SYNTHESES AND KINETIC STUDIES OF NITROGEN HETEROCYCLIC SULPHONES SULPHOXIDES AND SULPHIDES

a thesis

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William Vance Brown

Department of Medical Chemistry

John Curtin School of Medical Research

Australian National University

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The work described in this thesis was carried out by the candidate at the Australian National University. Where the work of others was employed, appropriate references have been given.

W. V. Brown

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NOMENCLATURE

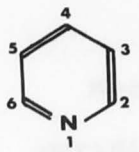
In this thesis the following nomenclature has been employed.

Alkyl-(or aryl-)sulphonyl has been used in describing a compound of the type $R\text{-}SO_2\text{-}R'$, e.g. 2-methylsulphonylpyridine, and in the discussion these compounds have frequently been referred to as sulphones.

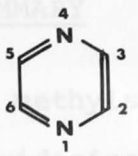
Alkyl-(or aryl-)sulphinyl has, similarly, been used in describing a compound of the general type R-SO-R', e.g. 2-methylsulphinylpyridine, and in this case the family name sulphoxide has been used when referring to these compounds generally.

Alkyl-(or aryl-)thio and sulphide, similarly, referred to compounds of the type R-S-R', e.g. 2-methylthiopyridine.

The heterocyclic ring systems discussed in this thesis are pyridine, pyrazine, pyridazine, pyrimidine, quinoline, isoquinoline, quinoxaline, phthalazine, cinnoline and quinazoline. The structures and numbering of these heterocycles are given below:-



Pyridine



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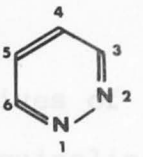
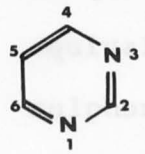
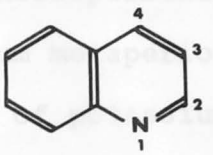


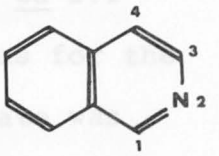
Pyridazine



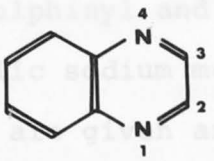
Pyrimidine



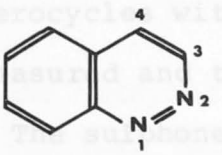
Quinoline



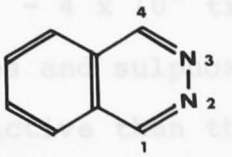
Isoquinoline



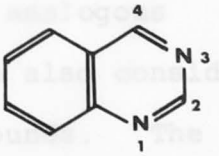
Quinoxoline



Cinnoline



Phthalazine



Quinazoline

SUMMARY

Methylsulphonyl and methylsulphinyl derivatives of pyridine, pyrazine, pyridazine, quinoline, isoquinoline, quinoxaline, cinnoline and phthalazine were prepared by oxidation of the corresponding methylthio compounds. The sulphoxides were prepared by oxidation with 1 equivalent of m-chloroperbenzoic acid or ca 1.2 equivalents of sodium metaperiodate, whereas for the sulphones an excess of potassium permanganate was used. Also prepared were the corresponding derivatives of quinoxaline in which the methyl group was replaced by either ethyl, isopropyl, or t-butyl.

The kinetics of reaction of these methylsulphonyl, methylsulphinyl and methylthio heterocycles with methanolic sodium methoxide were measured and the results are given and discussed. The sulphones and sulphoxides were found to have similar reactivities and to be considerably more reactive (35-120 times) than the corresponding chloro compounds. The methylthio compounds, though, were much less reactive (5×10^3 - 4×10^5 times) than the analogous sulphones and sulphoxides, and were also considerably less reactive than the chloro compounds. The

effects of activation by ring nitrogen atoms and annelation were in qualitative agreement with results obtained by earlier workers in studies of the reactivities of chloro compounds.

Replacement of the methyl group by larger alkyl groups in the three series led to reduced reactivity, and this reduction was largest for the sulphoxides and least for the sulphides.

Physical properties, i.e. ionization constants, ultraviolet, infrared and n.m.r. spectra were recorded and are discussed. The ionization constants clearly showed the powerful electron withdrawal of the methylsulphonyl and methylsulphinyl groups especially in the α position.

Potentially useful reactions of the methylsulphonyl heterocycles with various nucleophiles (viz. sodium hydroxide, sodium hydrogen sulphide, sodium cyanide, ammonia, methylamine, n-propylamine, and hydrazine hydrate) were found generally to proceed smoothly and in good yield.

CONTENTS

CHAPTER 1

INTRODUCTION

A study of nitrogen heterocyclic sulphides, sulphoxides and sulphones involves simultaneously a study of the comparative reactivities of the various heterocycles concerned and of the chemistry and effects of the sulphur-containing substituents. This introductory chapter begins with an account of previous work on the preparation and reactions of some of these compounds. Then are discussed the results of previous kinetic studies on the displacement, with anionic nucleophiles, of the chloro substituent in relevant heterocyclic ring systems; and the main theories on the mechanism of this replacement.

I Previous Work on the Preparation and Reactions of Nitrogen Heterocyclic Sulphides, Sulphoxides and Sulphones

The following discussion is limited to derivatives of pyridine, pyrazine, pyrimidine and pyridazine and the ring systems formed by the annelation of these heterocycles with one benzene ring.

a) Sulphides

i Preparation

The methods of preparation of alkyl- and aryl-thio heterocycles are well known and have been widely reported in the literature so they will not be discussed in detail here.

Briefly these main methods are, alkylation of the corresponding mercapto heterocycle, e.g. methylation of 1A with methyl iodide in aqueous sodium hydroxide to give 1B, displacement of another substituent (usually halo) by the appropriate mercaptide ion, and ring closure incorporating the alkyl- or aryl-thio group into the molecule.

ii Reactions

The only quantitative work on the nucleophilic displacement of the alkyl- or aryl-thio group from nitrogen heterocycles appears to be that by Brown and Foster (1966 a, b) on the butylaminolysis of various alkylthiopyrimidines (1C and 1D). They reported that a methylthio group was replaced from 10^4 to 2×10^5 times less readily than was the chloro substituent, and that the reactivity of the alkylthiopyrimidines tended to decrease with increasing size of the alkyl group.

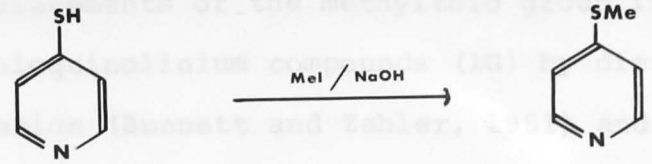
Previous qualitative aminolyses of alkyl- or aryl-thio heterocycles have been reported fairly widely, usually in the highly activated pyrimidines and quinazolines. Aminolyses of alkylthiopyrimidines have been extensively used in the preparation of potential antimalarials (Curd and Rose, 1946; Curd, Davis and Rose, 1946; Hull, Lovell, Openshaw, Payman and Todd, 1946; Curd, Raison and Rose, 1946; Curd, Davis, Owen, Rose and Tuey, 1946a, b; Curd, Richardson and Rose, 1946; Basford, Curd and Rose, 1947; Hull, Lovell, Openshaw and Todd, 1947). Cresswell and Strauss (1963) reported the facile displacement (10-20 min.; refluxing in aqueous solution) of the 2-methylthio group from 4-amino-6-hydroxy(or amino)-2-methylthio-5-nitrosopyrimidine by several amines; ammonia, on the other hand, gave a poor yield of amine with the 6-hydroxy compound and none at all with the 6-amino derivative.

In the quinazoline series, Leonard and Curtin (1946) reported the replacement of a 4-methylthio group by various amines, and Curd, Hoggarth, Landquist and Rose (1948) reported displacement of the 4-p-chlorophenylthio group from substituted quinazolines by amines.

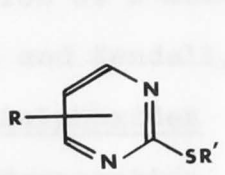
Cheeseman (1957) mentioned preliminary work on replacement of the methylthio group in 2-methylthio-quinoxaline by alcoholic methylamine and dimethylamine and claimed it went less readily than the chloro compound.

Displacement of alkyl- or aryl-thio groups by other nucleophiles have been reported. Koppel, Springer, Robins and Cheng (1961) and Daves, Baiocchi, Robins and Cheng (1961) recorded displacements of the 2-methylthio group from substituted pyrimidines (e.g. 1E) by hydrosulphide anion, to give the mercapto compound (e.g. 1F) and Falco, Hitchings, and Russell (1949), Matsukawa and Ohta (1949,a,b) and Bretschneider and Egg (1967) have reported the acid hydrolyses of substituted 2-alkyl- and aryl-thiopyrimidines to give the corresponding hydroxy compounds. Reactions of 4-arylthioquinazolines with hydroxide ions (Curd, et al., 1948) and 4-alkylthioquinazolines with alkoxide ions (Legrand and Lozac'h, 1963) have been observed.

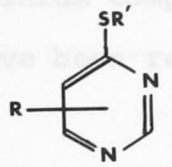
The methylthio group in 4-hydroxy-2-methylthio-pyrimidine and 5-ethoxycarbonyl-4-methyl-2-methylthio-pyrimidine has been replaced by the hydrazino group on treatment of these compounds with hydrazine hydrate in ethanol (Chi and Wu, 1957).



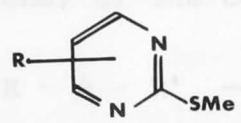
1A 1B

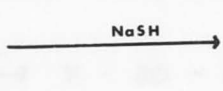


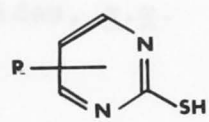
1C



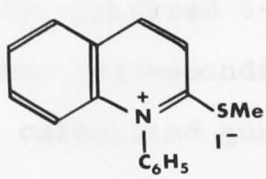
1D



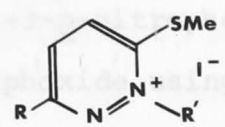




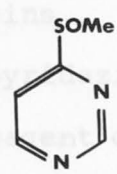
1E 1F



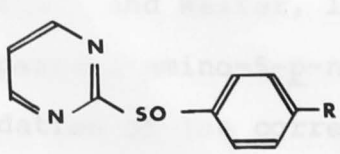
1G



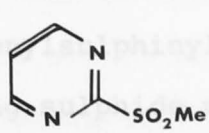
1H



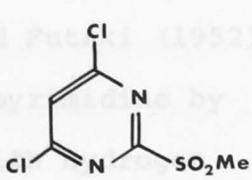
1J



1K



1L



1M

Replacements of the methylthio group in 2-methylthioquinolinium compounds (1G) by diethylmalonate anion (Bunnett and Zahler, 1951) and in 3-methylthiopyridazinium compounds (1H) by the zwitterion of 2-methylbenzothiazolinium compounds (Duffin and Kendall, 1959) also have been recorded.

b) Sulphoxides

i Preparation

The few heterocyclic sulphoxides hitherto reported were made by oxidation, under controlled conditions, of the corresponding sulphides, e.g.

$$R - S - R' \xrightarrow{'O'} R - SO - R'$$

Hydrogen peroxide, usually in acetic acid, has been most widely used. Gregory, Overend and Wiggins (1949) oxidised 6-methyl-3-p-nitrophenylthiopyridazine to the corresponding sulphoxide using this reagent or the calculated quantity of potassium permanganate. Oxidation of 6-methylthionicotinamide with hydrogen peroxide in acetone gave 6-methylsulphinylnicotinamide (Forrest and Walker, 1948). Yanagita and Futaki (1952) prepared 2-amino-5-p-nitrophenylsulphinylpyrimidine by oxidation of the corresponding sulphide with hydrogen peroxide and Hill and Krause (1964) prepared

3-chloro-6-methylsulphinylpyridazine similarly. Carpenter and Shaw (1965) prepared several 5-alkylsulphinyl-2,4-dihydroxypyrimidines by oxidation of the corresponding sulphides with hydrogen peroxide, or fuming nitric acid. These reagents were also used in the preparation of 2,4-dihydroxy-5-methylsulphinylpyrimidine (Bretschneider and Egg, 1967) and various alkylsulphinylhalopyridines (Johnston, 1967). Hydrogen peroxide also was used in the preparation of 2-methylsulphinylpyridine (Courtot and Zwilling, 1938) but full details were not given. Shaw, Bernstein, Losee and Lott have reported the preparation of 2-benzylsulphinylpyridine by the oxidation of 2-benzylthiopyridine by 1 equivalent of perbenzoic acid in chloroform. Brown and Ford (1967) used 1 equivalent of m-chloroperbenzoic acid in chloroform to prepare methylsulphinyl- and phenylsulphinylpyrimidines; but for 2-methylsulphinylpyrimidine, aqueous sodium metaperiodate was used.

ii Reactions

The only quantitative work on the nucleophilic displacement of the methyl- or phenyl-sulphinyl group appears to be recent work by Brown and Ford (1967) and Ford (1968) in the pyrimidine series. They

reported kinetics of replacement of the substituent in 2- and 4-methylsulphinylpyrimidine, (e.g. 1J) by n-pentylamine in dimethylsulphoxide and found it to be a good leaving group; rather better than chloro and similar to methylsulphonyl. They also reported kinetics of reaction of some p-substituted 2-phenylsulphinylpyrimidines (1K) with aqueous sodium hydroxide. A few qualitative reactions such as the reactions of 4-methylsulphinylpyrimidine, with sodium hydroxide to give 4-hydroxypyrimidine, and with propanolic sodium propoxide to give 4-propoxypyrimidine; the oxidation of 2-methylsulphinylpyrimidine (m-chloroperbenzoic acid) to the sulphone and its reduction (hydriodic acid) to the corresponding sulphide were also reported.

c) Sulphones

i Preparation

Heterocyclic sulphones have been reported fairly widely in the literature. In several papers series of related sulphones have been prepared for biological screening. The most common method of preparation was the oxidation of the corresponding sulphide, e.g.: $R - S - R' \xrightarrow{'O'} R - SO_2 - R'$ and for this purpose several oxidising agents have been used.

Sprague and Johnson (1935), and Johnson and Sprague (1938) used chlorine gas in water to prepare various 2-ethylsulphonylpyrimidines from the corresponding ethylthio compounds. In some cases, especially at higher temperatures, they observed simultaneous formation of the corresponding chloro compound. Similarly Nyberg and Cheng (1964) oxidised 3-chloro-6-methylthiopyridazine and 4-chloro-6-methylthiopyrimidine to the corresponding methylsulphonyl compounds using chlorine in aqueous methanol.

Hydrogen peroxide, usually in acetic acid (i.e. peracetic acid) was widely used. By this means Cheeseman (1957) prepared 2-methylsulphonylquinoxaline, from the corresponding sulphide. Similarly various substituted ethylthio- and phenylthio-pyrimidines were oxidised to the sulphones (Klötzer, 1961; Hoffmann-la Roche, 1963). Kukolja and Cvetnić (1962) prepared 2,6-dimethoxy-4-methylsulphonyl- (or benzylsulphonyl-) pyrimidines using hydrogen peroxide in formic acid to oxidise the corresponding sulphides.

Potassium permanganate, usually in aqueous acetic acid, has also been frequently used to perform the oxidation of heterocyclic sulphides to sulphones.

As early as 1900 Marckwald, Klemm, and Trabert used this reagent in the preparation of various pyridine sulphones. Takahashi and Ueda (1953) also used this reagent to prepare various substituted 2- and 3-methylsulphonylpyridines and similarly Bednyagina and Postovskii (1956) prepared several 1-alkylsulphonyl-4-phenylphthalazines.

Various other oxidising agents have been used occasionally. Colonna (1941) used chromic oxide and sulphuric acid to oxidise 5-nitropyridine-2-thiosalicylic acid to the corresponding sulphone and Caldwell and Sayin (1952) oxidised 2-acetamido-5-*p*-nitrophenylthiopyridine to the sulphone using chromic acid in acetic acid. Johnston (1967) used potassium chromate in sulphuric acid, and fuming nitric acid, to prepare several alkylsulphonylhalopyridines. Brown and Ford (1967) used *m*-chloroperbenzoic acid in chloroform to convert 4- and 5-methylthiopyrimidines to the sulphones. They also used this reagent to oxidise 2-methylsulphinylpyrimidine to 2-methylsulphonylpyrimidine.

Another preparative route to sulphones, most commonly used for arylsulphonyl heterocycles, is the replacement of the chloro substituent in a chloro

heterocycle by the appropriate sulphinate ion, e.g.:

$$R - Cl + R' - SO_2^- \longrightarrow R - SO_2 - R' + Cl^-.$$

Morren (1959a) prepared 3-chloro-6-p-tolylsulphonylpyridazine and 3,6-di-p-tolylsulphonylpyridazine from 3,6-dichloropyridazine and sodium-p-toluenesulphinate. 2-Amino-4-methyl-6-p-aminophenylsulphonylpyrimidine and its 6-p-acetamidophenylsulphonyl analogue were prepared from 2-amino-6-chloro-4-methylpyrimidine with potassium p-aminobenzenesulphinate (or its acetylated derivative) in ethanol using traces of copper dust and iodine as catalysts (Semonsky and Cerny, 1951).

Occasionally heterocyclic sulphones have been made by ring closure incorporating a sulphonyl group into the molecule. Substituted arylsulphonylpyrimidines (Atkinson, Shaw, and Sugowdz, 1957) and quinolines (Tröger and Menzel, 1921-1922) have been made in this way.

ii Reactions

Kinetic studies of the replacement of the methylsulphonyl group in the 2- and 4-positions of pyrimidine (e.g. 1L) by n-pentylamine and cyclohexylamine in dimethylsulphoxide have been made by Brown and Ford (1967). They found it to be a good leaving

group being somewhat more labile than chloro and of similar reactivity to the methylsulphinyl group. The displacement of substituted 2-phenylsulphonyl groups in the 2-position of pyrimidine by n-pentylamine and hydroxide ion (Ford, 1968) was also studied. Qualitative reactions of pyrimidine sulphones with a range of nucleophiles (azide, cyanide, hydrazine, hydroxide, ethoxide and butoxide) to give the expected product were also recorded.

Though no quantitative work had been done prior to the above, several reports of nucleophilic displacements in sulphonyl heterocycles had been described, and it had been recognized (Bunnett and Zahler, 1951, excepted) that the alkyl- or aryl-sulphonyl group was a comparable (or better) leaving group than a chlorine substituent. Sprague and Johnson (1936) first reported the displacement of an ethylsulphonyl group from the 2-position of substituted pyrimidines by ethoxide ion, hydroxide ion, aniline and ammonia; and acid hydrolysis to give the hydroxy compound was also recorded. They commented on the similarity of these reactions with those of the corresponding chloro compounds, and they were unable to replace a 4-chloro substituent in 4-chloro-2-ethylsulphonyl pyrimidines

by ethoxide ion without simultaneously replacing the 2-ethylsulphonyl group. Similar reactions of substituted 2-ethylsulphonylpyrimidines with hydroxide ion, alkoxide ions, ammonia and hydrochloric acid have been reported by Chi and Ling (1956 a,b; 1957 a,b).

Reactions of 4,6-dichloro-2-methylsulphonylpyrimidine (1M) with hydroxide ion (Koppel, Springer, Robins and Cheng, 1961) and ethylenimine (Koppel, Springer, and Cheng, 1961) gave preferential displacement of the 2-methylsulphonyl group and they commented that methylsulphonyl was a better leaving group than the chloro substituent. Displacement of the methylsulphonyl group in substituted 2-methylsulphonylpyrimidines by ammonia and amines has been reported (Nairn and Tieckelmann, 1960).

There have been several reports of the replacement of alkyl-or aryl-sulphonyl groups from substituted pyrimidines by sulphanilamide anion. Shepherd, Taft, and Krazinski (1961) and Taft and Shepherd (1962) reported that the displacement of the methylsulphonyl group in pyrimidines (e.g. 1N) with sulphanilamide anion went very much more readily than for the corresponding chloro compounds and attributed this to a

specific hydrogen bond stabilization of the transition state (1 O). Other similar displacements have been recorded by Hoffmann-la Roche (1963), Spofa (1963), Klötzer (1961) and Kukolja and Cvetnić (1962).

Acid and alkaline hydrolyses of several 1-alkylsulphonyl-4-phenylphthalazines have been reported (Bednyagina and Sokolov, 1959) and also hydrolysis of 4-phenyl-1-p-nitrophenylsulphonyl-phthalazine with sodium hydroxide (Bednyagina and Postovskii, 1956). Morren (1956 a,b,c) has reported the displacement of the arylsulphonyl group from 3-p-tolylsulphonylpyridazines by ammonia, sodium hydrogen sulphide, sodium alkyl mercaptides, sodium alkoxides and sodium p-aminobenzenesulphonamide. Forrest and Walker (1948) observed the replacement of the methylsulphonyl group from substituted pyridines by methanol and ammonia to give methoxy- and amino-pyridines; and Cheeseman (1957) observed the displacement of the substituent in 2-methylsulphonylquinoxaline with sodium hydroxide.

There have been reports of preferential displacement of the chloro substituent in heterocycles substituted with chloro and methylsulphonyl groups.

Nyberg and Cheng (1964) observed that in 3-chloro-6-methylsulphonylpyridazine (1P) and 4-chloro-6-methylsulphonylpyrimidine (1Q), the chlorine substituent is displaced by various amines. This was probably due to the activation effect of the methylsulphonyl group. An extreme case of this phenomenon occurred with 3-methoxy-6-methylsulphonylpyridazine (1R) when the methoxy group was preferentially displaced by sulphanilamide anion (Shepherd and Fedrick, 1965).

II Previous Kinetic Studies on Nucleophilic Displacements of the Chloro substituent from Substituted Azines

Previous kinetic studies on nitrogen heterocycles have been mainly confined to displacement of halo substituents (chloro principally) and much of this work has been on displacement by amines. The following discussion will be restricted to studies on the displacement by charged nucleophiles (because of its relevance to the present work) of chloro substituents from the ring systems covered in this thesis.

Kinetic studies of nucleophilic displacement by methanolic methoxide ion of the chlorine substituent in 2-, 3-, and 4-chloropyridines (Liveris and Miller, 1963; Kato, Hayashi, and Anzai, 1967), 3-chloro-

pyridazine (Hill and Krause, 1964), 2- and 4-chloroquinolines (Illuminati and Marino, 1958; Belli, Illuminati, and Marino, 1963) 2-chloroquinoxaline and 4-chlorocinnoline (Illuminati, 1964) have been made.

Chapman and Russell-Hill (1956) studied the reactions of most of the above compounds and 1-chlorophthalazine with sodium ethoxide in ethanol and Chan and Miller (1967) studied the reactions of 3- and 4-chloropyridazines and 2-chloropyrazine with p-nitrophenoxide anion in methanol.

The main points from the above work are discussed below.

a) Activation by ring nitrogen atoms

Insertion of an aza group into a chlorobenzene or a chloronaphthalene α or γ to the substituent produced a substantial increase in the ease of replaceability. Thus, 2-chloroquinoline reacted 6.9×10^9 times faster than β-chloronaphthalene with ethoxide ion (Chapman and Russell-Hill, 1956). This activation by aza groups was of the same order as that produced by an exocyclic nitro group in the γ position but somewhat less in the α position (Chapman and Russell-Hill, 1956).

Insertion of a second aza group into pyridines or quinolines also produced considerable activation. This effect was greatest when it was placed α or γ to the leaving group, but was still considerable when placed β. 4-Chlorocinnoline with sodium ethoxide in ethanol reacted 7.3×10^3 fold faster than did 4-chloroquinoline (Chapman and Russell-Hill, 1956). The appreciable activation by a β ring nitrogen was also observed by Chan and Miller (1967) in the monocyclic series and has been attributed to the inductive effect of the aza group (Illuminati, 1964). Thus in all cases the diazines were considerably more reactive than the corresponding monoazines.

b) Alpha versus gamma activation by ring nitrogen atoms

Liveris and Miller (1963) reported that at 100° 4-chloropyridine reacted 12 times faster than 2-chloropyridine with methanolic sodium methoxide, similarly Chapman and Russell-Hill (1956) found the former to be more reactive with ethanolic sodium ethoxide.

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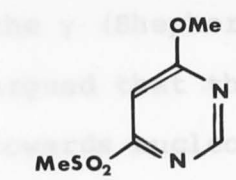
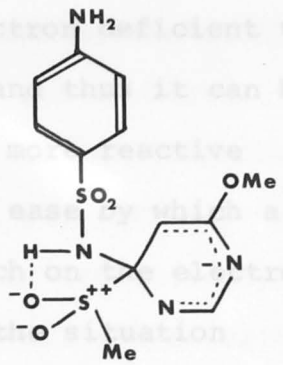
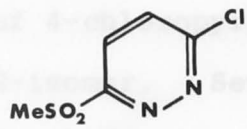


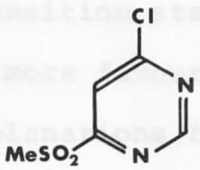
1N



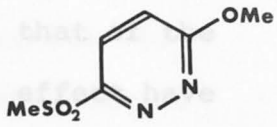
1O



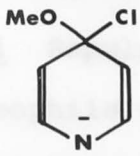
1P



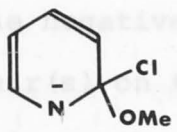
1Q



1R

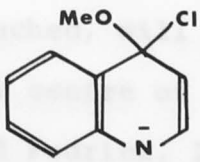


1S

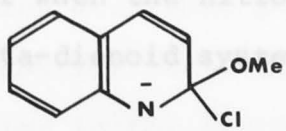


1T

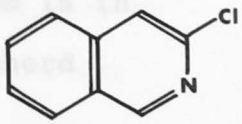
1U



1V



1W



1X

α position of pyridine was more electron deficient than the γ (Shepherd and Fedrick, 1965) and thus it can be argued that this position should be more reactive towards nucleophiles. However the ease by which a reaction proceeds depends not so much on the electron density in the ground state but on the situation prevailing in the transition state. It would seem, therefore, that the transition state for the reaction of 4-chloropyridine is more favoured than that of the 2-isomer. Several explanations for this effect have been offered.

i The greater stability of the para-quinonoid type transition state (1S) as opposed to its ortho-quinonoid (1T) counterpart (Chapman and Rees, 1954).

ii Repulsion between the negatively charged nucleophile and the lone pair(s) on the ring nitrogen atoms when attack is at the α position (Shepherd and Fedrick, 1965; Edwards and Pearson, 1962).

iii Localisation energy in producing (1U), or some form approaching it as the transition state is reached, will be lower when the nitrogen atom is in the centre of the penta-dienoid system (Shepherd and Fedrick, 1965).

With the pyridazines, Chan and Miller (1967) observed slightly higher reactivity for 4-chloropyridazine with p-nitrophenoxide anion in methanol, than for the 3-isomer; and somewhat surprisingly found that 2-chloropyrazine which was activated by α and β ring nitrogen atoms (like 3-chloropyridazine) was more reactive than either.

In the benzene annelated series, e.g. 2- and 4-chloroquinolines, the positional differences were less marked and variable. This is probably due to some loss of resonance energy in the transition state of the 4-compound (1V) relative to that of the 2-isomer (1W).

c) Effect of annelation with a benzene ring

Annelation of a monocyclic heterocycle with a benzene ring usually produced a considerable increase in the ease of replacement of the substituent. At 90^{o} 4-chloroquinoline reacted 8-fold faster with ethanolic sodium ethoxide than did 4-chloropyridine (Chapman and Russell-Hill, 1956). This was probably due to the greater area available for delocalisation of charge in the transition state (1V; 1W) and was manifest in a reduction in the activation energy.

An exception to this rule occurred when an azine nitrogen and a leaving group were in positions 2 and 3 relative to each other, e.g. 3-chloroisoquinoline (1X) which was less reactive than 2-chloropyridine.

d) Theoretical calculations

Two main methods have been used in attempts to calculate relative reactivities and both are summarised by Shepherd and Fedrick (1965). The first, which has been mentioned earlier, involved calculations of electron densities of different positions in the ground state and usually failed to predict the greater reactivity of the 4-position of pyridine. The other involved estimation of theoretical activation energies ($\Delta U - \Delta U^{o}$) referring to the absolute zero (Longuet-Higgins, 1950 a,b) and although apparently unsuccessful in the azabenzene series, has been found to be qualitatively correct for the reactions of a limited range of chloroazanaphthalenes with piperidine (Chapman and Russell-Hill, 1956). However the theory assumed a constant entropy of activation and was therefore not applicable to reactions involving charged nucleophiles which do not meet this criterion. Evans and

Polanyi (1936) suggested that if $\Delta S^{\ddagger}$ was not constant, then the heats of activation at absolute zero were better related to the logarithm of the rate at the reaction temperature than to the activation energy; accordingly Chapman and Russell-Hill (1956) plotted the logarithms of the reaction rates with ethanolic ethoxide ion against calculated activation energies and found a semi-quantitative fit for only a limited range of compounds. Qualitatively however its conclusions were fairly well borne out by experiments.

In short, then, it appears that while theoretical calculations have been sometimes useful qualitatively e.g. they predicted the poor reactivity of 3-chloroisoquinoline (1X), they were unreliable quantitatively and will therefore be treated with caution in this thesis.

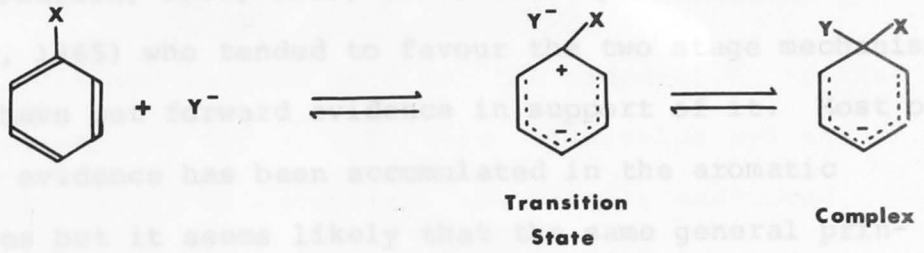
III The Mechanisms of Nucleophilic Heteroaromatic Substitution

Reactions between chloro substituted azabenzenes and azanaphthalenes with charged nucleophiles are invariably bimolecular and have not been

observed to be catalysed appreciably by acid or base. Two principal mechanisms for this bimolecular process have been proposed. Bunnett and Zahler (1951) pointed out that due to stereochemical and quantum mechanical considerations there was no acceptable transition state model in which benzenoid resonance was maintained. They therefore proposed a two-stage mechanism (Fig.1) which involved an intermediate σ complex of 'some' stability in which the carbon atom at the site of attack changes from sp^2 to sp^3 hybridisation and in which, depending on the species involved, either stage may be rate determining.

In the absence of "critical evidence in its favour" Chapman (1955) regarded this mechanism as "an unnecessary and complicating postulate" and preferred to formulate a simple one stage bimolecular mechanism (Fig.2) involving simultaneous bond making and breaking. Although the nature of the transition state was not clear he regarded that given in Fig.2 as providing a good guide to its structure, but pointed out that this formulation is "not intended to imply that the C-X bond is necessarily unaltered or that the C-Y bond is fully formed."

FIG 1


Transition
State
Complex

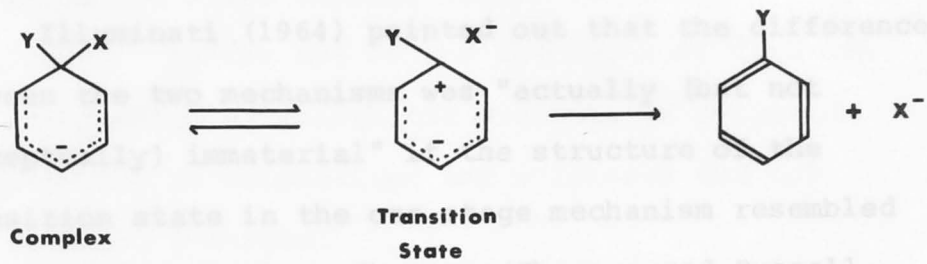
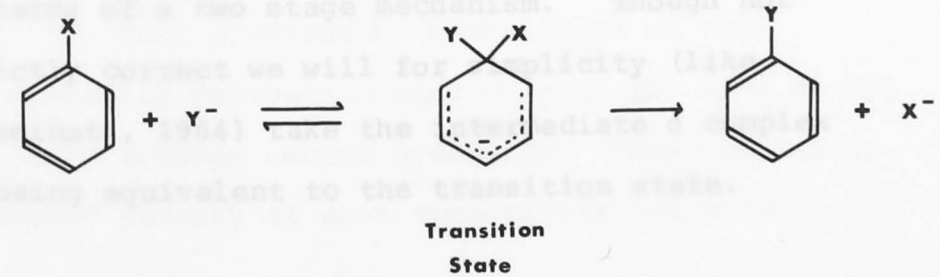

Complex
Transition
State

FIG 2


Transition
State

The question of mechanism has been much discussed by reviewers (Bunnett, 1958; Illuminati, 1964; Shepherd and Fedrick, 1965; Ross, 1963; and Capon, Perkins and Rees, 1965) who tended to favour the two stage mechanism and have put forward evidence in support of it. Most of this evidence has been accumulated in the aromatic series but it seems likely that the same general principles may apply in displacements from heterocycles.

Illuminati (1964) pointed out that the difference between the two mechanisms was "actually (but not conceptually) immaterial" if the structure of the transition state in the one stage mechanism resembled that of the σ complex; Chapman (Chapman and Russell-Hill, 1956) seemed prepared to concede this point. The difference between the mechanisms is usually kinetically not detectable and this is the case for the kinetics described in this thesis. However as the bulk of the evidence appears to support it, the reaction parameters will be discussed, where necessary, in terms of a two stage mechanism. Though not strictly correct we will for simplicity (like Illuminati, 1964) take the intermediate σ complex as being equivalent to the transition state.

CHAPTER 2

PREPARATION OF COMPOUNDS

Various methods used for the preparation of the three compound types, alkylthio, alkylsulphinyl and alkylsulphonyl heterocycles, are briefly mentioned. The methods which were used in this work are described and where appropriate, results are tabulated. At the end of the chapter some data are presented which establish the products of oxidation of sulphides as sulphoxides and sulphones and not the isomeric N-oxides.

I Alkylthio Compounds

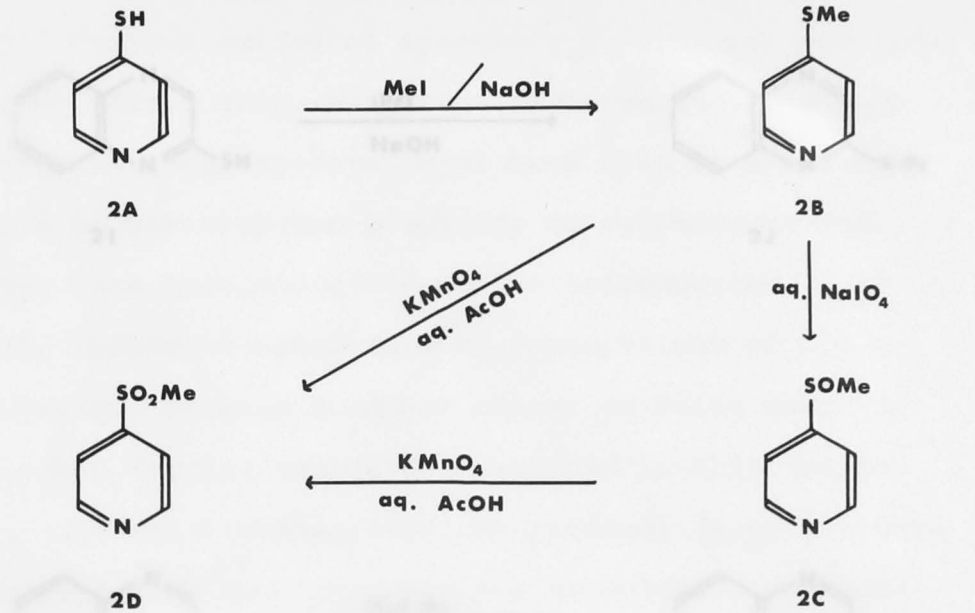
Alkylthio heterocycles have most frequently been prepared by alkylation of the mercapto compound or by reaction of the chloro heterocycle with the appropriate mercaptide ion as outlined in the Introduction.

In this work, the methylthio heterocycles (e.g. 2B) were prepared by methylation of the corresponding mercapto compound (e.g. 2A) with methyl iodide in aqueous sodium hydroxide. These reactions proceeded readily at room temperature and were

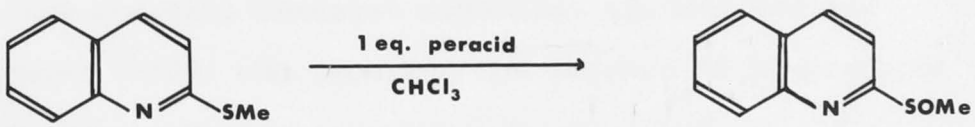
summarised by Albert and Barlin (1959, 1962). Compounds for kinetic studies were purified by column chromatography (alumina/chloroform) and crystallisation.

2-Ethylthioquinoxaline (Cuiban, Ionesco, Bala and Steresco, 1963) and the previously unknown 2-isopropylthioquinoxaline (2J) were similarly prepared from 2-mercaptoquinoxaline (2I) with the appropriate alkyl iodide in sodium hydroxide but in these cases more severe conditions were required and the reactions were carried out under reflux. The compounds were purified by column chromatography (alumina/chloroform), and recrystallisation in the case of 2-ethylthioquinoxaline, and distillation for the liquid 2-isopropylthioquinoxaline.

This method was not successful for 2-t-butylthioquinoxaline (2L). It was, however, prepared in good yield by refluxing 2-chloroquinoxaline (2K) with sodium t-butyl mercaptide in aqueous ethanol and purified by thin layer chromatography (silica gel/benzene) and crystallisation.

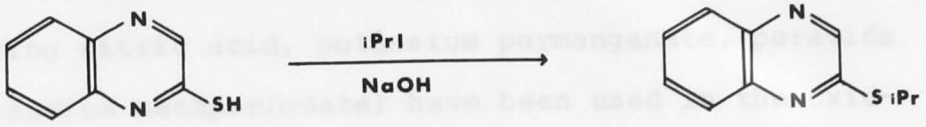


2A 2B 2D 2C

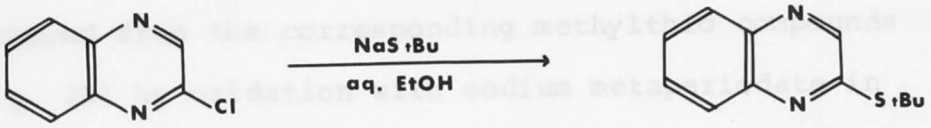


2E 2F

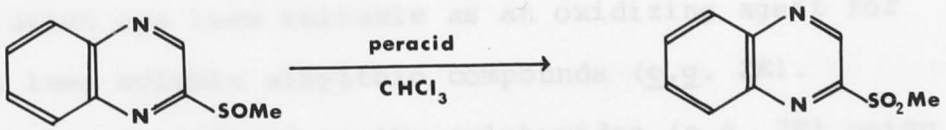
2G 2H



2I 2J



2K 2L



2M 2N

II Alkylsulphinyl Compounds

Various oxidising agents (viz. hydrogen peroxide, fuming nitric acid, potassium permanganate, peracids or sodium metaperiodate) have been used in the oxidation of heterocyclic sulphides to sulphoxides and these have been discussed in the Introduction. Of these sodium metaperiodate or 1 equivalent of m-chloroperbenzoic acid was chosen as being most suitable for the compounds described in this thesis.

2- and 4-Methylsulphinylpyridines (e.g. 2C) were prepared from the corresponding methylthio compounds (e.g. 2B) by oxidation with sodium metaperiodate in water. The reaction proceeded at room temperature but a small quantity of sulphone was formed and a little starting material remained; cf. Leonard and Johnson (1962) who reported the absence of by-products with this reagent.

The above reagent which was used in aqueous solution was less suitable as an oxidizing agent for the less soluble alkylthio compounds (e.g. 2E). These were oxidised to the sulphoxides (e.g. 2F) using 1 equivalent of m-chloroperbenzoic acid in chloroform. The solutions of the reactants were initially mixed slowly, generally at 0°, and then allowed to stand

overnight at room temperature. This method worked well and usually only traces of by-products were formed.

Purification of these compounds posed some problems at first as some were low melting and distillation was undesirable because 4-methylsulphinylpyridine was found to decompose on vacuum distillation. However purification was achieved by column (alumina/chloroform) and thin layer (alumina/ether and chloroform) chromatography and recrystallisation from an appropriate solvent. The reagent used and yield of sulphoxide formed, in each case, are given in Table 1.

III Alkylsulphonyl Compounds

Several reagents (viz. chlorine, hydrogen peroxide, potassium permanganate, peracids, chromic acid and fuming nitric acid) have been used by other workers to oxidise alkylthio heterocycles to the corresponding sulphones and these have been discussed in the Introduction.

Of these reagents hydrogen peroxide was not tried because of reported complications.

Sometimes when the oxidation was expected to proceed to the sulphone the reaction stopped at the

TABLE 1

Preparation of alkylsulphinyl compounds by oxidation of alkylthio compounds

Product	Oxidising agent	Yield %
2-MeSO pyridine	$NaIO_4$	75
4-MeSO pyridine	$NaIO_4$	31
2-MeSO pyrazine	peracid*	37
3-MeSO pyridazine	peracid	47
4-MeSO pyridazine	peracid	32
2-MeSO quinoline	peracid	64
4-MeSO quinoline	peracid	64
1-MeSO isoquinoline	peracid	73
4-MeSO cinnoline	peracid	48
1-MeSO phthalazine	peracid	41
2-MeSO quinoxaline	peracid	46
2-EtSO quinoxaline	peracid	67
2-t-BuSO quinoxaline	peracid	53

* m-chloroperbenzoic acid

formation of sulphoxide (Gregory, Overend and Wiggins, 1949). Chi and Chen (1957 a,b; 1958) using hydrogen peroxide in ethanol above a certain concentration reported the oxidation proceeding beyond the sulphone to the hydroxy compound and Cheeseman (1957) when preparing 2-methylsulphonylquinoxaline reported simultaneous formation of 2-methylsulphonylquinoxaline-4-oxide and 2,3-dihydroxyquinoxaline.

Chromic acid and fuming nitric acid were avoided because of difficulties of usage.

Chlorine gave variable results with 3- and 4-methylthiopyridazine. In aqueous methanol with 3-methylthiopyridazine (2G) at -20° a 70% yield of the sulphone (2H) was obtained, but with 4-methylthiopyridazine under the same conditions the desired product was not obtained. Other workers, Brown and Ford (1967), Sprague and Johnson (1935), also obtained variable results with this reagent.

The oxidation of 3- and 4-methylthiopyridazine to the sulphones using m-chloroperbenzoic acid in chloroform was attempted but a mixture of products was obtained.

A widely reported and apparently very successful reagent was potassium permanganate in aqueous acetic

acid and this was found to be very successful for the preparation of the alkylsulphonyl compounds described in this thesis. The oxidation of the alkylthio compound (e.g. 2B) was quickly and easily performed and the product (e.g. 2D) was usually obtained in a high degree of purity and in good yield. Purification was achieved by recrystallisation or distillation except for 1-methylsulphonylphthalazine which had to be chromatographed over alumina in chloroform to remove traces of 1-hydroxyphthalazine. The yields obtained from the permanganate oxidations in all cases are listed in Table 2.

Several alkylsulphonyl compounds (e.g. 2D) were also prepared by oxidation of the corresponding sulphoxide (e.g. 2C) with potassium permanganate in acetic acid. The experimental procedure and purification of the product were similar to those used when the starting material was the corresponding sulphide. 2-Methylsulphinylquinoxaline (2M) was also oxidised to 2-methylsulphonylquinoxaline (2N) using m-chloroperbenzoic acid in chloroform; it was purified by recrystallisation from cyclohexane. Details of these oxidations of sulphoxides are given in Table 3.

TABLE 2

Preparation of alkylsulphonyl compounds by oxidation of alkylthio compounds with potassium permanganate

Product	Yield %
2-$MeSO_2$ pyridine	83
4-$MeSO_2$ pyridine	88
2-$MeSO_2$ pyrazine	69
3-$MeSO_2$ pyridazine	74
4-$MeSO_2$ pyridazine	49
2-$MeSO_2$ quinoline	68
4-$MeSO_2$ quinoline	68
1-$MeSO_2$ isoquinoline	71
4-$MeSO_2$ cinnoline	57
1-$MeSO_2$ phthalazine	56
2-$MeSO_2$ quinoxaline	71
2-$EtSO_2$ quinoxaline	69
2-$iPrSO_2$ quinoxaline	58
2-t-$BuSO_2$ quinoxaline	66

TABLE 3

Oxidation of sulphoxides to sulphones

Product	Oxidising agent	Yield
4-$MeSO_2$ pyridine	$KMnO_4$	67
3-$MeSO_2$ pyridazine	$KMnO_4$	63
2-$MeSO_2$ quinoline	$KMnO_4$	81
4-$MeSO_2$ quinoline	$KMnO_4$	43
4-$MeSO_2$ cinnoline	$KMnO_4$	36
2-$MeSO_2$ quinoxaline	$KMnO_4$	83
2-$MeSO_2$ quinoxaline	peracid*	69
2-$EtSO_2$ quinoxaline	$KMnO_4$	70

* m-chloroperbenzoic acid

Compounds prepared in this work (sulphones, sulphoxides and sulphides) except 1-methylsulphonylphthalazine, were stable to storage for periods of weeks (often much longer) and no special precautions were necessary. 1-Methylsulphonylphthalazine however gradually decomposed to give 1-hydroxyphthalazine, probably due to absorption of water (it was extremely hygroscopic), and subsequent hydrolysis.

The oxidations of sulphides conceivably could have involved either oxidation on sulphur and/or on nitrogen. The evidence available from this work, viz. products of reactions, and the infrared and n.m.r. spectra of the products of oxidation were consistent with their being sulphoxides and sulphones and not isomeric N-oxides. Thus reactions with methanolic sodium methoxide yielded the methoxy heterocycles in good yield and the infrared spectra showed characteristic peaks at 1040-1070 cm^{-1} for the sulphoxides, and at 1125-1170 and 1310-1325 cm^{-1} for the sulphones (cf. Bellamy, 1958). The n.m.r. signal of the methyl group shifted downfield by 0.3-0.4τ in each case in going from the methylthio to the methylsulphinyl compound and a similar downfield shift was observed on further oxidation to the methylsulphonyl compound.

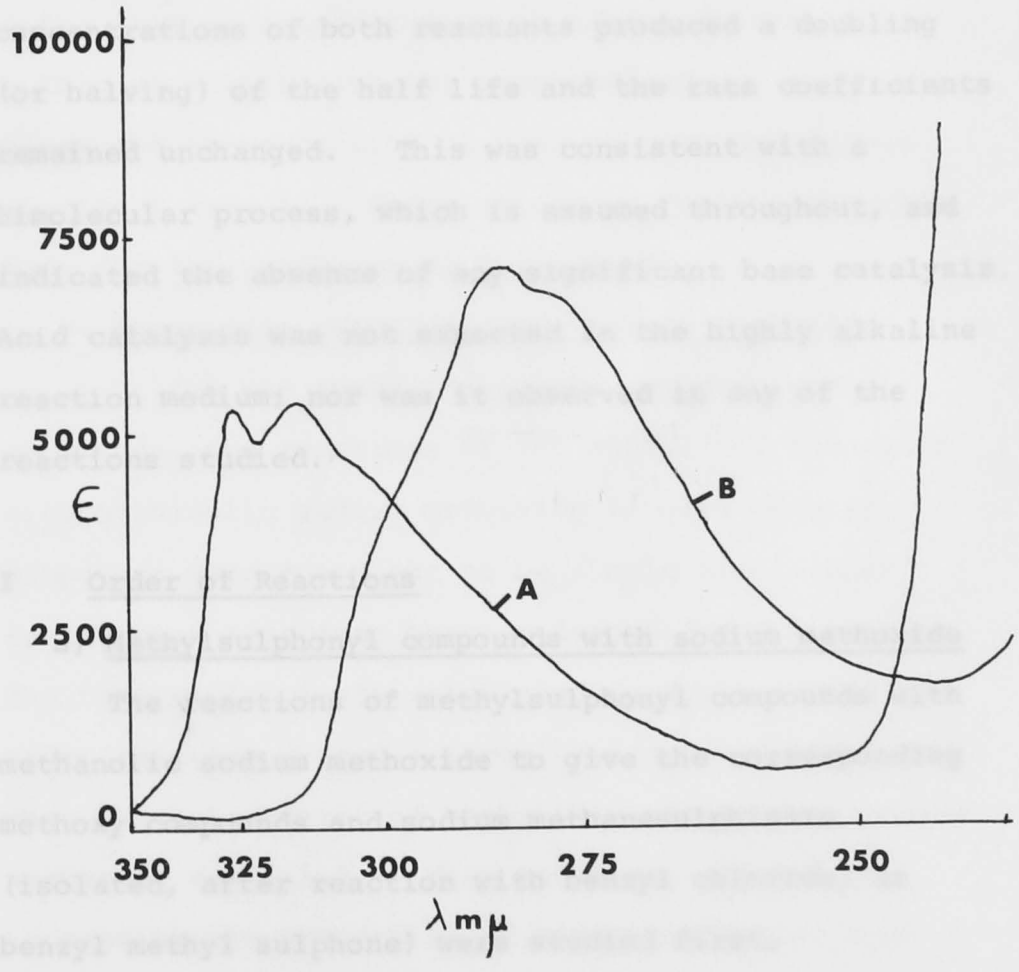
CHAPTER 3

KINETICS OF REACTION OF METHYLSULPHONYL, METHYLSULPHINYL AND METHYLTHIO HETEROCYCLES WITH SODIUM METHOXIDE

The kinetics of reaction of methylsulphonyl, methylsulphinyl and methylthio heterocycles with methanolic sodium methoxide have been studied spectrophotometrically. The ultraviolet wavelength used for analysis of the reaction mixture was chosen so as to give the maximum difference in absorption between the starting material and the methoxy compound produced; sometimes the appearance of a peak due to methoxy compound was followed and at other times the disappearance of an absorption peak in the reactant was used. An example of the spectral changes observed (with 4-methylsulphonylquinoline and methanolic sodium methoxide at 65^{o}) is shown in Fig.3. In all cases (with the two exceptions discussed in Section II) the reaction, as indicated by the ultraviolet spectra, proceeded smoothly to give the corresponding methoxy heterocycle as the only heterocyclic product (the ultraviolet spectrum of a reaction sample corresponding

FIG 3

Ultraviolet spectra of 4-methylsulphonyl-(A) and 4-methoxy-quinoline (B)



to t_∞ was that of the methoxy compound). This complete conversion to methoxy compound indicated that the reactions were 'clean' (i.e. free from any significant quantities of by-products) and that the reactions were not appreciably reversible (Chapman, Parker, and Soanes, 1954). The reactants were also stable in methanol alone, under the conditions of the kinetic runs. In every case halving (or doubling) the concentrations of both reactants produced a doubling (or halving) of the half life and the rate coefficients remained unchanged. This was consistent with a bimolecular process, which is assumed throughout, and indicated the absence of any significant base catalysis. Acid catalysis was not expected in the highly alkaline reaction medium; nor was it observed in any of the reactions studied.

I Order of Reactions

a) Methylsulphonyl compounds with sodium methoxide

The reactions of methylsulphonyl compounds with methanolic sodium methoxide to give the corresponding methoxy compounds and sodium methanesulphinate (isolated, after reaction with benzyl chloride, as benzyl methyl sulphone) were studied first,

$$\underline{e.g.}\quad R\text{-}SO_2Me + NaOMe \rightarrow ROMe + NaSO_2Me$$

The reactions were bimolecular and obeyed second order kinetics and the rate constants were calculated using the usual second order expression:

$$\underline{k} = \frac{2.303}{t(a-b)} \log \frac{b}{a} \frac{(a-x)}{(b-x)}$$

where $\underline{k}$ was the rate coefficient in $l.mole^{-1}\ sec.^{-1}$,

$\underline{a}$ the initial concentration of methoxide ion,

$\underline{b}$ that of methylsulphonyl compound and

$\underline{x}$ was the concentration of methoxy compound formed at time t (sec.). Where necessary corrections were made for the expansion of the solvent.

b) Methylthio compounds with sodium methoxide

Unlike the reactions of the methylsulphonyl compounds, the reactions of the methylthio compounds with methanolic sodium methoxide to give methoxy compounds were found not to be simple bimolecular replacement reactions obeying second order kinetics. The rate coefficients calculated as for a second order reaction showed a large upward trend with time when the molar ratio of methylthio compound to sodium methoxide was 1:1.7. This trend was reduced by increasing the proportion of sodium methoxide used.

Also complete conversion of the methylthio compound to methoxy compound was observed when only 30% of the molar equivalent of sodium methoxide was employed. However these reactions were found to be first order with respect to methylthio compound, and the rate varied directly with the initial sodium methoxide concentration. The equation employed in the calculations was:

$$\underline{k} = \frac{2.303}{at} \log \frac{b}{b-x}$$

(The rate constants were corrected for solvent expansion.) This result was consistent with a bimolecular process (as indicated by the doubling of times of 50% reaction on halving concentrations of reactants) in which the initial concentration of sodium methoxide was maintained throughout the reaction. It was postulated that the sodium methyl sulphide initially produced was oxidised to dimethyl disulphide (presumably by atmospheric oxygen) and that simultaneously sodium methoxide was regenerated, e.g.

$$2RSMe + 2MeO^- \rightarrow 2ROMe + 2MeS^-$$

$$2MeS^- + \text{'O'} + 2CH_3OH \rightarrow MeSSMe + 2CH_3O^- + H_2O \quad .$$

Evidence in support of this interpretation was obtained by identification of dimethyl disulphide in the reaction mixture. The trace of water produced from the low concentrations of reagents did not produce any observable complications.

That such oxidations of simple aliphatic mercaptides to disulphides proceed readily in alkaline solution with atmospheric oxygen was supported by the work of Xan, Wilson, Roberts, and Horton (1941). Accordingly we titrated with iodine samples of ethyl mercaptan (used instead of methyl mercaptan because of ease of handling) and sodium methoxide which had been heated in a sealed tube under conditions similar to those of the kinetic studies. It was found that the ethyl mercaptide anion was readily consumed. (Solutions for titration were acidified, and then quickly titrated.)

c) Methylsulphinyl compounds with sodium methoxide

The reactions of methylsulphinyl compounds with sodium methoxide to give the methoxy compounds and presumably initially sodium methanesulphenate (NaSOMe), behaved in a manner intermediate between those of methylsulphonyl and methylthio compounds.

Whereas the reactions of methylsulphonyl compounds and sodium methoxide obeyed second order kinetics, and those of methylthio compounds apparent first order kinetics, the reactions of methylsulphinyl compounds and sodium methoxide were found to fit best an order of 1.5. (Calculations of the second order rate coefficients gave an upward trend with time, and increase of methoxide ion concentration decreased this effect.) The reactions were bimolecular but the sodium methanesulphenate produced, like other compounds of this type (Kharasch, 1961; Kharasch and Bruice, 1951), was very unstable and presumably underwent a series of reactions leading to the formation of sodium methanesulphinate and dimethyl disulphide, _e.g._

$$RSOMe + {}^{-}OMe \rightarrow ROMe + {}^{-}SOMe$$

$${}^{-}SOMe + CH_3OH + \text{'O'} \rightarrow MeSO_2^{-} + MeSSMe + CH_3O^{-} + H_2O$$

The former was isolated after reaction with benzyl chloride, as benzyl methyl sulphone and the latter was identified in the reaction mixture. Although the exact nature of these changes was not known, the rate studies indicated that only _ca_ 0.5 molar equivalents of sodium methoxide per mole of methyl-

sulphinyl compound were consumed, and the overall reaction had order approximately 1.5. The equation giving the best fit for calculation of the rate coefficients for the methylsulphinyl compounds is given below:

$$\underline{k} = \frac{2.303}{t(\frac{a-b}{2})} \log \frac{b(\frac{a-x}{2})}{a(b-x)}$$

(Rate coefficients were corrected for solvent expansion or contraction where necessary.)

Further experimental evidence in support of this interpretation was obtained by adding fractional equivalents only of sodium methoxide to the reaction mixture and permitting the reaction to proceed as far as possible. Thus with 0.00, 0.15, 0.30, and 0.45 molar equivalents of sodium methoxide, the production of 4-methoxyquinoline from 4-methylsulphonylquinoline at 90° proceeded to 7, 35, 59 and 85% respectively.

II Anomalous Behaviour of 4-Methylsulphinylcinnoline and 4-Methylsulphinylpyridazine

As was mentioned earlier nearly all of the methylthio, methylsulphinyl and methylsulphonyl compounds with sodium methoxide reacted to give the

methoxy compounds as the only heterocyclic product. There were, however, two exceptions namely 4-methylsulphinylcinnoline and 4-methylsulphinylpyridazine which, in addition to the methoxy compound also gave the corresponding methylthio compound (to the extent of 25% and 6% respectively). This unusual change e.g. that for 4-methylsulphinylcinnoline and sodium methoxide is given in Fig.4, was first detected on examination of the ultraviolet spectra of the reaction mixtures, then confirmed by n.m.r. (which showed peaks clearly due to the previously established methoxy and methylthio compounds), thin layer chromatography and finally by separation and isolation of the products. The separation was effected by thin layer chromatography using silica gel or alumina and ether. Kinetics of nucleophilic displacement of the methylsulphinyl group by methoxide ion were calculated for the pyridazine which gave reasonable rate coefficients, but not for the cinnoline which, not unexpectedly, did not give constant rate coefficients. Preliminary work indicated that the formation of methylthio compounds was independent of the sodium methoxide concentration. The mechanism

of this reaction was not clear, nor was its restriction to these two compounds. Bunnett, Garbisch and Pruitt (1957) found that 2,4-dinitrodiphenyl sulphoxide reacted with piperidine to give 26% 2,4-dinitrodiphenyl sulphide and suggested that the benzenesulphenate anions produced may have given thiophenoxide ions which then acted as a nucleophile. Alternatively the methanesulphenate anion produced may have undergone oxidation with simultaneous reduction of the methylsulphinyl compound; or a simple disproportionation could have been involved.

III Discussion of Kinetic Results

The kinetics of reaction of methylthio, methylsulphinyl and methylsulphonyl derivatives of pyridine, pyrazine, pyridazine, quinoline, isoquinoline, quinoxaline, cinnoline and phthalazine with sodium methoxide in methanol have been studied and the results are given in Tables 4-6 of this Chapter.

In Table 4 are given representative examples of kinetic runs of methylthio, methylsulphinyl and methylsulphonyl heterocycles with sodium methoxide which showed that regular kinetics were observed

usually from ca 10% to ca 80% reaction when the rate coefficients were calculated using the expressions given above. The standard deviation was in general 3% or less and the rate coefficients were corrected to allow for expansion or contraction of the solvent methanol. The results of all the kinetic experiments are given in Table 5, and in Table 6 are given reaction parameters, viz.: the energy of activation, E; the Arrhenius factor, log A; and the transition state parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, calculated for the various reactions. Also, for comparison, some calculated rate coefficients, standardised at chosen temperatures, are included in Table 6. The results of these kinetic studies are discussed below.

a) Comparative reactivities of methylsulphonyl and methylsulphinyl compounds

The data presented in Tables 5 and 6 showed that there was little difference in reactivity between corresponding methylsulphonyl and methylsulphinyl compounds and this was consistent with findings by Brown and Ford (1967) with pyrimidine sulphones and sulphoxides. In most cases the reactivity of the sulphoxide varied from 0.5 (in the 2-position of pyridine) to 1.1 (in the 2-position of pyrazine) times

TABLE 4

Reactions of methoxide ions

4-Methylthiopyridazine at 110°

Methoxide ion 0.01097N, methylthio compound 0.004M.

Time (min.)	20.0	43.0	67.5	101.4	135.0	178.8	218.0	266.0	340.0
Reaction (%)	8.3	17.1	25.5	36.0	45.1	54.0	61.7	69.0	77.5
10^3k	6.60	6.64	6.64	6.71	6.76	6.61	6.72	6.69	6.69

Mean 10^3k = 6.67 ± 0.06; after correction for solvent expansion, 7.37.

1-Methylthiophthalazine at 100.95°

Methoxide ion 0.00498 N, methylthio compound 0.003 M.

Time (min.)	90.0	190.0	300.0	420.0	550	700	878	1105	1425
Reaction (%)	12.5	24.8	35.8	46.8	56.7	64.8	72.9	80.7	88.3
10^3k	4.95	5.02	4.94	5.01	5.09	5.04	4.97	4.96	5.06

Mean 10^3k = 5.00 ± 0.05; after correction for solvent expansion, 5.48.

4-Methylsulphinylquinoline at 50°

Methoxide ion 0.00652 N, methylsulphinyl compound 0.0038 M.

Time (min.)	86	173	278.5	399	551	723	920	1180	1500
Reaction (%)	9.9	17.9	26.9	36.2	46.1	54.4	62.1	70.7	78.1
10^3k	3.12	3.05	3.01	3.05	3.10	3.07	3.03	3.06	3.05

Mean 10^3k = 3.06 ± 0.03; after correction for solvent expansion, 3.16.

2-Methylsulphinylpyrazine at 40°

Methoxide ion 0.00563 N, methylsulphinyl compound, 0.000792 M.

Time (min.)	24.0	50.1	77.9	109.9	145.9	183.8	231.9	288.0	358.0	445.0
Reaction (%)	8.4	17.7	25.7	32.5	41.4	49.4	57.4	64.9	73.2	80.2
10^2k	1.08	1.15	1.13	1.07	1.10	1.11	1.11	1.11	1.12	1.12

Mean 10^2k = 1.11 ± 0.02; after correction for solvent expansion, 1.13.

2-Methylsulphonylpyridine at 108.7°

Methoxide ion 0.0123 N, methylsulphonyl compound, 0.0082 M.

Time (min.)	107	189.3	299.6	368	454	622	720	926	1101
Reaction (%)	13.3	21.2	29.4	34.6	40.9	49.4	54.7	61.6	66.2
10^3k	1.81	1.80	1.74	1.76	1.84	1.84	1.88	1.86	1.83

Mean 10^3k = 1.82 ± 0.04; after correction for solvent expansion, 1.97.

TABLE 4 continued

2-Methylsulphonylpyrazine at 49.9°

Methoxide ion 0.00238 N, methylsulphonyl compound, 0.00144 M.

Time (min.)	19.2	44.9	78.2	157.6	197.5	243.2	286	346
Reaction (%)	6.6	14.2	22.4	38.1	44.4	50.1	55.3	60.9
$10^2\underline{k}$	2.45	2.47	2.44	2.45	2.46	2.45	2.46	2.48

Mean $10^2\underline{k}$ = 2.46 ± 0.02; after correction for solvent expansion, 2.55.

2-Methylsulphonylquinoline at 60.0°

Methoxide ion 0.0104 N, methylsulphonyl compound, 0.00605 M.

Time (min.)	93.6	186.0	300.0	408.0	505.0	608.5	1047.7	1152.0	1277.0
Reaction (%)	13.5	24.2	35.3	42.9	48.8	55.1	72.1	74.1	76.5
$10^3\underline{k}$	2.68	2.59	2.63	2.57	2.55	2.60	2.68	2.62	2.58

Mean $10^3\underline{k}$ = 2.61 ± 0.05; after correction for solvent expansion, 2.72.

TABLE 5

Kinetic results for the reactions of methylthio, methylsulphinyl and methylsulphonyl compounds with methoxide ions

Temp.[a] (°C)	10^3[MeO$^-$]	10^3[Subst.]	$10^3 k$ [b]	$10^3 k$ [c] corr.	$t_{½}$ [d]	$t_{½}/t'_{½}$ [e]	$t_{½}/t'_{½}$ [f] calc.	An.λ(mμ)[g]	pH [h]
				2-Methylthiopyrazine					
129.9	8.77	3.49	2.50	2.83				322	6.0
139.9	8.77	3.49	5.15	5.90				322	6.0
150.0	8.77	3.49	10.5	12.1	122			322	6.0
150.0	4.33	1.70	10.5	12.1	246	2.03	2.02	322	6.0
				3-Methylthiopyridazine					
129.6	10.96	4.00	1.69	1.92				250	6.0
140.0	10.96	4.00	3.96	4.54	265			250	6.0
140.0	5.48	2.00	3.89	4.45	555	2.09	2.00	250	6.0
150.0	10.96	4.00	8.44	9.75				250	6.0
				4-Methylthiopyridazine					
90.1	10.96	4.00	1.29	1.40				270	6.0
100.0	10.96	4.00	2.96	3.24				270	6.0
110.0	10.96	4.00	6.67	7.37	157			270	6.0
110.0	5.48	2.00	6.62	7.32	314	2.00	2.00	270	6.0
				2-Methylthioquinoxaline					
90.0	7.26	4.41	3.135	3.39				360	6.0
101.0	7.26	4.40	7.245	7.94	223			360	6.0
101.0	3.63	2.21	7.24	7.94	436	1.96	2.00	360	6.0
109.3	7.26	4.41	13.1	14.5				360	6.0
				4-Methylthiocinnoline					
80.1	2.96	1.73	9.37	10.01				350	6.0
90.2	2.96	1.73	21.3	23.1	184			350	6.0
90.2	5.91	3.45	21.3	23.1	94	1.96	2.00	350	6.0
99.95	2.96	1.73	42.8	46.8				350	6.0

TABLE 5 continued

1-Methylthiophthalazine

90.0	10.00	6.00	2.25	2.44				300	6.0
100.95	9.96	5.99	4.96	5.44	235			300	6.0
100.95	4.98	3.00	5.00	5.48	463	1.97	2.00	300	6.0
109.3	10.00	6.00	8.79	9.71				300	6.0

2-Methylsulphinylpyridine

100.0	17.84	8.00	0.433	0.479				240	6.0
110.5	17.84	8.00	1.075	1.19	634			240	6.0
110.5	8.92	4.00	1.04	1.15	1320	2.08	2.00	240	6.0
120.1	17.84	8.00	2.645	2.96				240	6.0

4-Methylsulphinylpyridine

80.0	11.15	4.125	1.75	1.87				265	9.0
90.0	11.15	4.09	4.12	4.46	262			265	9.0
90.0	5.575	2.05	4.17	4.52	520	1.98	2.00	265	9.0
100.0	11.15	4.125	9.84	10.8				265	9.0

2-Methylsulphinylpyrazine

30.0	11.26	1.59	4.30	4.32				295	6.0
40.0	11.26	1.59	11.3	11.5	91			295	6.0
40.0	5.63	0.792	11.1	11.3	188	2.06	2.00	295	6.0
50.0	11.26	1.59	27.8	28.8				295	6.0

3-Methylsulphinylpyridazine

30.1	8.30	3.53	6.76	6.81				240	6.0
40.0	8.30	3.52	15.8	16.1	94			240	6.0
40.0	4.15	1.76	16.05	16.3	189	2.01	2.00	240	6.0
49.9	8.30	3.52	37.4	38.7				240	6.0

4-Methylsulphinylpyridazine

10.0	2.82	0.883	13.4	13.2				247	1.5
19.8	2.82	0.884	36.6	36.4	118	2.03	2.00	247	1.5
19.8	5.63	1.765	37.1	36.9	58			247	1.5
30.0	2.82	0.882	96.2	96.7				247	1.5

TABLE 5 continued

2-Methylsulphinylquinoline

60.0	9.42	5.50	2.18	2.28				288	6.0
70.0	9.42	5.51	5.22	5.51	257			288	6.0
70.0	4.71	2.76	4.93	5.21	544	2.11	2.00	288	6.0
79.9	9.42	5.50	12.4	13.3				288	6.0

4-Methylsulphinylquinoline

49.7	6.52	3.80	3.06	3.16				320	9.0
59.7	6.52	3.80	7.58	7.93				320	9.0
69.9	6.51	3.80	18.1	19.1	106			320	9.0
69.9	3.255	1.90	18.4	19.4	206	1.94	2.00	320	9.0

1-Methylsulphinylisoquinoline

30.0	22.53	1.313	1.26	1.27				330	6.0
40.0	22.53	1.312	3.33	3.39				330	6.0
50.0	22.53	1.312	8.365	8.63	63			330	6.0
50.0	11.26	1.310	8.11	8.37	128	2.03	2.02	330	6.0

2-Methylsulphinylquinoxaline

5.0	0.778	0.497	103	100.5				238	6.0
14.8	0.778	0.496	240	237	68.5			238	6.0
14.8	1.56	0.992	236	233	35.5	1.93	2.00	238	6.0
24.9	0.778	0.495	548	548				238	6.0

1-Methylsulphinylphthalazine

-3.9	0.796	0.500	130	125.5				227	6.0
5.0	1.59	1.00	296	289	27.3			227	6.0
5.0	0.796	0.500	309	301	52	1.90	2.00	227	6.0
14.85	0.795	0.500	740	731				227	6.0

2-Methylsulphonylpyridine

108.7	12.3	8.19	1.82	1.97				272	6.0
117.0	12.3	8.19	3.97	4.33				272	6.0
127.9	12.3	8.19	10.85	12.2	108			272	6.0
127.9	6.15	4.095	10.4	11.8	230	2.13	2.00	272	6.0

4-Methylsulphonylpyridine

90.4	11.09	6.15	6.91	7.47	183			268	9.0
90.4	6.55	3.62	6.94	7.52	310	1.67	1.67	268	9.0
100.1	5.24	2.99	15.4	16.8				268	9.0
110.5	3.92	2.82	36.3	40.2				268	9.0

TABLE 5 continued

2-Methylsulphonylpyrazine

29.9	7.13	4.01	3.86	3.89				292	6.0
39.9	4.75	2.88	9.74	9.97				292	6.0
49.9	4.75	2.88	24.3	25.2	120			292	6.0
49.9	2.38	1.44	24.6	25.5	243	2.02	2.00	292	6.0

3-Methylsulphonylpyridazine

30.2	7.15	3.95	9.65	9.71				266	6.0
40.1	4.11	2.38	23.2	23.6				266	6.0
50.6	4.52	2.54	56.9	58.6	53			266	6.0
50.6	2.26	1.27	56.1	57.8	108	2.04	2.00	266	6.0

4-Methylsulphonylpyridazine

20.25	2.90	1.90	50.8	50.6				247	1.0
30.3	2.32	1.58	121	122	52.5			247	1.0
30.3	1.16	0.791	120	121	104	1.98	2.00	247	1.0
39.7	0.695	0.475	268	273				247	1.0

2-Methylsulphonylquinoline

60.0	10.39	6.05	2.61	2.72				254	6.0
70.1	10.39	6.05	6.47	6.84	212			254	6.0
70.1	5.19	3.096	6.11	6.46	440	2.07	2.01	254	6.0
80.0	10.39	6.07	14.9	15.9				254	6.0

4-Methylsulphonylquinoline

49.9	5.23	3.05	2.68	2.77				325	9.0
60.3	10.46	6.05	7.01	7.33	190			325	9.0
60.3	5.23	3.04	6.90	7.20	390	2.05	2.00	325	9.0
69.7	5.23	3.05	15.0	15.8_5				325	9.0

1-Methylsulphonylisoquinoline

59.1	10.39	6.08	5.19	5.42	255			270	6.0
59.1	5.195	3.06	4.97	5.19	535	2.10	2.00	270	6.0
70.2	5.195	3.06	12.2	12.9				270	6.0
80.25	5.195	3.06	28.5	30.4				270	6.0

TABLE 5 continued

2-Methylsulphonylquinoxaline

5.2	0.831	0.480	88.3	86.1				242	6.0
14.9	0.831	0.480	212	209	79			242	6.0
14.9	0.415	0.241	216	213	155	1.97	2.00	242	6.0
24.8	0.831	0.480	505	505				242	6.0

4-Methylsulphonylcinnoline

5.0	1.50	0.90	55.6	54.3				286	6.0
15.1	2.99	1.80	136	134	34			286	6.0
15.1	1.50	0.90	139	137	66	1.94	2.00	286	6.0
24.9	1.50	0.90	284	284				286	6.0

1-Methylsulphonylphthalazine

5.0	1.70	0.99	49.2	48.0				256	6.0
15.1	1.70	0.99	119	117_5	33.8			256	6.0
15.1	3.40	1.985	121	120	68	2.01	2.00	256	6.0
24.8	1.70	0.99	264	264				256	6.0

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a ± 0.1^{o}. b In $l.mole^{-1}sec.^{-1}$; the standard deviation was usually below 3%. Calculated on the basis of a bimolecular reaction, which is second order for methylsulphonyl compounds, apparent first order for methylthio compounds, and has apparent order 1.5 for methylsulphinyl compounds. c Corrected for solvent expansion or contraction. d Time for 50% reaction, in min. e The ratio of $t_{\frac{1}{2}}$ for two experiments at different concentrations. f Calculated values from the concentrations of reactants employed. g Analytical wavelength for determination of percentage reaction. h pH of buffer solutions used to stop the reactions and for spectroscopic measurements.

TABLE 6

Rate coefficients and Arrhenius parameters for reactions with methoxide ions

Compound	Temp. (°C)	$10^3 k$ ($l.mole^{-1}sec^{-1}$)	E [a] ($kcal.mole^{-1}$)	log A [b]	$\Delta H^{\ddagger}$ [a] ($kcal.mole^{-1}$)	$-\Delta S^{\ddagger}$ [c] ($kcal.mole^{-1}deg.^{-1}$)
2-Methylsulphinyl-pyridine	110.5	1.15	26.6	12.2	25.8	5.2
2-Methylsulphonyl-pyridine	110.0	2.23[d]	28.7	13.7	27.9	-1.7
4-Methylsulphinyl-pyridine	110.0	24.1[d]	22.9	11.44	22.2	8.6
4-Methylsulphonyl-pyridine	110.5	40.2	23.1	11.7	22.4	7.5
2-Methylthio-pyrazine	110.0	0.566[d]	24.6	10.76	23.8	11.9
2-Methylsulphinyl-pyrazine	30.0	4.32	18.5	10.98	17.9	10.3
2-Methylsulphonyl-pyrazine	29.9	3.86	18.3	10.8	17.7	11.2
3-Methylthio-pyridazine	110.0	0.335[d]	27.3	12.0	26.5	6.4
3-Methylsulphinyl-pyridazine	30.1	6.81	16.9	10.0	16.3	14.8
3-Methylsulphonyl-pyridazine	30.2	9.71	17.1	10.3	16.5	13.5
4-Methylthio-pyridazine	110.0	7.37	23.0	10.96	22.2	10.8
4-Methylsulphinyl-pyridazine	30.0	96.7	17.0	11.25	16.4	8.5
4-Methylsulphonyl-pyridazine	30.3	121	15.7	10.4	15.1	13.0
2-Methylsulphinyl-quinoline	60.0	2.28	20.9	11.05	20.2	10.2
2-Methylsulphonyl-quinoline	60.0	2.72	20.7	11.0	20.0	10.4
4-Methylsulphinyl-quinoline	59.7	7.93	19.7	10.8	19.1	11.4
4-Methylsulphonyl-quinoline	60.3	7.20	19.4	10.6	18.8	12.3
1-Methylsulphinyl-isoquinoline	60.0	20.7[d]	18.6	10.5	18.0	12.5
1-Methylsulphonyl-isoquinoline	60.0	5.62[d]	19.55	10.55	18.9	12.5
2-Methylthio-quinoxaline	110.0	15.3[d]	20.8	10.04	20.1	15.0
2-Methylsulphinyl-quinoxaline	30.0	815 [d]	14.0	10.0	13.4	14.8
2-Methylsulphonyl-quinoxaline	30.0	776 [d]	14.8	10.6	14.3	12.1

TABLE 6 continued

4-Methylthio-cinnoline	110.0	96.3[d]	20.4	10.6	19.7	12.2
4-Methylsulphinyl-cinnoline	30.0	~1300	-	-	-	
4-Methylsulphonyl-cinnoline	30.0	418[d]	13.6	9.43	13.0	17.2
1-Methylthio-phthalazine	110.0	10.2[d]	19.7	9.26	19.0	18.6
1-Methylsulphinyl-phthalazine	30.0	2610[d]	14.6	10.9	14.1	10.3
1-Methylsulphonyl-phthalazine	30.0	398[d]	14.15	9.8	13.6	15.6

a Accurate to ±0.4 kcal.mole^{-1}.

b Accurate to ±0.3 unit.

c Accurate to ± 1 unit.

d Calculated from the experimental results.

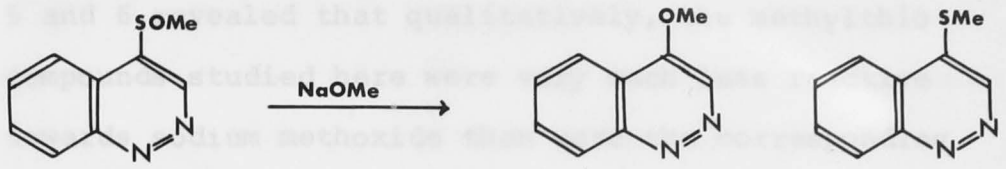
that of the corresponding sulphone. Exceptions to this were the 1-positions of phthalazine and isoquinoline; the 4-position of cinnoline was not considered because the figure quoted for 4-methylsulphinylcinnoline at 30° in Table 6 was considered unreliable for reasons given previously. In the 1-positions of phthalazine and isoquinoline the sulphoxides (3A, 3B) were appreciably more reactive than the sulphones (6.5 and 3.7 times respectively). Here the leaving group was between a ring nitrogen atom and the annelating benzene ring, and it well may have been that under these conditions steric factors were responsible for the relatively easier displacement of the methylsulphinyl group.

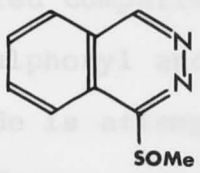
Differences in the energies of activation between the sulphones and corresponding sulphoxides were usually small and displayed no distinct pattern. Both the methylsulphonyl and methylsulphinyl groups were found to be good leaving groups and this point will be further illustrated later by reference to the corresponding chloro compounds.

b) Comparative reactivities of methylthio compounds and their methylsulphonyl (and methylsulphinyl) analogues

Examination of the data presented in Tables

FIG 4





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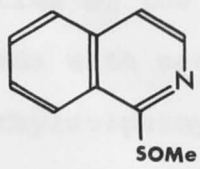

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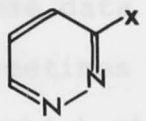

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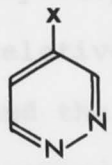

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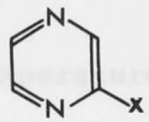

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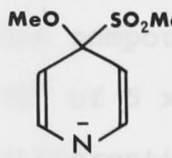

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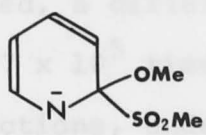

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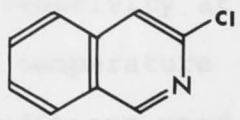

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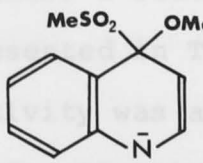
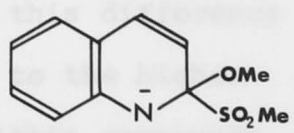


3I



3J

5 and 6 revealed that qualitatively, the methylthio compounds studied here were very much less reactive towards sodium methoxide than were the corresponding sulphones and sulphoxides, and that the methylthio group was, thus, a relatively poor leaving group. A detailed comparison of the reactivities of the methylsulphonyl and methylthio compounds with sodium methoxide is attempted in Table 7 (methylsulphinyl compounds are not included as they are very similar in reactivity to the methylsulphonyl compounds). These data include the relative rates at 30^{o} (sometimes calculated) and the calculated temperatures at which the methylthio compounds would react at a rate equal to that of the corresponding methylsulphonyl compounds at 30^{o}. These figures showed clearly, for the compounds examined, a difference in reactivity at 30^{o} of 5×10^{3} to 3.7×10^{5} times, and a temperature differential for reactions, under the conditions used, of $100\text{-}145^{o}$. Brown and Ford (1967) found in the pyrimidines, a reactivity differential of $>10^{5}$. The data presented in Table 6 showed that this difference in reactivity was attributable mainly to the higher energy of activation, E, of the methylthio compounds.

TABLE 7

Comparison of reactivity of methylthio and methylsulphonyl heterocycles with methoxide ion

Compound	Rate coefficient calculated at 30°	Ratio of reactivity at 30° SO_2Me/SMe	Temperature required for $k_{SMe}=k_{SO_2Me}$ at 30° [a]
2-Methylthio-pyrazine	1.14×10^{-7}	3.41×10^{4}	134.0°
3-Methylthio-pyridazine	2.62×10^{-8}	3.71×10^{5}	149.9
4-Methylthio-pyridazine	2.52×10^{-6}	4.76×10^{4}	149.0
2-Methylthio-quinoxaline	1.13×10^{-5}	6.87×10^{4}	174.3
4-Methylthio-cinnoline	8.18×10^{-5}	5.11×10^{3}	132.2
1-Methylthio-phthalazine	1.10×10^{-5}	3.60×10^{4}	173.3

a This is the calculated temperature for reactions of methylthio compounds at which the reaction rate is the same as shown by the methylsulphonyl analogues at 30°.

This difference, from the methylsulphonyl compounds was found to vary between 5.55 (for the 1-position of phthalazine) and 10.2 (for the 3-position of pyridazine) kcal. $mole^{-1}$. On the other hand variations in the frequency factor, log A, did not display a distinct pattern.

c) Comparative reactivities of chloro heterocycles with their methylsulphonyl, methylsulphinyl and methylthio analogues

It was of interest to compare the reactivities of heterocyclic methylthio, methylsulphinyl and methylsulphonyl compounds towards sodium methoxide with those of the corresponding chloro compounds and rate constants and reaction parameters of methylsulphonyl compounds and corresponding chloro compounds are presented in Table 8; and a comparison of the reactivities of methylthio compounds and their chloro analogues is given in Table 9. (Due to the great similarity between the reactivities of the sulphones and sulphoxides, the former were taken as representative of both groups.) The data in Table 8 revealed that the methylsulphonyl compounds were more reactive, and at the temperatures given (of the same order as those used experimentally) this greater reactivity

TABLE 8

Comparison of reactivity of methylsulphonyl and chloro heterocycles with methoxide ion

Compound	Temp. (^{o}C)	$10^{3}k$ [e] ($l.mole^{-1}sec^{-1}$)	E ($kcal.mole^{-1}$)	$-\Delta S^{\ddagger}$ ($kcal.mole^{-1}deg.^{-1}$)
2-Chloropyridine [a]	110.0	0.0385[f]	28.9	5.33
2-Methylsulphonylpyridine	110.0	2.23[f]	28.7	-1.7
4-Chloropyridine [a]	110.0	0.405[f]	25.2	10.4
4-Methylsulphonylpyridine	110.5	40.2	23.1	7.5
3-Chloropyridazine [b]	30.0	0.0902[f]	19.3	15.4
3-Methylsulphonylpyridazine	30.2	9.71	17.1	13.5
2-Chloroquinoline [c]	60.0	0.0451[f]	24.2	7.0
2-Methylsulphonylquinoline	60.0	2.72	20.7	10.4
4-Chloroquinoline [c]	60.0	0.0610[f]	21.2	17.2
4-Methylsulphonylquinoline	60.3	7.20	19.4	12.3
2-Chloroquinoxaline [d]	30.0	16.4[f]	16.7	13.6
2-Methylsulphonylquinoxaline	30.0	776[f]	14.8	12.1
4-Chlorocinnoline [d]	30.0	10.1[f]	15.8	17.7
4-Methylsulphonylcinnoline	30.0	418[f]	13.6	17.2

a Liveris and Miller (1963).

b Hill and Krause (1964).

c Belli, Illuminati, and Marino (1963).

d Illuminati (1964).

e To enable direct comparison to be made some coefficients have been normalised at specific temperatures.

f This rate coefficient has been obtained by calculation.

TABLE 9

Comparison of reactivity of methylthio and chloro heterocycles with methoxide ion

Compound	Rate coefficient calculated at 30°	Ratio of reactivity at 30° Cl/SMe	Temperature[a] required for $k_{SMe}=k_{Cl}$ at 30°
3-Chloro-pyridazine[b]	9.02×10^{-5}	3.44×10^{3}	96.6
2-Chloro-quinoxaline[c]	1.64×10^{-2}	1.45×10^{3}	111.0
4-Chloro-cinnoline [c]	1.01×10^{-2}	1.23×10^{2}	80.2

a This is the calculated temperature for reactions of methylthio compounds at which the rate is the same as shown by the chloro analogues at 30°.

b J.H.M. Hill and J.G. Krause (1964).

c G. Illuminati (1964).

varied from 41 (in the case of the 4-position of cinnoline) to 118 times (for the 4-position of quinoline). Except in the case of the 2-position of pyridine, where differences in the frequency factor were responsible, the greater reactivities of the methylsulphonyl compounds, as opposed to the chloro compounds, were reflected mainly in the lower energies of activation of the former (usually by 1.8 to 3.5 kcal.mole^{-1}). Various reports in the literature (e.g. Brown and Ford, 1967; Sprague and Johnson, 1936; Shepherd, Taft and Krazinski, 1961; see Introduction) claimed that the methylsulphonyl group was at least as good, or better, as a leaving group than was the chloro substituent, and these findings were well borne out by our quantitative work.

Unlike the sulphones the methylthio compounds were less reactive than their chloro analogues. The data in Table 9 showed that the chloro derivatives were from 1.2×10^2 to 3.4×10^3 times more reactive than their methylthio analogues, and that for the methylthio compounds to have the same reactivities as the chloro compounds, at 30°, increases of between 50 and 81° in temperatures of reactions were required.

Comparison of the data for the methylthio compounds presented in Table 6 with those for some of the chloro analogues given in Table 8 revealed that the greater reactivities of the latter were reflected in lower values of the energies of activation while differences in the frequency factors were variable. Brown and Foster (1966 a,b) also recorded large differences in the rates of aminolyses of substituted 2-chloro- and 2-methylthio-pyrimidines.

d) Positional effects in monocyclic systems

Previous workers have shown that a substituent in the 4-position of pyridine is more readily replaced by nucleophiles than the same substituent in the 2-position (see Introduction for summary). This was also true for 2- and 4-methylsulphinyl- and methylsulphonyl-pyridines where the ratio of reactivity at the 4-position to that at the 2-position was 18 for the sulphones and 21 for the sulphoxides (at 110°). Similarly the 4-substituted pyridazines (3D; where the substituent is γ to one aza group) reacted more readily than did the 3-isomers (3C; where the substituent is α to one aza group) in the sulphides, sulphoxides and sulphones. The largest value of

this ratio was 22.0 for the sulphides (at 110°) and it was least, 12.4, for the sulphones (at 30°). The greater reactivities of the γ substituted compounds, usually associated with lower energies of activation, have been attributed (Shepherd and Fedrick, 1965) to greater stabilisation of the transition states (e.g. 3F) relative to those of the α substituted isomers (e.g. 3G). Apparent exceptions were the 3- and 4-methylsulphinylpyridazines where the difference in reactivity was reflected mainly in the log A values.

In the 3-position of pyridazine (3C) and the 2-position of pyrazine (3E) the substituent was activated by α and β ring nitrogen atoms and thus these compounds might be expected to show similar reactivities. This was observed, and in the cases of the sulphones and sulphoxides the 3-pyridazine compounds were a little more reactive, but in the sulphides, 2-methylthiopyrazine, was slightly more reactive.

These results were somewhat different from those reported by Chan and Miller (1967), who found that with sodium p-nitrophenoxide, 4-chloropyridazine was

only very slightly (1.5 times) more reactive than its 3-isomer and 2-chloropyrazine was more reactive than either.

e) Effects of annelation with a benzene ring

Two general effects of annelation of a benzene ring to a heterocycle were observed in this work. These were general increases in reactivity of the annelated species as compared with their non-annelated monocyclic counterparts, and decreases in positional selectivity.

Annelations of substituted azabenzenes previously have been observed (Chapman and Russell-Hill, 1956) to produce considerable increases in reactivity except when they gave the less reactive 3-substituted 2-aza-naphthalenes (e.g. 3H). In this work, however, none of the compounds studied had this configuration and it was expected that all systems would show increases in reactivity on annelation. In fact, an increase in reactivity was observed in each case and these increases in reactivity are summarised in Table 10. These increased reactivities varied from 3.5 on annelation of 4-methylsulphonylpyridazine to give 4-methylsulphonylcinnoline, to 3240 for annelation of

TABLE 10

Annelation effect on reactivity

Monocycle	Position of substituent	Bicycle	Position of substituent	Ratio of Reactivity of bicycle / Reactivity of monocycle: Sulphide	Sulphoxide	Sulphone
Pyridine	2	Quinoline	2	-	356 [a]	366 [a]
Pyridine	2	Isoquinoline	1	-	3240 [a]	760 [a]
Pyridine	4	Quinoline	4	-	30 [a]	18 [a]
Pyrazine	2	Quinoxaline	2	27 [b]	188 [c]	201 [c]
Pyridazine	3	Phthalazine	1	30 [b]	383 [c]	41 [c]
Pyridazine	4	Cinnoline	4	13 [b]	-	3.5 [c]

[a] At 60°. [b] At 110°. [c] At 30°.

2-methylsulphinylpyridine to give 1-methylsulphinylisoquinoline. These increased reactivities were reflected in lower energies of activation even though the frequency factors were also lower. These effects have been attributed (Chapman and Russell-Hill, 1956) to the greater area available for delocalisation of the charge in the transition states of the annelated compound (e.g. 3I, 3J).

Inspection of Table 10 showed that annelation had a greater activating effect on 2-substituted heterocycles than their 4-isomers. This was probably due to loss of some resonance energy in the transition states of the 4-compounds (e.g. 3I) relative to those of the 2-isomers (e.g. 3J).

As a result of the aza-groups inducing greater reactivity at the γ positions, and annelation greater reactivity at the α positions, positional effects became variable in the benzene fused series. In the quinolines, 4-methylsulphinyl- and sulphonyl-quinolines were slightly more reactive than their 2-substituted counterparts but this difference was much less than in the corresponding pyridines. 1-Methylsulphinylisoquinoline was more reactive than 4-methylsulphinyl-

quinoline but the corresponding sulphone was less. With the diazines the picture was still more variable and reactivities were in the order: 4-methylthiocinnoline > 2-methylthioquinoxaline > 1-methylthiophthalazine for the sulphides; 1-methylsulphinylphthalazine > 4-methylsulphinylcinnoline > 2-methylsulphinylquinoxaline for the sulphoxides; and 2-methylsulphonylquinoxaline > 4-methylsulphonylcinnoline > 1-methylsulphonylphthalazine for the sulphones. The last order was the same as found by Chapman and Russell-Hill (1956) for reactions of chloro compounds with ethoxide ion. (The high reactivities of 1-methylsulphinyl-isoquinoline and phthalazine have been discussed earlier.)

f) Activation due to ring nitrogen atoms

Data on the displacements of the methylsulphonyl or methylsulphinyl groups (or indeed methylthio groups) from monosubstituted benzenes or naphthalenes were not available and hence it was not possible to give any value for the activation by the first ring nitrogen atom in the α and γ monosubstituted pyridines, quinolines and isoquinolines studied here.

The effects of addition of a second ring nitrogen

atom placed β to the leaving group were measurable in the sulphones and sulphoxides (but not in the sulphides because of the absence of information in the monoaza systems). This produced a considerable increase in reactivity and was of the order observed by earlier workers (e.g. Chapman and Russell-Hill, 1956) for displacements of chloro substituents. This increased activation has been attributed to inductive electron withdrawal by the ring nitrogen atom placed β to the leaving group (Illuminati, 1964). Thus 2-methylsulphinylpyrazine reacted 9 times as fast with sodium methoxide at 30° as 2-methylsulphinylpyridine at 100°; and 4-methylsulphonylcinnoline at 15° reacted 19 times as fast as 4-methylsulphonylquinoline at 60°. This increased reactivity was reflected in a considerable reduction in energy of activation (between 11.6 and 4.0 kcal. $mole^{-1}$) even though the frequency factor was also usually lower.

g) Theoretical calculations

Many attempts have been made to correlate reactivities of substituted nitrogen heterocyclic molecules toward nucleophiles with calculations of electron densities or localisation energies, and these

have been summarised by Albert (1959), Ridd (1963), and Shepherd and Fedrick (1965). In the past most of these studies have been on the reactivities of chloro heterocycles.

In this work we sought to see if any correlation existed between these calculations and the reactivities of the compounds, studied in this thesis, with sodium methoxide in methanol. However, it should be pointed out that in such approaches calculations related to the ring system and no allowance was made for the effect of variations in the nature of the leaving group or nucleophile. Differences in the relative reactivities of sulphides, sulphoxides and sulphones were observed but these were usually small and the sulphone series, only, was taken for comparison.

i Comparison of reactivities with calculated electron densities

Attempted correlations of reactivities with calculated electron densities should be treated with extreme caution for the reasons that many calculations of electron densities of ring systems currently under investigation have been made, and in many of these widely varying and conflicting values were obtained;

and that the nature of the transition states are probably a more accurate guide to reactivity than the ground state electron densities.

Black, Brown, and Heffernan (1967) used a "variable electronegativity self consistent field (V.E.S.C.F.)" method to calculate electron densities (Table 11) for the range of heterocycles covered in this thesis and we have examined results given in this work for possible correlations. The two series of compounds in which the leaving group was activated by α and γ ring nitrogen atoms were considered separately and some correlations were observed. Thus the reactivities of 4-methylsulphonyl-pyridine, quinoline, pyridazine and cinnoline with sodium methoxide were, qualitatively, in the same order as decreases in the calculated electron densities of these positions. The correlation was not so satisfactory in the α activated series but a general increase in reactivity, as the electron density decreased, was observed. Correlation failed completely when the two series were compared because the calculations of Black et al (1967) showed that the positions α to the ring

TABLE 11

Electron densities and potential energies of activation

Heterocycle	Ring position	q [a]	q [b]	$\Delta U - \Delta U^{\circ}$ [c]
pyridine	2	0.964	0.962	
pyridine	4	0.984	0.955	
pyrazine	2	0.960		
pyridazine	3	0.951		
pyridazine	4	0.980		
quinoline	2	0.956	0.947	$\frac{12\delta}{24}$
quinoline	4	0.981	0.943	$\frac{12\delta}{33}$
isoquinoline	1	0.956		$\frac{12\delta}{33}$
phthalazine	1	0.953		$\frac{20\delta}{33}$
quinoxaline	2	0.953		$\frac{15\delta}{24}$
cinnoline	4	0.978		$\frac{20\delta}{33}$

a Obtained from figures given by Black, Brown, and Heffernan (1967). b Coulson (1961).
c Chapman and Russell-Hill (1956).

nitrogen had greater electron deficiencies than those γ but the experimental results showed clearly that the γ substituted heterocycles were more reactive.

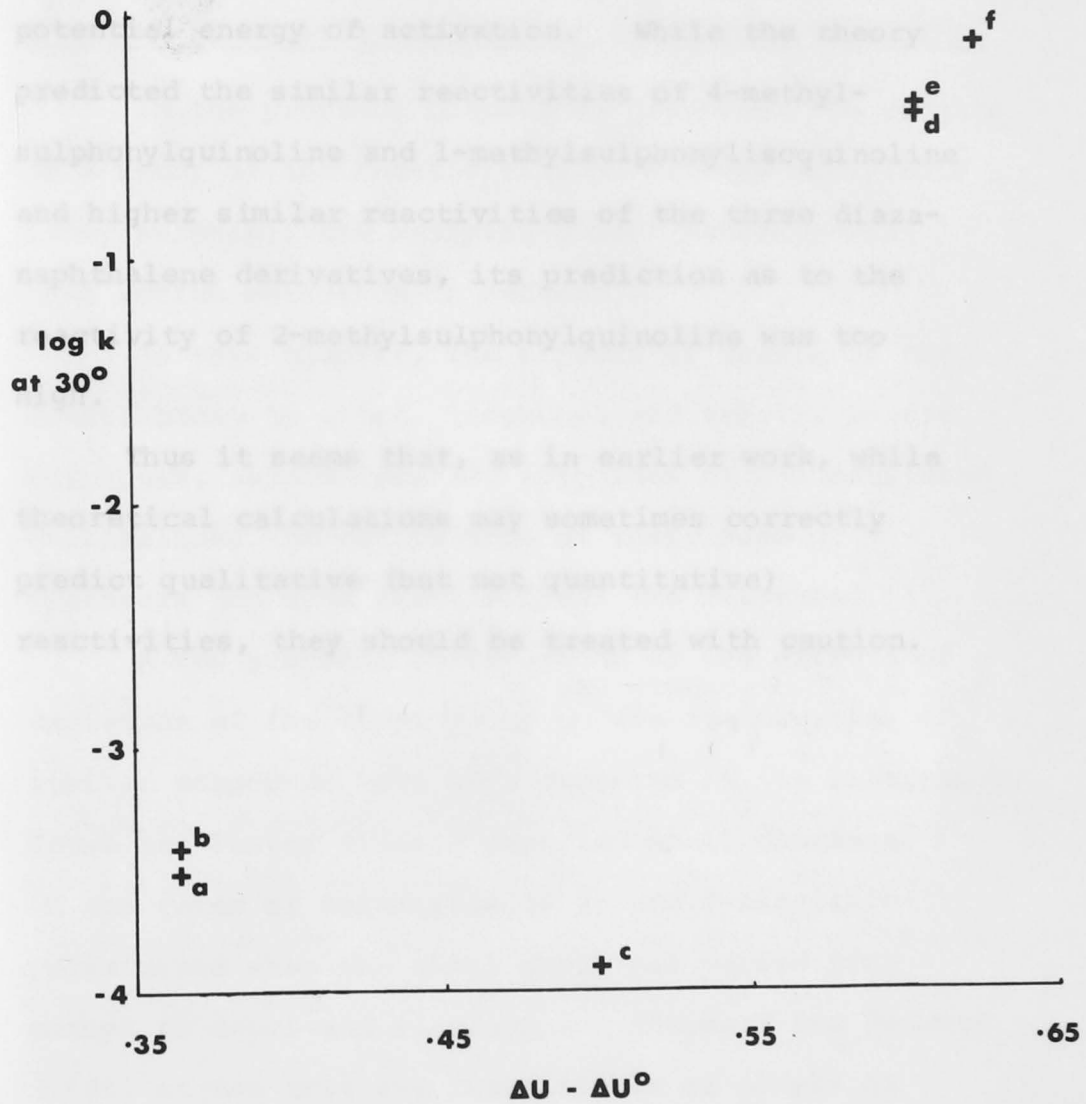
Coulson (1961) gave values for the electron densities of the 2- and 4-positions of pyridine and quinoline (Table 11) in which the reported electron densities, contrary to those usually quoted (Shepherd and Fedrick, 1965), were lower at the 4-positions and the electron deficiencies were in the same relative order as the reactivities of the relevant compounds with sodium methoxide.

ii Correlation of reactivities with localisation energies

An attempt has been made to correlate reactivities of various methylsulphonyl azanaphthalenes with potential energies of activation (Table 11) obtained by calculation from the localisation approach of Longuet-Higgins (1950 a,b), as applied by Chapman and Russell-Hill (1956) to the reactions of chloro azanaphthalenes. Because the entropies of activation for the reactions studied here were not constant (Chapman and Russell-Hill, 1956) the value of log k was taken as being a better reflection of the heat of

FIG 5

Graph of $\Delta U - \Delta U^{o}$ against log k for reactions of methylsulphonyl compounds with sodium methoxide



a 1-$MeSO_2$ isoquinoline

b 4-$MeSO_2$ quinoline

c 2-$MeSO_2$ quinoline

d 1-$MeSO_2$ phthalazine

e 4-$MeSO_2$ cinnoline

f 2-$MeSO_2$ quinoxaline

activation at the absolute zero (Evans and Polanyi, 1936) than $\Delta H^{\ddagger}$. These results are given in Fig.5, in which log $\underline{k}$ is plotted against the calculated potential energy of activation. While the theory predicted the similar reactivities of 4-methylsulphonylquinoline and 1-methylsulphonylisoquinoline and higher similar reactivities of the three diazanaphthalene derivatives, its prediction as to the reactivity of 2-methylsulphonylquinoline was too high.

Thus it seems that, as in earlier work, while theoretical calculations may sometimes correctly predict qualitative (but not quantitative) reactivities, they should be treated with caution.

CHAPTER 4

EFFECT OF VARIATION OF ALKYL GROUP ON THE REACTIVITIES OF ALKYL-SULPHONYL-, SULPHINYL- and THIO-QUINOXALINES

In the previous chapter we presented the results of a study of the reactivities of various methylthio, methylsulphinyl and methylsulphonyl heterocycles with sodium methoxide in methanol.

In this chapter, the effects of change of the methyl group to ethyl, isopropyl and t-butyl in the sulphones, sulphoxides and sulphides of 2-substituted quinoxalines (chosen because of their ease of synthesis and high reactivities) are described.

A few previous observations of the effects of variation of the alkyl group on the reactivities of similar compounds have been reported in the literature. Brown and Foster (1966a) reported small decreases in the rates of aminolyses of 2- and 4-alkylthio-pyrimidines when the alkyl group was varied from methyl to ethyl and isopropyl. Shepherd and Fedrick (1965) stated that the reactivities of alkyl- or aryl-sulphonyl groups ($R\text{-}SO_2\text{-}$) in heterocycles appeared to decrease with increases in the size of

the R- groups and Alekseeva and Postovskii (1954) found that the rates of hydrolysis of 2-alkylsulphonylbenzothiazoles decreased as the size of the alkyl group increased. Brown and Ford (1967) also reported that 2-methylsulphonylpyrimidine was slightly more reactive towards amines than 2-phenylsulphonylpyrimidine.

I Order of Reactions

The alkylthio-, alkylsulphinyl- and alkylsulphonylquinoxalines reacted smoothly with methanolic sodium methoxide to give 2-methoxyquinoxaline in high yield (as indicated by the ultraviolet spectra and by isolation of the product). The kinetics of these reactions were followed spectrophotometrically (Table 13 gives the relevant data) and rate coefficients were calculated assuming apparent orders of 1, 1.5 and 2 for the reactions of sulphides, sulphoxides and sulphones respectively. These reactions behaved exactly as for the methyl analogues and no additional complications were observed under the conditions of the kinetic runs.

II Discussion of Kinetic Results

The results of the kinetic experiments are given in Tables 12-14. In Table 12 are given some typical runs for reactions with sodium methoxide in methanol and these showed regular kinetics. The results of all kinetic experiments are given in Table 13, and in Table 14 are given reaction parameters, viz.: the energy of activation, E; the Arrhenius factor, log A; and the transition state parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ and rate constants, standardised where necessary at chosen temperatures. Also, for comparison, the values for the methyl analogues (from Chapter 3) are included in Table 14.

Examination of the figures in Tables 13 and 14 showed that the reactivities of the alkylthioquinoxalines changed only to a small extent on variation of the alkyl group and they decreased slightly with increasing size of that group. Thus 2-methylthioquinoxaline was ca 1.8 times more reactive towards methoxide ion at 90°, than was 2-t-butylthioquinoxaline.

In the sulphoxide and sulphone series the rates of reaction with sodium methoxide, were affected

TABLE 12

Reactions of methoxide ions

2-Isopropylthioquinoxaline at 100.2°

Methoxide ion 0.01115 N, 2-isopropylthio compound 0.00394 M.

Time (min.)	32	68	106	150	200	262	330	410	529
Reaction (%)	9.1	18.3	27.9	36.3	45.4	54.9	62.8	70.1	79.8
$10^3 k$	4.44	4.45	4.60	4.49	4.52	4.55	4.47	4.41	4.50

Mean $10^3 k$ = 4.49 ± 0.06; after correction for solvent expansion, 4.91.

2-Ethylsulphinylquinoxaline at 30.0°

Methoxide ion 0.002075 N, 2-ethylsulphinyl compound 0.000545 M.

Time (min.)	3.2	10.1	14.0	18.5	24.0	30.6	37.9	48.1	62.9
Reaction (%)	8.1	23.7	31.4	39.1	48.4	56.7	64.0	72.5	81.8
10 k	2.15	2.18	2.22	2.21	2.29	2.29	2.28	2.31	2.33

Mean 10 k = 2.25 ± .06; after correction for solvent expansion, 2.26.

2-t-Butylsulphonylquinoxaline at 40.0°

Methoxide ion 0.00223 N, 2-t-butylsulphonyl compound 0.000900 M.

Time (min.)	10.2	21.1	32.9	48.1	64.8	84.0	110.1	139.1	174.0	218.2
Reaction (%)	8.9	16.6	24.6	33.2	41.4	49.8	59.0	62.6	73.7	80.0
$10^2 k$	6.95	6.65	6.74	6.78	6.79	6.93	7.04	7.07	7.09	7.00

Mean $10^2 k$ = 6.90 ± 0.15; after correction for solvent expansion, 7.01.

TABLE 13

Kinetic results[a] for the reactions of alkylthio-, alkylsulphinyl-, and alkylsulphonyl-quinoxalines with methoxide ions

Temp.[b] (°C)	10^3[MeO$^-$]	10^3[substrate]	$10^3 k$ [c]	$10^3 k$ [d] corr.	$t_{½}$ [e]	$t_{½}/t'_{½}$ [f]	$t_{½}/t'_{½}$ [g] calc.	An.λ(mμ) [h]
			2-Ethylthioquinoxaline					
90.0	8.91	4.04	2.50	2.71				360
100.2	8.91	4.04	5.47	5.99				360
110.4	8.91	4.04	11.8	13.1	109			360
110.4	4.455	2.02	11.6	12.8	219	2.01	2.00	360
			2-Isopropylthioquinoxaline					
90.0	11.15	3.94	2.10	2.28				360
100.2	11.15	3.94	4.49	4.91				360
110.4	11.15	3.94	9.66	10.69	104			360
110.4	5.575	1.97	9.46	10.48	210	2.02	2.00	360
			2-t-Butylthioquinoxaline					
80.0	20.75	1.85	.760	.813				360
90.1	20.75	1.85	1.76	1.90				360
100.1	20.75	1.85	3.58	3.92	152			360
100.1	10.37	0.93	3.61	3.95	315	2.07	2.00	360
			2-Ethylsulphinylquinoxaline					
10.0	4.15	1.09	43.7	42.9	67			238
10.0	2.075	0.547	44.3	43.5	131	1.96	2.00	238
20.0	2.075	0.545	100.1	99.5				238
30.0	2.075	0.545	225	226				238
			2-t-Butylsulphinylquinoxaline					
30.0	10.37	0.908	5.64	5.67				241
40.0	20.75	0.910	12.5	12.8	44.5			241
40.0	10.37	0.908	12.4	12.6	90.5	2.03	2.02	241
50.0	10.37	0.908	26.4	27.2				241

TABLE 13 continued

			2-Ethylsulphonylquinoxaline					
10.0	1.995	1.001	74.0	72.6	91.5			242
10.0	0.998	0.500	74.7	73.4	185	2.02	2.00	242
20.0	0.998	0.500	175	174				242
30.0	0.998	0.500	361	364				242
			2-Isopropylsulphonylquinoxaline					
20.0	0.998	0.501	71.3	70.9				242
30.0	0.998	0.500	160	161	85	1.97	2.00	242
30.0	1.995	1.00	156	157	43			242
39.9	0.998	0.500	323	329				242
			2-t-Butylsulphonylquinoxaline					
30.0	2.23	0.898	31.7	31.9				242
40.0	2.23	0.900	69.0	70.1	87			242
40.0	1.115	0.450	68.0	69.1	171	1.97	2.00	242
50.0	2.23	0.900	141	145				242

a pH 6 buffer was used to stop the reaction and for spectroscopic measurements.

b $\pm 0.1^{o}$. c In $l.mole^{-1}sec^{-1}$; the standard deviation was usually below 3%.

d Corrected for solvent expansion or contraction. e Time for 50% reaction, in min.

f The ratio of $t_{\frac{1}{2}}$ for two experiments at different concentrations.

g Calculated assuming a bimolecular reaction, which was apparent first order for alkylthio-quinoxalines, had order 1.5 for alkylsulphinyl-quinoxalines, and second order for alkylsulphonyl-quinoxalines. h Analytical wavelength for determination of percentage reaction.

TABLE 14

Rate coefficients and Arrhenius parameters for reactions with methoxide ions

Compound	Temp. (°C)	$10^3 k$ (l.mole^{-1}sec^{-1})	E [a] (kcal.mole^{-1})	$\Delta H^{\ddagger}$ [a] (kcal.mole^{-1})	log A [b]	$-\Delta S^{\ddagger}$ [c] (kcal.mole^{-1}deg.$^{-1}$)
2-MeS quinoxaline	90.0	3.39	20.8	20.1	10.0_4	15.0
2-EtS quinoxaline	90.0	2.71	21.2	20.4	10.1_5	14.6
2-i-PrS quinoxaline	90.0	2.28	20.9	20.1	9.9_8	15.3
2-t-BuS quinoxaline	90.1	1.90	20.5	19.8	9.6	17.0
2-MeSO quinoxaline	30.0	815	14.0	13.4	10.0	14.8
2-EtSO quinoxaline	30.0	226	14.1_5	13.6	9.5_4	16.8
2-t-BuSO quinoxaline	30.0	5.67	15.2_5	14.6	8.7_4	20.7
2-$MeSO_2$ quinoxaline	30.0	776	14.8	14.3	10.6	12.1
2-$EtSO_2$ quinoxaline	30.0	364	13.9	13.3	9.6	16.6
2-i-$PrSO_2$ quinoxaline	30.0	161	14.0	13.4	9.3	18.0
2-t-$BuSO_2$ quinoxaline	30.0	31.9	14.7	14.1	9.1	18.8

[a] Accurate to ± 0.3 kcal.mole^{-1}. [b] Accurate to ± 0.3 unit. [c] Accurate to ± 1 unit.

to a greater extent on variation of the alkyl group; and again the rates decreased with increasing sizes. For example, at 30° 2-methylsulphonylquinoxaline was ca 24 times more reactive than 2-t-butylsulphonylquinoxaline and 2-methylsulphinylquinoxaline was ca 140 times more reactive than its t-butyl analogue.

These decreases in reactivity with increasing size of the alkyl group were reflected, in general, by a decrease in the log A term, with only minor fluctuations in energies of activation. An apparent exception was 2-t-butylsulphinylquinoxaline where, in addition to a substantially reduced log A term 8.7 relative to 10.0 for the methyl analogue, the energy of activation was also somewhat higher.

These observed effects most likely were due mainly to steric factors but electronic effects may have contributed also. As the size of the leaving group is increased, nucleophilic attack would have become more difficult due to steric hindrance, and it is probable that the less bulky sulphides would have been least affected. Support for this hypothesis was provided by the fact that the decreased reactivities of the quinoxalines substituted by the

bigger groups were reflected, mainly, in decreased values of the frequency factors.

Alternatively the electron release (hyper-conjugation) by the alkyl group would have also increased with the size of the group and this would have rendered nucleophilic replacement more difficult. Evidence of this electron release was provided by the acid strengths of the alkyl mercaptans (Kreevoy, Eichinger, Stary, Katz, and Sellstedt, 1964; Yabroff, 1940)* which were found to decrease as the group size increased.

Hence from these studies it was obvious that, though the differences in reactivity were not great (small for sulphides), the methylthio, methylsulphinyl and methylsulphonyl heterocycles were more reactive than their higher alkyl counterparts and thus would be better reaction intermediates.

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* The acid strength of isopropylmercaptan was calculated using the method of Barlin and Perrin (1966).

CHAPTER 5

PHYSICAL PROPERTIES

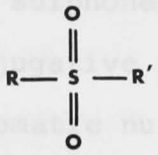
This chapter begins with a discussion of the nature and bonding of the sulphone and sulphoxide groups. Then the ionization constants, n.m.r., ultraviolet and infrared spectra of the sulphones and sulphoxides studied in this work are recorded and discussed. N.m.r. spectra of the sulphides, for which other physical data were published earlier by Albert and Barlin (1959; 1962) are also given.

I Nature of the Sulphone and Sulphoxide Groups

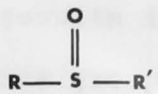
There is some doubt about the electronic structure of the sulphones and sulphoxides concerning the participation of the 'd' orbitals in the sulphur oxygen bonds and the ability of these groups to participate in resonance interactions (Szmant, 1961). Cilento (1960) regarded the sulphur oxygen bondings as being double covalent (5A, 5B) to a marked extent (especially in the sulphones), due to 'd' orbital participation, rather than single coordinate bonds

(5C, 5D) and he summarised evidence (quantum mechanics, bond lengths, heats of formation, dipole moments, etc.) for the existence of this double bond character. Burg (1961) also discussed bonding in sulphones and sulphoxides in terms of 'd' orbital participation and multiple bond character and Amstutz, Hunsberger, and Chessick (1951) regarded the structure of the sulphones as being best described by a resonance hybrid of the type (5E) and the sulphoxides as having some double bond character. Therefore, it seems likely that double bond participation is important in both sulphones and sulphoxides and this suggests the possibility of mesomeric electron withdrawal by these groups, when substituted in an aromatic ring, as shown in (5F)(Heppolette and Miller, 1956).

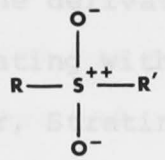
Evidence that methylsulphonyl groups do have indeed a mesomeric effect was provided by Heppolette and Miller (1956) and Kotch, Krol, Verkade, and Wepster (1952) who studied its effect on reaction rates of benzene derivatives. Shepherd and Fedrick (1965) also discussed the effect of methylsulphonyl groups on reactions of substituted azines in terms of resonance as well as induction. Fehnel and Carmack (1950) studied the ultraviolet spectra of substituted



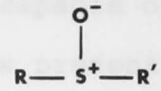
5A



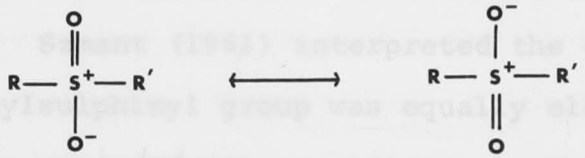
5B



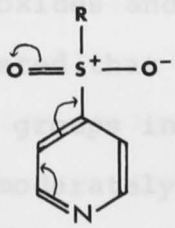
5C



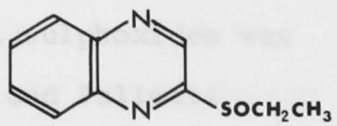
5D



5E



5F



5G

phenyl sulphones and interpreted their results in terms of conjugative interaction of the sulphone group with the aromatic nucleus and Rogers, Barrow and Bordwell (1956) came to similar conclusions on the basis of electric moments and infrared spectra of methyl phenyl sulphone derivatives when other groups capable of conjugating with the sulphone group were present. However, Strating (1961) interpreted the meta directing influence of a sulphone group in electrophilic aromatic substitution in terms of an inductive effect only.

With the sulphoxides evidence for conjugation was less strong. Szmant (1961) interpreted the evidence that the methylsulphinyl group was equally electron withdrawing in para and meta positions, in terms of the exclusive operation of the inductive effect. Koch (1950), on the basis of ultraviolet spectra, proposed a small degree of conjugation in phenyl sulphoxides and Leandri, Mangini and Passerini (1957) suggested that conjugation between the sulphoxide and nitro groups in p-nitrophenyl phenyl sulphoxides was only moderately strong. Ghersetti and Pallotti (1963) found, in the infrared spectra of phenyl

sulphoxides only small substituent influences, and suggested only slight conjugation between the phenyl and sulphoxide groups.

Thus it seems that the electron withdrawal by the sulphone and sulphoxide groups when attached to aromatic systems is principally by the inductive mechanism but resonance may be significant in the sulphones and possibly also to a lesser extent in the sulphoxides.

II Ionization Constants

The ionization constants of the sulphones and sulphoxides described in this thesis are given (where a determination was possible) in Table 15. Also included for comparison are those of the parent heterocycles.

a) Sulphones

Examination of the ionization constants clearly showed the powerful electron withdrawal of the methylsulphonyl group. In the 2- and 4-positions of pyridine it lowered the pK_a values by 6.7 and 3.6 units respectively (6.5 and 3.4 for the corresponding 2- and 4-positions of quinoline) and in the pyrazine

and the 3-position of pyridazine, where protonation occurred on the nitrogen β to the methylsulphonyl group the lowering of pK_a was 3.1 and 3.3 units respectively. (4-Methylsulphonylpyridazine is believed to protonate on N-1 or N-2, see discussion of n.m.r. spectra.)

The base weakening by the methylsulphonyl group was in the order $\alpha >> \gamma > \beta$, and this was consistent with electron withdrawal principally by the inductive effect but also with a contribution by a mesomeric effect. (The inductive base weakening by the chloro substituent was in the order $\alpha > \beta > \gamma$.) This was in accord with the nature of the sulphone group discussed previously.

b) Sulphoxides

The ionization constants showed that the methylsulphinyl group also effected considerable electron withdrawal, which was, however, less than that of the methylsulphonyl group. This electron withdrawal, as indicated by the decrease in pK_a, was particularly strong when the group was placed in the α position to the basic centre and was much less when the group was placed in the γ position.

In the 2- and 4-positions of pyridine, the

decrease in pK_a was 5.4 and 2.3 units whereas in quinoline it was 5.2 and 2.05 respectively. In pyrazine and the 3-position of pyridazine, where protonation took place on the nitrogen β to the methylsulphinyl group, the lowering was 2.1 and 2.95 respectively. Unlike the sulphones, therefore, the base weakening effect was no longer consistently $\alpha >> \gamma > \beta$ but was best described (on the data available) as $\alpha >> \beta \simeq \gamma$. This was consistent with the electron withdrawal by the inductive effect (Szmant, 1961) but a small resonance contribution could not be ruled out. As for the sulphones the data from ionization constants were, thus, consistent with earlier work on the nature of the sulphoxide group.

III Ultraviolet and Infrared Spectra

The ultraviolet spectra of the methylsulphonyl and methylsulphinyl heterocycles are given in Table 15, and those of the quinoxaline derivatives in which the methyl group has been replaced by other alkyl groups in Table 16. In many cases there were some similarities between the ultraviolet spectra of the sulphoxides and corresponding sulphones. These

TABLE 15

PK_a Values and ultraviolet spectra [a]

Compound	Ionization (water, 20°)					Spectroscopy in water [i]		
	Charged species involved [b]	pK_a	Spread (±)	Concn. (M)	A.w.l. [c] ($m\mu$)	λ_{max} ($m\mu$)	log ε	pH [j]
Pyridine	+	5.23 [d]						
2-SOMe	0	-				227, 256, 263, 268	3.42, 3.47, 3.55, 3.50	6.0
	+	-0.16	0.04	0.00012	281	280	3.75	-2.6
2-SO_2Me	0	-				253, 258, 264	3.46, 3.51, 3.36	9.0
	+	-1.50	0.03	0.00003	262	259	3.86	-4.0
4-SOMe	0	-				238, 257, 262, 271	3.48, 3.55, 3.54, 3.38	6.0
	+	2.94	0.02	0.00012	285	225, 257, 263, 270, 287	3.26, 3.66, 3.76, 3.72, 3.38	0.0
4-SO_2Me	0	-				268	3.49	7.0
	+	1.62	0.03	0.00003	270	269	3.72	-0.8
Pyrazine	+	0.65 [e]				-		
2-SOMe	0	-				272, 308-9	3.76, 2.90	6.0
	+	-1.48	0.04	0.00005	296	233, 269-71, 287	3.52, 3.61, 3.58	-4.0
2-SO_2Me	0	-				259, 264, 270, 310	3.80, 3.86, 3.74, 2.78	6.0
	+	-2.47	0.05	0.00008	280	273	3.90	-5.0
Pyridazine	+	2.33 [d]				-		
3-SOMe	0	-				240, 298	3.36, 2.54	6.0
	+	-0.62	0.06	0.0001	275	256	3.50	-2.8
3-SO_2Me	0	-				244, 249, 255, 303-4	2.88, 2.88, 2.67, 2.49	9.0
	+	-1.01	0.07	0.0006	310	244	3.09	-3.4
4-SOMe	0	-				258, 306-8	3.51, 2.69	6.0
	+	0.22	0.03	0.0001	315	274, 312-3	3.28, 3.26	-2.0
4-SO_2Me	0	-				252, 256, 262, 324	3.33, 3.34, 3.16, 2.46	7.0
	+	-1.06	0.06	0.00005	235	245-7	3.42	-3.2

TABLE 15 continued

Quinoline	+	4.93[f]				-		
2-SOMe	0	-				231, 300, 308, 313, 321	4.57, 3.60, 3.64, 3.60, 3.62	6.0
	+	-0.27	0.07	0.000015	330	244, 330	4.58, 4.06	-2.8
2-SO_2Me	0	-				235, 299	4.75, 3.61	6.0
	+	-1.53	0.08	0.00005	350	246, 306, 320, 347	4.68, 3.76, 3.95, 3.46	-4.0
2-OMe	0	-				232, 237, 259, 265, 294, 307, 313, 320[k]	4.27, 4.18, 3.49, 3.48, 3.24, 3.49, 3.43, 3.51	6.0
	+	3.17[f]				218, 228, 235, 239, 243, 307	4.12, 4.03, 4.25, 4.40, 4.44, 3.93	0.2
4-SOMe	0	-				232, 234, 298, 306, 320	4.38, 4.39, 3.69, 3.70, 3.64	6.0
	+	2.88	0.02	0.000025	316	239, 323	4.52, 3.92	0.0
4-SO_2Me	0	-				236, 239, 302, 314, 324	4.43, 4.42, 3.65, 3.74, 3.73	6.0
	+	1.57	0.03	0.00003	332	243, 329	4.50, 3.89	-1.6
Isoquinoline	+	5.46[f]				-		
1-SOMe	0	-				222, 267, 277, 287, 315, 325	4.63, 3.49, 3.55, 3.48, 3.59, 3.65	6.0
	+	0.90	0.02	0.00003	347	237, 279, 305, 345-6	4.57, 3.58, 3.32, 3.78	-2.0
1-SO_2Me	0	-				227, 281, 324	4.58, 3.45, 3.63	6.0
	+	-0.83	0.06	0.00003	320	243, 283, 293, 308, 352	4.63, 3.22, 3.27, 3.13, 3.61	-3.2
1-OMe	0	-				262, 270, 281, 298, 309, 320	3.65, 3.78, 3.71, 3.32, 3.52, 3.50	6.0
	+	3.05[f]				220, 227, 234, 255, 264, 274, 304, 318, 330	4.60, 4.56, 4.36, 3.59, 3.57, 3.43, 3.46, 3.71, 3.69	0.2
Quinoxaline	+	0.56[f]				-		
2-SOMe	0	-				239, 324	4.54, 3.89	6.0
	+	-1.36	0.07	0.000025	350	250, 345	4.52, 3.91	-4.0
2-SO_2Me	0	-				241, 321	4.60, 3.84	6.0
	+	-1.66	0.04	0.00002	340	251, 343	4.62, 4.00	-4.2

TABLE 15 continued

Cinnoline	+	2.29[g]			
4-SOMe	0	-	231, 304, 331	4.55, 3.65, 3.56	6.0
	+	[h]	-		
4-SO_2Me	0	-	235, 308, 337	4.55, 3.57, 3.46	6.0
	+	[h]	-		
Phthalazine	+	3.47[d]	-		
1-SOMe	0	-	225, 279	4.56, 3.58	6.0
	+	[h]	-		
1-SO_2Me	0	-	228, 281	4.58, 3.49	6.0
	+	[h]	-		

[a] Relevant data for the corresponding methylthio compounds are given in Albert and Barlin (1959) and Albert and Barlin (1962). [b] 0, Neutral species; +, cation. [c] Analytical wavelength for spectroscopic determinations of pK_a. [d] Albert, Goldacre, and Phillips (1948). [e] Chia and Trimble (1961). [f] Albert and Phillips (1956). [g] Osborn, Schofield, and Short (1956). [h] Instability of the compound in strong acid solutions prevented determination of the pK_a value. [i] Shoulders and inflexions are underlined. [j] pH Values below 0 have been obtained in solutions of sulphuric or hydrochloric acids to which Hammett acidity functions (c.f. Paul and Long, 1957) have been assigned. [k] The spectrum differs slightly from that recorded at pH 6.8 by Mason (1957).

TABLE 16

Ultraviolet spectra [a]

Substituted Quinoxaline	$\lambda_{max.}$ (mμ)	log ε
2-SMe [b]	241, 265, 361	4.19, 4.16, 3.91
2-SEt	242, 265, 358	4.16, 4.14, 3.95
2-S Pr^i	242, 266, 358	4.19, 4.10, 3.94
2-S Bu^t	243, 266, 332-3, 350	4.43, 3.81, 3.79, 3.75
2-SOMe	239, 324	4.54, 3.89
2-SOEt	239, 325	4.55, 3.90
2-SO Bu^t	240, 327	4.58, 3.91
2-SO_2Me	241, 321	4.60, 3.84
2-SO_2Et	241, 321	4.65, 3.85
2-SO_2 Pr^i	242, 321	4.64, 3.87
2-SO_2 Bu^t	242, 321	4.64, 3.86

a For the neutral molecule in aqueous buffer at pH 6.0.

b Albert and Barlin (1962).

similarities were most striking in the benzene fused diazines (i.e. quinoxaline, cinnoline and phthalazine) but with some of the more complicated spectra peak correlations were not clear. Generally (but not invariably) the absorption maxima of the sulphones were at a slightly higher wavelength than those of the sulphoxide. Correlations of absorption maxima between cation and neutral molecules were not always clear but generally formation of the cations from the neutral molecules appeared to produce small bathochromic shifts.

The sulphones and sulphoxides of the benzene fused heterocycles all showed characteristic intense absorption maxima at short wavelengths (220-240 mμ) which were missing in the monocyclic series.

Replacement of the methyl group by other larger alkyl groups had only a slight effect (<3 mμ) on the ultraviolet spectra of the neutral molecules. 2-t-Butylthioquinoxaline apparently was an exception as its spectrum showed a somewhat greater variation.

The ultraviolet spectra of the methoxy compounds required for the kinetic studies but not in

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Replacement of the methyl group by other larger alkyl groups had only a slight effect (<3 mμ) on the ultraviolet spectra of the neutral molecules. 2-t-Butylthioquinoxaline apparently was an exception as its spectrum showed a somewhat greater variation.

The ultraviolet spectra of the methoxy compounds required for the kinetic studies but not in

Table 15 are given [for 2-methoxypyridine, 2-methoxypyrazine, 3-methoxypyridazine and 4-methoxypyridazine (Mason, 1957; 1959); for 4-methoxypyridine (Spinner, 1963); for 4-methoxyquinoline (Ewing and Steck, 1946; Tucker and Irvin, 1951; Hearn, Morton and Simpson, 1951); for 2-methoxyquinoxaline (Cheeseman, 1958); and for 1-methoxyphthalazine and 4-methoxycinnoline (Albert and Barlin, 1962)], in the literature.

b) Infrared spectra

The infrared spectra of the sulphones showed characteristic peaks at 1125-1170 and 1310-1325 cm^{-1}, and those of sulphoxides at 1040-1070 cm^{-1} (Bellamy, 1958), attributed to the sulphur oxygen bond stretching modes. As mentioned in Chapter 2 these infrared data provided strong evidence for these compounds being sulphones and sulphoxides and not isomeric N-oxides.

IV N.m.r. Spectra

The n.m.r. spectra of the methylthio, methylsulphinyl and methylsulphonyl heterocycles are given in Table 17 and those of the alkyl protons of various alkylthio, alkylsulphinyl and alkylsulphonyl derivatives of quinoxaline in Table 18.

TABLE 17

Nuclear magnetic resonance spectra at 33.5°

Compound	Species [b]	Chemical shifts[a] (τ) of protons						
		2	3	4	5	6 [p]	8	CH_3-
Pyridine [c]	0	1.50	3.015	2.64	3.015	1.50	-	
2-SMe	0	-	∿2.75	2.4	2.9	1.42	-	7.39
	+	-	2.0	1.5	2.2	1.4	-	7.17
2-SOMe	0	-	∿2.05	∿2.05	2.67	1.40	-	7.20
	+	-	∿1.45	1.1	1.6	0.80	-	6.67
2-SO_2Me	0	-	1.9	1.8	2.3	1.13	-	6.72
	+	-	0.9	1.1	1.35	0.7	-	6.30
4-SMe	0	1.46	2.79	-	2.79	1.46	-	7.49
	+	1.44	2.10	-	2.10	1.44	-	7.27
4-SOMe	0	1.23	2.42	-	2.42	1.23	-	7.23
	+	0.90	1.55	-	1.55	0.90	-	6.89
4-SO_2Me	0	0.91	2.06	-	2.06	0.91	-	6.86
	+	0.57	1.16	-	1.16	0.57	-	6.40
Pyrazine [d]	0	1.37	1.37	-	1.37	1.37	-	
2-SMe	0	-	1.42	-	1.71	1.54	-	7.39
	+	-	0.97	-	1.32	0.70	-	7.19
2-SOMe	0	-	0.77	-	1.29	1.40	-	7.10
	+	-	∿0.65 [f]	-	0.92	0.30	-	6.75
2-SO_2Me	0	-	0.55	-	0.99	1.16	-	6.69
	+	-	0.39	-	0.68	0.14	-	6.43
Pyridazine [d]	0		0.76	2.46	2.46	0.76	-	
3-SMe	0	-	-	2.5	2.7	0.98	-	7.24
	+	-	-	1.4	1.6	0.56	-	7.22
3-SOMe	0	-	-	1.80	2.22	0.73	-	7.00
	+	-	-	0.9	0.9	0.07	-	6.70
3-SO_2Me	0	-	-	1.65	2.09	0.43	-	6.52
	+	-	-	0.8	0.9	-0.05	-	6.35
4-SMe	0	-	0.9	-	2.7	1.0	-	7.43
	+	-	0.60	-	1.69	0.74	-	7.15
4-SOMe	0	-	0.6	-	2.12	0.6	-	7.13
	+	-	0.0	-	0.97	0.1	-	6.74
4-SO_2Me	0	-	0.25	-	1.93	0.3	-	6.83
	+	-	-0.30	-	0.67	-0.2	-	6.37

TABLE 17 continued

Quinoline [g] [j]	0	1.19	2.74	2.00	2.31	2.57[m]	1.94	-
2-SMe	0	-	∿2.75	∿2.05	2.1-2.6	2.1-2.6	∿1.95	7.27
	+	-	2.3	1.38	1.9-2.3	1.9-2.3	1.9-2.3	7.06
2-SOMe	0	-	∿1.65	1.35	1.8-2.2	1.8-2.2	1.7	6.97
	+	-	∿1.55	0.60	1.5-2.0	1.5-2.0	1.5-2.0	6.65
2-SO_2Me	0	-	∿1.75	1.43	1.85-2.25	1.85-2.25	∿1.65	6.58
	+	-	1.9-2.6	0.18	1.9-2.6	1.9-2.6	1.9-2.6	6.13
4-SMe	0	1.12	2.78	-	1.75	∿2.15[e]	1.75	7.40
	+	1.39	2.55	-	2.05-2.35	2.05-2.35	2.05-2.35	7.26
4-SOMe	0	0.68	1.8	-	1.5-2.1	2.1	1.6	7.05
	+	0.54	1.40	-	1.6-1.9	1.6-1.9	1.6-1.9	6.80
4-SO_2Me	0	0.68	1.75	-	1.15	∿2.05	1.57	6.71
	+	0.27	1.1	-	0.85-1.65	1.5	0.85-1.65	6.32
Isoquinoline [g] [k]	0	-	1.55	2.50	2.29	2.43[n]	2.14	-
1-SMe	0	-	1.53	2.55	2.05-2.45	2.05-2.45	∿1.65	7.25
	+	-	∿1.95	2.2	1.9-2.2	1.9-2.2	1.9-2.2	7.07
1-SOMe	0	-	∿1.35	∿2.25	2.2-2.5	2.2-2.5	1.2	7.01
	+	-	1.08	1.21	1.45-1.75	1.45-1.75	1.45-1.75	6.67
1-SO_2Me	0	-	1.42	2.1	2.0-2.25	2.0-2.25	0.91	6.45
	+	-	0.9	0.9	1.4	1.4	0.8	6.08
Quinoxaline [g] [l]	0	1.27	1.27	-	1.94	2.33	1.94	-
2-SMe	0	-	1.23	-	1.8-2.0	2.1-2.3	1.8-2.0	7.29
	+	-	0.57	-	∿1.65	∿1.65	∿1.65	6.92
2-SOMe	0	-	0.30	-	1.6-2.0	1.6-2.0	1.6-2.0	6.90
	+	-	0.50	-	1.5	1.5	1.5	6.51
2-SO_2Me	0	-	0.32	-	1.55-1.75	1.8-2.0	1.55-1.75	6.53
	+	-	0.1 [f]	-	1.3	1.3	1.3	6.30
Cinnoline [g] [l]	0	-	0.78	∿2.25	∿2.25	∿2.25	1.52	-
4-SMe	+	-	0.81	-	∿1.85	1.9-2.2	1.40[g]	7.28
	+	-	0.59	-	1.55-1.75	1.55-1.75	1.55-1.75	6.91
4-SOMe	0	-	0.02	-	∿1.95	∿1.95	1.15[g]	6.96
	+[h]	-	-	-	-	-	-	-
4-SO_2Me	0	-	0.04	-	1.1	1.8	1.1	6.67
	+[h]	-	-	-	-	-	-	-

TABLE 17 continued

Phthalazine [g] [l]	0	-	-	0.56	2.07	2.15	2.07	-
1-SMe	0	-	-	0.60	1.9	1.9	1.75	7.12
	+	-	-	0.02	1.45-1.7	1.45-1.7	1.45-1.7	7.15
1-SOMe	0	-	-	0.23	1.7-1.85	1.7-1.85	0.66	6.71
	+[h]	-	-	-	-	-	-	-
1-SO_2Me	0	-	-	0.19	∿1.75	∿1.75	0.96	6.28
	+[i]	-	-	-0.81	0.85	∿1.15	0.7	6.11

a Tetramethylsilane was used as internal reference except in acid solutions when sodium 3-trimethylsilylpropanesulphonate was employed. Where the signal was easily distinguishable and separate from other signals, the chemical shift was given to 2 decimal places; otherwise it was given to the nearest 0.05τ (one decimal place or ∿ sign), or when assignment was not clear it was given over a range as indicated.

b 0 refers to neutral molecules in $CDCl_3$; + to the cation in DCl-D_2O or D_2SO_4-D_2O.

c Pople, Schneider, and Bernstein (1959); recorded as pure liquid.

d Tori and Ogata (1964).

e Chemical shift of the 7-proton was 2.3τ.

f Assumed to be beneath the water peak.

g Assigned to the 8-proton (rather than 5) as by Black and Heffernan (1965).

h Instability in acid prevented determination of the n.m.r. spectrum.

i Decomposition occurred in acid solution but was sufficiently slow to permit determination of the spectrum.

j Black and Heffernan (1964).

k Black and Heffernan (1966).

l Black and Heffernan (1965).

m Chemical shift of the 7-proton was 2.39 τ.

n Chemical shift of the 7-proton was 2.51 τ.

p This was also the chemical shift for the 7-proton in bicyclic systems except where otherwise stated.

q Spectra recorded in carbon tetrachloride

TABLE 18

Chemical shifts of alkyl group protons [a] in substituted quinoxalines

Quinoxaline compound [b]	Chemical Shift (τ) [c] n=0 (sulphide)	n=1 (sulphoxide)	n=2 (sulphone)
2-SO_nC<u>H</u>$_3$	7.29s	6.90s	6.53s
2-SO_nC<u>H</u>$_2$C<u>H</u>$_3$	6.68q	6.78o	6.42q
2-SO_nC<u>H</u>$_2$C<u>H</u>$_3$	8.57t	8.70t	8.59t
2-SO_nC<u>H</u>$(CH_3)_2$	5.80h	-	6.12h
2-SO_nCH$(C\underline{H}_3)_2$	8.50d	-	8.59d
2-SO_nC$(C\underline{H}_3)_3$	8.33s	8.67s	8.50s

a The relevant protons are underlined in the Table.

b Neutral molecule in $CDCl_3$.

c Values are marked s, for singlet; d, doublet; t, triplet; q, quartet; h, heptet; and o, octet.

a) N.m.r. spectra of alkyl protons

The signals due to the protons of the methyl group in methylthio, methylsulphinyl and methylsulphonyl groups were seen as sharp singlets in the region $\tau = 6 \rightarrow 7.5$. In all cases progressive downfield shifts were observed on increase of the oxidation state of the sulphur atom, this was probably due to electron withdrawal by the oxygen atoms and consequent deshielding of the methyl groups. Cationisation also usually produced downfield shifts of the signals due to the protons of the methyl group but these were variable and with 1-methylthiophthalazine a slight upfield shift was observed.

When the methyl group was replaced by other alkyl groups in substituted quinoxalines the expected signals were observed (i.e. a quartet and triplet for ethyl, a heptet and doublet for isopropyl, and a singlet for t-butyl) except for 2-ethylsulphinylquinoxaline (5G) where the expected quartet appeared as an octet. This was presumably due to the asymmetry and anisotropy of the sulphoxide group leading to non-equivalence of the methylene protons. Non-equivalence of methylene protons adjacent to a

sulphoxide group also has been reported by Nishio (1967) and Taddei (1965).

Unlike those of the methyl groups the proton signals of the higher alkyl groups did not show regular downfield shifts as the oxidation state of the sulphur increased but variable changes were observed. These signals were usually seen at highest field in the sulphoxides. This was probably due to restricted rotation about the carbon sulphur bond and shielding in favoured steric configurations, due to the anisotropy of the sulphur containing groups.

b) N.m.r. spectra of the monocyclic ring protons

These were analysable by inspection, J *para* being assumed to be greater than J *meta* for pyrazines (Tori and Ogata, 1964).

Comparison of the spectra of the neutral molecules of the methylsulphonyl and methylsulphinyl compounds with those of the parent ring systems revealed downfield chemical shifts of all protons, due to electron withdrawal by the sulphone or sulphoxide groups. As has been observed in pyridines (Smith and Schneider, 1961), protonation shifts were least for hydrogen atoms adjacent to the cationic

centre. Thus in the 2-substituted pyrazines, which protonated on N-4, shifts were least for 3-H and 5-H. in 4-methylsulphonylpyridazine, however, protonation shifts for 3-H and 6-H were 0.55 and 0.50, in 4-methylsulphinylpyridazine 0.6 and 0.5, and in 4-methylthiopyridazine 0.3 and 0.26; this could indicate that protonation occurred on N-1 and N-2.

c) N.m.r. spectra of bicyclic ring protons

The complexity of the spectra made complete analysis by inspection impossible and in many cases it was only possible to assign a proton to a range of τ values. Hence it was difficult to draw any definite conclusions from these spectra. In general, though, it seemed that the methylsulphonyl and methylsulphinyl groups produced downfield shifts of protons as compared with the parent compounds. Protonation shifts were variable and sometimes upfield movements were observed.

In the quinoxaline series replacement of the methyl group by other alkyl groups had little effect on the spectra of the ring protons (Taddei, 1965).

CHAPTER 6

QUALITATIVE REACTIONS

I Some Useful Preparative Reactions using Methylsulphonyl Compounds

The great potential usefulness of alkyl (or aryl)-sulphonyl compounds as intermediates, because of their ease of synthesis and high reactivities, has been recognised by Shepherd and Fedrick (1965) and Brown and Ford (1967), but previous studies of nucleophilic displacements of methylsulphonyl (or alkyl- or aryl-sulphonyl) groups have been largely confined to the pyrimidine series and few reactions of the compounds in heterocyclic systems discussed in this thesis have been reported (see Introduction).

In this study, which clearly established the usefulness of these compounds, the methylsulphonyl heterocycles were allowed to react with various nucleophiles, viz., aqueous sodium hydroxide, aqueous sodium hydrogen sulphide, sodium cyanide in dimethylformamide, aqueous ammonia (sometimes with added ammonium chloride), aqueous methylamine,

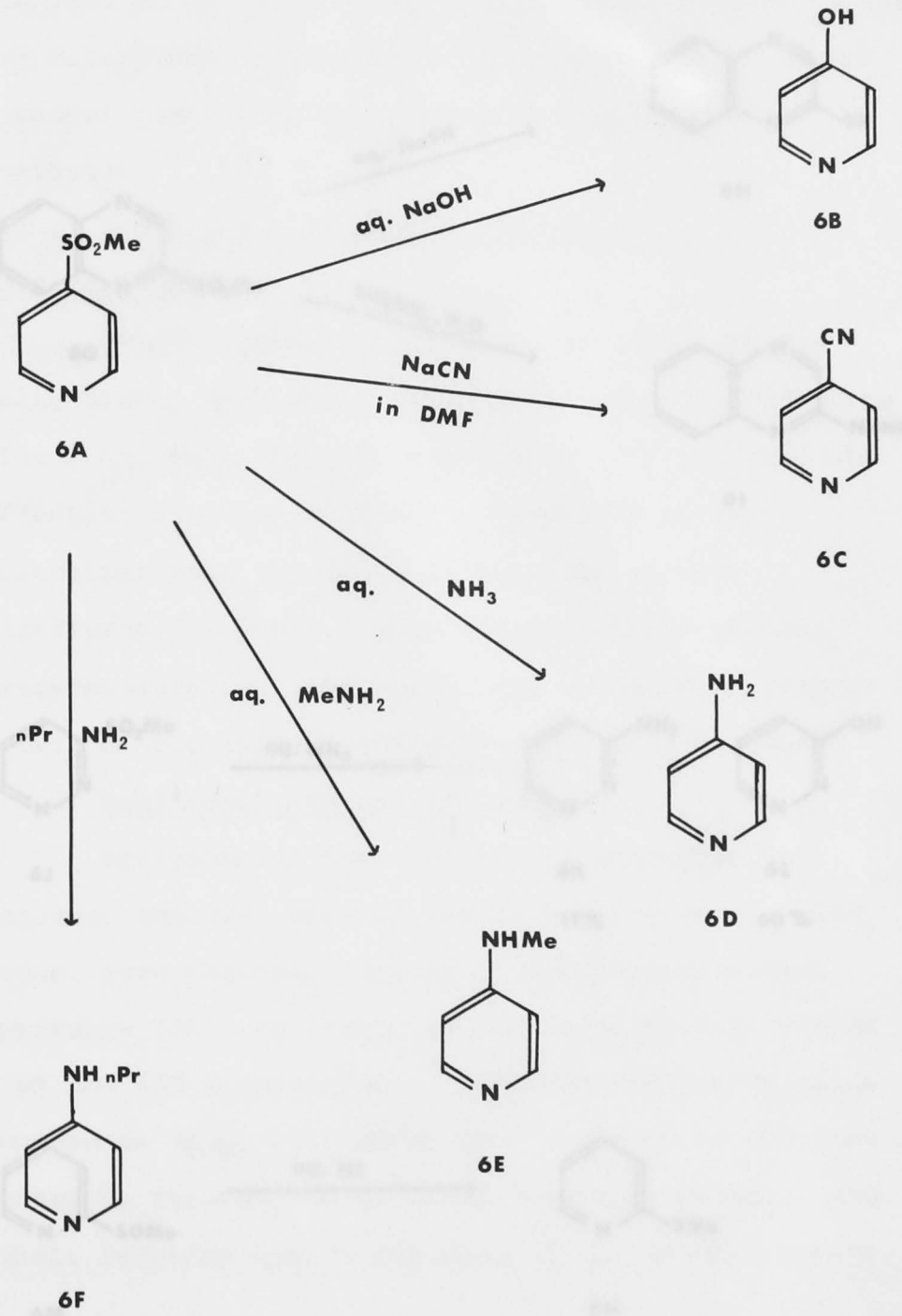
n-propylamine, and hydrazine hydrate. The reactions were usually found to proceed well and give good yields of the expected products. Full details of this work are given in the Experimental chapter and certain aspects are discussed below.

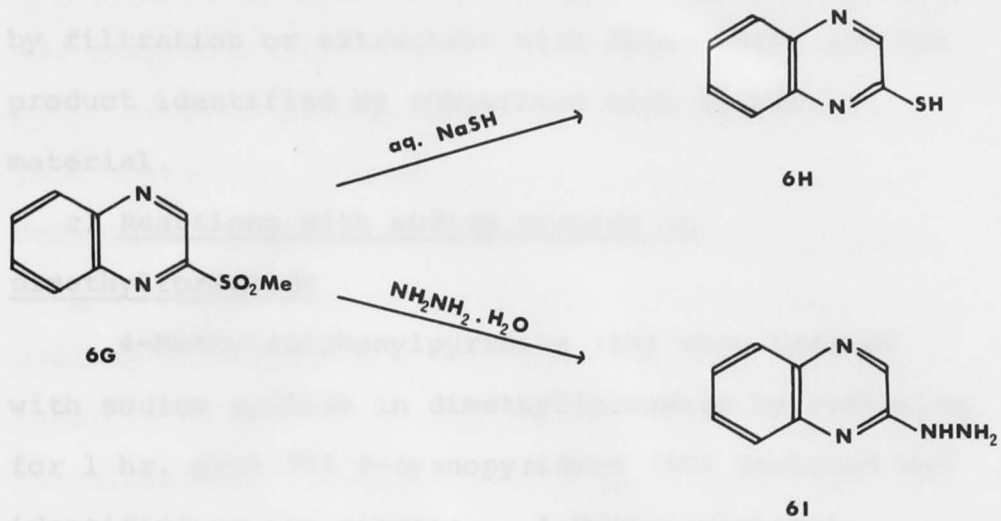
a) Reactions with aqueous sodium hydroxide

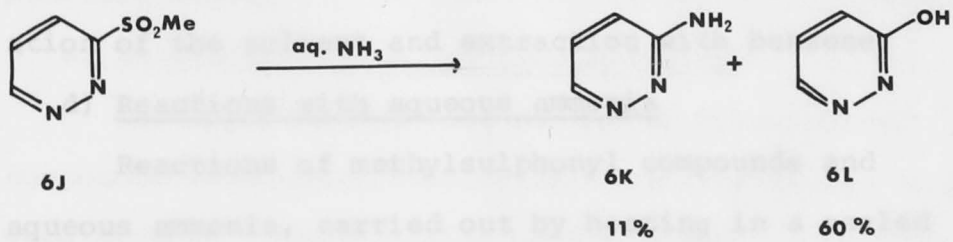
All of the methylsulphonyl compounds (e.g. 6A) when allowed to react with N sodium hydroxide solution (see Table 19 of Chapter 7 for times and temperatures), gave good yields of the hydroxy compounds (e.g. 6B). These were isolated either as the picrate or free base by crystallisation or sublimation and identified by melting point and, where possible, mixed melting point.

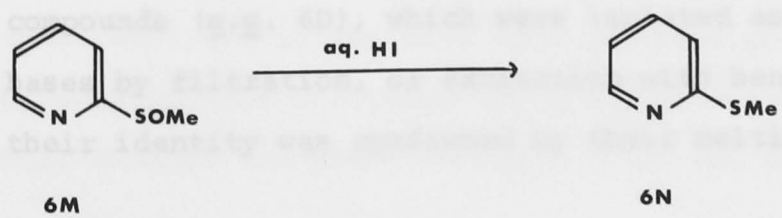
b) Reactions with aqueous sodium hydrogen sulphide

Aqueous sodium hydrogen sulphide solution was made by bubbling hydrogen sulphide through N sodium hydroxide solution till neutral to phenolphthalein. Samples of chosen methylsulphonyl compounds (3-methylsulphonylpyridazine, 4-methylsulphonyl-quinoline, and 2-methylsulphonylquinoxaline; 6G) were heated with this sodium hydrogen sulphide solution to give the corresponding mercapto compounds (e.g. 6H)


OH
N
6B
aq. NaOH
SO2Me
N
6A
NaCN
in DMF
CN
N
6C
aq. NH3
aq. MeNH2
nPr NH2
NH2
N
6D
NHMe
N
6E
NH nPr
N
6F


aq. NaSH
SH
6H
SO2Me
6G
NH2NH2 . H2O
NHNH2
6I


SO2Me
aq. NH3
NH2
OH
+
6J
6K
11 %
6L
60 %


aq. HI
SOMe
SMe
6M
6N

in good yield (81 to 86%). These were isolated either by filtration or extraction with chloroform, and the product identified by comparison with authentic material.

c) Reactions with sodium cyanide in dimethylformamide

4-Methylsulphonylpyridine (6A) when treated with sodium cyanide in dimethylformamide by refluxing for 1 hr. gave 75% 4-cyanopyridine (6C) isolated and identified as its picrate. 4-Methylsulphonylcinnoline when treated with the same reagent (refluxed for 5 min.) gave the previously unknown 4-cyanocinnoline (68%) which was isolated by evaporation of the solvent and extraction with benzene.

d) Reactions with aqueous ammonia

Reactions of methylsulphonyl compounds and aqueous ammonia, carried out by heating in a sealed tube, gave variable results. 4-Methylsulphonylpyridine (6A) and cinnoline gave satisfactory yields (69 and 63% respectively) of the corresponding amino compounds (e.g. 6D), which were isolated as the free bases by filtration, or extraction with benzene, and their identity was confirmed by their melting points.

The previously unknown 4-aminocinnoline picrate also was prepared.

However aqueous ammonia and 3-methylsulphonylpyridazine (6J) or 2-methylsulphonylquinoline gave only 11 and 22% respectively of the amino compounds (e.g. 6K)(isolated as picrates); but the corresponding hydroxy compounds (e.g. 6L) were isolated (as the free base) in 60 and 63% yields respectively. When these reactions were carried out with added ammonium chloride to suppress the concentration of hydroxide ion by the common ion effect, the yields of 3-aminopyridazine and 2-aminoquinoline improved to 42% and 50% respectively.

e) Reactions with aqueous methylamine

The reactions of most of the methylsulphonyl compounds with aqueous methylamine (heat; sealed tube) were studied. High yields of methylamino compounds (e.g. 6E) were usually obtained and isolation and identification were either as free bases or picrates. Sometimes amine salt was present (usually by adding conc. HCl) and in the case of 3-methylsulphonylpyridazine this increased the yield from 43 to 65%. Full details are given in Table 20 in the Experimental

chapter. New compounds were 3- and 4-methylamino-pyridazine, 1-methylaminoisoquinoline and the picrate of 4-methylaminocinnoline.

f) Reactions with n-propylamine

The reactions of all 11 methylsulphonyl compounds with n-propylamine (undiluted) to give the corresponding n-propylamino compounds (e.g. 6F) were carried out by heating in sealed tubes (full details are given in Table 21 in the Experimental chapter). Generally good yields were obtained (63 to 93%) except for 1-methylsulphonylphthalazine which gave only 39% of 1-n-propylaminophthalazine. Isolation and identification were either as free bases (sublimation and/or crystallisation) or as the picrate depending on the nature of the n-propylamino compound. All these compounds were new except for 2-n-propylamino-pyridine and quinoline.

g) Reactions with hydrazine hydrate

Certain methylsulphonyl compounds (2-methylsulphonylquinoline, 2-methylsulphonylquinoxaline (6G), and 4-methylsulphonylcinnoline) were refluxed with hydrazine hydrate. On cooling and dilution, the expected hydrazino compound (e.g. 6I) crystallised

and its identity was confirmed by melting point or elemental analysis. Yields were good, ranging from 67 to 91%.

II Reduction of Sulphoxides

It has been recorded (Brown and Ford, 1967) that simple pyrimidine sulphoxides were reduced by hydriodic acid to give the corresponding sulphides. Accordingly several sulphoxides (2-methylsulphinylquinoxaline, 2-methylsulphinylpyridine (6M) and 4-methylsulphinylquinoline) were heated with hydriodic acid on a steam bath. In all cases the corresponding methylthio compound (e.g. 6N) was isolated as the picrate (melting point and mixed melting point; yields ranged from 44 to 89%).

Oxidation of the sulphoxides by potassium permanganate or m-chloroperbenzoic acid to the corresponding sulphones has been discussed under the preparation of alkylsulphonyl compounds (Chapter 2).

CHAPTER 7

EXPERIMENTAL

Analyses were by Dr J.E.Fildes and her staff in the Department of Medical Chemistry, Australian National University, Canberra. Solids for analysis were dried at 25°/1 mm. except for some higher melting-materials (m.p. >130°) which were dried at 100°.

All melting points recorded below were taken in 'Pyrex' glass capillaries and are uncorrected.

Compounds were examined for impurities by paper chromatography on Whatman No.1 paper with butan-2-ol/5N-acetic acid (7:3) as solvent, and by thin layer chromatography on alumina (Merck P.F. 254 + 366) or silica gel (Merck P.F. 254 + 366) with ether and chloroform. Solid compounds for kinetic studies were purified by chromatography and/or crystallisation to constant m.p., and liquids by distillation. Exceptions were the low melting 2- and 4-methylsulphinylpyridines which were purified by chromatography to constant ultraviolet absorption spectra.

4-Methylsulphinylpyridine was also purified through the picrate but the free base was unstable to distillation under reduced pressure.

All new compounds are underlined at their first mention in the body of the text. (As in the Journal of the Chemical Society, names which are paragraph headings are also underlined but this does not indicate that the compound is new.)

PYRIDINES

2-Methylsulphinylpyridine.— 2-Methylthiopyridine (2 g.; Renault, 1955) in water (30 ml.) was stirred at 25° while sodium metaperiodate (3.4 g.) in water (30 ml.) was added slowly. The mixture was stirred overnight and extracted with chloroform. The chloroform extract was dried (Na_2SO_4) and evaporated to leave an oil, which was purified by thin layer chromatography (alumina/ether) and finally by column chromatography (alumina/chloroform) to give 2-methylsulphinylpyridine (1.7 g.)(Found: C, 51.1; H, 4.9; N, 9.9. C_6H_7NOS requires C, 51.0; H, 5.0; N, 9.9%). [Courtot and Zwilling (1938) reported the preparation of 2-methylsulphinylpyridine but did not give full experimental details or an elemental analysis.]

2-Methylsulphonylpyridine.— 2-Methylsulphonylpyridine was prepared from 2-methylthiopyridine by oxidation with potassium permanganate (Marckwald, Klemm, and Trabert, 1900). The reaction mixture was decolourised with sulphur dioxide, adjusted to pH 7, and the product extracted with chloroform and distilled. It had b.p. 120°/0.7 mm. (Found: C, 45.7; H, 4.7; N, 9.3; S, 20.3. Calc. for $C_6H_7NO_2S$: C, 45.7; H, 4.5; N, 8.9; S, 20.35%).

2-Methoxypyridine.—(a) 2-Methylsulphonylpyridine (0.100 g.) and methanolic sodium methoxide (5 ml.; 0.43N) were heated at 150° for 6 hr. The reaction mixture was diluted with water, adjusted to pH 7, and extracted with chloroform. The extract was dried (Na_2SO_4) and the solvent distilled off leaving an oil which with ethanolic picric acid gave yellow crystals of 2-methoxypyridine picrate (0.09 g.; 42%), m.p. and mixed m.p. 159-160° (from ethanol).

(b) 2-Methoxypyridine picrate, for comparison, was prepared from 2-bromopyridine and sodium methoxide by a method similar to that used (Grave, 1924) with 2-chloropyridine (Found: C, 42.5; H, 3.1; N, 16.6. $C_{12}H_{10}N_4O_8$ requires C, 42.6; H, 3.0; N, 16.6%).

(c) 2-Methylsulphinylpyridine (0.100 g.) was heated with sodium methoxide solution (3 ml., 0.4N) at 120° for 3 hr. The mixture was diluted with water and extracted with chloroform. The extract was dried (Na_2SO_4), the chloroform removed by fractionation and ethanolic picric acid added to the residue to give 2-methoxypyridine picrate (0.185 g.; 77%), m.p. and mixed m.p. 160-161° (from ethanol).

4-Methylsulphinylpyridine.— 4-Methylthiopyridine (2 g.; King and Ware, 1939) in water (30 ml.) was stirred at 25° while a solution of sodium meta-periodate (3.4 g.) in water (30 ml.) was added slowly. The mixture was then stirred overnight and extracted with chloroform. The chloroform extract was dried (Na_2SO_4) and evaporated to leave an oil. This was purified by thin layer chromatography (alumina/ether) and with ethanolic picric acid gave 4-methyl-sulphinylpyridine picrate (3.5 g.), m.p. 132° (from ethanol) (Found: C, 38.8; H, 2.7; N, 15.2. $C_{12}H_{10}N_4O_8S$ requires: C, 38.9; H, 2.7; N, 15.1%). The picrate was dissolved in sodium bicarbonate solution and extracted with chloroform. The extract was washed with sodium bicarbonate solution and water (2X), dried (Na_2SO_4), concentrated and

chromatographed over alumina in chloroform to give 4-methylsulphinylpyridine (0.7 g.) as a colourless oil which slowly solidified, m.p. 37-38° (Found: C, 50.6; H, 5.25; N, 10.0%).

4-Methylsulphonylpyridine.— 4-Methylsulphonylpyridine m.p. 82° (from benzene-hexane; lit., 81°) was prepared as described by King and Ware (1939). (b) 4-Methylsulphinylpyridine (0.200 g.) in acetic acid (10 ml., 6N) was shaken at 25° while potassium permanganate (0.3 g.) in water (20 ml.) was added over 0.5 hr. The mixture was chilled in ice, decolourised with sulphur dioxide, neutralised with ammonia and extracted with chloroform. The chloroform extract was dried (Na_2SO_4) and evaporated to give 4-methylsulphonylpyridine (0.150 g.), m.p. and mixed m.p. 81° (from benzene-hexane).

4-Methoxypyridine.—(a) 4-Methylsulphinylpyridine (0.100 g.) was heated in a sealed tube with sodium methoxide solution (10 ml., 0.2N) at 80° for 6 hr. The mixture was then diluted with water, the methanol removed by fractionation, and the product extracted with chloroform. The extract was dried (Na_2SO_4), the solvent removed by fractionation, and

addition of ethanolic picric acid to the residue gave 4-methoxypyridine picrate (0.205 g., 85%), m.p. 170-171° (from ethanol)(Renshaw and Conn, 1937, give 171-172°).

(b) 4-Methylsulphonylpyridine (0.100 g.) and methanolic sodium methoxide (5 ml.; 0.43N) were heated at 150° for 6 hr. The mixture was evaporated to dryness and extracted with chloroform; the product with aqueous picric acid gave 4-methoxypyridine picrate (0.075 g., 35%), m.p. 170-171° (from water)(no depression of the m.p. was observed on admixture with the sample prepared above)(Found: C, 42.9; H, 3.0; N, 16.7%).

PYRAZINES

2-Methylthiopyrazine was prepared as described by Albert and Barlin (1962). It had m.p. 45-46° (from light petroleum, b.p. 60-80°)(Cheeseman, 1960, gives 45-47.5°).

2-Methylsulphinylpyrazine.— A solution of m-chloroperbenzoic acid (3.58 g.; 77.7%) in chloroform (100 ml.) was added slowly to a stirred solution of 2-methylthiopyrazine (2.1 g.) in chloroform (50 ml.) at 0°, and then the mixture was allowed to stand

overnight at 20°. The chloroform solution was washed with aqueous sodium bicarbonate and water, dried (Na_2SO_4) and evaporated. The oil obtained was purified by thin layer chromatography (alumina/ether) and by crystallisation from hexane-cyclohexane to give white crystals of 2-methylsulphinylpyrazine (0.9 g.), m.p. 66-67° (Found: C, 42.3; H, 4.4; N, 19.85; S, 22.4. $C_5H_6N_2OS$ requires C, 42.25; H, 4.3; N, 19.7; S, 22.5%).

2-Methylsulphonylpyrazine.— 2-Methylthiopyrazine (0.500 g.) was dissolved in acetic acid (14 ml.; 8N) and a solution of potassium permanganate (1 g.) in water (8 ml.) added with stirring at 25° during 0.5 hr. This mixture was decolourised by passing in sulphur dioxide, neutralised with ammonia, and extracted with chloroform. The chloroform extract was dried (Na_2SO_4) and evaporated to give a colourless oil which solidified on cooling and was twice sublimed (150°/0.5 mm.) to give 2-methylsulphonylpyrazine (0.42 g.), m.p. 47-48° (Found: C, 38.4; H, 3.9; N, 17.7; S, 20.15. $C_5H_6N_2O_2S$ requires C, 38.0; H, 3.8; N, 17.7; S, 20.2%).

2-Methoxypyrazine.- Three experiments were carried out as follows: (a) 2-Methylthiopyrazine (0.002 g.) was heated with sodium methoxide solution (2 ml.; 0.01N) at 150° for 24 hr. (b) 2-Methylsulphinylpyrazine (0.009 g.) was heated with sodium methoxide solution (40 ml.; 0.01N) at 50° for 24 hr. (c) 2-Methylsulphonylpyrazine (0.005 g.) and methanolic sodium methoxide (3 ml.; 0.02N) were heated at 87° for 3 hr. In each case complete conversion into 2-methoxypyrazine was apparent. [Appropriate dilution of the reaction mixtures at pH 6.0 and -1.5 gave solutions with the ultraviolet absorption spectra of the neutral molecule (cf. Mason, 1957) and cation (cf. Mason, 1959) respectively.]

PYRIDAZINES

3-Methylthiopyridazine.- This compound, prepared as described by Duffin and Kendall (1959) had m.p. 42° (from light petroleum, b.p. 40-60°)(lit., 37-38°).

3-Methylsulphinylpyridazine.- A solution of m-chloroperbenzoic acid (3.53 g.; 77.7%) in chloroform (100 ml.) was added slowly to a stirred solution of 3-methylthiopyridazine (2.10 g.) in chloroform (50 ml.),

and the mixture was then allowed to stand overnight at 20°C. The chloroform solution was washed with sodium bicarbonate solution and water, dried, and evaporated. The oil obtained was purified by thin layer chromatography in ether over alumina and then crystallised from benzene-cyclohexane to give colourless crystals of 3-methylsulphinylpyridazine (1.1 g.), m.p. 65° (Found: C, 42.1; H, 4.3; N, 19.8; S, 22.6%).

3-Methylsulphonylpyridazine.—(a) To 3-methylthiopyridazine (0.290 g.) in acetic acid (6 ml.; 16N), potassium permanganate (0.75 g.) in water (9 ml.) was added slowly with stirring at 25° and stirring continued for 0.5 hr. The mixture was cooled in ice, decolourised by passing in sulphur dioxide, adjusted to pH 8 with ammonia, and extracted with chloroform. The extract was dried (Na_2SO_4) and evaporated to yield 3-methylsulphonylpyridazine (0.270 g.), m.p. 87° [from benzene-light petroleum (b.p. 60-80°)] (Found: C, 37.8; H, 3.7; N, 17.7; S, 20.4%).

(b) 3-Methylthiopyridazine (0.500 g.) was dissolved in water (10 ml.) and methanol (3 ml.). The solution was cooled to -20° and chlorine passed in for 1 hr. The cold solution was adjusted to pH 7

with aqueous potassium carbonate, and extracted with chloroform. The extract was dried (Na_2SO_4), concentrated, and chromatographed over alumina (6 in.) to give 3-methylsulphonylpyridazine (0.440 g.), m.p. and mixed m.p. with the sample prepared above, 87° [from benzene-light petroleum (b.p. 60-80°)].

(c) 3-Methylsulphinylpyridazine (0.200 g.) in acetic acid (5 ml.; 6N) was shaken at 20° while potassium permanganate solution (0.3 g.) in water (10 ml.) was added over 0.5 hr. The mixture was chilled in ice, decolourised with sulphur dioxide, neutralised and extracted with chloroform. The chloroform extract was dried (Na_2SO_4) and evaporated and the product crystallised from benzene-light petroleum (b.p. 60-80°) to give 3-methylsulphonylpyridazine (0.140 g.), m.p. and mixed m.p. [with sample from (a)], 87-88°.

3-Methoxypyridazine.—(a) 3-Methylthiopyridazine (0.100 g.) and methanolic sodium methoxide (20 ml.; 0.1N) were heated at 120° for 18 hr. The mixture was then diluted with water, fractionated to remove the methanol, and extracted with chloroform. The extract was dried (Na_2SO_4) and the solvent removed by fractionation. The oily residue, with ethanolic

picric acid, gave 3-methoxypyridazine picrate (0.140 g.; 52%), m.p. 111-112° (from ethanol)(Itai and Igeta, 1954 give 111°).

(b) 3-Methylsulphinylpyridazine (0.105 g.) and sodium methoxide solution (5 ml.; 0.4N) were refluxed for 0.5 hr. The mixture was diluted with water, neutralised, and the methanol removed by fractionation. Ethanolic picric acid was added to the residue and 3-methoxypyridazine picrate (0.235 g.; 93%) crystallised, m.p. 110-111° (from ethanol).

(c) 3-Methylsulphonylpyridazine (0.100 g.) and methanolic sodium methoxide (5 ml.; 0.43N) were refluxed for 30 min. The reaction mixture was diluted with water, neutralised, and extracted with chloroform. The chloroform extract was dried (Na_2SO_4) and the solvent evaporated to give an oily residue which with ethanolic picric acid gave yellow crystals of 3-methoxypyridazine picrate (0.080 g.; 37%), m.p. 111° (from ethanol)(Found: C, 39.1; H, 2.6; N, 20.3. Calc. for $C_{11}H_9N_5O_8$: C, 38.95; H, 2.7; N, 20.65%).

4-Methylthiopyridazine.— 4-Methylthiopyridazine was prepared as described by Albert and Barlin (1962)

but was purified by column chromatography in chloroform over alumina and crystallised from light petroleum (b.p. 40-60°). It had m.p. 44-45° (Found: C, 47.8; H, 4.9; N, 22.1. Calc. for $C_5H_6N_2S$: C, 47.6; H, 4.8; N, 22.2%). The picrate had m.p. 155-157° (from ethanol)(Albert and Barlin, 1962, give 149-150.5°)(Found: C, 36.8; H, 2.7; N, 19.6. Calc. for $C_{11}H_9N_5O_7S$: C, 37.2; H, 2.55; N, 19.7%).

4-Methylsulphinylpyridazine.— m-Chloroperbenzoic acid (5.99 g.; 77.7%) dissolved in chloroform (150 ml.) was added slowly with stirring to 4-methylthiopyridazine (3.34 g.) in chloroform (80 ml.) at 0°. After standing overnight at 0° the chloroform solution was washed with sodium bicarbonate solution and water (the washings were repeatedly extracted with chloroform) and evaporated to yield an oil which was subjected to thin layer chromatography in chloroform-ether (6:4) over alumina. The product crystallised from benzene-cyclohexane to give 4-methylsulphinylpyridazine (1.2 g.), m.p. 92-93° (Found: C, 42.0; H, 4.4; N, 19.6; S, 22.5%).

4-Methylsulphonylpyridazine.— 4-Methylthiopyridazine (0.120 g.) in acetic acid (2 ml.; 16N) was

stirred at room temperature while potassium permanganate (0.25 g.) in water (2.5 ml.) was added during 0.5 hr. The mixture was cooled, decolourised by passing in sulphur dioxide and adjusted to pH 7 with ammonia. Extraction with chloroform gave 4-methylsulphonylpyridazine (0.073 g.), m.p. 144° (from ethanol) (Found: C, 38.0; H, 3.9; N, 18.0; S, 20.3%).

4-Methoxypyridazine.—(a) 4-Methylthiopyridazine (0.100 g.) and methanolic sodium methoxide (20 ml.; 0.1N) were heated at 100° for 15 hr. The mixture was diluted with water, neutralised, and the product extracted with chloroform. The extract, was dried (Na_2SO_4) and the solvent removed by fractionation. Treatment of the oily residue with ethanolic picric acid gave 4-methoxypyridazine picrate (0.201 g.; 75%), m.p. 143° (Itai and Kamiya, 1963, give 143-144°).

(b) 4-Methylsulphonylpyridazine (0.100 g.) and methanolic sodium methoxide (5 ml.; 0.43N) were refluxed for 0.5 hr. The reaction mixture was diluted with water, neutralised, and extracted with chloroform. The chloroform extract was dried (Na_2SO_4) and the solvent evaporated to give an oily

residue which with ethanolic picric acid gave yellow crystals of 4-methoxypyridazine picrate (0.150 g.; 70%), m.p. and mixed m.p. with sample from (a), 143-144° (Found: C, 39.0; H, 2.4; N, 20.6%).

4-Methylsulphinylpyridazine with sodium methoxide solution.— A mixture of 4-methylsulphinylpyridazine (0.500 g.) and methanolic sodium methoxide (20 ml.; 0.2N) was allowed to stand at 25°/15 min., then diluted with water (25 ml.) and neutralised with dilute hydrochloric acid. The methanol was evaporated on a steam bath and the aqueous solution extracted with chloroform. The extract was dried (Na_2SO_4), the solvent evaporated and the components were separated by thin layer chromatography in ether over alumina.

The upper band, after extraction with chloroform, evaporation, and treatment with ethanolic picric acid, gave 4-methylthiopyridazine picrate (0.080 g.; 6.4%), m.p. and mixed m.p. with an authentic specimen 155-156° (from ethanol).

The lower band, after extraction with chloroform, evaporation, and treatment with ethanolic picric acid, gave 4-methoxypyridazine picrate (0.840 g.; 70.5%), m.p. and mixed m.p. with an authentic sample 143-144° (from ethanol).

QUINOLINES

2-Methylsulphinylquinoline.– 2-Methylthioquinoline (0.500 g.; Albert and Barlin, 1959) in chloroform (15 ml.) was stirred at 0° while m-chloroperbenzoic acid (0.635 g.) in chloroform (15 ml.) was added slowly. The mixture was then left to stand overnight at 20° and washed with sodium bicarbonate solution and water, and extracted with chloroform. The chloroform extract was dried (Na_2SO_4) and evaporated to give the product which was purified by chromatography in chloroform over alumina, and crystallised from benzene-light petroleum (b.p. 40-60°) to give 2-methylsulphinylquinoline (0.350 g.), m.p. 52° (Found: C, 62.3; H, 4.7; N, 7.3. $C_{10}H_9NOS$ requires C, 62.8; H, 4.75; N, 7.3; S, 16.7%).

2-Methylsulphonylquinoline.–(a) This was prepared as described by Larivé, Collet and Dennilauler (1956) from 2-methylthioquinoline with potassium permanganate in acetic acid. It had m.p. 101-102° (lit., 100°) (Found: C, 57.6; H, 4.5; N, 6.9; S, 15.4. Calc. for $C_{10}H_9NO_2S$: C, 58.0; H, 4.3; N, 6.8; S, 15.45%).

(b) 2-Methylsulphinylquinoline (0.150 g.) in acetic acid (5 ml.; 6N) was shaken at 20° while potassium permanganate (0.2 g.) in water (10 ml.) was added over 0.5 hr. The mixture was chilled in ice, decolourised with sulphur dioxide, to reveal a white precipitate, and filtered. The product was recrystallised from benzene-cyclohexane to give 2-methylsulphonylquinoline (0.132 g.), m.p. and mixed m.p. with sample from (a), 102°.

2-Methoxyquinoline.—(a) 2-Methylsulphinylquinoline (0.035 g.) and sodium methoxide (1 ml.; 0.4N) were heated at 85° for 3 hr. The mixture was diluted with water, neutralised, the methanol evaporated and aqueous picric acid added to precipitate 2-methoxyquinoline picrate (0.064 g.; 90%), m.p. 182° (from ethanol)(Fuson, Jackson, and Grieshaber, 1951, give 179-180°).

(b) 2-Methylsulphonylquinoline (0.12 g.) and methanolic sodium methoxide (5 ml.; 0.3N) were heated at 110° for 1 hr. The solvent was evaporated and the residue extracted with chloroform. The oily product with ethanolic picric acid gave 2-methoxyquinoline picrate (0.19 g.; 85%), m.p. 182-183° (from ethanol). No depression of the m.p. was

observed on admixture with a sample from (a) (Found: C, 49.7; H, 3.0; N, 14.35. Calc. for $C_{16}H_{12}N_4O_8$: C, 49.5; H, 3.1; N, 14.4%).

4-Methylsulphinylquinoline.– 4-Methylthioquinoline (1.00 g.; Albert and Barlin, 1959) in chloroform (30 ml.) was stirred at 0° while m-chloroperbenzoic acid (1.27 g.; 77.7%) in chloroform (30 ml.) was added dropwise over 1 hr. The mixture was then left to stand overnight at 20° and washed with sodium bicarbonate solution and water. The chloroform extract was dried (Na_2SO_4) and evaporated, the oily residue with ethanolic picric acid gave 4-methylsulphinylquinoline picrate (2.1 g.), m.p. 212° (Found: C, 45.9; H, 3.05; N, 13.4. $C_{16}H_{12}N_4O_8S$ requires C, 45.7; H, 2.9; N, 13.3%).

This picrate was dissolved in aqueous sodium bicarbonate and the solution extracted with chloroform. The product obtained crystallised from cyclohexane to give white crystals of 4-methylsulphinylquinoline (0.70 g.), m.p. 85-86° (Found: C, 62.7; H, 5.0; N, 7.25; S, 16.6%).

4-Methylsulphonylquinoline.–(a) A solution of 4-methylthioquinoline (1.2 g.) in acetic acid

(30 ml.; 6N) was stirred at room temperature while potassium permanganate (2.1 g.) in water (50 ml.) was added dropwise during 0.5 hr. The mixture was filtered, the black solid extracted three times with boiling benzene, and the extract evaporated. The 4-methylsulphonylquinoline (0.96 g.) crystallised from benzene-hexane and had m.p. 147-148° (Found: C, 58.4; H, 4.4; N, 7.0; S, 15.2%).

(b) 4-Methylsulphinylquinoline (0.150 g.) in glacial acetic acid (2 ml.) was shaken at 25° while potassium permanganate (0.200 g.) in water (15 ml.) was added over 0.5 hr. The mixture was chilled in ice and filtered; the black residue was extracted with boiling benzene and the product recrystallised from benzene-light petroleum (b.p. 60-80°) to give 4-methylsulphonylquinoline (0.070 g.), m.p. and mixed m.p. with a sample from (a), 147-148°.

4-Methoxyquinoline.—(a) 4-Methylsulphinylquinoline (0.020 g.) and methanolic sodium methoxide (28 ml.; 0.015N) were refluxed for 12 hr., the methanol was evaporated and the residue dissolved in ethanol and treated with ethanolic picric acid to give crystals of 4-methoxyquinoline picrate (0.037 g.; 90%), m.p. 200-201° (from ethanol)(Backeberg, 1933, gives 203°).

(b) 4-Methylsulphonylquinoline (0.050 g.) and methanolic sodium methoxide (2 ml.; 0.4N) were heated at 87° for 2 hr. The mixture was evaporated to dryness and the product extracted into chloroform. The chloroform extract was evaporated and the oily residue with ethanolic picric acid gave crystals of 4-methoxyquinoline picrate (0.057 g.; 61%), m.p. and mixed m.p. with a sample from (a), 202°.

ISOQUINOLINES

1-Methylsulphinylisoquinoline.— To 1-methylthioisoquinoline (1.105 g.; Albert and Barlin, 1959) in chloroform (30 ml.), m-chloroperbenzoic acid (1.404 g.; 77.7%) in chloroform (30 ml.) was added slowly with stirring at 0°. After standing overnight at 20° the chloroform solution was washed with aqueous sodium bicarbonate and water, dried (Na_2SO_4), concentrated and chromatographed over alumina to give an oil (0.88 g.) which slowly solidified. It was recrystallised from benzene-light petroleum (b.p. 60-80°) to give 1-methylsulphinylisoquinoline, m.p. 65-66° (Found: C, 62.45; H, 4.9; N, 7.1%).

1-Methylsulphonylisoquinoline.— To a stirred solution of 1-methylthioisoquinoline (0.5 g.) in acetic acid (10 ml.; 6N), potassium permanganate (1.0 g.) in water (20 ml.) was added dropwise during 0.5 hr. After chilling, the mixture was decolourised by sulphur dioxide and the precipitate filtered off and recrystallised from benzene-hexane to give 1-methylsulphonylisoquinoline (0.42 g.), m.p. 153-154° (Found: C, 58.0; H, 4.5; N, 6.7; S, 15.7%).

1-Methoxyisoquinoline.—(a). 1-Methylsulphinylisoquinoline (0.100 g.) was heated with sodium methoxide solution (1 ml.; 0.4N) at 50° for 2 hr. The mixture was diluted with water, neutralised, and aqueous picric acid added to give 1-methoxyisoquinoline picrate (0.125 g.; 62%), m.p. 170-171° (from water)(Robison and Robison, 1958, give m.p. 163.5-165.5°).
(b) 1-Methylsulphonylisoquinoline (0.12 g.) and methanolic sodium methoxide (5 ml.; 0.3N) were heated at 110° for 1 hr.; and the solvent was evaporated. The product, obtained by extraction with chloroform, gave, with ethanolic picric acid, 1-methoxyisoquinoline picrate (0.19 g.; 85%), m.p. 170-171° (from ethanol). No depression was observed when mixed with a sample from (a)(Found: C, 49.15; H, 3.1; N, 14.5%).

(c) 1-Methoxyisoquinoline was also prepared from 1-hydroxyisoquinoline, as described by Albert and Phillips (1956), through 1-chloroisoquinoline (Gabriel and Colman, 1900) with sodium methoxide. It had b.p. 138-140°/*ca* 25 mm. (Albert and Phillips give 135-136°/21 mm.).

CINNOLINES

4-*Methylthiocinnoline*.— This product, prepared as described by Castle, Ward, White, and Adachi (1960) had m.p. 97-98° (*lit.*, 98°).

4-*Methylsulphinylcinnoline*.— A solution of 4-methylthiocinnoline (3.00 g.) in benzene (50 ml.) and light petroleum (20 ml.; b.p. 60-80°) was stirred at 20° while *m*-chloroperbenzoic acid (3.785 g.; 77.7%) in benzene (60 ml.) and light petroleum (20 ml.; b.p. 60-80°) was added slowly and stirring continued overnight. The product was filtered off, chromatographed in chloroform over alumina and recrystallised from benzene-light petroleum (b.p. 60-80°) to give yellow crystals of 4-*methylsulphinylcinnoline* (1.56 g.), m.p. 157° (Found: C, 56.1; H, 4.1; N, 14.8; S, 16.8. $C_9H_8N_2SO$ requires C, 56.25; H, 4.2; N, 14.6; S, 16.7%).

4-Methylsulphonylcinnoline.—(a) 4-Methylthiocinnoline (1.00 g.) in acetic acid (20 ml.; 8N) was stirred at room temperature while potassium permanganate (1.5 g.) in water (30 ml.) was added during 0.5 hr. The mixture was chilled and decolourised by sulphur dioxide. The product was collected and recrystallised from benzene-cyclohexane to give yellow needles of 4-methylsulphonylcinnoline (0.67 g.), m.p. 183-184° (Found: C, 51.7; H, 3.8; N, 13.3; S, 15.35. $C_9H_8N_2O_2S$ requires C, 51.9; H, 3.85; N, 13.5; S, 15.4%).

(b) 4-Methylsulphinylcinnoline (0.200 g.) was dissolved in glacial acetic acid (3 ml.) and potassium permanganate (0.25 g.) in water (10 ml.) added over 0.5 hr. with shaking at 25°. The mixture was chilled in ice, decolourised with sulphur dioxide and filtered. The product was recrystallised from benzene-cyclohexane to give 4-methylsulphonylcinnoline (0.077 g.), m.p. and mixed m.p. with sample from (a), 183-184°.

4-Methoxycinnoline.—(a) 4-Methylthiocinnoline (0.200 g.) was refluxed with methanolic sodium methoxide (10 ml.; 0.4N) for 3 hr. The mixture was diluted with water, neutralised and the methanol

removed by fractionation. The residue was extracted with chloroform and the extract dried (Na_2SO_4) and evaporated to leave a pale pink solid. This was recrystallised from light-petroleum (b.p. 60-80°) to give 4-methoxycinnoline (0.130 g.; 71%), m.p. 126° (Schofield and Simpson, 1945, give 127-128°).

(b) 4-Methylsulphinylcinnoline (0.200 g.) was refluxed with methanolic sodium methoxide (10 ml.; 0.4N) for 2 hr. The mixture was then diluted with water, neutralised, and the methanol fractionated. The mixture was then extracted with chloroform, and the chloroform extract dried (Na_2SO_4), chromatographed over alumina, and evaporated to give 4-methoxycinnoline (0.135 g.; 81%), m.p. 127° (light petroleum, b.p. 60-80°).

(c) 4-Methylsulphonylcinnoline (0.20 g.) and methanolic sodium methoxide were refluxed for 5 min., and the solvent was evaporated. The residue was diluted with water and extracted with ether to yield 4-methoxycinnoline (0.08 g.; 52%), m.p. 128-129° (from light-petroleum, b.p. 60-80°). No depression was observed on admixture with samples from (a) and (b).

4-Methylsulphinylcinnoline with sodium methoxide under mild conditions.— 4-Methylsulphinylcinnoline (0.140 g.) in methanolic sodium methoxide (40 ml.; 0.02N)

was allowed to stand at 25° for 15 min. Water was then added, the solution neutralised to pH 7, the methanol evaporated, and the solution extracted with chloroform. This extract gave a solid which was shown by n.m.r. to be ca 75% 4-methoxycinnoline and 25% 4-methylthiocinnoline. The products were separated by thin layer chromatography (silica gel/ether) to give 4-methoxycinnoline (0.070 g.; 60%), m.p. and mixed m.p. with authentic specimen, 126° (from hexane); and 4-methylthiocinnoline (0.025 g.; 20%), m.p. and mixed m.p. with authentic specimen, 96° (from hexane).

PHTHALAZINES

1-Methylthiophthalazine was prepared as described by Albert and Barlin (1962) and had m.p. 76-77° (lit., 75-77°).

1-Methylsulphinylphthalazine.— 1-Methylthiophthalazine (1.00 g.) in chloroform (30 ml.) was stirred at 0° while m-chloroperbenzoic acid (1.27 g.) in chloroform (30 ml.) was added slowly. The mixture was left to stand overnight at 20° and washed with sodium bicarbonate solution and water. The chloroform extract was dried (Na_2SO_4), concentrated, and chromatographed over alumina

in chloroform. The eluate was evaporated and the product recrystallised from cyclohexane to give white crystals of 1-methylsulphinylphthalazine (0.45 g.), m.p. 105° (Found: C, 56.0; H, 4.05; N, 14.8%).

1-Methylsulphonylphthalazine.— A solution of 1-methylthiophthalazine (0.60 g.) in 6N acetic acid (18 ml.) was stirred at room temperature while potassium permanganate (1.2 g.) in water (30 ml.) was added during 0.5 hr. The mixture was chilled, decolourised by passing sulphur dioxide, and neutralised with ammonia to pH 7. Extraction with chloroform gave a mixture of 1-methylsulphonylphthalazine and 1-hydroxyphthalazine. This chloroform solution was chromatographed over alumina (8 in.) and the first fraction gave after crystallisation from benzene-light petroleum (b.p. 60-80°), 1-methylsulphonylphthalazine (0.40 g.), m.p. 156° (Found: C, 51.5; H, 3.6; N, 13.5; S, 15.1%). (This material is hygroscopic and reacts with the water absorbed to give the corresponding hydroxy compound. It is, however, sufficiently stable in solution to permit determination of the spectrum of the neutral molecule and also rate coefficients.)

1-Methoxyphthalazine.—(a) 1-Methylthiophthalazine (0.100 g.) was heated in a sealed tube with sodium

methoxide solution (20 ml.; 0.1N) at 115° for 3 hr. The mixture was then diluted with water, neutralised, and the methanol evaporated. Addition of aqueous picric acid gave 1-methoxyphthalazine picrate (0.203 g.; 92%), m.p. 161-162° (from ethanol)(Hayashi, Higashino, Iijima, Kono, and Doihara, 1962, give 139-140°).

(b) 1-Methylsulphinylphthalazine (0.100 g.) was refluxed with sodium methoxide solution (4 ml.; 0.4N) for 5 min. Water was then added, the mixture neutralised and the methanol evaporated. Addition of aqueous picric acid gave 1-methoxyphthalazine picrate (0.183 g.; 90%), m.p. 160-161° (from water).

(c) A mixture of 1-methylsulphonylphthalazine (0.100 g.) and methanolic sodium methoxide (4 ml.; 0.4N) was refluxed for 5 min., and the solvent evaporated. The mixture was extracted in chloroform, and, after evaporation of the solvent, the product, with ethanolic picric acid, gave 1-methoxyphthalazine picrate (0.135 g.; 72%), m.p. 161-162° (from ethanol)(Found: C, 46.5; H, 3.0; N, 17.9. Calc. for $C_{15}H_{11}N_5O_8$: C, 46.3; H, 2.85; N, 18.0%).

(d) An authentic specimen of the picrate prepared from 1-methoxyphthalazine (von Rothenburg, 1895) also had

m.p. 161-162° and gave no depression on admixture with samples from (a), (b), and (c).

QUINOXALINES

2-Methylthioquinoxaline was prepared as described by Cheeseman (1957) and had m.p. 45-46° (from light petroleum, b.p. 60-80°)(lit., 46-47°).

2-Methylsulphinylquinoxaline.– 2-Methylthioquinoxaline (0.500 g.) in chloroform (15 ml.) was stirred at 0° while m-chloroperbenzoic acid (0.632 g.) in chloroform (15 ml.) was added slowly. The mixture was left to stand overnight at 20° and washed with sodium bicarbonate solution and water. The extract was dried (Na_2SO_4) and evaporated. The solid product was purified by chromatography (alumina/chloroform) and recrystallised from cyclohexane to give 2-methylsulphinylquinoxaline (0.250 g.), m.p. 102-103° (Found: C, 56.15; H, 4.2; N, 14.9; S, 16.6%).

2-Methylsulphonylquinoxaline.–(a) A solution of 2-methylthioquinoxaline (0.100 g.) in acetic acid (2 ml.; 8N) was stirred at room temperature, while potassium permanganate (0.150 g.) in water (5 ml.) was added over 0.5 hr., and then decolourised with

sulphur dioxide. The white precipitate was filtered off and recrystallised from cyclohexane, to give 2-methylsulphonylquinoxaline (0.084 g.), m.p. 125-126° (Cheeseman, 1957, gives 126-127°)(Found: C, 51.5; H, 3.9; N, 13.6; S, 15.4%).

(b) 2-Methylsulphinylquinoxaline (0.200 g.) in acetic acid (5 ml.; 9N) was shaken at 20° while potassium permanganate (0.3 g.) in water (15 ml.) was added over 0.5 hr. The mixture was chilled in ice, decolourised with sulphur dioxide and filtered. The product was recrystallised from cyclohexane to give 2-methylsulphonylquinoxaline (0.180 g.), m.p. and mixed m.p. with a sample from (a), 126°.

(c) 2-Methylsulphinylquinoxaline (0.140 g.) in chloroform (5 ml.) was stirred at 25° while m-chloroperbenzoic acid (0.170 g.) in chloroform (10 ml.) was added slowly. The mixture was then left to stand overnight at 25°, washed with sodium bicarbonate solution and water. The extract was dried (Na_2SO_4), evaporated, and the product recrystallised from cyclohexane to give 2-methylsulphonylquinoxaline (0.105 g.), m.p. and mixed m.p. with a sample from (a), 125-126°.

2-Ethylthioquinoxaline was prepared as described by Cuiban, Ionesco, Bala, and Steresco (1963), and had m.p. 47-48° (lit., 47°).

2-Ethylsulphinylquinoxaline.— 2-Ethylthioquinoxaline (0.5 g.) in chloroform (20 ml.) was treated with m-chloroperbenzoic acid (0.558 g.; 77.7%), as described for 2-methylsulphinylquinoxaline, to give 2-ethylsulphinylquinoxaline (0.365 g.), m.p. 55° (from cyclohexane-light petroleum, b.p. 60-80°)(Found: C, 58.4; H, 5.05; N, 13.6; S, 15.5. $C_{10}H_{10}N_2SO$ requires C, 58.25; H, 4.9; N, 13.6; S, 15.5%).

2-Ethylsulphonylquinoxaline.—(a) 2-Ethylthioquinoxaline (0.300 g.) in acetic acid (4 ml.) was treated with potassium permanganate (0.6 g.) in water (30 ml.), as described for 2-methylsulphonylquinoxaline, to give 2-ethylsulphonylquinoxaline (0.240 g.), m.p. 122-123° (from cyclohexane)(Found: C, 54.4; H, 4.5; N, 12.6; S, 14.4. $C_{10}H_{10}N_2SO_2$ requires C, 54.05; H, 4.5; N, 12.6; S, 14.4%).

(b) To 2-ethylsulphinylquinoxaline (0.080 g.) in 6N acetic acid (4 ml.) was added potassium permanganate (0.160 g.) in water (10 ml.) with shaking at 20° over 0.5 hr. The mixture was chilled in ice, decolourised with sulphur dioxide, and the precipitate recrystallised

from cyclohexane to give 2-ethylsulphonylquinoxaline (0.060 g.), m.p. and mixed m.p. with a sample from (a), 122°.

2-Isopropylthioquinoxaline.– 2-Mercaptoquinoxaline (8 g.; Wolf, Wilson, and Tishler, 1954) was refluxed with isopropyl iodide (6 ml.) in sodium hydroxide solution (100 ml.; 1N) for 2 hr. The mixture was extracted with chloroform and the chloroform extract dried (Na_2SO_4) and evaporated to leave a yellow oil. This was distilled under reduced pressure, chromatographed over alumina in chloroform, and redistilled to give 2-isopropylthioquinoxaline (5 g.)(b.p. 140°/0.5 mm.)(Found: C, 64.6; H, 5.9; N, 14.0; S, 15.6. $C_{11}H_{12}N_2S$ requires C, 64.7; H, 5.9; N, 13.7; S, 15.7%).

2-Isopropylsulphonylquinoxaline.– 2-Isopropylthioquinoxaline (0.300 g.) was dissolved in glacial acetic acid (3 ml.) and treated with potassium permanganate (0.6 g.) in water (20 ml.), as for 2-methylsulphonylquinoxaline, to give 2-isopropylsulphonylquinoxaline (0.200 g.), m.p. 106° (from cyclohexane)(Found: C, 56.0; H, 5.25; N, 12.3;

S, 13.5. $C_{11}H_{12}N_2SO_2$ requires C, 55.9; H, 5.1; N, 11.9; S, 13.55%).

2-t-Butylthioquinoxaline.– To 2-chloroquinoxaline (6.1 g.)(Gowenlock, Newbold, and Spring, 1945) in ethanol (10 ml.) was added a solution of t-butyl mercaptan (2.5 ml.) and sodium hydroxide (1 g.) in water (20 ml.) under nitrogen. The mixture was then refluxed under nitrogen for 5 hr., cooled, neutralised, and extracted with chloroform. The extract was dried (Na_2SO_4) and evaporated to leave a brown oil. This was distilled (b.p. 120°/0.7 mm.), chromatographed (thin layer; silica gel/benzene) and crystallised from light petroleum (b.p. 40-60°) to give 2-t-butylthioquinoxaline (6.6 g.), m.p. 60-61° (Found: C, 66.0; H, 6.3; N, 12.7; S, 14.4. $C_{12}H_{14}N_2S$ requires C, 66.0; H, 6.5; N, 12.8; S, 14.7%).

2-t-Butylsulphinylquinoxaline.– 2-t-Butylthio-quinoxaline (0.500 g.) in chloroform (20 ml.) was treated with m-chloroperbenzoic acid (0.512 g.; 77.7%) in chloroform (20 ml.), as described for 2-methyl-sulphinylquinoxaline, to give 2-t-butylsulphinyl-quinoxaline (0.285 g.), m.p. 99-100° (from cyclohexane-

light petroleum; b.p. 60-80°)(Found: C, 61.6; H, 6.0; N, 11.9; S, 13.5. $C_{12}H_{14}N_2SO$ requires C, 61.5; H, 6.0; N, 12.0; S, 13.7%).

2-t-Butylsulphonylquinoxaline.— 2-t-Butylthio-quinoxaline (1.00 g.) in acetic acid (10 ml.) was treated with potassium permanganate (2 g.) in water (65 ml.), as described for 2-methylsulphonyl-quinoxaline, to give 2-t-butylsulphonylquinoxaline (0.75 g.), m.p. 123° (from cyclohexane)(Found: C, 57.3; H, 5.55; N, 11.3; S, 12.5. $C_{12}H_{14}N_2SO_2$ requires C, 57.6; H, 5.6; N, 11.2; S, 12.8%).

2-Methoxyquinoxaline.—(a) 2-Methylthio-quinoxaline (0.100 g.) was heated with methanolic sodium methoxide (20 ml.; 0.1N) at 115° for 3 hr. The mixture was then diluted with water, neutralised, and the methanol removed by evaporation. On addition of aqueous picric acid there separated 2-methoxyquinoxaline picrate (0.176 g.; 80%), m.p. 142° (from ethanol)(Cheeseman, 1955, gives 141-142°). Similarly 2-ethylthio-, 2-isopropylthio- and 2-t-butylthio-quinoxalines, with methanolic sodium methoxide, gave 2-methoxyquinoxaline picrate in yields of 64%., 63%., and 73% respectively.

(b) 2-Methylsulphinylquinoxaline (0.100 g.) was refluxed with sodium methoxide solution (10 ml.; 0.1N) for 5 min. Water was then added, the mixture neutralised, and the methanol evaporated. Aqueous picric acid was added and 2-methoxyquinoxaline picrate precipitated (0.180 g.; 89%), m.p. 141° (from ethanol). Similarly 2-ethylsulphinyl- and 2-t-butylsulphinyl-quinoxalines, with sodium methoxide solution, gave 2-methoxyquinoxaline picrate in yields of 95% and 80% respectively.

(c) 2-Methylsulphonylquinoxaline (0.10 g.) and methanolic sodium methoxide (6 ml.; 0.3N) were refluxed for 15 min., and the methanol was evaporated. The oily product was extracted with chloroform; and, with ethanolic picric acid, gave 2-methoxyquinoline picrate (0.07 g.; 37%), m.p. 142° (from ethanol). Similarly 2-ethylsulphonyl-, 2-isopropylsulphonyl- and 2-t-butylsulphonyl-quinoxalines with methanolic sodium methoxide, gave 2-methoxyquinoline picrate in yields of 75%, 83% and 82% respectively. (No depression of the m.p. was observed on admixture of the sample prepared from 2-methylsulphonyl-quinoxaline with the other samples.)

PREPARATIVE REACTIONS OF METHYLSULPHONYL COMPOUNDS WITH VARIOUS NUCLEOPHILES

Reactions of methylsulphonyl compounds with aqueous sodium hydroxide.— The methylsulphonyl compound (0.1 g.) and N-sodium hydroxide (3 ml.) were heated together. The conditions of reaction, the methods of isolation and the yields are summarised in Table 19.

Reactions of methylsulphonyl compounds with aqueous sodium hydrogen sulphide

3-Mercaptopyridazine.— 3-Methylsulphonylpyridazine (0.100 g.) and aqueous sodium hydrogen sulphide (2 ml.; 1N) were heated in a sealed tube at 100° for 2 hr. The mixture was adjusted to pH 2 and extracted with chloroform to give 3-mercaptopyridazine (0.070 g.; 85%) which crystallised from water and had m.p. 169-170° (Duffin and Kendall, 1959, give 170°).

4-Mercaptoquinoline.— 4-Methylsulphonylquinoline (0.100 g.) and sodium hydrogen sulphide (2 ml.; 1N) were heated in a sealed tube at 100° for 15 hr. The mixture was adjusted to pH 4, cooled, the solid filtered off and sublimed (160°/0.7 mm.) to give 4-mercaptoquinoline (0.068 g.; 81%), m.p. 158-160°. (Albert and Barlin, 1959, give 158-162°).

TABLE 19

Reactions of methylsulphonyl compounds (0.1g.) with N-sodium hydroxide (3 ml.)

Product	Conditions of reaction	Method of isolation[a]	Product: Hydroxy-compound Yield (g.; %)	M.p. (°)	Picrate of hydroxy-compound Yield (g.; %)	M.p. (°)	Lit. M.p. (°)
2-Hydroxypyridine (picrate)	145°/12hr.	A			0.145 70	173-174	170-172 [b]
4-Hydroxypyridine (picrate)	145/12hr.	A			0.148 72	240-241	236-238 [c]
2-Hydroxypyrazine	90/2hr.	B	0.030 50	186			187-188 [d]
3-Hydroxypyridazine	90/1hr.	B	0.035 58	105			103 [e]
4-Hydroxypyridazine	100/10min.	B	0.042 69	248-249[f]			250-251 [g]
2-Hydroxyquinoline	100/2hr.	C	0.059 85	195-196[f]			198-199 [h]
4-Hydroxyquinoline (picrate)	100/2hr.	A			0.175 95	183-184[i]	-
1-Hydroxyisoquinoline	100/2hr.	C	0.055 79	207-208[f]			208 [j]
2-Hydroxyquinoxaline	95/15min.[k]	C		97			261-264 [k]
4-Hydroxycinnoline	100/30min.	C	0.060 86	233-234[f]			236 [l]
1-Hydroxyphthalazine	100/30min.	C	0.058 83	184 [f]			182 [m]

[a] Methods of isolation were as follows: A, the reaction mixture was adjusted to pH 7 and the addition of aqueous picric acid gave yellow crystals of the picrate which were recrystallised from water; B, the reaction mixture was adjusted to pH ca 7, evaporated to dryness, and the hydroxy-compound vacuum-sublimed from the residue at 100-130°/ca 0.5 mm., except for 4-hydroxypyridazine which was sublimed at 200°/0.7 mm.; C, the reaction mixture was neutralised (pH 7) and on cooling there separated white crystals of the hydroxy-compound. [b] Shaw (1949). [c] Wibaut and Broekman (1959). [d] Erickson and Spoerri (1946). [e] Homer, Gregory, Overend, and Wiggins (1948). [f] No depression of the m.p. was observed on admixture with an authentic specimen. [g] Eichenberger, Rometsch, and Druey (1956). [h] Friedländer and Ostermaier (1881). [i] Found: C, 48.1; H, 2.6; N, 14.7. $C_9H_7NO:C_6H_3N_3O_7$ requires C, 48.2; H, 2.7; N, 15.0%. When crystallised from absolute ethanol, a picrate, m.p. 225° was obtained; this is probably 4-hydroxyquinoline, ½(picric acid)(Found: C, 55.0; H, 3.3; N, 13.4. $C_9H_7NO,½C_6H_3N_3O_7$ requires C, 55.5; H, 3.3; N, 13.5%). [j] Albert and Phillips (1956). [k] Cheeseman (1957). [l] Leonard and Boyd (1946). [m] Gabriel and Neumann (1893).

2-Mercaptoquinoxaline.— 2-Methylsulphonylquinoxaline (0.100 g.) and aqueous sodium hydrogen sulphide (2 ml.; 1N) were heated in a sealed tube at 100° for 1 hr. The reaction mixture was adjusted to pH 6 and chilled to give 2-mercaptoquinoxaline (0.072 g.; 86%), m.p. 203-204°. (Wolf, Wilson, and Tishler, 1954, give 204-205°).

Reactions of methylsulphonyl compounds with sodium cyanide in dimethylformamide

4-Cyanopyridine.— 4-Methylsulphonylpyridine (0.200 g.) and sodium cyanide (0.100 g.) in dimethylformamide (5 ml.) were refluxed for 1 hr. The dimethylformamide was distilled under reduced pressure and the residue treated with aqueous picric acid to give 4-cyanopyridine picrate (0.318 g.; 75%). It was recrystallised from water and had m.p. 197-199° (Ochiai and Suzuki, 1954, give 198-199°).

4-Cyanocinnoline.— 4-Methylsulphonylcinnoline (0.150 g.) and sodium cyanide (0.050 g.) in dimethylformamide (3 ml.) were refluxed for 5 min., and the dimethylformamide was distilled under reduced pressure. The residue was extracted three times with boiling benzene and the product obtained

crystallised from benzene-light petroleum (b.p. 60-80°) to give 4-cyanocinnoline (0.076 g.; 68%) as an orange solid, m.p. 139-140° (Found: C, 70.0; H, 3.5; N, 27.0. $C_9H_5N_3$ requires C, 69.7; H, 3.25; N, 27.1%).

Reactions of methylsulphonyl compounds with (a) aqueous ammonia and (b) aqueous ammoniacal ammonium chloride

4-Methylsulphonylpyridine with aqueous ammonia.– 4-Methylsulphonylpyridine (0.200 g.) and ammonium hydroxide (3 ml.; d, 0.91) were heated at 185° for 6 hr. The reaction mixture was boiled to remove most of the ammonia then adjusted to pH 4 and extracted with chloroform to remove any unchanged 4-methylsulphonylpyridine. The solution was then made strongly alkaline by addition of 5N-sodium hydroxide, evaporated to dryness, and the residue extracted with boiling benzene to give, after crystallisation from benzene-light petroleum (b.p. 60-80°), 4-aminopyridine (0.083 g.; 69%). It was sublimed (100°/0.7 mm.) and had m.p. 155-157° (Emmert and Dorn, 1915, give 158°). (The m.p. was not depressed on admixture with an authentic specimen.)

3-Methylsulphonylpyridazine with aqueous ammonia.- 3-Methylsulphonylpyridazine (0.200 g.) and ammonium hydroxide (6 ml.; d, 0.91) were heated in a sealed tube at 100° for 15 hr. The reaction mixture was then boiled to remove ammonia, cooled and divided into two equal parts. To the first part aqueous picric acid was added to give 3-aminopyridazine picrate (0.024 g.; 11%), m.p. 250-251° (from water) (Steck, Brundage, and Fletcher, 1954, give 249-250°). The second part was adjusted to pH 2, evaporated to dryness and the residue sublimed (100°/0.7 mm.) to give 3-hydroxypyridazine (0.036 g.; 60%), m.p. 102° (Homer, Gregory, Overend, and Wiggins, 1948, give 103°).

3-Methylsulphonylpyridazine with aqueous ammoniacal ammonium chloride.- 3-Methylsulphonylpyridazine (0.100 g.), ammonium hydroxide (3 ml.; d, 0.91) and ammonium chloride (0.32 g.) were heated at 100° for 12 hr. The mixture was then boiled to remove ammonia and addition of aqueous picric acid gave 3-aminopyridazine picrate (0.085 g.; 42%), m.p. 249-250°.

2-Methylsulphonylquinoline with aqueous ammonia.- 2-Methylsulphonylquinoline (0.100 g.) and ammonium hydroxide (2 ml.; d, 0.91) were heated at 140° for 15 hr. The mixture was boiled to remove ammonia and on cooling there separated 2-hydroxyquinoline (0.043 g.; 63%), m.p. 197-198° (Friedländer and Ostermaier, 1881, give 198-199°). (The m.p. was not depressed on admixture with an authentic specimen.) Addition of aqueous picric acid to the filtrate gave 2-aminoquinoline picrate (0.039 g.; 22%), m.p. 256-257° (from ethanol) (Chichibabin and Sazepina, 1918, give 255-256°).

2-Methylsulphonylquinoline with aqueous ammoniacal ammonium chloride.- 2-Methylsulphonylquinoline (0.100 g.), ammonium hydroxide (3 ml.; d, 0.91) and ammonium chloride (0.16 g.) were heated at 140° for 15 hr. The solution was boiled to remove ammonia and addition of aqueous picric acid gave 2-aminoquinoline picrate (0.090 g.; 50%), m.p. 257-258°.

4-Methylsulphonylcinnoline with aqueous ammonia.- 4-Methylsulphonylcinnoline (0.100 g.) and ammonium hydroxide (2 ml.; d, 0.91) were heated in a sealed

tube at 100° for 15 hr. and on cooling there precipitated 4-aminocinnoline (0.032 g.; 46%), m.p. 213-214° (from water) (Keneford, Schofield, and Simpson, 1948, give 212-213°). The filtrate was boiled to remove excess ammonia and addition of aqueous picric acid gave 4-aminocinnoline picrate (0.030 g.; 17%), m.p. 280° (Found: C, 45.3; H, 2.8; N, 22.3. $C_{14}H_{10}N_6O_7$ requires C, 44.9; H, 2.7; N, 22.5%).

Reactions of methylsulphonyl compounds with n-propylamine and aqueous methylamine.— The results and conditions of reaction of methylsulphonyl compounds (0.1 g. each) with aqueous methylamine and liquid n-propylamine are listed in Tables 20 and 21 respectively.

Reactions of methylsulphonyl compounds with hydrazine hydrate

2-Hydrazinoquinoline.— 2-Methylsulphonylquinoline (0.100 g.) and hydrazine hydrate (2 ml.; 98%) were refluxed for 1 hr. The mixture was concentrated and the residue diluted with water, boiled, and on cooling there separated 2-hydrazinoquinoline (0.062 g.; 81%), m.p. 142-143° (Perkin and Robinson, 1913, give 142-143°).

TABLE 20

Reactions of methylsulphonyl compounds (0.1g.) with aqueous methylamine

Product	Aqueous methylamine (ml.; %soln.)	Cond. of reaction °/hr	Method of isolation[a]	Product: Amine (g.; %)m.p.	Product: Amine picrate (g.; %)m.p.	Analyses of product: Found C	Found H	Found N	Calculated C	Calculated H	Calculated N
2-Methylamino-pyridine (picrate)	1.5 25	190/24	A		0.129 60 191-2°[b]						
4-Methylamino-pyridine	1.0 25	180/6	B	0.058 84 126°[c]							
3-Methylamino-pyridazine (picrate)	3.0 30	110/6	A		0.092 43 209	38.8	3.0	24.8	39.1	3.0	24.85
	2.0[d] 25	100/18	A		0.139 65 208-9						
4-Methylamino-pyridazine	2.0[d] 40	100/15	B[e]	0.013 19 77-8		55.4	6.5	38.1	55.0	6.5	38.5
4-Methylamino-pyridazine (picrate)	2.0[d] 40	100/15	A		0.168 78 192-3	39.0	2.9	24.6	39.1	3.0	24.85
4-Methylamino-quinoline	2.0 25	170/15	C	0.061 80 228-9[f g]		75.5	6.3	17.5	75.9	6.4	17.7
1-Methylamino-isoquinoline (picrate)	2.0[d] 40	140/15	A		0.141 76 197-8	49.4	3.4	18.2	49.6	3.4	18.1
4-Methylamino-cinnoline	2.0 25	90/18	C	0.049 64 228-30[h i]							
4-Methylamino-cinnoline (picrate)	2.0 25	90/18	A		0.173 92 253-5[j]	46.4	3.0	21.5	46.4	3.1	21.65

a Methods of isolation were as follows: A, the reaction mixture was boiled to remove excess of methylamine and aqueous picric acid added to precipitate the picrate which was then recrystallised from water; B, the reaction mixture was made strongly alkaline with 5N-sodium hydroxide, evaporated to dryness, and the residue was extracted with boiling benzene and the product recrystallised from benzene-light petroleum (b.p. 60-80°); C, a white precipitate separated from the reaction mixture.

b Pentimalli (1964) gives m.p. 192-193°. c Wibaut and Broekman (1961) give m.p. 124.5-125°.

d 10N-Hydrochloric acid (0.25 ml.) was also added to the reaction mixture. e Product not recrystallised but sublimed at 100°/0.5 mm. f Product recrystallised from benzene. g Suzuki (1961) gives m.p. 224°.

h It was recrystallised from water. A depression of the m.p. was observed on admixture with 4-hydroxycinnoline of m.p. 236°. i Atkinson and Taylor (1955) give m.p. 229°. j The product was recrystallised from ethanol.

TABLE 21

Reactions of methylsulphonyl compounds (0.1g.) with n-propylamine (1 ml.)

Product [a]	Conditions of reaction °/hr.	Product				Solvent for recryst.	Analyses of Product						Molecular formula
		Amine (%)	Amine m.p.(°)	Amine picrate (%)	Amine picrate m.p.(°)		Found C	Found H	Found N	Calculated C	Calculated H	Calculated N	
2-n-Propylamino-pyridine (picrate)	165/80			76	150-152 [b]	aq. ethanol	46.1	4.0	19.2	46.0	4.1	19.2	$C_{14}H_{15}N_5O_7$
4-n-Propylamino-pyridine	165/48	67	73-74			benzene -hexane	70.6	9.0	20.7	70.55	8.9	20.6	$C_8H_{12}N_2$
2-n-Propylamino-pyrazine (picrate)	150/18			63	176-177	ethanol	42.7	3.7	22.6	42.6	3.85	22.95	$C_{13}H_{14}N_6O_7$
3-n-Propylamino-pyridazine	150/12	93	85			benzene -hexane	61.4	8.0	30.2	61.3	8.1	30.6	$C_7H_{11}N_3$
4-n-Propylamino-pyridazine	111/18	71	109			benzene -hexane	61.4	8.2	30.3	61.3	8.1	30.6	$C_7H_{11}N_3$
2-n-Propylamino-quinoline (picrate)	145/12			76	196-197 [c]	ethanol							
4-n-Propylamino-quinoline	160/36	78	173-174			hexane	77.3	7.5	15.1	77.4	7.6	15.0	$C_{12}H_{14}N_2$
1-n-Propylamino-isoquinoline (picrate)	160/36			71	203-204	aq. ethanol	52.05	4.2	16.9	52.05	4.1	16.9	$C_{18}H_{17}N_5O_7$
2-n-Propylamino-quinoxaline (picrate)	110/12			70	178-179	water	49.1	4.0	20.3	49.0	3.9	20.2	$C_{17}H_{16}N_6O_7$
4-n-Propylamino-cinnoline	110/12	74	169-170			benzene -cyclo-hexane	70.9	7.0	22.4	70.6	7.0	22.4	$C_{11}H_{13}N_3$
1-n-Propylamino-phthalazine (picrate)	70/30min.			39	138-139	water	49.0	3.6	20.0	49.0	3.9	20.2	$C_{17}H_{16}N_6O_7$

a The method of isolation was as follows: the reaction mixture was made strongly alkaline with 5N-sodium hydroxide, evaporated to dryness, the residue extracted with boiling benzene (3 X) and the benzene evaporated. The product was sublimed or distilled onto a cold-finger condenser at ca 100-120°/0.5 mm. It was then either recrystallised or the picrate prepared as indicated. b Katritzky and Waring (1962) give m.p. 149-150.5° but Slotta and Franke (1930) give m.p. 163°. c Luthy, Bergstrom and Mosher (1949) give m.p. 196-196.5°.

2-Hydrazinoquinoxaline.— 2-Methylsulphonylquinoxaline (0.100 g.) and hydrazine hydrate (2 ml.; 98%) were refluxed for 45 min. and the mixture diluted with hot water (5 ml.). On cooling there separated crystals of 2-hydrazinoquinoxaline (0.051 g.; 67%), m.p. 166° (Asano, 1958, gives 167°).

4-Hydrazinocinnoline.— 4-Methylsulphonylcinnoline (0.100 g.) and hydrazine hydrate (2 ml.; 98%) were refluxed for 1 hr., the mixture diluted with water and on cooling 4-hydrazinocinnoline (0.070 g.; 91%) separated. It was recrystallised from aqueous ethanol as orange-red plates and had m.p. 285° (decomp.) (Alder and Niklas, 1954, give 229 and 301°*) (Found: C, 59.8; H, 4.9; N, 34.9. Calc. for $C_8H_8N_4$: C, 60.0; H, 5.0; N, 35.0%).

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* An orange-red form crystallised from the reaction mixture and had m.p. 301°, after boiling with ethanol and recrystallisation a yellow form, m.p. 229°, was obtained.

EVIDENCE FOR INTERPRETATION OF VARIABLE REACTION ORDERS

Benzyl methyl sulphone from 4-methylsulphonylquinoline.– A mixture of 4-methylsulphonylquinoline (0.200 g.) and sodium methoxide (3 ml.; 0.4M) was refluxed for 1 hr., diluted with water (6 ml.), the methanol removed by fractionation and the 4-methoxyquinoline extracted into chloroform. The aqueous solution was refluxed with benzyl chloride (0.4 g.) for 1 hr., and on cooling there precipitated benzyl methyl sulphone (0.080 g.; 53%), m.p. 126° (from benzene-cyclohexane) (Bradley, 1938, gives 126°).

Benzyl methyl sulphone from 4-methylsulphinylquinoline.– Under an atmosphere of N_2, a mixture of 4-methylsulphinylquinoline (0.400 g.) and sodium methoxide (4 ml.; 0.4M) was refluxed for 1 hr. It was then diluted with water (10 ml.) and the methanol removed by distillation. The aqueous layer was extracted with chloroform (to remove methoxy compound), and then refluxed with benzyl chloride (0.4 ml.) for 1 hr. Extraction of the reaction mixture with chloroform, followed by recrystallisation from benzene-cyclohexane gave benzyl methyl sulphone (0.050 g.; 16% of total

sulphur), m.p. 125-126°, not depressed on admixture with the product isolated above.

Identification of dimethyl disulphide in reaction of 2-methylsulphinylquinoxaline with sodium methoxide.— Two portions each of a mixture of 2-methylsulphinylquinoxaline (0.150 g.) and methanolic sodium methoxide (1 ml.; 0.4N) were allowed to stand in stoppered flasks at 25°. After 5 min. one portion of the reaction mixture was found to require a negligible quantity of a 0.5% solution of iodine in methanol to give a permanent colouration. (Likewise with 2-methylsulphonylquinoxaline.) (This indicated the absence of methyl mercaptan in the reaction mixture under conditions which were known to produce significant replacement of the methylsulphinyl group.)

The other portion of the reaction mixture was allowed to stand for 3 hr., then the liquid was distilled from a steam bath. The distillate on examination with a Varian Aerograph Series 120 gas chromatograph fitted with a flame ionization detector showed a significant peak due to dimethyl disulphide (and a large peak due to methanol). The identity of

dimethyl disulphide was established by addition of a little authentic material.

Identification of dimethyl disulphide in reaction of 2-methylthioquinoxaline with sodium methoxide.- 2-Methylthioquinoxaline (0.100 g.) and sodium methoxide solution (1 ml.; 0.4N) were heated at 80° for 48 hr. The liquid was distilled from a steam bath and the distillate examined by vapour phase chromatography. Dimethyl disulphide was clearly identified as described above.

Another sample of 2-methylthioquinoxaline (0.100 g.) and sodium methoxide (20 ml.; 0.1N) was heated at 100°/15 hr. This mixture was quickly diluted with water, acidified and titrated against a 0.5% iodine solution. Iodine uptake was 3.5 ml. (23% of the calculated quantity for complete conversion to and retention of methyl mercaptan).

Ethyl mercaptan and sodium methoxide at 80°.- A stock solution of ethyl mercaptan (0.42 ml.) in methanol (100 ml.) was prepared. Portions (5 ml.) were heated with methanolic sodium methoxide solution (5 ml.; 0.1N) in a sealed tube at 80° for 6 hr., the tubes were opened and the contents quickly diluted with water, acidified and titrated with a

0.5% solution of iodine in methanol. Uptake of iodine solution was 0.46 ml., whereas titration of a stock solution (5 ml.) directly required 7.0 ml.

Reaction of 4-methylsulphinylquinoline with a deficiency of sodium methoxide in methanol.— A solution of 4-methylsulphinylquinoline (0.0291 g.) in methanol (20 ml.) was prepared and 4 portions (1 ml.) placed in separate tubes. Methanolic sodium methoxide solution (4.64×10^{-3}N) corresponding to 0.00, 0.15, 0.30, and 0.45 molar equivalents was added to separate tubes, which were sealed and heated at 90° for 9 hr. Appropriate dilution of the reaction mixtures with buffer and examination of the ultraviolet spectra revealed 7, 35, 59 and 85% conversion to 4-methoxyquinoline respectively.

REDUCTIONS OF SULPHOXIDES WITH HYDROGEN IODIDE

Reduction of 2-methylsulphinylquinoxaline.— 2-Methylsulphinylquinoxaline (0.100 g.) and hydriodic acid (5 ml.; 15%) were warmed at 50° for 15 min. The mixture was cooled, neutralised with potassium hydroxide solution and extracted with chloroform.

The chloroform extract was dried (Na_2SO_4) and evaporated, and the residue with aqueous picric acid gave 2-methylthioquinoxaline picrate (0.093 g.; 44%), m.p. and mixed m.p. with an authentic sample, 127-128° (Cheeseman, 1957, gives 127-128°).

Reduction of 2-methylsulphinylpyridine.– 2-Methylsulphinylpyridine (0.085 g.) and hydriodic acid (6 ml.; 15%) were heated on a steam bath for 0.5 hr. The mixture was cooled in ice, neutralised with potassium hydroxide solution and extracted with chloroform. The extract was dried and the solvent fractionated and addition of aqueous picric acid to the residue gave 2-methylthiopyridine picrate (0.110 g.; 52%), m.p. 161-162° (Marckwald, Klemm, and Trabert, 1900, give 155°). A sample prepared from 2-methylthiopyridine (Renault, 1955) also melted at 161-162° and showed no depression on admixture with the above sample.

Reduction of 4-methylsulphinylquinoline.– 4-Methylsulphinylquinoline (0.090 g.) was heated with hydriodic acid (3 ml.; 64%) on a steam bath at 95° for 30 min. The mixture was then cooled, made alkaline with aqueous potassium hydroxide and extracted with chloroform. Evaporation of the

extract gave an oil which with aqueous picric acid gave 4-methylthioquinoline picrate (0.170 g.; 89%), m.p. 211-212°, not depressed on admixture with a sample prepared from 4-methylthioquinoline (Albert and Barlin, 1959)(Found: C, 47.2; H, 2.9; N, 13.9. $C_{16}H_{12}N_4O_7S$ requires C, 47.5; H, 3.0; N, 13.9%).

Methanol.— AnalaR methanol was dried by Lund and Bjerrum's (1931) method and fractionated through a column of glass helices; the first 10% of the distillate was discarded.

Sodium Methoxide Solution.— Clean sodium was dissolved in methanol, and the concentration determined by titration with standard acid.

PHYSICAL MEASUREMENTS

Ionization constants.— These were determined spectrophotometrically as described by Albert and Serjeant (1962). Solutions above pH 2.5 were made in aqueous buffers (Perrin, 1963), standardised with a glass electrode, between pH 1 and 2.5 dilute solutions of hydrochloric acid of known pH were used, and, at greater acidity, standard solutions of sulphuric or hydrochloric acid to which Hammett

acidity functions had been assigned (Paul and Long, 1957). The pK_a values were found by measuring the ultraviolet absorption (ε) at constant concentrations of the compound at a chosen wavelength over a range of pH values (usually at intervals of 0.2 units over a range of approximately ±0.8 units from the estimated pK_a value); extinction values in solutions, of such a pH as to give entirely neutral molecule (ε_M) and cation (ε_{MH^+}) were also recorded and the pK_a calculated from the expression

$$pK'_a = pH - \log \frac{(\varepsilon_{MH^+} - \varepsilon)}{(\varepsilon - \varepsilon_M)}$$

Values for the ionization constants given are the mean of about 9 such pK'_a terms. Stability of the cations in solution was checked by neutralisation.

Ultraviolet spectra were recorded on a Perkin-Elmer Spectracord model 4000 recording spectrophotometer, or a Unicam S.P.800 ultraviolet spectrophotometer, and the $\lambda_{max.}$ and ε values checked on an 'Optica' CF4 manual instrument. (The Optica was also used for measuring the ultraviolet absorption of solutions used in determinations of ionization constants and rate coefficients.)

Solutions were in aqueous buffers or standard acid solutions (as described for ionization constants) and were at least 2 pH units from the measured pK_a value.

Infrared spectra of liquids were recorded as such and solids as Nujol mulls using a Unicam S.P.200 spectrophotometer.

N.m.r. spectra were recorded at 60 Mc./sec. and 33.5° on a Perkin-Elmer R10 spectrometer. Chemical shifts are given on the τ scale; tetramethylsilane was used for internal reference except in acid solutions when sodium 3-trimethylsilylpropane-sulphonate was employed. Where required portions of the spectra were expanded.

Kinetic Procedure.— At temperatures greater than ca 50° methanol solutions which were 1.7 - 8.2 x 10^{-3}M in reactant and 2.9 - 17.8 x 10^{-3}N in sodium methoxide were heated in sealed tubes in a thermostat. The tubes were chilled briefly, and the contents diluted with buffer to 50 ml.

At temperatures less than ca 50° (for each compound the same method was used throughout), a weighed quantity of reactant was dissolved quickly in a known volume of methanolic sodium methoxide (0.7 - 22.5 x 10^{-3}N) in the thermostat, and samples

(2 ml.) were withdrawn at specified times and quenched in buffer solution.

The ultraviolet absorption at the specified wavelength was then determined for each sample and the rate coefficients calculated from the expressions given in Chapter 3. Where necessary, corrections were made for expansion (or contraction) of the solvent.

For each run, about 9 samples covering at least 10-60% reaction (usually more) and those corresponding to 't_o' and 't_∞' (ca 30 times the half-life of the reaction and corresponding to 98-100% reaction) were examined.

Each reaction was studied at three temperatures covering a 20^o range and a graph drawn of log $\underline{k}$ against $^1/T$ (T=temperature ^oA). From the slope of the resulting straight line the energy of activation (E) was calculated (E = -2.303R x slope). The frequency factor (log A) and the transition state parameters, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were calculated from the following expressions:

$$\log A = \log \underline{k} + \frac{E}{2.303\ RT} \quad (\equiv \log \underline{k} - \frac{\text{slope}}{T})$$

$$\Delta H^{\ddagger} = E - RT$$

$$\Delta S^{\ddagger} = 2.303R[\log A - \log T] - 49.2$$

(R, the universal gas constant, = 1.987 cal.deg.$^{-1}$mole^{-1}.)

REFERENCES

A. Albert, 1959. "Heterocyclic Chemistry", Athlone Press, London, Chapters III and IV.

A. Albert and G. B. Barlin, 1959. J. Chem. Soc., 2384.

A. Albert and G. B. Barlin, 1962. J. Chem. Soc., 3129.

A. Albert, R. Goldacre, and J. Phillips, 1948. J. Chem. Soc., 2240.

A. Albert and J. N. Phillips, 1956. J. Chem. Soc., 1294.

A. Albert and E. P. Serjeant, 1962. "Ionization Constants of Acids and Bases", Methuen, London.

K. Alder and H. Niklas, 1954. Annalen, 585, 97.

I. A. Alekseeva and I. Ya. Postovskii, 1954. Zhur. obshchei Khim., 24, 1814.

E. D. Amstutz, I. M. Hunsberger, and J. J. Chessick, 1951. J. Amer. Chem. Soc., 73, 1220.

K. Asano, 1958. J. Pharm. Soc. Japan, 78, 729.

C. M. Atkinson and A. Taylor, 1955. J. Chem. Soc., 4236.

M. R. Atkinson, G. Shaw, and G. Sugowdz, 1957. J. Chem. Soc., 3207.

O. G. Backeberg, 1933. J. Chem. Soc., 618.

G. B. Barlin and D. D. Perrin, 1966. Quart. Rev., 20, 75.

F. R. Basford, F. H. S. Curd, and F. L. Rose, 1947. Brit. Pat., 593,499. (Chem. Abs., 1948, 42, 2291.)

N. P. Bednyagina and I. Ya. Postovskii, 1956. Zhur. obshchei Khim., 26, 2279.

N. P. Bednyagina and S. V. Sokolov, 1959. Nauch. Doklady vysshei Shkoly, Khim. i khim. Tekhnol. (Moscow), No.2, 338. (Chem. Abs., 1959, 53, 21971.)

L. J. Bellamy, 1958. "The Infra-red Spectra of Complex Molecules", Methuen, London, 2nd ed., p.350 et seq.

M. L. Belli, G. Illuminati, and G. Marino, 1963. Tetrahedron, 19, 345.

P. J. Black, R. D. Brown, and M. L. Heffernan, 1967. Austral. J. Chem., 20, 1305.

P. J. Black and M. L. Heffernan, 1964. Austral. J. Chem., 17, 558.

P. J. Black and M. L. Heffernan, 1965. Austral. J. Chem., 18, 707.

P. J. Black and M. L. Heffernan, 1966. Austral. J. Chem., 19, 1287.

W. Bradley, 1938. J. Chem. Soc., 458.

H. Bretschneider and H. Egg, 1967. Monatsh., 98, 1577.

D. J. Brown and P. W. Ford, 1967. J. Chem. Soc. (C), 568.

D. J. Brown and R. V. Foster, 1966a.
Austral. J. Chem., 19, 1487.

D. J. Brown and R. V. Foster, 1966b.
Austral. J. Chem., 19, 2321.

J. F. Bunnett, 1958. Quart. Rev., 12, 1.

J. F. Bunnett, E. W. Garbisch Jr., and K. M. Pruitt,
1957. J. Amer. Chem. Soc., 79, 385.

J. F. Bunnett and R. E. Zahler, 1951.
Chem. Rev., 49, 273.

A. B. Burg, 1961, in "Organic Sulfur Compounds",
Vol.1, ed. N. Kharasch, Pergamon Press, London, p.30.

W. T. Caldwell and A. N. Sayin, 1952.
J. Amer. Chem. Soc., 74, 4314.

B. Capon, M. J. Perkins, and C. W. Rees, 1965.
Org. Reaction Mechanisms, 133, et seq.

J. M. Carpenter and G. Shaw, 1965. J. Chem. Soc., 3987.

R. N. Castle, H. Ward, N. White, and K. Adachi, 1960.
J. Org. Chem., 25, 570.

T. L. Chan and J. Miller, 1967.
Austral. J. Chem., 20, 1595.

N. B. Chapman, 1955.
Chem. Soc. Special Publ. No.3, p.155.

N. B. Chapman, R. E. Parker, and P. W. Soanes, 1954. J. Chem. Soc., 2109.

N. B. Chapman and C. W. Rees, 1954. J. Chem. Soc., 1190.

N. B. Chapman and D. Q. Russell-Hill, 1956. J. Chem. Soc., 1563.

G. W. H. Cheeseman, 1955. J. Chem. Soc., 1804.

G. W. H. Cheeseman, 1957. J. Chem. Soc., 3236.

G. W. H. Cheeseman, 1958. J. Chem. Soc., 108.

G. W. H. Cheeseman, 1960. J. Chem. Soc., 242.

Y-F. Chi and S-F. Chen, 1957a. Sci. Sinica, 6, 111. (Chem. Abs., 1957, 51, 16485.)

Y-F. Chi and S-F. Chen, 1957b. Sci. Sinica, 6, 477. (Chem. Abs., 1958, 52, 6360.)

Y-F. Chi (Ch'ih) and S-F. Chen (Ch'en), 1958. J. Gen. Chem. U.S.S.R. (Eng. Trans.), 28, 1533.

Y-F. Chi and Y-C. Ling, 1956a. Sci. Sinica, 5, 205. (Chem. Abs., 1957, 51, 14742.)

Y-F. Chi and Y-C. Ling, 1956 b. Acta Chim. Sinica, 22, 3. (Chem. Abs., 1958, 52, 5419).

Y-F. Chi and Y-C. Ling, 1957a. Sci. Sinica, 6, 633. (Chem. Abs., 1958, 52, 7329.)

Y-F. Chi and Y-C. Ling, 1957b. Sci. Sinica, 6, 643. (Chem. Abs., 1958, 52, 7329.)

Y-F. Chi and Y-L. Wu, 1957. Hua Hsüeh Hsüeh Pao, 23, 145. (Chem. Abs., 1958, 52, 14626.)

A. S-C. Chia and R. F. Trimble,Jr., 1961. J. Phys. Chem., 65, 863.

A. E. Chichibabin and E. W. Sazepina, 1918. J. Russ. Phys. Chem. Soc., 50, 553. (Chem. Zentr., 1923, III, 1023.)

G. Cilento, 1960. Chem. Rev., 60, 147.

M. Colonna, 1941. Boll. sci. Fac. Chim. ind. Bologna, 145. (Chem. Abs., 1943, 37, 4399.)

C. A. Coulson, 1961. "Valence", Oxford University Press, London, 2nd edn. p. 258.

C. Courtot and J. P. Zwilling, 1938. Congr. Chim. ind., Compt. rend. 18me Congr., Nancy, 1938, 796.

R. M. Cresswell and T. Strauss, 1963. J. Org. Chem., 28, 2563.

F. Cuiban, M. Ionesco, H. Bala, and M. Steresco, 1963. Bull.Soc. chim. France, 356.

F. H. S. Curd, M. I. Davis, E. C. Owen, F. L. Rose, and G. A. P. Tuey, 1946a. J. Chem. Soc., 370.

F. H. S. Curd, M. I. Davis, E. C. Owen, F. L. Rose, and G. A. P. Tuey, 1946b. J. Chem. Soc., 720.

F. H. S. Curd, M. I. Davis, and F. L. Rose, 1946. J. Chem. Soc., 351.

F. H. S. Curd, E. Hoggarth, J. K. Landquist, and F. L. Rose, 1948. J. Chem. Soc., 1766.

F. H. S. Curd, C. G. Raison, and F. L. Rose, 1946. J. Chem. Soc., 366.

F. H. S. Curd, D. N. Richardson, and F. L. Rose, 1946. J. Chem. Soc., 378.

F. H. S. Curd and F. L. Rose, 1946. J. Chem. Soc., 343.

G. D. Daves,Jr., F. Baiocchi, R. K. Robins, and C. C. Cheng, 1961. J. Org. Chem., 26, 2755.

G. F. Duffin and J. D. Kendall, 1959. J. Chem. Soc., 3789.

J. O. Edwards and R. G. Pearson, 1962. J. Amer. Chem. Soc., 84, 16.

K. Eichenberger, R. Rometsch, and J. Druey, 1956. Helv. Chim. Acta, 39, 1755.

B. Emmert and W. Dorn, 1915. Ber., 48, 687.

A. E. Erickson and P. E. Spoerri, 1946. J. Amer. Chem. Soc., 68, 400.

M. G. Evans and M. Polanyi, 1936.
Trans. Faraday Soc., 32, 1333.

G. W. Ewing and E. A. Steck, 1946.
J. Amer. Chem. Soc., 68, 2181.

E. A. Falco, G. H. Hitchings, and P. B. Russell, 1949.
J. Amer. Chem. Soc., 71, 362.

E. A. Fehnel and M. Carmack, 1950.
J. Amer. Chem. Soc., 72, 1292.

P. W. Ford, 1968. Ph. D. Thesis.
Australian National University.

H. S. Forrest and J. Walker, 1948. J. Chem. Soc., 1939.

P. Friedländer and H. Ostermaier, 1881.
Ber., 14, 1916.

R. C. Fuson, H. L. Jackson, and E. W. Grieshaber, 1951.
J. Org. Chem., 16, 1529.

S. Gabriel and J. Colman, 1900. Ber., 33, 980.

S. Gabriel and A. Neumann, 1893. Ber., 26, 521.

S. Ghersetti and M. Pallotti, 1963. Gazzetta, 93, 1000.

A. H. Gowenlock, G. T. Newbold, and F. S. Spring, 1945.
J. Chem. Soc., 622.

T. B. Grave, 1924. J. Amer. Chem. Soc., 46, 1460.

H. Gregory, W. G. Overend, and L. F. Wiggins, 1949. J. Chem. Soc., 2066.

E. Hayashi, T. Higashino, C. Iijima, Y. Kono, and T. Doihara, 1962. J. Pharm. Soc. Japan, 82, 584.

J. M. Hearn, R. A. Morton, and J. C. E. Simpson, 1951. J. Chem. Soc., 3318.

R. L. Heppolette and J. Miller, 1956. J. Chem. Soc., 2329.

J. H. M. Hill and J. G. Krause, 1964. J. Org. Chem., 29, 1642.

F. Hoffmann-la Roche, 1963. French Pat., 1,341,774. (Chem. Abs., 1964, 60, 10698.)

R. F. Homer, H. Gregory, W. G. Overend, and L. F. Wiggins, 1948. J. Chem. Soc., 2195.

R. Hull, B. J. Lovell, H. T. Openshaw, L. C. Payman, and A. R. Todd, 1946. J. Chem. Soc., 357.

R. Hull, B. J. Lovell, H. T. Openshaw, and A. R. Todd, 1947. J. Chem. Soc., 41.

G. Illuminati, 1964. Adv. Heterocyclic Chem., 3, 285.

G. Illuminati and G. Marino, 1958.
J. Amer. Chem. Soc., 80, 1421.

T. Itai and H. Igeta, 1954.
J. Pharm. Soc. Japan, 74, 1195.

T. Itai and S. Kamiya, 1963.
Chem. Pharm. Bull. (Tokyo), 11, 1059.

T. B. Johnson and J. M. Sprague, 1938.
J. Amer. Chem. Soc., 60, 1622.

H. Johnston, 1967. U.S. Pat. 3,296,272.
(Chem. Abs., 1967, 66, 104903.)

T. Kato, H. Hayashi, and T. Anzai, 1967.
Chem. Pharm. Bull. (Tokyo), 15, 1343.

A. R. Katritzky and A. J. Waring, 1962.
J. Chem. Soc., 1544.

J. R. Keneford, K. Schofield, and J. C. E. Simpson,
1948. J. Chem. Soc., 358.

N. Kharasch, 1961. "Organic Sulfur Compounds",
Vol.1, Pergamon Press, London, p.375.

N. Kharasch and T. C. Bruice, 1951.
J. Amer. Chem. Soc., 73, 3240.

H. King and L. L. Ware, 1939. J. Chem. Soc., 873.

W. Klötzer, 1961. Monatsh., 92, 1212.

H. P. Koch, 1950. J. Chem. Soc., 2892.

H. C. Koppel, R. H. Springer, and C. C. Cheng, 1961. J. Org. Chem., 26, 1884.

H. C. Koppel, R. H. Springer, R. K. Robins, and C. C. Cheng, 1961. J. Org. Chem., 26, 792.

A. Kotch, L. H. Krol, P. E. Verkade, and B. M. Wepster, 1952. Rec. Trav. chim., 71, 108.

M. M. Kreevoy, B. E. Eichinger, F. E. Stary, E. A. Katz, and J. H. Sellstedt, 1964. J. Org. Chem., 29, 1641.

S. Kukolja and Z. Cvetnić, 1962. Croat. Chem. Acta, 34, 115.

H. Larivé, P. Collet, and R. Dennilauler, 1956. Bull. Soc. chim. France, 1443.

G. Leandri, A. Mangini, and R. Passerini, 1957. J. Chem. Soc., 1386.

L. Legrand and N. Lozac'h, 1963. Bull. Soc. chim. France, 1161.

N. J. Leonard and S. N. Boyd,Jr., 1946. J. Org. Chem., 11, 419.

N. J. Leonard and D. Y. Curtin, 1946.
J. Org. Chem., 11, 349.

N. J. Leonard and C. R. Johnson, 1962.
J. Org. Chem., 27, 282.

M. Liveris and J. Miller, 1963. J. Chem. Soc., 3486.

H. C. Longuet-Higgins, 1950a.
J. Chem. Phys., 18, 265.

H. C. Longuet-Higgins, 1950b. Nature, 166, 139.

H. Lund and J. Bjerrum, 1931. Ber., 64, 210.

N. G. Luthy, F. W. Bergstrom, and H. S. Mosher,
1949. J. Amer. Chem. Soc., 71, 1109.

W. Marckwald, W. Klemm, and H. Trabert, 1900.
Ber., 33, 1556.

S. F. Mason, 1957. J. Chem. Soc., 5010.

S. F. Mason, 1959. J. Chem. Soc., 1253.

T. Matsukawa and B. Ohta, 1949a.
J. Pharm. Soc. Japan, 69, 489.

T. Matsukawa and B. Ohta, 1949b.
J. Pharm. Soc. Japan, 69, 491.

H. G. Morren, 1959a. Belg. Pat. 574,204.
(Chem. Abs., 1960, 54, 5714.)

H. G. Morren, 1959b. Belg. Pat. 579,291.
(Chem. Abs., 1960, 54, 9968.)

H. G. Morren, 1959c. Belg. Pat. 577,515.
(Chem. Abs., 1960, 54, 5715.)

J. G. Nairn and H. Tieckelmann, 1960.
J. Org. Chem., 25, 1127.

M. Nishio, 1967. Chem. Pharm. Bull. (Tokyo), 15, 1669.

W. H. Nyberg and C. C. Cheng, 1964.
J. Heterocyclic Chem., 1, 1.

E. Ochiai and Y. Suzuki, 1954.
Pharm. Bull. (Tokyo), 2, 247

A. R. Osborn, K. Schofield, and L. N. Short, 1956.
J. Chem. Soc., 4191.

M. A. Paul and F. A. Long, 1957. Chem. Rev., 57, 1.

L. Pentimalli, 1964. Gazzetta, 94, 458.

W. H. Perkin and R. Robinson, 1913.
J. Chem. Soc., 1973.

D. D. Perrin, 1963. Austral. J. Chem., 16, 572.

J. A. Pople, W. G. Schneider, and H. J. Bernstein, 1959. "High-Resolution Nuclear Magnetic Resonance", McGraw-Hill, New York.

J. Renault, 1955. Ann. Chim. (France), 10, 135.

R. R. Renshaw and R. C. Conn, 1937. J. Amer. Chem. Soc., 59, 297.

J. Ridd, 1963, in "Physical Methods in Heterocyclic Chemistry", ed. A. R. Katritzky, Academic Press, New York, p.109.

M. M. Robison and B. L. Robison, 1958. J. Amer. Chem. Soc., 80, 3443.

M. T. Rogers, G. M. Barrow, and F. G. Bordwell, 1956. J. Amer. Chem. Soc., 78, 1790.

S. D. Ross, 1963. Prog. in Phys. Org. Chem., 1, 31.

R. von Rothenburg, 1895. J. prakt. Chem., 51, 140.

K. Schofield and J. C. E. Simpson, 1945. J. Chem. Soc., 512.

M. Semonsky and A. Cerny, 1951. Chem. Listy, 45, 156. (Chem. Abs., 1952, 46, 1556.)

E. Shaw, 1949. J. Amer. Chem. Soc., 71, 67.

E. Shaw, J. Bernstein, K. Losee, and W. A. Lott, 1950. J. Amer. Chem. Soc., 72, 4362.

R. G. Shepherd and J. L. Fedrick, 1965. Adv. in Heterocyclic. Chem., 4, 145.

R. G. Shepherd, W. E. Taft, and H. M. Krazinski, 1961. J. Org. Chem., 26, 2764.

K. H. Slotta and W. Franke, 1930. Ber., 63, 678.

I. C. Smith and W. G. Schneider, 1961. Canad. J. Chem., 39, 1158.

E. Spinner, 1963. J. Chem. Soc., 3855.

Spofa, 1963. Belg. Pat., 633,513. (Chem. Abs., 1964, 61, 1877.)

J. M. Sprague and T. B. Johnson, 1935. J. Amer. Chem. Soc., 57, 2252.

J. M. Sprague and T. B. Johnson, 1936. J. Amer. Chem. Soc., 58, 423.

J. Strating, 1961, in "Organic Sulfur Compounds", Vol.1, ed. N. Kharasch, Pergamon Press, London, p.146.

E. A. Steck, R. P. Brundage, and L. T. Fletcher, 1954. J. Amer. Chem. Soc., 76, 3225.

Y. Suzuki, 1961. J. Pharm. Soc. Japan, 81, 1146.

H. H. Szmant, 1961, in "Organic Sulfur Compounds", Vol.1, ed. N. Kharasch, Pergamon Press, London, p.154.

F. Taddei, 1965. Boll. sci. Fac. Chim. ind.Bologna, Suppl., 23 (2-3). 273. (Chem. Abs., 1965, 63, 17851.)

W. E. Taft and R. G. Shepherd, 1962.
J. Medicin. Pharmaceut. Chem., 5, 1335.

T. Takahashi and K. Ueda, 1953.
J. Pharm. Soc. Japan, 73, 442.

K. Tori and M. Ogata, 1964.
Chem. Pharm. Bull. (Tokyo), 12, 272.

J. Tröger and W. Menzel, 1921-1922.
J. prakt. Chem., 103, 188.

G. F. Tucker and J. L. Irvin, 1951.
J. Amer. Chem. Soc., 73, 1923.

J. P. Wibaut and F. W. Broekman, 1959.
Rec. Trav. chim., 78, 593.

J. P. Wibaut and F. W. Broekman, 1961.
Rec. Trav. chim., 80, 309.

F. J. Wolf, R. M. Wilson,Jr., and M. Tishler, 1954.
J. Amer. Chem. Soc., 76, 2266.

J. Xan, E. A. Wilson, L. D. Roberts, and N. H. Horton, 1941. J. Amer. Chem. Soc., 63, 1139.

D. L. Yabroff, 1940. Ind. Eng. Chem., 32, 257.

M. Yanagita and R. Futaki, 1952. J. Pharm. Soc. Japan, 72, 236.

TABLE OF NEW COMPOUNDS*

2-Methoxypyridine picrate

4-Methylsulphinylpyridine and picrate

4-n-Propylaminopyridine

2-Methylsulphinylpyrazine

2-Methylsulphonylpyrazine

2-n-Propylaminopyrazine picrate

3-Methylaminopyridazine picrate

3-Methylsulphinylpyridazine

3-Methylsulphonylpyridazine

3-n-Propylaminopyridazine

4-Methylaminopyridazine and picrate

4-Methylsulphinylpyridazine

4-Methylsulphonylpyridazine

4-n-Propylaminopyridazine

2-Methylsulphinylquinoline

4-Hydroxyquinoline picrate

4-Methylsulphinylquinoline and picrate

4-Methylsulphonylquinoline

4-Methylthioquinoline picrate

4-n-Propylaminoquinoline

1-Methylaminoisoquinoline picrate

1-Methylsulphinylisoquinoline

1-Methylsulphonylisoquinoline

1-n-Propylaminoisoquinoline picrate

4-Aminocinnoline picrate

4-Cyanocinnoline

4-Methylaminocinnoline picrate

4-Methylsulphinylcinnoline

4-Methylsulphonylcinnoline

4-n-Propylaminocinnoline

1-Methylsulphinylphthalazine

1-Methylsulphonylphthalazine

1-n-Propylaminophthalazine picrate

2-t-Butylsulphinylquinoxaline

2-t-Butylsulphonylquinoxaline

2-t-Butylthioquinoxaline

2-Ethylsulphinylquinoxaline

2-Ethylsulphonylquinoxaline

2-Methylsulphinylquinoxaline

2-n-Propylaminoquinoxaline picrate

2-Isopropylsulphonylquinoxaline

2-Isopropylthioquinoxaline

* Underlining of 'picrate' indicates that only the picrate is a new compound.

PUBLICATIONS

G. B. Barlin and W. V. Brown, J. Chem. Soc.(B), 1967, 648.

G. B. Barlin and W. V. Brown, J. Chem. Soc.(B), 1967, 736.

G. B. Barlin and W. V. Brown, J. Chem. Soc.(C), 1967, 2473.

G. B. Barlin and W. V. Brown, J. Chem. Soc.(B), 1968,

submitted for publication, Paper No. 8/788.

Kinetics of Reactions in Heterocycles. Part II.[1] Replacement of the Methylsulphonyl Group in Substituted Pyridines, Pyridazines, and Pyrazine by Methoxide Ion

By **G. B. Barlin** and **W. V. Brown**, Department of Medical Chemistry, John Curtin School of Medical Research, Australian National University, Canberra, Australia

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Kinetics of Reactions in Heterocycles. Part II.[1] Replacement of the Methylsulphonyl Group in Substituted Pyridines, Pyridazines, and Pyrazine by Methoxide Ion

By G. B. Barlin and W. V. Brown, Department of Medical Chemistry, John Curtin School of Medical Research, Australian National University, Canberra, Australia

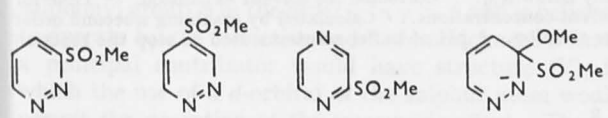
Kinetic study of the reactions of methylsulphonylpyridines, pyridazines, and pyrazine with methoxide ion shows that the methylsulphonyl group is very readily replaced. Where direct comparison is possible, as in the 3-substituted pyridazines, it is found that the methylsulphonyl compound is *ca.* 90 times more reactive than the chloro-compound, at 40·2°.

The preparation of new methylsulphonyl compounds is described. Ionisation constants and ultraviolet and nuclear magnetic resonance spectra are recorded and discussed.

REPLACEMENT of the methylsulphonyl group in substituted nitrogen heterocycles has been little studied and the only quantitative work is that on the reactivity of methylsulphonylpyrimidines with n-pentylamine in dimethyl sulphoxide.[2]

We have commenced a quantitative study of the displacement of the methylsulphonyl group from other heterocyclic derivatives with nucleophiles, and now report the results obtained with the monocyclic azines and methoxide ion. It is assumed that the main features of the reaction mechanism, which is almost certainly bimolecular, are common to all the compounds studied. In the absence of any experimental evidence to decide between a one-stage and a two-stage mechanism, we will, for simplicity, discuss the reaction parameters from the viewpoint of the former. Table 1 lists details of some typical kinetic experiments, Table 2 summarises all kinetic results, and Table 3 lists parameters derived from the kinetic studies. Sample results (Table 1) show no significant trend, and indicate freedom from side reactions; values of $t_{\frac{1}{2}}$ (Table 2) strongly indicate second-order kinetics, consistent with the bimolecular mechanism.

The values given in Table 3 show that the substituent in 4-methylsulphonylpyridine is more reactive than that in the 2-isomer, consistent with the considerably lower energy of activation, although the frequency factor, as given by log A, is also lower. These results agree with those obtained for ethoxydechlorination of pyridines,[3] where at 90° the γ-position is five times more reactive than the α-position. Similarly in 3- and 4-methylsulphonylpyridazine, (I) and (II), where the leaving group is placed β to one ring nitrogen and α or γ



(I) (II) (III) (IV)

to another, the 4-methylsulphonyl compound is found to be the more reactive, and as the frequency factors, log A, are almost the same, the greater reactivity is due to a lower energy of activation. 2-Methylsulphonylpyrazine (III), which is also activated by β and α ring-nitrogen atoms, shows considerable but lower reactivity, and the energy of activation is higher than that for similarly activated 3-methylsulphonylpyridazine. The reason for the greater reactivity of the latter is probably the electron withdrawal by the β ring nitrogen, which lowers the energy of formation of the transition state (IV) below that required for the pyrazine (III). The introduction of another doubly bound ring-nitrogen β to the leaving group in a methylsulphonylpyridine brings about a considerable increase in reactivity and a large decrease in energy of activation.

Direct comparison of the displacements of the methylsulphonyl and chloro-groups is at present possible only for the 3-position of pyridazine. From the figures given by Hill and Krause [4] for 3-chloropyridazine with methoxide ion at 40·2°, where k is $2{\cdot}56 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$, the energy of activation is 19·3 kcal. mole^{-1}, and $\Delta S^{\ddagger}$ is −15·4 units. Comparison of these results with those given in Tables 2 and 3 for the methylsulphonyl compound reveals that the latter is *ca.* 90 times more reactive than the chloro-compound, and this greater reactivity can be attributed mainly to a lower energy of activation.

The greater reactivity of the methylsulphonyl compared with the chloro-group is also indicated by comparing the results for 2- and 4-methylsulphonylpyridine (Table 3) with those for the reaction of 2- and 4-chloropyridine [3] with ethoxide ion in ethanol (a reagent which with 2- and 4-chloroquinoline [3] does not differ greatly in nucleophilicity from methoxide ion in methanol [5]).

Ionisation Constants and Ultraviolet Spectra (*Table* 4).—The ionisation constants clearly show the powerful electron withdrawal of the methylsulphonyl group. In the 2- and 4-positions of pyridine it reduces the pK_a values by 6·73 and 3·61 units respectively, and in pyrazine and the 3-position of pyridazine where protonation occurs on the nitrogen β to the methylsulphonyl group, the reduction is 3·12 and 3·34 units, respectively. 4-Methylsulphonylpyridazine is believed to protonate on N-1 or N-2 (see discussion of n.m.r. spectra). Thus the base-weakening by the methyl-

[1] G. B. Barlin, preceding Paper, is regarded as Part I.
[2] D. J. Brown and P. W. Ford, *J. Chem. Soc.* (*C*), 1967, 568.
[3] N. B. Chapman and D. Q. Russell-Hill, *J. Chem. Soc.*, 1956, 1563.
[4] J. H. M. Hill and J. G. Krause, *J. Org. Chem.*, 1964, **29**, 1642.
[5] M. L. Belli, G. Illuminati, and G. Marino, *Tetrahedron*, 1963, **19**, 345.

TABLE 1

Reactions of methoxide ions

4-Methylsulphonylpyridine at 110·5°

Methoxide ion 0·0039N, methylsulphonyl compound 0·0028M.

Time (min.)	18·3	51·5	75·7	104·6	136	172	208·2	262
Reaction (%)	13·9	32·3	41·2	50·2	57·9	65·0	69·8	75·1
10^2k	3·61	3·69	3·60	3·61	3·62	3·68	3·65	3·57

Mean $10^2k = 3·63 \pm 0·04$; after correction for solvent expansion, 4·02.

4-Methylsulphonylpyridazine at 30·3°

Methoxide ion 0·00116N, methylsulphonyl compound 0·00079M.

Time (min.)	15·4	34·6	56	84	128·2	170·7	215	270·2	342·5
Reaction (%)	11·3	22·8	33·1	43·4	56·4	65·2	71·7	78·1	83·5
$10k$	1·19	1·17	1·18	1·17	1·22	1·24	1·21	1·26	1·19

Mean $10k = 1·20 \pm 0·03$; after correction for solvent expansion, 1·21.

2-Methylsulphonylpyrazine at 49·9°

Methoxide ion 0·00238M, methylsulphonyl compound 0·00144M.

Time (min.)	19·2	44·9	78·2	157·6	197·5	243·2	286	346
Reaction (%)	6·6	14·2	22·4	38·1	44·4	50·1	55·3	60·9
10^2k	2·45	2·47	2·44	2·45	2·46	2·45	2·46	2·48

Mean $10^2k = 2·46 \pm 0·02$; after correction for solvent expansion, 2·55.

TABLE 2

Kinetic results for the reactions of methylsulphonyl compounds with methoxide ions

Temp.[a]	10^3[MeO$^-$]	10^3[$-SO_2Me$]	10^3k [b]	10^3k [c] corr.	$t_{\frac{1}{2}}$ [d]	$t_{\frac{1}{2}}/t'_{\frac{1}{2}}$ [e]	$t_{\frac{1}{2}}/t'_{\frac{1}{2}}$ [f] calc.	An. λ (mμ) [g]	pH [h]
				2-Methylsulphonylpyridine					
108·7°	12·3	8·19	1·82	1·97				272	6·0
117·0	12·3	8·19	3·97	4·33				272	6·0
127·9	12·3	8·19	10·85	12·2	108			272	6·0
127·9	6·15	4·095	10·4	11·8	230	2·13	2·00	272	6·0
				4-Methylsulphonylpyridine					
90·4	11·09	6·15	6·91	7·47	183			268	9·0
90·4	6·55	3·62	6·94	7·52	310	1·67	1·67	268	9·0
100·1	5·24	2·99	15·4	16·8				268	9·0
110·5	3·92	2·82	36·3	40·2				268	9·0
				3-Methylsulphonylpyridazine					
30·2	7·15	3·95	9·65	9·71				266	6·0
40·1	4·11	2·38	23·2	23·6				266	6·0
50·6	4·52	2·54	56·9	58·6	53			266	6·0
50·6	2·26	1·27	56·1	57·8	108	2·04	2·00	266	6·0
				4-Methylsulphonylpyridazine					
20·25	2·90	1·90	50·8	50·6				247	1·0
30·3	2·32	1·58	121	122	52·5			247	1·0
30·3	1·16	0·791	120	121	104	1·98	2·00	247	1·0
39·7	0·695	0·475	268	273				247	1·0
				2-Methylsulphonylpyrazine					
29·9	7·13	4·01	3·86	3·89				292	6·0
39·9	4·75	2·88	9·74	9·97				292	6·0
49·9	4·75	2·88	24·3	25·2	120			292	6·0
49·9	2·38	1·44	24·6	25·5	243	2·02	2·00	292	6·0

[a] ±0·1°. [b] In l. mole^{-1} sec.$^{-1}$; the standard deviation was usually below 3%. [c] Corrected for solvent expansion. [d] Time for 50% reaction, in min. [e] The ratio of $t_{\frac{1}{2}}$ for two experiments at different concentrations. [f] Calculated by assuming a second order reaction. [g] Analytical wavelength for determination of percentage reaction. [h] pH of buffer solutions used to stop the reaction and for spectroscopic measurements.

TABLE 3

Rate coefficients and Arrhenius parameters for reactions with methoxide ions

	Temp.	10^3k (l. mole^{-1} sec.$^{-1}$)	E [a] (kcal. mole^{-1})	log A [b]	$\Delta H^{\ddagger}$ [a] (kcal. mole^{-1})	$\Delta S^{\ddagger}$ [c] (cal. mole^{-1} deg.$^{-1}$)
2-Methylsulphonylpyridine	108·7°	1·97	28·7	13·7	27·9	+1·7
4-Methylsulphonylpyridine	110·5	40·2	23·1	11·7	22·4	−7·5
3-Methylsulphonylpyridazine	30·2	9·71	17·1	10·3	16·5	−13·5
4-Methylsulphonylpyridazine	30·3	121	15·7	10·4	15·1	−13·0
2-Methylsulphonylpyrazine	29·9	3·86	18·3	10·8	17·7	−11·2

[a] Accurate to ±0·4 kcal. mole^{-1}. [b] Accurate to ±0·3 unit. [c] Accurate to ±1 unit.

TABLE 4

Physical properties (pK_a and spectra)

Compound	Ionisation (water, 20°): Charged species involved [a]	pK_a	Spread (±)	Concn. (M)	An. λ [b] (mμ)	Spectroscopy in water [e]: $\lambda_{max.}$ (mμ)	log ε	pH [f]
Pyridine	—					—	—	—
	+	5·23 [c]				—	—	—
2-SO_2Me ...	0	—				253, 258, 264	3·46, 3·51, 3·36	9·0
	+	−1·50	0·03	0·00003	262	259	3·86	−4·0
4-SO_2Me ...	0	—				268	3·49	7·0
	+	1·62	0·03	0·00003	270	269	3·72	−0·8
Pyridazine ...	0	—				—	—	—
	+	2·33 [c]				—	—	—
3-SO_2Me ...	0	—				244, 249, *255*, 303—304	2·88, 2·88, *2·67*, 2·49	9·0
	+	−1·01	0·07	0·0006	310	*244*	*3·09*	−3·4
4-SO_2Me ...	0	—				*252*, 256, *262*, 324	*3·33*, 3·34, *3·16*, 2·46	7·0
	+	−1·06	0·06	0·00005	235	245—247	3·42	−3·2
Pyrazine ...	0	—				—	—	—
	+	0·65 [d]				—	—	—
2-SO_2Me ...	0	—				*259*, 264, *270*, 310	*3·80*, 3·86, *3·74*, 2·78	6·0
	+	−2·47	0·05	0·00008	280	273	3·90	−5·0

[a] 0 Refers to the neutral species, + to the cation. [b] Analytical wavelength for spectroscopic determinations of pK_a. [c] A. Albert, R. Goldacre, and J. N. Phillips, *J. Chem. Soc.*, 1948, 2240. [d] A. Chia and R. Trimble, *J. Phys. Chem.*, 1961, **65**, 863. [e] Shoulders and inflexions in italics. [f] pH Values below 0 have been obtained in solutions of sulphuric acid to which Hammett acidity functions (cf. M. A. Paul and F. A. Long, *Chem. Rev.*, 1957, **57**, 1) have been assigned.

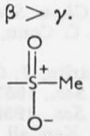
TABLE 5

N.m.r. spectra

Compound	Species †	Solvent	Chemical shifts (τ) of protons: 2	3	4	5	6	CH_3
Pyridine								
2-SO_2Me	0	$CDCl_3$		1·9m	1·8m	2·3m	1·13m	6·72
	+	10N-DCl		0·9m	1·1m	1·35m	0·7m	6·30
4-SO_2Me	0	$CDCl_3$	0·91q	2·06q		2·06q	0·91q	6·86
	+	2N-HCl	0·57q	1·16q		1·16q	0·57q	6·40
2-SMe	0	$CDCl_3$		2·75m	2·4m	2·9m	1·42m	7·39
	+	N-DCl		2·0m	1·5m	2·2m	1·4m	7·17
4-SMe	0	$CDCl_3$	1·46q	2·79q		2·79q	1·46q	7·49
	+	N-DCl	1·44q	2·10q		2·10q	1·44q	7·27
Pyridazine								
3-SO_2Me	0	$CDCl_3$			1·65q	2·09q	0·43q	6·52
	+	5N-DCl			0·8m	0·9m	−0·05m	6·35
4-SO_2Me	0	$CDCl_3$		0·25m		1·93q	0·3m	6·83
	+	5N-DCl		−0·30m		0·67m	−0·2m	6·37
3-SMe	0	$CDCl_3$			2·5m	2·7m	0·98q	7·24
	+	N-DCl			1·4m	1·6m	0·56m	7·22
4-SMe	0	$CDCl_3$		0·9m		2·7q	1·0m	7·43
	+	N-DCl		0·60d		1·69q	0·74d	7·15
Pyrazine								
2-SO_2Me	0	$CDCl_3$		0·55d		0·99d	1·16d	6·69
	+	9M-D_2SO_4		0·39		0·68d	0·14q	6·43
2-SMe	0	$CDCl_3$		1·42d		1·71d	1·54q	7·39
	+	5N-DCl		0·97		1·32d	0·70q	7·19

* τ Values are for singlets except where otherwise indicated; d doublet, q quartet, and m multiplet. † 0 Refers to the neutral molecule, + to the cation.

sulphonyl group is in the order $\alpha > \gamma > \beta$ and is believed to operate by the inductive and mesomeric mechanisms; a principal contributor would have structure (V), in which the use of a *d*-orbital of the sulphur atom would permit the operation of the mesomeric effect. The inductive base-weakening by the chloro-group in pyridine is less than that shown by the methylsulphonyl group and is in the order $\alpha > \beta > \gamma$.



(V)

Nuclear Magnetic Resonance Spectra.—The n.m.r. spectra of neutral molecules and cations are given in Table 5. The spectra were analysable by inspection, J_{para} being assumed to be greater than J_{meta} for pyrazines.[6]

Comparison of the spectra of the neutral molecules of the methylsulphonyl compounds with those of the parent ring systems [6,7] reveals downfield chemical shifts of all protons, due to electron withdrawal by the methyl-

[6] K. Tori and M. Ogata, *Chem. Pharm. Bull.* (*Tokyo*), 1964, **12**, 272.

[7] J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill, New York, 1959.

sulphonyl group. As has been observed in pyridines,[8] protonation shifts are least for hydrogen atoms adjacent to the cationic centre. Thus, in 2-methylsulphonyl- and 2-methylthio-pyrazine, which protonate on N-4, shifts are least for 3-H and 5-H. In 4-methylsulphonylpyridazine, however, protonation shifts for 3-H and 6-H are 0·55 and 0·50, and in 4-methylthiopyridazine 0·30 and 0·26; this could indicate that protonation occurs on N-1 and N-2.

EXPERIMENTAL

All compounds were examined for impurities by paper chromatography on Whatman No. 1 paper with (*a*) 3% aqueous ammonium chloride, and (*b*) butan-1-ol–5N-acetic acid (7 : 3). Analyses were by Dr. J. E. Fildes and her staff. Solids for analysis were dried at 20°/20 mm. unless otherwise stated.

Ionisation constants were determined spectroscopically using the method of Albert and Serjeant [9] and the stability of the cations in strong acid was checked by careful neutralisation.

Ultraviolet spectra were recorded on a Perkin-Elmer Spectracord model 4000 recording spectrophotometer, and $\lambda_{max.}$ and ε values were checked on an Optica CF4 manual instrument. N.m.r. spectra were recorded at 60 Mc./sec. and 33·5° on a Perkin-Elmer R10 spectrometer. Chemical shifts are given on the τ scale; tetramethylsilane was used for internal reference except in acid solutions when sodium 3-trimethylsilylpropanesulphonate was employed. Where required, portions of the spectra were expanded.

Preparation of Compounds.—Methylsulphonyl compounds were prepared from the methylthio-compounds by oxidation with potassium permanganate in dilute acetic acid. Oxidations with chlorine or *m*-chloroperbenzoic acid were, in general, found to be less satisfactory.

2- *and* 4-*Methylsulphonylpyridines.*—2-Methylsulphonylpyridine was prepared from 2-methylthiopyridine [10] by oxidation with potassium permanganate.[11] The reaction mixture was decolourised with sulphur dioxide, adjusted to pH 7, and the product extracted with chloroform and distilled (Found: C, 45·7; H, 4·7; N, 9·3; S, 20·3. Calc. for $C_6H_7NO_2S$: C, 45·7; H, 4·5; N, 8·9; S, 20·35%).

4-Methylsulphonylpyridine, m. p. 82° (lit., 81°) (Found: C, 46·1; H, 4·5; N, 9·2; S, 20·1%) was prepared as described by King and Ware.[12]

2-*Methoxypyridine.*—2-Methylsulphonylpyridine (0·100 g.) and methanolic sodium methoxide (5 ml., 0·43N) were heated at 150° for 6 hr. The reaction mixture was diluted with water, neutralised to pH 7, and extracted with chloroform. The extract was dried (Na_2SO_4) and the solvent distilled off leaving an oil, which with ethanolic picric acid gave yellow crystals of 2-*methoxypyridine picrate* (0·09 g.), m. p. and mixed m. p. 159—160° (ethanol). 2-Methoxypyridine picrate for comparison was prepared from 2-bromopyridine and sodium methoxide by a method similar to that used [13] with 2-chloropyridine (Found: C, 42·5; H, 3·0; N, 16·6. $C_{12}H_{10}N_4O_8$ requires C, 42·6; H, 3·0; N, 16·6%).

4-*Methoxypyridine.*—4-Methylsulphonylpyridine (0·100 g.) and methanolic sodium methoxide (5 ml.; 0·43N) were heated at 150° for 6 hr. The mixture was evaporated to dryness and extracted with chloroform; the product with aqueous picric acid gave 4-methoxypyridine picrate (0·075 g.), m. p. 170—171° (water) (lit.,[14] 172—173°) (Found: C, 42·9; H, 3·0; N, 16·7%).

2-*Methylsulphonylpyrazine.*— 2-Methylthiopyrazine [15] (0·500 g.) was dissolved in acetic acid (14 ml.; 8N) and a solution of potassium permanganate (1 g.) in water (8 ml.) added with stirring at 25° during ½ hr. This mixture was cooled in ice, decolourised by passing in sulphur dioxide, adjusted to pH 7 with ammonia, and extracted with chloroform. The chloroform extract was dried (Na_2SO_4) and evaporated to a colourless oil, which solidified on cooling and was twice sublimed (150°/0·5 mm.) to give 2-*methylsulphonylpyrazine* (0·42 g.), m. p. 47—48° (Found: C, 38·4; H, 3·9; N, 17·7; S, 20·15. $C_5H_6N_2O_2S$ requires C, 38·0; H, 3·8; N, 17·7; S, 20·2%).

2-*Methoxypyrazine.*—2-Methylsulphonylpyrazine (0·005 g.) and methanolic sodium methoxide (3 ml.; 0·02N) were heated at 87° for 3 hr. Complete conversion into 2-methoxypyrazine was apparent (appropriate dilutions of the reaction mixture at pH 6·0 and pH −1·5 gave solutions with the ultraviolet spectra of the neutral molecule [16] and the cation [17] respectively).

3-*Methylsulphonylpyridazine.*—(*a*) To 3-methylthiopyridazine [18] (0·029 g.) in acetic acid (6 ml.; 16N), potassium permanganate (0·75 g.) in water (9 ml.) was added slowly with stirring at 25° and stirring was continued for 0·5 hr. The mixture was cooled in ice, decolourised by passing in sulphur dioxide, adjusted to pH 8 with ammonia, and extracted with chloroform. The extract was dried (Na_2SO_4) and evaporated to yield 3-*methylsulphonylpyridazine* (0·027 g.), m. p. 87° [benzene–light petroleum (b. p. 60—80°)] (Found: C, 37·8; H, 3·7; N, 17·7; S, 20·4%).

(*b*) 3-Methylthiopyridazine (0·500 g.) was dissolved in a mixture of methanol (3 ml.) and water (10 ml.), cooled to −20°, and chlorine passed for 1 hr. The cold solution was adjusted to pH 7 by careful addition of aqueous potassium carbonate, extracted with chloroform, and the extract dried (Na_2SO_4) and evaporated to give a yellow solid. This, in a small volume of chloroform, was chromatographed over alumina (6 in.) to give 3-methylsulphonylpyridazine (0·440 g.), m. p. and mixed m. p. with product of (*a*) 87°.

4-*Methylsulphonylpyridazine.*— 4-Methylthiopyridazine [15] (0·120 g.) in acetic acid (2 ml.; 16N) was stirred at room temperature while potassium permanganate (0·25 g.) in water (2·5 ml.) was added during 0·5 hr. The mixture was cooled, decolourised by passing in sulphur dioxide, and adjusted to pH 7 with ammonia. Extraction with chloroform gave 4-*methylsulphonylpyridazine* (0·073 g.), m. p. 144° (ethanol) (Found: C, 38·0; H, 3·9; N, 18·0; S, 20·3%).

3-*Methoxypyridazine.*— 3-Methylsulphonylpyridazine (0·100 g.) and methanolic sodium methoxide (5 ml.; 0·43N) were refluxed for 30 min. The reaction mixture was

[8] I. C. Smith and W. G. Schneider, *Canad. J. Chem.*, 1961, **39**, 1158.
[9] A. Albert and E. P. Serjeant, "Ionization Constants," Methuen, London, 1963.
[10] M. A. Phillips and H. Shapiro, *J. Chem. Soc.*, 1942, 584.
[11] W. Markwald, W. Klemm, and H. Trabert, *Ber.*, 1900, **33**, 1556.
[12] H. King and L. L. Ware, *J. Chem. Soc.*, 1939, 873.
[13] T. B. Grave, *J. Amer. Chem. Soc.*, 1924, **46**, 1460.
[14] R. R. Renshaw and R. C. Conn, *J. Amer. Chem. Soc.*, 1937, **59**, 297.
[15] A. Albert and G. B. Barlin, *J. Chem. Soc.*, 1962, 3129.
[16] S. F. Mason, *J. Chem. Soc.*, 1957, 5010.
[17] S. F. Mason, *J. Chem. Soc.*, 1959, 1253.
[18] G. F. Duffin and J. D. Kendall, *J. Chem. Soc.*, 1959, 3789.

diluted with
with chlorofo
(Na_2SO_4) and
which with et
3-methoxypyr
(lit.,[19] 111°) (I
$C_{11}H_9N_5O_8$: C,
4-*Methoxypy*
(0·100 g.) witl
the 3-isomer g
m. p. 143—14
2·4; N, 20·6%
Methanol.—
Bjerrum's [21] n
packed with g
was discarded.
Sodium Met
in methanol, a
with standard
Kinetic Pro
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[19] T. Itai and
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11, 1059.
[21] H. Lund a

diluted with water, neutralised to pH 7, and extracted with chloroform. The chloroform extract was dried (Na_2SO_4) and the solvent evaporated to give an oily residue which with ethanolic picric acid gave yellow crystals of 3-methoxypyridazine picrate (0·080 g.), m. p. 111° (ethanol) (lit.,[19] 111°) (Found: C, 39·1; H, 2·6; N, 20·3. Calc. for $C_{11}H_9N_5O_8$: C, 38·95; H, 2·7; N, 20·65%).

4-Methoxypyridazine.— 4-Methylsulphonylpyridazine (0·100 g.) with sodium methoxide as described above for the 3-isomer gave 4-methoxypyridazine picrate (0·150 g.), m. p. 143—144° (lit.,[20] 143—144°) (Found: C, 39·0; H, 2·4; N, 20·6%).

Methanol.—AnalaR methanol was dried by Lund and Bjerrum's [21] method and fractionated through a column packed with glass helices; the first 10% of the distillate was discarded.

Sodium Methoxide Solution.—Clean sodium was dissolved in methanol, and the concentration determined by titration with standard acid.

Kinetic Procedure.—At temperatures greater than 90°, methanol solutions (2 ml.) which were $2·8—8·2 \times 10^{-3}$M in methylsulphonyl compound and $4·0—12·0 \times 10^{-3}$N in sodium methoxide were heated in sealed tubes in a thermostat. The tubes were chilled briefly, and the contents diluted with buffer to 50 ml.

At temperatures less than 51°, a weighed quantity of methylsulphonyl compound was dissolved quickly in a known volume of methanolic sodium methoxide ($0·7—7·0 \times 10^{-3}$N) in the thermostat, and samples (2 ml.) were removed at specified times and quenched in buffer solution.

Ultraviolet absorption at the specified wavelength was then determined for each sample and the second-order rate coefficient calculated from the expression:

$$k = \frac{2·303}{t(a - b)} \log \frac{b\,(a - x)}{a\,(b - x)}$$

where a is the initial concentration of methoxide ion, b that of methylsulphonyl compound, x is the concentration of methoxy-compound formed at time t (sec.), and k the second-order rate coefficient in l. mole^{-1} sec.$^{-1}$. Where necessary, corrections were made for expansion of the solvent.

The methylsulphonyl compounds in methanol were stable at the temperatures of the kinetic runs, and with sodium methoxide at t_∞ the spectrum obtained was that of the pure methoxy-compound.

For each run, 9 samples covering at least 10—60% reaction, and also those corresponding to t_0 and t_∞ (at least 30 times the half-life of the reaction and corresponding to 98—100% reaction) were examined. Times for 50% reaction were determined in selected cases. Each reaction was studied at three temperatures, covering a 20° range.

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[6/1420 *Received, November 11th,* 1966]

[19] T. Itai and H. Igeta, *J. Pharm. Soc. Japan*, 1954, **74**, 1195.
[20] T. Itai and S. Kamiya, *Chem. Pharm. Bull. (Tokyo)*, 1963, **11**, 1059.
[21] H. Lund and J. Bjerrum, *Ber.*, 1934, **64**, 210.

Kinetics of Reactions in Heterocycles. Part III.[1] Replacement of the Methylsulphonyl Group from Quinoline, Isoquinoline, Quinoxaline, Cinnoline, and Phthalazine by Methoxide Ion

By **G. B. Barlin** and **W. V. Brown**, Department of Medical Chemistry, John Curtin School of Medical Research, Australian National University, Canberra, Australia

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Kinetics of Reactions in Heterocycles. Part III.[1] Replacement of the Methylsulphonyl Group from Quinoline, Isoquinoline, Quinoxaline, Cinnoline, and Phthalazine by Methoxide Ion

By G. B. Barlin and W. V. Brown, Department of Medical Chemistry, John Curtin School of Medical Research, Australian National University, Canberra, Australia

A kinetic study of the reactions of methylsulphonyl quinolines, isoquinoline, quinoxaline, cinnoline, and phthalazine with methoxide ion reveals a high reactivity. Direct comparisons with four of the corresponding chloro-compounds under similar conditions show that the methylsulphonyl compounds are from *ca.* 40 to 100 times more reactive, and this has been traced to the lower energy of activation of the latter compounds. Annelation effects which lead to enhanced reactivity but reduced selectivity are also discussed. The preparation of the methylsulphonyl compounds is described. Ionisation constants and ultraviolet and n.m.r. spectra are recorded.

In Part II [1] we discussed replacement of the methylsulphonyl by the methoxy-group in monocyclic azines. This work is now extended to quinolines, isoquinoline, quinoxaline, cinnoline, and phthalazine, in which the methylsulphonyl group is attached to the heterocyclic ring. Table 1 gives details of a typical kinetic experiment, Table 2 gives all the kinetic results, and Table 3 lists parameters derived from the kinetic studies.

Inspection of Tables 2 and 3 reveals that, at the temperatures employed, 4-methylsulphonylquinoline is more reactive than the 2-isomer, and this is manifest in a lower energy of activation, E (19·4 compared to 20·7 kcal. mole^{-1}); but the frequency factor, log A, is also lower. This greater reactivity of the 4-position is also in qualitative agreement with the results found for pyridines.[1] 1-Methylsulphonylisoquinoline is intermediate in reactivity between these two methylsulphonylquinolines.

The three diazines show less than a two-fold difference in their reactivities, at 15°. 2-Methylsulphonylquinoxaline (which has the highest energy of activation, 14·8 kcal. mole^{-1}) is the most reactive because of the significantly larger value of log A. The greater reactivity of 4-methylsulphonylcinnoline over 1-methylsulphonylphthalazine is, on the other hand, due to the lower energy of activation (13·6 compared to 14·1$_5$ kcal. mole^{-1}) despite a lower value of log A (9·4 and 9·8, respectively).

The effects of annelating a benzene ring are seen, by comparison of the results in Tables 2 and 3 with those for the monocyclicazines,[1] to lead to a significant increase in reactivity. Thus, 4-methylsulphonylpyridine with methoxide ion at 90·4° has a rate coefficient of $7{\cdot}52 \times 10^{-3}$ whereas that for 4-methylsulphonylquinoline at 69·7° is $15{\cdot}8 \times 10^{-3}$ l. mole^{-1} sec.$^{-1}$. Similar results have been observed in other heterocycles, and are attributed to the expanded region available for delocalisation of the charge in the transition state.[2] This enhanced reactivity is reflected in considerably lower values of the energy of activation of the annelated compounds despite lower values of the frequency factors. For 4-chloro-pyridine and -quinoline the values of E are 23·1 and 19·4 kcal. mole^{-1} and of log A are 11·7 and 10·6, respectively.

Annelation in the compounds studied is also seen to reduce differences in reactivity due to positional effects. Thus, in the pyridines [1] at 110° the ratio of reactivity of the 4-methylsulphonyl compound to the 2-isomer is *ca.* 20 whereas in the quinolines at 60° it is *ca.* 2·6. This diminution is probably due to loss of some resonance energy in the transition state of the 4-compound, *e.g.*, (I), relative to that in the 2-isomer (II). The relative

[1] Part II, G. B. Barlin and W. V. Brown, *J. Chem. Soc.* (*B*), 1967, 648.

[2] N. B. Chapman and D. Q. Russell-Hill, *J. Chem. Soc.*, 1956, 1563.

TABLE 1

Reactions of methoxide ions

1-Methylsulphonylisoquinoline at 59·1°; methoxide ion 0·0104N, methylsulphonyl compound 0·00608M

Time (min.)	44·2	84·5	133·0	180·2	241·7	308·1	394·3	495·3	680·7
Reaction (%)	12·7	22·7	32·2	40·1	48·7	55·5	64·0	70·4	79·5
10^3k (l. mole^{-1} sec.$^{-1}$)	5·17	5·18	5·18	5·15	5·20	5·16	5·25	5·20	5·25

Mean $10^3k = 5·19 \pm 0·04$; 5·42 after correction for solvent expansion.

TABLE 2

Kinetic results for the reactions of methylsulphonyl compounds with methoxide ions

Compound	Temp.[a] (°c)	10^3[MeO$^-$] (N)	10^3[RSO$_2$Me] (M)	10^3k [b]	Standard deviation (±)	$10^3k_{corr.}$ [c]	$t_{\frac{1}{2}}$ [d]	$t_{\frac{1}{2}}/t_{\frac{1}{2}}'$ [e]	$(t_{\frac{1}{2}}/t_{\frac{1}{2}}')$ (calc.) [f]	A.w.l.[g] (mμ)	pH [h]
2-Methylsulphonyl-quinoline	60·0	10·39	6·05	2·61	0·05	2·72				254	6·0
	70·1	10·39	6·05	6·47	0·07	6·84	212			254	6·0
	70·1	5·19	3·096	6·11	0·07	6·46	440	2·07	2·01	254	6·0
	80·0	10·39	6·07	14·9	0·03	15·9				254	6·0
4-Methylsulphonyl-quinoline	49·9	5·23	3·05	2·68	0·07	2·77				325	9·0
	60·3	10·46	6·05	7·01	0·15	7·33	190			325	9·0
	60·3	5·23	3·04	6·90	0·11	7·20	390	2·05	2·00	325	9·0
	69·7	5·23	3·05	15·0	0·3	$15·8_5$				325	9·0
1-Methylsulphonyl-isoquinoline	59·1	10·39	6·08	5·19	0·04	5·42	255			270	6·0
	59·1	5·195	3·06	4·97	0·09	5·19	535	2·10	2·00	270	6·0
	70·2	5·195	3·06	12·2	0·2	12·9				270	6·0
	80·25	5·195	3·06	28·5	0·6	30·4				270	6·0
2-Methylsulphonyl-quinoxaline	5·2	0·831	0·480	88·3	1·2	86·1				242	6·0
	14·9	0·831	0·480	212	4	209	79			242	6·0
	14·9	0·415	0·241	216	6	213	155	1·97	2·00	242	6·0
	24·8	0·831	0·480	505	7	505				242	6·0
4-Methylsulphonyl-cinnoline	5·0	1·50	0·90	55·6	0·9	54·3				286	6·0
	15·1	2·99	1·80	136	2	134	34			286	6·0
	15·1	1·50	0·90	139	2	137	66	1·94	2·0	286	6·0
	24·9	1·50	0·90	284	2	284				286	6·0
1-Methylsulphonyl-phthalazine	5·0	1·70	0·99	49·2	0·7	48·0				256	6·0
	15·1	1·70	0·99	119	3	117_5	33·8			256	6·0
	15·1	3·40	1·985	121	2	120	68	2·01	2·0	256	6·0
	24·8	1·70	0·99	264	4	264				256	6·0

[a] ±0·1°. [b] In l. mole^{-1} sec.$^{-1}$. [c] Corrected for solvent expansion. [d] Time (minutes) for 50% reaction. [e] The ratio of $t_{\frac{1}{2}}$ for two experiments at different concentrations. [f] Calculated by assuming second-order reaction. [g] Analytical wavelength for determination of percentage reaction. [h] pH of buffer solutions used to stop the reaction and for spectroscopic measurements.

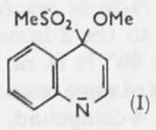
TABLE 3

Rate coefficients and Arrhenius parameters for reactions with methoxide ions

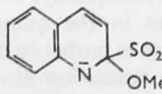
Methylsulphonyl compound	Temp. (°c)	10^3k (l. mole^{-1} sec.$^{-1}$)	E [a] (kcal. mole^{-1})	log A [b]	$\Delta H^{\ddagger}$ [a] (kcal. mole^{-1})	$-\Delta S^{\ddagger}$ [c] (kcal. mole^{-1} deg.$^{-1}$)
2-Methylsulphonylquinoline	60·0	2·72	20·7	11·0	20·0	10·4
4-Methylsulphonylquinoline	60·3	7·20	19·4	10·6	18·8	12·3
1-Methylsulphonylisoquinoline...	59·1	5·19	$19·5_5$	$10·5_5$	18·9	12·5
2-Methylsulphonylquinoxaline ...	14·9	209	14·8	10·6	14·3	12·1
4-Methylsulphonylcinnoline	15·1	137	13·6	9·4	13·0	17·2
1-Methylsulphonylphthalazine ...	15·1	117_5	$14·1_5$	9·8	13·6	15·6

[a] Accurate to ±0·3 kcal. mole^{-1}. [b] Accurate to ±0·3 unit. [c] Accurate to ±1 unit.

reactivity in the 4- and the 3-position of pyridazine at 30° is 12, but on annelation to 4-methylsulphonylcinnoline and 1-methylsulphonylphthalazine, at 15·1° the ratio has dropped to 1·2.



(I)



(II)

2-Methylsulphonylpyrazine is the least reactive of the diazines discussed in Part II but 2-methylsulphonylquinoxaline is the most reactive of the diazines listed here. Differences in conjugation in the transition state are probably important here too.

Data concerning the reactivity of methylsulphonyl and chloro-heterocycles with methoxide ion are in Table 4. Comparison of these results reveals that the methylsulphonyl compounds are very much more reactive. The superior reactivity of the methylsulphonyl compounds, calculated from the figures in Table 4, varies from 43 to 98 times (compare with the value of 90 obtained previously for the 3-position of pyridazine [1]). This higher reactivity is due primarily to the lower

TABLE 4

Rate coefficients and Arrhenius parameters for reactions with methoxide ions

Compound	Temp. (°c)	10^4k [c] (l. mole^{-1} sec.$^{-1}$)	E (kcal. mole^{-1})	$-\Delta S^{\ddagger}$ (kcal. mole^{-1} deg.$^{-1}$)
2-Chloroquinoline [a] ...	80·0	3·66 [d]	24·2	7·0
2-Methylsulphonylquinoline	80·0	159	20·7	10·4
4-Chloroquinoline [a] ...	80·0	3·7 [d]	21·2	17·2
4-Methylsulphonylquinoline	80·0	364 [d]	19·4	12·3
2-Chloroquinoxaline [b]	5·0	13·6	16·7	13·6
2-Methylsulphonylquinoxaline	5·2	861	14·8	12·1
4-Chlorocinnoline [b] ...	5·0	9·55 [d]	15·8	17·7
4-Methylsulphonylcinnoline	5·0	543	13·6	17·2

[a] M. L. Belli, G. Illuminati, and G. Marino, *Tetrahedron*, 1963, **19**, 345. [b] G. Illuminati, *Adv. Heterocyclic Chem.*, 1964, **3**, 285. [c] To enable direct comparison, some rate coefficients have been normalised at specific temperatures. [d] Obtained by calculation.

pounds with those for the chloro-compounds and ethoxide ion [2] shows similar values.

Ionisation Constants and Ultraviolet and N.m.r. Spectra (Tables 5 and 6).—The powerful electron withdrawal by the methylsulphonyl group is exemplified by 2-methylsulphonylquinoline and 1-methylsulphonylisoquinoline where the lowering of the pK_a by the methylsulphonyl group α to the basic centre is 6·5 and 6·3 units, respectively, and by the methylsulphonyl group γ to the centre in 4-methylsulphonylquinoline is 3·4 units. (Similarly, in pyridine the effects of the α and γ methylsulphonyl group are 6·7 and 3·6 units.[1]) The 2-methylsulphonyl group in pyrazine [1] was previously found to lower the pK_a value by 3·1 units, but the lowering in quinoxaline is now found to be 2·2.

The ultraviolet spectra of methoxy-compounds required for the kinetic studies, but not in Table 5, are given for 4-methoxyquinoline in ref. 3, for 2-methoxyquinoxaline in ref. 4, and for 4-methoxycinnoline and 1-methoxyphthalazine in ref. 5.

TABLE 5

pK_a Values and ultraviolet spectra

	Ionisation (water, 20°)					Spectroscopy in water [g]		
Compound	Charged species involved [a]	pK_a	Spread (±)	Concn. (M)	A.w.l. [b] (mμ)	$\lambda_{max.}$ (mμ)	log ε	pH [h]
Quinoline ...	+	4·93 [c]						
2-SO_2Me ...	0					235, 299	4·75, 3·61	6·0
	+	−1·53	0·08	0·00005	350	246, *306*, 320, *347*	4·68, *3·76*, 3·95, *3·46*	−4·0
2-OMe ...	0					232, *237*, 259, *265*, *294*, 307, 313, 320 [i]	4·27, *4·18*, 3·49, *3·48*, *3·24*, 3·49, 3·43, 3·51	6·0
	+	3·17 [c]				*218*, *228*, *235*, 239, 243, 307	*4·12*, *4·03*, *4·25*, 4·40, 4·44, 3·93	0·2
4-SO_2Me ...	0					236, 239, *302*, 314, 324	4·43, 4·42, *3·65*, 3·74, 3·73	6·0
	+	1·57	0·03	0·00003	332	243, 329	4·50, 3·89	−1·6
Isoquinoline	+	5·46 [c]						
1-SO_2Me ...	0					227, 281, 324	4·58, 3·45, 3·63	6·0
	+	−0·83	0·06	0·00003	320	243, *283*, 293, 308, 352	4·63, *3·22*, 3·27, 3·13, 3·61	−3·2
1-OMe ...	0					*262*, 270, 281, *298*, 309, 320	*3·65*, 3·78, 3·71, *3·32*, 3·52, 3·50	6·0
	+	3·05 [c]				220, *227*, *234*, 255, 264, 274, *304*, 318, 330	4·60, *4·56*, *4·36*, 3·59, 3·57, 3·43, *3·46*, 3·71, 3·69	0·2
Quinoxaline	+	0·56 [c]				—		
2-SO_2Me ...	0					241, 321	4·60, 3·84	6·0
	+	−1·66	0·04	0·00002	340	251, 343	4·62, 4·00	−4·2
Cinnoline ...	+	2·29 [d]				—	—	
4-SO_2Me ...	0					235, 308, 337	4·55, 3·57, 3·46	6·0
	+	[e]				—		
Phthalazine ...	+	3·47 [f]				—		
1-SO_2Me ...	0					228, 281	4·58, 3·49	6·0
	+	[e]				—		

[a] 0 Neutral species, + cation. [b] Analytical wavelength for spectroscopic determinations of pK_a. [c] A. Albert and J. N. Phillips, *J. Chem. Soc.*, 1956, 1294. [d] A. R. Osborn, K. Schofield, and L. N. Short, *J. Chem. Soc.*, 1956, 4191. [e] Instability of the compound in strong acid solutions prevented determination of the pK_a value. [f] A. Albert, R. Goldacre, and J. Phillips, *J. Chem. Soc.*, 1948, 2240. [g] Shoulders and inflexions in italics. [h] pH values below 0 have been obtained in solutions of sulphuric acid to which Hammett acidity functions have been assigned. [i] The spectrum differs from that recorded at pH 6·8 by S. F. Mason, *J. Chem. Soc.*, 1957, 5010.

energy of activation of the methylsulphonyl compounds. Although figures are not available for 1-chloroisoquinoline and 1-chlorophthalazine with methoxide ion, comparison of the results for the methylsulphonyl com-

[1] G. W. Ewing and E. A. Steck, *J. Amer. Chem. Soc.*, 1946, **68**, 2181; G. F. Tucker and J. L. Irvin, *ibid.*, 1951, **73**, 1923; J. M. Hearn, R. A. Morton, and J. C. E. Simpson, *J. Chem. Soc.*, 1951, 3318.

[4] G. W. H. Cheeseman, *J. Chem. Soc.*, 1958, 108.

[5] A. Albert and G. B. Barlin, *J. Chem. Soc.*, 1962, 3129.

EXPERIMENTAL

Compounds were examined for impurities by paper chromatography on Whatman No. 1 paper with (A) 3%

aqueous ammonium chloride, and (B) butan-1-ol–5N-acetic acid (7 : 3) as solvent, and also by thin-layer chromatography in chloroform over alumina.

Analyses were by Dr. J. E. Fildes and her staff. Solids for analysis were dried at 20°/20 mm. unless otherwise stated. Ionisation constants and ultraviolet and n.m.r. spectra were determined by methods described in Part II.[1]

2-Methylsulphonylquinoline.—This was prepared by oxidation of 2-methylthioquinoline [6] with potassium permanganate in acetic acid;[7] it had m. p. 101—102° (lit.,[7] 100°) (Found: C, 57·6; H, 4·5; N, 6·9; S, 15·4. Calc. for $C_{10}H_9NO_2S$: C, 58·0; H, 4·3; N, 6·8; S, 15·45%).

TABLE 6

Nuclear magnetic resonance spectra

Compound	Species [a]	Chemical shifts (τ) of protons: 2	3	4	5	6	7	8	CH_3
Quinoline									
2-SO_2Me	0		1·77	1·43	*b*	2·1	2·1	1·66	6·58
	+		*b*	0·18	*b*	*b*	*b*	*b*	6·13
4-SO_2Me	0	0·68	1·75		1·15	2·05	2·05	1·57	6·71
	+	0·27	1·12		*b*	1·5	1·5	*b*	6·32
2-SMe	0		2·75	2·05	*b*	*b*	*b*	1·95	7·27
	+		2·3	1·38	2·05	2·05	2·05	*b*	7·06
4-SMe	0	1·12	2·78		1·75	2·15	2·3	1·75	7·40
	+	1·39	2·55		2·2	2·2	2·2	2·2	7·26
iso*Quinoline*									
1-SO_2Me	0		1·42	2·08	2·05	2·05	2·05	0·91	6·45
	+		0·9	0·9	1·4	1·4	1·4	0·8	6·08
1-SMe	0		1·53	2·55	2·25	2·25	2·25	1·66	7·25
	+		1·95	2·22	2	2	2	2	7·07
Quinoxaline									
2-SO_2Me	0		0·32		1·65	1·9	1·9	1·65	6·53
	+		0·1 [c]		1·3	1·3	1·3	1·3	6·30
2-SMe	0		1·23		1·9	2·2	2·2	1·9	7·29
	+		0·57		1·65	1·65	1·65	1·65	6·92
Cinnoline									
4-SO_2Me	0		0·04		1·1	1·8	1·8	1·1	6·67
	+ [d]								
4-SMe	0		0·81		1·85	2·05	2·05	1·40	7·28
	+		0·59		1·65	1·65	1·65	1·65	6·91
Phthalazine									
1-SO_2Me	0			0·19	1·75	1·75	1·75	0·96	6·28
	+ [e]			−0·81	0·85	1·15	1·15	0·7	6·11
1-SMe	0			0·60	1·9	1·9	1·9	1·75	7·12
	+			0·02	1·6	1·6	1·6	1·6	7·15

[a] 0 refers to the neutral molecule in $CDCl_3$, + to the cation in DCl–D_2O except for 2-methylsulphonylquinoxaline which was in D_2SO_4–D_2O. [b] Assignment of peak not possible. [c] Assumed to be beneath the water peak. [d] Instability in acid prevented determination of the n.m.r. spectrum. [e] Decomposition occurred in acid solution but was sufficiently slow to permit determination of the spectrum.

4-Methylsulphonylquinoline.—A solution of 4-methylthioquinoline [6] (1·2 g.) in acetic acid (30 ml.; 6N) was stirred at room temperature while potassium permanganate (2·1 g.) in water (50 ml.) was added dropwise during 0·5 hr. The mixture was filtered, the black residue extracted three times with boiling benzene and the extract evaporated; the *product* crystallised from benzene–hexane (0·96 g.), m. p. 147—148° (Found: C, 58·4; H, 4·4; N, 7·0; S, 15·2%).

2-Methoxyquinoline.—2-Methylsulphonylquinoline (0·12 g.) and methanolic sodium methoxide (5 ml.; 0·3N) were heated in a sealed tube at 110° for 1 hr. The solvent was evaporated and the residue extracted with chloroform. The oily product with ethanolic picric acid gave 2-methoxyquinoline picrate (0·19 g.), m. p. 182—183° (from ethanol) (lit.,[8] 179—180°) (Found: C, 49·7; H, 3·0; N, 14·35. Calc. for $C_{16}H_{12}N_4O_8$: C, 49·5; H, 3·1; N, 14·4%).

Authentic 2-methoxyquinoline, prepared from 2-chloroquinoline and sodium methoxide,[9] had b. p. 78—80°/0·7 mm. (lit.,[9] 246—247°) (Found: C, 75·5; H, 5·8; N, 8·8. Calc. for $C_{10}H_9NO$: C, 75·45; H, 5·7; N, 8·8%).

4-Methoxyquinoline.—4-Methylsulphonylquinoline (0·050 g.) and methanolic sodium methoxide (2 ml.; 0·4N) were heated at 87° for 2 hr. The mixture was evaporated to dryness and the product extracted into chloroform. The liquid product gave, on addition of ethanolic picric acid, crystals of 4-methoxyquinoline picrate (0·057 g.), m. p. 202° (from ethanol) (lit.,[10] 203°).

1-Methylsulphonylisoquinoline.—To a stirred solution of 1-methylthioisoquinoline [6] (0·4 g.) in acetic acid (10 ml.; 6N), potassium permanganate (0·7 g.) in water (20 ml.) was added dropwise during 0·5 hr. After chilling, the mixture was decolourised by sulphur dioxide and the *product* filtered off, m. p. 153—154° (from benzene–hexane) (0·27 g.) (Found: C, 58·0; H, 4·5; N, 6·7; S, 15·7%).

[6] A. Albert and G. B. Barlin, *J. Chem. Soc.*, 1959, 2384.
[7] H. Larivé, P. Collet, and R. Dennilauler, *Bull. Soc. chim. France*, 1956, 1443.
[8] R. C. Fuson, H. L. Jackson, and E. W. Grieshaber, *J. Org. Chem.*, 1951, **16**, 1529.
[9] P. Friedlaender and H. Ostermaier, *Ber.*, 1882, **15**, 332.
[10] O. G. Backeberg, *J. Chem. Soc.*, 1933, 619.

1-*Methoxyisoquinoline*.— 1-Methylsulphonylisoquinoline (0·12 g.) and methanolic sodium methoxide (5 ml.; 0·3N) were heated at 110° for 1 hr., and the solvent was evaporated. The product, obtained by extraction with chloroform, gave with ethanolic picric acid, 1-methoxyisoquinoline picrate (0·19 g.), m. p. 170—171° (from ethanol) [lit.,[11] 163·5—165·5° (decomp.)] (Found: C, 49·15; H, 3·1; N, 14·5%).

1-Methoxyisoquinoline [12] was also prepared from 1-hydroxyisoquinoline [12] through 1-chloroisoquinoline [13] with sodium methoxide. It had b. p. 138—140°/*ca.* 25 mm. (lit.,[12] 135—136°/21 mm.).

2-*Methylsulphonylquinoxaline*.—2-Hydroxyquinoxaline [14] (8 g.) and phosphorus pentasulphide (16 g.) were refluxed in pyridine (250 ml.) for 40 min. The excess of phosphorus pentasulphide was decomposed by addition of water (150 ml.), and the mixture evaporated to dryness under reduced pressure. The residue was extracted with hot chloroform and the extract chromatographed over alumina in chloroform–ethanol (9 : 1). The eluate on evaporation gave quinoxaline-2-thiol (5 g.), m. p. 200—202° (lit.,[15] 204—205°). This product, on methylation [16] with methyl iodide and sodium hydroxide, gave 2-methylthioquinoxaline, m. p. 45—46° (lit.,[16] 46—47°).

A solution of 2-methylthioquinoxaline (0·100 g.) in acetic acid (2 ml.; 8N) was stirred at room temperature while potassium permanganate (0·150 g.) in water (5 ml.) was added during 0·5 hr., and then decolourised with sulphur dioxide. The white precipitate was filtered off and recrystallised from cyclohexane, to give 2-methylsulphonylquinoxaline (0·084 g.), m. p. 125—126° (lit.,[16] 126—127°) (Found: C, 51·5; H, 3·9; N, 13·6; S, 15·4. Calc. for $C_9H_8N_2O_2S$: C, 51·9; H, 3·85; N, 13·5; S, 15·4%).

2-*Methoxyquinoxaline*.— 2-Methylsulphonylquinoxaline (0·10 g.) and methanolic sodium methoxide (6 ml.; 0·3N) were refluxed for 15 min., and the methanol was evaporated. The oily product was extracted with chloroform; with ethanolic picric acid it gave 2-methoxyquinoxaline picrate (0·07 g.), m. p. 142° (from ethanol) (lit.,[17] 141—142°).

4-*Methylsulphonylcinnoline*.— 4-Methylthiocinnoline [18] (1·00 g.) in acetic acid (20 ml.; 8N) was stirred at room temperature while potassium permanganate (1·5 g.) in water (30 ml.) was added during 0·5 hr. The mixture was chilled and decolourised by sulphur dioxide. The product was collected and recrystallised from benzene–cyclohexane, to give yellow needles of 4-*methylsulphonylcinnoline* (0·67 g.), m. p. 183—184° (Found: C, 51·7; H, 3·8; N, 13·3; S, 15·35%).

4-*Methoxycinnoline*.—4-Methylsulphonylcinnoline (0·20 g.) and methanolic sodium methoxide (5 ml.; 0·4N) were refluxed for 5 min., and the solvent was evaporated. The residue was diluted with water (1 ml.) and extracted with ether, to yield 4-methoxycinnoline (0·08 g.), m. p. 128—129° [from light petroleum (b. p. 60—80°)] (lit.,[19] 127—128°.)

1-*Methylsulphonylphthalazine*.—A solution of 1-methylthiophthalazine [5] (0·60 g.) in 6N-acetic acid (18 ml.) was stirred at room temperature while potassium permanganate (1·2 g.) in water (30 ml.) was added during 0·5 hr. The mixture was chilled, decolourised by sulphur dioxide, and neutralised with ammonia to pH 7. Extraction with chloroform gave a mixture of 1-methylsulphonyl and 1-hydroxyphthalazine. This chloroform solution was chromatographed over alumina (8 in.), and the first fraction gave, after crystallisation from benzene–light petroleum (b. p. 60—80°), the *product* (0·40 g.), m. p. 156° (Found: C, 51·5; H, 3·6; N, 13·5; S, 15·1%). (This material is hygroscopic and reacts with the water absorbed to give the corresponding hydroxy-compound. It is, however, sufficiently stable in solution to permit determination of the spectrum of the neutral molecule and also rate coefficients.)

1-*Methoxyphthalazine*.—A mixture of 1-methylsulphonylphthalazine (0·100 g.) and methanolic sodium methoxide (4 ml.; 0·4N) was refluxed for 5 min., and the solvent evaporated. The mixture was extracted in chloroform, and, after evaporation of the solvent, the product, with ethanolic picric acid, gave 1-methoxyphthalazine picrate (0·135 g.), m. p. 161—162° (lit.,[20] 139—140°) (Found: C, 46·5; H, 3·0; N, 17·9. Calc. for $C_{15}H_{11}N_5O_8$: C, 46·3; H, 2·85; N, 18·0%). An authentic specimen of the picrate, prepared from 1-methoxyphthalazine,[21] had m. p. 161—162° and gave no depression on admixture with the above picrate.

Reagents and Kinetic Procedure.—These were essentially as described previously,[1] except that, for kinetic runs in the range 49—90°, the reagents were chilled thoroughly before mixing. The sealed tubes were then heated in the thermostat for the times specified.

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[11] M. M. Robison and B. L. Robison, *J. Amer. Chem. Soc.*, 1958, **80**, 3443.
[12] A. Albert and J. N. Phillips, *J. Chem. Soc.*, 1956, 1294.
[13] S. Gabriel and J. Colman, *Ber.*, 1900, **33**, 980.
[14] A. H. Gowenlock, G. T. Newbold, and F. S. Spring, *J. Chem. Soc.*, 1945, 622.
[15] F. J. Wolf, R. M. Wilson, and M. Tishler, *J. Amer. Chem. Soc.*, 1954, **76**, 2266.
[16] G. W. H. Cheeseman, *J. Chem. Soc.*, 1957, 3236.
[17] G. W. H. Cheeseman, *J. Chem. Soc.*, 1955, 1804.
[18] R. N. Castle, H. Ward, N. White, and K. Adachi, *J. Org. Chem.*, 1960, **25**, 570.
[19] K. Schofield and J. C. E. Simpson, *J. Chem. Soc.*, 1945, 512.
[20] E. Hayashi, T. Higashino, C. Iijima, Y. Kono, and T. Doihara, *J. Pharm. Soc. Japan*, 1962, **82**, 584.
[21] R. von Rothenburg, *J. prakt. Chem.*, 1895, **51**, 140.

Useful Reactions of Nucleophiles with Some Methylsulphonyl Derivatives of Nitrogen Heterocycles

By **G. B. Barlin** and **W. V. Brown**, Department of Medical Chemistry, John Curtin School of Medical Research, Australian National University, Canberra

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Useful Reactions of Nucleophiles with Some Methylsulphonyl Derivatives of Nitrogen Heterocycles

By G. B. Barlin and W. V. Brown, Department of Medical Chemistry, John Curtin School of Medical Research, Australian National University, Canberra

Methods are described for the preparation of hydroxy-, mercapto-, cyano-, amino-, methylamino-, n-propylamino-, and hydrazino-derivatives of pyridine, pyrazine, pyridazine, quinoline, isoquinoline, quinoxaline, cinnoline, and phthalazine by reaction of the corresponding methylsulphonyl compound with the appropriate nucleophile.

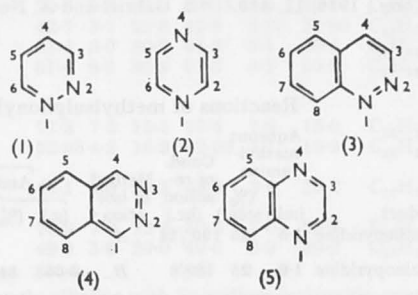
RECENT work [1,2] has shown that the methylsulphonyl derivatives of pyridine, pyrazine, pyridazine, quinoline, isoquinoline, quinoxaline, cinnoline, and phthalazine are about 40—100 times more reactive towards methoxide ions than are the corresponding chloro-compounds. These results suggested that other derivatives of these heterocycles could readily be prepared by the reaction of the methylsulphonyl compound with the appropriate nucleophile and an examination of these reactions was commenced.

The great potential usefulness of alkyl (or aryl) sulphonyl compounds as intermediates, because of their ease of synthesis and high reactivity, has been recognised by Shepherd and Fedrick,[3] and Brown and Ford,[4] but previous studies of nucleophilic displacements of methylsulphonyl (or alkyl- or aryl-sulphonyl) groups from derivatives of the ring systems discussed here have been restricted to a few isolated examples [3] and no systematic work has been undertaken. Forrest and Walker [5] observed the replacement of the methylsulphonyl group from substituted pyridines by methanol and ammonia to give methoxy- or amino-pyridines; the reactions of certain 3-methoxy-6-methylsulphonylpyridazines with sulphanilamide anions [6] have been examined; and replacement of the arylsulphonyl group from 3-arylsulphonylpyridazines by alkoxides,[7] by sodium hydrogen sulphide, and by alkyl mercaptides [8] has been observed.

In this study, the methylsulphonyl heterocycles were allowed to react with aqueous sodium hydroxide, aqueous sodium hydrogen sulphide, sodium cyanide in dimethylformamide, aqueous ammonia, aqueous ammoniacal ammonium chloride, aqueous methylamine, n-propylamine, and hydrazine hydrate.

With aqueous sodium hydroxide and aqueous sodium hydrogen sulphide, the methylsulphonyl compounds gave good yields of the hydroxy- (see Table 1) and mercapto-compounds, respectively; with sodium cyanide in boiling dimethylformamide, 4-methylsulphonylpyridine and 4-methylsulphonylcinnoline gave good yields of the cyano-compounds.

However, with ammonium hydroxide, variable results were obtained: 4-methylsulphonylpyridine with ammonium hydroxide at 185° gave a 69% yield of 4-aminopyridine but 3-methylsulphonylpyridazine with ammonium hydroxide at 100° gave 3-aminopyridazine (11%)



(1) Pyridazine; (2) Pyrazine; (3) Cinnoline; (4) Phthalazine; (5) Quinoxaline

and 3-hydroxypyridazine (60%). Addition of ammonium chloride to the aqueous ammoniacal mixture reduced the proportion of hydroxy-compound obtained, and increased that of the amino-compound.

The reactions of the methylsulphonyl compounds with aqueous methylamine (sometimes with added amine salt) and n-propylamine proceeded readily and in good yield (Tables 2 and 3). With hydrazine hydrate three selected methylsulphonyl compounds gave good yields of the hydrazino-compounds.

EXPERIMENTAL

Analyses were by Dr. J. E. Fildes and her staff. Solids for analysis were dried at 100° unless otherwise stated. Compounds were examined for the presence of impurities by paper chromatography on Whatman No. 1 paper with (*a*) 3% aqueous ammonium chloride and (*b*) butan-2-ol-5N-acetic acid (7 : 3) as solvent. Melting points were taken in ' Pyrex ' glass capillaries.

[1] G. B. Barlin and W. V. Brown, *J. Chem. Soc.* (*B*), 1967, 648.
[2] G. B. Barlin and W. V. Brown, *J. Chem. Soc.* (*B*), 1967, 736.
[3] R. G. Shepherd and J. L. Fedrick, *Adv. Heterocyclic Chem.*, 1965, **4**, 145.
[4] D. J. Brown and P. W. Ford, *J. Chem. Soc.* (*C*), 1967, 568.
[5] H. S. Forrest and J. Walker, *J. Chem. Soc.*, 1948, 1939.
[6] Reference 3, p. 199.
[7] H. G. Morren, *Belg. Pat.* 577,515/1959 (*Chem. Abs.*, 1960, **54**, 5715).
[8] H. G. Morren, *Belg. Pat.* 579,291/1959 (*Chem. Abs.*, 1960, **54**, 9968).

TABLE 1

Reactions of methylsulphonyl compounds (0·1 g.) with N-sodium hydroxide (3 ml.)

			Product						
			Hydroxy-compound			Picrate of hydroxy-compound			
			Yield			Yield			
Product	Conditions of reaction	Method of isolation [a]	(g.;	%)	M. p.	(g.;	%)	M. p.	Lit., m. p.
2-Hydroxypyridine (picrate)	145°/12 hr.	*A*				0·145	70	173—174°	170—172° [b]
4-Hydroxypyridine (picrate)	145/12 hr.	*A*				0·148	72	240—241	236—238 [c]
2-Hydroxypyrazine	90/2 hr.	*B*	0·030	50	186°				187—188 [d]
3-Hydroxypyridazine	90/1 hr.	*B*	0·035	58	105				103 [e]
4-Hydroxypyridazine	100/10 min.	*B*	0·042	69	248—249 [f]				250—251 [g]
2-Hydroxyquinoline	100/2 hr.	*C*	0·059	85	195—196 [f]				198—199 [h]
4-*Hydroxyquinoline* (*picrate*)	100/2 hr.	*A*				0·175	95	183—184	—
1-Hydroxyisoquinoline	100/2 hr.	*C*	0·055	79	207—208 [f]				208 [i]
2-Hydroxyquinoxaline	95/15 min. [k]	*C*		97					261—264 [k]
4-Hydroxycinnoline	100/30 min.	*C*	0·060	86	233—234 [f]				236 [l]
1-Hydroxyphthalazine	100/30 min.	*C*	0·058	83	184 [f]				182 [m]

[a] Methods of isolation were as follows: *A*, The reaction mixture was adjusted to pH 7 and the addition of aqueous picric acid gave yellow crystals of the picrate which were recrystallised from water; *B*, the reaction mixture was adjusted to pH *ca.* 7, evaporated to dryness, and the hydroxy-compound vacuum-sublimed from the residue at 100—130°/*ca.* 0·5 mm., except for 4-hydroxypyridazine which was sublimed at 200°/0·7 mm.; *C*, the reaction mixture was neutralised to pH 7 and on cooling there separated white crystals of the hydroxy-compound. [b] E. Shaw, *J. Amer. Chem. Soc.*, 1949, **71**, 67. [c] J. P. Wibaut and F. W. Broekman, *Rec. Trav. chim.*, 1959, **78**, 593. [d] A. E. Erickson and P. E. Spoerri, *J. Amer. Chem. Soc.*, 1946, **68**, 400. [e] Ref. 15. [f] No depression of the m. p. was observed on admixture with an authentic specimen. [g] K. Eichenberger, R. Rometsch, and J. Druey, *Helv. Chim. Acta*, 1956, **39**, 1755. [h] Ref. 16. [i] Found: C, 48·1; H, 2·6; N, 14·7. $C_9H_7NO{\cdot}C_6H_3N_3O_7$ requires C, 48·2; H, 2·7; N, 15·0%. When crystallised from absolute ethanol, a picrate, m. p. 225°, was obtained; this is probably 4-*hydroxyquinoline*,$\frac{1}{2}$(*picric acid*) (Found: C, 55·0; H, 3·3; N, 13·4. $C_9H_7NO,\frac{1}{2}C_6H_3N_3O_7$ requires C, 55·5; H, 3·3; N, 13·5%). [j] A. Albert and J. N. Phillips, *J. Chem. Soc.*, 1956, 1294. [k] G. W. H. Cheeseman, *J. Chem. Soc.*, 1957, 3236. [l] N. J. Leonard and S. N. Boyd, *J. Org. Chem.*, 1946, **11**, 419. [m] S. Gabriel and A. Neumann, *Ber.*, 1893, **26**, 521.

TABLE 2

Reactions of methylsulphonyl compounds (0·1 g.) with aqueous methylamine

					Product							Analyses of product (%)						
	Aqueous methyl-amine		Cond. of re-action	Method of isol-ation [a]	Amine			Amine picrate			Lit. m. p.	Found			Calculated			Molecular formula
Product	(ml.)	(% soln.)	(hr.)		(g.)	(%)	M. p.	(g.)	(%)	M. p.		C	H	N	C	H	N	
2-Methylaminopyridine (picrate)	1·5	25	190°/24	*A*				0·129	60	191—192°	192—193° [b]							
4-Methylaminopyridine	1·0	25	180/6	*B*	0·058	84	126°				124·5—125 [c]							
3-*Methylaminopyridazine* (*picrate*)	3·0	30	110/6	*A*				0·092	43	209		38·8	3·0	24·8	39·1	3·0	24·85	$C_{11}H_{10}N_6O_7$
	2·0 [d]	25	100/18	*A*				0·139	65	208—209								
4-*Methylaminopyridazine*	2·0 [d]	40	100/15	*B* [e]	0·013	19	77—78					55·4	6·5	38·1	55·0	6·5	38·5	$C_5H_7N_3$
4-*Methylaminopyridazine* (*picrate*)	2·0 [d]	40	100/15	*A*				0·168	78	192—193		39·0	2·9	24·6	39·1	3·0	24·85	$C_{11}H_{10}N_6O_7$
4-Methylaminoquinoline	2·0	25	170/15	*C*	0·061	80	228—229 [f]				224 [g]	75·5	6·3	17·5	75·9	6·4	17·7	$C_{10}H_{10}N_2$
1-*Methylaminoisoquinoline* (*picrate*)	2·0 [d]	40	140/15	*A*				0·141	76	197—198		49·4	3·4	18·2	49·6	3·4	18·1	$C_{16}H_{13}N_5O_7$
4-Methylaminocinnoline	2·0	25	90/18	*C*	0·049	64	228—230 [h]				229 [i]							
4-*Methylaminocinnoline* (*picrate*)	2·0	25	90/18	*A*				0·173	92	253—255 [j]		46·4	3·0	21·5	46·4	3·1	21·65	$C_{15}H_{12}N_6O_7$

[a] Methods of isolation were as follows: *A*, the reaction mixture was boiled to remove excess of methylamine and aqueous picric acid added to precipitate the picrate which was then recrystallised from water. *B*, The reaction mixture was made strongly alkaline with 5N-sodium hydroxide, evaporated to dryness, and the residue was extracted with boiling benzene and the product recrystallised from benzene–light petroleum (b. p. 60—80°). *C*, A white precipitate separated from the reaction mixture. [b] L. Pentimalli, *Gazzetta*, 1964, **94**, 458. [c] J. P. Wibaut and F. W. Brockman, *Rec. Trav. chim.*, 1961, **80**, 309. [d] 10N-Hydrochloric acid (0·25 ml.) was also added to the reaction mixture. [e] Product not recrystallised but sublimed at 100°/0·5 mm. [f] Product recrystallised from benzene. [g] Y. Suzuki, *J. Pharm. Soc. Japan*, 1961, **81**, 1146. [h] It was recrystallised from water. A depression of the m. p. was observed on admixture with 4-hydroxycinnoline of m. p. 236°. [i] C. M. Atkinson and A. Taylor, *J. Chem. Soc.*, 1955, 4236. [j] The product was recrystallised from ethanol.

Reactions of Methylsulphonyl Compounds with Aqueous Sodium Hydroxide.—The methylsulphonyl compound (0·1 g.) and N-sodium hydroxide (3 ml.) were heated together. The conditions of reaction, methods of isolation, and yields are summarised in Table 1.

Reactions of Methylsulphonyl Compounds with Aqueous Sodium Hydrogen Sulphide.—3-*Mercaptopyridazine.* 3-Methylsulphonylpyridazine (0·100 g.) and aqueous sodium hydrogen sulphide (2 ml.; 1N) were heated in a sealed tube at 100° for 2 hr. The mixture was adjusted to pH 2 and extracted with chloroform to give 3-mercaptopyridazine (0·070 g.; 85%) which crystallised from water and had m. p. 169—170° (lit.,[9] 170°).

4-*Mercaptoquinoline.* 4-Methylsulphonylquinoline (0·100 g.) and sodium hydrogen sulphide (2 ml.; 1N) were heated

[9] G. F. Duffin and J. D. Kendall, *J. Chem. Soc.*, 1959, 3789.

in a sealed tube at 100° for 15 hr. The mixture was adjusted to pH 4, cooled, and the solid filtered off and sublimed (160°/0·7 mm.) to give 4-mercaptoquinoline (0·068 g.; 81%), m. p. 158—160° (lit.,[10] 158—162°).

2-Mercaptoquinoxaline. 2-Methylsulphonylquinoxaline (0·100 g.) and aqueous sodium hydrogen sulphide (2 ml.; N) were heated in a sealed tube at 100° for 1 hr. The mixture was adjusted to pH 6 and chilled to give 2-mercaptoquinoxaline (0·072 g.; 86%), m. p. 203—204° (lit.,[11] 204—205°).

Reactions of Methylsulphonyl Compounds with Sodium Cyanide in Dimethylformamide.—4-Cyanopyridine. 4-Methylsulphonylpyridine (0·200 g.) and sodium cyanide (0·100 g.) in dimethylformamide (5 ml.) were refluxed for 1 hr. The dimethylformamide was distilled under reduced pressure and the residue treated with aqueous picric acid to give 4-cyanopyridine picrate (0·318 g.; 75%). It was recrystallised from water and had m. p. 197—199° (lit.,[12] 198—199°).

4-Cyanocinnoline. 4-Methylsulphonylcinnoline (0·150 g.) and sodium cyanide (0·050 g.) in dimethylformamide (3 ml.) were refluxed for 5 min., and the dimethylformamide was distilled under reduced pressure. The residue was extracted three times with boiling benzene and the product crystallised from benzene–light petroleum (b. p. 60—80°) to give *4-cyanocinnoline* (0·076 g.; 68%) as an orange solid, m. p. 139—140° (Found: C, 70·0; H, 3·5; N, 27·0. $C_9H_5N_3$ requires C, 69·7; H, 3·25; N, 27·1%).

Reactions of Methylsulphonyl Compounds with (a) *Aqueous Ammonia and* (b) *Aqueous Ammoniacal Ammonium Chloride.—4-Methylsulphonylpyridine with aqueous ammonia.* 4-Methylsulphonylpyridine (0·200 g.) and ammonium hydroxide (3 ml.; *d*, 0·91) were heated at 185° for 6 hr. The mixture was boiled to remove most of the ammonia then adjusted to pH 4 and extracted with chloroform to remove any unchanged 4-methylsulphonylpyridine. The solution was then made strongly alkaline by addition of 5N-sodium hydroxide, evaporated to dryness, and the residue extracted with boiling benzene to give, after crystallisation from benzene–light petroleum (b. p. 60—80°), 4-aminopyridine (0·083 g.; 69%). It was sublimed (100°/0·7 mm.) and had m. p. 155—157° (lit.,[13] 158°) not depressed on admixture with an authentic specimen.

3-Methylsulphonylpyridazine with aqueous ammonia.—3-Methylsulphonylpyridazine (0·200 g.) and ammonium hydroxide (6 ml.; *d*, 0·91) were heated in a sealed tube at 100° for 15 hr. The mixture was then boiled to remove ammonia, cooled, and divided into two equal parts. To the first part aqueous picric acid was added to give 3-aminopyridazine picrate (0·024 g.; 11%), m. p. 250—251° (from water) (lit.,[14] 249—250°). The second part was adjusted to pH 2 evaporated to dryness and the residue sublimed (100°/0·7 mm.) to give 3-hydroxypyridazine (0·036 g.; 60%), m. p. 102° (lit.,[15] 103°).

3-Methylsulphonylpyridazine with aqueous ammoniacal ammonium chloride. 3-Methylsulphonylpyridazine (0·100 g.)., ammonium hydroxide (3 ml.; *d*, 0·91), and ammonium chloride (0·32 g.) were heated at 110° for 12 hr. The mixture was then boiled to remove ammonia and addition of aqueous picric acid gave 3-aminopyridazine picrate (0·085 g.; 42%), m. p. 249—250°.

2-Methylsulphonylquinoline with aqueous ammonia. 2-Methylsulphonylquinoline (0·100 g.) and ammonium hydroxide (2 ml.; *d*, 0·91) were heated at 140° for 15 hr.

TABLE 3

Reactions of methylsulphonyl compounds (0·1 g.) with n-propylamine (1 ml.)

Product [a]	Conditions of reaction (hr.)	Product: Amine (%)	Product: Amine M. p.	Product: Amine picrate (%)	Product: Amine picrate M. p.	Solvent for recryst.	Analyses of product [b] (%): Found C	Found H	Found N	Calculated C	Calculated H	Calculated N	Molecular formula
2-n-Propylaminopyridine (picrate)	165°/80			76	150—152° [c]	1	46·1	4·0	19·2	46·0	4·1	19·2	$C_{14}H_{15}N_5O_7$
4-n-Propylaminopyridine	165/48	67	73—74°			2	70·6	9·0	20·7	70·55	8·9	20·6	$C_8H_{12}N_2$
2-n-Propylaminopyrazine (picrate)	150/18			63	176—177	3	42·7	3·7	22·6	42·6	3·85	22·95	$C_{13}H_{14}N_6O_7$
3-n-Propylaminopyridazine	150/12	93	85			2	61·4	8·0	30·2	61·3	8·1	30·6	$C_7H_{11}N_3$
4-n-Propylaminopyridazine	111/18	71	109			2	61·4	8·2	30·3	61·3	8·1	30·6	$C_7H_{11}N_3$
2-n-Propylaminoquinoline (picrate)	145/12			76	196—197 [d]	3							
4-n-Propylaminoquinoline	160/36	78	173—174			4	77·3	7·5	15·1	77·4	7·6	15·0	$C_{12}H_{14}N_2$
1-n-Propylaminoisoquinoline (picrate)	160/36			71	203—204	1	52·05	4·2	16·9	52·05	4·1	16·9	$C_{18}H_{17}N_5O_7$
2-n-Propylaminoquinoxaline (picrate)	110/12			70	178—179	5	49·1	4·0	20·3	49·0	3·9	20·2	$C_{17}H_{16}N_6O_7$
4-n-Propylaminocinnoline	110/12	74	169—170			6	70·9	7·0	22·4	70·6	7·0	22·4	$C_{11}H_{13}N_3$
1-n-Propylaminophthalazine (picrate)	70/30 min.			39	138—139	5	49·0	3·6	20·0	49·0	3·9	20·2	$C_{17}H_{16}N_6O_7$

[a] The method of isolation was as follows: the reaction mixture was made strongly alkaline with 5N-sodium hydroxide, evaporated to dryness, the residue extracted with boiling benzene (3×) and the benzene evaporated. The product was sublimed or distilled on to a cold-finger condenser at *ca.* 100—120°/0·5 mm. It was then either recrystallised or the picrate prepared as indicated; solvents for recrystallisation were (1) aqueous ethanol, (2) benzene–hexane, (3) ethanol, (4) hexane, (5) water, (6) benzene–cyclohexane. [b] Compounds melting below 130° were dried for analysis at 20°/0·5 mm. [c] A. R. Katritzky and A. J. Waring, *J. Chem. Soc.*, 1962, 1544 give m. p. 149—150·5° but K. H. Slotta and W. Franke, *Ber.*, 1930, **63**, 678 give m. p. 163°. [d] N. G. Luthy, F. W. Bergstrom, and H. S. Mosher, *J. Amer. Chem. Soc.*, 1949, **71**, 1109 give m. p. 196—196·5°.

[10] A. Albert and G. B. Barlin, *J. Chem. Soc.*, 1959, 2384.
[11] F. J. Wolf, R. M. Wilson, and M. Tishler, *J. Amer. Chem. Soc.*, 1954, **76**, 2266.
[12] E. Ochiai and Y. Suzuki, *Pharm. Bull.* (*Tokyo*), 1954, **2**, 247.
[13] B. Emmert and W. Dorn, *Ber.*, 1915, **48**, 687.
[14] E. A. Steck, R. P. Brundage, and L. T. Fletcher, *J. Amer. Chem. Soc.*, 1954, **76**, 3225.
[15] R. F. Homer, H. Gregory, W. G. Overend, and L. F. Wiggins, *J. Chem. Soc.*, 1948, 2195.

The mixture was boiled to remove ammonia and on cooling there separated 2-hydroxyquinoline (0·043 g.; 63%), m. p. 197—198° (lit.;[16] 198—199) not depressed on admixture with an authentic specimen. Addition of aqueous picric acid to the filtrate gave 2-aminoquinoline picrate (0·039 g.; 22%), m. p. 256—257 (from ethanol) (lit.,[17] 255—256°).

2-Methylsulphonylquinoline with aqueous ammoniacal ammonium chloride. 2-Methylsulphonylquinoline (0·100 g.), ammonium hydroxide (3 ml.; *d*, 0·91), and ammonium chloride (0·16 g.) were heated at 140° for 15 hr. The solution was boiled to remove ammonia and addition of aqueous picric acid gave 2-aminoquinoline picrate (0·090 g.; 50%), m. p. 257—258°.

4-Methylsulphonylcinnoline with aqueous ammonia. 4-Methylsulphonylcinnoline (0·100 g.) and ammonium hydroxide (2 ml.; *d*, 0·91) were heated in a sealed tube at 100° for 15 hr. and on cooling there precipitated 4-aminocinnoline (0·032 g.; 46%), m. p. 213—214° (from water), (lit.,[18] 212—213°). The filtrate was boiled to remove excess of ammonia and addition of aqueous picric acid gave 4-aminocinnoline *picrate* (0·030 g.; 17%), m. p. 280° (Found: C, 45·3; H, 2·8; N, 22·3. $C_{14}H_{10}N_6O_7$ requires C, 44·9; H, 2·7; N, 22·5%).

Reactions of Methylsulphonyl Compounds with n-Propylamine and Aqueous Methylamine.—The results and conditions of reaction of methylsulphonyl compounds (0·1 g. each) with aqueous methylamine and liquid n-propylamine are listed in Tables 2 and 3, respectively.

Reactions of Methylsulphonyl Compounds with Hydrazine Hydrate.—*2-Hydrazinoquinoline.* 2-Methylsulphonylquinoline (0·100 g.) and hydrazine hydrate (2 ml.; 98%) were refluxed for 1 hr. The mixture was concentrated and the residue diluted with water, boiled, and on cooling there separated 2-hydrazinoquinoline (0·062 g.; 81%), m. p. 142—143° (lit.,[19] 142—143°).

2-Hydrazinoquinoxaline. 2-Methylsulphonylquinoxaline (0·100 g.) and hydrazine hydrate (2 ml.; 98%) were refluxed for 45 min. and the mixture diluted with hot water (5 ml.). On cooling there separated crystals of 2-hydrazinoquinoxaline (0·051 g.; 67%), m. p. 166° (lit.,[20] 167°).

4-Hydrazinocinnoline. 4-Methylsulphonylcinnoline (0·100 g.) and hydrazine hydrate (2 ml.; 98%) were refluxed for 1 hr., the mixture was diluted with water, and on cooling 4-hydrazinocinnoline (0·070 g.; 91%) separated. It was recrystallised from aqueous ethanol as orange red plates and had m. p. 285° (decomp.) (lit.,[21] 229 and 301°) (Found: C, 59·8; H, 4·9; N, 34·9. Calc. for $C_8H_8N_4$: C, 60·0; H, 5·0; N, 35·0%).

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[16] P. Friedländer and H. Ostermaier, *Ber.*, 1881, **14**, 1916.
[17] A. E. Chichibabin and E. W. Sazepina, *J. Russ. Phys. Chem. Soc.*, 1918, **50**, 553 (*Chem. Zentr.*, 1923, *III*, 1023).
[18] J. R. Keneford, K. Schofield, and J. C. E. Simpson, *J. Chem. Soc.*, 1948, 358.
[19] W. H. Perkin and R. Robinson, *J. Chem. Soc.*, 1913, 1973.
[20] K. Asano, *J. Pharm. Soc. Japan*, 1958, **78**, 729.
[21] K. Alder and H. Niklas, *Annalen*, 1954, **585**, 97.