A STUDY OF THE SULPHONES AND SULPHOXIDES OF PYRIMIDINE AND RELATED HETEROCYCLES

a thesis

submitted for the

Degree of Doctor of Philosophy

in the

Australian National University

by

PHILLIP WILTON FORD

Department of Medical Chemistry

John Curtin School of Medical Research

Australian National University

February, 1968

CORRECTIONS

A Study of the Sulphones and Sulphoxides of Pyrimidine and related Heterocycles by P.W.Ford

p.5 line 20 for "4-p-acetamidophenyl-" read "4-p-acetamidophenylsulphonyl"

p.6 line 21 for "This" read "The instability"

p.7 line 3 for "This" read "The delocalization"

p.36 Table 6 in $4MeSO_2$ entry

for	6.63 ± 0.13	read 66.3 ± 1.3
	7.30 ± 0.11	73.0 ± 1.1
	8.64 ± 0.08	86.4 ± 0.08

p.37 Table 7 for " $2MeSO_2$ 8.8 -34" read 9.1 -43"

for " $4MeSO_2$ 7.8 -51" read " 7.8 -43"

p.43 footnote a) for "CH_3SO_2, 6.63; CH_3SO, 6.93"

read "CH_3SO_2, 6.87; CH_3SO, 7.03".

p.46 lines 3 and 4 delete "two doublets and triplet" insert "two triplets"

p.46 line 11 for "2,4-diamino-3-cyanopent-2-ene"

read " 2-amino-3-cyanopent-2-ene-4-imine"

p.55 delete "A number ..... was"

insert "Several 2-p-substituted-phenylsulphonyl- and -phenylsulphinyl-pyrimidines were".

p.101 line 9 insert "; the values were kindly determined by Mr. I. Pavelic."

Bibliography: insert " D.D.Perrin, 1965. Adv. Heterocyclic Chem., 4, 53-57."

22/2/13 (~~OUT~~BOUND) XEROX SUPP. TO BURROUGHS WELLCOME CO.
(3030 CORNWALLIS RD., RESEARCH TRIANGLE
PARK, N.C. 27709, USA)

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.

Phillip Ford.

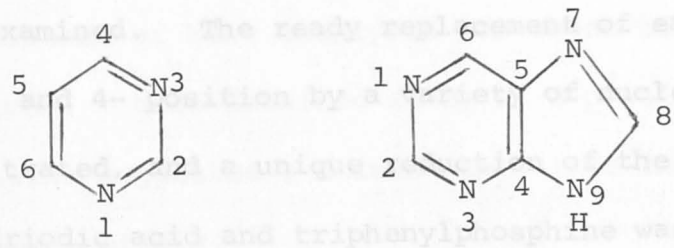
ACKNOWLEDGMENTS

I thank Dr. D.J. Brown for his most helpful supervision and encouragement, and Professor Adrien Albert for his interest in the work described. I am grateful to Dr. W.L.F. Armarego, Dr. T.J. Batterham, Dr. M.E.C. Biffin, Dr. D.D. Perrin and Dr. E. Spinner for helpful discussions. The fresh and iconoclastic comments of my colleague for two years, Dr. M.N. Paddon-Row have been invaluable. Dr. S. Middleton (Monash University), Dr. Q.N. Porter (University of Melbourne) and Dr. J. McLeod (Research School of Chemistry, A.N.U.) kindly determined the mass spectra.

I gratefully acknowledge the award of a C.S.I.R.O. Senior Postgraduate Studentship and wish to thank Mrs. K. English who typed this thesis.

NOMENCLATURE

Pyrimidine (a), and purine (b) are numbered as shown.



(a) (b)

The general nomenclature of the International Union of Pure and Applied Chemistry* is used and all substituents are written in alphabetical order as prefixes to the parent name. Those compounds which bear potentially tautomeric substituents in positions adjacent to a ring nitrogen are named conveniently as hydroxy, mercapto or amino derivatives, regardless of tautomeric form.

---

* The Chemical Society, "Handbook for Chemical Society Authors", London, 1960.

SUMMARY

Syntheses of 2-, 4-, and 5-methylsulphonylpyrimidine; 2-, 4-, and 5-methylsulphinylpyrimidine; 2-phenylsulphonylpyrimidine and 2-phenylsulphinylpyrimidine were carried out and the physical properties of the products were examined. The ready replacement of each group in the 2- and 4- position by a variety of nucleophiles was demonstrated, and a unique reduction of the 2-sulphones by hydriodic acid and triphenylphosphine was discovered. The kinetics of the displacement of the 2- and 4-sulphones and sulphoxides by pentylamine and cyclohexylamine were measured. Both groups proved to be more easily displaced from the 2-position than chlorine. The 4-sulphones and sulphoxides were more reactive than their 2-isomers.

5-Methylsulphonyl- and 5-methylsulphinyl-pyrimidine underwent ring opening when heated with amines without added solvent to give 2-methylsulphonyl-1,3-dipentyliminopropane and its analogues; the mechanism proposed involves attack by the amine at C-4 of the pyrimidine. Covalent hydration was demonstrated in the cations of the 5-sulphone and the 5-sulphoxide.

Several 2-p-substituted-phenylsulphonylpyrimidines and the corresponding sulphoxides were prepared. The

Hammett plots for their hydrolyses to 2-hydroxypyrimidine by aqueous sodium hydroxide were characterised by small values of the reaction constant (ρ); this implied poor transmission of electronic effects by the sulphone and sulphoxide groups. Both groups underwent pentylaminolysis and evidence of base catalysis was observed in two such reactions. More detailed study of 2-*p*-tolylsulphonylpyrimidine suggested a Meisenheimer-like intermediate in the aminolysis.

Methylation of 2-, 6-, and 8-methylthiopurine with diazomethane in ether was carried out and all the products were identified. The derived sulphones and sulphoxides were too unstable for precise measurement of the rates of their aminolysis, but approximate comparisons for displacement of methylthio and methylsulphonyl groups from purines were obtained. 3,9-Dimethyl-6-methylthiopurine underwent ring opening to give a substituted imidazole.

Solvent effects observed in the proton magnetic resonance spectra of the N-methylpurines proved useful in the assignment of structure. Such effects were shown to arise from the solute-induced reaction field; similar effects were seen to operate in several pyridines.

CONTENTS

(Chapter 5 continued)

Chapter 1

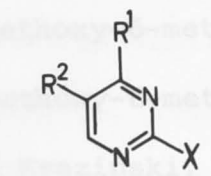
INTRODUCTION

The chemistry of pyrimidine sulphones and sulphoxides may be considered as both a study in pyrimidine chemistry *per se* and as an examination of some questions in the field of aromatic nucleophilic substitution reactions. This chapter begins with a historical note on previous work on the pyrimidine sulphones and sulphoxides followed by a brief discussion of several topics to which the results obtained will be related. These topics are the ease of displacement of methylsulphonyl and methylsulphinyl groups, the variation in reactivity with position in the pyrimidine ring and the mechanism of aromatic nucleophilic substitution in nitrogen heterocycles.

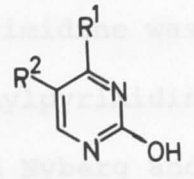
1. Preparation and Reactions of Pyrimidine Sulphones and Sulphoxides.

Sprague and Johnson, (1935) first investigated the alkylsulphonylpyrimidines, by preparing a series of 4 and/or 5 substituted 2-ethylsulphonylpyrimidines

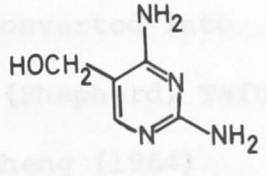
(1a-g, X=SO_2Et) by the action of chlorine on an aqueous suspension of the 2-ethylthiopyrimidines (1a-g, X=SEt) at a controlled low temperature [(higher temperatures led to the replacement of the ethylsulphonyl group by a chloro group: (1f, X=SO_2Et)→(1f, X=Cl)] . They recorded the acid hydrolysis of each sulphonylpyrimidine (1a-g, X=SO_2Et) to the corresponding 2-hydroxypyrimidine (11a-g) and later (Sprague and Johnson, 1936 and 1938), the displacement of the ethylsulphonyl group by aniline, ammonia, and hydroxide ion to give the corresponding 2-anilino-, amino-, and hydroxypyrimidines. Reduction of the sulphones with unspecified reagents was unsuccessful. The above methods (chlorine-water; chlorine-methanol) could not be extended to 2-ethylsulphonyl-4-hydroxypyrimidine from which uracil was the only product isolated (Sprague and Johnson, 1938), but were successful with other pyrimidines. Thus 5-acetoxymethyl-4-amino-2-methylthiopyrimidine was oxidised to the sulphone by chlorine and the methylsulphonyl group was displaced by ammonia with removal of the protecting acetyl group simultaneously (Nairn and Tieckelmann, 1960) to give the pyrimidine (III) (the protecting group was



(I)

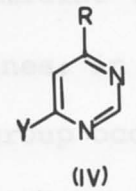


(II)

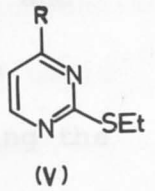


(III)

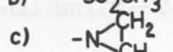
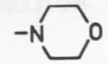
	R^1	R^2
a)	OEt	Me
b)	Cl	Me
c)	OEt	Br
d)	Cl	Br
e)	Cl	CO_2Et
f)	NH_2	CO_2Et
g)	OEt	H



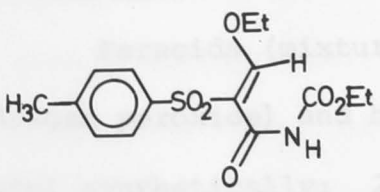
(IV)



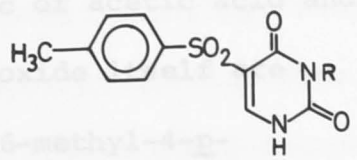
(V)

	R
a)	$-SCH_3$
b)	$-SO_2CH_3$
c)	
d)	$-N(CH_3)_2$
e)	$-NH-C_6H_4Br$
f)	

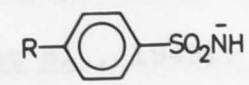
	R
a)	NH_2
b)	OEt
c)	OMe
d)	Cl



(VI)



(VII)



(VIII)

essential because no sulphone was isolated from the action of chlorine on the 5-hydroxymethylpyrimidine); 4-methoxy-6-methylthiopyrimidine was converted into 4-methoxy-6-methylsulphonylpyrimidine (Shepherd, Taft, and Krazinski, 1961); and Nyberg and Cheng (1964) oxidised 4-chloro-6-methylthiopyrimidine (IVa, Y=Cl) to the 6-methylsulphonylpyrimidine (IVb, Y=Cl) and allowed it to react with amines: in every case displacement of the chloro group occurred giving the amines (IVc-f, Y=SO_2Me). Sodium hypochlorite may also be used in this reaction. For example, 4,6-diamino-2-methylthiopyrimidine gave 4,6-diamino-2-methylsulphonylpyrimidine, but the methylsulphonyl group could not be replaced by a variety of amines or ammonia (Todd et al., 1949).

Peracids (mixtures of formic or acetic acid and hydrogen peroxide) and hydrogen peroxide itself are useful synthetically: 2-acetamido-6-methyl-4-p-nitrophenylthiopyrimidine was converted into the corresponding sulphone by peracetic acid at room temperature (Feld'man et al., 1949); Profft and Sitter (1963) oxidised 4-methyl-2-methylthio-6-phenylthiopyrimidine

to the disulphone with acetic acid/hydrogen peroxide mixtures; and 2-amino-5-p-nitrophenylthiopyrimidine was converted similarly into the 5-p-nitrophenyl sulphone (Yanagita, 1949). Hydrogen peroxide in ethanol converted each 4-substituted-2-ethylthiopyrimidine (Va-d) (Chi and Ling, 1956) to the sulphone and the ethylsulphonyl group was then displaced by ammonia to give the corresponding amino derivative or hydrolysed under acidic or basic conditions to the 2-hydroxypyrimidine. A fourth preparative method is the displacement of chloro groups by sulphinate anion although the postulated rearrangement (Brown, 1962a) may be unnecessary because attack by S rather than O appears to be the general rule. Thus 2-amino-4-chloro-6-methylpyrimidine on heating with sodium p-toluenesulphinate gave 2-amino-4-methyl-6-p-tolylsulphonylpyrimidine; 2,4-dichloro-6-methylpyrimidine gave the 4-methyl-2,6-bistolylsulphonylpyrimidine under similar conditions (Ohta and Suido, 1951); and 2-amino-4-chloro-6-methylpyrimidine reacted with p-acetamidosulphonamide anion (VIII, R=CH_3CONH-) to give 4-p-acetamidophenyl-2-amino-6-methylpyrimidine (Semenoský and Černý, 1951).

Few examples of 5-sulphones or sulphoxides of pyrimidine are known: chromium trioxide/acetic acid oxidised 2-acetamido-5-p-nitrophenylthiopyrimidine to a mixture of the 5-p-nitrophenyl-sulphonyl (and -sulphinyl)pyrimidines (Caldwell, 1952), and 2,4-dihydroxy-5-methylthiopyrimidine gave the corresponding 5-methylsulphinyl-pyrimidine with peracetic acid at -15°; at 0° it reacted further to give the sulphone in good yield (Bretschneider and Egg, 1967). This series of 5-alkylsulphonylpyrimidines was extended by oxidation of the corresponding 5-alkylthio-2,4-dihydroxypyrimidines with potassium permanganate. Fuming nitric acid in acetic acid gave the analogous 5-alkylsulphinylpyrimidines (Carpenter and Shaw, 1965), and cyclization with ammonia or primary amines of the ethoxyethylene derivative of p-tolylsulphonylacetylurethane (VI) yielded the 5-p-tolylsulphonyl-uracils (VII) (Shaw, Atkinson and Sugowdz, 1957). These three examples constitute the only known exceptions to the general observation that a hydroxyalkylsulphonylpyrimidine is too unstable to be isolated. This is probably due to the considerable stabilisation of the intermediate produced by nucleophilic

attack on the sulphone, through delocalisation of the negative charge on to the oxygen of the hydroxy group. This can occur only if the hydroxy and sulphonyl groups bear a meta relation to each other; with either group in the 5 position the other group cannot be meta to it.

Apart from the attempted nucleophilic displacements listed above, the only known substitution reactions of the sulphone group involve the use of sulphanilamide anion (VIII, R=NH_2), its acetyl derivative (VIII, R=$NHCOCH_3$), or the nitro compound (VIII, R=NO_2) (which may be reduced to the amine without reduction of the pyrimidine ring) (Yanagita and Futaki, 1952), all leading to pharmologically useful pyrimidine sulphonamides. For instance, 2,4-dimethoxy-6-methylsulphonylpyrimidine reacted with sodium salt of sulphanilamide to give the corresponding 6-sulphanilamidopyrimidine (Taft and Shepherd, 1962) and 4,5-dimethoxy-6-phenylsulphonylpyrimidine (Hoffman-LaRoche, 1964) and a series of 2-alkylsulphonyl-5-methoxypyrimidines (Spofa, 1964) reacted similarly with sulphanilamide anion to produce the corresponding sulphanilamidopyrimidines.

2. Positional Reactivity of the Pyrimidine Ring

The positional variation in reactivity of pyrimidine in nucleophilic substitution reactions has been the subject of a considerable number of qualitative comparisons leading to the reactivity order 4 > 2 ≫ 5 (Brown, 1962b), based on preparative reactions. However only two kinetic studies have been conducted: the reactivity order in the piperidino-dechlorination of several chloroalkylpyrimidines was 4 > 2 (Chapman and Rees, 1954), while displacement of halogen from several simple halogeno-pyrimidines by *p*-nitrophenolate anion (Miller and Chan, 1967) led to the same conclusion, although the simple chloropyrimidines gave the reactivity order 2 > 4 > 5, a result attributed to acid catalysis being more effective in the ortho position.

Examination of the preparative kinetics of the aminolyses of chloro-, alkoxy- and alkylthio-pyrimidines (Brown and Lyall, 1965; Brown and Foster, 1966) lead to the order 4 > 2, but interpretation of their data is uncertain as good first order kinetics were observed under conditions (amine: pyrimidine, 2-3:1) expected to give second order kinetics. A considerable change in

dielectric constant of the medium is also expected to occur during the reaction due to the liberation of alkanols, alkylthiols or hydrochloric acid.

The apparently greater ease of replacement of substituents at the 4-position (relative to those at the 2-position) is of considerable interest. The 2-position has been shown to be more electron deficient than the 4-position, by means of nuclear quadrupole resonance studies of ^{35}Cl substituents (Dewar and Lucken, 1958), and the ^{13}C-H coupling constants of simple methylpyrimidines (Reddy, Hopgood and Goldstein, 1962). Both the π-electron density and the localization energy (R. D. Brown and Heffernan, 1956) calculated from the molecular orbital method with inclusion of the relative electronegativity parameter predict the reactivity order $2 > 4 > 5$, for nucleophilic attack. Furthermore, S.C.F. L.C.M.O. calculations (Newton, Boer, and Lipscomb, 1966) led to the same conclusion of greater π-electron deficiency at 2-C. Thus both a simple coulombic theory of nucleophilic substitution (Albert, 1959), and the assumption that stabilisation of a transition state formed by donation of a lone pair

to the heterocyclic ring depends directly on the electron density at that position in the ground state, require that the 2-position be more reactive than the 4-position. This deduction contradicts the experimental results. A number of explanations have been suggested for the greater activating influence of a γ-nitrogen:

(i) repulsion between lone pairs on the ring nitrogen atom(s) and the incoming nucleophile (Edwards and Pearson, 1962).

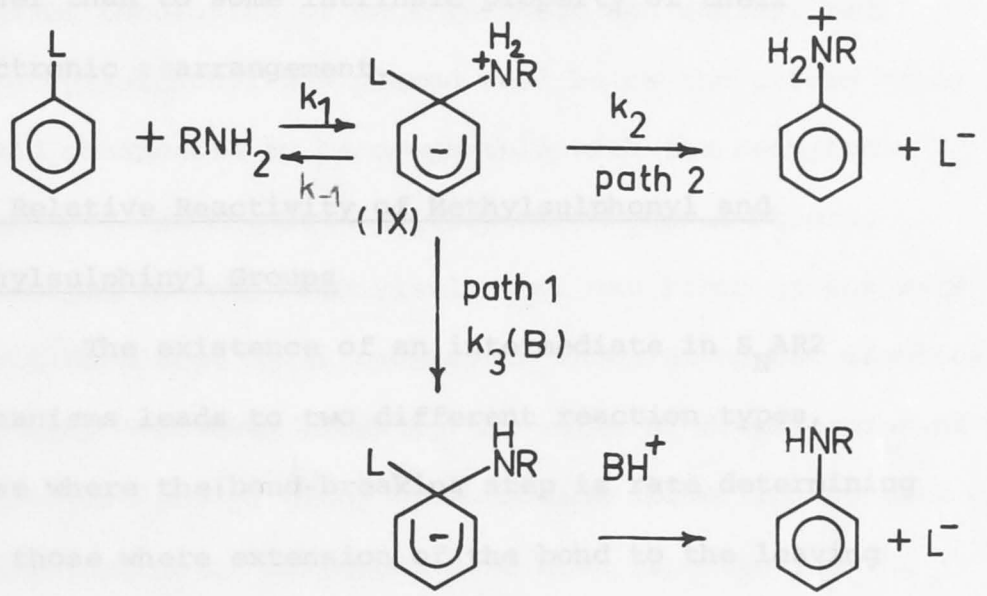
(ii) greater stability of the pentadienide anion with nitrogen in the centre (Shepherd and Fedrick, 1965b)

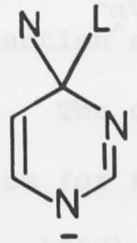
(iii) considering the intermediate (X) as having a p-quinonoid structure and hence being more stable than the corresponding o-quinonoid structure (XI) (Chapman and Rees, 1954).

However explanation (iii) appears to be invalid for the following reasons:

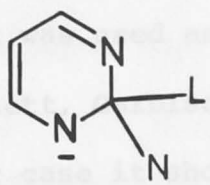
(i) Analogies between structures such as (X) and p-quinone are false as (X) lacks the cyclic conjugated system of p-quinone involving four filled bonding molecular orbitals. (X) has two filled bonding orbitals and one filled non-bonding orbital and lacks cyclic conjugation.

SCHEME. 1





(X)



(XI)

N = Attacking Nucleophile .

L = Leaving Group.

(ii) The greater stability of p-quinone relative to o-quinone may be due to the smaller dipole-dipole repulsions between the two C=O bonds in p-quinone rather than to some intrinsic property of their electronic rearrangement.

3. Relative Reactivity of Methylsulphonyl and Methylsulphinyl Groups

The existence of an intermediate in S_NAR2 mechanisms leads to two different reaction types, those where the bond-breaking step is rate determining and those where extension of the bond to the leaving group is not involved in the formation of the transition state, implying that for reactions in this latter class the reaction rate should be independent of the leaving group. The converse of this argument was used as evidence for the S_NAR2 mechanism (Bunnett, Garbisch, and Pruitt, 1957). However, in the former case it should be possible to define a sequency of "displaceability" which should be independent of the aromatic substrate and the attacking nucleophile except in cases of considerable "hardness" disparity (Pearson, 1962).

The literature is contradictory on the relative rates of displacement of chloro and methylsulphonyl groups (methylsulphinyl has hardly been considered). In the major tabulation of data (Bunnett and Zahler, 1951) methylsulphonyl was placed well below the chloro group and considered to be comparable with the methylthio group. In the 2,4-dinitrobenzene series chloro, methylsulphonyl, methylsulphinyl and bromo groups were all displaced by thiophenoxide anion at almost identical rates. However recently the rates of displacement of methylsulphonyl group by methoxide anion from several heteroaromatic compounds have been reported (Barlin and W.V. Brown, 1967). Comparison of this data with earlier results on the corresponding chloro compounds (Chapman and Russell-Hill, 1956; Hill and Krause, 1964) shows the greater displaceability of the methylsulphonyl group.

Some preparative results indicate that the relative order of displaceability is dependent upon the nucleophile. The methylsulphonyl group was more easily displaced by sulphanilamide anion than was either a trimethylammonium or a chloro substituent

from the 4-substituted-6-methoxypyrimidine (Taft and Shepherd, 1962). On the other hand, in 4-chloro-6-methylsulphonylpyrimidines the chloro group was displaced preferentially by a variety of amines* (Nyberg and Cheng, 1964).

In some cases the apparently greater reactivity of the methylsulphonyl group is sufficient to reverse the normal (see earlier) reactivity order (4 > 2), 4,6-dichloro-2-methylsulphonylpyrimidine reacted with sodium hydroxide to give 4,6-dichloro-2-hydroxypyrimidine (Koppel et al., 1961) and with ethyleneimine to give the 2-aziridino-4,6-dichloropyrimidine. Yet several 6-chloro-2-methylsulphonylpyrimidines reacted with ammonia in ethanol to give the corresponding 6-amino-2-methylsulphonylpyrimidines (Chi and Ling, 1956, 1957). However the relative reactivity was reversed when sulphanilamide anion was the nucleophile, the

---

* Due to the different activating effects of chloro and methylsulphonyl groups on each other this is not a strictly valid comparison. However it suggests that the rate disparity between chloro and methylsulphonyl is so small that activating effects determine the reaction course.

2-methylsulphonyl group being displaced in preference to the 4-chloro group (Geigy, 1958). Qualitative studies in the purine series indicate that the methylsulphonyl group is displaced at approximately the same rate as the chloro group (Noell and Robins, 1959).

4. Mechanisms for Nucleophilic Substitution

Two distinct mechanisms have been postulated for bimolecular aromatic substitution (Shepherd and Fedrick, 1965). In the first mechanism (Bunnett and Zahler, 1951) the substitution is considered to take place in two steps: one involves reversible addition of the incoming nucleophile to the aromatic ring position bearing the leaving group to give the intermediate (IX), analogous to a Meisenheimer complex; and the second step involves elimination of the leaving group from this intermediate with the formation of the product. Either the first, the second, or neither step may be rate determining, depending on the nature of the leaving group, the nucleophile, the substrate,

and the solvent. In the second mechanism (Chapman, 1955) stretching of the bond to the leaving group is considered to occur concurrently with the attachment of the nucleophile (the extent of bond making and breaking at any instant need not necessarily be the same). No intermediate is formed during the reaction.

Evidence for the intermediate complex mechanism is considered (Capon, Rees, and Perkins, 1965) to be quite conclusive for nucleophilic substitution in activated aromatic carbocyclic substrates. The more recent work discussed below has provided further support for this view, most of the evidence being derived from the displacement of halogens by an amine. This reaction is considered to proceed through the intermediate (IX) which may undergo base catalysed loss of a proton prior to the fast loss of the leaving group (path 1) or loss of the leaving group followed by rapid proton loss (path 2). Making the "steady state" approximation for the intermediate (IX), and provided $k_{-1} \gg k_3$ ie return of the intermediate predominates, the observed second order rate constant should be of the form (i) (Bunnett and Garst, 1965).

$$k_{observed} = k_1 + k_b [base] \quad \ldots (i)$$

where $k_{observed}$ is the observed second order rate constant k_1 is the extrapolated value of $k_{observed}$ at zero base concentration and [base] is the concentration of base*. Similarly the catalytic effect of added 1,4-diaza-(2.2.2)-bicyclooctane (DABCO) and pyridine on the reaction of *p*-anisidine with 2,4-dinitrofluorobenzene or 2,4-dinitrochlorobenzene in toluene has been noted (Bernasconi and Zollinger, 1966). Catalysis by the reacting amine has also been demonstrated in the reaction of 2,4-dinitrofluorobenzene with benzylamine, *N*-methylbenzylamine and morpholine in benzene (Bernasconi and Zollinger, 1967). The first example of base catalysis in a heteroaromatic nucleophilic displacement reaction was recently reported (Illuminati *et al.*, 1967) for the piperidino-dechlorination of 2- and 4-chloroquinoline, but the mechanistic interpretation

---

* Provided that the formation of IX is fast reaction of IX by two paths (one base catalysed) would lead to the same form of k_{obs}.

is not clear.

Indirect support for the above "intermediate" mechanism is provided by the success of rate constant calculations (Miller, 1963; Miller and Kendall, 1967), by methods which explicitly consider the reaction path to proceed through an intermediate complex.

Chapter 2

THE PREPARATION, REACTIONS AND REACTION KINETICS OF SIMPLE PYRIMIDINE SULPHONES AND SULPHOXIDES

Introduction

The preparation and physical properties of the simple pyrimidine sulphones and sulphoxides and the reactions of the 2- and 4- substituted compounds are described in this chapter. In addition, the kinetics of the displacement of the methylsulphonyl and methylsulphinyl groups by cyclohexylamine and pentylamine in dimethylsulphoxide were studied. It was shown that these groups were as easily displaced as the chloro group and that the positional reactivity of the pyrimidine ring was 4 > 2.

1. Preparation of the Sulphones and Sulphoxides

Several methods were used for the synthesis of the simple sulphones and sulphoxides from the corresponding alkylthio- or 2-arylthio-pyrimidines. Both 4- and 5-methylthiopyrimidine (1 mole) were oxidized at room temperature with two moles of m-chloroperbenzoic acid in chloroform to the corresponding methylsulphonyl-pyrimidines; at 0°, a similar oxidation with one mole

of m-chloroperbenzoic acid gave the methylsulphinyl-pyrimidine in good yield. 2-Phenylthiopyrimidine, prepared from sodium thiophenoxide and 2-chloropyrimidine, reacted similarly with one mole of m-chloroperbenzoic acid to give the 2-phenylsulphinylpyrimidine. 2-Phenylthio- and 2-methylthio- pyrimidine were also oxidized by aqueous chlorine at 3° to the corresponding sulphones*, but application of this method to 4-methylthiopyrimidine led only to a liquid of low boiling point, identified on the basis of its p.m.r. spectrum (singlet, 6.31 τ) and infrared spectrum (thin film: bands at 980, 1180, 1340, 1390, 3020 $cm.^{-1}$)

---

* Contrary to the pessimistic predictions of Kwart and Body (1965). The work of Robbins and Noell (1959) shows that Kwart's generalizations are only correct under the most forcing conditions.

as methanesulphonyl chloride*. Presumably the 4-methylsulphonylpyrimidine was formed, but the methylsulphonyl group was immediately displaced by water and the methylsulphinate anion converted by excess chlorine to methanesulphonyl chloride (Muth, 1955; Quaedvlieg, 1955). The methylsulphonyl group was not cleaved from the pyrimidine ring by chlorine, cf. formation of 2-methylsulphonylpyrimidine (see also Sprague and Johnson, 1938). 2-Phenylsulphonylpyrimidine was also prepared by heating 2-chloropyrimidine with sodium benzenesulphinate in dimethyl sulphoxide.

Oxidation of the alkyl and aryl thiopyrimidines with sodium metaperiodate to the corresponding sulphoxide (Leonard and Johnson, 1962) was attempted also. The

---

* Methanesulphonyl chloride has the following physical properties: p.m.r. spectrum: singlet at 6.31 . (Varian Associates, 1963); i.r. spectrum: 971, 1176, 1190, 1333, 1370, 1389, 3030 cm^{-1} (Simon, et al. 1956).

reaction was successful in making 2-methylsulphinyl-pyrimidine although it was found to be far slower (Table 1) than reported for previous examples (10 hr., reaction complete). Attempts to overcome the incomplete oxidation to the sulphoxide by raising the reaction temperature led to the formation of the sulphone as well (Table 1).

Table 1

Periodate oxidation of alkylthio- or arylthio- pyrimidines[a]

Pyrimidine	Temp.°C	Time (hr)	Relative proportions* (%) Sulphoxide	Thioether
2-methylthio	3	20	90	10
4-methylthio	3	20	34.5	65.5
	5	40	49.5	50.5
	50	3	40	5 (55% sulphone)
2-phenylthio	5	96	24.7	75.3

[a] Carried out in 0.5M aqueous sodium metaperiodate

* Estimated from p.m.r. integral.

2. Physical Properties and Reactions

The p.m.r., ultraviolet and infrared spectroscopic data (Tables 2 and 3) are conclusive evidence that the compounds are sulphones and sulphoxides rather than mono or di N-oxides. The presence of sulphoxide groups was confirmed by their ability to reduce acidic potassium iodide solutions to iodine.

The methyl peaks show downfield shifts of about 0.5τ on conversion of the methylthiopyrimidine to the sulphoxide; the formation of the sulphone produces a further downfield shift of 0.3τ, as expected for the increased effective electronegativity of the sulphur and the consequent deshielding of the methyl groups. The bands in the infrared spectra are within the accepted ranges for sulphoxides and sulphones (Bellamy, 1958). The ultraviolet spectra are shown below (Table 3).

The spectra and pK_a values of 5-methylsulphinyl- and 5-methylsulphonyl-pyrimidine are clearly anomalous and the origins of these effects, together with the results of attempted nucleophilic displacement reactions on these two compounds, are discussed in Chapter 3. The pK_a values of the 2- and 4-sulphoxides and sulphones

were too low to be determined: no spectral change occurred down to H_o-2*, at even lower H_o values the spectra of the methylsulphinyl- or methylsulphonyl-pyrimidine cation changed so rapidly to that of 2-hydroxy- or 4-hydroxy-pyrimidine cation that measurement was precluded. These results indicate that the methylsulphonyl and methylsulphinyl groups in either 2- or 4-position exert a strong base weakening effect in accord with their large positive σ^- values (Jaffe, 1953).

Both 2- and 4-methylsulphonyl and methylsulphinyl groups were easily displaced by a variety of nucleophiles. The results of these preparative experiments are summarised diagramatically in Figs. 1 - 3. However the reactions of 2-methylsulphonyl-pyrimidine with sodium fluoride, potassium iodide, or sodium thiocyanate in dimethylsulphoxide failed to give the expected 2-fluoro, 2-iodo, or 2-thiocyanato-pyrimidine.

---

* cf. pK_a of pyrimidine, 1.23 (Albert, Goldacre and Phillips, 1948).

Table 2

Infrared and p.m.r. spectra of pyrimidinyl sulphones and sulphoxides

Pyrimidine	Infrared bands ($cm.^{-1}$)	p.m.r. spectrum* (τ)	
		CH_3 group	Others
2-$MeSO_2^-$	1120, 1300	6.63	4+6-H (0.98(d)); 5-H (2.32(t)). $J_{4,5}$ = 5 cps.
4-$MeSO_2^-$	1115, 1160, 1320	6.69	2-H (0.55), 6-H (0.76(d)), 5-H (1.90(d.ofd.)). $J_{4,5}$ = 5 cps; $J_{2,5}$ = 1.5 cps.
5-$MeSO_2^-$	1120, 1130, 1180, 1310	6.87	2-H (0.36), 4+6-H (0.60)
2-$PhSO_2^-$	1132, 1300	-	4+6-H (0.95(d)), 5-H (2.42(t)). $J_{4,5}$ = 5 cps. Aromatic Multiplet 1.8τ singlet 2.25τ
2-MeSO	1070	6.95	4+6-H (0.87(d)), 5-H (2.22(t)). $J_{4,5}$ = 5 cps.

Table 2 (page 2)

4-MeSO	1050, 1075	7.01	2-H (0.65), 6-H (0.86(d)), 5-H (1.83(d.ofd.)). $J_{5,6}$ = 5 cps. $J_{2,5}$ = 1.5 cps.
5-MeSO	1055	7.03	2-H (0.50), 4+6-H (0.87)
2-PhSO	1060	-	4+6-H (1.05(d)), 5-H (2.0(t)). $J_{4,5}$ = 5 cps. Aromatics complex multiplet 2.4 - 2.6τ .

d = doublet t = triplet

* in $CDCl_3$ T.M.S. internal reference.

Table 3

Ionisation and ultraviolet spectra

Pyrimidine	pK_a[a]	λ_{max} ($\log\varepsilon$)[b]	solvent[c]
2-$MeSO_2$	<-3[d]	239(3.21), 243(3.23), <u>265</u>(2.41)	5.0
		240(3.27), 244(3.24)	E
4-$MeSO_2$	<0[d]	<u>229</u>(3.90), <u>250</u>(3.42), 277(2.93), <u>286</u>(2.89)	5.0
		229(3.77), <u>250</u>(3.42), 281(2.91), 288(2.86)	E
5-$MeSO_2$	0.97±0.04(264)	240(3.06), 243(3.06), <u>277</u>(2.63)	5.0
		265(3.68)	-1.5
		238(3.08), 286(2.52)	E
2-$PhSO_2$	<-3[d]	235(4.04), <u>267</u>(3.03)	5.0
		228(3.87), 267(3.08), 274(3.00)	E
2-MeSO	<-3[d]	247(3.57)	5.0
		250(3.56)	E
4-MeSO	<0[d]	254(3.63)	5.0
		258(3.61)	E

Table 3 (page 2)

5-MeSO	0.42±0.04 (276)	247 (3.44)	5.0
		269 (3.69)	-1.5
		250 (3.44)	E
2-PhSO	<-3[d]	226 (4.11)	5.0
		227 (4.13)	E
2-C_6H_{11}	4.04±0.02	237 (4.28), 308 (3.40)	7.0
		232 (4.25), 320 (3.40)	2.0
		235 (4.30), 312 (3.42)	E
2-NH_2NH	4.55±0.04	230 (4.12), 297 (3.39)	7.0
	-0.46±0.05	220 (4.03), 276 (3.31)	2.0
		233 (4.13), 300 (3.38)	E
2-C_5H_{11}	4.04[e]	237 (4.26), 309 (3.41)	7.0
		317 (3.51), 270 (4.26)	2.0
		238 (4.28), 310 (3.43)	E
4-C_5H_{11}	-	245 (4.21), 278 (3.49)	E

Table 3 (page 3)

[a] At 20°, measured spectrometrically (analytical wavelength given) by the usual methods (Albert and Serjeant, 1962).

[b] Inflexions in italics.

[c] Aqueous buffer of given pH value or 95% ethanol (E).

[d] Instability in highly acidic media precluded precise measurement.

[e] Brown and Harper, 1963.

FIGURE 1

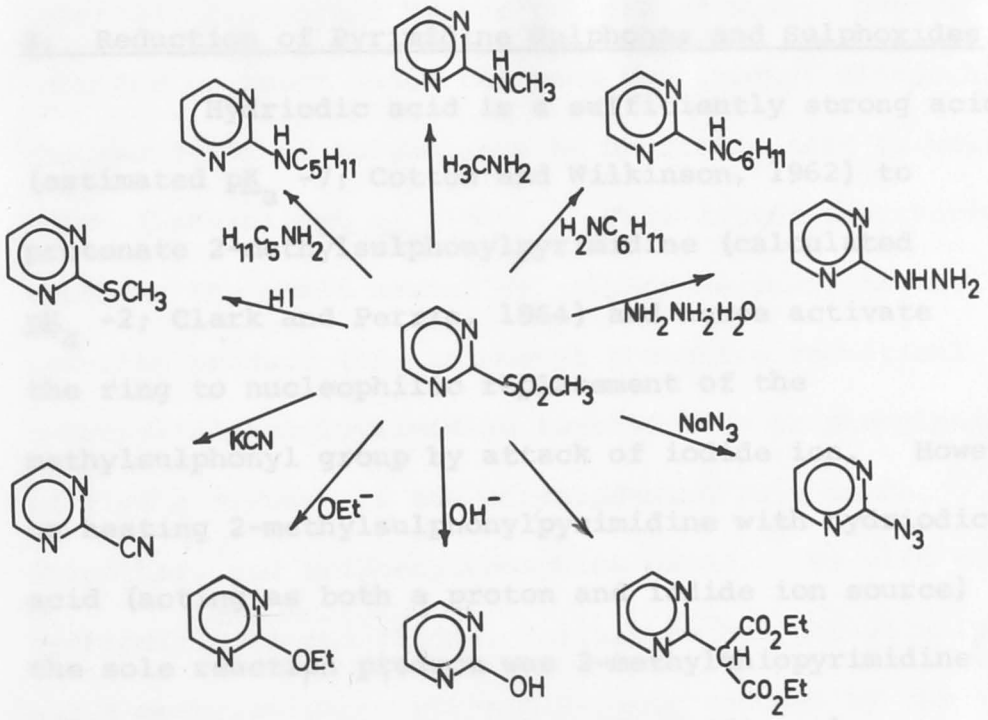
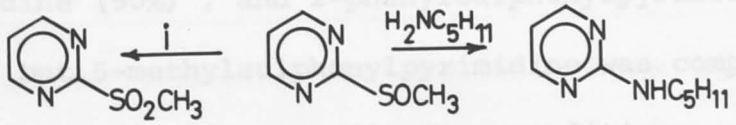
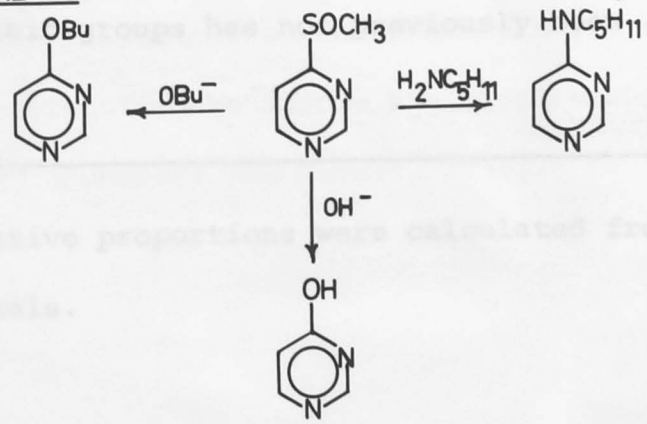


FIGURE 2



i = meta-Chloroperbenzoic Acid

FIGURE 3



3. Reduction of Pyrimidine Sulphones and Sulphoxides

Hydriodic acid is a sufficiently strong acid (estimated pK_a -7; Cotton and Wilkinson, 1962) to protonate 2-methylsulphonylpyrimidine (calculated pK_a -2; Clark and Perrin, 1964) and hence activate the ring to nucleophilic replacement of the methylsulphonyl group by attack of iodide ion. However on heating 2-methylsulphonylpyrimidine with hydriodic acid (acting as both a proton and iodide ion source) the sole reaction product was 2-methylthiopyrimidine (35% yield). 2-Phenylsulphonylpyrimidine also reacted with hydriodic acid to give 2-phenylthio-pyrimidine (90%)*, and 2-phenylsulphinylpyrimidine (10%), but 5-methylsulphonylpyrimidine was completely destroyed under the same reaction conditions.

The reduction of alkylsulphonyl groups to alkylthio groups has not previously been

---

* Relative proportions were calculated from p.m.r. integrals.

reported* (supported by the failure of methyl phenyl sulphone to react under the same conditions) although the reduction of sulphoxides by hydriodic acid is well known (Landini, et al. 1964). This latter observation explains the small amount of sulphoxide found in the reaction product (cf. triphenyl phosphine reduction). 2-Methylsulphonylpyrimidine reacted with triphenylphosphine to give a mixture of the corresponding sulphoxide, thioether, and triphenylphosphine oxide. As with the hydriodic acid reductions, neither methyl phenyl sulphone nor 5-methylsulphonylpyrimidine was reduced by the triphenylphosphine; similarly, 9-methyl-2-methylsulphonyl-

---

* The present consensus is adequately summarised as follows, "Eine Reduktion der Sulfone durch Einwirkung von Zink und Mineralsäuren oder durch Eintragen von Zink in das siedende Sulfon sowie auch Behandeln mit rauschender Jodwasserstoffsäure konnte bis jetzt nicht beobachtet werden" (Schöberl and Wagner, 1955).

purine did not react. Brief examination of the course of the reaction (Table 4) indicated that the reaction proceeded *via* the sulphoxide, the reduction of sulphoxides (but *not* sulphones) by triphenylphosphine being well known (Castrillon and Szmant, 1965).

Table 4

Reduction of 2-methylsulphonylpyrimidine by triphenylphosphine

Reaction time (hr.)	Relative proportions*		
	Sulphone	Sulphoxide	Thioether
14	20.6	34	45.4
36	4.7	39.5	56

* Calculated from p.m.r. spectra.

2-Methylsulphonylpyrimidine did not react with triethylphosphite. In this it behaved differently from 2-chloropyrimidine, which reacted readily to give the corresponding pyrimidin-2-ylphosphonate (Kosolapoff and Roy, 1961). Sodium borohydride in aqueous methanol neither reduced 2-methylsulphinylpyrimidine to 2-methylthiopyrimidine nor caused cleavage of the bond joining the pyrimidine ring and the sulphoxide

group to give pyrimidine. Aluminium amalgam in aqueous dioxane, known (Corey and Chaykowsky, 1965) to readily replace methylsulphinyl groups by hydrogen in a wide variety of β ketosulphoxides, caused complete destruction of the pyrimidine ring system.

The reduction of 2-methylsulphonylpyrimidine by triphenylphosphine may be formally considered as a Lewis acid-base reaction. The oxygen transfer reaction involves attack by the phosphorus of triphenylphosphine on the oxygen of the sulphone group. The ease of this attack will depend on the relative "softness" (Pearson and Songstad, 1967) of the phosphorus and oxygen atoms. As the oxygen atom (the Lewis acid) bears a formal negative charge it may be considered to be softer than the neutral phosphorus atom (the base).

However the considerable inductive withdrawal of electrons by the pyrimidine ring decreases this "softness disparity" and permits reaction; in contrast in methyl phenyl sulphone and 5-methylsulphonylpyrimidine the inductive withdrawal is absent or greatly reduced, the "softness" gap is too great, and reaction does not occur. The failure of even 2-methylsulphonylpyrimidine

to react with triethyl phosphite is explicable in this scheme. Triethyl phosphite would be a considerably harder base than triphenylphosphine due to the inductive withdrawal by the ethoxy groups, hence the difference in softness increases (despite the "hardening" effect of the pyrimidine ring) and no reaction occurs.

The exceptional reaction of 2-methylsulphonyl-pyrimidine with hydriodic acid may be explained in similar terms with iodide ion now acting as the Lewis base. However the detailed explanation depends on the choice of the actual mechanism from the various reasonable possibilities (Fig. 4). Having no experimental criteria as a guide they will not be further discussed except to mention the possible participation of the protonated ring nitrogen as a means of activating the oxygen atoms of the sulphone group (probably also protonated) towards displacement by iodide ion. Alternatively the unprotonated ring nitrogen may act as an acceptor for OH^+ from the sulphone group to give a protonated pyrimidine N-oxide which would then be reduced by the hydriodic acid (acidic iodide solutions will reduce some heterocyclic N-oxides; Katritzky, 1956).

FIGURE 4.

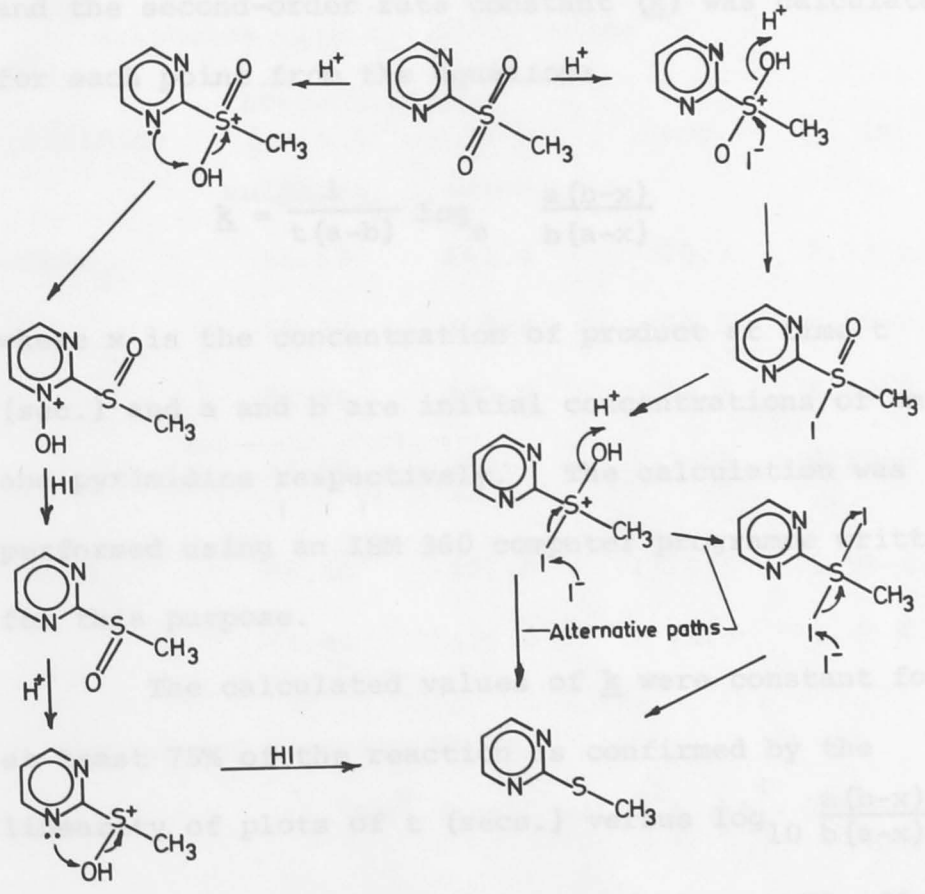


Figure 4. Possible mechanisms for the reduction of 2-methylsulphonylpyrimidine by hydriodic acid.

4. Kinetics

The appearance of the cyclohexylamino- or pentylamino-pyrimidine was followed spectrophotometrically, and the second-order rate constant ($\underline{k}$) was calculated for each point from the equation:

$$\underline{k} = \frac{1}{t(a-b)} \log_e \frac{a(b-x)}{b(a-x)}$$

where x is the concentration of product at time t (sec.) and a and b are initial concentrations of amine and pyrimidine respectively. The calculation was performed using an IBM 360 computer programme written for this purpose.

The calculated values of $\underline{k}$ were constant for at least 75% of the reaction as confirmed by the linearity of plots of t (secs.) versus $\log_{10} \frac{a(b-x)}{b(a-x)}$

The second order rate constant was not affected by varying the initial amine concentration, indicating the absence of base catalysis (Ross, 1964). The results are shown in Tables 5 and 6, together with the calculated values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ (Table 7).

Table 5

Kinetics of the reaction of 2-pyrimidinyl sulphones with cyclohexylamine[a]

Pyrimidine	concentrations (mole l^{-1} x 10^4) sulphone	amine	Temp.	k^b (x 10^4)
2-$MeSO_2$	55.69	442.4	70.3	2.73±0.10
	55.27	407.9	74.5	3.50±0.11
	55.84	383.2	79.5	4.42±0.09
	55.84	768.7	79.5	4.50±0.12
2-$PhSO_2$	65.96	421.0	74.5	2.96±0.09
	55.41	421.0	79.5	4.08±0.07

Calculated from the above:

Pyrimidine	$\Delta H^{\ddagger}$ (kcal. $mole^{-1}$)	$\Delta S^{\ddagger}$ (kcal. $mole^{-1}$ $deg.^{-1}$)
2-$MeSO_2$	13.0±0.4	-21 ± 4
2-$PhSO_2$	15.3±0.4	-31 ± 4

[a] In DMSO (dimethylsulphoxide).

[b] Second Order rate constant, l. $mole^{-1}$ $sec.^{-1}$.

Table 6

Kinetics of reaction with pentylamine in DMSO.

Pyrimidine	concentration ($mole^{-1} \times 10^4$)		temp.°C	k^a
	pyrimidine	amine		
2-$MeSO_2$	60.54	509.4	28.15	6.71±0.11
	63.97	498.2	33.35	8.84±0.09
	60.04	478.5	38.15	11.38±0.15
2-$PhSO_2$	61.26	509.4	28.15	5.36±0.10
	65.85	498.2	33.35	7.04±0.19
	64.56	478.5	38.15	9.13±0.16
4-$MeSO_2$	62.44	531.9	19.50	6.63±0.13
	61.58	482.3	21.50	7.30±0.11
	59.11	447.9	24.95	8.64±0.08
2-MeSO	88.03	482.4	29.50	3.11±0.08
	101.7	567.5	34.60	4.29±0.09
	74.8	558.3	39.90	5.53±0.08
4-MeSO	64.97	517.1	25.70	11.90
	75.41	452.7	29.85	14.20
	69.32	452.7	32.65	18.40
2-Cl	88.96	572.8	29.35	1.44±0.01
	84.43	543.3	36.20	2.19±0.04
	82.85	547.7	41.00	2.85±0.03
	170.7	109.5	41.0	2.90±0.02

[a] Second order rate constant, $l.mole^{-1}\ sec.^{-1} \times 10^4$.

Table 7

Energies and entropies of activation.

Pyrimidine	$\Delta H^{\ddagger}$ (kcal. mole^{-1})	$\Delta S^{\ddagger}$ (cal. mole^{-1} deg.$^{-1}$)
2-$MeSO_2$	8.8	-34
4-$MeSO_2$	7.8	-51
2-$PhSO_2$	9.3	-43
2-MeSO	10.8	-39
2-Cl	11.1	-44

For comparative purposes the relative rates of displacement of chlorine and methylsulphonyl groups from the 2-position of pyrimidine by hydroxide ion were measured (Table 8). Because of the great disparity in rates of reaction, the rate constant at 20° (the temperature at which the methylsulphonylpyrimidine/hydroxide ion kinetics were measured) for the 2-chloropyrimidine was determined by extrapolation from the values found at higher temperatures.

Table 8

2-Chloro- and 2-methylsulphonyl-pyrimidine/ hydroxide ion kinetics.

Pyrimidine	T^{o}	k^{*} (sec.$^{-1}$ x 10^{4})
2-Cl	49.8	9.28
	40.01	4.21
(extrapolated value)	20.0	0.79_{4}
2-$MeSO_2$	20.0	3010

* First order rate constant at 1M hydroxide ion, i.e. second-order rate constant; calculated from rates measured using 0.5M sodium hydroxide for 2-chloropyrimidine and 0.1M sodium hydroxide for 2-methylsulphonylpyrimidine.

5. Discussion

The preparative reactions described in the earlier portion of this chapter demonstrate the synthetic utility of the methylsulphonyl and methylsulphinyl groups in the preparation of a wide variety of simple 2- or 4-substituted-pyrimidines. These groups are replaced by the same nucleophiles as those that will displace chloride ion from chloropyrimidines (Brown,

1962 b) and in some cases these reactions take place under much milder conditions. The demonstrated ease of preparation of the sulphoxides and sulphones from the corresponding alkylthio- or arylthio-pyrimidines extends considerably the possibilities for using the alkylthio group in preparations; coupled with the ease of preparation of mercapto-pyrimidines by "primary synthesis" or thiation of hydroxypyrimidines (Brown, 1962 c) this makes synthetic routes *via* mercapto-pyrimidines much more attractive.

The kinetic results further demonstrate the greater reactivity of the 4-position relative to the 2-position in pyrimidine. This effect appears to be independent of the leaving group and the incoming nucleophile.

The reaction parameters for the displacements by cyclohexylamine and pentylamine indicate that the difference in rates arises from changes in both the energy and the entropy of activation. The entropy of activation is smaller for cyclohexylamine than for pentylamine presumably because the methylene groups attached to the *alpha* carbon are "held back", being

part of the chair form of cyclohexylamine (Eliel, et al, 1965), thus decreasing steric interference to attack by the amine group. No such effect operates in pentylamine. The rate difference (approx. a factor of 30) is similar to that observed in changing from n- to iso- propylamine in the amino-dechlorination of 2-chloro-4,6-dimethylpyrimidine (Brown and Lyall, 1964 and 1965).

The rates of replacement of the methylsulphonyl, methylsulphinyl, and chloro groups by pentylamine differ by less than a factor of 5. This similarity in rates is evidence (albeit weak) for the absence of an "element effect" (Bunnett, Garbisch and Pruitt, 1957), indicating that loss of the leaving group is not involved in the rate determining step. However, with hydroxide anion as nucleophile considerable differences in reaction rate were observed indicating that stretching of the carbon-sulphone and the carbon-chlorine bonds was involved in the formation of the transition state. The methylsulphonyl group is displaced faster than the chloro group due to greater delocalisation of the negative charge over the oxygen atoms of the sulphone group, in the bond breaking step.

Chapter 3

REACTIONS OF THE 5-METHYL -SULPHONYL- AND -SULPHINYL- PYRIMIDINES

Introduction

Attempted nucleophilic displacement of the 5-methylsulphinyl and 5-methylsulphonyl groups from pyrimidine by simple alkylamines did not give the expected 5-alkylaminopyrimidines but 2-substituted-3-iminopropylamines derived from the three adjacent carbon atoms of the pyrimidine ring and two molecules of amine. This section describes how the structure of the products was found, and proposes a reasonable mechanism. The formation of water adducts by 5-methylsulphonyl- and 5-methylsulphinyl-pyrimidinium cations is demonstrated.

1. Results of Ring Opening Reactions

Refluxing 5-methylsulphonylpyrimidine with pentylamine led to the evolution of ammonia and the isolation of a low melting point solid ($C_{14}H_{28}N_2O_2S$), obviously not the expected 5-pentylaminopyrimidine.

The reaction of the same sulphone with benzylamine or of the 5-methylsulphinylpyrimidine with pentylamine or benzylamine, gave similar compounds, $C_4H_6N_2X.2R$ (X=OS or O_2S; R=C_5H_{11} or C_7H_7), confirmed as monomers by a mass spectral molecular weight (m/e 272) for the 5-methylsulphinylpyrimidine/pentylamine product (see Fig. 2).

The infrared spectra (thin film or Nujol mull) of all products show bands at 1640 cm^{-1} (-C=N- stretch) while the sulphinyl or sulphonyl stretching frequency decreased relative to the starting sulphone or sulphoxide (Table 1), indicating attachment of this group to a less electronegative carbon (Bellamy, 1958). The N-H stretching frequency (3120 cm^{-1}), indicated strong hydrogen bonding while the absence of N-H deformation vibrations in the 1650 cm^{-1} region suggested the presence of a secondary amine.

The p.m.r. spectra of all the products are very similar (Table 2). Hence, only that of the product from 5-methylsulphonylpyrimidine/pentylamine reaction (Fig. 1(a)) will be discussed in detail: it shows a broad band at 8.6τ (12 protons) and complex multiplets

Table 1

Ultraviolet and infrared spectra of the products

Reactants	λ_{max}	$\log_{10}\varepsilon$	ν_{SO} [a] or ν_{SO_2} (cm^{-1})
5-$MeSO_2$ pyrimidine/pentylamine	298	4.13	1118, 1280
5-$MeSO_2$ pyrimidine/benzylamine	300.5	3.87	1140, 1280
5-MeSO pyrimidine/pentylamine	290	-	1028
5-MeSO pyrimidine/benzylamine	302	3.84	1019

[a] cf. 5-methylsulphonylpyrimidine ν_{SO_2} 1131, 1310 cm^{-1}

5-methylsulphinylpyrimidine ν_{SO} 1040 cm^{-1}

Table 2

P.m.r. spectra of the products

Reactants	assigned peak positions[c]			
	1,3-H	$-N-CH_2^+$	CH_3SO_2 or CH_3SO[a]	others
5-$MeSO_2$-pyrimidine/pentylamine	2.00	6.65	7.00	8.6*(b), 9.16(b)
5-$MeSO_2$-pyrimidine/benzylamine	1.83	5.39	6.97	2.65(C_6H_5)
5-MeSO-pyrimidine/pentylamine	2.15	6.59	7.26	8.55(b), 9.05(b)
5-MeSO-pyrimidine/benzylamine	2.03	5.38	7.27	2.65(C_6H_5)

*b = broad band, the value quoted is the maximum.

[a] cf. in the parent pyrimidine CH_3SO_2, 6.63; CH_3SO, 6.93.

[c] τ values, 5% solution in $CDCl_3$, TMS internal reference.

at 6.6τ (4 protons) and 9.1τ (6 protons) with sharp peaks at 1.99τ(2 protons) and 7.00τ (3 protons). The broad bands at 8.6, 9.1 and 6.6τ are typical of the n-pentylamino group (cf. n-pentylamine 7.35τ(2-methylene group), 8.7, 8.95τ). The single peak of the methylsulphonyl group at 7.00τ has moved upfield relative to its position in the pyrimidine indicating either (or both) a decrease in the ring current deshielding of the methyl group (loss of aromaticity) or a decrease in electronegativity at the carbon atom bearing the CH_3SO_2 group (Table 2). Thus the compound possessed two pentylamino groups, one methylsulphonyl group and two equivalent protons. A structure compatible with the above data was the hydrogen bonded iminopropenamine (I), provided that the tautomerisation, I $\rightleftharpoons$ II, is fast on a p.m.r. time scale. Further support for the structure was provided by the p.m.r. spectrum (Fig. 1(b)) of the double Schiff's base (III) prepared from malondialdehyde and n-butylamine (Paddon-Row, 1966). This shows that the iminoenamine (IV) was more stable than the alternative tautomer (III), presumably because of the more extensive

FIG. 1a

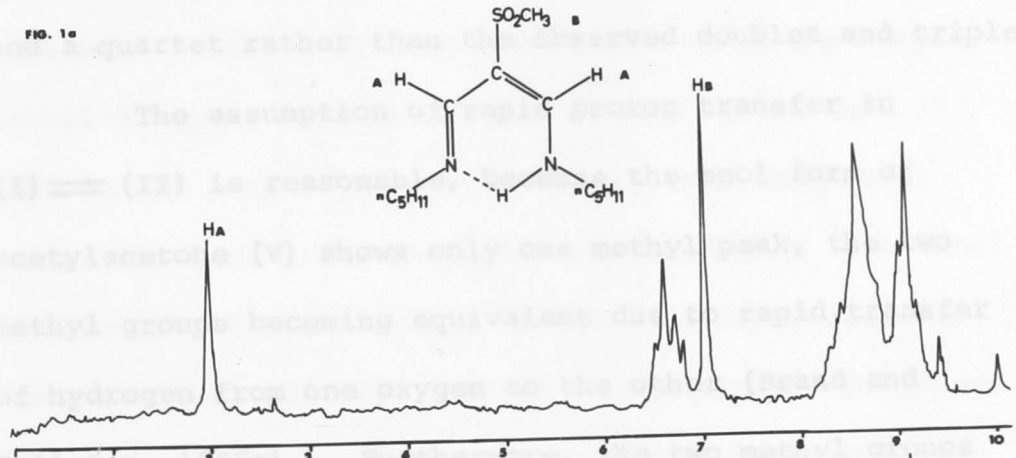
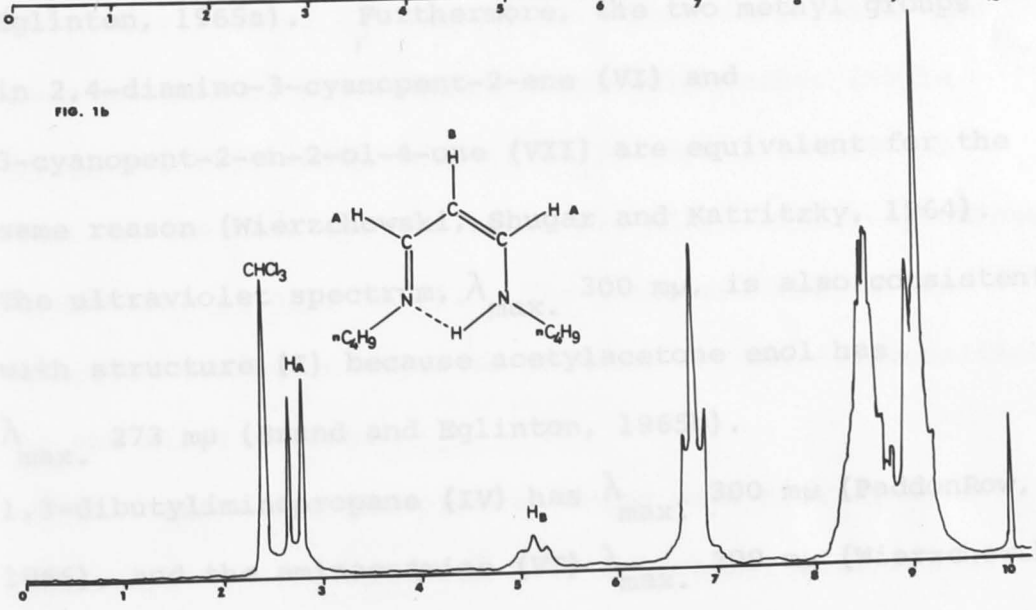

SO2CH3
B
A H
H A
HB
HA
nC5H11
nC5H11
0 1 2 3 4 5 6 7 8 9 10

FIG. 1b


B
H
A H
H A
CHCl3
HA
HB
nC4H9
nC4H9
0 1 2 3 4 5 6 7 8 9 10

conjugated system and the additional stabilisation due to hydrogen bonding. The p.m.r. spectrum showed no trace of the tautomer (III) which should show two doublets and a quartet rather than the observed doublet and triplet.

The assumption of rapid proton transfer in (I) $\rightleftharpoons$ (II) is reasonable, because the enol form of acetylacetone (V) shows only one methyl peak, the two methyl groups becoming equivalent due to rapid transfer of hydrogen from one oxygen to the other (Brand and Eglinton, 1965a). Furthermore, the two methyl groups in 2,4-diamino-3-cyanopent-2-ene (VI) and 3-cyanopent-2-en-2-ol-4-one (VII) are equivalent for the same reason (Wierzchowski, Shugar and Katritzky, 1964). The ultraviolet spectrum, $\lambda_{max.}$ 300 mμ, is also consistent with structure (I) because acetylacetone enol has $\lambda_{max.}$ 273 mμ (Brand and Eglinton, 1965b), 1,3-dibutyliminopropane (IV) has $\lambda_{max.}$ 300 mμ (PaddonRow, 1966), and the aminoenamine (VI) $\lambda_{max.}$ 298 mμ (Wierzchowski *et al.*, 1964).

In a similar way, structures (1a), (1b), and (1c) represent the other products in this series.

The mass spectrum* (Fig. 2) of the product from the 5-methylsulphinylpyrimidine/pentylamine reaction provided further support for the proposed structure (1c). The most abundant fragment ion (apart from the simple alkyl fragment ions at m/e 43, 41 and 29) was m/e 257, due to the loss of a methyl radical from the parent molecular ion. The $M-CH_3$ ion produced then lost water giving m/e 239 (metastable at 222.2; 257→239 requires metastable at 222.26). These rather unusual processes involving loss of H_2O and OH have been observed in the mass spectra of some simple alkyl sulphoxides (Bowie et al., 1966), while loss of CH_3SO (m/e 272→209) is seen in the mass spectra of simple alkyl aryl sulphoxides (Johnstone et al., 1967). The lower m/e end of the spectrum can be interpreted in terms of the decomposition of the alkyl chains.

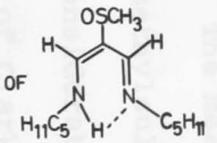
Replacing the primary amine with hydrazine or the sulphone or sulphoxide with 5-bromopyrimidine under a variety of reaction conditions led to decomposition

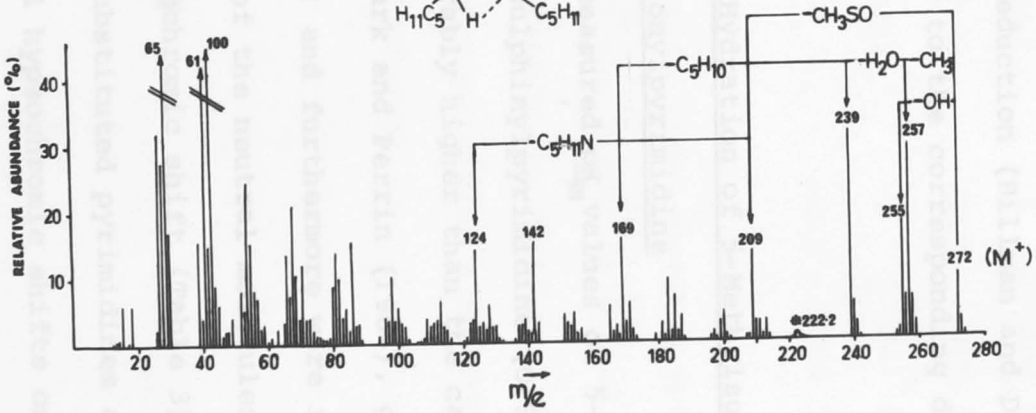
---

* Very kindly determined by Dr. S. Middleton, Monash University.

FIGURE, 2

MASS SPECTUM OF





to dark oils, from which no substituted pyrazoles (from hydrazine), bromoiminopropenamines, 5-hydrazino-, or 5-alkylaminopyrimidine could be isolated. Sodium borohydride reduction (Billman and Diesing, 1957) of compound (1a) to the corresponding diamine was also unsuccessful.

2. Covalent Hydration of 5-Methylsulphinyl and 5-Methylsulphonylpyrimidine

The measured pK_a values of 5-methylsulphonyl- and 5-methylsulphinylpyrimidine (0.97 and 0.42 respectively) were considerably higher than the calculated values (the method of Clark and Perrin (1964), gave -2.54 and -1.86 respectively) and furthermore were in reverse order. Protonation of the neutral molecules was associated with a large bathochromic shift (Table 3) while pyrimidine and simple substituted pyrimidines are recorded as showing small hypsochromic shifts on formation of the cation (Brown, 1962). These two phenomena characterise (Albert and Armarego, 1965) the formation of a covalent hydrate. This conclusion was confirmed by the p.m.r. spectra of the 5-sulphone and sulphoxide in dilute

Table 3

Ultraviolet spectra of 5-substituted pyrimidines

Substituent	pH	λ_{max} ($\log_{10}\varepsilon$)
5-methylsulphonyl	5	240 (3.06), 243 (3.06)
cation	-1.5	265 (3.68)
5-methylsulphinyl	5	247 (3.44)
cation	-1.5	269 (3.69)

hydrochloric acid. The observed spectra (Table 4) were consistent with the formation of the water adduct of the cation (VIII, X=$SOCH_3$ or SO_2CH_3). The cation of 5-methylsulphonylpyrimidine also added deuteromethanol in CD_3OD/HCl (Table 4).

Table 4

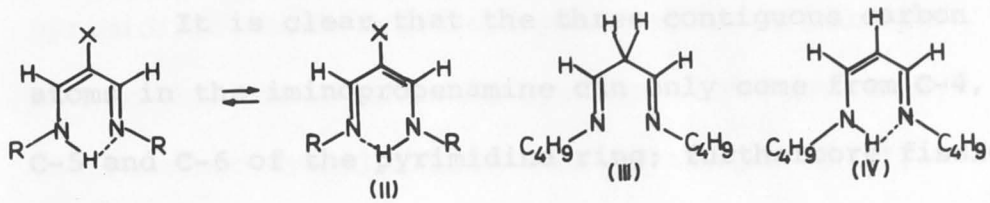
P.m.r. spectra of 5-substituted pyrimidines

5-substituent	solvent	peak positions* (assignment)
methylsulphonyl	D_2O	0.54(2-H), 0.65(4+6-H), 6.60(CH_3SO_2)
	1N-DCl/D_2O	1.40, 2.28(2-H+6-H), 3.79(CHOD), 6.71(CH_3SO_2)
	CD_3OD	0.57(2-H), 0.73(4+6-H), 6.74(CH_3SO_2)
	CD_3OD/HCl[a]	1.09, 2.22(2H, 6H), 3.92(CHOD), 6.84(CH_3SO_2)
methylsulphinyl	D_2O	0.66(2-H), 0.90(4+6-H), 6.93(CH_3SO)
	1N-DCl/D_2O	1.51, 2.62(2H, 6H), 3.80(CHOD), 7.04(CH_3SO)

[a] CD_3OD was saturated with HCl gas.

cf. The covalent hydrate of 5-nitropyrimidine cation (IX) which gives peaks at 1.34, 1.69 and 3.51τ (Biffin, Brown and Lee, 1967).

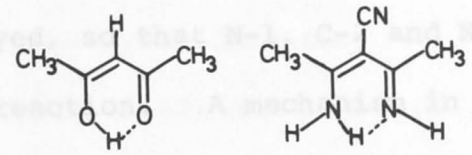
* τ values, internal reference sodium 3-trimethylsilyl-propane-1-sulphonate.



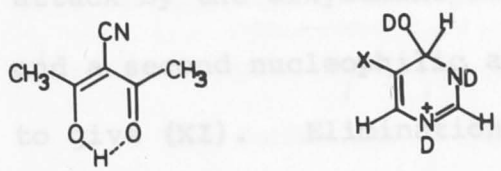
(II) (III) (IV)

(I) R = n-PENTYL
(Ia) R = BENZYL
X = SO_2CH_3

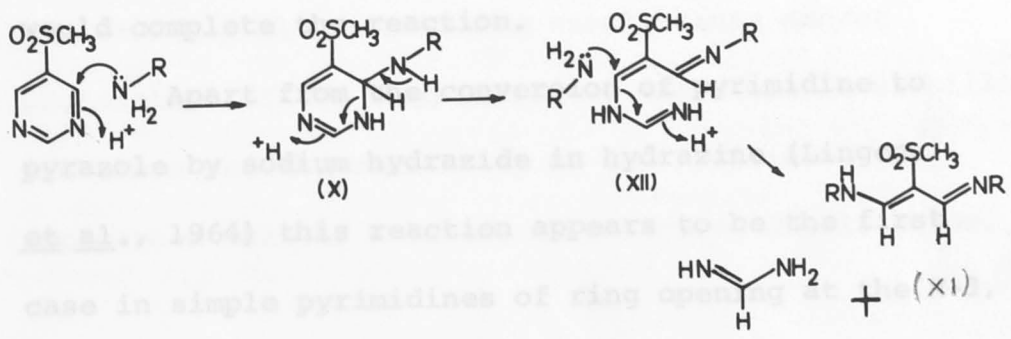
(Ib) R = n-PENTYL
(Ic) R = BENZYL
X = $SOCH_3$



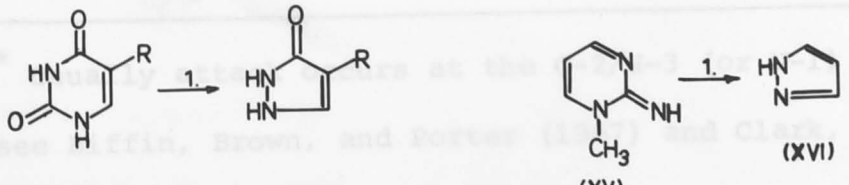
(V) (VI)



(VII) (VIII) (IX)



(X) (XII) (XI)



(XIII) (XIV) (XV) (XVI)

1, Hydrazine

3. Discussion

It is clear that the three contiguous carbon atoms in the iminopropenamine can only come from C-4, C-5 and C-6 of the pyrimidine ring; furthermore fission of the C-N bond in the alkylamine is most unlikely under the conditions employed, so that N-1, C-2 and N-3 must be eliminated in the reaction. A mechanism in accord with these deductions would involve initial attack by the alkylamine at C-4, ring opening to (X), and a second nucleophilic attack by the amine at C-6 to give (XI). Elimination of formamidine (XII) (detected as ammonia) in the basic reaction mixture would complete the reaction.

Apart from the conversion of pyrimidine to pyrazole by sodium hydrazide in hydrazine (Lingens et al., 1964) this reaction appears to be the first case in simple pyrimidines of ring opening at the N-3, C-4 bond* and loss of N-1+C-2+N-3, although this type

---

* Usually attack occurs at the C-2/N-3 (or N-1) bond, see Biffin, Brown, and Porter (1967) and Clark, Gelling, and Neath (1967).

of a reaction has been noted in some substituted pyrimidines which are vinylogous amides or amidines rather than fully aromatic systems. For instance, the reaction uracil (XIII; R=H) or thymine (XIII; R=CH_3) with hydrazine gave the pyrazolone (XIV) derived from C-4+C-5+C-6 of the pyrimidine ring (Lingens and Schneider-Bernlöhr, 1965) and 1-methyl-1,2-dihydro-2-iminopyrimidine (XV) with butylamine gave NN'-dibutyl-3-iminoprop-1-eneamine (IV) or with hydrazine, pyrazole (XVI) (Paddon-Row, 1966).

The formation of the water adduct and the nucleophilic attack at C-4 indicated that, with increasingly electronegative substituents and/or protonation of the ring nitrogen, the aromatic stability decreases and the reactivity of the pyrimidine ring approaches that of a series of polarized double bonds.

Chapter 4

2-ARYLSULPHONYL- AND 2-ARYLSULPHINYL-PYRIMIDINES. THE TRANSMISSION OF ELECTRONIC EFFECTS THROUGH THE SULPHONE AND SULPHOXIDE GROUP

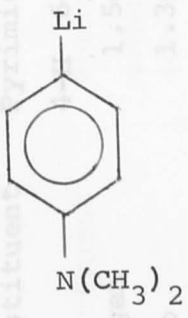
Introduction

A number of p-substituted-2-phenylsulphonyl- and -2-phenylsulphinyl-pyrimidines was prepared and the displacement of the sulphone and sulphoxide groups by pentylamine and hydroxide anion was investigated. From the relative insensitivity of the rate constants to variations in the nature of the substituent it is concluded that both sulphonyl and sulphinyl groups are poor transmitters of electronic effects. Apparent base catalysis of the reaction of 2-p-tolylsulphonylpyrimidine with pentylamine was observed and is considered to provide evidence for the presence of an intermediate in the nucleophilic displacement reaction.

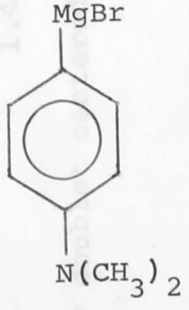
1. Preparation and Physical Properties

The 2-p-substituted-phenylthiopyrimidines, to be used as intermediate in the preparation of the corresponding 2-phenylsulphinyl- and 2-phenylsulphonyl-pyrimidines were prepared from 2-chloropyrimidine and the appropriate

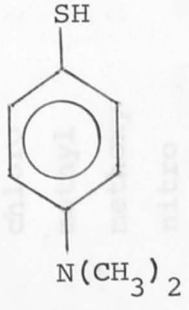
p-substituted-thiophenoxide anion. The required thiophenols were prepared by treatment of the corresponding Grignard reagent with sulphur (Leukart, 1904). This provided a new and better synthetic route to 4-dimethylaminothiophenol, previously prepared from p-dimethylaminophenyllithium (I) (Gilman, 1949) because the Grignard (II) could not be prepared in diethylether. More recently, Owen (1961) was able to utilize the greater solvating properties of tetrahydrofuran (Normant, 1954) to prepare the p-dimethylaminophenyl Grignard reagent (II). In our hands it reacted vigorously with sulphur to give p-dimethylaminothiophenol (III) in high yield. The p.m.r. and ultraviolet spectra of the phenylthiopyrimidines are recorded (Tables 1 and 2).



(I)



(II)



(III)

Table 1

P.m.r. spectra of 2-p-substituted-phenylthiopyrimidines

p-substituent	Pyrimidine protons			Phenyl ring protons		Jcps	Others	
	4-H	6-H	5-H					
Hydrogen		1.54	3.10	broad multiplet at 2.4				
chloro		1.36	2.91	2.25(d)	2.51(d)	9.4		
dimethylamino		1.36	3.03	2.42(d)	2.68(d)	9.1	NMe_2	5.46
methyl		1.38	2.45	2.35(d)	2.60(d)	8.6	CH_3	7.56
methoxy		1.36	2.48	2.29(d)	2.90(d)	9.1	OCH_3	6.09
nitro		1.49	3.03	1.75(d)	2.22(d)	9.1		

d = doublet centered at this τ value.

Table 2

Ultraviolet spectra of 2-p-substituted-phenylthiopyrimidines

p-substituent	pH	$\lambda_{max.}$ ($\log_{10}\varepsilon$)
chloro	5.0	224(4.08), 243(4.16)
methyl	5.0	250(4.11)
methoxy	5.0	248(4.23)
nitro	5.0	245(4.14), 319(3.87)

Table 3

P.m.r. spectra of 2-p-substituted-phenylsulphinyl- and phenylsulphonyl-pyrimidines*

p-substituent	Pyrimidine ring protons		Phenyl ring protons		J(cps)	Other
	4-H+6-H (doublet)	5-H (triplet)				
Sulphoxides						
Hydrogen	1.03	2.34	2.00	2.41	8.5	
chloro						
methyl	1.03	2.55	1.48	2.84	8.6	CH_3 7.10
methoxy	0.97	2.48	2.09	2.60	8.6	OCH_3 6.08
nitro	1.18	2.67	1.82	2.71	8.7	
Sulphones						
hydrogen	0.95	2.40	1.74	2.33	8	
chloro	1.11	2.56	1.98	2.67	8.6	
methyl	1.13	2.57	1.95	2.97	8.6	CH_3 7.58
methoxy	0.95	2.36	1.81	2.40	8.6	OCH_3 6.16
nitro**	0.97	2.21	1.65		8.6	

* In $CDCl_3$ TMS internal reference.

** Insoluble $CDCl_3$; in D^6 DMSO TMS internal reference.

Oxidation of the phenylthiopyrimidines (1 mole) with m-chloroperbenzoic acid (1 or 2 moles) gave the required phenylsulphinyl or phenylsulphonylpyrimidines (Table 3 and 4).

Table 4

Ultraviolet spectra of the 2-p-substituted-phenylpyrimidine sulphones and sulphoxides in 95% ethanol

p-Substituent	$\lambda_{max.}$; ($\log_{10}\varepsilon$)
Sulphoxides	
hydrogen	227(4.13)
	226(4.11)*, 227(4.13)*
chloro	
methyl	233(4.20)
methoxy	245(4.21)
nitro	254(4.11)
Sulphones	
hydrogen	235(4.04), 267^{i}(3.30)
	228(3.87)*, 267(3.08)*
chloro	240.5(3.19)
methyl	238.5(3.09)
methoxy	256(3.04)
nitro	

* pH 5 buffer

The infrared spectra of the sulphones and sulphoxides were also recorded (Table 5) to determine the effect of the p-substituent on the SO stretching frequency.

Table 5

Infrared spectra of 2-p-substituted phenylpyrimidinyl sulphones and sulphoxides

p-substituent	sulphone* (symmetrical vibration)	sulphoxide+
hydrogen	1150 cm^{-1}	1057 cm^{-1}
chloro	1150	1059
dimethylamino	1145	-
methyl	1149	1059
methoxy	1151	1061
nitro	not soluble	1058

* In CS_2 solution 0.1 mm cell Perkin Elmer 21 machine.

\+ Nujol mull, Unicam SP 200 machine.

The p-substituent had little effect on the SO or SO_2 frequencies showing that perturbations of the electron density in the aromatic ring caused little change in the SO bond character, indicating a low degree of conjugation between either the SO or SO_2 group

and the aromatic ring.

All substituted phenylsulphinyl and phenylsulphonyl pyrimidines reacted readily with pentylamine to give the expected 2-pentylaminopyrimidine. The crude product from reaction of pentylamine with either 2-*p*-nitrophenylsulphinyl-pyrimidine or 2-*p*-nitrophenylsulphonylpyrimidine was examined spectrophotometrically. No *p*-nitro-N-pentylaniline was detected (sensitivy *ca*. 1%).

2. Kinetics

The kinetics of the displacement of *p*-substituted benzenesulphinic acids by pentylamine from the 2-*p*-substituted phenylsulphonylpyrimidines were studied in anhydrous tertiary butanol, [redacted]. Preliminary experiments showed that no reaction occurred between the solvent and the sulphonylpyrimidine. The rate of appearance of 2-pentylaminopyrimidine was determined spectrophotometrically (at 308 mμ). The second order rate constant (k_2) (l mole^{-1} sec^{-1}) was calculated from the expression:

$$k_2 = \frac{2.303}{t(a-b)} \log_{10} \frac{a(b-x)}{b(a-x)} ,$$

where a and b are the initial concentrations (moles l^{-1}) of pentylamine and the phenylsulphonylpyrimidine respectively, and x is the concentration of 2-pentylaminopyrimidine at time t (seconds). The measurements were carried out at two different concentrations of amine to determine the presence or absence of base catalysis of the displacement reaction by the excess of pentylamine (Ross, 1964; Bunnett and Garst, 1965). The results are recorded in Table 6.

Table 6

Second-order rate constants for the reaction of 2-*p*-substituted-phenylsulphonylpyrimidines with pentylamine

Substituent	concentration (mole l^{-1}) sulphone $\times 10^4$	amine $\times 10^4$	k ($l.mole^{-1}sec^{-1}$) $\times 10^3$
hydrogen	4.118	14.72	1.11 ± 0.03
	3.831	29.45	1.14 ± 0.04
methyl	3.41	25.70	0.800 ± 0.02
	3.72	36.07	1.04 ± 0.02
methoxy	3.715	14.72	0.79_2 ± 0.04
	3.673	36.01	0.81_7 ± 0.04
chloro	3.211	5.00	1.36 ± 0.02
	3.213	5.14	1.68 ± 0.03

The second-order rate constant for the p-tolyl and p-chlorophenyl-sulphonylpyrimidine showed a considerable dependence on amine concentration and this dependence was reflected in the slight decrease in the second-order rate constant (k_2) as the reaction progressed and the pentylamine concentration decreased concomitantly (Table 7).

Table 7

Variation of rate* with the extent of the reaction of 2-p-tolylsulphonylpyrimidine+ with pentylamine

% reaction	k_2 (l. mole^{-1} sec^{-1})
5.6	0.834
14.1	0.827
20.4	0.804
25.4	0.812
35.6	0.812
43.9	0.807
51.4	0.792
58.1	0.787
61.4	0.785
67.0	0.779
77.5	0.775

* At 65.00 ±0.01°

+ Initial concentrations:

2-p-tolylsulphonylpyrimidine 3.41 x 10^{-3} mole $l.^{-1}$

pentylamine 25.7 x 10^{-3} mole $l.^{-1}$

This apparent dependence of the second order rate constant on pentylamine concentration was further investigated for 2-*p*-tolylsulphonylpyrimidine: the initial pentylamine concentration was varied while the 2-*p*-tolylsulphonylpyrimidine concentration was kept constant. The results (Table 8) show that the rate constant is dependent linearly (Fig. 1) on the initial amine concentration (as the pentylamine is present in considerable excess the initial concentration provides a good measure of the amine concentration throughout the reaction).

The effect is not a general one: addition of varying amounts of a tertiary amine (triethylamine*) at constant pentylamine concentration did not significantly alter the second order rate constant (Table 9) and (Fig. 1).

---

* The pK_a of triethylamine is comparable with that of pentylamine (10.7 and 10.6 respectively; Perrin, 1965) and hence is presumably an equally efficient base catalyst, yet unable to participate easily in the displacement reaction.

Table 8

Kinetics* of the reaction of 2-p-tolylsulphonyl-pyrimidine+ with pentylamine

Initial pentylamine conc. (mole $l.^{-1}$) x 10^3	Second-order rate constant ($l.\ mole^{-1} sec^{-1}$) x 10^3
12.85	0.765±0.03
25.7	0.80±0.02
54.21	0.94±0.01
73.56	1.025±0.03

* at 65.00°±0.01

\+ Initial concentration: 3.41 x 10^{-3} mole $l.^{-1}$

Table 9

Effect of added triethylamine on 2-p-tolylsulphonyl-pyrimidine*/pentylamine+ reaction kinetics

Triethylamine conc. (mole $l.^{-1}$) x 10^3	Second-order rate constant ($l.mole^{-1} sec^{-1}$) x 10^3
0	0.94±0.01
45.15	0.95_5±0.01
90.30	0.95_6±0.02

* Initial concentration: 3.41 x 10^{-3} mole $l.^{-1}$

\+ Initial concentration, pentylamine: 54.27 x 10^{-3} mole $l.^{-1}$

FIGURE 1. Rate constant dependence on amine concentration.

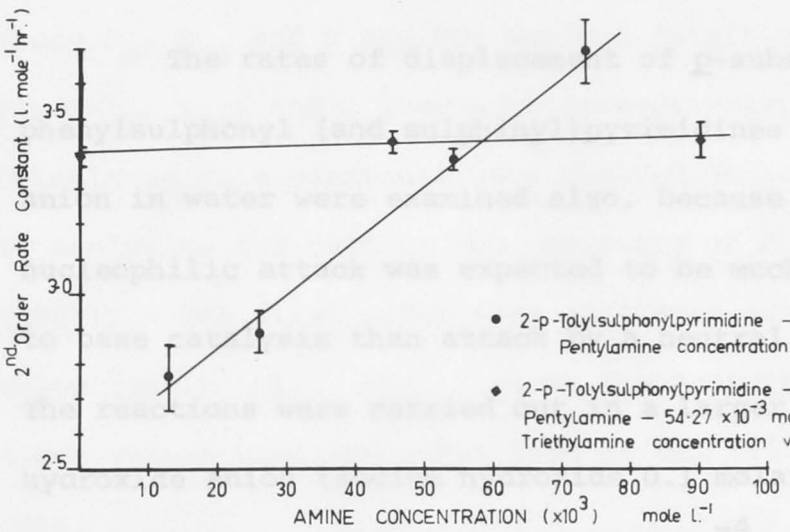
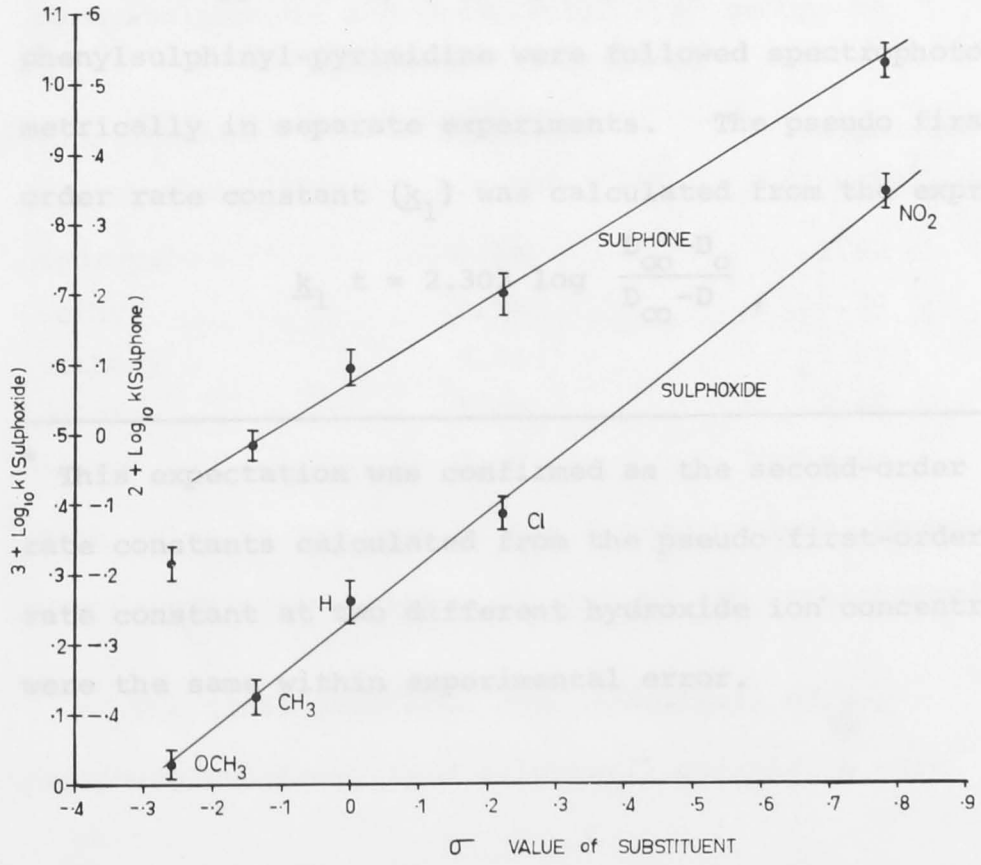


FIGURE 2. Hammett plots for p-substituted Phenyl Pyrimidinyl Sulphones and Sulphoxides / OH^- reactions.



The rates of displacement of p-substituted-phenylsulphonyl (and sulphinyl)pyrimidines by hydroxide anion in water were examined also, because an anionic nucleophilic attack was expected to be much less subject to base catalysis than attack by a neutral nucleophile.* The reactions were carried out in a larger excess of hydroxide anion (sodium hydroxide 0.1 molar, sulphonyl- or sulphinyl-pyrimidine approx. 3×10^{-4} molar) and the rates of appearance of the 2-hydroxypyrimidine anion and of disappearance of the phenylsulphonyl- or phenylsulphinyl-pyrimidine were followed spectrophotometrically in separate experiments. The pseudo first-order rate constant (k_1) was calculated from the expression:

$$k_1 \, t = 2.303 \log \frac{D_\infty - D_o}{D_\infty - D} ,$$

---

* This expectation was confirmed as the second-order rate constants calculated from the pseudo-first-order rate constant at two different hydroxide ion concentrations were the same within experimental error.

where D_o, D_∞ and D are the optical densities at times t_o, t_∞, and t (seconds) respectively. The calculated rate constants were checked in some cases by analysing the data by the technique of Guggenheim (1929). The first-order rate constants are shown below (Table 10). Fig. 2 shows the Hammett plot (the sigma values used are taken from Jaffe, 1953) of this data.

Table 10

First-order rate constants* for displacement of phenylsulphonyl- and phenylsulphinyl- groups by hydroxide ion (0.05 N)

p-substituent	sulphone $k \times 10^2$	sulphoxide $k \times 10^3$
hydrogen	1.26	1.82
methyl	0.96	1.34
methoxy	0.655	1.07
chloro	1.64_4	2.42
nitro	3.40	6.99

* Each value is the mean of six determinations, comprising three determinations taken at each of two wavelengths.

The final solutions from hydrolysis of 2-p-nitrophenylsulphonyl (and sulphinyl) pyrimidine were

examined spectroscopically for the presence of p-nitrophenolate anion. Although the detection limit was ca. 1% no p-nitro- phenolate anion was apparent in either product. This indicated that the relative rates of displacement of p-nitrophenyl sulphinate ion from pyrimidine and 2-pyrimidinyl sulphinate ion from p-nitrobenzene were at least 100:1, corresponding to a difference in activation energy (at 20^{o}) of more than 3.8 kcal. $mole^{-1}$.

(ii) Discussion.

The dependence of the second-order rate constant (k_2) of 2-p-tolylsulphonylpyrimidine on amine concentration may be described by equation (i).

$$k_2 = k_o + k_b \text{ (pentylamine)}$$

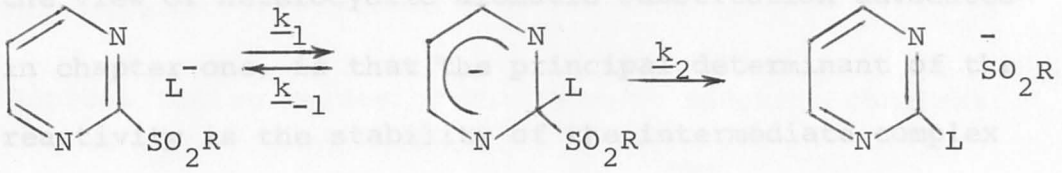
where: $k_o = 6.98 \times 10^{-4}$ l. $mole^{-1} sec^{-1}$

$k_b = 4.45 \times 10^{-3}$ $l.^2$ $mole^{-2} sec^{-1}$ ...(i)

The ratio k_b/k_o (6.37) is close to the values observed in the reaction of 2,4-dinitrofluorobenzene with butylamine (Bunnett and Garst, 1965) and of p-fluorobenzene with piperidine (Suhr, 1963). This mild acceleration

may be interpreted in terms of the previously described (Chapter 1) kinetic scheme for base catalysis of aromatic nucleophilic substitutions which pass through an intermediate. Apart from the recent results for 2- and 4-chloroquinoline (Illuminati *et al.*, 1967) this appears to be the first evidence for an intermediate such as (IX, Scheme 1, Chapter 1) in a heterocyclic nucleophilic substitution.

The Hammett plots give straight lines of slopes +0.60 and +0.77 for the *p*-substituted-phenylsulphones and -phenylsulphoxides respectively. The essential point about these results is the smallness of the *rho* values which are in the lower tail of the distribution of *rho* values for a variety of reactions analogous to this nucleophilic displacement (see Appendix at end of this Chapter). The interpretation of these values in terms of transmission of electronic effects by the sulphone or sulphoxide groups is complicated by not knowing which of the two possible steps (shown below) in the nucleophilic displacement is rate determining.



(IV)

If the attack of the nucleophile ($\underline{k}_1$) is rate determining, the small ρ values indicate that inductive transmission of electronic effects through the SO_2 and SO groups is small; the rate-determining factor would be the charge at the site of attack. Alternatively, if the bond breaking stage is rate determining, resonance effects between the developing sulphenate and sulphinate anion and the substituent groups must be slight; furthermore, the "normal" σ^- value for p-NO_2 groups may be correlated more satisfactorily than $\sigma^-_{NO_2^-}$ (NO_2 conjugated to a negative centre) thus indicating that little negative charge is developed in the rate determining step, or alternatively, that the SO_2 or SO group is poorly conjugated to the phenyl aromatic system and hence the substituent group cannot interact with the negative charge.

A different hypothesis which is compatible with

the view of heterocyclic aromatic substitution advocated in chapter one, is that the principal determinant of the reactivity is the stability of the intermediate complex (IV). The p-substituents are well removed from the conjugated system of (IV) and hence can exert little effect. The comparatively small difference between the rates of reaction of the sulphones or the sulphoxides supports the contention that the leaving group has little effect on the rate of reaction.

Appendix

Representative values of the Hammett reaction constant.

Reaction	temp.^{o}	rho value	Reference
$PhCO_2Ar^{*} + OH^{-} \rightarrow ArO^{-}$	0	0.98	Wiberg, 1964
$ArNHCOCH_3 + CH_3O^{-} \rightarrow ArNH_2$	30	2.15	Wiberg, 1964
$(ArO)_2PO_2CH_3 + C_4H_5N \rightarrow (ArO)_2PO_2^{-}$	30	1.1	Osborne, 1964
$ArCH_2CO_2Et + OH^{-} \rightarrow ArCH_2CO_2^{-}$	25	0.97	Norman and Ralph, 1963
$Ar.O.COCl + NO_3^{-} \rightarrow Ar.O.CO.NO_3$	10	1.50	Zahik and Schuetz, 1967
$^{+}RCO_2Et + OH^{-} \rightarrow RCO_2^{-}$	30	0.81	Fuchs and Bloomfield, 1963
$CH_3CO_2CH_2Ar + OH^{-} \rightarrow ArCH_2OH$	-	0.858	Wells, 1963
$ArCOCl + EtO^{-} \rightarrow ArCO_2Et$	0	1.987	Wells, 1963

* Ar = p-substituted-phenyl group.

\+ R = trans-2-aryl cyclopropane.

Chapter 5

REACTIONS AND KINETICS OF SOME PURINE SULPHONES AND SULPHOXIDES

Introduction

This chapter described the methylation of 2-, 6- and 8-methylthiopurine and how the structure of each product was found. Some of these products, 9-methyl-2(6- and 8-)methylthiopurine, were converted into the corresponding sulphones and sulphoxides, and the kinetics of the displacement of each methylsulphonyl or methylsulphinyl group by piperidine and hydroxide ion examined. Some solvent effects noted in the p.m.r. spectra of the methylthiopurines were investigated; similar effects were found in the spectra of simple pyridines.

1. Preparation of the 9-Methylpurine Sulphones and Sulphoxides

The 2-, 6- and 8-methylthio derivatives of 9-methylpurine required for the synthesis of the corresponding methylsulphinyl- and methylsulphonyl-purines were prepared by treatment of 2-, 6- and

8-methylthiopurine with diazomethane in ether. In each case two compounds were isolated. The 9-methyl-6(and 8)-methylthiopurines were identified by comparison of their physical properties with those reported in the literature (Elion *et al.*, 1959; Brown and Mason, 1957). 9-Methyl-2-methylthiopurine (III) was identified by comparison with authentic material synthesized unambiguously (Fig. 1) from 5-amino-2-mercapto-4-methylaminopyrimidine (I) *via* 2-mercapto-9-methylpurine (II).

The 9-methyl methylsulphonyl (and methylsulphinyl) purines were prepared by oxidation of the corresponding methylthio compound with *meta*-chloroperbenzoic acid. The infrared spectra nujol mull, bands at 1080, (S-O stretch); 1320, 1180 $cm.^{-1}$ (SO_2 stretch) confirmed the products as sulphones and sulphoxides rather than mono- and di-*N*-oxides. Furthermore, in the p.m.r. spectra the expected downfield shift of the methyl group attached to sulphur was observed (compare Tables 1 and 6).

Table 1

P.m.r. spectra of substituted 9-methylpurines*

Substituent	Peak positions (τ values)			
	NCH_3 or $SOCH_3$ / SO_2CH_3	2-H	6-H	8-H
2-methylsulphinyl	6.60 6.61	-	0.82	1.73
2-methylsulphonyl	5.90 6.53	-	0.62	1.52
6-methylsulphinyl	6.05 6.86	0.91	-	1.85
6-methylsulphonyl	6.00 6.52	0.91	-	1.65
8-methylsulphinyl	5.84 6.74	0.97	0.84	-
8-methylsulphonyl	5.84 6.44	0.91	0.79	-

* 5% solutions in $CDCl_3$; TMS internal reference

Table 2

Ultraviolet spectra of purines

Substituents	pH	Species	λ_{max} (mμ)	$\log_{10}\varepsilon$
9-methyl-2-methylthio	7	0	236,257.5,261,302	4.66,4.26,4.25,4.26
	0	+	248	4.21
9-methyl-6-methylthio	7	0	220,242,286	4.08,4.25,4.24
	0	+	224,299	4.01,4.23
9-methyl-8-methylthio	7	0	221,289	4.13,4.25
	0	+	238,301	4.16,4.15
7,8-dimethyl-2-methylthio	7	0	242,311	4.35,4.34
	0	+	238,320	4.40,4.20
3-methyl-6-methylthio	7	0	237,311	3.99,4.22
	0	+	316	4.295
3-methyl-8-methylthio	5	0	240^{i}, 318	4.32
	0	+	321	4.41
9-methyl-2-methylsulphinyl	7	0	272.5	3.93
9-methyl-2-methylsulphonyl	7	0	266	3.91

Table 2 (page 2)

9-methyl-6-methylsulphinyl	7	0	277	3.95
9-methyl-6-methylsulphonyl	7	0	280	3.93
9-methyl-8-methylsulphinyl	7	0	274	4.11
9-methyl-8-methylsulphonyl	7	0	271	4.10
9-methyl-2-piperidino[a]	7	0	232,257,332	4.43,4.02,3.71
	1.9	+	237,260,343	4.55,3.99,3.42
9-methyl-6-piperidino[a]	6.5	0	216,282	4.20,4.30
	1.3	+	213,275	4.20,4.27
9-methyl-8-piperidino[a]	6.5	0	212[i],224, 262[i],295	4.08,3.12, 4.18,3.71
	2.2	+	222,235[i], 242,312[i]	4.12,4.06, 3.44,4.11

[a] Barlin and Chapman, 1965.

2. Methylation of the Methylthiopurines

The structures of the by-products from the methylations, described above, were elucidated. The second compound from 6-methylthiopurine was shown to be 3-methyl-6-methylthiopurine (m.p., analysis [parent ion; m/e 180], and ultraviolet spectrum). Similarly the second compound ($C_7H_8N_4S$, parent ion; m/e 180) from 8-methylthiopurine is probably 3-methyl-8-methylthiopurine. Its p.m.r. spectrum showed N-methyl (5.88 τ) and S-methyl (7.27τ) groups as well as 2 aromatic protons. That the N-methyl group was at N-3 rather than N-1 or N-7 follows from the large bathochromic shift relative to the parent compound, which is characteristic of N-3-methylation (Elion, 1962; Neiman and Bergmann, 1965; Bergmann, Neiman, and Kleiner, 1966), i.e. 3-methyl-8-methylthiopurine, $\lambda_{max.}$, 240, 318 mμ; $\log_{10}\varepsilon$ 4.32, 4.41 (pH 5). cf. 8-Methylthiopurine $\lambda_{max.}$, 246, 290 mμ; $\log_{10}\varepsilon$ 3.59; 4.30 (pH 5) (Brown and Mason, 1957). In contrast N-7-methylation causes a small bathochromic shift ($\leqslant$5 mμ) Bergmann, 1964; Mason, 1954; Brown and Mason, 1957; Brown, Ford, and Tratt, 1967) while N-1-methylation had little effect (Elion, 1962; Balsiger et al., 1961).

The compound ($C_8H_{10}N_4S$, parent ion; m/e 180) from the methylation of 2-methylthiopurine, differed from the proceeding two compounds in having a C-methyl group in addition to S-methyl and N-methyl groups (p.m.r. spectrum in $CDCl_3$:NCH_3, 5.78; SCH_3, 7.16; CCH_3, 7.06; aromatic H, 1.69). The C-methyl group was located at C-8 because the aromatic proton peak moved upfield 0.3τ in D^6DMSO relative to its position in $CDCl_3$ (see later). The small bathochromic shift relative to the parent compound [3 mμ, after correcting for the shift due to the 8-methyl group (Mason, 1954)] is indicative of N-7-methylation.

The mass spectrum of the compound further supported the assignment of the methyl group to C-8. The fragmentation pattern for the 3-methyl-6(and 8)-methylthiopurines showed the loss of CH_2S followed by the loss of two moles of HCN. By analogy with the mass spectra of purine and the three simple methylpurines (Tatematsu, Goto and Matsuura, 1966), the first mole of HCN was lost from the pyrimidine ring, while the second mole was eliminated from the imidazole ring. However

the 7,8-dimethyl-2-methylthiopurine lost only one mole of HCN (from the pyrimidine ring by the above analogy) followed by elimination of a fragment m/e 41 (CH_3CN) from the imidazole ring, indicating that the methyl group was attached at C-8. Hence the compound was 7,8-dimethyl-2-methylthiopurine.

The formation of the different methylation products may be explained by the various reaction paths of the methyldiazonium cation, the normal intermediate (Gompper, 1963) in methylations with diazomethane*. In the 6-(and 8)methylthiopurines, the methyldiazonium ion formed by proton transfer from the purine was attacked by one of the adjacent negatively charged centres (N-3 or N-9) in the mesomeric anion (IV), before the solvent cage was disrupted. In 2-methylthiopurine, coordination of the positively charged nitrogen of the methyldiazonium

---

* The results are equally well rationalized in terms of the "direct methylation" mechanism (Arndt, 1953). Both mechanisms require the participation of a solvent-caged ion-pair.

cation to the sulphur lone pairs (V), stabilises the cation and orientates the methyl group for attack at N-9. Delocalisation of the positive charge to the sulphur may lead to formation of a less energetic methyl cation (Streitwieser and Schaeffer, 1957) able to move across the electron excessive imidazole ring to attack at C-8 (or N-7).

3. Ring Opening in 6-Methylthiopurine

(i) Preparation and structure of product.

Methylation of 6-methylthiopurine with methyl iodide/potassium carbonate in dimethyl sulphoxide (Beaman and Robins, 1963) gave the required 9-methyl-6-methylthiopurine (identified by comparison with authentic material) and another compound ($C_7H_8N_4O$; m/e 164). Its infrared spectrum (nujol) showed strong bands at 2200 cm^{-1} (-CN stretch), 1670 cm^{-1} (CO stretch of a secondary or tertiary amide; absence of bands in 3500-3200 cm^{-1} region suggested a tertiary amide), and 1570 cm^{-1} (-C=N- stretch). The p.m.r. spectrum*

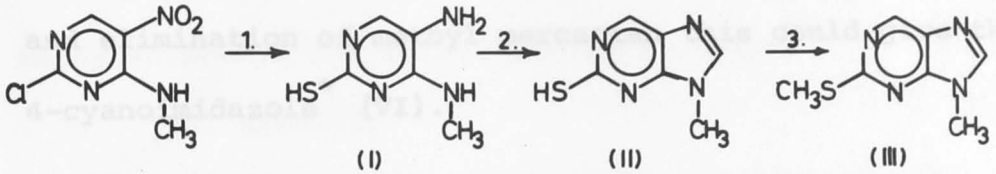
---

* The assignments reported here are supported by those of 1-methyl-5-methylcarbamoyl-4-methylformamidoimidazole (VIII, values as shown) (Dr. R. Hoskinson, Personal communication.

showed 2 protons at 0.93τ, and 2.60τ (assigned to the proton of a formamido group and the 2-proton of imidazole respectively) and two methyl groups at 6.24τ, (N-1-methyl group) and 6.63τ (4-methylformamido group). The structures (VI) and (VII) were consistent with the above data. Of these, the 4-cyano-1-methyl-5-methylformamidoimidazole (VI) was preferred to its 5-cyano isomer (VII), because a reasonable mechanism could be written (see below) for its formation from 9-methyl-6-methylthiopurine (the major product of the reaction) while no 7-methyl-6-methylthiopurine (which by the same mechanism would give the 5-cyanoimidazole) could be detected in the crude reaction mixture by p.m.r. spectroscopy. The mass spectrum was consistent with both (VI) and (VII), showing a parent ion at m/e 164 and loss of CO and HCN.

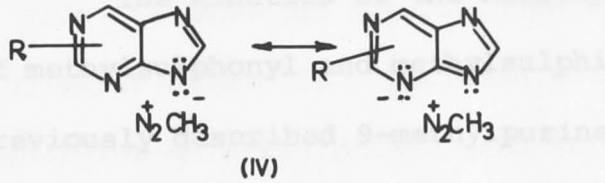
(ii) Probable mechanism of ring opening.

9-Methyl-6-methylthiopurine is known to be methylated at N-3 by the usual alkylating agents in aprotic solvents (Neimann and Bergmann, 1965), giving (IX). Nucleophilic attack (by hydroxide ion) at the 2-position, now activated by the adjacent positive

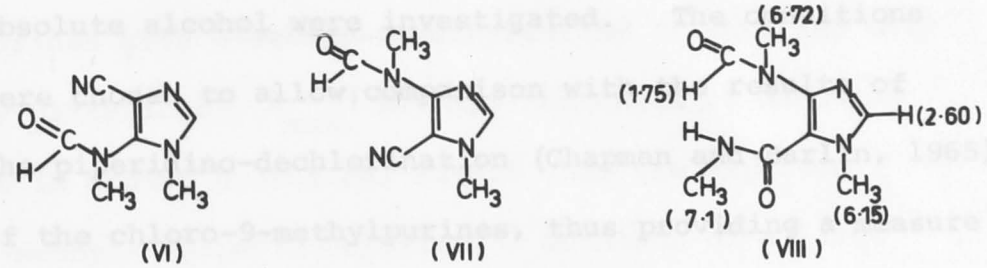


(I) (II) (III)

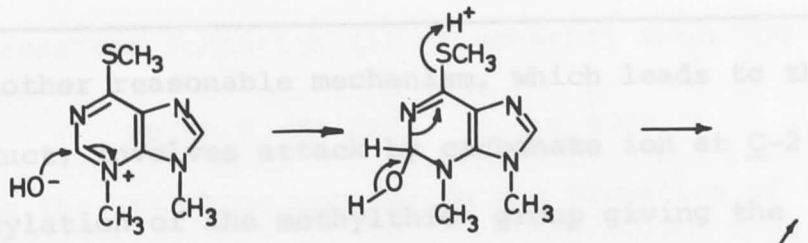
1, NaSH 2, HCO_2H / Reflux 3, CH_3I / OH^-



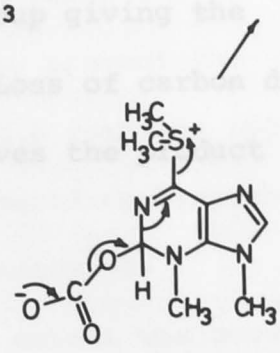
(IV) (V)



(VI) (VII) (VIII)



(IX) (X) (VI)



(XI)

charge, could yield (X); by concerted proton abstraction and elimination of methyl mercaptan this could give the 4-cyanoimidazole* (VI).

4. Kinetics

The kinetics of the nucleophilic displacement of methylsulphonyl and methylsulphinyl groups from the previously described 9-methylpurines by piperidine in absolute alcohol were investigated. The conditions were chosen to allow comparison with the results of the piperidino-dechlorination (Chapman and Barlin, 1965) of the chloro-9-methylpurines, thus providing a measure

---

* Another reasonable mechanism, which leads to the same product, involves attack by carbonate ion at C-2 and methylation of the methylthio- group giving the 6-dimethylsulphonium ion (XI). Loss of carbon dioxide and methyl sulphide, as shown, gives the product (VI).

of the relative ease of displacement of the chloro, methylsulphonyl and methylsulphinyl groups.

(i) Results.

All the 9-methyl-2(6 and 8)-methylsulphonyl (and methylsulphinyl) purines reacted with neat piperidine to give the expected piperidinopurines. However in 0.05 molar ethanolic piperidine solution both the 9-methyl-8-methylsulphonyl (and methylsulphinyl) purines gave 8-ethoxy-9-methylpurine (identified only by ultraviolet $\lambda_{max.}$ 272 mμ, unchanged on addition of 1N sodium hydroxide) rather than the expected 9-methyl-8-piperidinopurine. Addition of a large excess (0.1 molar) of piperidine hydrochloride to suppress the formation (i) of ethoxide anion (presumed

$$EtOH + HN(CH_2)_5 \rightleftharpoons EtO^- + H_2\overset{+}{N}(CH_2)_5 \quad \ldots\ldots (i)$$

to be the attacking species in the formation of the 8-ethoxy-9-methylpurine), failed to prevent the formation of the ethoxypurine. The reaction appeared to be accelerated by the added piperidine hydrochloride, suggesting that protonation of 9-methyl-8-methylsulphonylpurine to a minute extent was occurring and activating the ring towards nucleophilic attack by

the solvent (ethanol) rather than by ethoxide ion. 9-Methyl-8-methylsulphinylpurine reacted similarly.

Both 9-methyl-2-methylsulphonylpurine and the corresponding methylsulphinylpurine decomposed under reaction conditions (0.05 molar piperidine, 90°) estimated from the pyrimidine sulphone (Chapter 2) and purine sulphide (this chapter, see later) data to produce 50% reaction in 3 hours. The dark brown solution did not show the expected 9-methyl-2-piperidinopurine peak ($\lambda_{max.}$ 332 mμ). Lower temperatures gave the same result. Thus the 2-sulphones and sulphoxides displayed the same instability toward amines as did the 2-methylthiopurines (see later).

Before the kinetics of the reaction of the 6-methylsulphinyl and 6-methylsulphonyl derivatives of 9-methylpurine could be examined, it was necessary to devise means for following the reaction. Table 2 shows that there is considerable overlap in the ultraviolet spectra of 9-methyl-6-methylsulphonylpurine and the corresponding 6-piperidinopurine. However the ultraviolet spectra of 6-hydroxy-9-methylpurine anion ($\lambda_{max.}$ 254 mμ; Elion, 1962) does not overlap

that of the sulphone ($\lambda_{max.}$ 280 mμ). Thus "quenching" the reaction mixture in sodium hydroxide solution should convert the unreacted sulphone to the anion of the hydroxy compound and allow measurement of the 9-methyl-6-piperidinopurine concentration without interference. For this procedure to give accurate kinetic data the hydrolysis of the sulphone must be much faster than the aminolysis. The rates of reaction of the sulphones with sodium hydroxide were examined. The results (Table 3) indicate that under the conditions used (1N, NaOH; piperidine, approx. 10^{-3} molar) the hydrolysis is about 10^{4} times faster than the aminolysis.

Table 3

Hydrolysis rates* of 9-methylpurines (1N NaOH)

Substituent	k^{+} (l $mole^{-1} sec^{-1}$)
2-methylsulphinyl	2.46×10^{-3}
2-methylsulphonyl	8.43×10^{-3}
6-methylsulphinyl	1.92
6-methylsulphonyl	0.98
8-methylsulphinyl	6.02
8-methylsulphonyl	5.16

+ At 20°, probable error ± 3%.

* Average value from 3 runs at each of 2 different wavelengths.

Table 4

Kinetics of reaction with piperidine

Temperature (°)	10^2(piperidine)	10^4(purine)	$10^4 k$(sec^{-1})
9-methyl-6-methylsulphinylpurine			
9.65	3.983	1.991	5.110
16.90	3.983	1.991	7.37
24.68	3.983	1.111	10.81
24.68	7.866	1.111	21.76
31.65	3.983	1.111	14.71
9-methyl-6-methylsulphonylpurine			
26.01	1.166	1.186	1.235
37.85	1.166	1.186	2.584
37.85	2.322	1.186	5.277
46.25	1.166	1.186	4.072

The Arrhenius parameters calculated from the above data are:

Compound	k^* ($mole^{-1}$ 1 sec^{-1})	E (kcal. $mole^{-1}$)	$\log_{10} A$
9-methyl-6-methylsulphinylpurine	0.116	8.26	4.40
9-methyl-6-methylsulphonylpurine	.026	11.15	6.28
9-methyl-6-chloropurine [a]	.0288	11.3	6.30

[a] Barlin and Chapman, 1965

* Second order rate constant, at 40°

Using the above method the 6-methylsulphinyl and 6-methylsulphonyl derivatives of 9-methylpurine reacted normally and the rate constants for their reaction with piperidine in absolute alcohol are shown in Table 4.

The "preparative kinetics" of the displacement of methylthio groups from 2,9-dimethyl-6(and 8) methylthiopurine by n-butylamine were also investigated; 2-methylthiopurines were excluded because they were unchanged after 24 hours at 200° with.butylamine. It was expected that the 2-methyl group would increase the solubility of the purine in the amine. The 9-methyl group was inserted as a blocking group to prevent the formation of an anion (Sutcliffe and Robins, 1963). A large excess of butylamine was used and plots of time against log $\frac{D_\infty - D_o}{D_\infty - D}$ gave straight lines up to 80% reaction. The first order rate constants and half lives of the reactions are shown in Table 5.

Table 5

Kinetics of the reaction of methylthiopurines with butylamine[a]

Purine	Analytical Wavelength	$\underline{k}$[b] $(sec.^{-1}) \times 10^5$		$t_{\frac{1}{2}}$ (hr.)
2,9-dimethyl-6-methylthio				
	265	3.88	3.75	5.1
	272	3.78		
	292	3.57		
2,9-dimethyl-8-methylthio				
	255	1.39	1.5	12.6
	256	1.66		
	258	1.51		

Temperature: 150 ± 0.1^{o}

[a] Butylamine: purine molar ratio; 20:1

[b] First order rate constant.

An attempt was made to examine the rates of displacement of the methylsulphonyl group from the 2,9-dimethyl-6(and 8)methylsulphonylpurines using the same molar ratio of butylamine to purine. The methylsulphonylpurines were prepared from the corresponding methylthiopurines by the usual methods. However the purine sulphones (like the pyrimidinyl sulphones) displayed a very low solubility in butylamine, and reacted as they slowly dissolved. At 47^{o}, 2,9-dimethyl-

6-methylsulphonylpurine dissolved in about 10 minutes, but the reaction was complete in less than 20 minutes. For the 2,9-dimethyl-8-methylsulphonylpurine dissolution was complete after 15 minutes and, even at that time, no sulphone could be detected in the solution.

(ii) Discussion.

The results from the reaction with piperidine showed that the methylsulphonyl and methylsulphinyl groups were displaced at least as easily as the chloro group. The greater reactivity of the sulphoxide relative to the sulphone (approx. a factor of 4) was the reverse of that noted in respect of 4-methylsulphonyl and methylsulphinyl-pyrimidine. The greater reactivity of the sulphoxide is due to a decrease in activation energy which is partially compensated by a decrease in the "frequency factor" (log A) indicating that the transition state for the piperidine/sulphoxide reaction has a less positive entropy of activation. Presumably, approach of the amine is more constrained in the sulphoxide due to repulsions between the lone-pairs of the amine, of N-6, and of N-7, together with the partial double bond

character of the C-S bond arising from the p_{π}-d_{π} overlap between these two atoms cf. stabilisation of carbanions by adjacent sulphoxide groups (Cram et al., 1961).

Comparison of the butaminolysis reactions of the methylthiopurines and the rates of hydrolysis of the methylsulphonyl and methylsulphinyl-purine showed that the reactivity order depended on the nucleophile, being 6> 8 for the butaminolysis, and 8> 6 for the hydrolysis. A similar result has been noted in the chloro-9-methylpurines (Barlin and Chapman, 1965; Barlin, 1967). The theoretically predicted positional reactivities are contradictory: the coefficients of the lowest empty molecular orbital (Miller, Schmeising and Lykos, 1962) indicate an order of 6> 8> 2, the electron density predicts 6> 2> 8 (indicating failure of the "non-crossing" assumption; R. D. Brown, 1952), and the localisation energies (Pullman, 1959) require 6=8> 2. The rapidity of reaction of the methylsulphonylpurines with butylamine demonstrated qualitatively the much greater displacability of the sulphone group relative to the methylthio group.

5. Solvent Effects in P.m.r. Spectra

On changing the solvent from $CDCl_3$ to DMSO*, considerable differential shifts in peak positions were noted in the p.m.r. spectrum of a reaction mixture, which was obtained from the methylation of 6-methylthiopurine with diazomethane in ether. This observation suggested that the site of methylation might be determined from the p.m.r. spectra of the compound measured in these two solvents. To establish the relationship between structure and solvent shift, the p.m.r. spectra of all the N-methyl-methylthiopurines prepared in this study and of known structure were examined (Table 6). Peaks were assigned using:

(i) the order established (Schweizer et al., 1964; Matsuura and Goto, 1965) in purine, viz. 6< 2<8,

(ii) comparison of the spectra with those of various 9-methylpurines having other substituents in the ring.

---

* Throughout this section DMSO and dimethyl sulphoxide refer to the hexadeuterated compound $(CD_3)_2SO$.

Thus on changing the solvent from $CDCl_3$ to DMSO (Table 6) the 8-proton peak moved downfield 0.4 to 0.6τ, but the 2- and 6-proton peaks altered position (either upfield or downfield) by less than 0.15τ.

The peak positions of the various methyl groups were virtually unaltered by changing the solvent; the N-7-methyl group signal was always 0.3τ downfield with respect to the methyl signal in the corresponding 9-methylpurine.

This specific shift of the 8-proton peak cannot reasonably be attributed to association as the "internal shift"* of 6-chloro-9-methylpurine was practically insensitive to a nine-fold change+ in concentration

---

* The internal shift is defined as $\tau_8 - \tau_2$ for each solvent.

+ Klinck and Strothers (1962) consider a change in internal shift of 2-4 cps. normal for a 4-fold change in concentration when hydrogen bonding or association is absent.

Table 6

Chemical shifts of N-methylpurines in DMSO and $CDCl_3$

Purine	Proton	τ Value in DMSO	τ Value in $CDCl_3$	Δ*
9-methyl-2-methylthio				
	6-H	1.07	0.96	+0.11
	8-H	1.61	1.97	-0.36
	$2-SCH_3$	7.41	7.28	+0.13
	$9-NCH_3$	6.23	6.26	-0.03
9-methyl-6-methylthio				
	2-H	1.08	1.26	-0.18
	8-H	1.41	2.08	-0.67
	$6-SCH_3$	7.29	7.29	±0.00
	$9-NCH_3$	6.11	6.13	-0.02
9-methyl-8-methylthio				
	2-H	1.21	1.17	+0.04
	6-H	1.09	1.10	-0.01
	$8-SCH_3$	7.22	7.21	+0.01
	$9-NCH_3$	6.33	6.29	+0.04
6-chloro-9-methyl				
	2-H	1.25	1.29	-0.04
	8-H	1.36	1.91	-0.55
	$9-NCH_3$	6.12	6.08	+0.04
6,7-dimethyl-2-methylthio				
	8-H	1.60	2.13	-0.53
	$2-SCH_3$	7.20,	7.24,	
	$6-CH_3$	7.46	7.39	
	$7-NCH_3$	5.98	6.03	-0.05
6,9-dimethyl-2-methylthio				
	8-H	1.74	2.20	-0.46
	$2-SCH_3$	7.38,	7.24,	
	$6-CH_3$	7.44	7.39	
	$9-NCH_3$	6.27	6.21	+0.06

Table 6 (page 2)

2,9-dimethyl-6-methylthio			
	8-H	1.71	2.21	-0.50
	2-CH_3, 6-SCH_3	7.35, 7.35	7.30, 7.27	
	9-NCH_3	6.24	6.20	+0.04
6-butylamino-2,9-dimethyl			
	8-H	2.05	2.43	-0.38
	2-CH_3	7.50	7.46	+0.04
	9-NCH_3	6.36	6.27	-0.09

* $\Delta = \tau_{DMSO} - \tau_{CDCl_3}$

Table 7

Concentration dependance of internal shift*

Concentration (mole l^{-1})	Internal shift (cps)	
	$CDCl_3$	DMSO
0.05	39.1	7.3
0.13	39.4	7.7
0.25	39.4	7.5
0.45	37.8	6.7

* For 6-chloro-9-methylpurine

Table 8

Chemical shifts of some simple pyridines in DMSO and $CDCl_3$

Compound	Protons	τ value in DMSO	τ value in $CDCl_3$	$\Delta\tau$ (ppm)
Pyridine	2-H+6-H	1.45	1.42	+0.03
	3-H+5-H	2.33	2.45	-0.12
	4-H	2.60	2.71	-0.11
2-picoline	6-H	1.52, 1.59	1.51, 1.59	+0.01, 0
	3-H+5-H	2.74, 2.84	2.88, 2.99	-0.14, -0.15
	4-H	2.23, 2.37 2.48	2.36, 2.49 2.62	-0.13, -0.12 -0.14
	$2\text{-}CH_3$	7.55	7.48	+0.07
3-picoline	2-H+6-H	1.51	1.60	-0.09
	5-H	2.65, 2.73 2.77, 2.85	2.81, 2.89 2.94, 3.01	-0.16, -0.16 -0.17, -0.16
	4-H	2.32, 2.45	2.53, 2.65	-0.21, -0.20
	$3\text{-}CH_3$	7.72	7.74	-0.02
4-picoline	2-H+6-H	1.56	1.56	$\pm$0.00
	3-H+5-H	2.83	2.99	-0.16
	$4\text{-}CH_3$	7.69	7.73	-0.04
2,5-lutidine	3-H	2.98	3.06	-0.08
	4-H	2.60	2.73	-0.13
	6-H	1.75	1.73	+0.02

Table 8 (page 2)

2,5-lutidine	2-CH_3	7.60	7.54	+0.06
	5-CH_3	7.79	7.79	±0.00
2,6-lutidine	3-H+5-H	3.04	3.13	-0.09
	4-H	2.50	2.61	-0.11
	2-CH_3+6-CH_3	7.60	7.53	+0.07
3,4-lutidine	2-H	1.74	1.70	+0.04
	5-H	2.92	3.03	-0.11
	6-H	1.78	1.74	+0.04
	3-CH_3 4-CH_3	7.79	7.79	±0.00
3,5-lutidine	2-H+6-H	1.81	1.80	±0.01
	4-H	2.69	2.80	-0.11
	3-CH_3+5-CH_3	7.78	7.78	±0.00
2,4,6-collidine	3-H+5-H	3.23	3.23	±0
	2-CH_3	7.64	7.53	+0.11
	4-CH_3	7.79	7.75	+0.04

(Table 7) cf. the large concentration-dependent shifts in the p.m.r. spectrum of purine due to association (Chan et al., 1964).

To determine the generality of these specific solvent shifts, the p.m.r. spectra of some simple pyridines in $CDCl_3$ and DMSO were examined also (Table 8). The 3- and 5-proton, and the 4-proton peaks showed downfield shifts of 0.12 and 0.13τ respectively while the 2- and 6-proton peaks moved upfield by 0.02τ on changing from $CDCl_3$ to DMSO*.

Table 9

Solvent dependence of differential shifts

Compound	Proton	τ values in solvent (dielectric constant)			
		$CDCl_3$ (4.81)	DMSO (47.6)	Acetone (21.3)	Acetonitrile (37.5)
Pyridine	2-H+6-H	1.41	1.45	1.46	1.49
	4-H	2.43	2.34	2.34	2.37
	3-H+5-H	2.72	2.61	2.66	2.68
6-chloro-9-methylpurine	2-H	1.28	1.25	1.32	1.31
	8-H	1.90	1.36	1.57	1.76
	9-CH_3	6.06	6.11	6.05	6.16

* Average for all examples.

Discussion

The differential solvent shifts observed in the pyridines and the N-methylpurines may arise either from (i) complex formation (hydrogen bonded or charge transfer) between the solute and the solvent; provided that the complex is sufficiently stable the various protons would be shielded to different extents by the solvating molecule, and hence would show differential solvent shifts, or

(ii) from differential deshielding (Buckingham, 1960; Musher, 1962) of the various protons by the reaction field (Onsager, 1936) resulting from the interaction of the polar solute with the polar solvent.

The latter explanation is preferred for two reasons: similar differential shifts were observed in solvents of comparable dielectric constant but of considerably different solvating power suggesting that the important factor in the differential shielding is the dielectric constant of the medium (as required by the reaction field deshielding theories); the calculated shifts of the pyridine protons due to the reaction field (using both Buckingham's and Musher's parameters; see

appendix) are in reasonable agreement with the observed values (Table 10).

Extension of this theoretical treatment to the N-methylpurines is complicated, as the dipole moment and its direction are unknown. However, assuming the dipole moment is 4.5 D* and that it lies along the major axis of the purine, the calculated solvent shifts are also in reasonable agreement with the observed values (Table 10).

Table 10

Calculated differential solvent shifts

	Proton	Observed v shift	Calculated shift (a)	(b)
Pyridine				
	2-H+6-H	+0.03	-0.03	+0.08
	3-H+5-H	-0.12	-0.10	-0.11
	4-H	-0.11	-0.17	-0.21
Average shifts for N-methylpurines				
	2-H	-0.06	+0.15	
	6-H	+0.05	-0.10	
	8-H	-0.49	-0.38	

(a) Using Buckingham's (1960) parameters.

(b) Using Musher's (1962) parameters.

---

* The dipole moments of 6-chloro-9-ethyl-, 6-chloro-9-phenyl-, and 6-chloro-9-phenylethyl-purine are 4.75 D, 4.75 D, and 4.66 D respectively (Chou, Lin and Varma, 1967).

Appendix

Both Buckingham (1960) and Musher (1962) have shown that the change in proton screening constant ($\Delta\sigma$) for a proton experiencing an electric field E is given by:

$$\Delta\sigma = aE_z + bE^2$$

Where Ez is the component of the field along the X-H bond. However different values of the constants a and b were suggested, viz.

	a	b
Buckingham	-2×10^{-12}	-10^{-18}
Musher	-2.9×10^{-12}	-7.38×10^{-19}

The reaction field ($\vec{R}$) was calculated from the expression (Onsager, 1936):

$$\vec{R} = \frac{2(\epsilon-1)(n^2-1)}{3(2\epsilon+n^2)} \frac{\vec{\mu}}{\alpha}$$

Where ϵ is the dielectric constant of the solvent,

n the refractive index of the pure liquid (take n^2 as 2.5 throughout the calculation),

$\vec{\mu}$ the dipole moment of the solute, and

$\alpha = \frac{(n^2-1)}{(n^2+2)} r^3$, where r is the radius of the molecule (considered as a sphere).

Chapter 6

1. Introduction

Microanalyses were carried out by Dr. J.E. Fildes and assistant analysts Mrs. I. Komorowsky and Mrs. N. Rincic of this department.

Melting points were determined in "Pyrex" brand glass capillary tubes in an electrically heated copper block (Townson and Mercer Ltd., type V melting point apparatus), and are uncorrected.

The purity of compounds having sharp melting points was checked by ascending paper chromatography and thin layer chromatography. Whatman No.1 and No.4 papers were used with the following solvents (a) 3% aqueous ammonium chloride and (b) n-butanol/5N-acetic acid mixture. The thin layer chromatogram were carried out on 0.2 mm. alumina and silica plates (Merck, dried at 105^{o} for 2 hr.). The chromatograms were examined in ultraviolet light of wavelengths 254 mμ and 365 mμ . In addition, the plates were stained in an iodine bath.

Following the practice of the Chemical Society the names of new compounds are underlined (in lieu of italics) at their first mention in the body of the

experimental text. Names which are headings, however, are also underlined, but this does not mean that the compound is necessarily new. All new compounds are listed alphabetically in the appendix at the end of the experimental section.

2. Determination of Physical Constants

Ionisation constants were determined either by potentiometric or spectrophotometric means. The methods used are described by Albert and Serjeant (1962).

Ultraviolet spectra were obtained using a Shimadzu Recording Spectrophotometer RS 27, and the peaks checked on a Hilger "Uvispek" H700/301 quartz Spectrophotometer.

Infrared spectra were recorded on a Unicam SP 200 spectrophotometer.

Nuclear magnetic resonance spectra were measured on a Perkin Elmer R 10 spectrometer at 60 Mc/sec. and 33.5° by Mr. S. Brown. Chemical shifts are recorded as τ values. For aqueous media the sodium salt of 3-trimethylsilylpropane-1-sulphonic acid was used as internal reference, and for non-aqueous media tetramethylsilane was used as internal standard.

Mass spectra were kindly determined by Dr. J. McLeod (Research School of Chemistry, A.N.U.), Dr. S. Middleton (Monash University) and Dr. Q.N. Porter (University of Melbourne).

3. Preparation of Compounds

2-Methylsulphonylpyrimidine.- Chlorine was bubbled through a suspension of 2-methylthiopyrimidine (10 g., Boarland and McOmie, 1952) in water (100 ml.) until dissolution occurred. The temperature was maintained in the range 0 - 5° through the reaction. The reaction mixture was kept at 3° for 4 hr. then extracted with chloroform (3 x 75 ml.); the chloroform was evaporated, and the residue recrystallised from 95% ethanol giving 2-methylsulphonylpyrimidine (6.2 g.), m.p. 73-74°. Concentration of the filtrate gave a second crop (1.95 g.), m.p. 73° (Found: C, 37.9; H, 4.0; N, 17.7. $C_5H_6N_2O_2S$ requires C, 38.0; H, 3.8; N, 17.7%).

4-Methylsulphonylpyrimidine.- To

4-methylthiopyrimidine (6.3 g.; Albert and Barlin, 1962) in chloroform (100 ml.; -15°), 80% m-chloroperbenzoic acid (20.0 g.) in chloroform (350 ml., -15°) was added. The reaction mixture was maintained at room temperature for 16 hr. and then washed with saturated aqueous sodium sulphite solution (2 x 25 ml.) followed by 2N-sodium carbonate (2 x 100 ml.). Removal of chloroform left an oily residue, which crystallised from benzene-petroleum ether (40-60°), (1:3 v/v) giving 4-methylsulphonylpyrimidine (3.75 g.), m.p. 53-54° (Found: C, 38.0; H, 4.0; N, 17.7. $C_5H_6N_2O_2S$ requires C, 38.0; H, 3.8; N, 17.7%).

5-Methylthiopyrimidine.- Methanethiol from S-methylisothiouronium sulphate (49.0 g.) and sodium hydroxide (Phillips and Clarke, 1923; Windus and Shildneck, 1943) was passed into ethanolic sodium ethoxide (150 ml., 2.9 g. sodium). 5-Bromopyrimidine (15.9 g.; Bredereck, Gompper and Herlinger, 1958) was added and the solution refluxed for 12 hr. Sodium bromide was filtered off and the filtrate adjusted to pH 4 with dilute hydrochloric acid, and the ethanol evaporated under reduced pressure. The aqueous residue was extracted with chloroform (4 x 50 ml.). The chloroform

was evaporated and the residual oil distilled giving 5-methylthiopyrimidine (10.25 g.), b.p. 70-71°/2 mm. and m.p. 42° (Found: C, 48.0; H, 5.3; N, 21.9. $C_5H_6N_2S$ requires C, 47.6; H, 4.8; N, 22.2%).

5-Methylsulphonylpyrimidine.- 5-Methylthiopyrimidine was oxidised by m-chloroperbenzoic acid in the same manner as 4-methylthiopyrimidine giving 5-methylsulphonylpyrimidine (55%), m.p. 135-136° (from 95% ethanol) (Found: C, 38.3; H, 3.6; N, 17.7. $C_5H_6N_2O_2S$ requires C, 38.0; H, 3.8; N, 17.7%).

2-Phenylthiopyrimidine.- 2-Chloropyrimidine (11.5 g.; Kogon, Minin and Overberger, 1955) in ethanol was added to an ethanolic solution of sodium thiophenoxide (prepared from thiophenol, 11.0 g., in ethanolic sodium ethoxide, 210 ml., from 2.5 g. sodium). The solution was refluxed (2 hr.), refrigerated, and the sodium chloride filtered off. The ethanol was evaporated and the residue, suspended in water (200 ml.), was then extracted with chloroform (3 x 100 ml.). The chloroform was removed under reduced pressure and the residual oil distilled, giving 2-phenylthiopyrimidine (11.1 g.), b.p. 144-146°/0.8 mm. m.p. 45°. An analytical

sample was purified by thin layer chromatography (Found: C, 63.6; H, 4.4; N, 14.9. $C_{10}H_8N_2S$ requires C, 63.8; H, 4.3; N, 14.9%).

2-Phenylsulphonylpyrimidine.- (a) 2-Chloropyrimidine (3.5 g.), sodium benzenesulphinate (5.0 g.) and anhydrous DMSO (25 ml.) were heated on a steam bath for 5 hr. The cooled and filtered solution was evaporated *in vacuo* at 60° and the residue extracted with hot chloroform (2 x 50 ml.). Evaporation gave 2-phenylsulphonylpyrimidine (3.45 g.), m.p. 99-100° (from 95% ethanol) (Found: C, 54.4; H, 3.8; N, 12.7; S, 14.2. $C_{10}H_8N_2O_2S$ requires C, 54.5; H, 3.7; N, 12.7; S, 14.5%).

(b) Oxidation of 2-phenylthiopyrimidine (5.0 g.) with aqueous chlorine (as above) gave 2-phenylsulphonylpyrimidine (4.2 g.) identified by mixed m.p., infrared and p.m.r. spectrum, and thin layer chromatography.

2-Methylsulphinylpyrimidine.- 2-Methylthiopyrimidine (10.0 g.) was dissolved in aqueous 0.5 M sodium meta-periodate (165 ml.) at 5°. After stirring for 16 hr. at 20°, the precipitated sodium iodate was

filtered off, washed with chloroform (25 ml.) and the filtrate extracted with chloroform (3 x 50 ml.). The chloroform was evaporated from the combined washings and extract, and the residual oil distilled giving 2-methylsulphinylpyrimidine (6.0 g.), b.p. 152-4°/0.5 mm. (Found: C, 42.5; H, 4.4; S, 22.2. $C_5H_6N_2OS$ requires C, 42.3; H, 4.3; S, 22.5%).

4-Methylsulphinylpyrimidine.- To 4-methylthiopyrimidine (4.6 g.) in chloroform (100 ml.) cooled to -15°, 80% m-chloroperbenzoic acid (7.4 g.) in chloroform (150 ml.) similarly cooled was added. After standing for 15 hr. at 0°, the reaction mixture was washed with aqueous N-sodium carbonate solution (2 x 25 ml.). The residue on evaporation of the solvent was recrystallised from benzene/petroleum ether (40-60°) (1:3, v/v) giving 4-methylsulphinylpyrimidine (3.4 g.), m.p. 47-49° (Found: C, 42.25; H, 4.5; N, 14.6. $C_5H_6N_2OS$ requires C, 42.3; H, 4.3; N, 14.7%).

5-Methylsulphinylpyrimidine.- This was prepared from 5-methylthiopyrimidine as for the the 4-isomer (see above) in 84% yield, m.p. 84-86° (from ethanol). An analytical sample of the sulphoxide was purified by thin

layer chromatography to remove a trace of the corresponding sulphone (Found: C, 42.1; H, 4.1; N, 14.4%).

2-Phenylsulphinylpyrimidine.- 2-Phenylthiopyrimidine (5.0 g.) was oxidised with meta-chloroperbenzoic acid as was 4-methylthiopyrimidine above. After removing a trace of sulphone by thin layer chromatography on alumina, 2-phenylsulphinylpyrimidine (2.5 g.) had m.p. 118-119° (from benzene) (Found: C, 59.2; H, 4.0; N, 13.7. $C_{10}H_8N_2OS$ requires C, 58.8; H, 3.95; N, 13.7%).

Reactions of 2-methylsulphonylpyrimidine

(a) With sodium azide

2-Methylsulphonylpyrimidine (2.0 g.) and sodium azide (2.5 g.) in anhydrous dimethylformamide (Fluka puriss., 4 ml.) were heated on a steam bath for 3 hr. The reaction mixture was cooled and diluted with chloroform (25 ml.) and the sodium methyl sulphinate filtered off. The filtrate was evaporated to dryness in vacuo and the residue recrystallised from benzene giving 2-azidopyrimidine (0.9 g.), m.p. 123-125°, undepressed on admixture with material made (Sirakawa, 1958; Temple and Montgomery, 1965) by treating

2-hydrazinopyrimidine with nitrous acid (Found: C, 39.9; H, 2.5; N, 57.3. Calc. for $C_4H_3N_5$: C, 39.7; H, 2.5; N, 57.8%).

(b) With potassium cyanide

The sulphone (2.0 g.) and potassium cyanide (2.0 g.) in dimethyl formamide (10 ml.) were heated on a steam bath (4 hr.). The reaction mixture was cooled, diluted with chloroform (25 ml.) and filtered. The filtrate was evaporated under reduced pressure and the residue sublimed (50°, 0.1 mm.) giving 2-cyanopyrimidine (0.55 g.), m.p. 42-43° (lit, 42°; Robba, 1960) (Found: C, 56.8; H, 3.1; N, 39.8. Calc. for $C_5H_3N_3$: C, 57.1; H, 2.9; N, 40.0%).

(c) With cyclohexylamine

The sulphone (2.0 g.), cyclohexylamine (5.0 ml.) and absolute ethanol (25 ml.) were refluxed (4 hr.). The ethanol was removed under reduced pressure and the residue suspended in N-sodium hydroxide (10 ml.) and the suspension extracted with chloroform (4 x 15 ml.). The chloroform was evaporated and the residue sublimed (70°/0.5 mm.) giving 2-cyclohexylaminopyrimidine (0.8 g.), m.p. 92-94° (Found: C, 68.1; H, 8.7; N, 23.4.

$C_{10}H_{15}N_3$ requires C, 67.8; H, 8.5; N, 23.4%).

(d) With pentylamine

Pentylamine reacted with the sulphone similarly, to give 2-pentylaminopyrimidine (60%), b.p. 72-74°/0.4 mm. (Found: C, 65.2; H, 9.15; N, 25.5. Calc. for $C_9H_{15}N_3$: C, 65.4; H, 9.15; N, 25.4%). The derived picrate had m.p. 117-118° (from ethanol) (lit. 116-117°; Brown and Harper, 1963) (Found: C, 45.5; H, 4.7; N, 21.5. $C_{15}H_{18}N_6O_7$ requires C, 45.7; H, 4.6; N, 21.3%).

(e) With hydrazine

The 2-sulphone reacted with hydrazine hydrate similarly giving 2-hydrazinopyrimidine (45%), m.p. 112-113° (lit. 110°; Chesterfield, McOmie and Sayer, 1955) (Found: C, 43.4; H, 5.6; N, 51.2. Calc. for $C_4H_6N_4$: C, 43.6; H, 5.5; N, 50.4%).

The reaction of 2-hydrazinopyrimidine with nitrous acid gave 2-azidopyrimidine m.p. 123-125° (see above).

(f) With hydriodic acid

(i) 2-Methylsulphonylpyrimidine (1.5 g.) and hydriodic acid (SP. Gr. 1.94; 5.0 ml.) were heated together with occasional shaking on a steam bath for 10 min. The solution was decolourised by addition

of sodium sulphite and adjusted to pH 10 with solid sodium carbonate then extracted with chloroform. The chloroform was evaporated and the residual oil distilled giving 2-methylthiopyrimidine (0.35 g.), b.p. 70-71°/0.5 mm. Its p.m.r. and infrared spectra were identical with those of authentic material (Found: C, 47.8; H, 5.0. Calc. for $C_5H_6N_2S$: C, 47.6; H, 4.8%).

(ii) To 2-phenylsulphonylpyrimidine (2.0 g.) hydriodic acid (sp. gr. 1.94; 5 ml.) was added. The mixture became hot and was allowed to stand 2 min. then heated on the steam bath for 5 min., poured on to ice, and the reaction mixture worked up as above. The residual oil (1.69 g.) had two components, chromatographically identical with 2-phenylsulphonyl- and 2-phenylthio-pyrimidine by thin layer (2 solvents) and paper (2 solvents), relative proportions estimated from p.m.r. integrals of aromatic protons.

(iii) 5-Methylsulphonylpyrimidine (0.2 g.) was added to hydriodic acid (sp. gr. 1.94, 2 ml.) the mixture allowed to stand 10 min., heated on a steam bath 1 min. (copious evolution of methanethiol) then poured on to ice and the aqueous solution decolourised with

solid sodium sulphite. The solution was adjusted to pH 5 with solid sodium carbonate and extracted with chloroform (3 x 25 ml.). The chloroform was evaporated leaving a very small oily residue which contained neither starting material nor 5-methylthiopyrimidine.

(g) With sodium ethoxide

The sulphone (1.6 g.) was added to ethanolic sodium ethoxide (25 ml.; sodium 0.4 g.) and the solution refluxed for 1 hr. The cooled solution was diluted with water (10 ml.), adjusted to pH 4 with hydrochloric acid and the ethanol evaporated under reduced pressure. The residual solution was extracted with chloroform (3 x 25 ml.) and distillation gave 2-ethoxypyrimidine (0.4 g.), b.p. 46-48°/1.1 mm. Its p.m.r. and infrared spectra were identical with those of authentic material (Found: C, 58.3; H, 6.6. Calc. for $C_6H_8N_2O$: C, 58.05; H, 6.5%).

(h) With diethyl malonate ester anion

The sulphone (5.0 g.) in ethanol (100 ml.) was added to a solution of sodium diethyl malonate (diethyl malonate, 5.5 g., in absolute ethanol, 25 ml., added to ethanolic sodium ethoxide solution, 20 ml., from 0.8 g.

sodium). The solution was refluxed for 12 hr., cooled, the solid filtered off and the filtrate evaporated to dryness. The residue was dissolved in water, adjusted to pH 5 with hydrochloric acid and extracted with chloroform (3 x 25 ml.). The chloroform was evaporated and the oil (7.5 g.) twice distilled. The fraction (5.2 g.) b.p. 56°/0.35 mm. was diethyl-2-(2-pyrimidinyl)malonate. Its p.m.r., infrared and gas chromatographic retention time were identical with those of authentic material.

(i) With sodium hydroxide

The sulphone (1.0 g.) and 2N-sodium hydroxide (32 ml.) were allowed to stand for 2 hr. at 25°. The solution was adjusted to pH 4 with hydrochloric acid and evaporated to dryness. The residue was extracted with boiling ethyl acetate (5 x 10 ml.) giving 2-hydroxypyrimidine, identified with authentic material (Brown, 1950(a)) by paper chromatography (2 solvents), infrared spectra, and mixed melting point.

(j) With methylamine

The sulphone (0.75 g.) dissolved in ethanolic methylamine solution (33%, 10 ml.) was heated at 100°

in a sealed tube for 2 hr. The ethanol was evaporated and the residue recrystallised from cyclohexane giving 2-methylaminopyrimidine (0.175 g.), m.p. 59-61° (lit. 59-61°; Brown and Short, 1953), identified with authentic material by m.p., paper chromatography (2 solvents), and infrared spectra.

(k) Attempted reduction of 2-methylsulphinylpyrimidine

(i) To the sulphoxide (1.42 g.) dissolved in aqueous tetrahydrofuran (H_2O/T.H.F., 1:9 v/v; 100 ml.) was added aluminium amalgam (Corey and Chaykovsky, 1965), and the solution was kept at 50° for 1½ hr. Water (25 ml.) was added and the filtered solution was concentrated under reduced pressure. The concentrate (30 ml.) was extracted with chloroform (2 x 25 ml.). The oily residue from removal of the solvent did not contain detectable amounts of pyrimidine or 2-methylthiopyrimidine.

(ii) The sulphoxide (1.0 g.) was dissolved in 10% aqueous methanol (50 ml.), and sodium borohydride (0.5 g.) was added portionwise over 10 min. When gas evolution ceased, the solution was evaporated to dryness under reduced pressure and the white residue was

extracted with chloroform (2 x 25 ml.). The chloroform was removed and the residue (0.87 g.) shown to be unchanged 2-methylsulphinylpyrimidine by its p.m.r. and infrared spectrum and by thin layer chromatography.

Reactions of 2-methylsulphinylpyrimidine

(a) The sulphoxide (0.1 g.) and pentylamine (0.3 g.) were heated at 100° for 10 hr. The pentylamine was removed under reduced pressure and the residual oil added to ethanolic picric acid. The 2-pentylamino-pyrimidine picrate (0.17 g.; m.p. 117°) was identical with that prepared above.

(b) Addition of the sulphoxide (1 drop) to aqueous potassium iodide/dilute sulphuric acid resulted in the immediate liberation of iodine.

(c) m-Chloroperbenzoic acid (1.75 g.) in chloroform (150 ml.) cooled at -15°, was added to the sulphoxide (1.0 g.) in chloroform (100 ml.) at 0°. After 16 hr. at 20°, the chloroform solution was washed with saturated aqueous sodium sulphite (50 ml.) and N-sodium carbonate (50 ml.). The solvent was evaporated and recrystallisation of the white residue gave 2-methylsulphonylpyrimidine

(0.6 g.) identified with authentic material by mixed m.p. and infrared spectra.

Reactions of 4-methylsulphonyl- and 4-methylsulphinylpyrimidine

(a) With pentylamine

The sulphone (1.0 g.) was treated with pentylamine (2.5 ml.) as for its 2 isomer (above). The 4-pentylaminopyrimidine (0.43 g.) had b.p. 114-116°/0.4 mm. and m.p. 58-60° (lit. 61-62°; Hitchings and Russell, 1949) (Found: C, 65.55; H, 9.1; N, 25.6. Calc. for $C_9H_{15}N_3$: C, 65.4; H, 9.15; N, 25.4%).

(b) With butanol

The sulphone (4.0 g.) and butanolic sodium butoxide (20 ml.; sodium 0.7 g.) were warmed for 2 hr. Water (20 ml.) was added, the mixture was adjusted to pH 4 with dilute hydrochloric acid and then extracted with chloroform (3 x 25 ml.). The chloroform was evaporated and distillation gave an oil, b.p. 35-37°/1.1 mm. It was almost entirely 4-butoxypyrimidine but containing approx. 1% butanol as judged from gas chromatography. It was converted into 4-butoxypyrimidine picrate, m.p. 85-86° (Found: C, 44.2; H, 4.2; N, 18.5.

$C_{14}H_{15}N_5O_8$ requires C, 44.1; H, 4.0; N, 18.4%).

(c) With hydroxide anion

The sulphoxide (1.0 g.) was treated with aqueous N-sodium hydroxide (as above for 2-methylsulphonylpyrimidine). The resulting 4-hydroxypyrimidine was identified with authentic material (Brown, 1950(b)) by mixed m.p., infrared spectrum, and paper chromatography.

Reactions with triphenylphosphine

(a) 2-Methylsulphonylpyrimidine (0.1 g.) and triphenylphosphine (0.4 g.) were heated in a sealed tube (steam bath). At two intervals the tube was cooled and the components of the reaction mixture identified by the infrared and p.m.r. spectra and by thin layer chromatography (two solvents). The relative proportions of 2-methylthio-, 2-methylsulphinyl- and 2-methylsulphonylpyrimidine were determined from the integrals of relevant peaks in the p.m.r. spectrum.

(b) Methyl phenyl sulphone (0.3 g.) and triphenylphosphine (1.2 g.) were heated in a sealed tube at 100° for 15 hr. The contents of the tube were examined by p.m.r. and infrared spectroscopy, and by thin layer and gas chromatography. Neither thioanisole nor

methylsulphinylbenzene were detected.

(c) 5-Methylsulphonylpyrimidine and 9-methyl-2-methylsulphonylpurine

The sulphone (10 mg.) and triphenylphosphine (50 mg.) were allowed to react and examined as above. The corresponding thioether was not detected in either case.

1,3-Dibenzylimino-2-methylsulphonylpropane.- 5-Methylsulphonylpyrimidine (0.53 g.) and benzylamine (0.75 g.) were heated on a steam bath for 1 hr. The cooled solid was extracted with boiling light petroleum (b.p. 60-80°; 3 x 25 ml.). The remaining solid was recrystallised from benzene giving 5-methylsulphonylpyrimidine (0.10 g.) m.p. 135-137°. The solid from evaporation of extracts was recrystallised four times from cyclohexane giving NN'-dibenzyl-1,3-diimino-2-methylsulphonylpropane, (0.25 g.), m.p. 69-71° (Found: C, 65.5; H, 6.2; N, 8.7. $C_{18}H_{20}N_2O_2S$ requires C, 65.8; H, 6.1; N, 8.5%).

1,3-Dipentylimino-2-methylsulphonylpropane.- 5-Methylsulphonylpyrimidine (200 mg.) and pentylamine (Fluka puriss, 282 mg.) were heated on a steam bath

for 30 min. Further n-pentylamine (100 mg.) was added, and the heating was continued for 1.5 hr. The excess pentylamine was distilled (0.1 mm., 40°) and the residual oil was dissolved in chloroform (15 ml.). The solution was washed with 1N-sodium hydroxide (10 ml.) and dried over magnesium sulphate. After removal of solvent, the solid was twice recrystallised from light petroleum (b.p. 60-80°) to give 1,3-diimino-2-methylsulphonyl-NN'-dipentylpropane (80 mg.), m.p. 51-52°. (Found: C, 58.55; H, 9.5; S, 11.4. $C_{14}H_{28}N_2O_2S$ requires C, 58.6; H, 9.8; S, 11.1%).

1,3-Dipentylimino-2-methylsulphinylpropane.- 5-Methylsulphinylpyrimidine (0.4 g.) was allowed to react in a similar way to 5-methylsulphonylpyrimidine, with n-pentylamine. The resulting NN'-dipentyl-2-methylsulphinyl-1,3-diiminopropane (82 mg.) had m.p. 42-43° (Found: C, 60.9; H, 10.0. $C_{14}H_{28}N_2OS$ requires C, 61.7; H, 10.4%).

1,3-Dibenzylimino-2-methylsulphinylpropane.- 5-Methylsulphinylpyrimidine (1.0 g.) and benzylamine (1.65 g.) were heated together on the steam bath for 2 hr. Repeated recrystallisation of the reaction

mixture from cyclohexane gave NN'-dibenzyl-1,3-diimino-2-methylsulphinylpropane (0.36 g.) m.p. 96-98° (Found: C, 69.5; H, 6.5; N, 8.9. $C_{18}H_{20}N_2OS$ requires C, 69.2; H, 6.5; N, 9.0%).

p-Dimethylaminothiophenol.- p-Bromodimethylaniline (25 g.; Kosolapoff, 1953) in T.H.F.* (200 ml.) was added dropwise to magnesium turnings (5 g.; BDH Grignard reagent grade) and ethyl bromide (1 ml.) at a rate sufficient to maintain gentle boiling. On completion of the addition (3/4 hr.) the solution was refluxed for 1 hr., cooled, then finely powdered dry sulphur (5 g.) was added portionwise (CAUTION, vigorous reaction) and yellow solution refluxed for ½ hr. The cooled reaction mixture was brought to pH 5 with dilute hydrochloric acid, the THF layer decanted and the aqueous layer extracted with ether (2 x 100 ml.). The ether and THF layers were extracted with aqueous sodium hydroxide solutions (5%, 2 x 25 ml.). The alkaline layers were then adjusted to pH 5 with dilute hydrochloric acid and extracted with ether (2 x 50 ml.). The ether layers

---

* THF = Tetrahydrofuran (dried by distillation from lithium aluminium hydride).

were dried ($MgSO_4$) and the evaporation gave a foul smelling yellow oil. Distillation gave p-dimethylaminothiophenol (11.5 g.) b.p. 85-86° (0.1 mm.), m.p. 28-30° (lit. 28.5°; Leukart, 1904) p.m.r. ($CDCl_3$), A_2B_2 doublets at 2.58, 3.23 (J = 8.8 cps) NME_2 7.02 -SH 6.63 cf. SH of p-methylthiophenol 6.73 (spectrum No. 16 8, Varian Catalog of n.m.r. spectra).

2-p-Dimethylaminophenylthiopyrimidine.- 2-Chloropyrimidine (4.2 g.; Overberger and Kogon, 1954) in ethanol (50 ml.) was slowly added to a solution of sodium p-dimethylaminothiophenoxide, prepared from p-dimethylaminothiophenol (6.0 g.) in sodium ethoxide solution (25 ml., 1.5 M). The solution was refluxed for 2 hr. and allowed to stand overnight. The solid was filtered off, the filtrate evaporated to dryness, and the residue chromatographed (alumina 2 x 35 cm. column). Elution with either petroleum ether or benzene gave fractions which contained two components. The fractions were combined, and extracted with hot petroleum ether (60-80°, 4 x 50 ml.). The residual solid recrystallised from benzene giving 2-p-dimethylaminophenylthiopyrimidine m.p. 136-137° (2.76 g.)

concentration of the petroleum ether extracts to 75 ml. gave a further 1.23 g. m.p. 135-137° (Found: C, 62.4; H, 5.7; N, 18.1. $C_{12}H_{13}N_3S$ requires C, 62.0; H, 5.6; N, 18.5%).

The other 2-p-substituted-phenylthiopyrimidines listed below were prepared in a similar manner from the corresponding thiophenols and 2-chloropyrimidine.

		Found (%)			Calculated (%)		
p-Substituent	m.p.	C	H	N	C	H	N
chloro	73-74	54.3	3.2	12.5	53.4	3.2	12.6
methyl	56-57	65.2	4.8	13.9	65.3	5.0	13.9
methoxy	76	60.65	4.7	12.8	60.5	4.6	12.8
nitro	157-8	51.9	2.9	18.3	51.5	3.0	18.0

2-p-Methoxyphenylsulphinylpyrimidine.- m-Chloroperbenzoic acid (2.08 g.) in chloroform (50 ml.; 0°) was added to 2-p-methoxyphenylthiopyrimidine (2.18 g.) in cold chloroform (50 ml. -10°) and the solution was maintained at 3° overnight. The chloroform solution was washed with saturated aqueous sodium bicarbonate solution (2 x 25 ml.) and dried over a molecular sieve. The chloroform was evaporated and the residual solid recrystallised from ethanol giving 2-p-methoxyphenyl-sulphinylpyrimidine (1.48 g.) m.p. 101-103° (Found:

C, 56.3; H, 4.3; N, 12.1. $C_{11}H_{10}N_2SO$ requires C, 56.4; H, 4.3; N, 12.0%).

The 2-p-substituted-phenylsulphinylpyrimidines listed below were prepared in a similar manner from the corresponding phenylthiopyrimidine.

		Found(%)			Calculated(%)		
p-Substituent	m.p.	C	H	N	C	H	N
chloro	162-163	50.2	2.9	11.6	50.3	3.0	11.7
methyl	141-142	60.7	4.85	12.8	60.5	4.6	12.8
nitro	182-183	48.2	2.7	16.95	48.2	2.8	16.9

2-p-Tolylsulphonylpyrimidine.- m-Chloroperbenzoic acid (6.8 g.) in chloroform (150 ml.) was added to 2-p-tolylthiopyrimidine (3.0 g.) in chloroform (50 ml.). The reaction mixture was maintained at -10° for 1 hr. then allowed to stand at room temperature for 48 hr. The chloroform solution was washed with sodium bisulphite (20 ml. satd.) and then with saturated aqueous sodium bicarbonate solution (2 x 50 ml.), and dried over a molecular sieve. The residual solid from evaporation recrystallised from ethanol givine 2-p-tolylsulphonylpyrimidine (1.12 g.) m.p. 135-136°. Concentration of the filtrate gave a further 2 crops: 1.04 g., m.p. 134-136°; and 0.44 g.,

m.p. 133-135°.

The other 2-p-substituted-phenylsulphonylpyrimidines listed below were prepared in a similar manner, from the corresponding phenylthiopyrimidines.

		Found(%)			Calculated(%)		
p-Substituent	m.p.°	C	H	N	C	H	N
chloro	150-2	47.4	2.6	11.1	47.2	2.8	11.0
methoxy	127-8	52.8	4.1	11.4	52.8	4.0	11.2
nitro	215	44.9	2.55	16.1	45.3	2.7	15.85

2-Mercapto-9-methylpurine.- 5-Amino-2-mercapto-4-methylaminopyrimidine (1.0 g.) (Brown, 1957(a)) in formic acid (5 ml.) was refluxed for 2 hr. The excess of formic acid was removed under reduced pressure and the residue dissolved in 1N-sodium hydroxide, filtered, and reprecipitated (pH 5). Recrystallisation from water gave 2-mercapto-9-methylpurine (0.64 g.) as a pale yellow solid decomposing without melting at 220° (Found: C, 42.85; H, 3.6; N, 32.7. $C_6H_6N_4S$ requires C, 43.4; H, 3.6; N, 33.7%).

9-Methyl-2-methylthiopurine.- (a) 2-Mercapto-9-methylpurine (1.0 g.) was suspended in 1N-sodium hydroxide solution (6 ml.), methyl iodide (0.38 ml.)

was added, and the mixture was shaken for ½ hr. Refrigeration overnight gave 9-methyl-2-methylthiopurine (0.87 g.) m.p. 131-132° (Found: C, 46.85; H, 4.5; N, 31.0. $C_7H_8N_4S$ requires C, 46.65; H, 4.5; N, 31.1%).

(b) To 2-methylthiopurine (3.0 g.) suspended in ether (200 ml.) was added ethereal solution of diazomethane (1.5 g., in 50 ml.). The solution was stirred overnight at room temperature. Removal of the ether left a red tar which was extracted with boiling cyclohexane (5 x 50 ml.). The residue from evaporation was chromatographed (BDH deactivated* alumina), 1.2 x 25 cm. column. Elution with benzene gave 9-methyl-2-methylthiopurine (1.79 g.) identical with authentic material (infrared, p.m.r. spectra and T.L.C. in two solvents). Its m.p. 131-132°, was undepressed by admixture with authentic material. Further elution with benzene gave fractions containing two components. Elution with chloroform (when benzene elution gave no

---

* Deactivated by refluxing in ethylacetate for 2 hr.

more material) gave 7,8-dimethyl-2-methylthiopurine (0.2 g.) m.p. 158-159° (from cyclohexane) (Found: C, 49.4; H, 5.3; N, 28.9; S, 16.5. $C_8H_{10}N_4S$ requires C, 49.5; H, 5.2; N, 28.8; S, 16.5%).

9-Methyl-6-methylthiopurine.- (a) 6-Methylthiopurine (1.5 g.; Elion, Burgi and Hitchings, 1952) in ethereal diazomethane solution (1.5 g. in 25 ml.) was stirred overnight. The solid was recrystallised from benzene and gave 3-methyl-6-methylthiopurine (0.51 g.), m.p. 163-164° (lit., 163-164°; Jones and Robins, 1962), u.v. λ_{max} 237, 311; $\log_{10}\varepsilon$ 3.99; 4.22 [lit. (Bergmann et al., 1961): λ_{max} 236, 312 mm. $\log_{10}\varepsilon$ 4.09, 4.32].

The ethereal filtrate was evaporated to dryness and the solid chromatographed (BDH alumina 1.5 x 25 cm. column). Elution with benzene-chloroform (8:1, v/v) gave 9-methyl-6-methylthiopurine (10.2 g.), m.p. 169-170° (lit., 170-171°; Robins and Lin, 1957). The melting point was undepressed on admixture with authentic material.

(b) 6-Methylthiopurine (7.5 g.), anhydrous potassium carbonate (4.5 g.), and methyl iodide (3.5 ml.) were stirred together in dimethyl sulphoxide (3.0 ml.) for

12 hr. at 35°. Most of the solvent was removed under reduced pressure (<60°) and the components of the mixture separated by liquid-liquid extraction (6 tubes $CHCl_3/H_2O$ 50 ml. of each). Tube 1, $CHCl_3$ layer, gave 1.52 g. 6-methylthio-9-methylpurine. The $CHCl_3$ layers of tubes 2 - 4 were combined, the solvent removed and the solid chromatographed. Elution with benzene gave 9-methyl-6-methylthiopurine (1.75 g.), m.p. 169-171°. Tube 5 $CHCl_3$; the solvent was removed and the residue recrystallised from hexane-benzene (1:1, v/v) giving 4-cyano-1-methyl-5-methylformamidoimidazole (0.48 g.) m.p. 118-120°. (Found: C, 51.2; H, 4.7; N, 33.8. $C_7H_8N_4O$ requires C, 51.2; H, 4.9; N, 34.1%).

9-Methyl-8-methylthiopurine.- 8-Methylthiopurine (1.5 g.) was methylated using the procedure described for 2- or 6-methylthiopurine. Chromatography (as before) gave 3-methyl-8-methylthiopurine (0.14 g.) m.p. 166-167° (Found: C, 47.1; H, 4.7; N, 31.1. $C_7H_8N_4S$ requires C, 46.45; H, 4.8; N, 31.1%). Evaporation of the ether filtrate gave a scarlet tarry solid. Thin layer chromatography (10 x 40 cm. silica (Merck) plates; methanol) gave 9-methyl-8-methylthiopurine (0.73 g.) m.p. 151-152° (lit., 147-148°; Brown and Mason,

1957); undepressed by admixture with authentic material. It had the same R_F as authentic material on paper chromatography in two solvents.

9-Methyl-2-methylsulphonylpurine.- To 9-methyl-2-methylthiopurine (1.0 g.) in chloroform 0°, 50 ml.) m-chloroperbenzoic acid (85%, 2.7 g.) in chloroform (0°, 75 ml.) was added and the solution maintained at 0° (2 hr.) then 25° overnight. The chloroform solution was washed with saturated sodium bisulphite (25 ml.) and 5% sodium bicarbonate solutions (2 x 25 ml.) and dried over molecular sieve (Linde 4A). The chloroform was removed and the residual solid recrystallised from methanol gave 9-methyl-2-methylsulphonylpurine (0.62 g.), m.p. 167-168° (Found: C, 40.0; H, 3.8; N, 26.35. $C_7H_8N_4O_2S$ requires C, 39.6; H, 3.8; N, 26.4%).

9-Methyl-2-methylsulphinylpurine.- 9-Methyl-2-methylsulphinylpurine was prepared in a similar manner to 9-methyl-2-methylsulphonylpurine, but using only 1 mole equivalent of m-chloroperbenzoic acid. It had m.p. 186-187° (Found: C, 42.7; H, 4.0; N, 28.4. $C_7H_8N_4OS$ requires C, 42.85; H, 4.1; N, 28.55%).

The 9-methyl,6-(and 8)methylsulphinylpurines and the 9-methyl-6-(and 8)methylsulphonylpurines were prepared in a similar manner to their respective 2-isomers.

Substituent in 9-Methylpurine	m.p.°	Analysis C	H	N
6-Methylsulphonyl	210-212 (decomp.)	39.6	4.4	26.4
6-Methylsulphinyl	168-170	42.4	4.1	29.1
8-Methylsulphonyl	133-135	39.8	3.9	26.3
8-Methylsulphinyl	144-145	42.5	4.7	28.7

2,9-Dimethyl-6-methylsulphonylpurine.- 2,9-Dimethyl-6-methylsulphonylpurine was prepared in a similar manner to 9-methyl-6-methylsulphonylpurine (above). It had m.p. 202-204° (Found: C, 42.5; H, 4.6; N, 24.7. $C_8H_{10}N_4O_2S$ requires C, 42.5; H, 4.5; N, 24.8%).

2,9-Dimethyl-8-methylsulphonylpurine was similarly prepared, m.p. 139-140° (Found: C, 42.6; H, 4.7; N, 24.9%).

9-Methyl-2-piperidinopurine.- (a) 9-Methyl-2-methylsulphonylpurine (0.1 g.) and piperidine (0.5 ml.) were refluxed for 6 hr. The solvent was removed and

the residue extracted with chloroform (2 x 20 ml.). The solvent was removed, and the residue was recrystallised from cyclohexane giving 2-piperidino-9-methylpurine (57 mg.) m.p. 135-136° (lit. 135.5-136.5°; Barlin and Chapman, 1965).

(b) 9-Methyl-2-piperidinopurine, similarly prepared from 9-methyl-2-methylsulphinylpurine, had m.p. 135-136°, undepressed on admixture with material prepared above.

9-Methyl-6-piperidinopurine.- (a) 9-Methyl-6-methylsulphonylpurine (0.15 g.) and piperidine (0.25 ml.) in ethanol (2 ml.) were refluxed together for 1 hr. The solvent was evaporated and the residue in water adjusted to pH 8 with aqueous sodium carbonate. The solution was extracted with chloroform (3 x 15 ml.). The chloroform layers were dried (molecular sieve) and evaporated. The residue was recrystallised twice (cyclohexane) giving 9-methyl-6-piperidinopurine (81 mg.) m.p. 82-83° (lit. 65-66°; Barlin and Chapman, 1965) (Found: C, 61.1; H, 7.0; N, 32.1. Calc. for $C_{11}H_{15}N_5$: C, 60.8; H, 7.0; N, 32.2%). The infrared and p.m.r. spectra, and T.L.C. (in two solvents) were

identical with those of 9-methyl-6-piperidinopurine prepared from 6-chloro-9-methylpurine (see below). 9-Methyl-6-methylsulphinylpurine reacted similarly to give 9-methyl-6-piperidinopurine m.p. 82-83° undepressed by admixture with authentic material prepared below.

(b) 6-Chloro-9-methylpurine (0.3 g.) and piperidine (0.5 ml.) were refluxed (1½ hr.) in absolute ethanol (15 ml.). The ethanol was removed under reduced pressure and the residue extracted with hot benzene (3 x 10 ml.). The benzene extracts were combined and the benzene removed. The residual solid was recrystallised from cyclohexane giving 9-methyl-6-piperidinopurine (0.135 g.) m.p. 82-83° (lit. 65-66°; Barlin and Chapman, 1965) (Found: C, 61.1; H, 7.0; N, 32.1. Calc. for $C_{11}H_{15}N_5$: C, 60.8; H, 7.0; N, 32.2%). The infrared and p.m.r. spectra and T.L.C. (2 solvents) were identical with those of 9-methyl-6-piperidinopurine prepared from 9-methyl-6-methylsulphonyl-(and methylsulphinyl-)purine (see above).

9-Methyl-8-piperidinopurine was prepared similarly to the 2-isomer (100°; 1 hr.) from both 8-methylsulphonyl-9-methyl-8-methylsulphonyl- and

9-methyl-8-methylsulphinyl-purine m.p. 90-91° and 89.5-90.5° respectively (lit. 89.5-91°; Barlin and Chapman, 1965). There was no depression of m.p. on admixture of the specimens.

4. Measurement of Rates

(a) Hydrolysis of methylsulphinyl and methylsulphonyl derivatives of 9-methylpurine:

For the 6- and 8-substituted compounds a rapid reaction apparatus was used (Perrin, 1965). For the 2-substituted compounds the sample was maintained in a thermostated cell (20.0°) and its optical density measured periodically. Plots of $\log_{10} \frac{D_{\infty}-D_o}{D_{\infty}-D}$ versus time gave straight lines passing through the origin from which k, the first order rate constant, was calculated.

(b) Aminolysis of the methylsulphinyl and methylsulphonyl-9-methylpurine:

Aliquots (5 ml.) were removed from the reaction mixture (98.8% ethanol) maintained at constant temperature by a thermostatted water bath, and quenched in 15 ml. 1N-sodium hydroxide. The optical density at the $\lambda_{max.}$ of the 9-methylpiperidinopurine was measured

and the first order rate constant calculated from plots of $\log \frac{a}{a-x}$ versus time. These values were checked in some cases by applying the method of Guggenheim (1926). The optical density at "infinite time" (15 half lives) corresponded to 98-100% reaction indicating the absence of decomposition or reversible reactions.

BIBLIOGRAPHY

A. Albert, 1959. "Heterocyclic Chemistry," Athlone Press, London, p.61.

A. Albert and W.L.F. Armarego, 1965. Adv. Heterocyclic Chem., 4, 1.

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

F. Arndt, 1953. "Organic Analysis", Eds., Mitchell et al., Interscience, New York, vol.1, pp.197-241.

R.W. Balsiger, A.L. Fikes, T.P. Johnston, and J.A. Montgomery, 1961. J. Org. Chem., 26, 3446.

G.B. Barlin, 1967. J. Chem. Soc.(B), 954.

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

G.B. Barlin and N.B. Chapman, 1965. J. Chem. Soc., 3017.

A.G. Beaman and R.K. Robins, 1963. J. Org. Chem., 28, 2310.

L.J. Bellamy, 1958. "Infrared spectra of complex organic molecules", Methuen, London, p.203, 247, and 358.

F. Bergmann, Z. Neiman, and M. Kleiner, 1966. J. Chem. Soc.(C), 10.

F. Bergmann, M. Kleiner, Z. Neiman, and M. Rashi, 1964. Israel J. Chem., 2, 185.

F. Bergmann, G. Levin, A. Kalmus, and H. Kwienty-Govrin, 1961. J. Org. Chem., 26, 1504.

C.F. Bernasconi and H. Zollinger, 1966. Helv. Chim. Acta, 49, 2570.

C.F. Bernasconi and H. Zollinger, 1967. Helv. Chim. Acta, 50, 3.

M.E.C. Biffin, D.J. Brown, and T.C. Lee, 1967. J. Chem. Soc.(C), 573.

M.E.C. Biffin, D.J. Brown, and Q.N. Porter, 1967. Tetrahedron Letters, 2029.

J.H. Billman and A.C. Diesing, 1957. J. Org. Chem., 22, 1068.

M.P.V. Boarland and J.F.W. McOmie, 1952. J. Chem. Soc., 3716.

J.H. Bowie, D.H. Williams, S.O. Lawesson, J.O. Madsen, C. Nolde, and G. Schroll, 1966. Tetrahedron, 22, 3515.

J.C.D. Brand and G. Eglinton, 1965a. "Applications of spectroscopy," Oldbourne Press, London, p.68.

J.C.D. Brand and G. Eglinton, 1965b. ibid. p.174

H. Bredereck, R. Gompper, and H. Herlinger, 1958. Chem. Ber., 91, 2830.

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

D.J. Brown, 1950a. Nature, 165, 1010.

D.J. Brown, 1950b. J. Soc. Chem. Ind., 69, 353.

D.J. Brown, 1957. J. Appl. Chem., 7, 115.

D.J. Brown, 1962. "The Pyrimidines", Interscience, New York, p.492.

D.J. Brown, 1962a. ibid. p.298.

D.J. Brown, 1962b. ibid. p.13.

D.J. Brown, 1962c. ibid. p.274.

D.J. Brown, P.W. Ford, and K. Tratt, 1967. J. Chem. Soc.(C), 1445.

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

D.J. Brown and J.S. Harper, 1963. J. Chem. Soc., 1276.

D.J. Brown and J.M. Lyall, 1964. Austral. J. Chem., 17, 794.

D.J. Brown and J.M. Lyall, 1965. Austral. J. Chem., 18, 741 and 1811.

D.J. Brown and S.F. Mason, 1957. J. Chem. Soc., 682.

D.J. Brown and L.N. Short, 1953. J. Chem. Soc., 331.

R.D. Brown, 1952. Quart. Rev., 6, 63.

A.D. Buckingham, 1960. Canad. J. Chem., 38, 300.

R.D. Brown and M.L. Heffernan, 1956. Austral. J. Chem., 9, 83.

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

J.F. Bunnett and R.H. Garst, 1965. J. Amer. Chem. Soc., 87, 3875.

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

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

B. Capon, M.J. Perkins, and C.W. Rees, 1965. "Organic Reaction Mechanisms," Interscience, London, vol.1, p.133-140.

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

J.P.A. Castrillon and H.H. Szmant, 1965. J. Org. Chem., 30, 1338.

N.B. Chapman, 1955. Chem. Soc. Special Publn., No.3, p.157.

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.

S.I. Chan, M.P. Schweiser, P.O.P. Ts'o, and G.K. Helmkamp, 1964. J. Amer. Chem. Soc., 86, 4182.

J. Chesterfield, J.F.W. McOmie, and E.R. Sayer, 1955. J. Chem. Soc., 3478.

Y.F. Chi and Y.C. Ling, 1956. Sci. Sinica, 5, 205.

Y.F. Chi and Y.C. Ling, 1957. Sci. Sinica, 6, 633.

T.C. Chou, H.H. Lin, and R. Varma, 1967. J. Chem. Soc.(B), 410.

J. Clark, I. Gelling, and G. Neath, 1967. Chem. Comm., 859.

J. Clark and D.D. Perrin, 1964. Quart. Rev., 18, 309.

E.J. Corey and M. Chaykovsky, 1965. J. Amer. Chem. Soc., 87, 1345.

F.A. Cotton and G. Wilkinson, 1962. "Advanced Inorganic Chemistry", Interscience, New York, p.139.

D.J. Cram, D.A. Scott, and W.D. Nielsen, 1961. J. Amer. Chem. Soc., 83, 3696.

M.J.S. Dewar and E.A.C. Lucken, 1958. J. Chem. Soc., 2653.

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

E.L. Eliel, N.L. Allinger, S.J. Angyal, and G.A. Morrison, 1965. "Conformational Analysis", Interscience, New York, p.42.

G.B. Elion, 1962. J. Org. Chem., 27, 2478.

G.B. Elion, E. Burgi, and G.H. Hitchings, 1952. J. Amer. Chem. Soc., 74, 411.

G.B. Elion, I. Goodman, W. Lange, and G.H. Hitchings, 1959. J. Amer. Chem. Soc., 81, 1898.

I.Kh. Feld'man, V.M. Merlis, and Yu.M. Rozanova, 1949. Zhur. Obshchei. Khim., 19, 1683.

R. Fuchs and J.J. Bloomfield, 1963. J. Org. Chem., 28, 910.

J.R. Geigy, 1963. Fr. P. 1,339,747; through Chem. Abstr., 60, 5518 (1964).

H. Gilman and L. Fullhart, 1949. J. Amer. Chem. Soc., 71, 1478.

R. Gompper, 1963. Adv. Heterocyclic Chem., 2, 246.

E.A. Guggenheim, 1929. Phil. Mag., 2, 538.

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

G.H. Hitchings and P.B. Russell, 1949. J. Chem. Soc., 2454.

F. Hoffman-LaRoche and Co., 1964. Fr. Pat., 1,341,774, through Chem. Abstr., 60, 10698 (1964).

G. Illuminati, G. Marino, and Sleiter, 1967. J. Amer. Chem. Soc., 89, 3510.

H.H. Jaffe, 1953. Chem. Rev., 53, 191.

R.A.W. Johnstone, I.D. Entwhistle, and D.J. Millard, 1967. J. Chem. Soc.(C), 302.

J.W. Jones and R.K. Robbins, 1962. J. Amer. Chem. Soc., 84, 1914.

A.R. Katritzky, 1956. Quart. Rev., 10, 395.

R.E. Klinck and J.B. Strothers, 1962. Canad. J. Chem., 40, 1071.

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

I.C. Kogon, R. Minin, and C.G. Overberger, 1955. Org. Synth., 35, 34.

G.M. Kosolapoff, 1953. J. Amer. Chem. Soc., 75, 3596.

G.M. Kosolapoff and C.H. Roy, 1961. J. Org. Chem., 26, 1895.

H. Kwart and R.W. Body, 1965. J. Org. Chem., 30, 1188.

D. Landini, F. Montanari, H. Hogeveen, and G. Maccagnani, 1964. Tetrahedron Letters, 2691.

R. Leukart, 1904. J. prakt. Chem., 41, 208.

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

F. Lingens and H. Schneider-Bernlöhr, 1964. Angew. Chem., Int. Edn., 3, 379.

F. Lingens and H. Schneider-Bernlöhr, 1965. Annalen, 686, 134.

S.F. Mason, 1954. J. Chem. Soc., 2071.

S. Matsuura and T. Goto, 1965. J. Chem. Soc., 623.

J. Miller, 1963. J. Amer. Chem. Soc., 85, 1628.

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

J. Miller and F.H. Kendall, 1967. J. Chem. Soc.(B), 119.

R.L. Miller, H.N. Schmeising, and P.G. Lykos, 1962. J. Amer. Chem. Soc., 84, 4623.

J.I. Musher, 1962. J. Chem. Phys., 37, 34.

F. Muth, 1955. In Houben-Weyl, "Methoden der Organischen Chemie", Thieme, Stuttgart, 4th edn., vol.9, p.540.

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

M.D. Newton, F.P. Boer, and W.N. Lipscomb, 1966. J. Amer. Chem. Soc., 88, 2367.

Z. Neiman and F. Bergmann, 1965. Israel J. Chem., 3, 85.

C.W. Noell and R.K. Robins, 1959. J. Amer. Chem. Soc., 81, 5997.

R.O.C. Norman and P.D. Ralph, 1963. J. Chem. Soc., 5431.

H. Normant, 1954. Compt. rend., 239, 1510.

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

M. Ohta and R. Suido, 1951. J. Pharm. Soc. Japan, 71, 511. Through Chem. Abstr., 46, 4549 (1952).

L.O. Onsager, 1936. J. Amer. Chem. Soc., 58, 1486.

D.W. Osborne, 1964. J. Org. Chem., 29, 3570.

C.G. Overberger and I.C. Kogon, 1954. J. Amer. Chem. Soc., 76, 1065.

T.C. Owen, 1961. J. Chem. Soc., 465.

M.N. Paddon-Row, 1966. Ph. D. Thesis, pp.83 et seq., Canberra.

R.G. Pearson, 1963. J. Amer. Chem. Soc., 85, 3533.

R.G. Pearson and J. Songstad, 1967. J. Amer. Chem. Soc., 89, 1827.

D. D. Perrin, 1965. "Dissociation constants of organic bases in aqueous solution", Butterworths, London, p. 28 and 46.

R. Phillips and H.T. Clarke, 1923. J. Amer. Chem. Soc., 45, 1755.

E. Profft and L. Sitter, 1963. Arch. Pharm., 296, 151.

B. Pullman, 1959. J. Chem. Soc., 1621.

M. Quaedvlieg, 1955. In Houben-Weyl, Methoden der Organischen Chemie, Thieme, Stuttgart, 4th Edn., vol.9, p.397.

G.S. Reddy, R.T. Hopgood, and J.H. Goldstein, 1962. J. Amer. Chem. Soc., 84, 336.

M. Robba, 1960. Ann. Chim. (France), (13), 5, 351.

R.K. Robins and H.H. Lin, 1957. J. Amer. Chem. Soc., 79, 490.

R.K. Robins and C.W. Noell, 1959. J. Amer. Chem. Soc., 81, 5997.

S.D. Ross, 1964. In "Progress in Physical Organic Chemistry", Eds. Cohen, Streitwieser, and Taft, Interscience, New York, vol.1, p.31.

A. Schöberl and A. Wagner, 1955. In "Houben-Weyl, Methoden der Organischen Chemie", Thieme, Stuttgart, 4th Edn. vol.9, p.243.

M.P. Schweizer, S.I. Chan, G.K. Helmkamp, and P.O.P. T'so, 1964. J. Amer. Chem. Soc., 86, 696.

M. Semenoský and A. Černý, 1951. Chem. Listy., 45, 156. Through Chem. Abstr., 46, 1556 (1952).

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

R.G. Shepherd and J.L. Fedrick, 1965. Adv. Heterocyclic Chem., 4, 155 et seq.

R.G. Shepherd and J.L. Fedrick, 1965b. Adv. Heterocyclic Chem., 4, 179.

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

A. Simon, H. Kriegsmann and H. Dutz, 1956. Chem. Ber., 89, 1883.

K. Sirakawa, 1958. Jap. p.777/1957. Through Chem. Abstr., 52, 4699 (1958).

Spofa, 1964. Belg. Pat., 633,513; through Chem. Abstr., 61, 1877 (1964).

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

A. Streitwieser and W.D. Schaeffer, 1957. J. Amer. Chem. Soc., 79, 2888.

H. Suhr, 1963. Annalen, 689, 109.

E.Y. Suttcliffe and R.K. Robbins, 1963. J. Org. Chem., 28, 1662.

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

A. Tatematsu, T. Goto, and S. Matsuura, 1966. Nippon Kagaku Zasshi, 87, 71. Through Chem. Abstr., 65, 14605 (1966).

C. Temple and J.A. Montgomery, 1965. J. Org. Chem., 30, 826.

A.R. Todd, K.J.M. Andrews, N. Anand, and A. Topham, 1949. J. Chem. Soc., 2490.

Varian Associates, 1963. "N.m.r. Spectra Catalog", vol.2, 4.

P.R. Wells, 1963. Chem. Rev., 63, 184 (Table IX, reactions Nos. 65a, 90a).

K.B. Wiberg, 1964. "Physical Organic Chemistry", Wiley, International Edition, Tokyo, 404.

K.L. Wierzchowski, D. Shugar, and A.R. Katritzky, 1964. J. Amer. Chem. Soc., 85, 827.

W. Windus and P.R. Shildneck, 1943. Org. Synth., Col. Vol. II, 345.

M. Yanagita and R. Futaki, 1952. J. Pharm. Soc. Japan, 72, 236. Through Chem. Abstr., 47, 6424 (1952).

M.J. Zahik and R.D. Schuetz, 1967. J. Org. Chem., 32, 300.

INDEX OF COMPOUNDS*

* Compounds underlined are new.

Others

PUBLICATIONS

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

D.J. Brown, P.W. Ford, and K.H. Tratt, J. Chem. Soc.(C), 1967, 1445.

D.J. Brown, P.W. Ford and M.N. Paddon-Row, J. Chem. Soc.(C), 1968, submitted for publication. (Paper 8/033)

Simple Pyrimidines. Part X.[1] The Formation and Reactivity of 2-, 4-, and 5-Pyrimidinyl Sulphones and Sulphoxides

By **D. J. Brown** and **P. W. Ford**, Department of Medical Chemistry, Australian National University, Canberra, Australia

Reprinted from

JOURNAL
OF
THE CHEMICAL SOCIETY

SECTION C
Organic Chemistry

1967

Simple Pyrimidines. Part X.[1] The Formation and Reactivity of 2-, 4-, and 5-Pyrimidinyl Sulphones and Sulphoxides

By D. J. Brown and P. W. Ford, Department of Medical Chemistry, Australian National University, Canberra, Australia

The hitherto unknown sulphones (2-, 4-, and 5-methylsulphonyl- and 2-phenylsulphonyl-pyrimidine) and sulphoxides (2-, 4-, and 5-methylsulphinyl- and 2-phenylsulphinyl-pyrimidine) are prepared from the corresponding thioethers by oxidative methods. 2-Phenylsulphonylpyrimidine is also made from 2-chloropyrimidine with sodium benzenesulphinate. The 2- and 4-derivatives undergo a variety of ready nucleophilic displacement reactions on a preparative scale, and second-order rate constants for their aminolysis by pentylamine or cyclohexylamine in dimethyl sulphoxide are reported. These figures indicate that the sulphones and sulphoxides are a little more reactive than the corresponding chloropyrimidines, and $>10^5$-times as reactive as the thioethers from which they are derived. Both 2-sulphones undergo an unprecedented reduction by hydriodic acid to 2-methyl (or phenyl) thiopyrimidine. The base-weakening effect of sulphonyl or sulphinyl substituents on pyrimidine is marked in the 2- and 4-derivatives but minimal in the 5-isomers.

DESPITE their potential use as intermediates,[2] pyrimidine sulphones have been little studied and pyrimidine sulphoxides remain practically unknown.[3] We now describe the preparation (by representative methods) and some typical displacement reactions of 2-, 4-, and 5-methylsulphonylpyrimidine; of the corresponding methylsulphinyl derivatives; and of 2-phenylsulphinyl- and 2-phenylsulphonyl-pyrimidine. In addition, we have measured the rates for aminolysis of the 2- and 4-sulphones and sulphoxides so that their reactivities may be compared with those of the corresponding chloro-,[4,5] methoxy-,[6] and methylthio-pyrimidines.[6]

Syntheses and Nature.—Oxidation of appropriate thioethers with two molar proportions of *m*-chloroperbenzoic acid at room temperature gave 4- and 5-methylsulphonylpyrimidine. When only one mole of oxidant was used at 0°, the corresponding methylsulphinyl derivatives were formed, and 2-phenylsulphinylpyrimidine was also made in this way. 2-Methylthio- and 2-phenylthio-pyrimidine were converted by aqueous chlorine into the corresponding sulphones, but the method was unsatisfactory for oxidising 4-methylthiopyrimidine: of the several products, only methanesulphonyl chloride [7] (n.m.r.: singlet at τ 6·31; i.r. bands at 980, 1180, 1340, 1390, and 3020 cm.$^{-1}$) could be isolated in quantity. 2-Phenylsulphonylpyrimidine was also made by heating 2-chloropyrimidine with sodium benzenesulphinate (cf. precedents [8]), and 2-methylsulphinylpyrimidine by oxidising the thioether with periodate.[9] A similar oxidation of 2-phenylthiopyrimidine was only 33% completed after 96 hr.; this contrasts with the rapid oxidation of simple phenylthioethers.

The pyrimidine sulphones and sulphoxides are reason-

[1] Part IX, T. J. Batterham, D. J. Brown, and M. N. Paddon-Row, *J. Chem. Soc.* (*B*), 1967, 171.

[2] W. H. Nyberg and C. C. Cheng, *J. Heterocyclic Chem.*, 1964, **1**, 1; R. G. Shepherd, W. E. Taft, and H. M. Krazinski, *J. Org. Chem.*, 1961, **26**, 2764; D. J. Brown, "The Pyrimidines," Interscience, New York, 1962, p. 300.

[3] J. M. Carpenter and G. Shaw, *J. Chem. Soc.*, 1965, 3987.

[4] N. B. Chapman and C. W. Rees, *J. Chem. Soc.*, 1954, 1190.

[5] D. J. Brown and J. M. Lyall, *Austral. J. Chem.*, 1964, **17**, 794; 1965, **18**, 741 and 1811.

[6] D. J. Brown and R. V. Foster, *Austral. J. Chem.*, 1966, **19**, 1487, 2321.

[7] A. Simon, H. Kriegsmann, and H. Dutz, *Chem. Ber.*, 1956, **89**, 1883; "N.M.R. Spectra Catalog," Varian Associates, 1963, vol. 2, no. 347.

[8] M. Semonský and A. Černý, *Chem. listy*, 1951, **45**, 156; (*Chem. Abs.*, 1952, **46**, 1556).

[9] N. J. Leonard and C. R. Johnson, *J. Org. Chem.*, 1962, **27**, 282.

ably stable crystalline solids, but 4-methylsulphonylpyrimidine is exceptional: even at 0°, it changes in a few days to high-melting yellow material which lacks an i.r. absorption band at 1140 cm.$^{-1}$. That each of these compounds is indeed a sulphoxide or sulphone, rather than the isomeric mono- or di-*N*-oxide follows from the n.m.r. spectra. Thus the methyl signal is shifted downfield *ca.* τ 0·5 on oxidation of each methylthiopyrimidine to a sulphoxide, and a further similar shift occurs from sulphoxide to sulphone. In addition, each sulphoxide shows a characteristic [10] i.r. absorption at 1040—1080 cm.$^{-1}$, and each sulphone at 1140 and 1320 cm.$^{-1}$.

TABLE 1

Ionisation and ultraviolet spectra

Pyrimidine	pK_a [a]	$\lambda_{max.}$ (log ε) [b]	Solvent [c]
2-$MeSO_2$-	< -3 [d]	239 (3·21), 243 (3·23), *265 (2·41)*	5·0
		240 (3·27), 244 (3·24)	E
4-$MeSO_2$- ...	< 0 [d]	*229 (3·90)*, *250 (3·42)*, 277 (2·93), *286 (2·89)*	5·0
		229 (3·77), *250 (3·13)*, 281 (2·91), 288 (2·86)	E
5-$MeSO_2$- ...	0·97 ± 0·04 (264)	240 (3·06), 243 (3·06), *277 (2·63)*	5·0
		265 (3·68)	−1·5
		238 (3·08), 286 (2·52)	E
2-$PhSO_2$- ...	< -3 [d]	235 (4·04), *267 (3·30)*, 228 (3·87), 267 (3·08), 274 (3·00)	5·0
			E
2-MeSO-	< -3 [d]	247 (3·57)	5·0
		250 (3·56)	E
4-MeSO-	< 0 [d]	254 (3·63)	5·0
		258 (3·61)	E
5-MeSO-	0·42 + 0·04 (276)	247 (3·44)	5·0
		269 (3·69)	−1·5
		250 (3·44)	E
2-PhSO-	< -3 [d]	226 (4·11)	5·0
		227 (4·13)	E
2-$C_6H_{11}NH$-	4·04 ± 0·02 (340)	237 (4·28), 308 (3·40)	7·0
		232 (4·25), 320 (3·10)	2·0
		235 (4·30), 312 (3·42)	E
2-NH_2NH- ...	4·55 ± 0·04	230 (4·12), 297 (3·39)	7·0
	−0·46 ± 0·05 (297)	220 (4·03), 276 (3·31)	2·0
		233 (4·13), 300 (3·38)	E
2-$C_5H_{11}NH$-	4·04 [e]	237 (4·26), 309 (3·41)	7·0
		317 (3·51), 270 (4·26)	2·0
		238 (4·28), 310 (3·43)	E
4-$C_5H_{11}NH$-	—	245 (4·21), 278 (3·49)	E

[a] Measured at 20° spectrometrically (analytical wavelength given) by methods described by A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Methuen, London, 1962. [b] Inflexions in italics. [c] Aqueous buffer of given pH value or 95% ethanol (E). [d] Instability in highly acidic media precluded precise measurement. [e] D. J. Brown and J. S. Harper, *J. Chem. Soc.*, 1963, 1276.

The base-weakening effect of sulphonyl and sulphinyl groupings is particularly evident when they are situated at the 2- or 4-position: thus no spectral change occurred down to H_0 −2, indicating pK_a values at least 4 units below that of pyrimidine; at lower H_0 values the change towards the spectrum of the appropriate hydroxypyrimidine was so rapid as to preclude observation of cation formation. As expected, when the same groups were situated at the 5-position they were far less activated towards nucleophilic attack. In addition, they had less effect on the basic centres, each pK_a value being depressed <1 unit below that of pyrimidine (pK_a 1·3).

Reactions.—The synthetic potential of pyrimidine sulphones and sulphoxides is exemplified better in the following reactions of the simple derivatives than in the meagre record [2,3] of their more highly substituted analogues. 2-Methylsulphonylpyrimidine reacted in dimethylformamide with sodium azide or potassium cyanide to give 2-azido- or 2-cyano-pyrimidine, respectively; with ethanolic alkylamines, hydrazine, or sodium ethoxide to give 2-alkylamino-, 2-hydrazino-, or 2-ethoxy-pyrimidine; with aqueous sodium hydroxide to give 2-hydroxypyrimidine; and with 2N-hydrochloric acid to give the same product [$t_{\frac{1}{2}}$ (25°) = 4·8 hr.]. It failed to react in dimethyl sulphoxide with sodium fluoride, iodide, or thiocyanate despite the enhanced nucleophilicity of such ions in that solvent,[11] but in hydriodic acid it was reduced to 2-methylthiopyrimidine [$t_{\frac{1}{2}}$ (98°) = 10 min.], a result in marked contrast to the resistance of other sulphones to reduction.[12] 2-Phenylsulphonylpyrimidine underwent similar reduction at a comparable rate, but 5-methylsulphonylpyrimidine gave no thioether. This suggests that a ring nitrogen atom in α-position to the alkylsulphonyl group may be necessary for intra-molecular oxygen transfer from sulphur to nitrogen followed by reduction [13] of the *N*-oxide. 2-Methylsulphinylpyrimidine underwent reduction, as do simple sulphoxides,[14,15] with hydriodic acid, and it was aminolysed by pentylamine. In addition, it was oxidised to the 2-sulphone by *m*-chloroperbenzoic acid, in good yield. 4-Methylsulphonylpyrimidine reacted with butanolic sodium butoxide to give 4-butoxypyrimidine, and underwent aminolysis; 4-methylsulphinylpyrimidine was shown to undergo alkaline hydrolysis and to react with sodium propoxide. 5-Methylsulphonyl- and 5-methylsulphinyl-pyrimidine both reacted abnormally with amines: the nature and formation rates of the products are being studied.

Aminolysis Rates.—Previous studies [5,6] on the relative aminolysis rates of chloro-, alkoxy-, and alkylthiopyrimidines have been conducted under preparative conditions in systems without added solvent. Because of their high reactivity, meaningful results could not be obtained under such conditions for the reactions of the 2- and 4-sulphones and sulphoxides with primary n-alkylamines. Rather than resort to the less reactive s- or t-alkylamines or to dialkylamines, we have followed the aminolyses of these pyrimidines in dimethyl sulphoxide solution. The resulting second-order rate constants may be compared semi-quantitatively with those derived in ethanol,[4] or without solvent [5,6] because, in addition, we have measured (as a link) the rate for pentylaminolysis of 2-chloropyrimidine in dimethyl sulphoxide. Ethanol was avoided as solvent in

[10] L. J. Bellamy, "Infrared Spectra of Complex Molecules," Methuen, London, 2nd edn., 1958, p. 350 *et seq.*
[11] A. J. Parker, *Adv. Org. Chem.*, 1965, **5**, 1.
[12] E. O. Beckmann, *J. prakt. Chem.*, 1878, **17**, 439.
[13] C. C. J. Culvenor, *Rev. Pure Appl. Chem.* (*Australia*), 1953, **3**, 83.
[14] T. Zincke, *Annalen*, 1918, **416**, 86.
[15] G. Moderna, G. Scorrano, D. Landini, and F. Montanari, *Tetrahedron Letters*, 1966, 3309.

the present measurements because of spectral evidence that an appreciable proportion of ethoxypyrimidine was being formed from the 2-methylsulphone and dilute ethanolic amine during preliminary runs; in contrast, the same sulphone was unaffected by anhydrous dimethyl sulphoxide at 95° for 24 hr.

the methylsulphonyl, phenylsulphonyl, methylsulphinyl, or chloro substituent as a leaving group from pyrimidine; the rates of aminolytic displacement of these groups from the 2-position at the same temperature differ at most by a factor of 5 in favour of the sulphur-containing groups. Although $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values differ significantly, they

TABLE 2

Rates of aminolysis

Pyrimidine and concn. (M × 10⁴)	Amine [a] and concn. (M × 10⁴)	Temp.	10⁴k [b] (l. mole⁻¹ sec.⁻¹)	Anal. λ (mμ)	$\Delta H^{\ddagger}$ [c] (kcal. mole⁻¹)	$\Delta S^{\ddagger}$ [d] (kcal. mole⁻¹ deg.⁻¹)
2-$MeSO_2^-$ ... 55·69	c, 442·4	70·3	2·73 ± 0·10 (66)			
55·27	407·9	74·5	3·50 ± 0·11 (83)			
55·84	383·2	79·5	4·42 ± 0·09 (85)			
55·84	768·7	79·5	4·50 ± 0·12 (80)	310	13·0	−21
60·54	p, 509·4	28·15	6·71 ± 0·11 (85)			
63·97	498·2	33·35	8·84 ± 0·09 (80)			
60·04	478·5	38·15	11·38 ± 0·15 (77)	309	8·8	−34
2-$PhSO_2^-$ ... 65·96	c, 421·0	74·5	2·96 ± 0·09 (67)			
55·41	421·0	79·5	4·08 ± 0·07 (90)	310	15·3	−31
61·26	p, 509·4	28·15	5·36 ± 0·10 (78)			
65·85	498·2	33·35	7·04 ± 0·19 (85)			
64·56	478·5	38·15	9·13 ± 0·16 (83)	309	9·3	−43
2-$MeSO^-$ ... 88·03	p, 482·4	29·5	3·11 ± 0·08 (66)			
101·7	567·5	34·6	4·29 ± 0·09 (75)			
74·48	558·3	39·9	5·53 ± 0·08 (73)	309	10·8	−39
4-$MeSO_2^-$ ... 62·44	p, 531·9	19·5	6630 ± 0·13 (90)			
61·58	482·3	21·5	7300 ± 0·11 (95)			
59·11	447·9	24·95	8640 ± 0·08 (93)	278	7·8	−51
4-$MeSO^-$ [e] ... 69·47	p, 517·1	25·7	1190			
75·41	452·7	29·85	1420			
69·32	452·7	36·25	1840	278	—	—
2-Cl^- ..... 88·96	p, 572·8	29·35	1·44 ± 0·01 (82)			
84·43	543·3	36·2	2·19 ± 0·04 (83)			
82·85	547·7	41·0	2·85 ± 0·03 (60)			
170·07	1095·4	41·0	2·90 ± 0·02 (65)	309	11·1	−44

[a] Cyclohexylamine (c) or *n*-pentylamine (p). [b] Second-order rate constant and standard deviation; reaction followed from <10% to % in parenthesis. [c] Maximum estimated uncertainty ± 0·4 units, except cyclohexylamine displacements (±0·7). [d] Maximum estimated uncertainty ±4 units. [e] *k* values are approximate; rectilinearity lost beyond 50% reaction.

The sulphones apparently react with amines thus:

$$R{\cdot}SO_2Me + R'NH_2 \longrightarrow R{\cdot}NH{\cdot}R' + MeSO_2H$$

but, in aprotic dimethyl sulphoxide, without the subsequent salt formation:

$$MeSO_2H + R'NH_2 \longrightarrow RN^+H_3{\cdot}MeSO_2^-$$

because the plot:

$$t/\log_{10}\frac{a(b-x)}{b(a-x)}$$

is rectilinear in all but one case over at least 75% of each reaction. The fate of the group displaced from pyrimidine sulphoxides during aminolysis is unknown, but again it does not bind any amine. The rate constants were calculated by the expression:

$$k = \frac{1}{t(a-b)}\log_e\frac{a(b-x)}{b(a-x)}$$

and the results are given in Table 2.

It is clear from these that there is little to choose between do so in a compensating way. There appears to be no previous data on heterocyclic sulphoxides as substrates for nucleophilic attack,[2,16] but the approximate equivalence of chloro and alkylsulphonyl substituents as leaving groups in pyrimidines is in agreement with kinetic observations of the reactions between sodium methoxide and the sulphones of other monocyclic [17] and bicyclic [18] azines, and with a similar qualitatively-based conclusion [16] in respect of such groups attached to heterocycles in general. In the benzene series, literature [19] on the relative reactivities is quite contradictory. The above equivalence, taken in conjunction with round figures previously derived [6] for the relative ease of displacing chloro- and methylthio-substituents in the pyrimidine series, indicates that an improvement of >10^5-fold in aminolysis rate may be expected whenever an alkylthiopyrimidine is oxidised to the corresponding sulphone or sulphoxide before reaction with an amine.

Both 4-methylsulphonyl- and 4-methylsulphinylpyrimidine undergo aminolysis more rapidly than do

[16] R. G. Shepherd and J. L. Fedrick, *Adv. Heterocyclic Chem.*, 1965, **4**, 146.

[17] G. B. Barlin and W. V. Brown, *J. Chem. Soc.* (*B*), 1967, in the press.

[18] G. B. Barlin and W. V. Brown, personal communication.

[19] J. F. Bunnett, E. W. Garbisch, and K. M. Pruitt, *J. Amer. Chem. Soc.*, 1957, **79**, 385; J. F. Bunnett and W. D. Merritt, *ibid.*, p. 5967; J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, 1951, **49**, 273.

their respective 2-isomers, therein being parallel to the corresponding pairs of chloro-,[4,5] alkylthio-,[6] and alkoxypyrimidines.[6] The approximately 30-fold decrease in rate, evident when n-pentylamine is replaced by cyclohexylamine as nucleophile of the sulphones, is similar to the 25-fold decreases recorded [5] when n- is replaced by s-butylamine, and n- by iso-propylamine, in the aminolyses of 2-chloro-4,6-dimethylpyrimidine.

EXPERIMENTAL

Analyses were done by Dr. J. E. Fildes and her staff. Ultraviolet spectra were recorded on a Shimadzu model RS27 spectrophotometer and peaks checked on a Uvispec manual instrument. N.m.r. spectra were measured at 60 Mc./sec.

2-Methylsulphonylpyrimidine.—Chlorine was bubbled through a suspension of 2-methylthiopyrimidine [20] (10 g.) in water (100 ml.) at 0—5° until dissolution occurred. After a further 2 hr. in ice, the solution was adjusted to pH 8 with solid potassium carbonate. Chloroform extraction afforded the colourless *sulphone* (6·2 g.), m. p. 73—74° (from 95% ethanol) (Found: C, 37·9; H, 4·0; N, 17·7. $C_5H_6N_2O_2S$ requires C, 38·0; H, 3·8; N, 17·7%).

4-Methylsulphonylpyrimidine.—4-Methylthiopyrimidine [21] (6·3 g.) in chloroform (100 ml.) at −15° was treated with similarly cooled 80% *m*-chloroperbenzoic acid (20 g.) in chloroform (350 ml.). After it had stood at 20° for 16 hr., the reaction mixture was washed with saturated aqueous sodium sulphite solution (2 × 50 ml.) followed by 2N-sodium carbonate (2 × 100 ml.). Removal of chloroform gave the *4-sulphone* (3·75 g.), m. p. 53—54° (from benzene–light petroleum) (Found: C, 38·0; H, 4·0; N, 17·7. $C_5H_6N_2O_2S$ requires C, 38·0; H, 3·8; N, 17·7%).

5-Methylsulphonylpyrimidine.—The methanethiol from *S*-methylthiourea sulphate (49 g.) and base [22] was passed into ethanolic sodium ethoxide (150 ml.; sodium, 2·9 g.). 5-Bromopyrimidine [23] (15·9 g.) was added, and the solution was heated under reflux for 12 hr. The filtrate was adjusted with hydrochloric acid to pH 4 and evaporated under reduced pressure. An aqueous solution of the residue was extracted with chloroform (4 × 50 ml.) and distillation of the extract gave *5-methylthiopyrimidine* (10·25 g.), b. p. 70—71°/2 mm. and m. p. 42—43° (Found: C, 48·0; H, 5·3; N, 21·9. $C_5H_6N_2S$ requires C, 47·6; H, 4·8; N, 22·2%). Oxidation with *m*-chloroperbenzoic acid as above thence afforded *5-methylsulphonylpyrimidine* (55%), m. p. 135—136° (from 95% ethanol) (Found: C, 38·3; H, 3·6; N, 17·7. $C_5H_6N_2O_2S$ requires C, 38·0; H, 3·8; N, 17·7%).

2-Phenylsulphonylpyrimidine.—(*a*) 2-Chloropyrimidine [24] (3·5 g.), sodium benzenesulphinate (5·0 g.), and anhydrous dimethyl sulphoxide (25 ml.) were heated on the steam-bath for 5 hr. After cooling, the filtered solution was evaporated *in vacuo* at 60° and the residue was extracted with hot chloroform (2 × 50 ml.). Evaporation gave the *phenylsulphone* (3·45 g.), m. p. 99—100° (from 95% ethanol) (Found: C, 54·4; H, 3·8; N, 12·7; S, 14·2. $C_{10}H_8N_2O_2S$ requires C, 54·5; H, 3·7; N, 12·7; S, 14·5%).

(*b*) 2-Chloropyrimidine (11·5 g.) in ethanol (150 ml.) was added to a solution of sodium ethoxide (from sodium, 2·5 g.) and thiophenol (11·0 g.) in ethanol (210 ml.). The solution was heated under reflux for 2 hr., cooled, and filtered. The residue from evaporation was dissolved in water (200 ml.) and extracted with chloroform. Distillation gave *2-phenylthiopyrimidine* (11·1 g.), b. p. 144—146°/0·8 mm. and m. p. 45°. An analytical sample was purified chromatographically (Found: C, 63·6; H, 4·2; N, 14·9. $C_{10}H_8N_2S$ requires C, 63·8; H, 4·3; N, 14·9%). Oxidation of this thioether (5·0 g.) with aqueous chlorine as above gave the phenylsulphone (4·2 g.), identified by mixed m. p.

2-Methylsulphinylpyrimidine.—2-Methylthiopyrimidine [20] (10·0 g.) was dissolved in aqueous 0·5M-sodium metaperiodate (165 ml.) at 5°. After gentle stirring at 20° for 16 hr., the solid was removed and the filtrate extracted with chloroform. Distillation of the extract gave the *sulphoxide* (6·0 g.), b. p. 152—154°/0·5 mm. (Found: C, 42·5; H, 4·4; S, 22·2. $C_5H_6N_2OS$ requires C, 42·3; H, 4·3; S, 22·5%).

4-Methylsulphinylpyrimidine.—4-Methylthiopyrimidine [21] (4·6 g.) in chloroform (100 ml.) was treated at −15° with 80% *m*-chloroperbenzoic acid (7·4 g.) in chloroform (150 ml.). After 15 hr. at 0°, the solution was twice washed with N-sodium carbonate. Evaporation of the chloroform gave the *4-sulphoxide* (3·4 g.), m. p. 47—49° (from benzene–light petroleum) (Found: C, 42·25; H, 4·5; N, 19·6. $C_5H_6N_2OS$ requires C, 42·3; H, 4·3; N, 19·7%).

5-Methylsulphinylpyrimidine.—Prepared as its 4-isomer above, the *5-sulphoxide* required final purification by thin-layer chromatography on alumina to remove a trace of sulphone. It had m. p. 84—86° (from ethanol) (Found: C, 42·1; H, 4·1; N, 19·4%).

2-Phenylsulphinylpyrimidine.— 2-Phenylthiopyrimidine (5·0 g.) was oxidised with *m*-chloroperbenzoic acid as was 4-methylthiopyrimidine above. After removing a trace of sulphone by thin-layer chromatography on alumina, *2-phenylsulphinylpyrimidine* (2·5 g.), had m. p. 118—119° (from benzene) (Found: C, 59·2; H, 4·0; N, 13·7. $C_{10}H_8N_2OS$ requires C, 58·8; H, 3·95; N, 13·7%).

Reactions of 2-Methylsulphonylpyrimidine.—(*a*) 2-Methylsulphonylpyrimidine (2·0 g.) and sodium azide (2·5 g.) were heated in dimethylformamide (4·0 ml.) on the steam-bath for 3 hr. The cooled mixture was diluted with chloroform (25 ml.), and filtered. Evaporation of the filtrate *in vacuo* gave 2-azidopyrimidine (0·9 g.), m. p. 123—125° (from benzene), undepressed on admixture with material made [25] by treating 2-hydrazinopyrimidine with nitrous acid (Found: C, 39·9; H, 2·5; N, 57·3. Calc. for $C_4H_3N_5$: C, 39·7; H, 2·5; N, 57·8%).

(*b*) The sulphone (2·0 g.), potassium cyanide (2·0 g.), and dimethylformamide (10 ml.) were heated at 100° for 4 hr. Addition of chloroform (25 ml.), filtration, and evaporation gave 2-cyanopyrimidine (0·55 g.) which, after sublimation (0·5 mm.), had m. p. 42—43° (lit.,[26] 42°) (Found: C, 56·8; H, 3·1; N, 39·8. Calc. for $C_5H_3N_3$: C, 57·1; H, 2·9; N, 40·0%).

(*c*) The sulphone (2·0 g.), cyclohexylamine (5·0 ml.), and ethanol (25 ml.) were heated under reflux for 4 hr.

[20] M. P. V. Boarland and J. F. W. McOmie, *J. Chem. Soc.*, 1952, 3716.
[21] A. Albert and G. B. Barlin, *J. Chem. Soc.*, 1962, 3129.
[22] R. Phillips and H. T. Clarke, *J. Amer. Chem. Soc.*, 1923, **45**, 1755; W. Windus and P. R. Shildneck, *Org. Synth.*, Coll. Vol. II, 1943, 345.
[23] H. Bredereck, R. Gompper, and H. Herlinger, *Chem. Ber.*, 1958, **91**, 2830.
[24] I. C. Kogon, R. Minin, and C. G. Overberger, *Org. Synth.*, 1955, **35**, 34.
[25] K. Sirakawa, Jap. P. 777/1957 (*Chem. Abs.*, 1958, **52**, 4699); C. Temple and J. A. Montgomery, *J. Org. Chem.*, 1965, **30**, 826.
[26] M. Robba, *Ann. Chim.* (*France*), 1960, [13], **5**, 351.

After removing ethanol, the residue was treated with aqueous sodium hydroxide and extracted with chloroform. Evaporation and sublimation (70°/0·5 mm.) gave *2-cyclohexylaminopyrimidine* (0·8 g.), m. p. 92—94° (Found: C, 68·1; H, 8·7; N, 23·4. $C_{10}H_{15}N_3$ requires C, 67·8; H, 8·5; N, 23·7%).

(*d*) Pentylamine similarly gave 2-pentylaminopyrimidine (60%), b. p. 72—74°/0·4 mm. (Found: C, 65·2; H, 9·1; N, 25·5. Calc. for $C_9H_{15}N_3$: C, 65·4; H, 9·15; N, 25·4%), identified as its picrate, m. p. 117—118° (lit.,[27] 116—117°) (Found: C, 45·5; H, 4·7; N, 21·5. Calc. for $C_{15}H_{18}N_6O_7$: C, 45·7; H, 4·6; N, 21·3%).

(*e*) Hydrazine similarly gave 2-hydrazinopyrimidine (45%), m. p. 112—113° (lit.,[28] 110°) (Found: C, 43·4; H, 5·6; N, 51·2. Calc. for $C_4H_6N_4$: C, 43·6; H, 5·5; N, 50·9%).

(*f*) The sulphone (1·5 g.) was heated on the steam-bath for 10 min. with hydriodic acid (sp. gr. 1·94; 5·0 ml.). The cooled mixture was added to ice. After treatment with sodium sulphite and subsequent adjustment with solid potassium carbonate to pH 10, the solution was extracted with chloroform. Distillation gave 2-methylthiopyrimidine (0·35 g.), b. p. 70—71°/0·5 mm.; its n.m.r. spectrum was identical with that of authentic material (Found: C, 47·8; H, 5·0. Calc. for $C_5H_6N_2S$: C, 47·6; H, 4·8%).

(*g*) The sulphone (1·0 g.) and 2N-sodium hydroxide (32 ml.) were set aside for 2 hr. at 25°. The solution was adjusted to pH 4 with hydrochloric acid and evaporated to dryness. Extraction with boiling ethyl acetate gave 2-hydroxypyrimidine, identified with authentic material[29] by paper chromatography and mixed m. p.

(*h*) A solution of the sulphone (1·6 g.) in ethanolic sodium ethoxide (25 ml.; sodium, 0·4 g.) was heated under reflux for 1 hr., cooled, and diluted with water (10 ml.). After adjustment to pH 4 (with hydrochloric acid) and partial evaporation, the residual mixture was extracted with chloroform (3 × 25 ml.). Distillation gave 2-ethoxypyrimidine (0·4 g.), b. p. 46—48°/1·1 mm. (lit.,[30] 77—78°/20 mm.) (Found: C, 58·3; H, 6·6; N, 23·0. Calc. for $C_6H_8N_2O$: C, 58·05; H, 6·5; N, 22·6%).

Reactions of 2-Methylsulphinylpyrimidine.—(*a*) The sulphoxide (0·1 g.) and pentylamine (0·3 g.) were heated at 100° for 10 hr. After removing the excess of pentylamine under reduced pressure, the residual oil was added to alcoholic picric acid. The 2-pentylaminopyrimidine picrate (0·17 g.), m. p. 117°, was identical with that prepared above.

(*b*) The sulphoxide underwent immediate reaction in aqueous potassium iodide–sulphuric acid with liberation of iodine.

(*c*) A solution of 75% *m*-chloroperbenzoic acid (1·75 g.) in chloroform (150 ml.) was added to the sulphoxide (1·0 g.) in chloroform (100 ml.) at 0°. After 16 hr., the chloroform solution was washed successively with saturated aqueous sodium sulphite (50 ml.) and N-sodium carbonate (50 ml.) Evaporation and recrystallisation of the residue from ethanol gave 2-methylsulphonylpyrimidine (0·6 g.), identified with authentic material by mixed m. p. and i.r. spectra.

Reactions of 4-Methyl-sulphonyl(and -sulphinyl)pyrimidine.—(*a*) The sulphone (1·0 g.) was treated with pentylamine as was its isomer above. The 4-pentylaminopyrimidine (0·43 g.), had b. p. 114—116°/0·4 mm. and m. p. 58—60° (lit.,[31] 61—62°) (Found: C, 65·55; H, 9·1; N, 25·6. Calc. for $C_9H_{15}N_3$: C, 65·4; H, 9·15; N, 25·4%).

(*b*) The sulphone (4·0 g.) and butanolic sodium butoxide (20 ml.; sodium, 0·7 g.) were warmed for 2 hr. Water (20 ml.) was added and the mixture was adjusted to pH 4 and extracted with chloroform. Distillation *in vacuo* gave an oil (2·2 g.) containing some butanol. It was converted into *4-butoxypyrimidine picrate*, m. p. 85—86° (Found: C, 44·2; H, 4·2; N, 18·5. $C_{14}H_{15}N_5O_8$ requires C, 44·1; H, 4·0; N, 18·4%).

(*c*) The sulphoxide (1·0 g.) was treated with aqueous sodium hydroxide as was the 2-methylsulphonylpyrimidine above. The resulting 4-hydroxypyrimidine was identified with authentic material[32] by mixed m. p. and i.r. spectra.

(*d*) The sulphoxide (3·1 g.) was treated with propanolic sodium propoxide as was the sulphone above with butoxide. The resulting distillate was converted into *4-propoxypyrimidine picrate*, m. p. 92—93° (from ethanol) (Found: C, 42·7; H, 3·7; N, 18·9. $C_{13}H_{13}N_5O_8$ requires C, 42·5; H, 3·6; N, 19·1%).

Rate Measurements.—Dimethyl sulphoxide (Fluka: purum) was purified by sodium hydride (triphenylmethane indicator) and distilled *in vacuo*. Pentylamine and cyclohexylamine (Fluka: puriss.) were homogeneous on gas chromatography.

Separate dimethyl sulphoxide solutions of the pyrimidine and the amine were brought to temperature, mixed, and thermostatted. Samples were taken at intervals and each was diluted immediately with cold 95% ethanol in an appropriate (>20-fold) excess, thus decreasing the rate of reaction to a negligible figure (experimentally verified). The alkylaminopyrimidine content of each was estimated spectrometrically at a predetermined wavelength. Reference spectra are given in Table 1; other data in Table 2.

We thank Professor A. Albert for discussion, and Messrs. S. E. Brown, I. Pavelic, and D. T. Light for assistance. P. W. F. thanks the C.S.I.R.O. for a Senior Postgraduate Studentship.

[6/1321 *Received, October 17th,* 1966]

[27] D. J. Brown and J. S. Harper, *J. Chem. Soc.*, 1963, 1276.
[28] J. Chesterfield, J. F. W. McOmie, and E. R. Sayer, *J. Chem. Soc.*, 1955, 3478.
[29] D. J. Brown, *Nature*, 1950, **165**, 1010.
[30] D. J. Brown and R. V. Foster, *J. Chem. Soc.*, 1965, 4911.
[31] G. H. Hitchings and P. B. Russell, *J. Chem. Soc.*, 1949, 2454.
[32] D. J. Brown, *J. Soc. Chem. Ind.*, 1950, **69**, 353.

Purine Studies. Part V.[1] Formation and Aminolysis of Some Methylthiopurines

By **D. J. Brown, P. W. Ford,** and **K. H. Tratt,** Department of Medical Chemistry, John Curtin School of Medical Research, Canberra, Australia

Reprinted from

JOURNAL
OF
THE CHEMICAL SOCIETY

SECTION C
Organic Chemistry

1967

Purine Studies. Part V.[1] Formation and Aminolysis of Some Methylthiopurines

By D. J. Brown, P. W. Ford, and K. H. Tratt, Department of Medical Chemistry, John Curtin School of Medical Research, Canberra, Australia

Syntheses of 6,7- and 6,9-dimethyl-2-methylthiopurine, 2,9-dimethyl-6-methylthiopurine, 9-benzyl-8-methyl- and 2,9-dimethyl-8-methyl-thiopurine, and related compounds are described. The 2-methylthiopurines are unaffected by butylamine at 200°, but the dimethyl-6(and 8)-methylthiopurines undergo apparent first-order-butylaminolysis under preparative conditions at rates comparable with simple 4-methylthiopyrimidines; 9-benzyl-8-methylthiopurine is decomposed by such treatment. The recorded ionisation constants and ultraviolet spectra are used to confirm some of the structures involved.

STUDIES [2,3] on the relative ease of aminolysis of chloro-, alkoxy-, and alkylthio-pyrimidines under preparative conditions, recently extended to 2-chloropteridines and 2-chloropurines,[4] are now widened to include the reactions of some methylthiopurines with butylamine. For reasons already outlined,[4] the ease of aminolysis of a substituent in the pyrimidine ring of a purine, *e.g.*, (I), might be expected to approximate to that of the corresponding pyrimidine, whatever the leaving group. A substituent in the 8-position of purine appears to be intermediate in reactivity between the 2- and the 6-isomer as judged by the monochloro-9-methylpurines.[5] Data on aminolyses of simple alkylthiopurines are minimal, being confined to a few qualitative observations: *e.g.*, 6(or 8)-methylthiopurine heated with aqueous dimethylamine at 140° for 24 hr. gives the corresponding dimethylaminopurine in reasonable yield, but 2-methylthiopurine under similar conditions slowly yields 4,5-diamino-2-methylthiopyrimidine without any replacement of the sulphide group.[6]

For the present study, 2-, 6-, and 8-methylthiopurines were prepared, each bearing a 7- or 9-methyl group to preclude anion formation during aminolysis, and an additional *C*-methyl group to assist mutual solubility of the purine and butylamine without added solvent.

6,9-Dimethyl-2-methylthiopurine (I; R = SMe) was made from 2-chloro-4-methyl-6-methylamino-5-nitropyrimidine [4] by treating it with sodium hydrogen sulphide to give the 5-amino-2-mercaptopyrimidine (II; R = SH); this underwent direct cyclisation in formic acid to the mercaptopurine (I; R = SH), which was subsequently *S*-methylated. 6,9-Dimethylpurine (I; R = H) was made for comparison by desulphurising the intermediate (II; R = SH) and similarly cyclising the resulting diamine (II; R = H). 6,7-Dimethyl-2-methylthiopurine (III; R = SMe) was prepared from 4,5-diamino-6-methyl-2-methylthiopyrimidine [7] by reduction (with lithium aluminium hydride) of the formyl group in the 5-formamido-derivative to give the diamine (IV; R^1 = SMe, R^2 = H), reformylation of this to the methylformamido-derivative (IV; R^1 = SMe, R^2 = CHO), and thermal cyclisation. Again, the parent purine (III; R = H) was made similarly *via* the desulphurised intermediate (IV; $R^1 = R^2$ = H).

It can be seen (Experimental section) that the above cyclisations leading to 7-methylpurines needed much more vigorous conditions than those yielding 9-methylpurines. It might be thought that this phenomenon, also observed in a related case,[8] results from the 4-amino-5-methylaminopyrimidine intermediates for 7-methylpurines being formylated on the less hindered 4-substituent instead of on the 5-substituent as do other such diamines.[8,9] However, much confirmation for the 5-acetylated structures (IV; R^2 = CHO) is evident in the following considerations. 4-Aminopyrimidines are stronger bases than 5-aminopyrimidines: compare pyrimidine (pK_a 1·3) with 4-aminopyrimidine (5·7) and 5-aminopyrimidine (2·5).[10] Hence the basic properties of a 4,5-diaminopyrimidine are associated with the vinylogous guanidine system involving the 4-amino-group and the ring nitrogens, rather than with the more isolated 5-amino-group; hence acylation of a 4-amino-group should have a greater base-weakening effect than acylation of a 5-amino-group. Thus, in practice, acylation of 4-aminopyrimidine (pK_a 5·7) or its 5-ethoxycarbonyl-2-methyl derivative (4·5) produces a decrease of 3 units in basic strength for the acetamido-analogues, pK_a 2·75 and 1·4, respectively (see Table 1;

[1] Part IV, A. Albert, *J. Chem. Soc.* (*B*), 1966, 438.
[2] D. J. Brown and J. M. Lyall, *Austral. J. Chem.*, 1964, **17**, 794; 1965, **18**, 741, 1811.
[3] D. J. Brown and R. V. Foster, *J. Chem. Soc.*, 1965, 4911; *Austral. J. Chem.*, 1966, **19**, 1487, 2321; M. E. C. Biffin, D. J. Brown, and T.-C. Lee, *Austral. J. Chem.*, 1967, **20**, 1041.
[4] D. J. Brown, B. T. England, and J. M. Lyall, *J. Chem. Soc.* (*C*), 1966, 226.
[5] G. B. Barlin and N. B. Chapman, *J. Chem. Soc.*, 1965, 3017.
[6] A. Albert and D. J. Brown, *J. Chem. Soc.*, 1954, 2060.
[7] R. N. Prasad, C. W. Noell, and R. K. Robins, *J. Amer. Chem. Soc.*, 1959, **81**, 193.
[8] D. J. Brown and S. F. Mason, *J. Chem. Soc.*, 1957, 682.
[9] W. Wilson, *J. Chem. Soc.*, 1948, 1157; D. J. Brown, *J. Appl. Chem.*, 1955, **5**, 358.
[10] D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution," Butterworths, London, 1965.

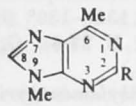
TABLE 1

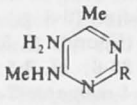
Ionisation constants and ultraviolet spectra

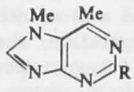
Compound	pK_a *	$\lambda_{max.}$ (log ε) †	pH
Purine			
9-Benzyl-8-mercapto		313 (4·23), *256* (*3·31*), 232 (3·78)	4·5
cation	1·69 ± 0·04 (350)	333 (4·06), 241 (3·90)	−0·5
anion	7·11 ± 0·05 (272)	314 (4·21), 235 (3·95)	9·5
9-Benzyl-8-methylthio		289 (4·23), *254* (*3·58*), *225* (*4·08*), *215* (*4·27*)	6·0
cation	2·84 ± 0·02 (314)	302 (4·14), 237 (4·14)	0·0
6-Butylamino-2,9-dimethyl		271 (4·20), 213 (4·29)	8·0
cation	5·01 ± 0·02 (294)	268 (4·15), *211* (*4·22*)	2·0
8-Butylamino-2,9-dimethyl		296 (4·13), 256 (3·75), 221 (4·21)	8·0
cation	5·45 ± 0·04 (325)	*305* (*3·94*), 287 (3·98), 229—225 (4·26), 219 (4·27)	2·0
6,9-Dimethyl		262 (3·89)	6·0
cation	3·2 ± 0·04 (282)	265 (3·81), 210 (*ca.* 4·4)	0·0
2,9-Dimethyl-6-methylthio		*293* (*4·21*), 288 (4·22), *228* (*4·07*), 221 (4·16)	5·0
cation	2·05 ± 0·03 (315)	305 (4·19), 225 (4·08)	0·0
2,9-Dimethyl-8-methylthio		292 (4·25), 250 (3·59), 222 (4·21)	7·0
cation	3·83 ± 0·03 (315)	302 (4·13), 239 (4·27), *224* (*4·05*)	1·5
6,7-Dimethyl-2-methylthio		306 (3·74), *225* (*4·00*), 238 (4·34)	5·0
cation	2·27 ± 0·02 (335)	312 (3·67), 247 (4·21), 232 (4·14)	0·0
6,9-Dimethyl-2-methylthio		297 (3·89), 259 (3·89), 234 (4·27)	7·0
cation	2·65 ± 0·04 (298)	309 (3·57), 273 (4·03), 244 (4·28)	−1·0
2-Mercapto-6,9-dimethyl		337 (3·37), 289 (4·33), 250 (4·19)	4·0
cation	*ca.* 0 ‡	372 (3·19), 294 (4·32), *250* (*3·94*), 237 (4·04)	−1·5
anion	8·01 ± 0·02 (290)	321 (3·82), 274 (4·13), 239 (4·28)	11·0
8-Mercapto-2,9-dimethyl		314 (4·44), *258* (*3·50*), 235 (4·11)	5·5
cation	2·87 ± 0·03 (345)	330 (4·31), *281* (*3·57*), 243 (4·21)	0·5
anion	7·61 ± 0·03 (273)	315 (4·30), *263* (*3·62*), 236 (4·19)	10·0
Thiazolo[5,4-d]*pyrimidine*			
5-Methyl-7-methylamino		*294* (*3·69*), *273* (*4·00*), 269 (4·01), 225 (4·14)	7·0
cation	3·71 ± 0·02 (312)	*300* (*3·57*), 271 (4·10), 218 (4·18)	1·5
Pyrimidine			
4-Acetamido §		262 (4·01), 232 (4·01)	5·0
cation	2·76 ± 0·03 (276)	268 (4·26)	0·4
4-Amino-5-formamido ‖		279 (3·62), 233 (3·97)	7·0
cation	4·45 ± 0·02 (260)	253 (3·99)	2·0
4-Amino-5-formamido-2-methylthio ¶		293 (3·84), 251 (4·02), 223 (4·25)	6·0
cation	3·71 ± 0·03 (307)	*286* (*3·82*), 243 (4·37)	1·0
5-Amino-2-mercapto-4-methyl-6-methylamino		*310* (*3·85*), *280* (*4·14*), 257 (4·40)	6·5
cation	3·04 ± 0·04 (266)	295 (4·22), 243 (4·06)	1·0
anion	11·50 ± 0·04 (252)	*305* (*3·83*), 274 (4·11), 234 (4·23)	13·5
5-Amino-4-mercapto-2-methyl-6-methylamino		329 (4·24), 242 (4·19), *231* (*4·16*)	6·0
cation	2·82 ± 0·02 (348)	*360* (*3·14*), 307 (4·24), 248 (4·20), *244* (*4·19*)	0·0
anion	10·44 ± 0·03 (345)	310 (4·11), 236—240 (4·20), 228 (4·22)	13·0
4-Amino-6-methyl-5-methylamino		279 (3·72), 240 (3·73)	9·0
cation	6·12 ± 0·02 (310)	277 (3·89)	4·0
5-Amino-2-methyl-4-methylamino	7·45 ± 0·04 (280)	—	
5-Amino-4-methyl-6-methylamino		284 (3·91), 260 (3·90)	9·5
cation	6·82 ± 0·03 (315)	290 (4·11)	3·5
4-Amino-6-methyl-5-methylamino-2-methylthio		293 (3·82), 258 (3·92), 220 (4·18)	8·0
cation	5·41 ± 0·02 (247)	281 (3·93), 241 (4·31)	3·0
5-Amino-2-methyl-4-methylamino-6-methylthio		303 (3·59), 222 (4·16)	9·0
cation	6·02 ± 0·02 (335)	311 (4·05), *230* (*3·92*), *221* (*3·93*)	3·5
4-Amino-6-methyl-5-methylformamido		—	
cation	4·57 ± 0·04 (250)		
4-Amino-6-methyl-5-methylformamido-2-methylthio		286 (3·86), 251 (4·10), 224 (4·28)	7·0
cation	4·02 ± 0·01 (344)	*275* (*4·00*), 242 (4·44)	1·5
4-Chloro-2-methyl-6-methylamino-5-nitro	<1·0 **	350 (3·64), *262* (*3·59*), 232 (4·23)	5·0
5-Formamido-2-methyl-4-methylamino-6-methylthio		286 (3·85), 241 (4·38), *230* (*4·27*)	6·5
cation	3·92 ± 0·03 (316)	285 (4·12), 245 (4·15), *225* (*3·99*)	1·5
Pteridine			
8-Benzyl-7,8-dihydro-7-oxo		306 (3·94), *266* (*3·54*), *255* (*3·64*), 251 (3·65), *216* (*4·32*)	4·0
cation	0·79 ± 0·03 (344)	*302* (*3·89*), 295 (3·89), 280 (3·90), *221* (*4·24*)	−1·5

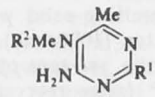
* Measured at 20° spectrometrically by methods of A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Methuen, London, 1962. † In aqueous buffers of given pH; inflexions in italics. ‡ Measurement impeded by dication; spectrum for mixed species. § Prep.: D. J. Brown and L. N. Short, *J. Chem. Soc.*, 1953, 331. ‖ Prep.: D. J. Brown, *J. Appl. Chem.*, 1955, **5**, 358. ¶ Prep.: ref. 6. ** Unstable at and below pH 0.

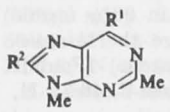
also refs. 10 and 11); on the other hand, 5-acylation of 4,5-diaminopyrimidine (pK_a 6·0) or its 2-methylthio-derivative (5·0) produces only a lowering of *ca* 1·5 units for the 5-formamido-analogues, pK_a 4·45 and 3·7, respectively. Hence the observed decrease (see Table 1) of *ca.* 1·5 units on formylation of 4-amino-6-methyl-5-methylaminopyrimidine (IV; $R^1 = R^2 = H$) and its 2-methylthio-derivative (IV; $R^1 = SMe$, $R^2 = H$) is indicative of acylation at the 5- rather than the 4-substituent.

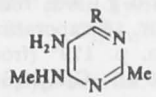

(I)

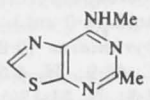

(II)


(III)


(IV)


(V)


(VI)


(VII)

2,9-Dimethyl-6-methylthiopurine (V; $R^1 = SMe$, $R^2 = H$) was approached by initial monoaminolysis of 4,6-dichloro-2-methyl-5-nitropyrimidine to give its 4-chloro-6-methylamino-analogue which reacted with sodium hydrogen sulphide to give the mercaptodiamine (VI; R = SH). Formylation and cyclisation give, not the purine (V; $R^1 = SH$, $R^2 = H$), but 2-methyl-7-methylaminothiazolo[5,4-*d*]pyrimidine (VII) which was identified by its lack of acidity, and its close similarity in basic strength and spectra to known [8,12] homologues. Accordingly, the mercaptodiamine was first *S*-methylated, then formylated, and finally cyclised to the purine (V; $R^1 = SMe$, $R^2 = H$). The isomeric purine (V; $R^1 = H$, $R^2 = SMe$) was made from the same mercaptodiamine (VI; R = SH) by desulphurisation, cyclisation with thiourea to the purine (V; $R^1 = H$, $R^2 = SH$), and final *S*-methylation. The analogous 9-benzyl-8-methylthiopurine was made similarly from the known [13] 5-amino-4-benzylaminopyrimidine, here prepared by an improved route. The intermediate was confirmed in structure by its reaction with ethyl ethoxyglycollate to give 8-benzyl-7,8-dihydro-7-oxopteridine, closely similar in ultraviolet spectrum to the known [14] 8-methyl homologue.

Both the 2-methylthiopurines (I and III; R = SMe) failed to react with butylamine at 200° in 24 hr.; 9-benzyl-8-methylthiopurine was decomposed by such treatment but remained unaffected under more gentle conditions. However, the 6- and the 8-methylthiopurine (V; $R^1 = SMe$, $R^2 = H$) and (V; $R^1 = H$, $R^2 = SMe$) reacted cleanly at 150—180° with butylamine to give the corresponding 6- and 8-butylaminopurines in good yield. The rates of these two aminolyses were followed spectrometrically at 150°, with a 20 : 1 molar ratio of amine to purine in order to achieve homogeneity without an added solvent. Plots of log ΔD against time were rectilinear over at least 80% of each reaction. The average first-order rate constants, $3{\cdot}75 \times 10^{-5}$ and $1{\cdot}5 \times 10^{-5}$ sec.$^{-1}$, respectively, indicated that the 6-methylthiopurine (V; $R^1 = SMe$, $R^2 = H$) underwent aminolysis about 2·5 times more easily than the 8-methylthio-isomer, a result in good agreement with the *ca.* 3-fold increase observed [5] for the rate of aminolysis of 6-chloro-9-methylpurine compared with its 8-chloro-isomer. Moreover, the rate constant for the 6-methylthiopurine was close enough to that of the corresponding 4-methylthiopyrimidine (estimated from existing data [3] as about 1×10^{-6} sec.$^{-1}$ under similar conditions) to be again consistent with our postulate [4] that corresponding purines and pyrimidines undergo similar nucleophilic replacements at broadly similar rates.

EXPERIMENTAL

Analyses were by Dr. J. E. Fildes and her staff; ultraviolet spectra by Mr. A. Arandjelović; and ionisation constants by Messrs. D. T. Light and I. Pavelić. The homogeneity of each compound was checked by paper chromatography.

5-Amino-2-mercapto-4-methyl-6-methylaminopyrimidine.—2-Chloro-4-methyl-6-methylamino-5-nitropyrimidine [4] (20 g.) was stirred on the steam-bath for 1 hr. with M-sodium hydrogen sulphide (700 ml.). The cooled solution was adjusted to pH 5 by adding acetic acid and any solid discarded. The filtrate was evaporated almost to dryness and the brown product removed. Dissolution in hot 0·5N-sodium hydroxide (100 ml.), treatment with charcoal, and neutralisation of the filtrate with 5N-sulphuric acid gave the orange *mercaptopyrimidine* (78%) which, recrystallised from water, had m. p. 280—285° (decomp.) (Found: N, 33·0. $C_6H_{10}N_4S$ requires N, 32·9%).

5-Amino-4-methyl-6-methylaminopyrimidine.—The above mercapto-derivative (3·0 g.) dissolved in hot 0·5N-ammonia solution (75 ml.) was stirred with Raney nickel (15 g., weighed wet) under reflux for 30 min. The filtrate and washings from the nickel were evaporated and the residue recrystallised from benzene to give the *diamine*, m. p. 165—167° (Found: N, 40·3. $C_6H_{10}N_4$ requires N, 40·55%).

6,9-Dimethylpurine.—The diamine (0·5 g.) and formic acid (98%; 1·0 ml.) were refluxed for 10 min. The solution was evaporated *in vacuo* and then twice more with ethanol (4 ml.). The residue was repeatedly extracted with boiling light petroleum (b. p. 60—80°) and the extracts evaporated. The hygroscopic *purine* (0·4 g.) sublimed (90°/0·1 mm.) and then had m. p. 103° (Found: C, 57·05; H, 5·6; N, 38·0. $C_7H_8N_4$ requires C, 56·75; H, 5·4; N, 37·8%).

[11] S. Mizukami and E. Hirai, *J. Org. Chem.*, 1966, **31**, 1199.
[12] G. B. Elion, W. H. Lange, and G. H. Hitchings, *J. Amer. Chem. Soc.*, 1956, **78**, 2858.
[13] J. A. Montgomery and C. Temple, *J. Amer. Chem. Soc.*, 1960, **82**, 4592.
[14] D. J. Brown and S. F. Mason, *J. Chem. Soc.*, 1956, 3443.

2-Mercapto-6,9-dimethylpurine.— 5-Amino-2-mercapto-4-methyl-6-methylaminopyrimidine (2·0 g.) and formic acid (98%; 10 ml.) were refluxed for 1 hr. After removal of formic acid, the *mercaptopurine* recrystallised from water as yellow needles (2·05 g.), m. p. 285° (decomp.) (Found: C, 47·0; H, 4·55; N, 31·1. $C_7H_8N_4S$ requires C, 46·7; H, 4·5; N, 31·1%).

6,9-Dimethyl-2-methylthiopurine.—The mercaptopurine (1·2 g.) in N-sodium hydroxide was shaken with methyl iodide for 15 min. The mass was diluted with a little water and the solid was collected. The *methylthiopurine* (1·2 g., from water) had m. p. 128° (Found: C, 49·7; H, 5·3. $C_8H_{10}N_4S$ requires C, 49·5; H, 5·2%).

4-Amino-5-formamido-6-methyl-2-methylthiopyrimidine.—4,5-Diamino-6-methyl-2-methylthiopyrimidine [7] (4·0 g.) was refluxed in 98% formic acid (25·0 ml.) for 1 hr. The residue from evaporation was dissolved in water (150 ml.) and treated with carbon. Adjustment of the solution to pH 5 gave the *formamidopyrimidine* (3·2 g.), m. p. 235° (from water) (Found: C, 42·3; H, 4·8; N, 28·3. $C_7H_{10}N_4OS$ requires C, 42·4; H, 5·1; N, 28·3%). A sample heated at 240° for 10 min. gave 6-methyl-2-methylthiopurine (70%), m. p. 293—294° (after sublimation) (lit.,[7] 290—294°).

4-Amino-6-methyl-5-methylamino-2-methylthiopyrimidine.—The above formamidopyrimidine (2·0 g.) was dissolved in hot pyridine (60 ml.). This solution (kept at 50°) was added dropwise to a stirred solution of lithium aluminium hydride (2·0 g.) in ether (300 ml.) under nitrogen. After refluxing and stirring for a further 2 hr., ethyl acetate (25 ml.) was added cautiously, followed by water (25 ml.) and then 5N-sodium hydroxide (40 ml.). The organic layer was decanted and the sludge was washed with ethyl acetate (2 × 50 ml.). The combined solutions were evaporated, and the residue twice evaporated with water (100 ml.) to remove pyridine. The residual *5-methylamino-2-methylthio-derivative* (1·2 g.) had m. p. 120—121° (from water) (Found: C, 46·0; H, 6·4; N, 30·1. $C_7H_{12}N_4S$ requires C, 45·65; H, 6·6; N, 30·4%).

4-Amino-6-methyl-5-methylformamido-2-methylthio-pyrimidine.—The 5-methylamino-2-methylthiopyrimidine (1·5 g.) was refluxed in 98% formic acid (15·0 ml.) for 90 min. The oily residue from evaporating the acid under reduced pressure was diluted with water (15 ml.) and adjusted to pH 8 with 10N-sodium hydroxide. Refrigeration gave the *methylformamidopyrimidine* (1·35 g.), m. p. 166—167° (from benzene) (Found: C, 45·4; H, 5·9; N, 26·4. $C_8H_{12}N_4OS$ requires C, 45·3; H, 5·7; N, 26·4%).

6,7-Dimethyl-2-methylthiopurine.—The methylformamidopyrimidine (1·0 g.) was heated at 270—280° for 20 min. Sublimation (160°/0·01 mm.) then gave the *purine* (0·6 g.), m. p. 174—175° (from benzene) (Found: C, 49·5; H, 5·2. $C_8H_{10}N_4S$ requires C, 49·5; H, 5·2%).

4-Amino-6-methyl-5-methylaminopyrimidine.—The above 5-methylamino-2-methylthiopyrimidine (0·8 g.) was refluxed for 2 hr. in water (90 ml.) with Raney nickel (10 g., weighed wet). The filtered solution was evaporated to dryness and the residue was extracted with boiling ethyl acetate. Removal of solvent gave the *methylaminopyrimidine* (0·25 g.), m. p. 133—135° (from light petroleum) (Found: C, 51·95; H, 7·1; N, 40·0. $C_6H_{10}N_4$ requires C, 52·2; H, 7·3; N, 40·55%).

4-Amino-6-methyl-5-methylformamidopyrimidine.— The above diamine (0·4 g.) was refluxed with 98% formic acid (5·0 ml.) for 2 hr. A solution of the residue from evaporation in water (2 ml.) was adjusted to pH 7—8. Repeated chloroform extraction gave the *methylformamidopyrimidine* (0·3 g.), m. p. 178—179° (from benzene) (Found: C, 51·0; H, 6·5; N, 33·2. $C_7H_{10}N_4O$ requires C, 50·6; H, 6·1; N, 33·7%). Cyclisation was unsuccessful.

4-Chloro-2-methyl-6-methylamino-5-nitropyrimidine.—Aqueous methylamine (40% w/v; 16·0 ml.) was adjusted to pH 8 with glacial acetic acid and then added during 10 min. to a stirred solution of 4,6-dichloro-2-methyl-5-nitropyrimidine [15] (10·0 g.) in dioxan (100 ml.) kept at 20—25°. After a further hour's stirring ice-cold water (500 ml.) was added. The resulting solid was filtered off, washed with cold water, and dried *in vacuo* at room temperature. The *nitropyrimidine* (6·8 g.) had m. p. 138—139° (from light petroleum) (Found: C, 35·6; H, 3·6; N, 27·8. $C_6H_7ClN_4O_2$ requires C, 35·6; H, 3·5; N, 27·65%).

5-Amino-4-mercapto-2-methyl-6-methylaminopyrimidine.—The above nitropyrimidine (6·0 g.) was stirred on the steam-bath for 1 hr. with 2N-sodium hydrogen sulphide (100 ml.). The cooled solution was adjusted to pH 5 with acetic acid, and the resulting solid was removed and extracted with boiling water (1000 ml.). On refrigeration, the extract deposited the *mercaptopyrimidine* (4·0 g.), decomposing about 272° (after recrystallisation from water) (Found: C, 42·35; H, 5·8; N, 33·0. $C_5H_{10}N_4S$ requires C, 42·35; H, 5·9; N, 32·9%).

5-Methyl-7-methylaminothiazolo[5,4-d]*pyrimidine.*— The mercaptopyrimidine (1·0 g.) was refluxed in 98% formic acid (5·0 ml.) for 2 hr. Evaporation gave the *thiazolo-pyrimidine* (0·9 g.), m. p. 179° (from benzene) (Found: C, 46·9; H, 4·5; N, 30·9;. $C_7H_8N_4S$ requires C, 46·7; H, 4·5; N, 31·1%).

5-Amino-2-methyl-4-methylamino-6-methylthiopyrimidine.—The same mercaptopyrimidine (2·0 g.) in N-sodium hydroxide (30 ml.) was shaken with methyl iodide (1·9 g.) for 30 min. After refrigeration, the solid was dried at room temperature. The *methylthiopyrimidine* (2·0 g.) had m. p. 108° (from water) (Found, for a sample dried at 75°/0·01 mm.: C, 45·4; H, 6·7; N, 30·25. $C_6H_{12}N_4S$ requires C, 45·6; H, 6·6; N, 30·4%).

5-Formamido-2-methyl-4-methylamino-6-methylthio-pyrimidine.—The above methylthiopyrimidine (1·9 g.) was refluxed with 98% formic acid (20 ml.) for 2 hr. Evaporation and crystallisation from ethanol gave the *formamidopyrimidine* (1·8 g.), m. p. 222—223° (after sublimiation at 130°/0·02 mm.) (Found: C, 44·95; H, 6·0; N, 25·9. $C_8H_{12}N_4OS$ requires C, 45·3; H, 5·7; N, 26·4%).

2,9-Dimethyl-6-methylthiopurine.—The above formamidopyrimidine (1·0 g.) was plunged into a bath at 250—260° and kept there for 5 min. after the initial reaction had subsided. Any sublimate was returned to the melt. Subsequent sublimation (75°/0·01 mm.) gave the *purine* (0·9 g.), m. p. 106—107° (from light petroleum) (Found: C, 49·8; H, 5·5; N, 28·7. $C_8H_{10}N_4S$ requires C, 49·5; H, 5·2; N, 28·85%).

6-Butylamino-2,9-dimethylpurine.—The above purine (0·4 g.) was heated with butylamine (2·0 ml.) in a sealed tube at 175° for 24 hr. The residue from evaporation was triturated with water, and the resulting solid was dried ($CaCl_2$). Crystallisation from cyclohexane gave the *butylaminopurine* (0·38 g.), m. p. 97—98° (Found: C, 59·9; H, 7·9; N, 32·2. $C_{11}H_{17}N_5$ requires C, 60·25; H, 7·8; N, 31·95%).

[15] J. Baddiley and A. Topham, *J. Chem. Soc.*, 1944, 678; A. Albert, D. J. Brown, and H. C. S. Wood, *J. Chem. Soc.*, 1954, 3832.

8-Mercapto-2,9-dimethylpurine.— 5-Amino-4-mercapto-2-methyl-6-methylaminopyrimidine (10·0 g.) was refluxed for 90 min. with Raney nickel (40 g., weighed wet) in water (250 ml.) containing 15N-ammonia (15 ml.). The filtrate and washings were evaporated to dryness, and the residue was extracted with boiling benzene (2 × 150 ml.). Removal of solvent gave *5-amino-2-methyl-4-methylaminopyrimidine* (65%), m. p. 103—105° (from cyclohexane) (Found: C, 51·8; H, 7·3; N, 40·9. $C_6H_{10}N_4$ requires C, 52·15; H, 7·3; N, 40·55%). This pyrimidine (4·0 g.) was heated with thiourea (12·0 g.) at 230—240° for 10 min. Isolation as the benzyl analogue (below) gave the *mercaptopurine* (60%), m. p. ∢310° (from water) (Found: C, 46·4; H, 4·7; N, 31·4. $C_7H_8N_4S$ requires C, 46·7; H, 4·5; N, 31·1%).

2,9-Dimethyl-8-methylthiopurine.—The above purine (3·0 g.) was stirred for 1 hr. in N-sodium hydroxide (20 ml.) with methyl iodide (3·0 g.). The solution was adjusted to pH 7 and evaporated to dryness. The residue was extracted with boiling benzene (2 × 100 ml.). Removal of solvent gave the *methylthiopurine* (85%), m. p. 136—137° (from light petroleum) (Found: C, 49·2; H, 5·4; N, 28·7. $C_8H_{10}N_4S$ requires C, 49·5; H, 5·2; N, 28·85%).

8-Butylamino-2,9-dimethylpurine.—The above methylthiopurine (0·5 g.) and butylamine (5·0 ml.) were heated at 185° for 24 hr. Evaporation gave the butylaminopurine (60%), m. p. 155—156° (from cyclohexane) (Found: C, 60·15; H, 8·1; N, 31·7. $C_{11}H_{17}N_5$ requires C, 60·25; H, 7·8; N, 31·9%).

5-Amino-4-benzylaminopyrimidine.— 5-Amino-4,6-dichloropyrimidine [16] (3·25 g.) was warmed on the steam-bath with benzylamine (4·2 g.) until the mixture became homogeneous (10 min.) and then for a further 15 min. during which time the mixture solidified. After grinding with cold water and recrystallisation from aqueous ethanol, 5-amino-4-benzylamino-6-chloropyrimidine (83%) had m. p. 206° (cf. Greenberg *et al.*,[17] 64% yield, m. p. 207—209°, from a lengthy procedure). This chloropyrimidine (3·0 g.) was hydrogenated at 25°/1 atm. over 5% palladium-on-carbon (2·0 g.) with magnesium oxide (2·5 g.) in 50% aqueous ethanol (160 ml.). The filtrate and washings were diluted with 2N-sodium carbonate (75 ml.) and evaporated to dryness. Extraction with boiling benzene and subsequent evaporation gave 5-amino-4-benzylaminopyrimidine (70%), m. p. 136° (from benzene) (cf. m. p. 136—137° for material made [11] in lower yield from 5-amino-4α-benzylhydrazino-6-chloropyrimidine). The diamine (0·3 g.), ethyl ethoxyglycollate [18] (0·6 g.), and water (3·0 ml.) were heated on a steam-bath for 30 min. Refrigeration gave *8-benzyl-7,8-dihydro-7-oxopteridine* (0·28 g.), m. p. 111—112° (from light petroleum) (Found: C, 65·6; H, 4·3; N, 23·2. $C_{13}H_{10}N_4O$ requires C, 65·5; H, 4·2; N, 23·5%).

9-Benzyl-8-mercaptopurine.— 5-Amino-4-benzylaminopyrimidine (2·0 g.) and thiourea (4·0 g.) were heated at 200—210° for 15 min. The cooled material was dissolved in hot N-sodium hydroxide (30 ml.), treated with carbon, and filtered. Adjustment of the filtrate to pH 5 gave the *purine* (60%), m. p. 234—235° (from 50% aqueous ethanol) (Found: C, 59·7; H, 4·2; N, 22·9. $C_{12}H_{10}N_4S$ requires C, 59·5; H, 4·2; N, 23·1%).

9-Benzyl-8-methylthiopurine.—The above mercaptopurine (1·6 g.) in 0·2N-sodium hydroxide (40 ml.) was stirred with methyl iodide (1·0 g.) for 1 hr. The collected *methylthiopurine* (80%) had m. p. 126—127° (from 50% aqueous ethanol) (Found: C, 61·4; H, 4·8; N, 21·8. $C_{13}H_{12}N_4S$ requires C, 60·9; H, 4·7; N, 21·9%).

TABLE 2

Rates of butylaminolysis at 150°

Purine	Analytical λ (mμ)	10^5k (sec.$^{-1}$)	$t_{\frac{1}{2}}$ (hr.)
2,9-Me_2-6-SMe ...	265	3·88	
	272	3·78	
	292	3·57	
		Av. 3·75	5·13
2,9-Me_2-8-SMe ...	255	1·39	
	256	1·66	
	258	1·51	
		Av. 1·5	12·6

Reaction Rates.—Ten aliquot portions of a mixture containing the methylthiopurine and butylamine (in molar ratio 1 : 20) were heated in sealed Pyrex tubes at 150·1° ± 0·1° for periods covering >80% of the reaction (cf. ref. 3). Each was cooled immediately and suitably diluted with 95% ethanol so that the change in ultraviolet absorption at a given wavelengths (Table 2) could be followed. For the 8-methylthiopurine such analytical wavelengths were limited necessarily to a small range between two slopes.

We thank Professor A. Albert for discussions, and the C.S.I.R.O. for a Senior Postgraduate Studentship (to P. W. F.).

[7/117 *Received, January 30th,* 1967]

[16] E. C. Taylor, J. W. Barton, and W. W. Paudler, *J. Org. Chem.*, 1961, **26**, 4961.

[17] S. M. Greenberg, L. O. Ross, and R. K. Robins, *J. Org. Chem.*, 1959, **24**, 1314.

[18] W. Rigby, *J. Chem. Soc.*, 1950, 1907.