



"Thiol - thione Equilibria in nitrogenous Heterocyclic
Mercapto - compounds".



a Thesis
submitted for the
Degree of Doctor of Philosophy
in the
Australian National University
by
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The work described in this Thesis was carried out by the candidate at the Australian National University. Where the work of others was employed, appropriate references are given.

C. B. Barlow

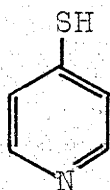
I sincerely thank Professor Adrien Albert for most helpful supervision, interest and encouragement throughout this work, and Dr. D.J. Brown for most helpful advice.

Grateful acknowledgement is also made to the Australian National University for the award of a Scholarship and General Motors - Holden's for the award of a Post - graduate Research Fellowship.

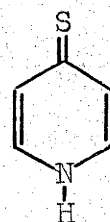
NOMENCLATURE.

In this thesis the following nomenclature has been employed.

Mercapto - compound has been used to describe the tautomeric mixture at equilibrium and carries no implication of structure. For example "4-mercaptopyridine" is used to describe the tautomeric mixture of (I \longleftrightarrow II)

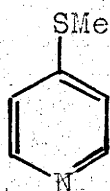


(I)



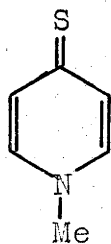
(II)

The term "thiol" has been used to refer to structures of the type (I) and the term "thione" or "thioamide" (a vinylogous thioamide in this case) have been used to refer to structures of the type (II). S-methyl derivative or methylmercapto - compound have been used to describe derivatives of the "thiol" structure in which the hydrogen atom on sulphur has been replaced by a methyl - group. For example "4-methylmercaptopyridine" is represented by the structure (III)



(III)

N-methyl derivative or N-methyl thione have been used to describe derivatives of the "thione" or "thioamide" form in which the hydrogen on nitrogen has been replaced by a methyl - group. For example N(1)-methylpyrid-4-thione is represented by the structure (IV).



(IV)

Table of New Compounds.

3-Benzoylmercaptopyridine
3-Methylmercaptopyridine and hydrochloride
3-Mercaptopyridine methochloride
3-Benzoylmercaptopyridine methiodide
1-Methylpyrid-4-thione
3-Mercaptoquinoline
3-Benzoylmercaptoquinoline
Di-3-quinolyl disulphide
3-Methylmercaptoquinoline and hydrochloride
3-Methylmercaptoquinoline methiodide
3-Mercaptoquinoline methiodide and methochloride
3-Benzoylmercaptoquinoline methiodide
4-Mercaptoquinoline
4-Methylmercaptoquinoline
Di-4-quinolyl sulphide
Quinoline-5-sulphonyl chloride
5-Mercaptoquinoline
5-Benzoylmercaptoquinoline
Di-5-quinolyl disulphide
5-Methylmercaptoquinoline
5-Mercaptoquinoline methiodide
5-Benzoylmercaptoquinoline methiodide
5-Benzoylmercaptoquinoline methyl hydrogen sulphate
6-Methylmercaptoquinoline
6-Methylmercaptoquinoline methiodide
6-Mercaptoquinoline methiodide and methochloride
6-Benzoylmercaptoquinoline methiodide
8-Methylmercaptoquinoline hydriodide
Di-8-quinolyl disulphide methiodide periodide
8-Methylmercaptoquinoline methiodide periodide
1-Mercaptoisoquinoline
1-Methylmercaptoisoquinoline
3-Mercaptoisoquinoline
3-Benzoylmercaptoisoquinoline
3-Methylmercaptoisoquinoline hydrochloride
2-Methylmercaptopyrazine
1-Methylpyraz-2-thione
1-Methylquinoxal-2-thione
1-Methylpyrimid-2-thione
4-Methylmercaptopyrimidine
1-Methylpyrimid-6-thione
1-Methylpyrimid-4-thione

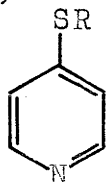
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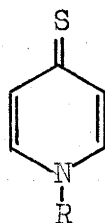


SECTION I.INTRODUCTION.Opening Remarks.

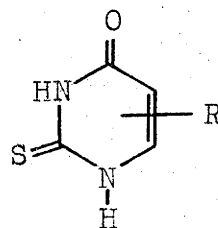
Two different tautomeric forms may be written for monoaza-heterocyclic mercapto-compounds, one with the mobile hydrogen atom on sulphur and the other with the mobile hydrogen on nitrogen. For example 4-mercapto-pyridine may exist in the tautomeric forms: (I; R = H) or (II; R = H).



(I)



(II)



(III)

Additional NH forms are possible for polyaza-heterocyclic mercapto-compounds.

The tautomerism of the mercapto-derivatives of six-membered rings has been little examined. Isolated qualitative studies of the tautomerism have been undertaken but no quantitative approach to the problem has previously been attempted.

The present investigation was undertaken with the aim of elucidating the structure of simple nitrogenous heterocyclic mercapto-compounds in water because of their relationship to the biologically important 2-thiouracil derivatives which may be represented as (III).

In the present work the mercapto - compounds have been studied by reference to fixed tautomeric forms in which the mobile hydrogen atom was replaced by an immobile methyl - group e.g. (I and II; R = Me). This can be done because changes in ultraviolet absorption spectra and ionization constants are small upon N- or S-methylation. Finally, by employing ionization constants, the ratio of the tautomers at equilibrium in monoaza - heterocyclic mercapto - compounds was calculated.

HISTORICAL OUTLINE.

Previous work on the tautomerism of nitrogenous heterocyclic mercapto - compounds in which the heterocyclic compound is composed of six-membered rings is discussed below, and that involving five - membered heterocyclic rings is given in Appendix I .
Mercapto - derivatives of Six - membered Rings.

That tautomerism of six-membered ring nitrogenous heterocyclic mercapto - compounds is possible is illustrated by the production of 1-methylpyrid-2-thione, and 2-methylmercaptopyridine by the action of diazomethane on 2-mercaptopyridine as shown by Renault (1955). A quantitative study of this type of tautomerism has never been undertaken and only isolated cases of a qualitative study in various solvents (mostly non-aqueous) have been recorded. Generally these are incomplete in that all possible tautomeric forms were not investigated, even when only two forms were possible. Most of the qualitative work on the tautomerism of heterocyclic mercapto - compounds composed of six - membered rings, particularly in aqueous media, has been concentrated on diaza - compounds, and generally directed at elucidation of the structure of 2-thiouracil.

The only conclusive qualitative study of tautomerism involving six - membered ring heterocyclic

mercapto - compounds in water is that of Marshall and Walker (1951) with 2-mercaptopyrimidines in which it was shown by comparison of ultraviolet absorption spectra with N- and S-methyl derivatives that the mercapto - compound exists largely in the NH form.

The available evidence is presented separately below for studies in water (because of its importance to the present study), and in non-aqueous media.

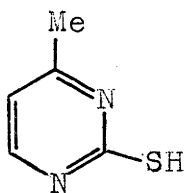
Evidence in aqueous solution. Previous studies of the tautomerism of six - membered ring nitrogenous heterocyclic mercapto - compounds in water have been limited to ultraviolet absorption spectral studies.

In 1949, Hannan, Liebllich, and Renfrew examined the ultraviolet absorption spectra of some C-substituted 2- and 4-mercaptoquinolines and some S-butyl derivatives in aqueous acid, aqueous alkali and 95% ethanol. They reached no conclusions on the structure of the mercapto - compounds mainly because they attempted to draw similarities to the hydroxy - analogues for which the results and reasoning of Ewing and Steck (1946) are now known to be in error *

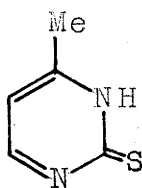
* In the absence of pK values (see Albert and Phillips (1956)), Ewing and Steck did not obtain the pure ionic species in solution for spectral study.

The whole of this work is confused by lack of knowledge of the pK values. However, examination of the authors' results shows that the ultraviolet absorption spectra of the mercapto - compound and its S-alkyl derivatives are quite different. Further, the hypsochromic shift observed on conversion of the molecule of the mercapto - compound into either the cation or anion as well as the bathochromic shift observed on conversion of the molecule of the S-alkyl derivative to the cation, is in agreement with the observations recorded in this thesis for a much larger number of heterocyclic substances.

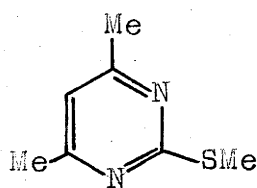
Marshall and Walker (1951) attempted the first systematic qualitative study of the tautomerism of six - membered ring heterocyclic mercapto - compounds. They compared the ultraviolet absorption spectra of the pure species (molecules or ions) with the corresponding species of its N- and S-methyl derivatives in which the mobile hydrogen atom of the two tautomeric forms was replaced by an immobile methyl - group.



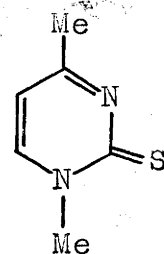
(IV)



(V)

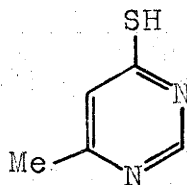


(VI)



(VII)

The ultraviolet absorption spectra of 4-methyl-2-mercaptopyrimidine (IV \longleftrightarrow V) and its N-methyl derivative (VII) and 6-methyl-S-methyl derivative (VI) showed quite clearly that the mercapto - compound exists mainly in the NH form. Marshall and Walker also examined the ultraviolet absorption spectra of 6-methyl-4-mercaptopyrimidine (VIII) and showed it to be quite different from that of its S-methyl derivative.

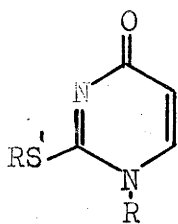


(VIII)

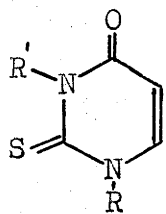
The ultraviolet absorption spectra in water of 2-thiouracil and some derivatives have been measured by a number of workers (Elion, Ide, and Hitchings, (1946); Stuckey, (1949); and Shugar and Fox, (1952)) but the structure of 2-thiouracil has not been completely established. For structural considerations of 2-thiouracil, only the data presented by Shugar and Fox need be considered.

There are six possible tautomeric forms of 2-thiouracil shown as (IX) to (XIV) ($R = R' = H$) below. Structures (IX), (XII) and (XIII) can be rejected by comparison of the ultraviolet absorption spectra of their dimethyl derivatives ($R = R' = Me$) (whose constitution follows from their synthesis) with that

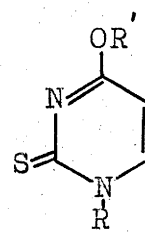
of 2-thiouracil, from which they are quite different.



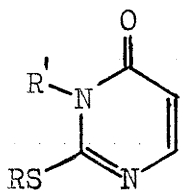
(IX)



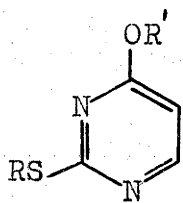
(X)



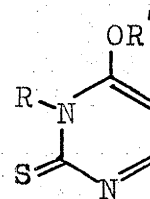
(XI)



(XII)



(XIII)



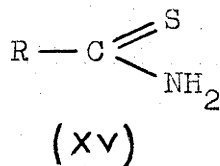
(XIV)

The ultraviolet absorption spectra of 1-methyl-, 3-methyl-, and 1:3-dimethyl-2-thiouracil and 2-thiouracil are all similar, indicating that 2-thiouracil may have the structure (X) but compounds of the fixed structural types (XI) or (XIV) have not been available for study. Brown, Hoerger, and Mason (1955) have shown that 2- and 4-hydroxypyrimidine exist mainly in the NH form and the evidence given in this thesis shows that 2-mercaptopyrimidine exists mainly in the NH form. Hence it appears unlikely that either structure (XI) or (XIV) ($R = R' = H$) could represent that of 2-thiouracil (Schneider and Halverstadt (1948) from infrared absorption studies have shown that structures (XI) and (XIV), ($R = R' = H$) are unlikely for 2-thiouracil in non-aqueous solution).

Evidence in non-aqueous media. A greater variety of examples are available on the structure of tautomerisable thioamides in non-aqueous media.

Infrared spectral studies have been rather inconclusive mainly because the absorption band (2500 - 2600 cm.^{-1}) due to the -SH group is weak and there has been considerable doubt as to the location of the thiocarbonyl absorption band.*

Raman spectral studies by Kohlrausch and Wagner (1940) indicate that thioamides have the structure (XV) because bands which are indicative of the SH group are absent.



* Marvel, Radzitzky, and Brader (1955) have shown that dithiolesters and thioamides absorb strongly in the 1170 - 1265 cm.^{-1} region of the infrared due to the thiocarbonyl - group and Mecke and Mecke (1956) have shown that piperid-2-thione and trimethylene-thiourea (cyclic thioamides) absorb in the 1100 - 1200 cm.^{-1} region due to the thiocarbonyl - group. See Davies and Jones (1958).

Magnetic susceptibility studies by Clow and Thompson (1936) also indicate that thioacetamide has the structure (XV, R = Me.).

In the field of heterocyclic thioamides, Penfold (1953b) has studied electron density projections of solid 2-mercaptopyridine and although the results are inconclusive \times , (because of technical difficulties) the C - S bond was found to have 65% double bond character.

In addition, support for the thiocarbonyl structure of heterocyclic mercapto - compounds is provided by ultraviolet absorption spectral studies which are given below.

Morton and Stubbs (1939) were the first to attempt a study of the tautomerism of six - membered ring nitrogenous heterocyclic mercapto - compounds by ultraviolet absorption spectral studies. They examined 4-methyl-2-mercaptoquinoline and its S-alkyl derivative in ethanol and found the spectra to be quite different and concluded that the mercapto - compound must possess the thione structure. Unfortunately, they did not confirm this by examining the N-alkyl derivative.

\times In contrast, α -pyridone was clearly resolved by Penfold (1953a) and the NH form shown to predominate.

Ross (1951) examined the ultraviolet absorption spectra of 4-mercaptopyridine and its S-alkyl derivative in alcoholic solution and found them to be quite different. Again the N-methyl derivative was not examined. The ultraviolet absorption spectra of 4-mercaptopyridine underwent a hypsochromic shift on conversion to the cation or anion (greater on conversion to the cation). These results are in accord with the results obtained in aqueous solution in the present work, but in isolation were able to contribute little to solving the problem.

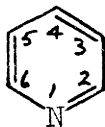
Acheson, Burstall, Jefford, and Sansom (1954) have examined the ultraviolet absorption spectra of 5-mercapto-acridine and its N- and S-methyl derivatives in methanol and have shown that the mercapto - compound exists mainly in the NH form.

Badger and Buttery (1956) found for 8-mercapto-quinoline that the long - wavelength absorption band (in the visible region) in alcohol and aqueous alcohol is suppressed in less polar solvents and at higher temperatures. The suppression of the long - wavelength absorption bands by less polar solvents has been observed by Mason (1957) with hydroxy - heterocyclic compounds and has been attributed to suppression of the NH tautomer.

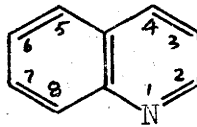
Dipole moment measurements have been applied to the study of tautomerism of one heterocyclic mercapto - compound. Schneider and Halverstadt (1948) measured the dipole moments in dioxane of 2-thiouracil and compounds of fixed structural types (IX,) (X,) (XII,) and (XIII,) ($R = R' = Me$) and found that, of these, the structure (X) was preferred for 2-thiouracil. Compounds of fixed structural types (XI) and (XIV) were not available for study but infrared studies of 2-thiouracil indicated the presence of a carbonyl group, absorbing at 1700 cm.^{-1} . Neither of the structures (XI) or (XIV) possess a carbonyl group so that such structures for 2-thiouracil are unlikely in non-aqueous solution.

Scope of the present work.

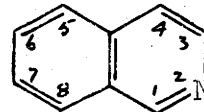
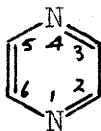
The work described in this thesis covers the preparation of the three mercapto-pyridines and their N- and S-methyl derivatives, six mercaptoquinolines and their N- and S-methyl derivatives (excluding the N-methyl derivative of 8-mercaptoquinoline), 1-mercapto-isoquinoline and its N- and S-methyl derivative, 3-mercaptoisoquinoline and its S-methyl derivative, 2-mercapto-pyrazine and quinoxaline and their N(1)- and S-methyl derivatives, the N-methyl derivative of 2-mercapto^opyrimidine, and the N(1)-, N(3)- and S-methyl derivatives of 4-mercaptopyrimidine.



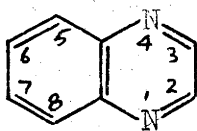
Pyridine



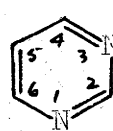
Quinoline

isoQuinoline

Pyrazine



Quinoxaline



Pyrimidine

The ionization constant(s) of each compound have been determined by potentiometric titration or by spectrophotometry. The ultraviolet absorption spectra of the molecule, monocation, and where possible the anion of the compounds listed above have also been determined in aqueous solution.

The tautomerism of the mercapto - compounds has been examined qualitatively by reference to the ultraviolet absorption spectra of the mercapto - compound and its N- and S-methyl derivatives and quantitatively (for the monoaza-heterocyclic compounds) by reference to the ionization constants from which the proportion of the two tautomers at equilibrium (water, 20°) has been calculated.

SECTION II.DISCUSSION OF THE ORGANIC CHEMICAL EXPERIMENTAL PROCEDURES.Methods of Preparation.

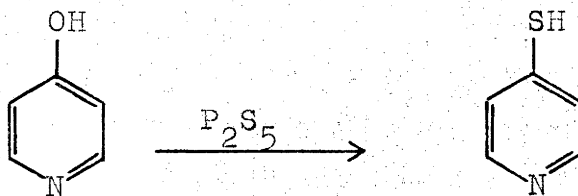
The various general methods available for preparing the desired substances will first be reviewed, and their suitability for different isomers indicated. After this, details will be given of the application of these methods to the production of the substances required.

(1) Mercapto - compounds. From the preparative point of view, two classes of these are distinguishable, (i) when the mercapto - group is α or γ to a ring-nitrogen atom, and (ii) when it is not.



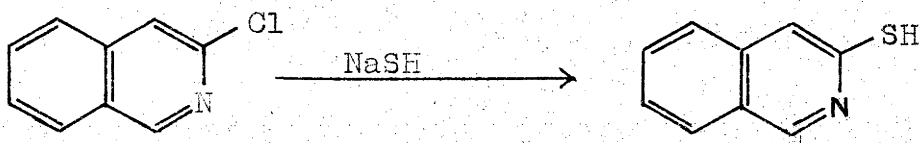
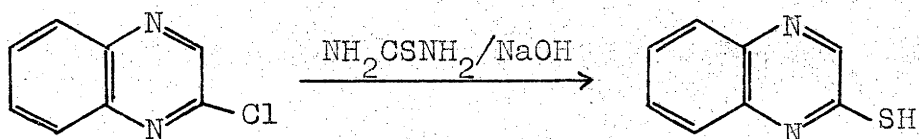
(i) The mercapto - compounds with the mercapto - group α or γ to the ring-nitrogen atom were obtained either (a) from the hydroxy-analogue by the action of phosphorus pentasulphide in pyridine, in tetralin (b.p. $207^{\circ}/760$ mm.), or without a solvent.

For example:



or (b) from the corresponding chloro-or bromo - compound by the action of thiourea followed by sodium hydroxide or by the action of sodium (or potassium) hydrogen sulphide.

For example:

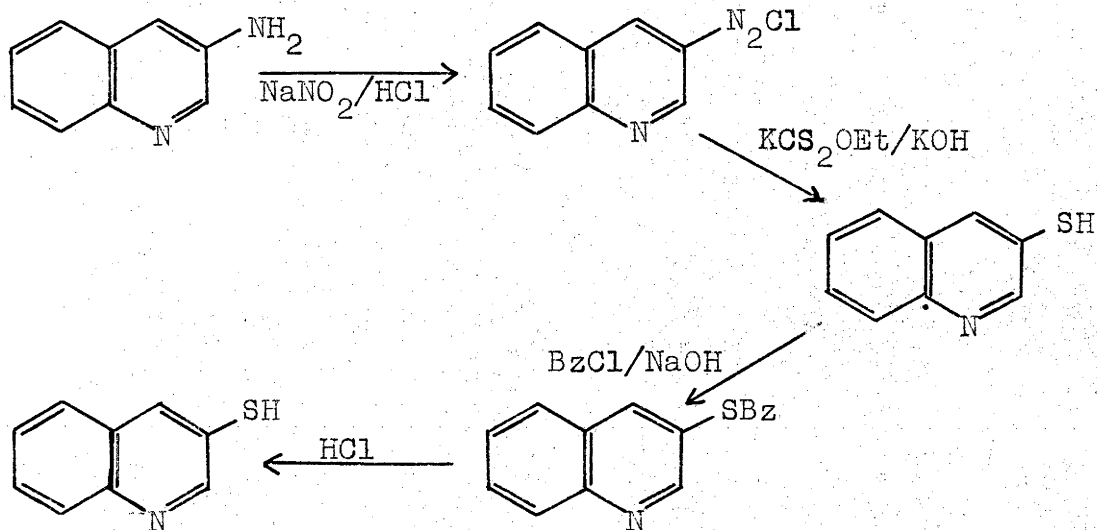


Except in the case of 3-mercaptoisoquinoline (which was isolated as its S-benzoate), the α - and γ - mercapto - compounds were first isolated in the free condition. Their tendency to aerial oxidation is small.

(ii) When the mercapto - group was not α or γ to the ring-nitrogen atom, the desired substance was obtained by one of the following procedures and isolated as the S-benzoate, from which the mercapto - compound was readily obtained by acid hydrolysis.

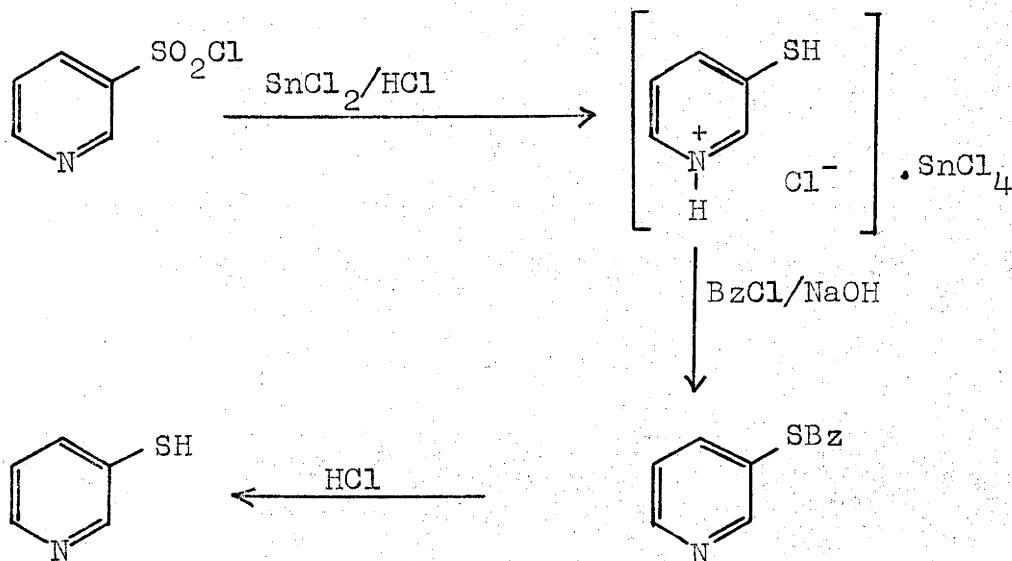
(a) From the corresponding amine by diazotization and treatment with potassium ethyl xanthate.

For example:

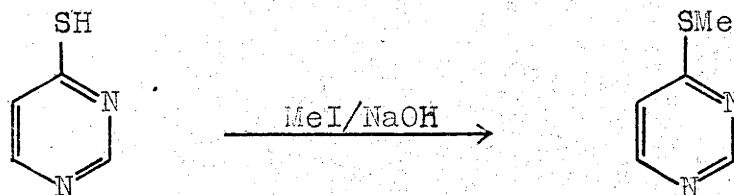


(b) By the reduction of the corresponding sulphonyl chloride with stannous chloride and hydrochloric acid.

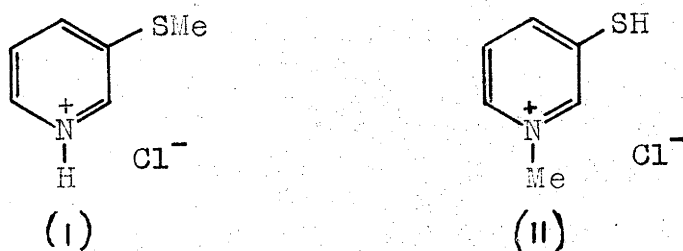
For example:



(2) S-Methyl derivatives. S-Methyl derivatives of the mercapto - compounds were prepared by direct methylation. For example:

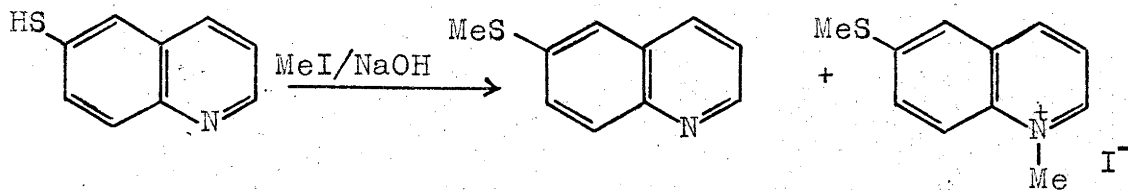


The methylating agents employed were diazomethane and dimethyl sulphate, or, more commonly, methyl iodide with ca. 1 equivalent of sodium hydroxide. The methylmercapto - compound, frequently isolated as the hydrochloride, was examined by paper chromatography in both butanol + acetic acid and 3% aqueous ammonium chloride for freedom from the N-methyl isomer. By isolation as the hydrochloride, e.g. (I), mixed melting points could also be taken with the N-methyl isomer, e.g. (II)

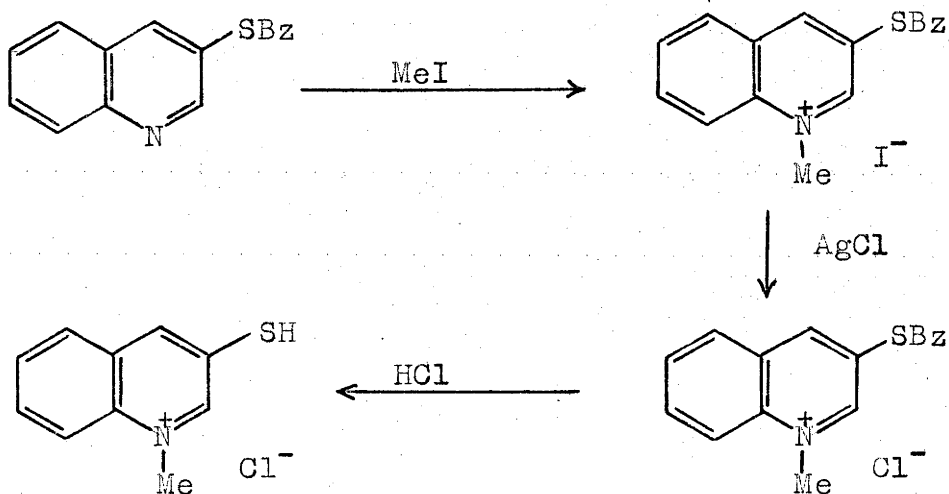


Methylation of the mercapto - compound with methyl iodide frequently gave small amounts of the methiodide of the methylmercapto - compound.

For example:



(3) N-Methyl derivatives. Many of the N-methyl derivatives were obtained by quaternizing the corresponding benzoylmercapto-compounds, exchanging the anion if necessary, and then hydrolysing the protective group. For example:

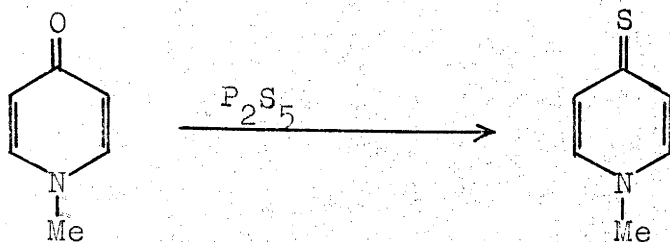


It was found necessary to exchange the anion by using silver salts before the protective group was hydrolysed, otherwise, insoluble silver mercaptides were produced.

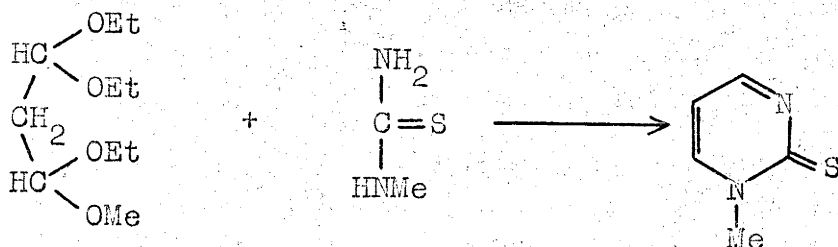
The N-methyl derivatives of α - and γ -thio - compounds were prepared from the well known oxygen-

analogues by the action of phosphorus pentasulphide in benzene, in pyridine or without a solvent.

For example:



In one case where this synthesis failed, the preparation was achieved as shown below.



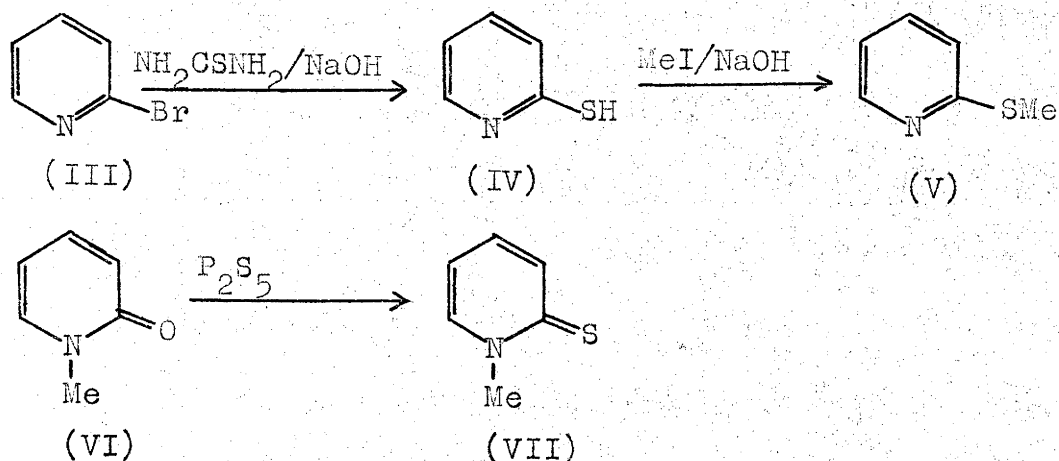
Synthesis of the Compounds Required.

Pyridine:

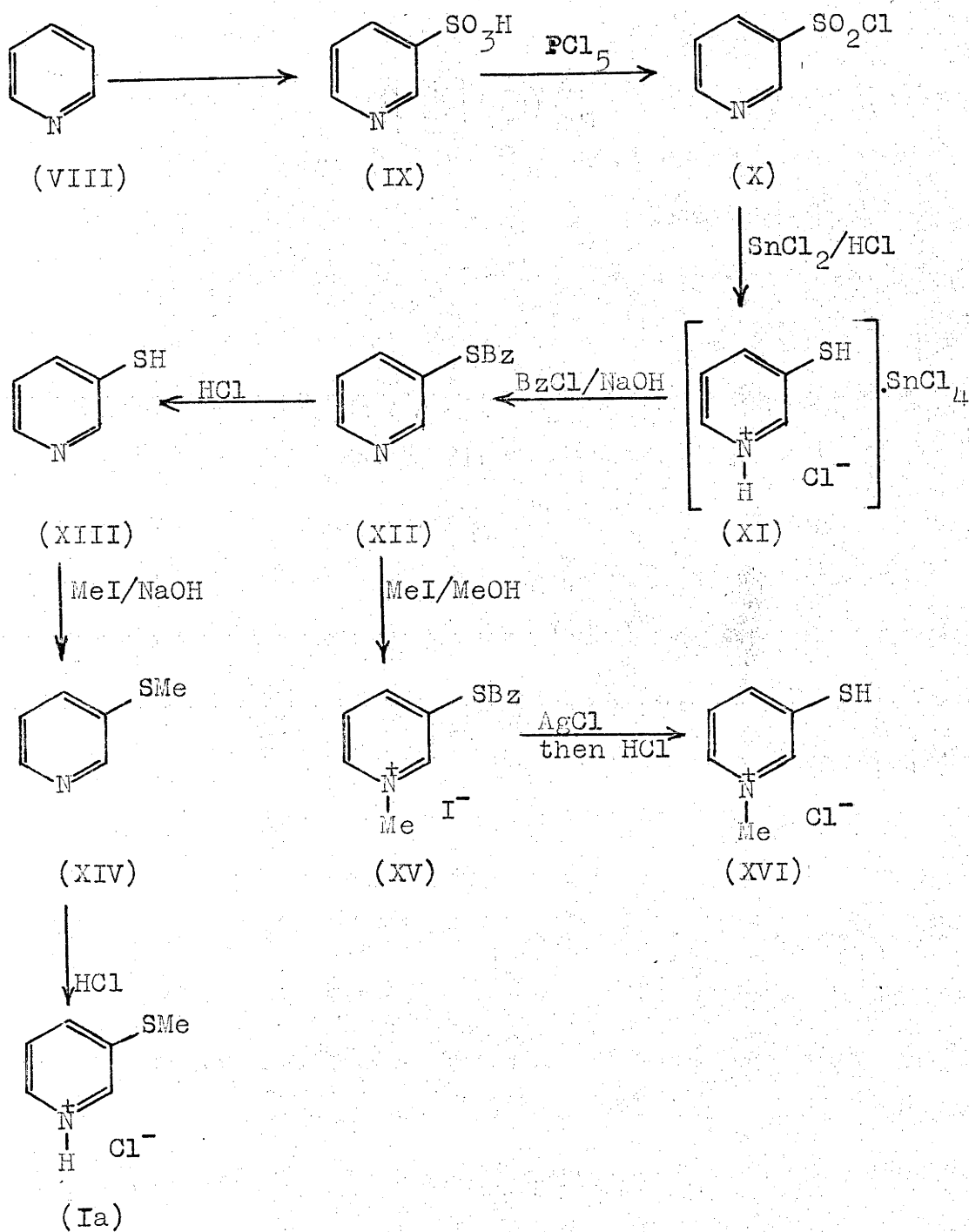


the 2-position. The substances required for the present investigation are 2-mercaptopyridine, 2-methylmercaptopyridine and 1-methylpyrid-2-thione. The preparation of all three compounds is described in the literature. In the present study 2-mercaptopyridine (IV) was prepared by the action of thiourea and sodium hydroxide on 2-bromopyridine (III) according to Phillips and Shapiro

(1942). It was methylated with methyl iodide and sodium hydroxide as described by Renault (1955) to give 2-methylmercaptopyridine (V). 1-Methylpyrid-2-thione (VII) was prepared from the pyridone (VI) and phosphorus pentasulphide according to Renault (1953).



Pyridine: the 3-position. The substances required for the present investigation are 3-mercaptopyridine, 3-methylmercaptopyridine, and 3-mercaptopyridine-N-methohalide. Of these only the first was known. The references to the preparation of 3-mercaptopyridine are (i) a patent reference by Steiger (1950, 1951) to the reduction of pyridine-3-sulphonyl chloride with stannous chloride and hydrochloric acid and (ii) a reference by Wuest and Sakel (1951) to the reaction of 3-bromopyridine with potassium hydrogen sulphide and copper powder in propylene glycol. The preparation of the compounds required in the present study is shown in Scheme A.



SCHEME A.

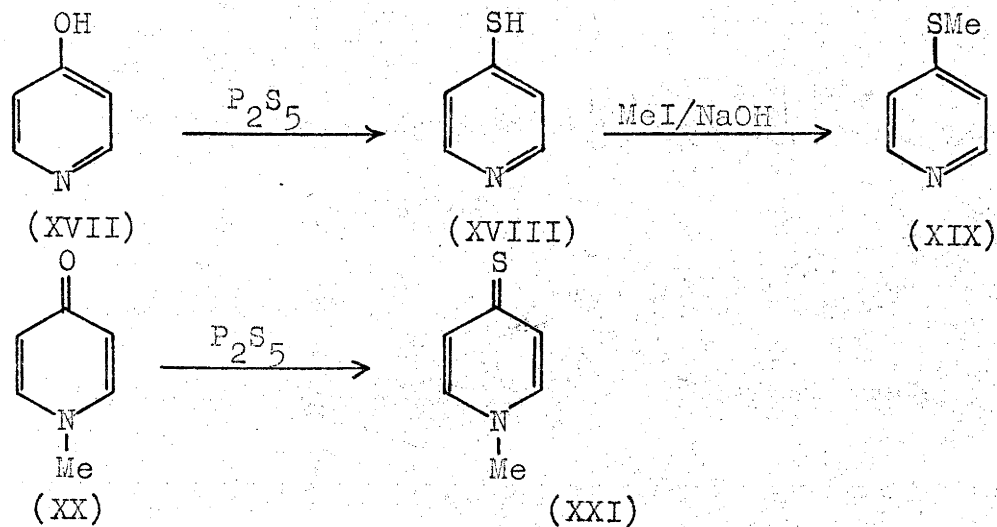
Pyridine (VIII) was sulphonated with fuming sulphuric acid (20% free SO_3) at 220° as described by McElvain and Goese (1943) rather than at the higher temperature (300°) employed by Zienty (1948). The pyridine-3-sulphonic acid (IX) was converted by the action of phosphorus pentachloride to pyridine-3-sulphonyl chloride (X) in accordance with Zienty (1948) and the product reduced with stannous chloride and hydrochloric acid as outlined by Steiger (1950, 1951). The mercapto-compound separated from the reaction mixture as the stannic chloride double salt (XI). The 3-mercapto-pyridine was best isolated as the S-benzoate (XII) which was free from disulphide and could be readily purified from inorganic impurities. The mercapto - compound (XIII) could be readily recovered from its S-benzoate by hydrolysis with 6N-hydrochloric acid in an atmosphere of carbon dioxide as employed previously by Edinger (1908), and by Ponci and Gialdi (1954) for the preparation of 8- and 6-mercaptoquinoline from their respective S-benzoates. The methylation of 3-mercaptopyridine with methyl iodide and sodium hydroxide was found to proceed smoothly to give 3-methylmercaptopyridine (XIV). Quaternization of 3-benzoylmercaptopyridine with methyl iodide in methanol proceeded readily at 20° and higher temperatures were avoided because of the ease of removal of the benzoyl-group in a number of cases to be described below.

The 3-benzoylmercaptoquinoline methiodide (XV) was hydrolysed with hydrochloric acid, the product shaken with silver chloride and the 3-mercaptopyridine methochloride (XVI) purified. However, it is preferable to exchange the anion before hydrolysis to the mercapto-compound because of the formation of insoluble silver mercaptides. That this product (XVI) was different to 3-methylmercaptopyridine hydrochloride (1a) was shown by mixed m.p. and by considerable differences in R_F on paper chromatograms in butanol + acetic acid, and 3% aqueous ammonium chloride.

Pyridine: the 4-position. The substances required for the present investigation are 4-mercaptopyridine, 4-methylmercaptopyridine and 1-methylpyrid-4-thione. All three substances are now known. However, 1-methylpyrid-4-thione was not described by Jones and Kátritzky (1958) until it had been prepared in the present work, and its ultraviolet absorption spectrum published by Albert and Barlin (1958).

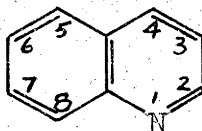
4-Mercaptopyridine (XVIII) was prepared from 4-hydroxypyridine (XVII) by the action of phosphorus pentasulphide and methylated with methyl iodide and sodium hydroxide to give 4-methylmercaptopyridine (XIX) as described by King and Ware (1939). 1-Methylpyrid-4-thione (XXI) was prepared by heating the oxygen-analogue (XX) with phosphorus pentasulphide. The properties

agree with those described by Jones and Katritzky.



SCHEME B.

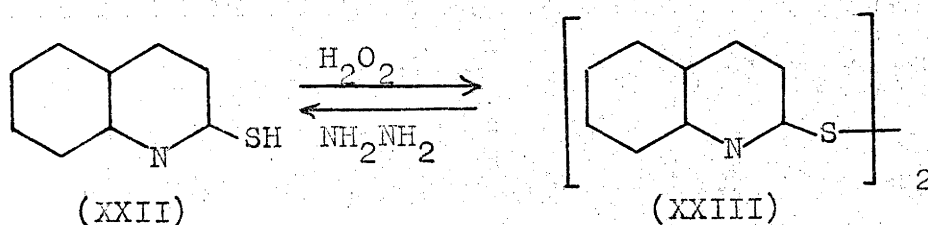
Quinoline:



the 2-position. The substances required for the present investigation are 2-mercaptoquinoline, 2-methylmercaptoquinoline and 1-methylquinol-2-thione. All three substances were known. 2-Mercaptoquinoline (XXII) and 2-methylmercaptoquinoline both of which are well known were made by the action of phosphorus pentasulphide in pyridine (cf. Klingsberg and Papa (1951)) on 2-hydroxyquinoline. (This reaction had previously been carried out in the absence of a solvent by Roos (1888)) and the 2-mercaptoquinoline methylated with dimethyl sulphate and sodium hydroxide according to Beilenson and Hamer (1939). 1-Methylquinol-2-thione was prepared by the action of

phosphorus pentasulphide on the oxygen-analogue as described by Gutbier (1900). The reactions involved are analogous to those shown in Scheme B, p. 24 for the 4-position of pyridine.

In anticipation of future preparations of mercapto-compounds by reduction of disulphides, di-2-quinolyl disulphide (XXIII) (prepared by oxidation of 2-mercaptoquinoline with hydrogen peroxide) was reduced with hydrazine hydrate to 2-mercaptoquinoline (XXII). The method was adopted from that employed by Katz and Schroeder (1954) for the preparation of (2:4-dichlorobenzal) thiosalicylhydrazide by reduction of its disulphide or 2-(2:4-dichlorobenzalamino) benzisothiazolone.



Quinoline: the 3-position. The substances requires for the present investigation are 3-mercaptoquinoline, 3-methylmercaptoquinoline and 3-mercaptoquinoline-N-methohalide. All three compounds were unknown. 3-Mercaptoquinoline (XXVI) was prepared from 3-aminoquinoline (XXIV) by diazotization and reaction with potassium ethyl xanthate similar to the method described by Tarbell and Fukushima (1947) for the preparation of m-methylmercaptotoluene from m-toluidine. The 3-mercapto-

quinoline was isolated as the S-benzoate (XXV) from which the mercapto - compound, which exists in two crystalline forms was readily obtained by acid hydrolysis. Attempts to prepare the ammonium salt of 3-mercaptoquinoline were unsatisfactory. Di-3-quinolyl disulphide (XXXII) was readily produced when 3-mercaptoquinoline was mixed with dilute hydrogen peroxide. (Roos (1888) prepared di-2-quinolyl disulphide by oxidizing 2-mercaptoquinoline with dilute hydrogen peroxide).

Methylation of 3-mercaptoquinoline with methyl iodide and sodium hydroxide produced not only 3-methylmercaptoquinoline (XXVII) but also a small amount of 3-methylmercaptoquinoline methiodide (XXVIII). The purification of 3-methylmercaptoquinoline was found to be best effected through the hydrochloride (XXIX) from which the free base can be regenerated with alkali. This hydrochloride, (XXIX) was found to be quite different from its N-methyl isomer, 3-mercaptoquinoline methochloride (XXXI); the m.p's were depressed on admixture and differences in R_F were observed when the samples were chromatographed on paper in both butanol + acetic acid and in 3% aqueous ammonium chloride.

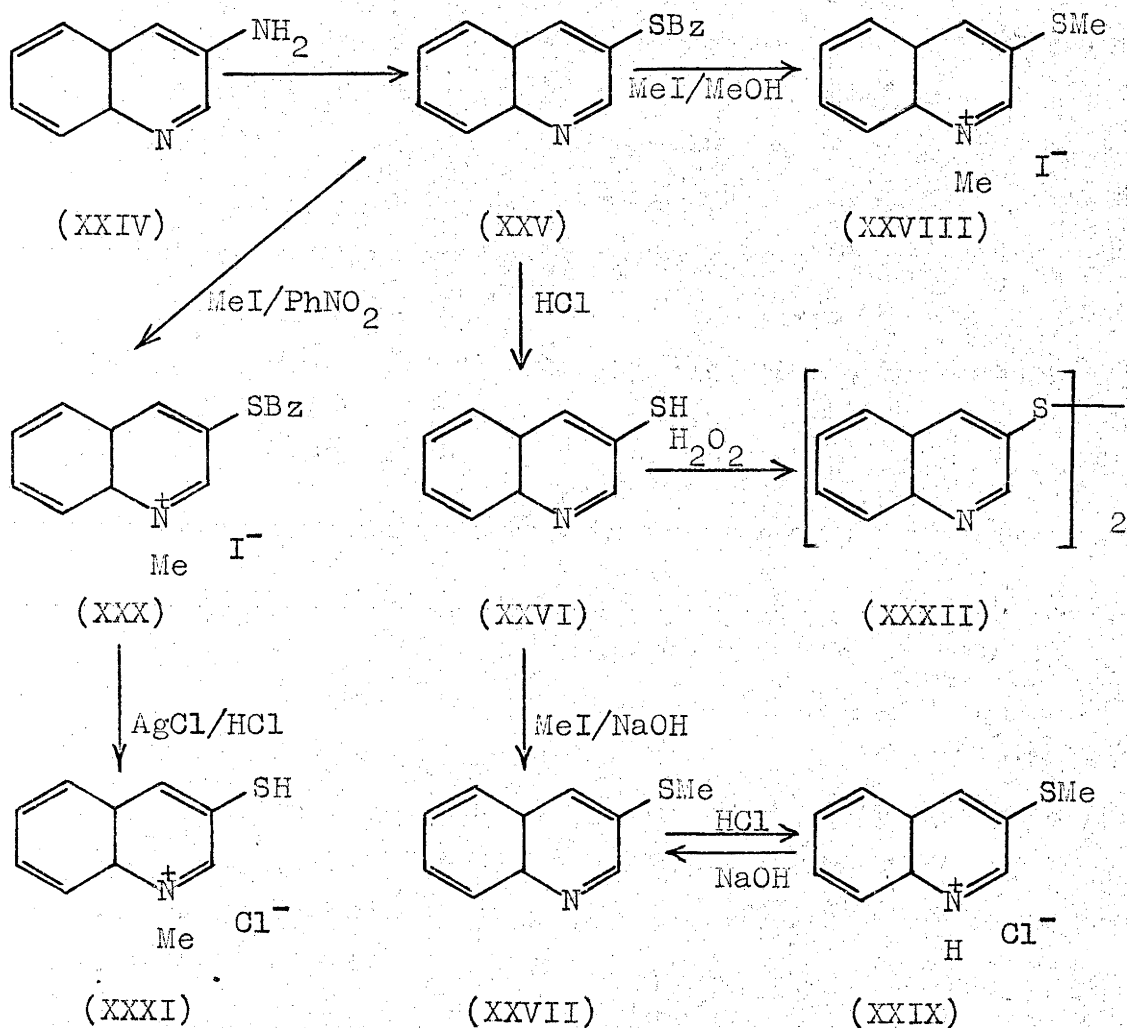
3-Mercaptoquinoline methochloride (XXXI) was prepared by quaternizing 3-benzoylmercaptoquinoline with methyl iodide in methanol at 20° to give 3-benzoylmercaptoquinoline methiodide (XXX), the anion exchanged

by shaking with silver chloride and the protecting group hydrolysed with acid. When the quaternization was attempted at 100°, the benzoyl - group was removed and the product isolated as 3-methylmercaptoquinoline methiodide (XXVIII). A similar reaction occurred with 8-benzoylmercaptoquinoline but at 20°. The reason for the removal of the benzoyl - group and substitution by the methyl - group is believed to be due to the observation that the formation of thiol esters from mercaptans or thiophenols and an acid is an equilibrium process. The free mercaptan, as it was released from the S-benzoyl ester, reacted with the methylating agent. Support for this hypothesis is given by the observation that when 8-benzoylmercaptoquinoline is boiled with ethanol, the solution becomes red, probably due to the formation of free 8-mercaptoquinoline. Examples of this equilibrium have been quoted by Connor (1943). The reactions described above are shown in Scheme C.

Quinoline: the 4-position. The substances required for the present investigation are 4-mercaptoquinoline, 4-methylmercaptoquinoline and 1-methylquinol-4-thione. The first two compounds were unknown.

1-Methylquinol-4-thione had previously been prepared by Campaigne, Cline, and Kaslow (1950) by the action of sodium hydrogen sulphide on 4-chloroquinoline methiodide. In the present work 4-mercaptoquinoline was prepared from 4-hydroxyquinoline by heating with phosphorus

pentasulphide. 4-Mercaptoquinoline could be recrystallised from both benzene and toluene but tenaciously retained the solvent, even when heated at $115^{\circ}/0.01$ mm.. The product was purified by sublimation.

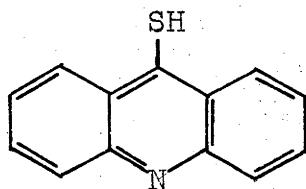


SCHEME C.

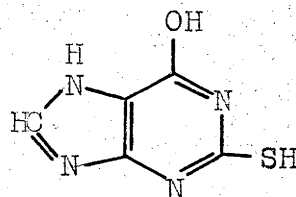
Methylation of 4-mercaptoquinoline with methyl iodide and sodium hydroxide gave 4-methylmercaptoquinoline but attempted methylation with dimethyl sulphate and

sodium hydroxide gave 1-methylquinol-4-one, apparently by hydrolysis of the mercapto - group followed by methylation of the hydroxy - compound on nitrogen. The product was identified as 1-methylquinol-4-one by mixed m.p. and chromatography on paper in both butanol + acetic acid and also in 3% aqueous ammonium chloride.

Hydrolysis of a mercapto - group under the conditions of methylation has been encountered before (Renault (1951) found that 2-mercapto-3:4:5:6-tetrahydropyridine with sodium hydroxide and alkyl sulphates gave 2-hydroxy-3:4:5:6-tetrahydropyridine). Nitrogenous heterocyclic mercapto - compounds methylate rapidly and exclusively on sulphur whereas their hydroxy-analogues methylate much more slowly and generally on the ring-nitrogen atom. (e.g. Edinger and Arnold (1901) found that 5-mercapto-acridine (XXXIII) with methyl iodide and sodium ethoxide methylated exclusively on sulphur, and Eckert and Steiner (1914) found that 5-hydroxyacridine with dimethyl sulphate and potassium hydroxide methylates on nitrogen. Elion, Lange, and Hitchings (1956) prepared 6-hydroxy-2-methyl-mercaptapurine (XXXIV) in 95% yield from 6-hydroxy-2-mercaptapurine with dimethyl sulphate and sodium hydroxide at 30°. However, Bergstrom (1944) quotes examples where methylation with diazomethane takes place on oxygen and mentions the production of 2-methoxypyridine from 2-hydroxypyridine).

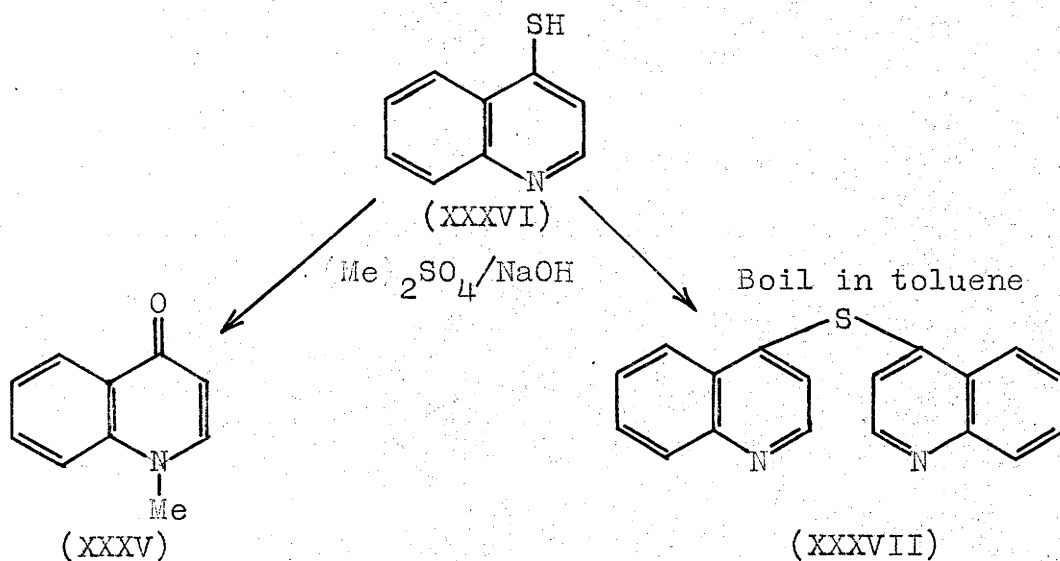


(XXXIII)



(XXXIV)

1-Methylquinol-4-thione was prepared by the action of phosphorus pentasulphide on the oxygen-analogue (XXXV). 1-Methylquinol-4-one was prepared from 4-hydroxyquinoline by the action of dimethyl sulphate on the potassium salt, the method was adapted from that employed by Eckert and Steiner (1914) for the preparation of N(10)-methylacrid-5-one. This method was considered preferable to that described by Späth and Kolbe (1922) who methylated 4-hydroxyquinoline with methyl iodide and sodium methoxide in methanol at 100°.



One unexpected reaction shown by 4-mercaptoquinoline was its conversion, on refluxing with toluene, to di-4-quinolyl monosulphide (XXXVII). The product was

insoluble in dilute sodium hydroxide and analysed correctly for the sulphide. The sulphur analysis was approximately half that of the expected disulphide. Many examples of the oxidation of mercapto - compounds to sulphides appear in the literature. King and Ware (1939) found that 4-mercaptopyridine is oxidised by chlorine to di-4-pyridyl sulphide (and 4-chloropyridine); and Cole (1957) found that an alkaline solution of p-nitromercapto-benzene absorbs oxygen and is oxidised to di-p-nitrophenyl sulphide and di-p-nitrophenyl disulphide. They attribute the ease of oxidisation to the presence of the nitro - group.

The reactions not shown diagrammatically above are analogous to those shown in Scheme B, p.24 for the 4-position of pyridine.

Quinoline: the 5-position. The substances required for the present investigation are 5-mercaptoquinoline, 5-methylmercaptoquinoline and 5-mercaptoquinoline-N-methohalide. All three compounds were unknown. The approach adopted in the present work was similar to that employed for 3-mercaptopyridine and its N- and S-methyl derivatives.

Quinoline was sulphonated with fuming sulphuric acid (20% free SO_3) in the presence of mercury as described by Grier (1952). Under these conditions quinoline-5-sulphonic acid (XXXV) was produced, but, in the absence

of mercury McCasland (1946) found that sulphonation occurred in the 8-position. Quinoline-5-sulphonyl chloride (XXXIX) was prepared by the action of phosphorus pentachloride on the sulphonic acid. The position of the substituent was proven by hydrolysis of the purified sulphonyl chloride to quinoline-5-sulphonic acid, fusion X of which with alkali at 260° gave 5-hydroxyquinoline (XL) in 64% overall yield. The m.p. was not depressed on admixture with 5-hydroxyquinoline of other origin. Quinoline-5-sulphonyl chloride was reduced with stannous chloride and hydrochloric acid and the mercapto - compound isolated as the S-benzoate (XLI). Acid hydrolysis of 5-benzoylmercaptoquinoline (XLI) gave 5-mercaptoquinoline (XLII) which crystallised as a red monohydrate, passing to the anhydrous form, a light pink solid when dried over phosphorus pentoxide. (Edinger (1908) found that 8-mercaptoquinoline gives a red hydrate which on drying passes to the anhydrous compound, a violet liquid). 5-Mercaptoquinoline was oxidised by dilute hydrogen peroxide to the disulphide (XLIII). Methylation of 5-mercaptoquinoline with methyl iodide and sodium hydroxide gave 5-methylmercaptoquinoline (XLIV) which was purified

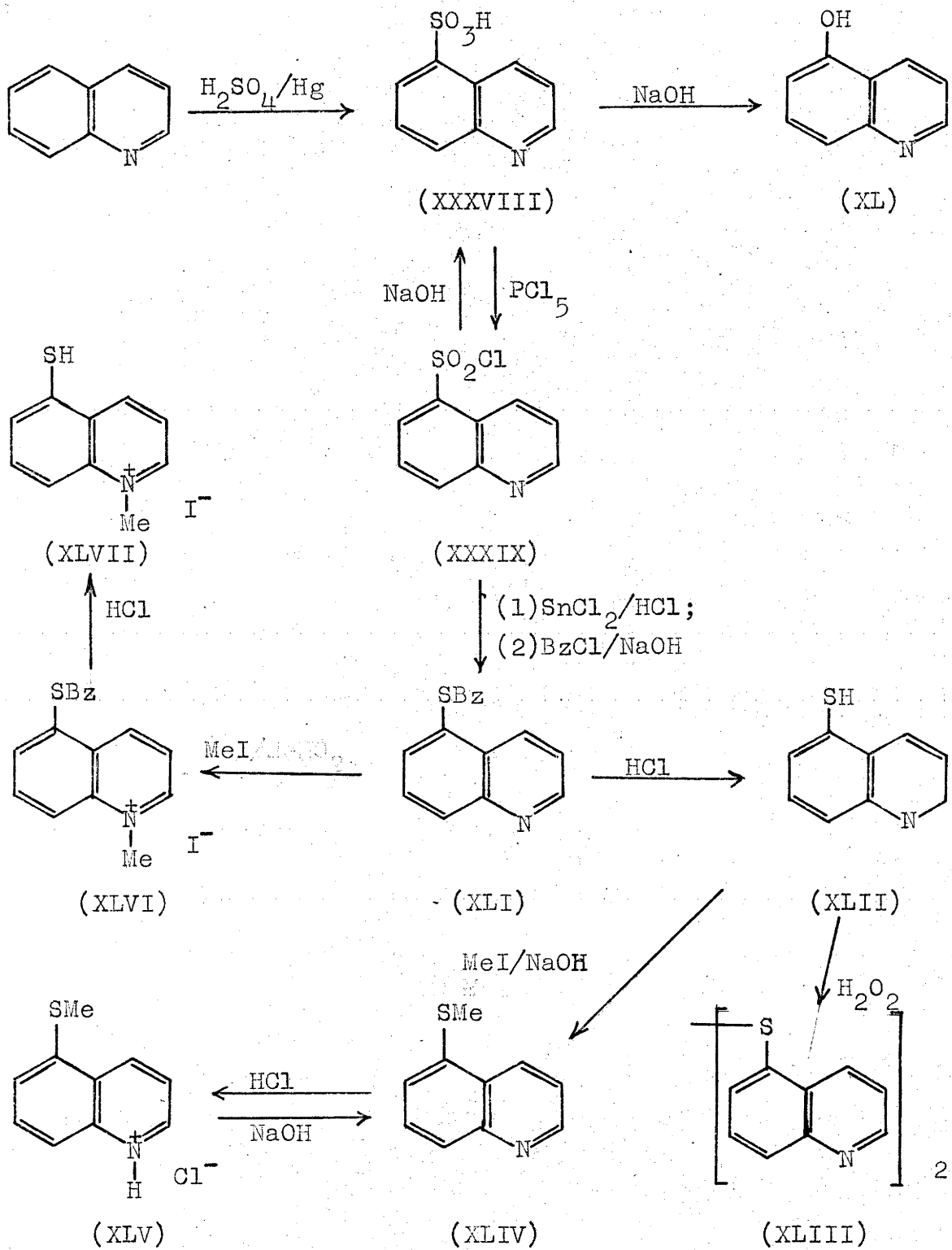
X The temperature of the fusion was of the order of that used by Koelsch and Alberton (1953) for the conversion of isoquinoline-5-sulphonic acid to 5-hydroxyisoquinoline by fusion with a mixture of sodium and potassium hydroxides at 230° .

through its hydrochloride (XLV).

5-Benzoylmercaptoquinoline (XLI) was quaternized both by methyl iodide in nitromethane at 20° and by dimethyl sulphate in nitrobenzene at 20°, to give respectively the methiodide (XLVI) and the methyl hydrogen sulphate (Renault (1955) has prepared the methyl hydrogen sulphate of 2-methylmercaptopyridine). Acid hydrolysis of 5-benzoylmercaptoquinoline methiodide (XLVI) gave 5-mercaptoquinoline methiodide (XLVII). The anion of 5-benzoylmercaptoquinoline methiodide was exchanged by shaking with silver chloride and the methochloride hydrolysed with acid. The 5-mercaptoquinoline methochloride unlike the methiodide could not be satisfactorily crystallised.

The reactions described above are shown diagrammatically in Scheme D.

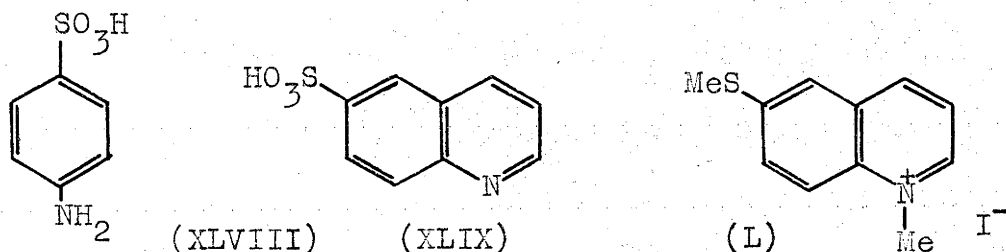
Quinoline: the 6-position. The substances required for the present investigation are 6-mercaptoquinoline, 6-methylmercaptoquinoline and 6-mercaptoquinoline-N-methohalide. Only the first was known. It had been prepared by Ponci and Gialdi (1954) by a process analogous to that outlined above for 5-mercaptoquinoline. The position of the substituent in the starting material, quinoline-6-sulphonic acid (XLIX), was fixed by its synthesis from sulphanilic acid (XLVIII). The 6-mercaptoquinoline was prepared as described above and purified by distillation under reduced pressure. The sodium salt



SCHEME D.

as prepared by Ponci and Gialdi was found to be unsatisfactory.

6-Methylmercaptoquinoline and 6-mercaptoquinoline methochloride were made similarly to the 5-isomer. 6-Mercaptoquinoline methochloride and 6-mercaptoquinoline methiodide were both prepared. Methylation of 6-mercaptoquinoline with methyl iodide and sodium hydroxide gave 6-methylmercaptoquinoline and a small amount of 6-methylmercaptoquinoline methiodide (L). The procedures employed were the same as those shown diagrammatically in Scheme D, p. 34 for the 5-position.



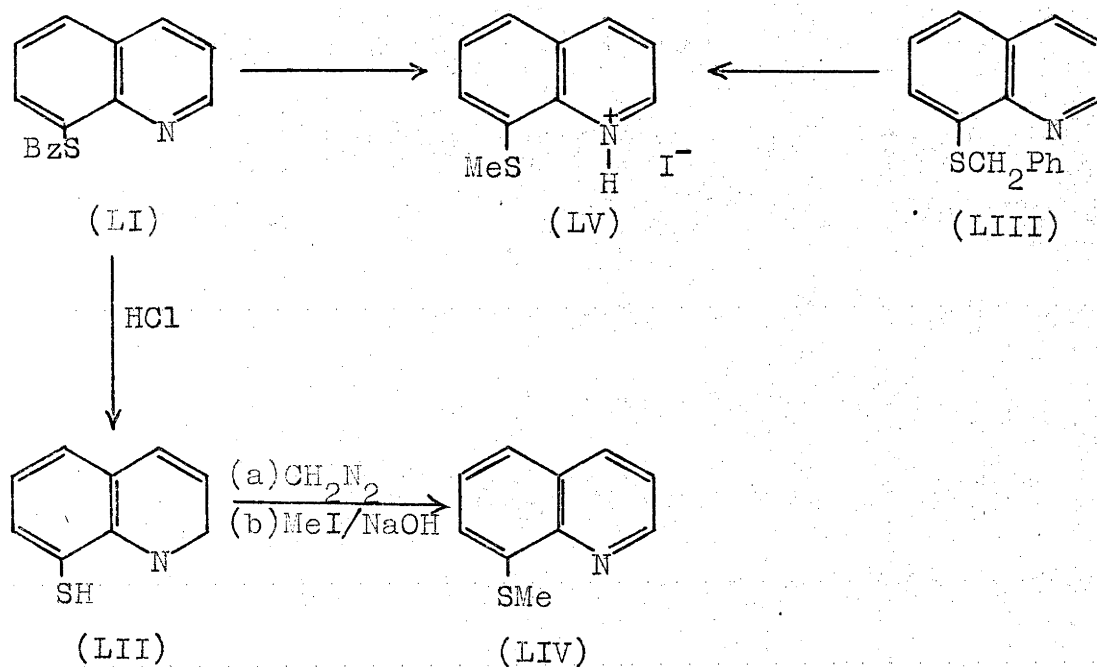
Quinoline: the 8-position. The substances required for the present investigation are 8-mercaptoquinoline, 8-methylmercaptoquinoline and 8-mercaptoquinoline-N-methohalide. The first two substances were known. 8-Mercaptoquinoline has been prepared several times from the sulphonic acid, a method originally described by Edinger (1908); the preparation of 8-methylmercaptoquinoline has been described by Taylor (1951) by methylation of 8-mercaptoquinoline with methyl iodide and sodium hydroxide. Although one would expect methylation to take place on sulphur the structure had not been

proven nor was the N-methyl isomer known. All attempts to prepare the N-methyl isomer in the present work failed.

The method as described by Edinger (1908) was found most suitable for the preparation of 8-mercaptoquinoline (LII), the sulphonic acid being most conveniently prepared according to McCasland (1946) by sulphonating quinoline with fuming sulphuric acid (30% free SO_3) in the absence of a catalyst. (N.B. In the presence of mercury, the 5-isomer is produced).

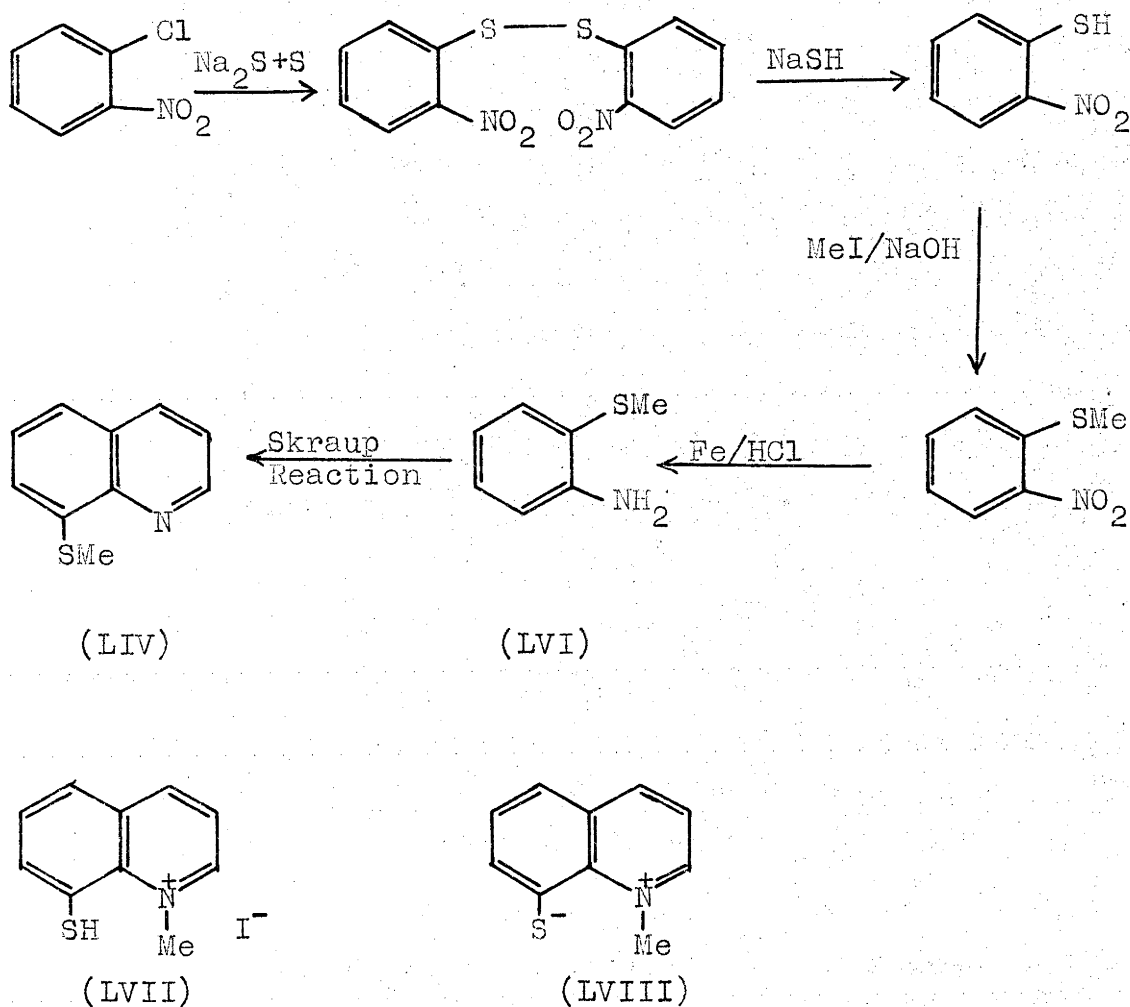
8-Benzoylmercaptoquinoline (LI), 8-benzylmercaptoquinoline (LIII) and di-8-quinolyl disulphide (LIX) were also prepared as described by Edinger. The reactions in the preparation are analogous to those shown in Scheme D. p. 34 for the 5-isomer.

8-Methylmercaptoquinoline (LIV) was prepared by a number of methods. 8-Mercaptoquinoline was methylated with diazomethane, and with methyl iodide and sodium hydroxide; and 8-benzoylmercaptoquinoline and 8-benzylmercaptoquinoline with methyl iodide in methanol at 20° and at 100° respectively gave 8-methylmercaptoquinoline hydriodide (LV) from which the base was recovered by the action of alkali.



SCHEME E.

The structure of the methylated product was proved by its synthesis from *o*-methylmercaptoaniline (LVI) by a Skraup reaction under conditions similar to those used by King and Sherrad (1942) for the synthesis of 8-methoxyquinoline. This is the first methylmercaptoquinoline to be prepared by a Skraup reaction. The series of reactions employed in the preparation are outlined in Scheme F.



SCHEME F.

The following attempts to prepare 8-mercaptoquinoline methiodide (LVII) or its anhydro-base (LVIII) failed.

(i) (a) Di-8-quinolyl disulphide (LIX) and dimethyl sulphate in nitrobenzene at 150° gave a product, the analysis of which did not correspond to any of the expected N-methyl derivatives of the disulphide. (This method is similar to that used by Grandmougin and

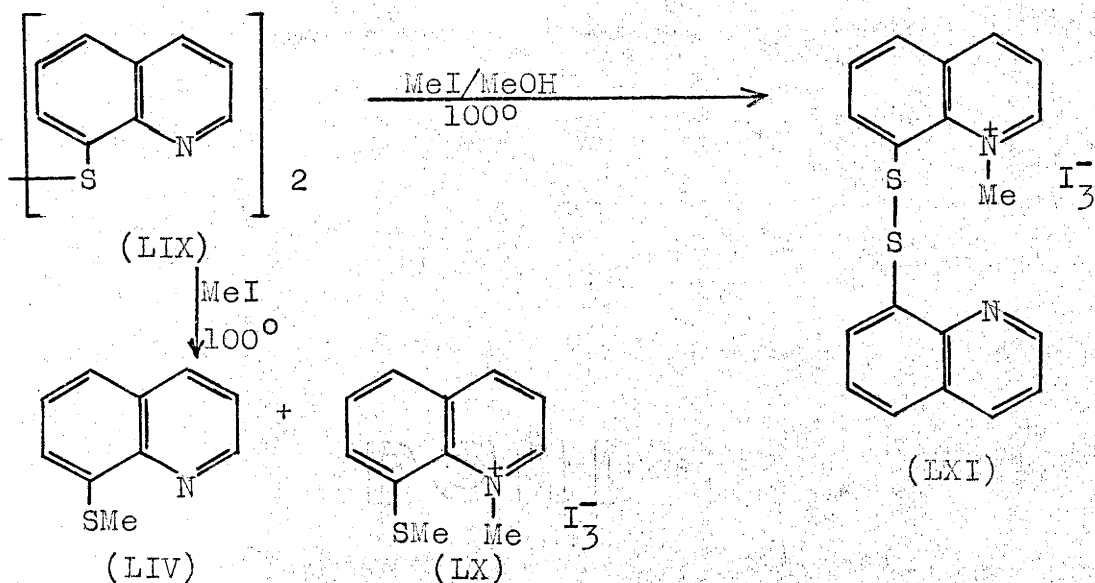
Smirous (1913) for the preparation of 3:6-diamino-10-methylacridinium salts). Reduction of the product was not attempted.

(b) Di-8-quinolyl disulphide and methyl iodide at 100° gave 8-methylmercaptoquinoline (LIV) and 8-methylmercaptoquinoline methiodide periodide (LX). The deep colouration of the periodide was discharged by sulphur dioxide, presumably by conversion to the iodide as found by Ullmann and Maag (1907) for N-phenylacridinium compounds.

(c) Di-8-quinolyl disulphide and methyl iodide in methanol at 100° gave di-8-quinolyl disulphide methiodide periodide (LXI). The deep colouration of the periodide was discharged by sulphur dioxide.

Reduction of the monomethiodide periodide was not attempted because of the similar properties expected for the two products.

The reactions involved in (b) and (c) are shown below.



(ii) (a) 8-Benzoylmercaptoquinoline and methyl iodide in methanol at 20° for 2 days gave 8-methylmercaptoquinoline hydriodide.

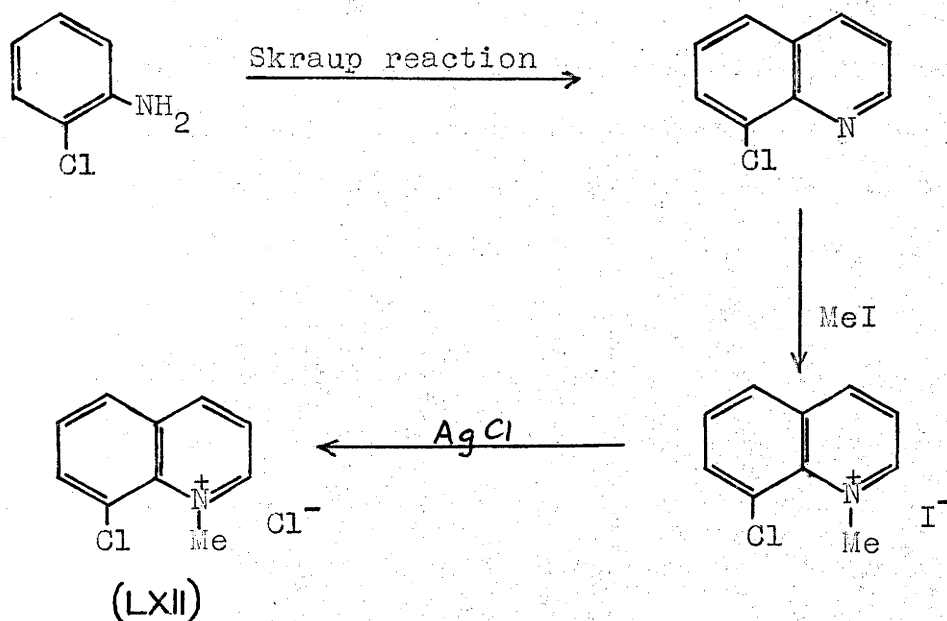
(b) 8-Benzylmercaptoquinoline and methyl iodide in methanol at 100° gave 8-methylmercaptoquinoline hydriodide.

See Scheme E p. 37 and p.27 for discussion.

(iii) (a) 8-Chloroquinoline methochloride (LXII) and thiourea in alcohol at 150° did not react. McCasland (1946) found that 8-chloroquinoline with thiourea did not give 8-quinolineisothiuronium chloride and thence 8-mercaptoquinoline.

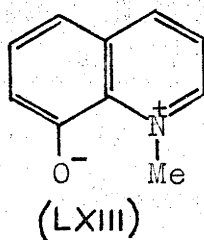
(b) 8-Chloroquinoline methochloride and alcoholic sodium hydrogen sulphide at 175° did not react.

The preparation of the compounds involved in this study is shown in Scheme G below.

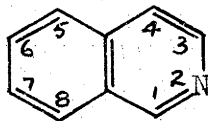


SCHEME G.

(iv) "Diazoxine" (LXIII) (the anhydride of 8-hydroxy-quinoline methohydroxide, prepared as described by Phillips and Keon (1951)) did not react with phosphorus pentasulphide. The reaction was attempted in refluxing benzene (used by Arndt and Kalischek (1930) in the preparation of N-phenyl-4-thio²-chelidamic acid ester), in toluene (used by Arndt (1932) in the preparation of N- γ -pyridylpyrid-4-thione) and in xylene.



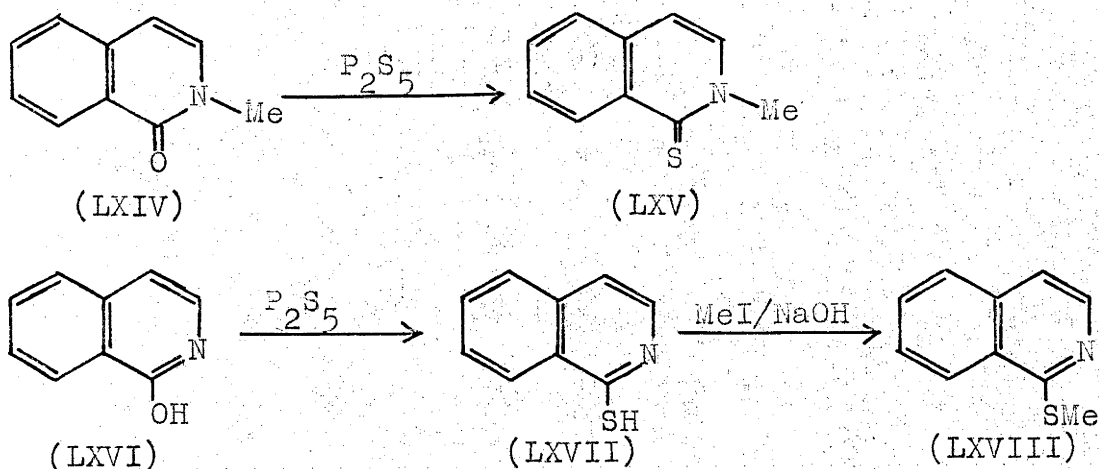
Isoquinoline:



the 1-position. The substances required for the present investigation are 1-mercaptoisoquinoline, 1-methylmercapto-isoquinoline and 2-methylisoquinol-1-thione (LXV) of these, only the last was known. It had been prepared as described by White and Brooker (1950), and Peak and Stansfield (1952). In the present study it was prepared from 2-methylisoquinol-1-one (LXIV) and phosphorus pentasulphide without a solvent.

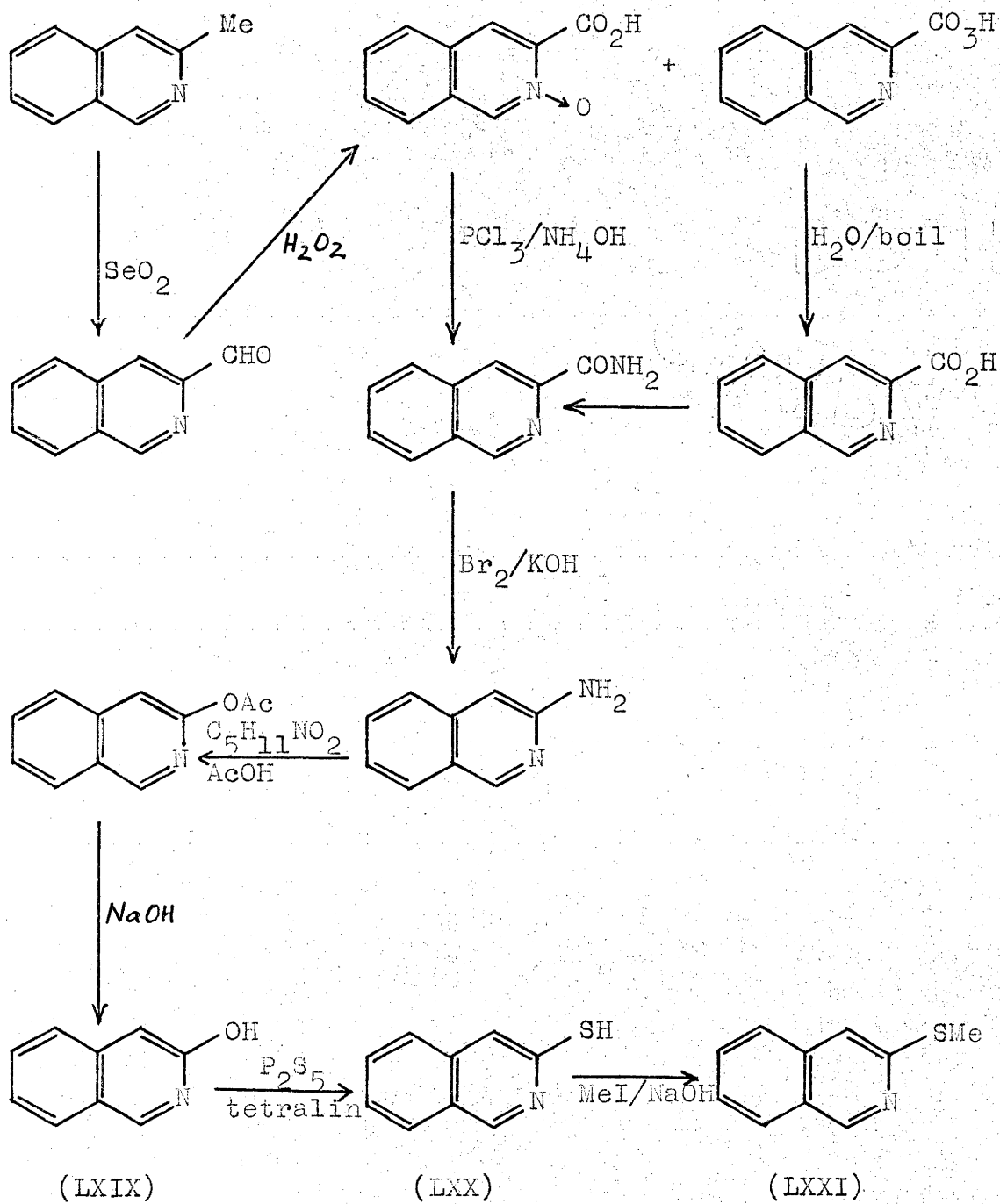
The unknown 1-mercaptoisoquinoline (LXVII) was prepared from 1-hydroxyisoquinoline (LXVI) and phosphorus pentasulphide and on methylation with methyl iodide and sodium hydroxide gave the unknown 1-methylmercapto-

isoquinoline (LXVIII).



Isoquinoline: the 3-position. The substances required for the present investigation are 3-mercaptoisoquinoline, 3-methylmercaptoisoquinoline and 3-mercaptoisoquinoline-N-methohalide. All three compounds were unknown.

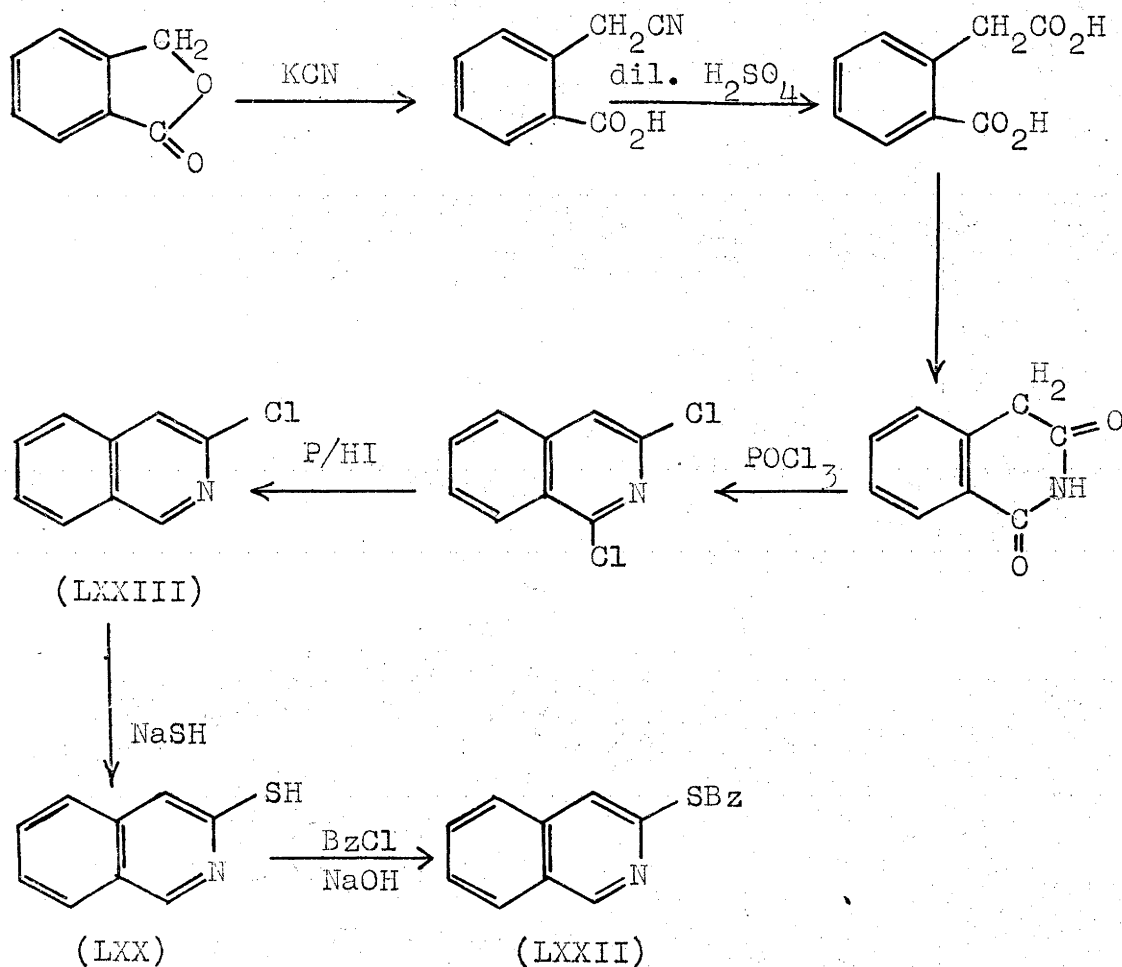
3-Mercaptoisoquinoline was prepared in small yield from 3-hydroxyisoquinoline (LXIX) and phosphorus pentasulphide in tetralin (Elion and Hitchings (1947) thiated uracils and thiouracils with phosphorus pentasulphide in tetralin) at 180° , and from 3-chloroisoquinoline (LXXIII) and sodium hydrogen sulphide at 205° . Methylation of 3-mercaptoisoquinoline gave 3-methylmercaptoisoquinoline (LXXI) which was isolated as the hydrochloride. The preparation of 3-mercaptoisoquinoline methochloride was not attempted. The steps involved in the preparation of 3-mercaptoisoquinoline and 3-methylmercaptoisoquinoline through 3-hydroxyisoquinoline are outlined in Scheme H.



SCHEME H.

Below 180° the reaction of 3-hydroxyisoquinoline and phosphorus pentasulphide did not proceed and the starting material was recovered unchanged.

The preparation of 3-mercaptoisoquinoline (LXX) through 3-chloroisoquinoline (LXXIII) is shown in Scheme J.

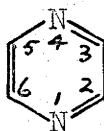


SCHEME J.

The reaction of 3-chloroisoquinoline with sodium hydrogen sulphide did not proceed readily. When the reaction was carried out under less vigorous conditions

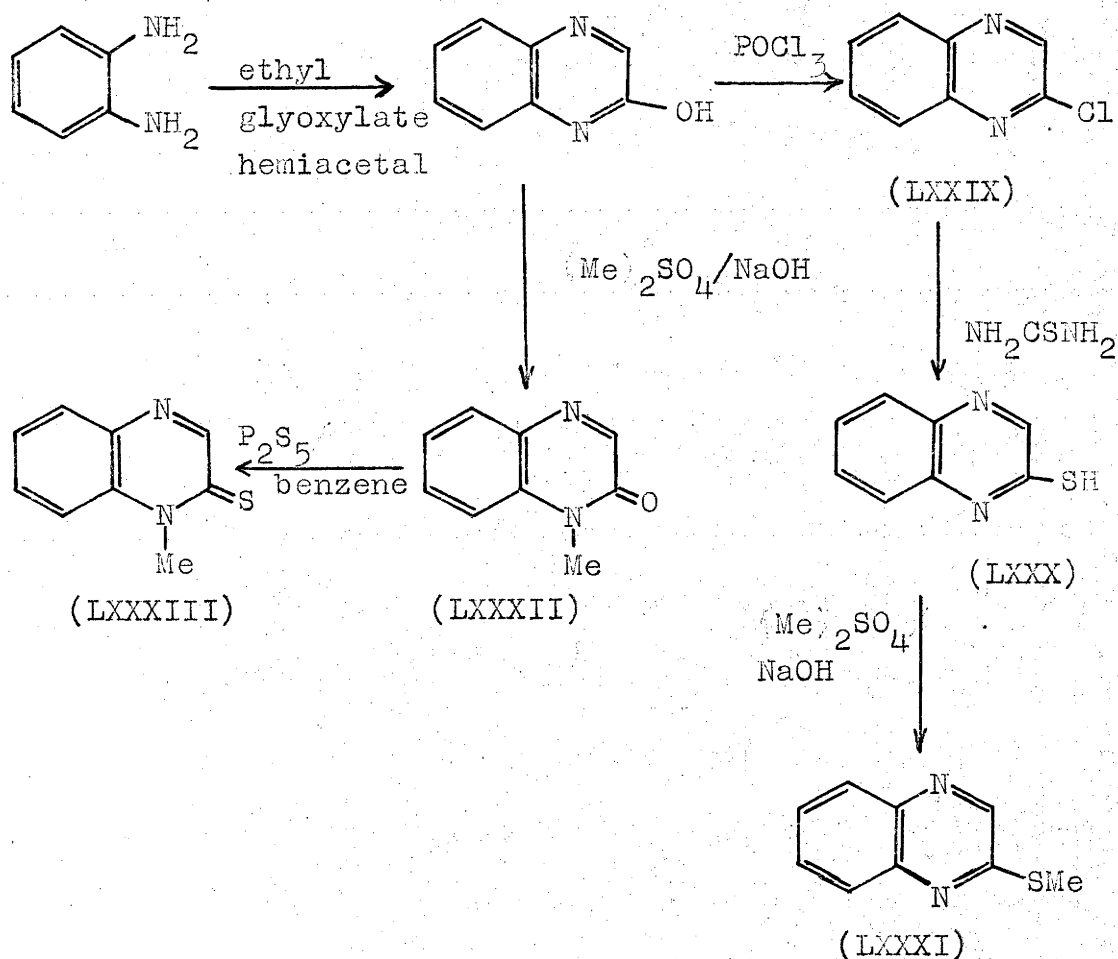
than those described (210° for 70 hours), considerable quantities of 3-chloroisoquinoline were recovered unchanged. The product was best isolated as the benzoate (LXXII). The failure of 3-chloroisoquinoline to react with p-chloroaniline and 3-diethylaminoethylamine has been commented upon by Haworth and Robinson (1948).

Pyrazine:



the 2-position. The substances required for the present investigation are 2-mercaptopyrazine, 2-methylmercaptopyrazine and 1-methylpyraz-2-thione. Of these, only the first was known. It has been prepared by Roblin and Clapp (1950) by the action of potassium hydrogen sulphide on 2-chloropyrazine. A better method was found in the present work, viz, from 2-hydroxypyrazine (LXXIV) with phosphorus pentasulphide in pyridine. Methylation of 2-mercaptopyrazine with methyl iodide and sodium hydroxide gave 2-methylmercaptopyrazine (LXXVI). 1-Methylpyraz-2-thione (LXXVIII) was prepared from its oxygen-analogue (LXXVII) by reaction with phosphorus pentasulphide in pyridine. The steps involved in the synthesis are shown in Scheme K.

(1954), and 2-methylmercaptoquinoxaline (LXXXI) by Cheeseman (1957). 2-Mercaptoquinoxaline was prepared from 2-chloroquinoxaline (LXXIX) and thiourea as described by Wolf, Wilson, and Tishler, and methylated with dimethyl sulphate and sodium hydroxide. (Cheeseman used methyl iodide and sodium hydroxide). 1-Methylquinoxal-2-thione (LXXXIII) was prepared from the oxygen-analogue (LXXXII) with phosphorus pentasulphide in benzene. The series of reactions is shown in Scheme L.



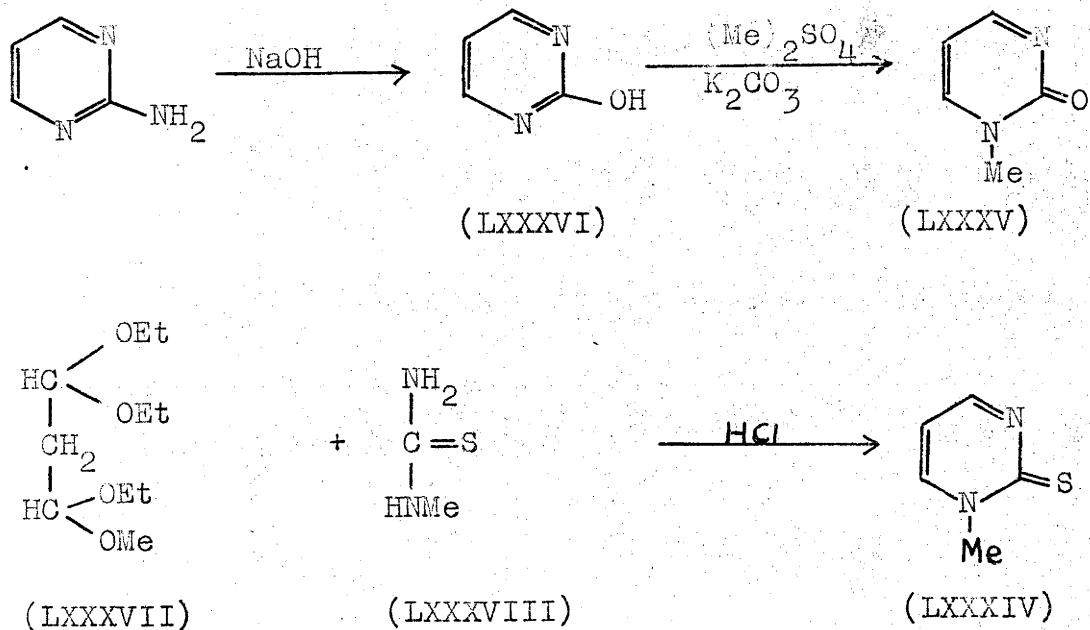
SCHEME L.

Pyrimidine:

the 2-position. The substances required for the present investigation are 2-mercaptopyrimidine, 2-methylmercaptopyrimidine and 1-methylpyrimid-2-thione. Of these, the first two were known and their relevant constants and ultraviolet absorption spectra at various pH values determined by Boarland and McOmie (1952). The preparation of only 1-methylpyrimid-2-thione (LXXXIV) was required. 1-Methylpyrimid-2-thione could not be prepared from 1-methylpyrimid-2-one (LXXXV) ~~X~~ and phosphorus pentasulphide under a variety of conditions, ranging from refluxing benzene to tetralin at 180°. Its synthesis however, was achieved from commercial malondialdehyde tetra-acetal (LXXXVII) and N-methylthiourea (LXXXVIII) in the presence of hydrochloric acid. (Adapted from Hale and Williams (1915) who prepared 1:4:6-trimethylpyrimid-2-thione from acetylacetone and N-methylthiourea in ethanolic hydrochloric acid).

The reactions involved in the above preparations are shown diagrammatically in Scheme M.

~~X~~ best prepared from 2-hydroxypyrimidine (LXXXVI) with dimethyl sulphate and potassium carbonate.

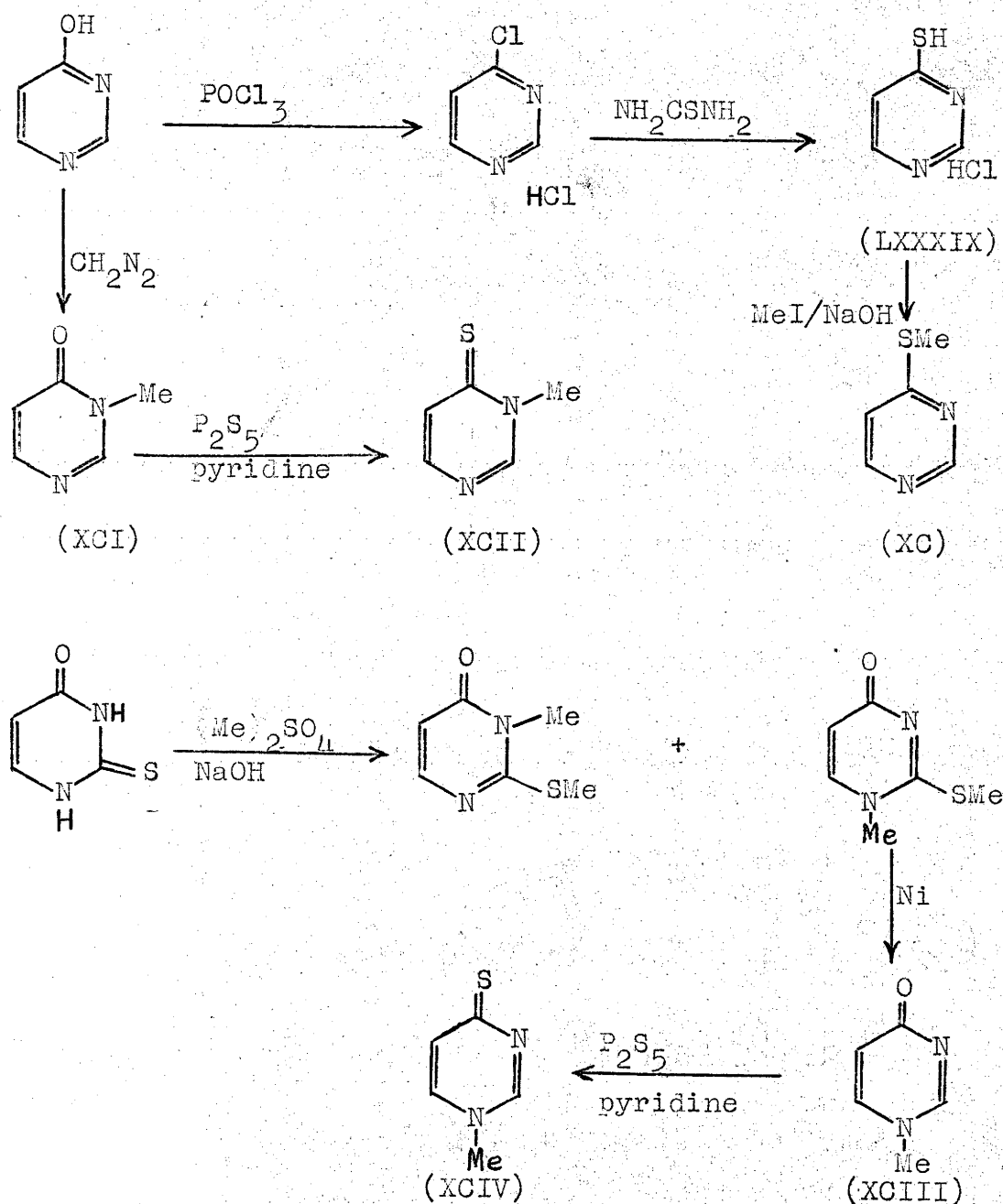
SCHEME M.

Pyrimidine: the 4-position. The substances required for the present investigation are 4-mercaptopyrimidine, 4-methylmercaptopyrimidine, 1-methylpyrimid-6-thione and 1-methylpyrimid-4-thione. Of these only the first was known. It had been prepared, and its ionization constants and its ultraviolet absorption spectrum at various pH values determined by Boarland and McOmie (1952). The other compounds required, 4-methylmercaptopyrimidine, 1-methylpyrimid-6-thione and 1-methylpyrimid-4-thione were prepared as described below.

4-Methylmercaptopyrimidine (XC) was prepared by methylation of 4-mercaptopyrimidine (LXXXIX) with methyl

iodide and sodium hydroxide. 1-Methylpyrimid-6-thione (XCII) and 1-methylpyrimid-4-thione (XCIV) were prepared from their oxygen-analogues (XCI;XCIII) by refluxing with phosphorus pentasulphide in pyridine.

The steps in the syntheses are shown in Scheme N.

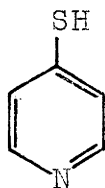


SCHEME N

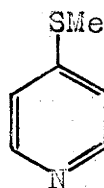
SECTION III.QUALITATIVE AND QUANTITATIVE METHODS OF EVALUATION OF TAUTOMERISMQualitative.

The extent of tautomerism of nitrogenous heterocyclic mercapto - compounds was found to be revealed most readily by ultraviolet spectroscopy. Infrared spectroscopy was considered unsuitable for reasons given below.

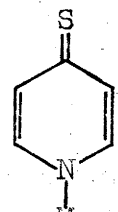
The ultraviolet absorption spectra, in water, of the neutral molecule and various ionic species of the mercapto - compound and its N- and S-methyl derivatives were determined. The ultraviolet absorption spectrum of the tautomerisable mercapto - compound was then compared with those of the two forms in which the mobile hydrogen had been replaced by an immobile methyl - group. e.g. The ultraviolet absorption spectrum of the molecule of 4-mercaptopyridine (I) was compared with those of the neutral molecule of 4-methylmercaptopyridine (II) and 1-methylpyrid-4-thione (III).



(I)



(II)



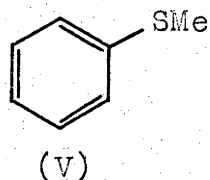
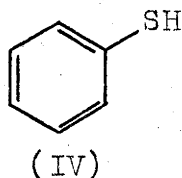
(III)

The results of these comparisons are dealt with in the "Discussion of Results" p. 67.

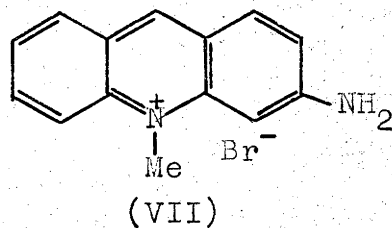
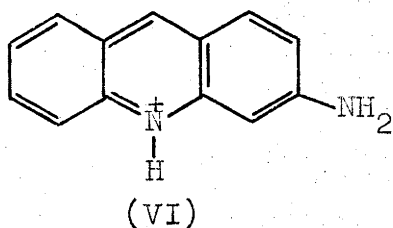
The success of this method in studies of tautomerism depends on the virtual optical transparency of the methyl

group when attached to carbon, oxygen, nitrogen or sulphur atoms. The following evidence supports this assumption in the present studies.

1. Methyl on sulphur. The ultraviolet absorption spectra of the molecule of mercaptobenzene (IV) and methylmercaptobenzene (V) in water are shown in Fig. 1. It can be seen that the shoulder at 275 $m\mu$ in mercaptobenzene has undergone only a very slight shift to 280 $m\mu$ in methylmercaptobenzene.



2. Methyl on Nitrogen. Examination of the figures given by Craig and Short (1945) and Turnbull (1945) show that the ultraviolet absorption spectra of 2-aminoacridine cation (proton on the ring-nitrogen atom) (VI) in 66% aqueous methanol is almost identical with that of 2-aminoacridine methobromide (VII) in water.



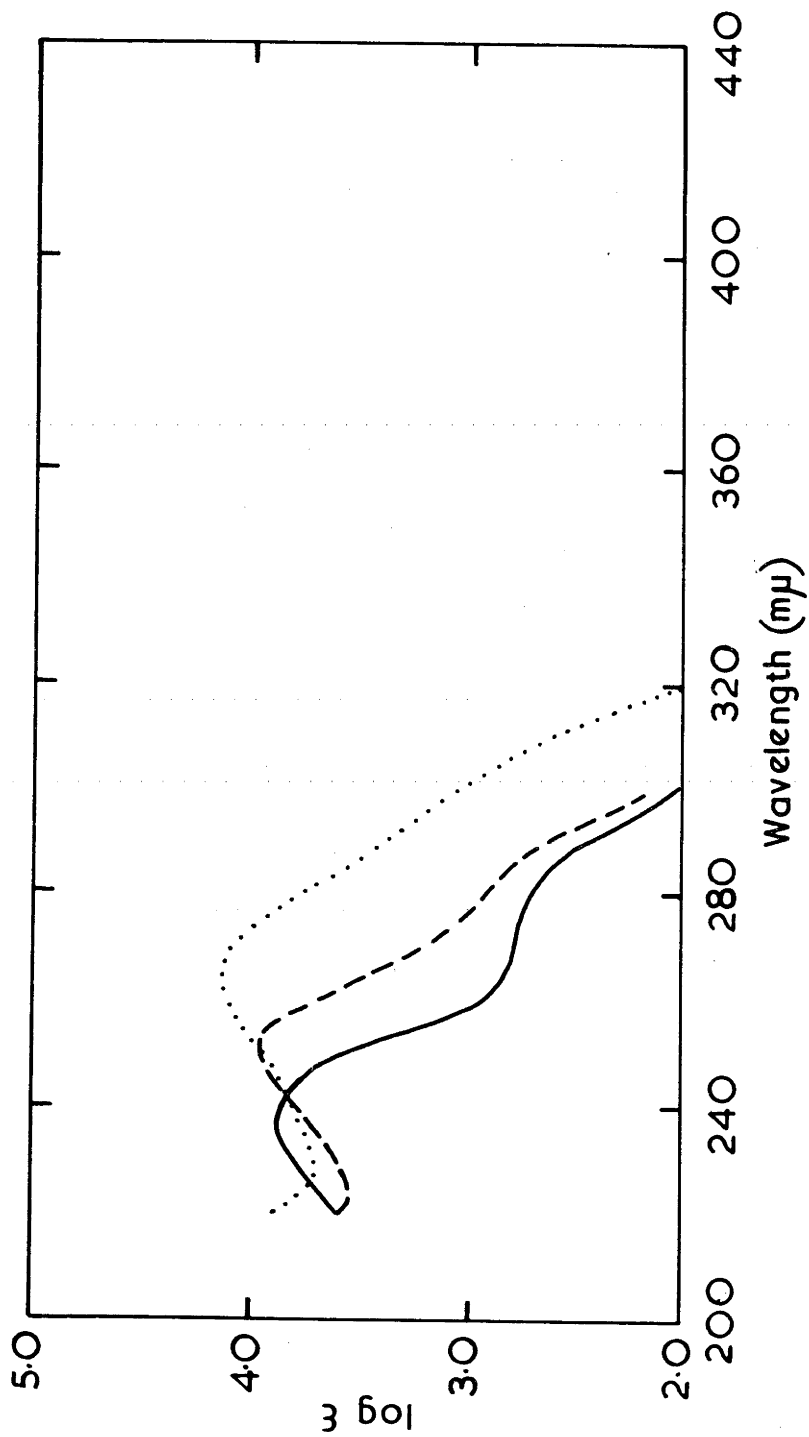


Fig. 1. — Molecule of mercaptobenzene
..... Anion of mercaptobenzene
--- Methylmercaptobenzene



The spectral data are given in the following table.

Compound.	$\lambda_{\max.}$ μ	$\log \epsilon_{\max.}$
2-aminoacridine (monocation)	278;366;460	4.65;4.20;4.15
2-aminoacridine methobromide.	276;370;465	4.60;4.12;4.10

The method of substitution of mobile hydrogen atoms with immobile methyl - groups has been applied to the qualitative study of tautomerism in nitrogenous heterocyclic mercapto - compounds by a number of workers.

Morton and Stubbs (1939) and Hasan and Hunter (1936) studies the tautomerism of 2-mercaptobenzo-thiazoles; Morton and Stubbs (1939) that of 2-mercapto-4-methylquinoline; Acheson, Burstall, Jefford and Samson (1954) that of 5-mercaptoacridine; Boarland and McOmie (1952) and Marshall and Walker (1951) that of 2- and 4-mercaptopyrimidines; and Shugar and Fox (1952) that of 2-thiouracil.

In the present work, no quantitative use has been made of ultraviolet spectra for determination of the tautomeric ratios of the two forms at equilibrium. This method has been applied by Mason (1957) to the tautomerism of N-heteroaromatic hydroxy - compounds but a more accurate method is provided by potentiometry which was preferred for the present work.

Infrared spectroscopy was not employed in the present study of thiol-thione tautomerism in nitrogenous heterocyclic mercapto - compounds for the following

reasons.

- (1) There is still uncertainty concerning the position of the thiocarbonyl (C = S) absorption band.
- (2) The absorption of the SH group is weak and can easily be masked.
- (3) The absorption peak for the NH group is not easily identified unambiguously.
- (4) Infrared spectroscopy cannot be used in water, and hence the biological interest of these studies would be nullified.

Quantitative.

A quantitative approach has been made to the tautomerism of nitrogenous heterocyclic mercapto - compounds from a study of the ionization constants. The method was developed by Ebert (1926) for the determination of zwitterionic ratios in aminoacids. In the present field its use has been extended by Edsall and Blanchard (1933) (described in Cohn and Edsall, 1943). It has since been applied to a study of tautomerism in N-heteroaromatic hydroxy - compounds by Tucker and Irvin

(1951), Albert and Phillips (1956) and Mason (1958) ✕
 It has now extended to nitrogenous heterocyclic
 mercapto - compounds. Since the initial publication,
 Albert and Barlin (1958); Jones and Kitritzky (1958)
 have published some data on 2- and 4-mercaptopyridine.
 The derivation of the relevant expressions is as follows:
 Consider 4-mercaptopyridine; the two ionization
 equilibria or proton exchanges exhibited by 4-mercapto-
 pyridine are shown in Fig. 2, together with the thiol-
 thione tautomerism postulated for this compound.

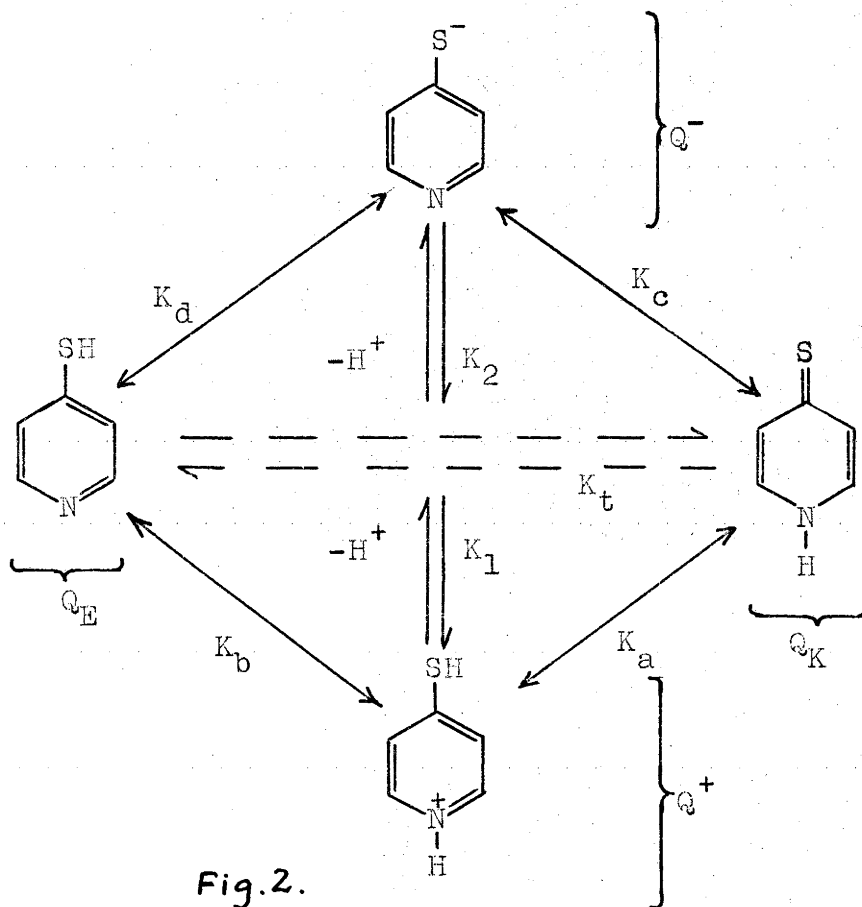
Other resonance structures are possible but are
 less significant. Only one of the possible Kekule
 structures is shown for each species and the structures
 comprising a resonance hybrid are enclosed by brackets.

✕ Two equations given by Mason are in error.

Equation (4), $K_t = \frac{K_{\text{OMe}}}{K_1} - 1$ should read $K_t = \frac{K_1}{K_{\text{OMe}}} - 1$

and equation (5), $K_t = \frac{1}{\left[\frac{K_{\text{NMe}}}{K_1} - 1 \right]}$ should read $K_t = \frac{1}{\left[\frac{K_1}{K_{\text{N}^{\wedge}\text{Me}}} - 1 \right]}$

The following symbols are used to represent the various species shown in Fig. 2: Q_E , the non-ionized pyridthiol; Q_K , the non-ionized pyridthione which is in tautomeric equilibrium with Q_E ; Q^+ , the cation formed by addition of a proton to Q_E or Q_K ; Q^- , the anion formed by removal of a proton from Q_E or Q_K .



Ionization equilibria (proton exchanges) between species are indicated by single arrows. The thiolthione tautomerism between Q_E and Q_K is represented by two broken arrows directly linking these two forms.

However, it should be emphasized that this carries no implication regarding the mechanism of the tautomerisation (the most probable mechanism of tautomerisation involves the ionization steps shown in the upper and lower parts of Fig. 2 with the ionic species Q^- and Q^+ as intermediates).

The various ionization equilibria can be formulated in terms of the intrinsic constants, K_a , K_b , K_c , and K_d by the following equations in which parentheses represent activities.

Considering the equilibrium between the cation and the neutral molecule, the cation may lose a proton from either the sulphur or the ring-nitrogen atom. The two dissociation constants are:

$$K_a = (H^+) (Q_K) / (Q^+) \quad \dots\dots\dots(1)$$

$$K_b = (H^+) (Q_E) / (Q^+) \quad \dots\dots\dots(2)$$

Likewise each of the two forms (thiol and thione) may lose a hydrogen ion to form the anion and the two dissociation constants are:

$$K_c = (H^+) (Q^-) / (Q_K) \quad \dots\dots\dots(3)$$

$$K_d = (H^+) (Q^-) / (Q_E) \quad \dots\dots\dots(4)$$

The constants K_a , K_b , K_c and K_d cannot be determined directly. However, two ionization constants, K_1 and K_2 , can be evaluated experimentally either by

potentiometric titration or by spectrophotometry and were found to be widely separated.

The constants, K_1 and K_2 , are defined and are related to the intrinsic constants as

$$K_1 = (H^+) (Q_E + Q_K) / (Q^+) = K_a + K_b \dots\dots\dots(5)$$

$$K_2 = (H^+) (Q^-) / (Q_E + Q_K) = (K_c \times K_d) / (K_c + K_d) \dots\dots\dots(6)$$

The tautomeric equilibrium between the thiol and thione (Q_E and Q_K) can be described in terms of the constant

K_t

$$K_t = (Q_K) / (Q_E) = K_a / K_b = K_d / K_c \dots\dots\dots(7)$$

In determining the ionization constants

potentiometrically it is assumed that the equilibrium between the tautomeric forms Q_E and Q_K is instantaneous and independent of pH. This appears to be the case with the compounds examined because no drifts were observed during potentiometric titration, K_t can therefore be assumed to be a true constant.

With these assumptions, ionization constants X can be evaluated as outlined in the "Experimental".

The two ionization constants of 4-mercaptopyridine can also be evaluated spectrophotometrically in as much as non-ionized 4-mercaptopyridine and the two ionized species, Q^+ and Q^- , have distinct and characteristic absorption spectra. Presumably the two

* These classical ionization constants are evaluated in terms of concentrations rather than activities. The thermodynamic ionization constant and the classical ionization constant (as determined using concentrations) are related approximately by the equation

$$pK_a \text{ (thermodynamic)} = pK_a \text{ (as determined)} + 0.5 \sqrt{I}$$

where I is the ionic strength at half - neutralisation. Albert and Phillips (1956) have calculated the following corrections for conversion of the pK_a (as determined) to the pK_a (thermodynamic): An acid titrated at the following molarities should have the quantities in parenthesis added to the pK_a values as determined: 0.05 molar (0.08); 0.02 molar (0.05); 0.01 molar (0.03); 0.002 molar (0.02); 0.0005 molar (0.01). For bases, these quantities are subtracted.

tautomers, Q_E and Q_K , differ in absorption spectra, but there appears to be no satisfactory procedure for obtaining the characteristic absorption of each individual tautomer since it must be assumed that both are present in the equilibrium mixture at all times. With the additional assumption that K_t is a true constant (failure of the validity of this assumption would become apparent in deviation of the experimental data from the theoretical relationships employed), the ionization constants can be evaluated spectrophotometrically at selected wavelengths in buffered solutions (of known pH) of 4-mercaptopyridine. The ionization constants have essentially the significance of equations (5) and (6) with the exception that the ionization constants are expressed in terms of concentrations of the species Q_E , Q_K , Q^+ and Q^- rather than activities.

The procedure for evaluating the ionization constants is outlined in the Experimental section and is similar to that of Irvin and Irvin (1947, 1948).

If in addition to K_1 and K_2 , the value of any one of the four constants K_a , K_b , K_c or K_d is known, the value of the other three may be determined. Although it is not possible to determine the ionization constant of either of the two tautomers, it is possible to determine the cationic ionization constants of their

respective derivatives where the mobile hydrogen has been substituted by an immobile methyl - group.

For calculations in the present work, the cationic ionization constant of the S-methyl derivative (K_e) is assumed to be equal to that of the thiol tautomer and

$$K_b = (H^+) (Q_E) / (Q^+) = K_e \quad \dots\dots\dots(8)$$

Equation (8), in contrast to earlier equations which are exact, is approximate.

That this is a reasonable assumption is supported by the following evidence.

The pK_a values given by Hall and Sprinkle (1932) for aniline, o-, m-, p-methoxyaniline are respectively 4.58, 4.49, 4.20 and 5.29. In m-methoxyaniline, only the inductive effect (-I) is operating, and it is base weakening. The other isomers show the opposed influences of the -I and the (base - strengthening) mesomeric effect (+M). The pK_a values given by Kuhn (1928) for o-, m-, and p-hydroxyaniline are respectively 4.72, 4.17 and 5.50. Comparison of the m-derivatives shows that the inductive effect of methoxyl- and hydroxyl - groups are identical and this has been demonstrated with acids by Dippy (1939) e.g. 4.09 and 4.08 respectively for the pK_a values of m-methoxy- and m-hydroxy-benzoic acid. Inspection of the values for the o- and p-isomers reveals that the +M effects of methoxyl- and hydroxyl - groups are very similar, that

of the hydroxyl - group being somewhat greater. The maximum difference between the ionization constants of the hydroxy - and methoxy-anilines is 0.23 units. Figures are not available for the pK's of mercapto- and methylmercapto-anilines but it is expected that they would follow approximately the relationships of their oxygen - analogues.

However, the dipole moments given by Lumbroso and Marschalk (1952) for phenol and anisole are 1.60 and 1.28D respectively and for mercaptobenzene and methylmercaptobenzene 1.19 and 1.38D respectively. The difference in dipole moment between phenol and anisole (0.32D) is greater than that between mercaptobenzene and methylmercaptobenzene (0.19D). On this basis one would not expect the maximum difference in pK between the mercapto- and methylmercapto-anilines to exceed that of their oxygen - analogues i.e. 0.23 units. The assumption then that the pK of 4-methylmercaptopyridine is equal to that of the thiol - tautomer does not appear unreasonable and even if this assumption is in error to the extent of 0.23 units the order of the tautomeric ratio calculated as shown below is not significantly altered.

From the equations given above it can be derived that:

$$K_a = K_1 - K_b = K_1 - K_e$$

$$K_t = \frac{K_a}{K_b} = \frac{K_a}{K_e}$$

$$= \frac{(K_1 - K_e)}{K_e}$$

$$= \frac{K_1}{K_e} - 1$$

$$\begin{aligned} \text{and } K_t &= \text{antilog}(pK_e - pK_1) - 1 \\ &= \text{antilog}(pK_{\text{S-methyl}} - pK_{\text{mercaptan}}) - 1 \quad \dots(9) \end{aligned}$$

Similarly it can be derived that:

$$\frac{1}{K_t} = \text{antilog}(pK_{\text{N-methyl}} - pK_{\text{mercaptan}}) - 1 \quad \dots(10)$$

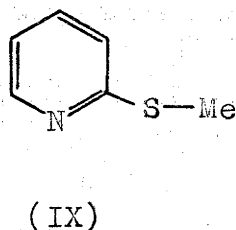
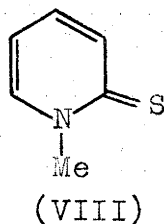
of these, equation (9) is by far the more serviceable. Equation (10) loses in accuracy because the differences are small in the present study and the error in the determination of the ionization constants becomes significant. The assumption in the derivation of (10) that the pK of the thione tautomer is equal to that of the N-methyl derivative is probably less justified than that involving the thiol tautomer and the S-methyl derivative.

Equation (9) (derived on the assumption that the

pK of the thiol tautomer is equal to that of its S-methyl derivative) was therefore selected to calculate the tautomeric ratios because the differences in pK used in the expression are considerable and do not suffer greatly from small inaccuracies of determination or of the assumption.

The equations derived above for 4-mercaptopyridine may be applied to the other mercapto - compounds studied. Possible exceptions are given below.

(1) When the mercapto - group is α to the ring-nitrogen, e.g. 2-mercaptopyridine, the methyl derivatives (VIII) and (IX) were examined.

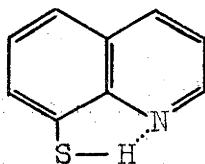


In (VIII) it is possible that steric hinderance by the methyl - group will effect the pK of the thione tautomer of the mercapto - compound. On the other hand it is most unlikely that steric hinderance in (IX) by the methyl - group will effect the pK of the thiol tautomer, which it is taken to represent.

Fortunately the exclusive use of the equation (9) in the present work means that the pK of the N-methyl derivative is not required for calculation of the tautomeric ratios.

(2) In one case however, that of 8-mercaptoquinoline, steric hindrance may be interfering. In (X) a naturally - existing hydrogen bond becomes impossible after methylation.

This could make the methylmercapto - compound a stronger base than the true thiol tautomer because hydrogen ions would have easier access to the methylmercapto - compound. Thus the tautomeric ratio of thione to thiol forms obtained from 8-mercaptoquinoline may be slightly too large.

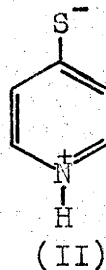
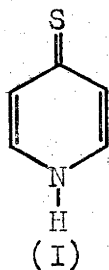


(X)

SECTION IV

DISCUSSION OF RESULTS.Ultraviolet Absorption Spectra.

Summary. A study of the ultraviolet absorption spectra of nitrogenous hetero-cyclic mercapto - compounds and their N- and S-methyl derivatives has given a clear demonstration that, in aqueous solution the tautomeric forms of the mercapto - compound with the mobile hydrogen atom on nitrogen are favoured over those with hydrogen on sulphur i.e., the thioamide form e.g. (I) or zwitterionic form e.g. (II) is preferred.



The ratio of NH tautomer to SH tautomer is even higher than the ratio of NH form to OH form found for the corresponding hydroxy - compound by Albert and Phillips (1956) and Mason (1957).

Ultraviolet absorption spectra have been obtained in aqueous solution for the neutral molecule and various ionic species of some mercapto - compounds (and their N- and S-methyl derivatives) of pyridine, quinoline, isoquinoline, pyrazine, quinoxaline and pyrimidine.

These spectra are given in Table 1 together with the pH of the aqueous solution in which the spectrum was determined. (The spectra were determined at least 2 pH units away from the relevant pK_a value (given in Table 2) unless the nearness of two pK 's made this impossible, in which case the isoelectric point was chosen).

The diaza - compounds (examples have been chosen with one ring-nitrogen atom α to the mercapto - group and the other α , δ or in a non-conjugated position) have been found to exist in the thioamide form with the mobile hydrogen favouring the nearer ring-nitrogen.

Table 1. Ultraviolet spectra of substances (in water at 20°). Values underlined refer to shoulders or inflexions.

No. Substance.	Neutral molecule or zwitterion			Proton gained (cation)			Proton lost (anion)			
	λ_{\max} (m μ)	log ϵ	pH	λ_{\max} (m μ)	log ϵ	pH ^a	λ_{\max} (m μ)	log ϵ	pH	
<u>PART 1 (ONE RING NITROGEN.)</u>										
2	2-Mercaptopyridine	273;345	4.03;3.87	4.7	238;302	3.79;3.94	-3.6	264;310	4.10;3.67	12.0
3	N-methyl	274;341	4.01;3.91	7.0	240;301	3.76;3.96	-3.6			
4	S-methyl	247;293	3.94;3.62	6.0	250;317	3.86;3.90	1.0			
5	3-Mercaptopyridine	232;290;362	4.15;4.09;3.37	5.1	221;255;310	4.06;3.89;3.50	0	219;269;313	3.99;4.13;3.41	10.0
6	N-methyl	236;294;369	4.12;4.07;3.34	7.0	224;258;314	4.07;3.86;3.45	0			
7	S-methyl	253;294	3.94;3.40	9.0	228;268;328	4.01;3.94;3.45	1.0			
8	4-Mercaptopyridine	231; <u>275</u> ;327	4.02; <u>3.12</u> ;4.34	4.7	223;282	3.90;4.23	-1.68	222;287	4.04;4.18	12.0
9	N-methyl	231; <u>275</u> ;333	3.89; <u>3.05</u> ;4.37	7.0	224;286	3.90;4.29	-0.90			
10	S-methyl	264	4.10	9.0	229;299	3.94;4.28	2.0			
12	2-Mercaptoquinoline	275;376	4.35;4.14	7.0	<u>240</u> ;261;342	<u>4.14</u> ;4.35;4.11	-2.5	266; <u>283</u> ;354	4.37; <u>4.03</u> ;3.94	12.0
13	N-methyl	274;371	4.38;4.14	7.0	237;260;338+ 345	4.06;4.39;4.13+ 4.13	-4.0			
14	S-methyl	257;338	4.36;3.82	7.0	240;266;353	4.07;4.20;4.15	0			

15	3-Mercaptoquinoline	224;264;289; <u>308</u> ;416	4.40;4.33;4.09; 3.89;3.54	4.21	241; <u>265</u> ;325; 357	4.56; <u>3.94</u> ;3.52; 3.62	-1.68	263;293;363	4.34;4.02;3.66	9.4
16	N-methyl	224;242;267; 292; <u>311</u> ;426	4.35;4.20;4.26; 4.03; <u>3.91</u> ;3.50	9.93	244; <u>270</u> ;324; 358	4.39; <u>3.80</u> ;3.61; 3.56	-0.13			
17	S-methyl	231;258; <u>290</u> ; 342	4.32;4.28; <u>3.72</u> ; 3.62	9.5	244+253; <u>280</u> ; 326;382	4.35+4.37; <u>3.94</u> ; 3.30;3.66	0			
18	4-Mercaptoquinoline	227; <u>240</u> ;264; 303+ <u>314</u> ;384	4.48; <u>4.13</u> ;3.84; 3.57+3.56;4.19	6.4	239;286;320+ 333	4.57;3.63;4.00+ 4.00	-1.20	225; <u>250</u> ;344	4.49; <u>4.05</u> ;4.04	13.
19	N-methyl	227; <u>240</u> ;268; 305+ <u>317</u> ;392	4.44; <u>4.07</u> ;3.85; 3.36+ <u>3.37</u> ;4.29	7.0	240;289;320+ 334	4.36;3.63;4.00+ 3.99	-2.01			
20	S-methyl	227;312	4.53;4.04	9.4	238; <u>250</u> ;347	4.52; <u>3.96</u> ;4.17	1.0			
21	5-Mercaptoquinoline	<u>254</u> ;278;322; 468	<u>4.07</u> ;4.27;3.23; 3.38	5.08	<u>238</u> ;259; <u>313</u> ; 323;373	<u>4.02</u> ;4.34; <u>3.44</u> ; 3.49;3.39	-1.68	260;374	4.34;3.65	13.
22	N-Methyl	<u>258</u> ;281;320; 466	<u>4.11</u> ;4.23;3.35; 3.53	7.0	<u>240</u> ;260; <u>312</u> ; 323;375	<u>3.97</u> ;4.23; <u>3.53</u> ; 3.60;3.47	1.0			
23	S-methyl	249; <u>314</u> ;320+ 332	4.24; <u>3.52</u> ;3.58+ 3.56	9.5	<u>244</u> ;266;316; 401	<u>3.96</u> ;4.29;3.03; 3.41	0			
24	6-Mercaptoquinoline	220;245;288; <u>322</u> ;430	4.30;4.18;4.26; <u>3.58</u> ;3.32	5.22	261;324;356	4.50;3.56;3.57	-1.68	<u>232</u> ;266; 299;368	<u>4.00</u> ;4.52; 3.85;3.65	13.

Table 1 (continued).

25	N-methyl	218;293; <u>330</u> ; 445	4.43;4.55; <u>3.64</u> ; 3.58	9.0	264;327;365	4.54;3.61;3.54	1.0			
26	S-methyl	254; <u>288</u> ;343	4.46; <u>3.66</u> ;3.57	9.4	272;382	4.47;3.61	0			
27	8-Mercaptoquinoline	254;280;323; 461	4.17;4.28;2.99; 3.24	5.0	242; <u>256</u> ; <u>313</u> ; 320; <u>340</u>	4.30; <u>4.08</u> ; <u>3.67</u> ; 3.72; <u>3.33</u>	-2.01	2.63;375	4.28;3.55	12.
28	S-methyl	251;337	4.34;3.62	9.5	242; <u>259</u> ; <u>312</u> ; 320; <u>350</u>	4.21; <u>4.13</u> ; <u>3.61</u> ; 3.65; <u>3.16</u>	0			
29	1-Mercaptoiso- quinoline	219; <u>232</u> ;261; 236;295;371	4.59; <u>4.01</u> ;3.68; <u>3.85</u> ;3.90;4.04	5.0	229;272; <u>284</u> ; 346;357	4.51;4.01; <u>3.81</u> ; 3.89;3.88	-4.20	<u>233</u> ;(250); 313;352	<u>3.88</u> ;(3.91); 3.77;3.89	13.0
30	N-methyl	222;263;295; 366	4.63;3.76;3.85; 4.02	7.0	233;271; <u>288</u> ; 347;360	4.53;3.94; <u>3.66</u> ; 3.80;3.82	-4.20			
31	S-methyl	<u>245</u> ;286+296; 330; <u>340</u>	<u>3.82</u> ;3.75+3.79; 3.79; <u>3.76</u>	9.0	225+230; <u>250</u> ; 278+283;343+ 361	4.46+4.44; <u>3.81</u> ; 4.02+3.94;3.93+ 3.98	-3.60			
32	3-Mercaptoiso- quinoline	260;313;415	4.44;4.24;3.47	4.0	245;284;356	4.42;3.58;3.61	-4.20	252;303;366	4.43;4.27; 3.22	12.0
33	S-methyl	246; <u>269</u> ;280+ 290;343	4.34; <u>3.89</u> ;3.97+ 3.91;3.25	9.4	233;252;285; 373	4.19;4.42;3.84; 3.53	1.0			

Table 1 (continued)

PART 2 (TWO RING NITROGENS)										
34	2-Mercaptopyrazine	227;279;382	3.53;4.09;3.82	3.48	260;291;448	<u>3.61</u> ;4.16;3.61	-2.95	226;270;344	3.72;4.05;3.70	9.2
35	N-methyl	222;279;375	3.56;4.07;3.81	7.0	<u>260</u> ;291;436	3.56;4.17;3.64	-2.95			
36	S-methyl	251; <u>300</u> ;322	3.89; <u>3.51</u> ;3.73	7.0	238;267;359	3.74;3.93;3.68	-2.35			
37	2-Mercapto- quinoxaline	280; <u>335</u> ;407	4.29; <u>3.40</u> ;4.07	4.3	291;370;488	4.39;5.33;3.88	-4.20	<u>250</u> ;275;386	<u>4.06</u> ;4.22;3.95	12.0
38	N(1)-methyl	273; <u>335</u> ;398	4.32; <u>3.47</u> ;4.08	7.0	289;365;472	4.40;3.43;3.91	-4.20			
39	S-methyl	241;265;361	4.19;4.16;3.94	7.5	256; <u>275</u> ;397	4.32; <u>3.96</u> ;3.93	-2.01			
40	2-Mercapto- pyrimidine ^c	278;346	4.33;3.42	4.9	208;285;378	3.37;4.51;3.18	0.0	231; <u>270</u>	3.69;4.23	13.0
41	N-methyl	279;344	4.26;3.45	9.0	283;378	4.34;3.14	-2.95			
42	S-methyl ^{cd}	250	4.12	6.98	214.5;255;310	3.39;4.16;3.54	0.0			
43	4-Mercapto- pyrimidine ^c	285;327	4.03;3.91	4.5	306	4.30	0.0	292-4	4.04	13.0
44	N(3)-methyl	287;322	4.03;3.91	7.15	304	4.23	-2.95			
45	N(1)-methyl	328	4.33	7.0	309	4.24	-2.01			
46	S-methyl	257;279	3.85;3.91	7.0	221;302	5.47;4.23	0.0			

Notes on Table 1.

- a. pH values below 0 have been obtained in solutions of sulphuric acid to which Hammett's acidity functions have been assigned.
- b. Spectrum of cation in agreement with that reported by Mangini and Passerini, Gazzetta, (1954), 54, 36.
- c. McOmie and Boarland, J. Chem. Soc., (1952), 3716.
- d. The basic pK_a of 4-methyl-2-methylmercaptopyrimidine given by Marshall and Walker J. Chem. Soc., (1951), 1004 is 1.95.

DEFINITION OF "SIMILAR"

In the following discussion of spectra, the term "similar" when used in comparing spectra implies that the spectra have the same number of absorption maxima and inflexions (a little variation of fine structure is permitted). The maximum tolerance allowed for the logarithm of the extinction coefficient is 0.20. The tolerances allowed for the wavelength (which are greater for the longer wavelengths to allow for the broader absorption regions) are shown below.

Wavelength μ	Tolerance μ
220 - 300	5
300 - 350	6
350 - 400	8
400 - 500	15

Monoaza-heterocyclic compounds.Neutral Molecules.

The ultraviolet absorption spectra are shown in Fig. 3 for the molecules of 3-mercaptopyridine and 3-methylmercaptopyridine (III, R = H) (at such pH values as to exclude any of the ionic species) together with 3-mercaptopyridine methochloride (V) adjusted in solution to a pH (see pK_a in Table 2) where it had lost the elements

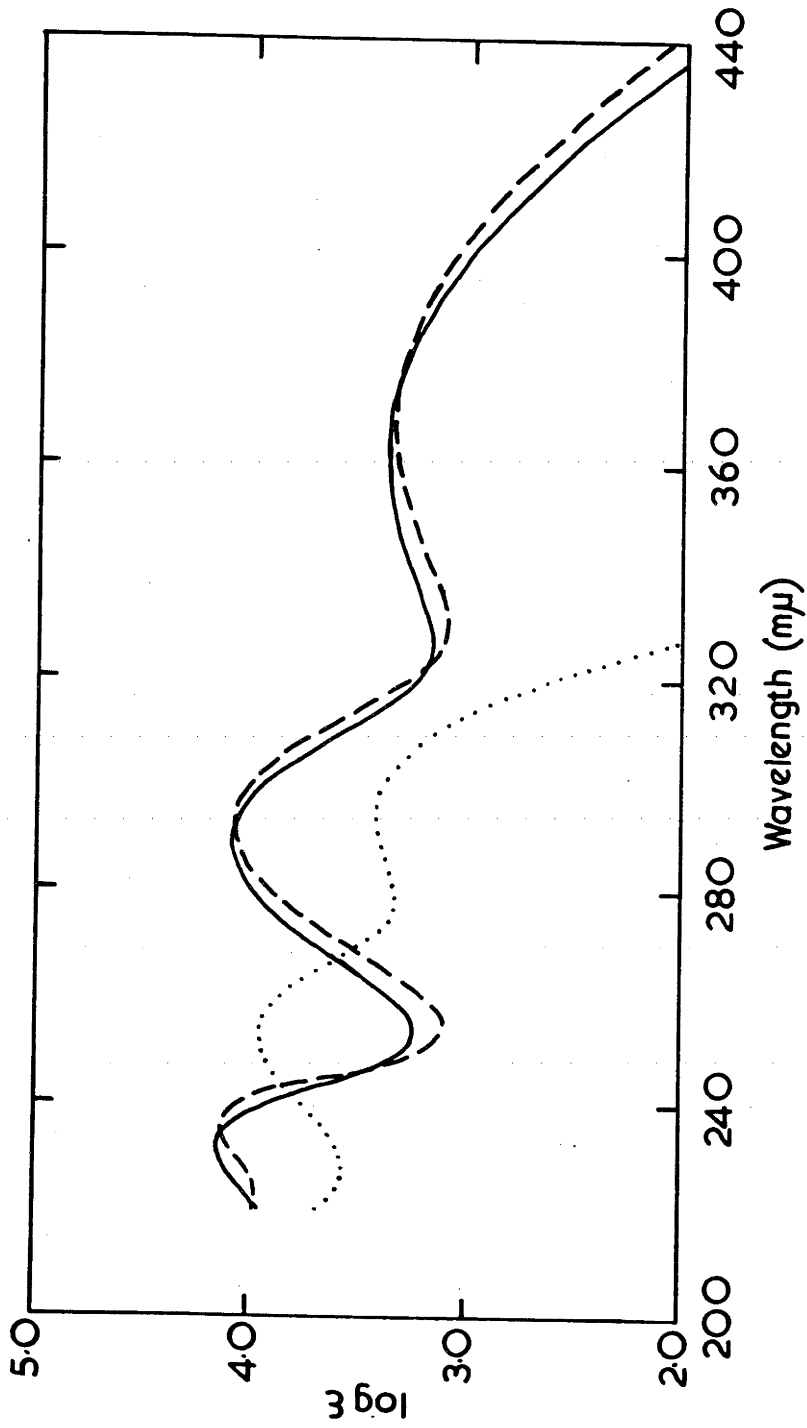
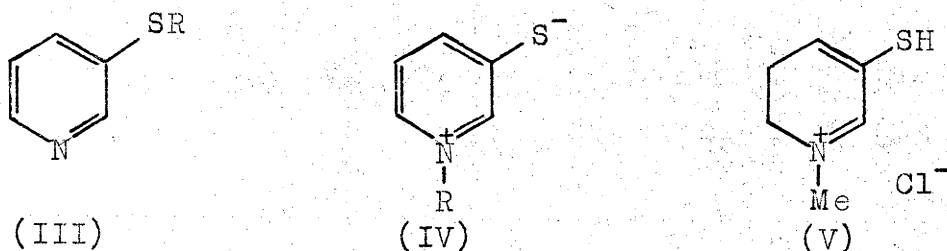


Fig.3. Neutral molecules of
— 3-mercaptopyridine
- - - N-methyl derivative
..... S-methyl derivative

of hydrogen chloride and was entirely the zwitterion (IV; R = Me). Fig. 3 shows quite clearly the similarity in the spectrum of 3-mercaptopyridine to that of its N-methyl derivative, and the difference from that of the S-methyl derivative.



The two tautomeric forms of 3-mercaptopyridine are (III, R = H) and (IV, R = H). It is evident from the above that of these, the zwitterion (IV, R = H) is preferred to the thiol (III, R = H) in aqueous solution. When the mercapto - group is α or γ to a ring-nitrogen atom, a third tautomeric form, the thioamide form (e.g. VI, R = H) is possible. It is evident that (VI, R = H) and (VIII, R = H) are likely to be canonical forms of a single resonance hybrid.

The spectra of the neutral molecules of 4-mercaptoquinoline and its N- and S-methyl derivatives are shown in Fig. 4. It can be seen that the spectrum of 4-mercaptoquinoline is similar to that of the N-methyl derivative (1-methylquinol-4-thione; (VI, R = Me)). Even the smallest characteristics of the spectrum of the N-methyl derivative are retraced in the spectrum of the mercapto - compound, although, there are small variations in the wavelengths of

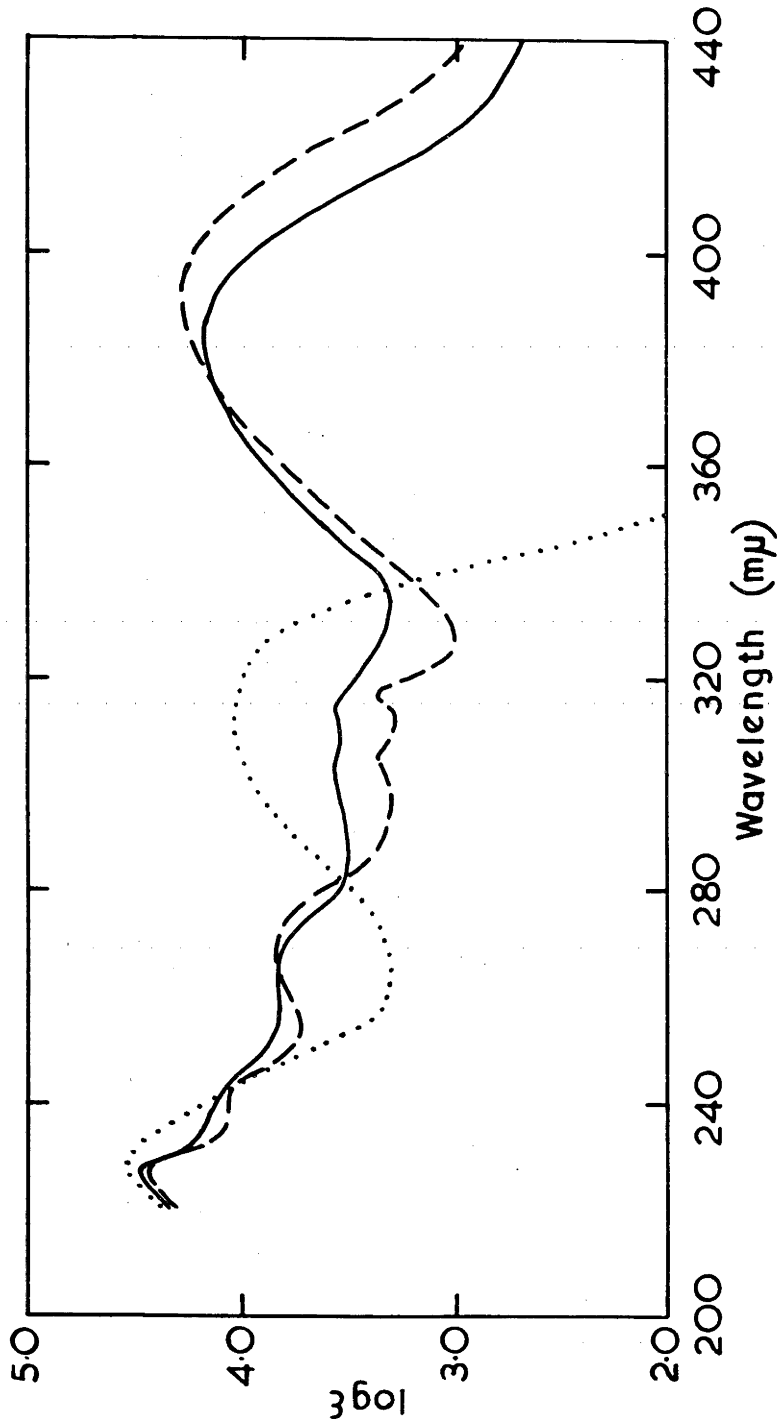
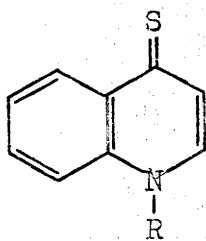
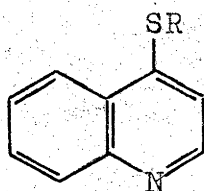


Fig.4. Neutral molecules of
— 4-mercaptoquinoline
- - - N-methyl derivative
..... S-methyl derivative

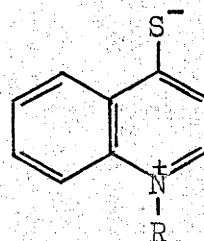
the absorption maxima. The spectrum of 4-mercaptoquinoline is quite different from that of the S-methyl derivative (VII, R = Me), the long - wavelength absorption band of the latter being at considerably shorter wavelengths than in the mercapto-compound.



(VI)



(VII)



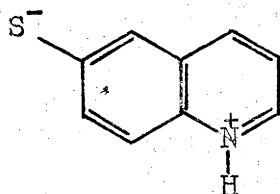
(VIII)

It is evident from this spectroscopic evidence that 4-mercaptoquinoline exists in aqueous solution predominately with the mobile hydrogen atom on the ring-nitrogen rather than on the sulphur.

Examining the situation more broadly it may be seen from the ultraviolet absorption spectra given in Table 1 Part 1 (for monoaza-heterocyclic compounds) that, for a particular mercapto - compound X, the spectra of the molecule of the mercapto - compound and the N-methyl derivative are similar. On the other hand, the spectra of the molecules of the mercapto- compound and the S-methyl derivative are quite different, in that the long wavelength absorption band of the S-methyl derivative lies at

X Although the spectra of 6-mercaptoquinoline and its N-methyl derivative are not "similar" by the above somewhat rigorous definition, they agree quite closely.

considerably shorter wavelengths (range 38-136 m μ) than that of the mercapto-compound. These relationships hold irrespective of the position of the mercapto - group. The two examples discussed above are therefore typical of the whole series. Even in 6-mercaptoquinoline where considerable spatial separation of charge is required in the zwitterion (IX) and where the spectral agreement is not good, the mobile hydrogen atom still favours the ring-nitrogen.



(IX)

In two cases, 8-mercaptoquinoline and 3-mercaptoisoquinoline the N-methyl derivative is unknown but, at least the usual difference between the spectra of the mercapto - compound and the S-methyl derivative was observed. These results contrast with those for hydroxy - compounds which have been determined by Mason (1957). He found that tautomerism of hydroxy-quinolines and -isoquinolines with the hydroxyl - group α or γ to the ring-nitrogen atom favours the NH tautomer, but when the hydroxyl - group is neither α nor γ to the ring-nitrogen, the OH tautomer is preferred. Metzler and Snell (1955) have also shown by ultraviolet spectroscopy that 3-hydroxypyridine exists equally as the enol and zwitterionic forms in neutral aqueous solution.

The present observations X show that isolated previous observations are part of a general pattern.

For example:

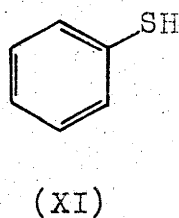
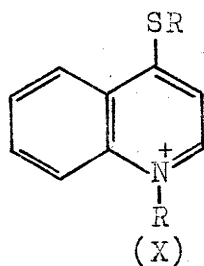
- (1) Acheson, Burstall, Jefford, and Sanson (1954) compared the ultraviolet absorption spectra of 5-mercaptoacridine and its N- and S-methyl derivatives in methanol and found a close resemblance between spectra of the mercapto - compound and the N-methyl derivative but no resemblance to that of the S-methyl derivative.
- (2) Morton and Stubbs (1939) found that the ultraviolet absorption spectra of 4-methyl-2-mercaptoquinoline and its S-methyl derivative in alcoholic solution are quite different.

X After the results reported here had been obtained and, in part, published (Albert and Barlin, 1958); Jones and Katritzky (1958) published some results on the tautomerism of 2- and 4-mercaptopyridine in aqueous solution. They compared the ionization constants and ultraviolet absorption spectra of the mercapto - compound with its N-methyl and S-benzyl derivatives and arrived at the same conclusions as found in the present study.

Examination of the ultraviolet absorption spectra of the molecule of the mercapto - compound given in Table 1 Part 1 shows that the mercapto - compounds with the mercapto - group β to the ring-nitrogen or in the adjoining benzene ring invariably absorb at a longer wavelength than those in which the mercapto - group is α or γ to the ring-nitrogen atom. It seems likely that the first group of compounds absorb at longer wavelengths due to the preponderance of the zwitterionic form e.g. (II). On the other hand, the mercapto - compounds with the mercapto - group α or γ to the ring-nitrogen, have structures modified by (or even predominately) the thioamide component of the resonance hybrid and the absorption at shorter wavelengths is most likely to be an expression of this difference in electronic distribution.

It can also be seen from Table 1 Part 1 that the spectrum of 8-mercaptoquinoline at long - wavelengths is almost identical with that of the 5-isomer.

Cations. Fig. 5 shows the ultraviolet absorption spectra of the cations of 4-mercaptoquinoline and its N- and S-methyl derivatives. All three compounds should give a cation e.g. (X) with similar spectra.



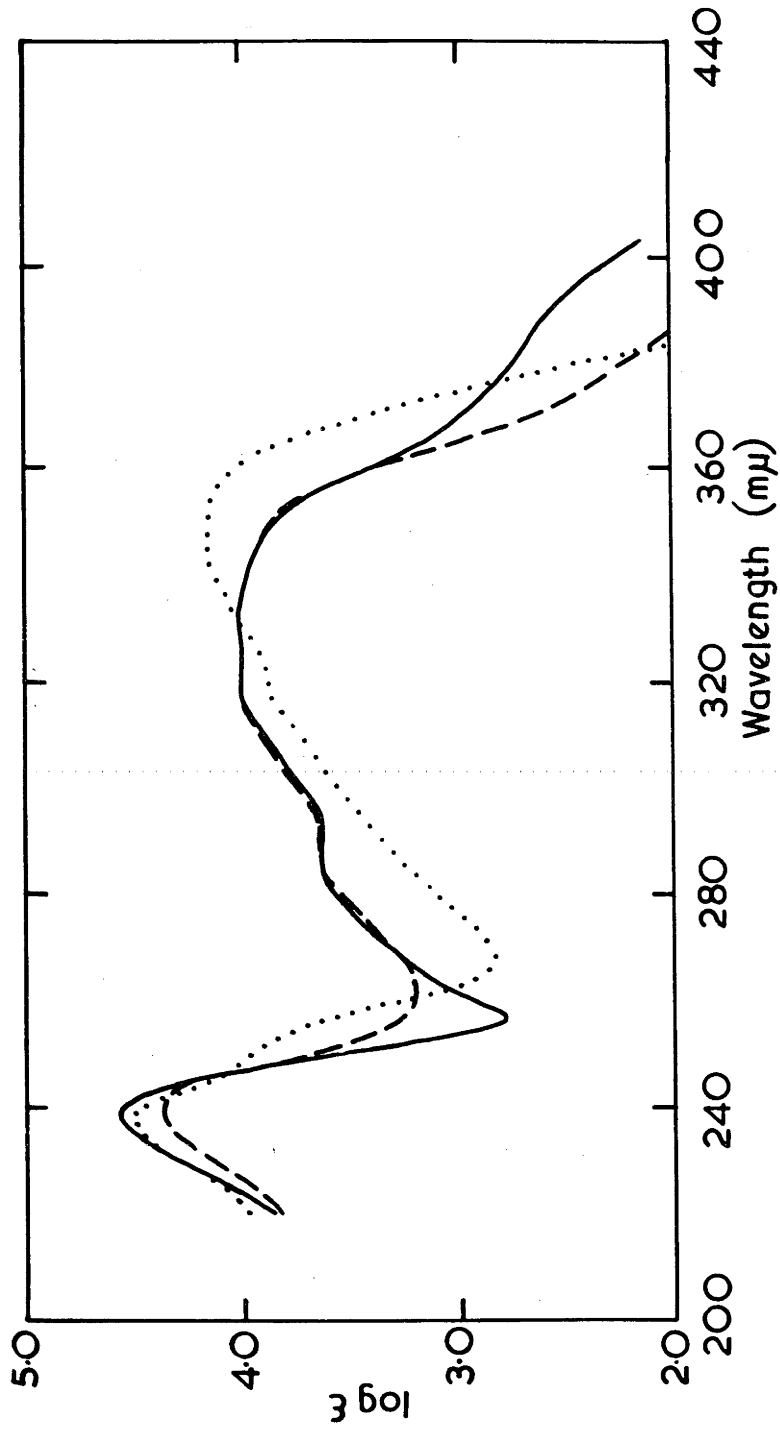


Fig.5. Cations of
—— 4-mercaptoquinoline
- - - N-methyl derivative
..... S-methyl derivative

It is seen from Fig. 5 that the spectra of the cations of 4-mercaptoquinoline and its N-methyl derivative are "similar" but the spectra of the mercapto - compound and the S-methyl derivative are not "similar" (as rigidly defined on p. 74). The long - wavelength absorption maximum exceeds the limits of similarity by 8 m μ but it may well be that S-methylation is more bathochromic in a cation than in a neutral molecule (see p.52 for the effect of S-methylation on the spectrum of mercaptobenzene).

Inspection of Table 1 Part 1 shows the similarity of the spectra of the cations of the mercapto - compound and the N-methyl derivative and the difference of the spectra of the cation of the mercapto - compound and the S-methyl derivative. *

It is also seen from Table 1 Part 1 that the long - wavelength absorption band of the molecule of the mercapto - compound and its N-methyl derivative recede to shorter wavelengths on conversion into the cation, however, when the molecule of the S-methyl derivative is converted into

* The differences are sometimes small e.g. the cations of 1-mercaptoisoquinoline and its S-methyl derivative; and the spectra of the cations of 8-mercaptoquinoline and its S-methyl derivative are "similar" (as defined on p. 74).

the cation, the long - wavelength absorption band undergoes a bathochromic shift to longer wavelengths (e.g. the absorption peak of 2-mercaptopyridine at 345 m μ . shifts to 302 m μ , and the absorption peak of 1-methylpyrid-2-thione at 341 m μ . shifts to 301 m μ , but the absorption peak of 2-methylmercaptopyridine at 293 m μ . shifts to 317 m μ , on conversion of the molecule into the cation). This clearly demonstrates the similar structures of the mercapto - compound and the N-methyl derivative.

The marked hypsochromic shift shown by the mercapto - compounds when converted from the molecule into the cation or anion has also been noted by Hannan, Lieblich, and Renfrew (1949) with substituted 2- and 4-mercaptoquinolines*. The authors also noted the bathochromic shift shown by the S-alkyl derivatives on passing from the molecule to cation.

Anions. Examination of Table 1 Part 1 shows that conversion of the molecule of the mercapto - compound into the anion moves the long - wavelength absorption peak of the molecule to shorter wavelengths (as is also the case for the cation, see above). The spectra of the molecule of 4-methylmercaptoquinoline and the anion of 4-mercaptoquinoline are shown in Fig. 6. The hypsochromic shift

* A similar observation was made by Tucker and Irvin (1951) for 4-hydroxyquinoline and its N- and O-methyl derivatives. (see Albert and Phillips (1956) for pK values).

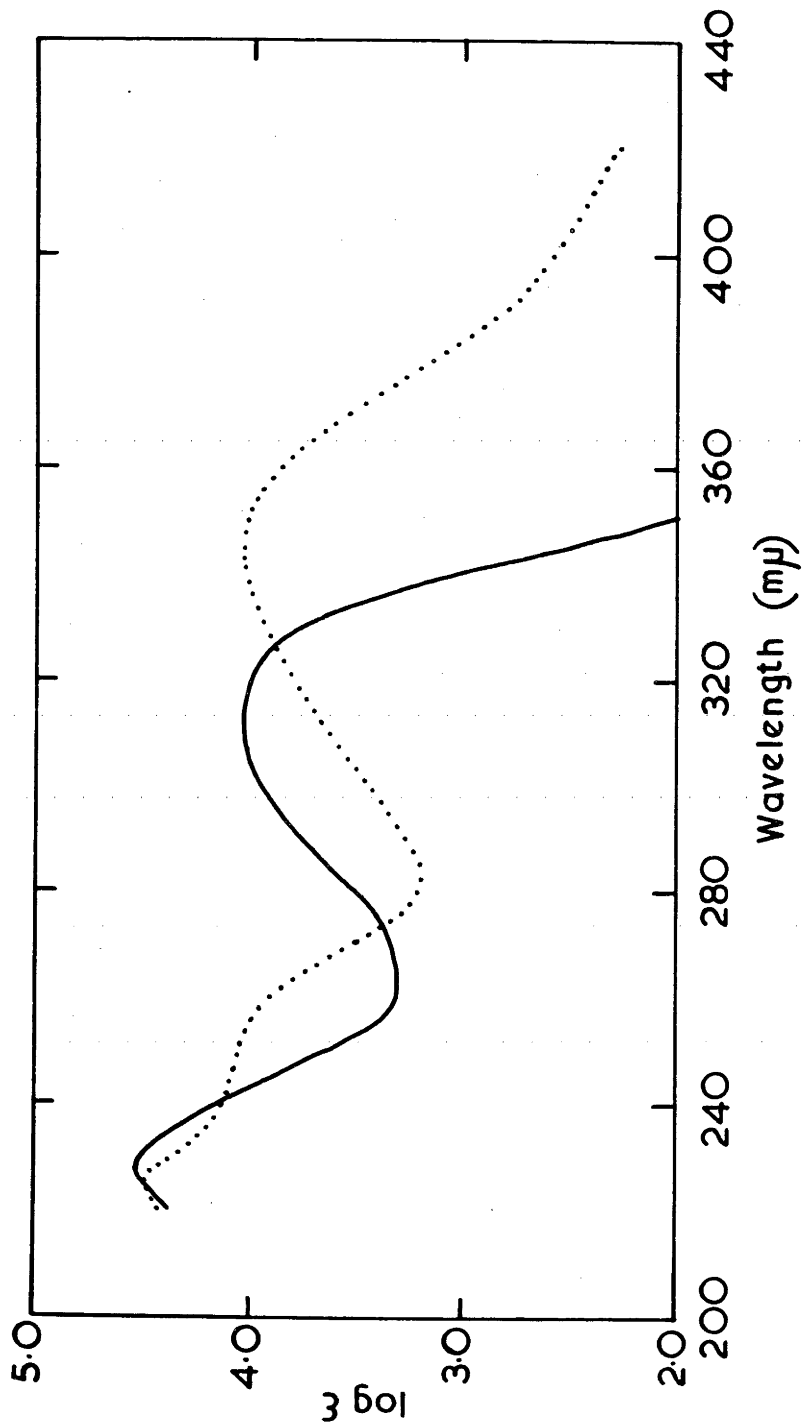


Fig. 6. — Neutral molecule of 4-mercaptoquinoline
..... Anion of 4-mercaptoquinoline

observed on conversion of a molecule to the anion (e.g. 40 μ for the long - wavelength absorption band of 4-mercaptoquinoline) is not as great as observed on conversion of a molecule into the cation (e.g. 51 μ for the long - wavelength absorption band of 4-mercaptoquinoline). It has been found that the spectrum of mercaptobenzene (XI, which cannot exist in a thione form) undergoes a bathochromic shift on conversion of the molecule into the anion and the spectra are shown in Fig. 1 X. Hence the contrast between mercaptobenzene and the heterocyclic mercapto - compounds is additional evidence against a thiol structure for the neutral molecule of the heterocyclic - compound.

The spectra of an anion and the corresponding cation are quite different[†].

X Similar bathochromic shifts were observed by Doub and Vandenbelt (1947) when phenol is converted to its anion.

† Jones and Katritzky (1958) incorrectly report analogous spectra for the anion and cation of both 2- and 4-mercaptopyridine and conclude that both species have similar π -electron distributions.

Diaza - heterocyclic compounds.

Neutral molecules. The ultraviolet absorption spectra of the neutral molecules of some diaza - heterocyclic mercapto - compounds and their N- and S-methyl derivatives are presented in Table 1 Part 2. It can be seen in each case that there is a very close resemblance between the spectra of the mercapto - compound and a N- methyl derivative and a difference from that of its S-methyl derivative. This clearly indicates the thione structure of the mercapto - compound. The long - wavelength absorption band of the S-methyl derivative is invariably at a shorter wavelength than that of either the mercapto - compound or its N-methyl derivative(s).

In diaza - heterocyclic mercapto - compounds, the mobile hydrogen atom may occupy one of two alternative positions on ring-nitrogen atoms.

In 2-mercaptopyrimidine both positions are identical but in 4-mercaptopyrimidine (XIV; R = H) they are not. The spectra of 4-mercaptopyrimidine and its N- and S-methyl derivatives are shown in Fig. 7. The spectrum of the molecule reported by McOmie and Boarland (1952) is similar to that of 1-methylpyrimid-6-thione (XII; R=H) but different to that of 1-methylpyrimid-4-thione (XIII; R = H) and 4-methylmercaptopyrimidine (XIV; R = Me).

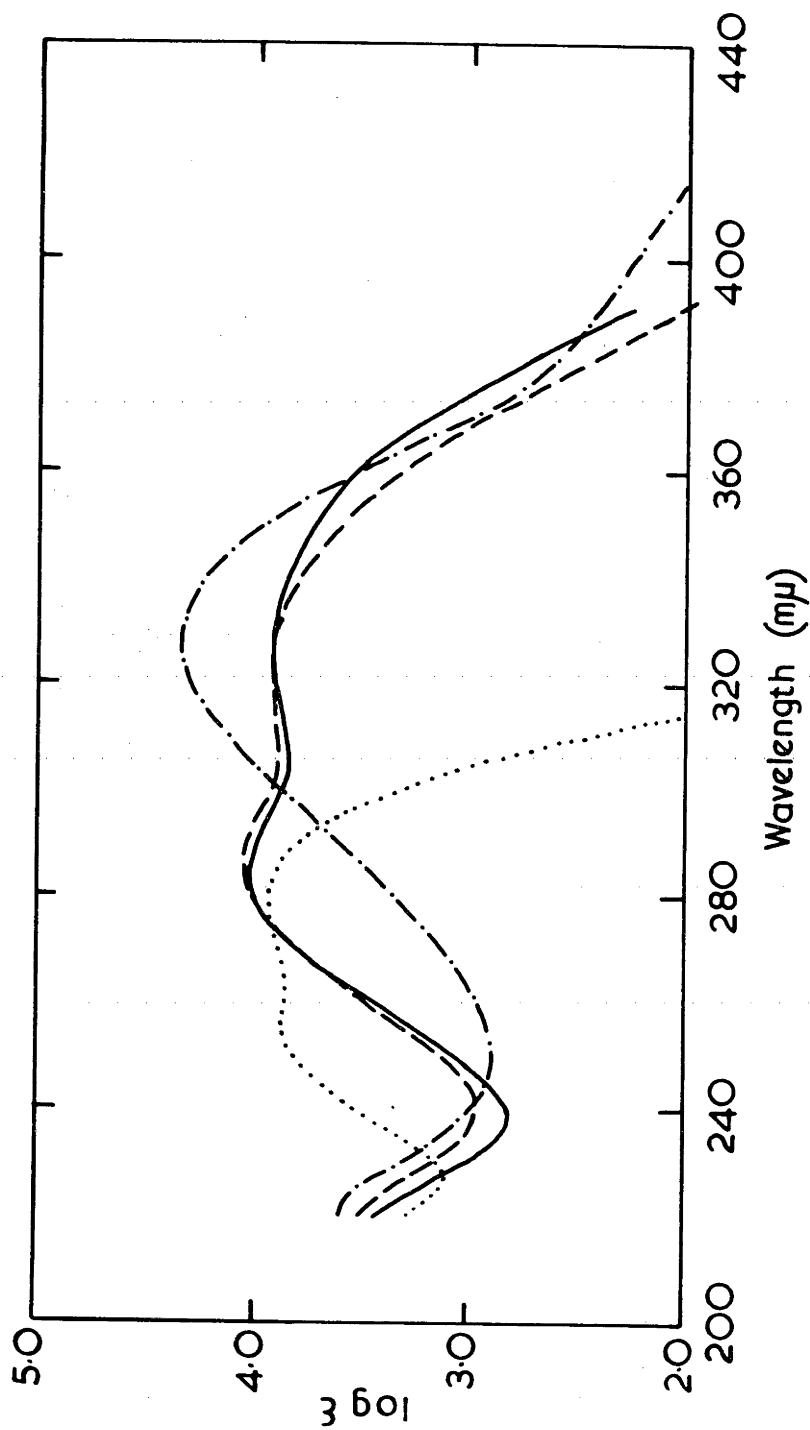
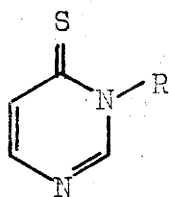


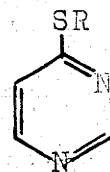
Fig.7. Neutral molecules of
— 4-mercaptopyrimidine
- - - l-methylpyrimid-6-thione
- · - · l-methylpyrimid-4-thione
..... 4-methylmercaptopyrimidine



(XII)



(XIII)

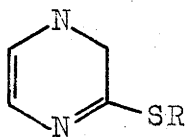


(XIV)

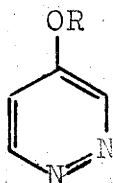
This clearly indicates that the structure (XII, R = H), with the mobile hydrogen atom on the nearer ring-nitrogen, is preferred. It is interesting that Brown, Hoerger, and Mason (1955) found this is also the preferred orientation in the hydroxy-analogue, 4-hydroxypyrimidine. Examination of the spectra of 2-mercaptopyrazine (XV, R=H) and its N(1)- and S-methyl derivatives clearly indicates the similarity in structure of the mercapto - compound and the N(1)-methyl derivative, but these are quite different from the S-methyl derivative.

The N(4)-methylpyrazine derivative was not prepared for the following reasons.

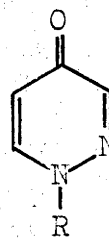
(1) Mason (1957) has found that in diaza - compounds with one ring-nitrogen atom either α or δ to the hydroxyl - group and the other in a non - conjugated position e.g. (XVI, R = H), the structure with the hydrogen on the conjugated nitrogen is favoured. This is understandable from the extra resonance energy available to the zwitterion with the proton on N(1), through the amide structure (XVII, R = H). The zwitterion however with



(XV)



(XVI)



(XVII)

the proton on N(4) enjoys no such resonance.

(2) The similarity of the spectra of the N(1)-methyl derivative to that of the mercapto - compound.

Cations. The ultraviolet absorption spectra of the cations of some diaza - heterocyclic mercapto - compounds and their N- and S-methyl derivatives are presented in Table 1 Part 2. As observed with monoaza -heterocyclic mercapto - compounds, the spectra of the cations of the mercapto - compound and its N-methyl derivatives are similar ~~X~~ and are generally quite different from that of the S-methyl derivative. Excluding 4-mercaptopyrimidine and its S-methyl derivative, the differences between the long - wavelength absorption maxima of the cations of the mercapto - compounds and its S-methyl derivative are from 68 to 91 μ , with the absorption maxima of the S-methyl derivatives at the shorter wavelengths. Hence it appears

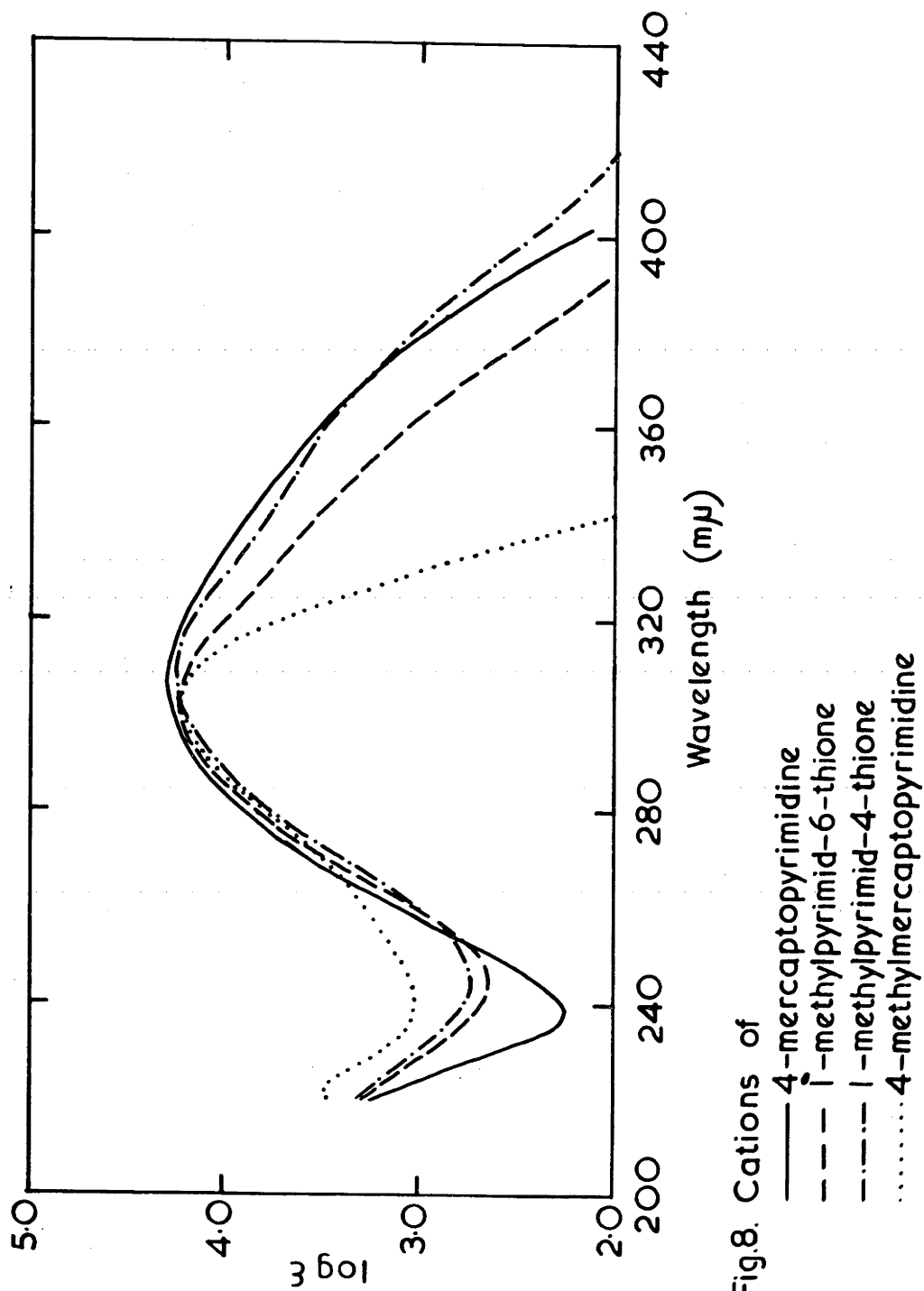
~~X~~ The difference in wavelength of the long - wavelength absorption maxima of the cations of 1-mercaptoquinoxaline and 1-methylquinoxal-2-thione exceed the limits of "similar" as defined on p. 74 by 1 μ .

unlikely that a common cation is produced by the mercapto - compound and its N- and S-methyl derivatives.

In contrast to the monoaza - compounds discussed above, conversion of the molecule of the mercapto - compound of diaza - heterocyclic compounds or their N-methyl derivatives into the cations produced a bathochromic shift of the long - wavelength absorption band, e.g. 2-mercaptopyrazine and its N-methyl derivative (excepting 4-mercaptopyridine and its N-methyl derivatives). The long - wavelength absorption band of the S-methyl derivatives as with the monoaza - heterocyclic compounds, undergoes a bathochromic shift on changing from molecule into cation. *

The spectra of the cations of 4-mercaptopyrimidine (XIV, R = H) and its N- and S-methyl derivatives are shown in Fig. 8. The agreement between the spectra of the mercapto - compound and both N-methyl derivatives (XII and XIII, R = Me) is particularly close but they are also similar to that of the S-methyl derivative (XIV, R=Me). The agreement between the spectra of both N-methyl derivatives and the mercapto - compound is probably consequent on the formation of similar chromophore systems on the addition of the proton. This has been

* Parallel observations were made by Marshall and Walker (1951) for some C-methyl derivatives of 2-mercaptopyrimidine and its N- and S-methyl derivatives.



postulated for 4-hydroxypyrimidine and its N-methyl derivatives by Brown, Hoerger, and Mason (1955).

Similarity to the S-methyl derivative may be fortuitous.

The long - wavelength absorption band of 4-mercaptopyrimidine \times and both N-methyl derivatives moves to shorter wavelengths on conversion of the molecule into the cation; that of the S-methyl derivative moves to longer - wavelengths as observed for the other S-methyl derivatives of heterocyclic mercapto - compounds.

Anions. The ultraviolet absorption spectra of the anions of some diaza - heterocyclic mercapto - compounds are presented in Table 1 Part 2 and the spectra of the anion of 4-mercaptoquinoline and the molecule of 4-methyl-mercaptoquinoline are shown in Fig. 6. As in the case of monoaza - heterocyclic mercapto - compounds, it can be seen that the long - wavelength absorption band of the anions is at a shorter wavelength than that of the molecule and that the spectra of the anion of the mercapto - compound and the molecule of the S-methyl derivative are quite different. It is clear from a study of the mono - substituted derivatives (see Fig. 6) that a

\times Parallel observations were made by Marshall and Walker (1951) with 6-methyl-4-mercaptopyrimidine and its S-methyl derivative.

comparison of the spectra of the S-methyl derivative with that of the anion of the mercapto - compound cannot be used to substantiate or eliminate the possibility of a thiol structure e.g. Shugar and Fox (1952) have attempted to resolve the structure of 2-thiouracil and have included this comparison.

Ionization Constants.

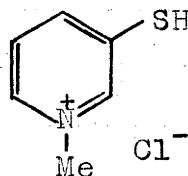
The pK'_a values, representing protons gained by the neutral molecule.

Monoaza - heterocyclic compounds. The ionization constants of the compounds examined are expressed as pK'_a values in Table 2 Part 1. Potentiometric and spectrophotometric methods were employed in the determinations and the experimental details are given in Section V.

For determination of the ionization constant by potentiometric titration, the substances in the form of neutral molecules, e.g. (XVIII, R = H or Me) were submitted to conditions of increasing acidity, but when the substance was in the form of a salt e.g. methochloride (XIX), it was submitted to decreasing acidity.



(XVIII)



(XIX)

The effect of different ionic strengths on the pK'_a value determined by potentiometric titration was also examined. For 4-methylmercaptopyridine it was found (see "Experimental", Section V) that in solutions of potassium chloride from 0 to 3 molar, the pK'_a value as determined by potentiometric titration rose from 5.98 to 6.48.

Table 2.

Ionization of Substances (in water at 20°).

No.	Substance	Proton gained			Proton lost			Analytical wavelength ^e m μ
		pK' _a	Spread ^a (\pm)	Concn. ^a (M)	pK _a	Spread ^a (\pm)	Concn. ^a (M)	
<u>PART 1 (ONE RING NITROGEN).</u>								
1	Pyridine	5.23 ^b						
2	2-Mercapto	-1.07	0.06	0.0001	9.97	0.03	0.01	345 (pK' _a)
3	N-methyl	-1.22	0.09	0.0001				341
4	S-methyl	3.62	0.02	0.01				
5	3-Mercapto	2.28	0.04	0.005	7.01	0.03	0.005	
6	N-methyl	2.27	0.06	0.005				
7	S-methyl	4.45	0.04	0.01				
8	4-Mercapto	1.43	0.07	0.000025	8.83	0.02	0.01	327 (pK' _a)
9	N-methyl	1.30 ^d	0.04	0.05				
10	S-methyl	5.97	0.04	0.01				
11	Quinoline	4.93 ^c						

Table 2 (continued)

12	2-Mercapto	-1.44	0.09	0.0001	10.21	0.04	0.0001	405(pK_a) and (pK'_a)
13	N-methyl	-1.6	0.1	0.0000125				385
14	S-methyl	3.71	0.05	0.00005				360
15	3-Mercapto	2.33	0.05	0.000025	6.13	0.03	0.000025	362 (pK_a) and 241 (pK'_a)
16	N-methyl	2.40	0.07	0.000025				426
17	S-methyl	3.88	0.03	0.000025				382
18	4-Mercapto	0.77	0.05	0.000025	8.83	0.02	0.000025	384(pK_a) and (pK'_a)
19	N-methyl	0.56	0.09	0.000025				392
20	S-methyl	5.31	0.03	0.000025				349
21	5-Mercapto	3.31	0.04	0.000025	6.48	0.07	0.000025	374(pK_a) and (pK'_a)
22	N-methyl	3.22	0.06	0.000025				466
23	S-methyl	4.50	0.03	0.000025				266
24	6-Mercapto	3.95	0.06	0.000025	6.5	0.1	0.000025	367(pK_a) 262(pK'_a)

Table 2 (continued)

25	N-methyl	4.12	0.03	0.000025				446
26	S-methyl	4.75	0.05	0.000025				272
27	8-Mercapto	2.05	0.04	0.000025	8.29	0.03	0.000025	280(pK _a) and (pK' _a)
28	S-methyl	3.50	0.01	0.000025				251
29	<u>iso</u> Quinoline	5.46 ^c						
30	1-Mercapto	-1.9	0.13	0.000025	10.82	0.04	0.000025	380(pK _a) and (pK' _a)
31	N-methyl	-2.13	0.08	0.000025				380
32	S-methyl	3.93	0.02	0.000025				362
33	3-Mercapto	0.39	0.06	0.000025	8.58	0.04	0.000025	416(pK _a) and (pK' _a)
34	S-methyl	3.41	0.04	0.000025				374
<u>PART 2 (TWO RING NITROGENS)</u>								
	Pyrazine	0.6 ^b						
35	2-Mercapto	-0.73	0.1	0.000025	6.32	0.03	0.005	382(pK' _a)
36	N-methyl	-0.45	0.1	0.000025				437

Table 2 (continued)

p. 99

37	S-methyl Quinoxaline	0.48 0.56 ^c	0.06	0.000025		359
38	2-Mercapto	-1.11 ^f			7.72 ^g	
39	N(1)-methyl					
40	S-methyl Pyrimidine	0.26 ^f 1.30 ^b				
41	2-Mercapto	1.3 ^h			7.2 ^h	
42	N-methyl	1.66	0.02	0.000025		344
43	S-methyl					
44	4-Mercapto	1 ^{hj}			6.7 ^h	
45	N(3)-methyl	0.56	0.08	0.000025		304
46	N(1)-methyl	1.16	0.01	0.000025		330
47	S-methyl	2.48	0.02	0.05		

Notes for Table 2.

- a. These results are given only for new determinations.
- b. Albert, Goldacre, and Phillips, J. Chem. Soc., (1948), 2240.
- c. Albert and Phillips J. Chem. Soc., (1956), 1294.
- d. Thermodynamic.
- e. An entry in this column means that the determination was spectroscopic (otherwise potentiometric).
- f. Cheeseman, J. Chem. Soc., (1958), 108.
- g. Determined in 50% ethanol by Cheeseman, J. Chem. Soc., (1958), 108.
- h. Boarland and McOmie, J. Chem. Soc., (1952), 3716.
- j. The basic pK_a of 6-methyl-4-mercaptopyrimidine given by Marshall and Walker, J. Chem. Soc., (1951), 1004 is 1.8.

Although the pK'_a as determined by potentiometric titration is effected by ionic strength, the small variations which would be encountered in the present study are not considered significant. Low pK'_a values correspond to weak bases.

It is seen from Table 2 Part 1 that the pK'_a values of each mercapto - compound and its N-methyl derivative are very near, and quite different, from that of its S-methyl derivative. The pK'_a values of the N- and S-methyl derivatives are more widely separated when the mercapto - group is α or δ to the ring-nitrogen atom; and closer together when a thioamide form is not possible (mercapto - group attached to the pyridine nucleus), or is in an adjacent benzene ring.

The results substantiate what has already been shown above with ultraviolet spectra, i.e. that the tautomeric equilibrium in the mercapto - compounds favours forms which have the mobile hydrogen atom on the ring-nitrogen.

Comparison of the results given in Table 2 Part 1 with those given by Albert and Phillips (1956) and Mason (1957) for the corresponding hydroxy - compounds shows that the mercapto - compounds are from 0.7 to 3.0 pK units weaker as bases than their hydroxy - analogues. The two series preserve much the same order of basic strength, the 1-isoquinoline derivative being the weakest base in each, followed by the 2-quinoline and 2-pyridine

derivatives. The N-methyl derivatives of the mercapto - and hydroxy - series also differ within similar limits. On the other hand the S- and the O-methyl derivatives differ by very little (e.g. the pK'_a range for: pK'_a O-methyl - pK'_a S-methyl is -0.34 to 0.88). This last observation accords with the knowledge that the inductive effects of the methylmercapto - and methoxy - groups are similar and the mesomeric effects are not greatly different in the benzene series e.g. Bordwell and Cooper (1952) and Hall and Sprinkle (1932) give the following pK'_a values; aniline (4.58); m-methylmercaptoaniline (4.05), m-methoxyaniline (4.20); p-methylmercaptoaniline (4.40) and p-methoxyaniline (5.29).

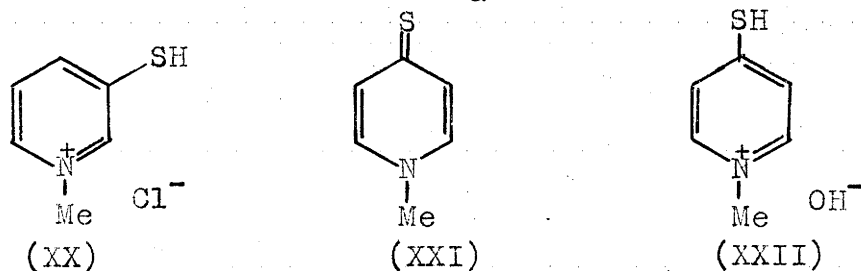
Figures are not available to compare the inductive effect of a mercapto - and an hydroxy - group on an aromatic base but the picture would be complicated by zwitterion formation.

In the methylmercaptopyridines, we have the opposing influences of the mesomeric electron release and the inductive electron withdrawal. In the 3-position only the inductive effect can operate and this is slightly base weakening, hence we find that 3-methylmercaptopyridine is only a slightly weaker base than pyridine.

However in the 2-and 4-positions the base weakening inductive effect is modified, by the base strengthening mesomeric effect. The pK'_a values of pyridine, and

2- and 4-methylmercaptopyridine are 5.23, 3.62 and 5.97 respectively. Hence the base strengthening mesomeric effect overcomes the base weakening inductive effect in the 4-position; but in the 2-position the inductive effect is more important. The above reasoning also applies to 2-, 3-, and 4-methylmercaptoquinoline.

The early work of Bredig (1894) indicated that quaternary compounds are strong bases; but this is not general for heteroaromatic bases e.g. the quaternary compound of 10-methylacridine has pK'_a 9.85 (given by Albert (1950)). In the present work the quaternary compounds e.g. (XX, or XXI which is XXII minus the elements of water) have been shown to be even weaker bases and may have negative pK'_a values.

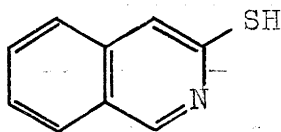


On the existing evidence, no explanation can be offered for the weakness of bases of the N-methyl derivatives relative to the S-methyl derivatives.

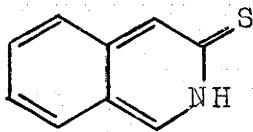
The mercapto - compounds with the mercapto - group α or γ to the ring-nitrogen atom (excepting 3-mercapto-isoquinoline) have pK'_a values from 4.5 to 5.8 pK units

below that of the S-methyl derivative. When the mercapto - group is β to the ring-nitrogen or in the benzene ring of quinoline, the pK'_a values are from 0.8 to 2.2 pK units below that of the S-methyl derivative. The pK'_a values of the mercapto - compound, irrespective of the position of the mercapto - group, have been found to vary only ± 0.2 pK units from that of the N-methyl derivative. In two cases that of the N-methyl derivative of 3- and 6-mercaptoquinoline, are the N-methyl derivatives stronger bases than the mercapto - compound but they are only very slightly so.

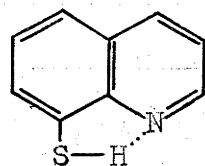
In 3-mercaptoisquinoline (XXIII) neither six-membered ring can have a true aromatic structure when the mercapto - compound is in the thione form (XXIV) and the pK'_a difference between the mercapto - compound and the S-methyl derivative (3.0 pK units) lies between the corresponding difference for the 2- and 3-isomers of quinoline (5.15 and 1.55 pK units respectively).



(XXIII)



(XXIV)



(XXV)

In 2-mercaptoquinoline the aromatic structure of the benzene ring is retained with the thione structure but in 3-mercaptoquinoline, the thione structure is not possible.

8-Mercaptoquinoline (XXV) is a weaker base than the 5-or 6-isomer. This is believed to be due to internal hydrogen bonding, making it a weaker base, in so far as the ring-nitrogen is not freely accessible to approach by the proton.

Diaza - heterocyclic compounds. Comparison of the ionization constants, expressed as pK'_a values (all the values are not known) for the compounds shown in Table 2 Part 2 shows that, as for monoaza-heterocyclic compounds the pK'_a value of the mercapto - compound is near to that of the N-methyl derivative which it has been shown to resemble spectroscopically but different from that of the S-methyl derivative.

In 2-mercapto-pyrazine and quinoxaline the pK'_a values of the N(1)-methyl derivatives are higher than that of the mercapto - compound.

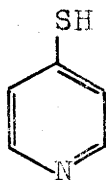
Comparison of the pK'_a values available with those given by Albert and Phillips (1956) for their oxygen-analogues show that the pK'_a values for the O-methyl derivative do not vary greatly from those found for the S-methyl derivatives. A similar observation was made with the monoaza -heterocyclic compounds (see p.102) and is attributed to the similar inductive and mesomeric effects of the O-methyl and S-methyl groups. The pK'_a values of the mercapto - compound and its N-methyl derivative are from 0.3 to 1.2 pK units lower than their

oxygen-analogues. This difference is not as great as with the monoaza - heterocyclic compounds but are similar to those found for diaza - heterocyclic mercapto - compounds by Marshall and Walker (1951).

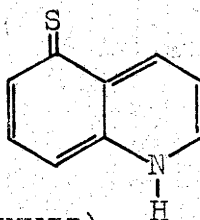
The effect of the introduction of the second ring-nitrogen atom is to decrease the basic strength of the S-methyl derivative e.g. the pK'_a values of 2-methylmercapto - pyridine and pyrazine and 4-methylmercaptopyrimidine are 3.62, 0.48 and 2.48 respectively and that of 2-methylmercapto-quinoline and quinoxaline are 3.71 and 0.26 respectively. This is the usual effect of introducing a second ring-nitrogen atom (see Albert, Goldacre, and Phillips (1948)).

The pK_a values representing protons lost by the neutral molecules.

Monoaza - heterocyclic compounds. The ionization constants of the heterocyclic mercapto - compounds as acids, expressed as pK_a values are given in Table 2 Part 1. Low pK_a values correspond to strong acids. Potentiometric and spectrophotometric methods were employed. For potentiometric titration, the substances as the neutral molecule e.g. (XXVI) were submitted to conditions of decreasing acidity.



(XXVI)



(XXVII)

It can be seen from Table 2 Part 1 that the pK_a values of the compounds in which the mercapto - group is α or γ to the ring-nitrogen atom are considerably higher i.e. are weaker acids, than those where it is not. This is due to the stabilization of the α - or γ -mercapto - compound by resonance and hence making them weaker acids. The resultant of the inductive and mesomeric effects of the mercapto - group are such that the α -mercapto - compounds are weaker acids than their γ -isomers e.g. the pK_a values of 2- and 4-mercapto-pyridine and quinoline as acids are 9.97, 8.83; 10.21 and 8.83 respectively. In 8-mercaptoquinoline (XXV) internal hydrogen bonding is also possible and it is a weaker acid than 5- or 6-mercaptoquinoline.

6-Mercaptoquinoline is an example in which the mercapto - group is in a position where it is least disturbed by inductive or mesomeric effects (only the 3-, 6- and 8-isomers can, from considerations of valency have no thioamide component). The acidic pK_a value of 5-mercaptoquinoline resembles that of the 6-isomer and suggest that the thioamide form (XXVII) does not stabilize the 5-isomer to any extent, although valency would permit it. This is in keeping with what is known (see Albert (1959), Brown and Mason (1956) and Mason (1957)) of the feeble energy available for transannular tautomerism, especially when the orthoquinonoid form

would be involved.

Comparison of the pK_a values of the mercapto - compounds and their hydroxy - analogues given by Albert and Phillips (1956) shows that as acids, the mercapto - compounds are from 1.5 to 2.4 pK units stronger than their hydroxy - analogues. The pK_a of mercaptobenzene has now been determined spectroscopically in water and found to be 6.7 ± 0.1 and may be compared with 9.98 for phenol given by Bordwell and Cooper (1952). In each case substitution of oxygen by sulphur results in acid strengthening.

In 3-mercaptoisoquinoline, resonance stabilization of the thione structure (XXIV) will not be as great as in the 1-isomer and hence 3-mercaptoisoquinoline is a stronger acid than 1-mercaptoisoquinoline.

Diaza - heterocyclic compounds. The ionization constants of some diaza - heterocyclic mercapto - compounds as acids, expressed as pK_a values are given in Table 2 Part 2.

It can be seen on comparison with the pK_a values given by Albert and Phillips (1956) for the hydroxy - analogues that the strength of the mercapto - compounds, as acids, are from 1.9 to 2.5 pK units stronger than their hydroxy-analogues. Similar observations have been made by Marshall and Walker (1951). This is

similar to the findings for monoaza - heterocyclic mercapto - compounds and mercaptobenzene.

From Table 2 it can be seen that the effect of introducing a second ring-nitrogen atom in the 4-position of a α -mercapto - compound or in the 3-position of a α or δ mercapto - compound is to increase acidity e.g. the pK_a of 2-mercaptopyrazine is 6.32 and of 2-mercaptopyridine is 9.97. The increase was from 2.1 to 3.7 pK units in the compounds examined. Similar observations were made by Albert and Phillips (1956) with heterocyclic hydroxy - compounds.

Tautomeric RatiosMonoaza - heterocyclic compounds.

The tautomeric ratio \bar{X} (K_t), the ratio of the NH form to the SH form, at equilibrium in an aqueous solution of the monoaza - heterocyclic mercapto - compound may be calculated by the equation:

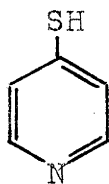
$$K_t = \text{antilog} (\text{pK}_{\text{S-methyl}} - \text{pK}_{\text{mercaptan}}) - 1 \dots (9)$$

where $\text{pK}_{\text{S-methyl}}$ is the basic pK of the S-methyl derivative and $\text{pK}_{\text{mercaptan}}$ is the basic pK of the mercapto - compound.

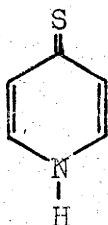
The derivation of this equation is given in Section III, "Qualitative and Quantitative Methods of Evaluation of Tautomerism". This approach assumes that the basic ionization constant of the thiol tautomer of the mercapto - compound although not directly determinable, will be practically identical with that of its S-methyl derivative and that the NH and SH tautomers e.g.

\bar{X} The tautomeric ratio has not been calculated from the ultraviolet absorption spectra as used by Mason (1957) for the determination of the tautomeric ratio in N-heteroaromatic hydroxy - compounds, because the method is suitable only when the ratio is of the order of unity.

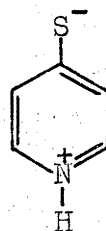
(XXVIII \longleftrightarrow XXIX, and XXVII), form a common cation e.g. (XXX).



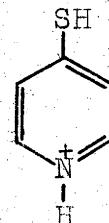
(XXVII)



(XXVIII)



(XXIX)



(XXX)

Ideally the basic pK_a value of the mercapto - compound should lie between those of its N- and S-methyl derivatives, however, in two cases the basic pK_a value of the mercapto - compound lies slightly below that of the N-methyl derivative, viz, in 3- and 6-mercaptoquinoline.

The tautomeric ratio of the NH form to the SH form for monoaza - heterocyclic mercapto - compounds in aqueous solution are given in Table 3 together with the ratio for the corresponding hydroxy - compound as determined by Albert and Phillips (1956) and Mason (1957).

Examination of Table 3 shows that the tautomeric ratio, the ratio of the NH form to the SH form, is quite high in all cases. Even in 6-mercaptoquinoline, where no thioamide form e.g. (XXXI) is possible and the NH tautomer must exist as the zwitterion (XXXII), the tautomeric ratio (K_t) is 5.

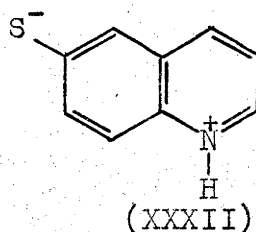
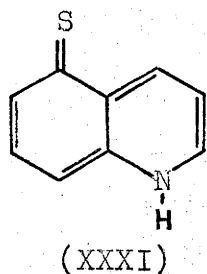
Table 3. Approximate ratios of forms having a hydrogen atom on nitrogen to those having hydrogen on sulphur (neutral molecules at equilibrium in water at 20°).

Pyridine			
2-Mercapto	49,000	2-Hydroxy	340 ^a
3-Mercapto	150	3-Hydroxy	1 ^{a,b}
4-Mercapto	35,000	4-Hydroxy	2,200 ^a
Quinoline			
2-Mercapto	140,000	2-Hydroxy	3,000 ^a
3-Mercapto	34	3-Hydroxy	0.06 ^b
4-Mercapto	110,000	4-Hydroxy	24,000 ^a
5-Mercapto	15	5-Hydroxy	0.05 ^b
6-Mercapto	5	6-Hydroxy	0.01 ^b
8-Mercapto	27	8-Hydroxy	0.04 ^b
<u>iso</u> Quinoline			
1-Mercapto	680,000	1-Hydroxy	18,000 ^a
3-Mercapto	1,000		

Notes to Table 3.

a. Albert and Phillips, J. Chem. Soc., (1956), 1294

b. Mason, J. Chem. Soc., (1957), 5010, which uses a spectroscopic method more suited to low values.



In 5-mercaptoquinoline, where the thioamide form (XXXI) is possible, the tautomeric ratio is not greatly affected but is higher than in the 6-isomer. This accords with the conclusions of Albert (1959), Brown, and Mason (1956), and Mason (1957) that energy available for transannular tautomerism is small, especially when an ortho-quinonoid form is involved.

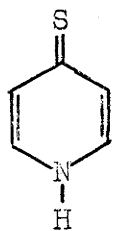
In 8-mercaptoquinoline, where the thioamide form is not possible (as for the 6-isomer), the tautomeric ratio is higher than for the 6-isomer. This effect may be accounted for by internal hydrogen bonding which has made 8-mercaptoquinoline a weaker base than would be expected if hydrogen bonding was not possible (see p. 66). Such bonding would make the tautomeric ratio, calculated from the pK'_a values of the mercapto - compound and its S-methyl derivative higher than otherwise expected.

When the mercapto - group is α or δ to the ring-nitrogen atom, the thioamide form (XXXIII) becomes an important contributor to the resonance hybrid and the NH form is further stabilized. It can be seen from

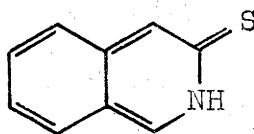
Table 3 that in these cases the ratio of NH form to SH form is very high indeed, being greatest in the case of 1-mercaptoisoquinoline.

It can also be seen from Table 3 that the tautomeric ratio is higher for the α -mercapto - compounds of pyridine and quinoline than it is for the δ -isomers.

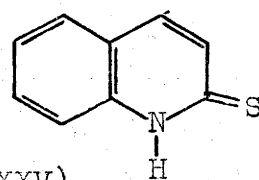
3-Mercaptoisoquinoline is a special case. Although the mercapto - group is α to the ring-nitrogen atom and a thioamide form is possible, the benzenoid structure of the benzene ring is replaced by an ortho-quinonoid structure in the thioamide form. Gore and Phillips (1949) present some evidence that the resonance of an orthoquinonoid ring in heteroaromatic chemistry is much less than that of a benzene ring.



(XXXIII)



(XXXIV)



(XXXV)

From Table 3 it is seen that the tautomeric ratio for 3-mercaptoisoquinoline is greater than that for 3-mercaptoquinoline for which a thioamide form is not possible, but considerably less than that of 2-mercaptoquinoline in which the benzenoid structure is not replaced in the thione form (XXXV).

It can also be seen from Table 3 that the addition

of a fused benzene ring in the 5:6 position of pyridine increases \times the tautomeric ratios of the α and γ -mercapto- compounds (the benzene ring extends the conjugation) but decreases the tautomeric ratio of the β -mercapto - compound where a thioamide form is not possible.

Practical experience in the handling of the substances under discussion indicates that compounds with high tautomeric ratios are quite stable but those with low tautomeric ratios are usually more or less easily oxidised in air.

Comparison of the tautomeric ratios of the mercapto - compounds with those of their hydroxy - analogues obtained by Albert and Phillips (1956) and Mason (1957) and given in Table 3 shows that the tautomeric ratio is much higher for mercapto - compounds than for their hydroxy - analogues.

\times Mason (1957) has shown with transannular heterocyclic hydroxy - compounds that the addition of a fused benzene ring, when it can conjugate with an amide form, enhances the value of the tautomeric ratio.

These results contrast with what has been predicted from methylation studies e.g. heterocyclic mercapto - compounds, ^{generally} methylate rapidly and exclusively on sulphur but heterocyclic hydroxy - compounds methylate much more slowly, usually on the ring-nitrogen atom. However, reaction rates are notoriously unreliable guides to tautomeric ratios, the tautomer present in smaller amount may be the more reactive and, as it is consumed in a reaction, it is regenerated by the tautomeric process.

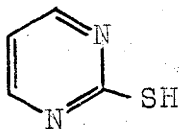
Some examples of the widely held (but mistaken) view that heterocyclic mercapto - compounds are in the SH form (on the grounds that they methylate on the sulphur atom) are afforded by (a) Campaigne, Cline, and Kaslow (1950) who considered the methylation (by King and Ware (1939)) of 4-mercaptopyridine with methyl iodide to give 4-methylmercaptopyridine indicated that 4-mercaptopyridine existed entirely as the thiol and (b) Gleu and Schaarschmidt (1939) who found similarly that mercapto-acridines gave exclusively the S-alkyl derivative upon alkylation and concluded that they exist principally in the thiol form.

The results obtained above for heterocyclic mercapto - compounds contrast with the results obtained by Albert and Phillips (1956) and Mason (1957) for their hydroxy - analogues. Albert and Phillips, and Mason found that generally when the hydroxy - group is

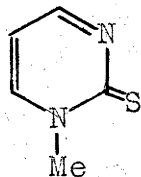
neither α or γ to the ring-nitrogen atom, or is in an adjoining benzene ring, the OH form was the predominant tautomer. In α - and γ -hydroxy - compounds where the NH form predominates, the tautomeric ratio for the γ - was much higher than for the α -hydroxy - compounds.

Diaza - heterocyclic compounds.

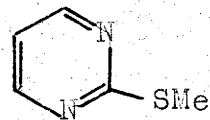
The calculation of the tautomeric ratio has not been extended to the diaza - heterocyclic mercapto - compounds under study because the experimental evidence makes it seem unlikely that a common cation is produced from the mercapto - compound e.g. (XXXVI), and its N- and S-methyl derivatives e.g. (XXXVII and XXXVIII respectively) (see page 90). With the exception of 4-mercaptopyrimidine and its S-methyl derivative, very considerable differences are observed in the ultraviolet absorption spectra given in Table 1 Part 2 for the cations of the diaza-heterocyclic mercapto - compounds and their S-methyl derivatives.



(XXXVI)



(XXXVII)



(XXXVIII)

In the monoaza - heterocyclic mercapto - compounds examined, differences of 4 to 28 $m\mu$ (average 18 $m\mu$) are observed in the long - wavelength absorption maxima of

the cations of the mercapto - compound and its S-methyl derivative and this is believed to be due to a special bathochromic effect of methylation on sulphur in a cation (see p. 83).

In the diaza - heterocyclic mercapto - compounds the difference is from 68 to 91 $m\mu$ (excluding 4-mercaptopyrimidine and its S-methyl derivative), and the long - wavelength absorption maxima of the S-methyl derivative lies at the shorter wavelength. Hence it appears unlikely that a common cation is produced.

Even in 4-mercaptopyrimidine and its S-methyl derivative the agreement may be fortuitous .

In spite of this lack of a basis for quantitative assessment, it is clear (from qualitative considerations of the ionization constants and ultraviolet absorption spectra) that for the diaza - heterocyclic mercapto - compounds examined, the NH form predominates over the SH form in aqueous solution.

SECTION V.EXPERIMENTAL.

Microanalyses were kindly carried out by Dr. J.E. Fildes and her Staff in the Department of Medical Chemistry, Australian National University, Canberra, and by Dr. K.W. Zimmermann and his Staff in the C.S.I.R.O. Microanalytical Laboratory, Melbourne.

All melting points recorded below were taken in soda-glass capillaries and are uncorrected.

Compounds were also examined for both fluorescing and absorbing impurities by paper chromatography using Whatman No. 1 paper. Both (a) 3% aqueous ammonium chloride and (b) n-butanol (7 volumes) + 5N-acetic acid (3 volumes) were used as solvents. The paper chromatograms were examined under ultraviolet light at two wavelengths, (a) with a mercury vapour lamp and Wood's glass filter (principally 365 m μ), and (b) with a mercury resonance lamp and Chance Brothers' OX7/19874 filter (principally 254 m μ). The last named combination proved particularly useful for impurities which absorb ultraviolet light, and which were seen as dark spots against the fluorescence of the paper.

Solid compounds for analysis were dried at 100°/0.1 mm., unless otherwise indicated.

All new compounds are underlined at their first mention in the body of the text. (As in the Journal of the Chemical Society, names which are paragraph headings

are also underlined but this does not indicate that the compound is new).

PYRIDINES.

2-Mercaptopyridine was prepared from 2-bromopyridine and thiourea as described by Phillips and Shapiro (1942) and had m.p. 130-132.5°. (Found: C, 54.5; H, 4.45; S, 29.1. Calculated for C₅H₅NS: C, 54.0; H, 4.5; S, 28.8%). (Phillips and Shapiro give m.p. 125°; Thirtle (1946) gives m.p. 128°; and Jones and Katritzky (1958) give m.p. 124-126°).

2-Methylmercaptopyridine. Methylation of 2-mercaptopyridine with methyl iodide and sodium hydroxide as described by Renault (1955) gave 2-methylmercaptopyridine, b.p. 100-104°/33 mm. (Renault reports b.p. 91°/22 mm.). Paper chromatography in aqueous ammonium chloride and butanol+acetic acid revealed no trace of the N-methyl isomer.

1-Methylpyrid-2-thione was prepared from 1-methylpyrid-2-one and phosphorus pentasulphide at 125-130° according to Renault (1953). The product melted at 90°. (Renault gives m.p. 89-90°).

Pyridine-3-sulphonic acid was prepared by sulphonating pyridine with fuming sulphuric acid (20% free SO₃) at 220° in the presence of mercuric sulphate according to McElvain and Goese (1943). The product had m.p. 343-346° (McElvain and Goese give m.p. 352-356°).

Pyridine-3-sulphonyl chloride was obtained by the action of phosphorus pentachloride on pyridine-3-sulphonic acid according to Zienty (1948).

Reduction of pyridine-3-sulphonyl chloride to 3-mercaptopyridine was effected with stannous chloride and hydrochloric acid as described by Steiger (1950) (1951). The 3-mercaptopyridine (= R) separated from the reaction mixture as the double salt $R.HCl.SnCl_4$ in 64% yield.

3-Benzoylmercaptopyridine. The above double salt (10g.) was ground with water, decomposed with sodium hydroxide, the solution heated to boiling and filtered. The cooled filtrate was shaken with benzoyl chloride (10 ml.), and the oil which separated soon solidified. It was collected and recrystallised from light petroleum (b.p. 60-80°) giving 3-benzoylmercaptopyridine as colourless needles (3.66g., 69%), m.p. 78.5-80.5°. (Found, for material dried at 55°/0.05 mm. : C, 66.9; H, 4.2. $C_{12}H_9ONS$ requires C, 66.95; H, 4.2%).

3-Mercaptopyridine. 3-Benzoylmercaptopyridine (1g.) was refluxed with 6N-hydrochloric acid (10 ml.) in an atmosphere of carbon dioxide for 1 hour. The benzoic acid (0.53g.; 93%) was extracted with chloroform and the cold aqueous solution adjusted to pH 4.4. The solution was again extracted with chloroform, the extract dried (Na_2SO_4) and the solvent evaporated giving 3-mercaptopyridine (0.45g.; 87%) as a yellow oil, which solidified on cooling

and recrystallised from a mixture of benzene and light petroleum (b.p. 60-80°) as bright yellow crystals, m.p. 81°. (Wuest and Sakel (1951) give m.p. 78-80°).

3-Methylmercaptopyridine. 3-Mercaptopyridine (2.5g. crude; 0.023 mole) in N-sodium hydroxide (24 ml.) was shaken with methyl iodide (1.5 ml.; 0.024 mole) for 2 hours. The alkaline solution was extracted with chloroform and after drying (Na_2SO_4) the solvent was evaporated. The 3-methylmercaptopyridine distilled as a colourless oil (1.71g.; 61%), b.p. 102°/17 mm. (Found: C, 57.6; H, 5.7; N, 10.9. $\text{C}_6\text{H}_7\text{NS}$ requires C, 57.6; H, 5.6; N, 11.2%). Paper chromatography in aqueous ammonium chloride and butanol+acetic acid revealed no trace of the N-methyl-analogue (see below).

3-Methylmercaptopyridine hydrochloride.

10N-Hydrochloric acid was added to 3-methylmercaptopyridine in alcohol and the solution evaporated to dryness under reduced pressure. The residue was recrystallised from an ethanol and benzene mixture giving 3-methylmercaptopyridine hydrochloride as a colourless solid, m.p. 156.5-158.5° which was depressed on admixture with 3-mercaptopyridine methochloride (see below). (Found: Cl, 21.7, 22.1. $\text{C}_6\text{H}_6\text{NClS}$ requires Cl, 21.9%).

3-Benzoylmercaptopyridine methiodide. 3-Benzoylmercaptopyridine (5.0g.; 0.023 mole) in methanol (30 ml.) was allowed to stand at ca. 20° with methyl iodide (2.5 ml.;



0.04 mole) for 2 days). The solvent was evaporated and the residue recrystallised from ethanol giving yellow 3-benzoylmercaptopyridine methiodide (4.95g.; 60%), m.p. 163°. (Found: C, 43.4; H, 3.3; N, 3.9, 4.0; S, 9.0. $C_{13}H_{12}ONIS$ requires C, 43.7; H, 3.4; N, 3.9; S, 9.0%).

3-Mercaptopyridine methochloride. 3-Benzoylmercaptopyridine methiodide (1g.) was refluxed with 6N-hydrochloric acid (10 ml.) in an atmosphere of carbon dioxide for 1 hour. After the benzoic acid (0.28g.; 80%) had been extracted with ether, the aqueous solution was shaken with freshly precipitated silver chloride (ca. 0.6g.) for 30 minutes. The solution was evaporated to dryness in a vacuum and the residue extracted with ethanol. Removal of the solvent gave 3-mercaptopyridine methochloride (0.27g.; 60%) which recrystallised from a mixture of ethanol and ethyl acetate; it had m.p. 182-183.5°. (Found: C, 44.5; H, 4.9; Cl, 22.2. C_6H_6NClS requires C, 44.6; H, 5.0; Cl, 21.9%). The m.p. of 3-methylmercaptopyridine hydrochloride was depressed on admixture with the above sample. Paper chromatography in aqueous ammonium chloride and butanol+acetic acid revealed considerable differences in R_F between these two isomers.

4-Hydroxypyridine was prepared as described by Bowden and Green (1954). Pyridine reacted with thionyl chloride to give 4-pyridylpyridinium dichloride which was hydrolysed to 4-hydroxypyridine, b.p. 194-206°/0.5 mm. (Riegel and

Reinhard (1926) give b.p. 257-260°/10 mm.).

4-Mercaptopyridine. 4-Hydroxypyridine reacted with phosphorus pentasulphide at 120° as described by King and Ware (1939) giving 4-mercaptopyridine, m.p. 179-189° (decomp). (Found: C, 54.0; H, 4.6. Calculated for C₅H₅NS: C, 54.0; H, 4.5%). Recorded m.p.'s. vary from 177° (Koenigs and Kinne (1921)) to 186° (King and Ware).

4-Methylmercaptopyridine. Methylation of 4-mercaptopyridine with methyl iodide as described by King and Ware (1939) gave 4-methylmercaptopyridine, m.p. 47°. (King and Ware recorded m.p. 44-45°). Paper chromatography in aqueous ammonium chloride and butanol+acetic acid revealed no trace of the N-methyl isomer.

1-Methylpyrid-4-one. 4-Hydroxypyridine was methylated with methyl iodide in methanol at 140° as described by Ruzicka and Fornasir (1920) to produce the hygroscopic 1-methylpyrid-4-one, b.p. 153-156°/0.05 mm. (Tschitschibabin and Ossetrowa (1925) give b.p. 230-233°/13 mm.).

1-Methylpyrid-4-thione. A mixture of 1-methylpyrid-4-one (3.72g.; 0.034 mole) and phosphorus pentasulphide (7.4g.; 0.033 mole) in a flask fitted with a short air condenser and drying tube was heated to 110°. A vigorous reaction ensued. The mixture was heated at 125° for 1 hour, cooled, and water (15 ml.) was added to decompose excess phosphorus pentasulphide. The solution was neutralised to pH 7, extracted with chloroform, the extract dried (K₂CO₃) and the solvent evaporated giving

orange 1-methylpyrid-4-thione (2.62g.; 61%), which was recrystallised from ethanol and had m.p. 168.5-170°.

(Found: C, 57.5; H, 5.5; N, 11.2, 11.3; S, 25.7. C_6H_7NS requires C, 57.6; H, 5.6; N, 11.2; S, 25.6%). (During the course of the present work, this substance was prepared by Jones and Katritzky (1958) who recorded m.p. 161-163°).

QUINOLINES.

2-Mercaptoquinoline. A mixture of 2-hydroxyquinoline (5g.; 0.035 mole) and phosphorus pentasulphide (8.53g.; 0.038 mole) in pyridine (51 ml.) was refluxed for 2 hours. The mixture was poured into hot water (330 ml.) with stirring, and the crude product (5.41g.) recrystallised from benzene as yellow plates (2.56g.; 46%), m.p. 178-179.5° (Fischer (1899) gives m.p. 175°).

Di-2-quinolyl disulphide was prepared by the oxidation of 2-mercaptoquinoline in aqueous ethanol with dilute hydrogen peroxide as described by Roos (1888.). The product had m.p. 139°. (Roos gives m.p. 137°).

Reduction of di-2-quinolyl disulphide to 2-mercaptoquinoline. Di-2-quinolyl disulphide (0.21g.) was suspended in a mixture of methanol (4 ml.) and pyridine (4 ml.) and hydrazine hydrate (1 ml; 100%) was added. The mixture allowed to stand and the disulphide slowly dissolved. After 30 minutes at 20°, a mixture of acetic acid (3 ml.) and water (13 ml.) was added and the almost pure mercapto-compound (0.07g.) m.p. 179°, was filtered off.

2-Methylmercaptoquinoline was prepared by the action of dimethyl sulphate on 2-mercaptoquinoline as described by Beilenson and Hamer (1939). The product, recrystallised from light petroleum (b.p. 60-80°), had m.p. 59°. (Beilenson and Hamer give m.p. 55°). Paper chromatography in aqueous ammonium chloride and butanol+acetic acid revealed no trace of the N-methyl isomer.

1-Methylquinol-2-one. Quinoline was converted to 1-methylquinol-2-one by the action of dimethyl sulphate and potassium ferricyanide according to Perkin and Robinson (1913). The product, once recrystallised from light petroleum (b.p. 60-100°), had m.p. 73°. (Perkin and Robinson give m.p. 74°).

1-Methylquinol-2-thione. Reaction of 1-methylquinol-2-one with phosphorus pentasulphide at 130° as described by Gutbier (1900) gave 1-methylquinol-2-thione, m.p. 115°. (Gutbier gives m.p. 118°).

3-Benzoylmercaptoquinoline. 3-Aminoquinoline (30g.; 0.21 mole) was added slowly to a well cooled, well stirred mixture of 10N-hydrochloric acid (42 ml.) and ice (42g.). A solution of sodium nitrite (15.3g.) in water (36 ml.) was then added during 15 minutes, keeping the temperature below 5°. The diazotized solution was added during 30 minutes to a well stirred solution of potassium ethyl xanthate (42g.; 0.26 mole; Cranendonk (1951)) in water (51 ml) at 45° and the mixture maintained at this temperature for

1 hour, during which time nitrogen was evolved, and the yellow solid which formed initially changed to a thick red oil. The reaction mixture was extracted with ether and the extract washed with 2.5N-sodium hydroxide (to remove any 3-hydroxyquinoline), and then with water. After drying (Na_2SO_4), the ether was evaporated and the residue was dissolved in ethanol (300 ml.), heated to boiling, potassium hydroxide (49g.) added slowly, and the mixture refluxed for 10 hours in an atmosphere of nitrogen. The ethanol was evaporated, the residue dissolved in water and the solution extracted with ether (discarded). The aqueous solution was shaken with benzoyl chloride (32 ml.) for a few minutes. The solid (54.3g.), was filtered off, and recrystallised from a mixture of benzene and light petroleum (b.p. 60-80°) giving 3-benzoylmercaptoquinoline, as colourless plates (37.8g.; 68%), m.p. 111°. (Found, for material dried at 20°/10mm.: C, 72.5; H, 4.3; N, 5.2, 5.3; S, 11.9. $\text{C}_{16}\text{H}_{11}\text{ONS}$ requires C, 72.5; H, 4.2; N, 5.3; S, 12.1%).

3-Mercaptoquinoline. 3-Benzoylmercaptoquinoline (1g.) was refluxed with 6N-hydrochloric acid (10 ml.) in an atmosphere of carbon dioxide for 1 hour. The benzoic acid was extracted with ether (discarded). The aqueous solution was chilled, adjusted to pH 4.5, extracted with ether, the extract dried (Na_2SO_4) and the solvent evaporated. There remained a red oil (0.55g.; 91%)

which was sublimed twice giving 3-mercaptoquinoline, m.p. 58° . (Found: C, 66.7; H, 4.5; N, 8.6, 8.7; S, 19.7. C_9H_7NS requires C, 67.05; H, 4.4; N, 8.7; S, 19.9%). 3-Mercaptoquinoline exists in two crystalline forms, a bright red and a pale pink crystalline solid, which were found to be interconvertible on sublimation, possessed the same m.p., and were indistinguishable on paper chromatography in both aqueous ammonium chloride and butanol+ acetic acid.

Di-3-quinolyl disulphide. To 3-mercaptoquinoline, suspended in aqueous alcohol, hydrogen peroxide (10%) was added until the red colour of the mercapto-compound disappeared giving di-3-quinolyl disulphide which was collected and recrystallised from aqueous ethanol as colourless needles, m.p. $150-151.5^{\circ}$. (Found: C, 67.4; H, 3.4; N, 8.6; S, 19.7, 19.8. $C_{18}H_{12}N_2S_2$ requires C, 67.5; H, 3.8; N, 8.7; S, 20.0%).

Di-3-quinolyl disulphide was also produced when an ammoniacal benzene solution of 3-mercaptoquinoline was exposed to the air.

Methylation of 3-mercaptoquinoline. 3-Mercaptoquinoline (from 5g.; 0.019 mole of 3-benzoylmercaptoquinoline) in N-sodium hydroxide was shaken with methyl iodide (1.5 ml.; 0.024 mole) and allowed to stand overnight. An oil and a yellow solid separated. The oil, 3-methylmercaptoquinoline, was extracted from the

aqueous solution with ether, and the solid, 3-methylmercaptoquinoline methiodide (0.41g.; 7%), which was insoluble in ether was filtered from the aqueous solution and recrystallised from ethanol as yellow needles, m.p. 245°. (Found: C, 41.6; H, 3.7; N, 4.4. $C_{11}H_{12}NIS$ requires C, 41.6; H, 3.8; N, 4.4%). The ethereal solution was dried (Na_2SO_4) and dry hydrogen chloride passed in to precipitate 3-methylmercaptoquinoline hydrochloride, which was filtered off, washed with ether, and decomposed with 2N-ammonia. The free base was extracted with ether, the extract dried (Na_2SO_4), and the solvent evaporated leaving an oil (2.67g.), which was distilled giving 3-methylmercaptoquinoline (1.76g.; 52%) as a pale yellow liquid, b.p. 112-113°/0.06 mm.; 118-119°/0.2 mm.. (Found: C, 68.2; H, 5.2; N, 7.9; S, 18.6. $C_{10}H_9NS$ requires C, 68.5; H, 5.5; N, 8.0; S, 18.3%).

3-Methylmercaptoquinoline hydrochloride. 3-Methylmercaptoquinoline was dissolved in ether and the yellow 3-methylmercaptoquinoline hydrochloride precipitated with dry hydrogen chloride. The product was collected, washed with ether, recrystallised from butanol and sublimed. It had m.p. 205-209°. (Found: S, 15.1. $C_{10}H_{10}NClS$ requires S, 15.15%).

3-Benzoylmercaptoquinoline with methyl iodide in methanol at 100°. 3-Benzoylmercaptoquinoline (0.2g.; 0.0008 mole), methyl iodide (0.1 ml.; 0.0016 mole) and methanol (6 ml.) were heated in a sealed tube at 100° for 5 hours. Evaporation of the solvent and recrystallisation of the residue from a mixture of methanol and ethanol gave 3-methylmercaptoquinoline methiodide (0.15g.; 63%), m.p. 240-242.5°. The m.p. was not depressed on admixture with 3-methylmercaptoquinoline methiodide obtained above by methylation of 3-mercaptoquinoline. (Found, for material dried at 20°/10mm. C, 41.5; H, 3.8; N, 4.4; S, 10.0. $C_{11}H_{12}NIS$ requires C, 41.6; H, 3.8; N, 4.4; S, 10.1%).

3-Benzoylmercaptoquinoline methiodide. (a) A mixture of 3-benzoylmercaptoquinoline (5g.; 0.019 mole), methyl iodide (3.5 ml.; 0.057 mole) and nitrobenzene (20 ml.) was allowed to stand at 20° for 8 days. The precipitate was collected and crystallised from methanol giving orange 3-benzoylmercaptoquinoline methiodide (5.38g.; 70%), m.p. 199-201°, which was depressed on admixture with 3-methylmercaptoquinoline methiodide. Paper chromatography in aqueous ammonium chloride and butanol+acetic acid revealed considerable differences in R_F between 3-benzoylmercaptoquinoline methiodide and 3-methylmercaptoquinoline methiodide. (Found, for material dried at 20°/10mm. : C, 50.0; H, 3.5; N, 3.4; S, 7.9. $C_{17}H_{14}ONIS$ requires C, 50.1; H, 3.5; N, 3.4; S, 7.9%).

(b) A mixture of 3-benzoylmercaptoquinoline (6g.; 0.023 mole), methyl iodide (3 ml.; 0.049 mole) and nitromethane (50 ml.) was set aside at 20° for 12 days. The precipitate was collected, and recrystallised from methanol, giving 3-benzoylmercaptoquinoline methiodide (3.36g.; 36%), m.p. 198.5-201.5°. The m.p. was not depressed on admixture with the product from (a).

3-Mercaptoquinoline methiodide. 3-Benzoylmercaptoquinoline methiodide (0.5g.) was refluxed with 6N-hydrochloric acid (6 ml.) in an atmosphere of carbon dioxide for 1 hour. The benzoic acid was extracted with ether, the aqueous solution evaporated to dryness under reduced pressure and the residue crystallised from a mixture of methanol and ethanol containing a little hydriodic acid, giving yellow 3-mercaptoquinoline methiodide, m.p. 229-231°. (Found: N, 4.6; S, 10.5. $C_{10}H_{10}NIS$ requires N, 4.6; S, 10.6%).

3-Mercaptoquinoline methochloride. 3-Benzoylmercaptoquinoline methiodide (1g.) was suspended in water and shaken with an excess of freshly precipitated silver chloride until the methiodide dissolved. The precipitate was filtered off, and the shaking with silver chloride repeated. The filtrate was evaporated to dryness in a vacuum and the residue of 3-benzoylmercaptoquinoline methochloride (0.73g.; 94%) refluxed for 1.25 hours with 6N-hydrochloric acid (10 ml.) in an atmosphere of carbon dioxide. The benzoic acid was extracted with ether, the

aqueous solution evaporated to dryness in a vacuum, and the residue crystallised from a mixture of methanol and ethyl acetate giving cream coloured 3-mercaptoquinoline methochloride, m.p. 261-262.5°. (Found, for material which had been allowed to reach equilibrium with water at 20°: C, 50.5; H, 5.1; N, 5.8, 5.9; S, 13.65. (C₁₀H₁₀NClS)₂·3H₂O requires C, 50.3; H, 5.5; N, 5.9; S, 13.4%).

2-Carbethoxy-4-hydroxyquinoline, was obtained by reacting aniline with ethyl sodio-ethoxalylacetate as described by Riegel, Albisetti, Lappin, and Baker (1946b). The crude 2-carbethoxy-4-hydroxyquinoline had m.p. 204-206°. (Riegel, Albisetti, Lappin, and Baker give m.p. 213°).

4-Hydroxyquinoline was obtained by hydrolysis and decarboxylation of 2-carbethoxy-4-hydroxyquinoline as described by Riegel, Albisetti, Lappin, and Baker (1946b). The 4-hydroxyquinoline had m.p. 200-201°. (Riegel, Albisetti, Lappin, and Baker give m.p. 200-201°).

4-Mercaptoquinoline. 4-Hydroxyquinoline (2g.; 0.014 mole) and phosphorus pentasulphide (4g.; 0.018 mole) were heated at 140° for 4 hours, and finally at 155° for 1 hour. The excess phosphorus pentasulphide was decomposed by warming with water (8 ml.) and the cold solution adjusted with sodium carbonate to pH 5.5. The mixture was extracted with chloroform, the extract dried (Na₂SO₄) and

the solvent evaporated leaving an orange residue (2.31g.) which crystallised from a large volume of toluene as yellow needles, (1.48g.; theoretical yield 2.22g.). The product sublimed at 125-135°/0.005 mm. giving 4-mercaptoquinoline as a waxy red product which later solidified. It had m.p. 158-162° (decomp). (Found: C, 67.0; H, 4.5; N, 8.5. C_9H_7NS requires C, 67.05; H, 4.4; N, 8.7%).

Methylation of 4-mercaptoquinoline (a) with methyl iodide and sodium hydroxide. 4-Mercaptoquinoline (1.16g.; 0.0072 mole) in N-sodium hydroxide (8 ml.) was shaken with methyl iodide (0.46 ml.; 0.0072 mole) for 30 minutes. The oil was extracted with chloroform and the extract dried (K_2CO_3). The solvent was evaporated and the product (1.22g.) extracted with boiling light petroleum (b.p. 60-80°). There remained an insoluble yellow solid (0.24g.) which was rejected. The extract was concentrated, and on cooling deposited colourless needles of 4-methylmercaptoquinoline (0.84g.; 67%), m.p. 70-72°. (Found, for material dried at 20°/10mm: C, 68.45; H, 5.3; N, 7.8. $C_{10}H_9NS$ requires C, 68.5; H, 5.2; N, 8.0%). Paper chromatography in aqueous ammonium chloride and butanol+acetic acid revealed no trace of the N-methyl isomer.

(b) with dimethyl sulphate and sodium hydroxide. 4-Mercaptoquinoline (0.75g.; 0.0047 mole) in N-sodium hydroxide (5 ml.) was shaken vigorously as dimethyl sulphate (1 ml.; 0.011 mole) was slowly added. 2N-Sodium hydroxide was

added from time to time to keep the solution alkaline. The mixture was extracted with chloroform, the extract dried (K_2CO_3) and the solvent evaporated. The residue (0.81g.) was recrystallised from a mixture of benzene and light petroleum (b.p. 80-100°) giving 1-methylquinol-4-one (0.28g.; 38%), m.p. 151-152.5°, which was not depressed on admixture with authentic 1-methylquinol-4-one (see below). (Found: C, 75.6; H, 5.7; N, 8.7, 8.8. Calculated for $C_{10}H_9ON$: C, 75.45; H, 5.7; N, 8.8%). Both samples gave identical spots when chromatographed on paper in both aqueous ammonium chloride and butanol+acetic acid. 4-Methylmercaptoquinoline was identified in the filtrate by paper chromatography alongside an authentic sample of 4-methylmercaptoquinoline.

Di-4-quinolyl sulphide. 4-Mercaptoquinoline was refluxed with charcoal in toluene for ca. 1 hour. The solution was filtered and the filtrate evaporated in a vacuum. The residue, which was insoluble in sodium hydroxide, was recrystallised from aqueous alcohol, giving colourless di-4-quinolyl sulphide, m.p. 146-147.5°. (Found: C, 74.5; H, 4.1; N, 9.5, 9.6; S, 11.1. $C_{18}H_{12}N_2S$ requires C, 75.0; H, 4.2; N, 9.7; S, 11.1%).

1-Methylquinol-4-one. 4-Hydroxyquinoline (1g.; 0.007 mole) was dissolved in a little water containing potassium hydroxide (2g.; 0.036 mole) and the solution evaporated to dryness in a vacuum. Dimethyl sulphate (1.5 ml.; 0.016 mole) was added to the residue and the

mixture warmed on a water bath. A reaction soon commenced and was moderated by cooling. The mixture was then warmed on the water bath for ca. 15 minutes, water (10 ml.) was added, and the mixture was extracted with chloroform. After drying (K_2CO_3), the solvent was evaporated giving 1-methylquinol-4-one (0.89g.; 81%) which crystallised from benzene. It had m.p. 150-152°. (Späth and Kolbe (1922) give m.p. 152°).

1-Methylquinol-4-thione. 1-Methylquinol-4-one (0.75g.; 0.0047 mole) and phosphorus pentasulphide (1.5g.; 0.0068 mole) were heated at 140-150° for 4 hours. The mixture was cooled, and excess phosphorus pentasulphide was decomposed by warming with water (5 ml.). The solution was neutralised with sodium carbonate to pH 7, and was extracted with chloroform. After drying (K_2CO_3) the solvent was evaporated and the crude 1-methylquinol-4-thione (0.80g.; 97%) recrystallised from ethanol as yellow needles m.p. 209-211°. (Campaigne, Cline, and Kaslow (1950) give m.p. 209-210°).

Quinoline-5-sulphonic acid was prepared by the action of fuming sulphuric acid (20% free SO_3) on quinoline in the presence of mercury as described by Grier (1954).

Quinoline-5-sulphonyl chloride. Quinoline-5-sulphonic acid (10g.) and phosphorus pentachloride (10g.) were heated to 130°, when a reaction commenced, and finally to 150°. The phosphorus oxychloride was removed under reduced pressure. After cooling, ice water and sodium bicarbonate

were added. The solid slowly dissolved, a white precipitate separated and was extracted with chloroform. After drying (Na_2SO_4) the solvent was evaporated and the oily quinoline-5-sulphonyl chloride (7.68g.; 71%) which solidified on cooling was recrystallised from light petroleum (b.p. $60-80^\circ$). The colourless product softened, without melting at $91-95^\circ$. (Found: C, 47.4; H, 2.4; S, 14.0. $\text{C}_9\text{H}_6\text{O}_2\text{NClS}$ requires C, 47.5; H, 2.7; S, 14.1%). The product produced only one spot when paper chromatographed in (i) aqueous ammonium chloride and (ii) butanol+acetic acid. The R_F in each case was considerably different from that of quinoline-5-sulphonic acid.

Conversion of quinoline-5-sulphonyl chloride to 5-hydroxyquinoline. Quinoline-5-sulphonyl chloride (2g.) was refluxed with N-sodium hydroxide (20 ml.) for 2.5. hours. The yellow solution was evaporated to dryness under reduced pressure. A sample of this residue when paper chromatographed in aqueous ammonium chloride and butanol+acetic acid gave, in each case, a spot identical with that obtained for quinoline-5-sulphonic acid. The quinoline-5-sulphonic acid and sodium chloride mixture was added to a mixture of sodium hydroxide (10.8g.) and water (1.0 ml.) at 260° , and kept at that temperature for 5 minutes. The reaction mixture was cooled, dissolved in water and filtered. The filtrate was adjusted with 10N-hydrochloric acid to pH 6.8. The pK_a values of 5-hydroxyquinoline are 5.20 and 8.54 (Albert and Phillips

(1956)) . The product extracted with hot chloroform, and after drying (Na_2SO_4), the solvent was evaporated and the cream coloured 5-hydroxyquinoline (0.81g.; 64%) was crystallised from a mixture of ethanol and benzene, followed by aqueous alcohol. It had m.p. $223-226^\circ$, which was not depressed on admixture with authentic 5-hydroxyquinoline (L. Light & Co.). The product and 5-hydroxyquinoline were indistinguishable when paper chromatographed in aqueous ammonium chloride and butanol+acetic acid.

Reduction of quinoline-5-sulphonyl chloride.

Quinoline-5-sulphonyl chloride (14.88g.) in 10N-hydrochloric acid (60 ml.) was added dropwise with stirring to a solution of $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (48g.) in 10N-hydrochloric acid (105 ml.). The mixture was warmed and a yellow precipitate separated. When the addition was complete, water (84 ml.) was added, and the mixture chilled overnight. The tin complex (18.7g.) was filtered off and dried in air.

5-Benzoylmercaptoquinoline was prepared by decomposing the above tin complex (18.7g.) with warm 2.5N-sodium hydroxide (250 ml.) in an atmosphere of nitrogen, filtering, and shaking the cold filtrate with benzoyl chloride (10 ml.) for 30 minutes. The oil which separated, solidified on chilling, and was filtered off. The crude product (13.77g.; 80% based on the sulphonyl chloride) was chromatographed in chloroform over alumina and the colourless 5-benzoylmercaptoquinoline crystallised from light

petroleum (b.p. 80-100°). It had m.p. 88°. (Found, for material dried at 60°/1mm.: C, 71.8; H, 4.45; N, 5.2, 5.25; S, 12.05. $C_{16}H_{11}ONS$ requires C, 72.5; H, 4.2; N, 5.3; S, 12.1%).

5-Mercaptoquinoline. 5-Benzoylmercaptoquinoline (4g.) was refluxed for 1 hour with 6N-hydrochloric acid (40 ml.) in an atmosphere of carbon dioxide. On cooling, benzoic acid separated and was extracted with ether. The aqueous solution was chilled and adjusted to pH 3 with 2.5N-sodium hydroxide. The 5-mercaptoquinoline monohydrate was filtered off and gave red crystals, m.p. 87.5-89°, from aqueous ethanol. (Found, for material dried at 20°/10mm. without a desiccating agent; C, 60.7; H, 5.0; N, 7.9, 7.8; S, 17.7. $C_9H_7NS.H_2O$ requires C, 60.3; H, 5.1; N, 7.8; S, 17.9%). When the product was dried at 20°/10mm. over P_2O_5 , a light pink solid, anhydrous 5-mercaptoquinoline was produced. (Found: C, 66.6; H, 4.4; S, 19.8. C_9H_7NS requires C, 67.05; H, 4.4; S, 19.9%).

Di-5-quinolyl disulphide. 5-Mercaptoquinoline was suspended in water and hydrogen peroxide (15%) was added. The red 5-mercaptoquinoline monohydrate soon disappeared giving a colourless solid, di-5-quinolyl disulphide, which was recrystallised from a mixture of benzene and light petroleum (b.p. 60-80°). It had m.p. 109°. (Found, for material dried 70°/1 mm. : C, 67.6; H, 3.8; N, 8.6; S, 19.65. $C_{18}H_{12}N_2S_2$ requires C, 67.5; H, 3.8; N, 8.7;

S, 20.0%). Aerial oxidation gave the same product.

5-Methylmercaptoquinoline. 5-Benzoylmercaptoquinoline (2.0g.; 0.008 mole) was refluxed for 1 hour with 6N-hydrochloric acid in an atmosphere of carbon dioxide, and the benzoic acid extracted with ether. The aqueous solution was made alkaline with 10N-sodium hydroxide and shaken with methyl iodide (0.5 ml.; 0.008 mole) for 15 minutes. The oil was extracted with ether, the extract dried (Na_2SO_4) and the solvent evaporated. The product (1.06g.; 80%) was dissolved in ether, dry hydrogen chloride was passed into the solution and the precipitate of 5-methylmercaptoquinoline hydrochloride crystallised from butanol. Subsequent sublimation gave a yellow solid, m.p. $241-243.5^\circ$, which was decomposed with 2N-ammonia. The product was extracted with ether, the extract dried (Na_2SO_4), the solvent evaporated and the 5-methylmercaptoquinoline distilled as an almost colourless oil, b.p. $104^\circ/0.09$ mm. (Found: C, 68.6; H, 5.2. $\text{C}_{10}\text{H}_9\text{NS}$ requires C, 68.5; H, 5.2%).

5-Benzoylmercaptoquinoline methiodide. 5-Benzoylmercaptoquinoline (0.2g.; 0.00075 mole) and methyl iodide (0.1 ml.; 0.0016 mole) in nitromethane (1 ml.) were set aside at 20° . After 7 days the mixture was chilled, the yellow precipitate collected and washed with ether. The 5-benzoylmercaptoquinoline methiodide (0.16g.; 52%) crystallised from ethanol. It had m.p. 207° . (Found: C, 50.3; H, 3.5; N, 3.4, 3.5; S, 8.0. $\text{C}_{17}\text{H}_{14}\text{ONIS}$

requires C, 50.1; H, 3.5; N, 3.4; S, 7.9%).

5-Mercaptoquinoline methiodide. 5-Benzoylmercaptoquinoline methiodide (0.4g.) and 6N-hydrochloric acid (5 ml.) were refluxed for 1 hour in an atmosphere of carbon dioxide, cooled, and the benzoic acid extracted with ether. The aqueous solution was evaporated to dryness under reduced pressure. The residue (0.19g.; 63%), recrystallised from ethanol containing a little hydriodic acid gave yellow 5-mercaptoquinoline methiodide, m.p. 189°. (Found: C, 39.5; H, 3.4; N, 4.5; S, 10.55. $C_{10}H_{10}NIS$ requires C, 39.6; H, 3.3; N, 4.6; S, 10.6%).

5-Benzoylmercaptoquinoline methyl hydrogen sulphate. Dimethyl sulphate (0.1 ml.; 0.001 mole) and 5-benzoylmercaptoquinoline (0.2g.; 0.0075 mole) in nitrobenzene (1 ml.) was allowed to stand at 20° for 5 days. The nitrobenzene was distilled with water under reduced pressure. The residue crystallised from a mixture of ethanol and ethyl acetate. 5-Benzoylmercaptoquinoline methyl hydrogen sulphate had m.p. 170-172°. (Found: C, 53.8; H, 4.1; N, 3.65. $C_{18}H_{17}O_5NS_2$ requires C, 54.1; H, 4.0; N, 3.7%).

Quinoline-6-sulphonic acid was prepared from sulphanilic acid, glycerol, nitrobenzene and sulphuric acid as described by Ponci and Gialdi (1954).

Quinoline-6-sulphonyl chloride. Quinoline-6-sulphonic acid was heated with phosphorus pentachloride as described by Ponci & Gialdi (1954). The product was recrystallised

once from light petroleum (b.p. 60-80°). It had m.p. 90°. (Ponci and Gialdi give m.p. 91°).

Reduction of quinoline-6-sulphonyl chloride.

Quinoline-6-sulphonyl chloride was reduced with stannous chloride and hydrochloric acid. The 6-mercaptoquinoline separated as the tin salt as described by Ponci and Gialdi (1954).

6-Benzoylmercaptoquinoline. The tin salt of 6-mercaptoquinoline above was dissolved in sodium hydroxide and benzoylated with benzoyl chloride according to Ponci and Gialdi (1954). The 6-benzoylmercaptoquinoline, once recrystallised from aqueous alcohol had m.p. 147-149°. (Ponci and Gialdi give m.p. 148-150°).

6-Mercaptoquinoline was prepared by acid hydrolysis of 6-benzoylmercaptoquinoline as described by Ponci and Gialdi (1954) and the red oil distilled, b.p. 114°/0.1 mm.. (Found; N, 8.55; S, 19.65. Calculated for C₉H₇NS, N, 8.7; S, 19.9%).

Methylation of 6-mercaptoquinoline. 6-Mercaptoquinoline (2.15g.; 0.013 mole), N-sodium hydroxide (13ml.) and methyl iodide (0.83 ml.; 0.013 mole) were shaken for 15 minutes and extracted with chloroform. There remained a yellow, chloroform and water insoluble material, 6-methylmercaptoquinoline methiodide (0.88g.; 21%) which was filtered off and crystallised from alcohol as yellow needles, m.p. 237-238.5°. (Found: C, 41.9; H, 4.0; N, 4.3; S, 10.0. C₁₁H₁₂NIS requires C, 41.6; H, 3.8;

N, 4.4; S, 10.1%).

The chloroform extract was dried (Na_2SO_4), the solvent was evaporated and the residue was extracted with light petroleum (b.p. 60-80°) giving 6-methylmercaptoquinoline (1.27g.; 54%) which crystallised from light petroleum (b.p. 60-80°) as colourless needles, m.p. 44-46°. (Found, for material dried 20°/10 mm: C, 68.9; H, 5.3; N, 7.8. $\text{C}_{10}\text{H}_9\text{NS}$ requires C, 68.5; H, 5.2; N, 8.0%).

6-Benzoylmercaptoquinoline methiodide. 6-Benzoylmercaptoquinoline (1.5g. 0.006 mole), methyl iodide (0.75 ml.; 0.012 mole), and methanol (6 ml.) were heated at 100° for 5 hours. The solvent was evaporated and the residue was recrystallised from a mixture of methanol and ethanol giving yellow 6-benzoylmercaptoquinoline methiodide (2.05g.; 89%), m.p. 205-207.5°. (Found: C, 50.2; H, 3.5; N, 3.4; S, 7.8. $\text{C}_{17}\text{H}_{14}\text{ONIS}$ requires C, 50.1; H, 3.5; N, 3.4; S, 7.9%).

6-Mercaptoquinoline methiodide. 6-Benzoylmercaptoquinoline methiodide (0.5g.) was refluxed with 6N-hydrochloric acid (6 ml.) in an atmosphere of carbon dioxide for 1 hour. The benzoic acid was extracted with ether, the aqueous solution evaporated to dryness under reduced pressure and the residue crystallised from methanol containing a little hydriodic acid giving 6-mercaptoquinoline methiodide, m.p. 225-227°. (Found: N, 4.5; S, 10.4. $\text{C}_{10}\text{H}_{10}\text{INS}$ requires N, 4.6; S, 10.6%).

6-Mercaptoquinoline methochloride. 6-Benzoylmercaptoquinoline methiodide (1g.) was shaken with freshly precipitated silver chloride (from 2g. AgNO_3) in water at 20° for 25 minutes. The precipitate was filtered off, washed thoroughly with ethanol, with water, and the filtrates evaporated. The residue, 6-benzoylmercaptoquinoline methochloride (0.76g.; 98%) was crystallised once from a mixture of ethanol and ethyl acetate giving yellow crystals (0.67g.), m.p. $180-182.5^\circ$. This product (0.67g.) was refluxed with 6N-hydrochloric acid (10 ml.) for 1.25 hours in an atmosphere of carbon dioxide, and the benzoic acid (0.24g.; 92%) extracted with ether. The aqueous solution was evaporated to dryness under reduced pressure at ca. 60° , and the 6-mercaptoquinoline methochloride (0.36g.; 80%) recrystallised from ethanol. The cream product had m.p. $219-221.5^\circ$. (Found: C, 56.4; H, 4.9; N, 6.75; S, 15.0. $\text{C}_{10}\text{H}_{10}\text{NClS}$ requires C, 56.7; H, 4.8; N, 6.6; S, 15.15%).

Quinoline-8-sulphonic acid was prepared by sulphonating quinoline with fuming sulphuric acid (30% free SO_3) as described by McCasland (1946).

Quinoline-8-sulphonyl chloride was prepared from phosphorus pentachloride and quinoline-8-sulphuric acid as described by Edinger (1908) and modified by McCasland (1946). The quinoline-8-sulphonyl chloride crystallised from a mixture of benzene and light petroleum (b.p. $80-100^\circ$).

It had m.p. 131° . Badger and Buttery (1956) give m.p. $128.5-129^{\circ}$; McCasland gives m.p. $124-126^{\circ}$; and Edinger gives m.p. 122° .

Reduction of quinoline-8-sulphonyl chloride to 8-mercaptoquinoline was achieved with stannous chloride and hydrochloric acid as described by Edinger (1908). The 8-mercaptoquinoline precipitated as the tin complex.

Di-8-quinolyl disulphide. 8-Mercaptoquinoline (as the tin complex) was oxidised with iodine in sodium hydroxide by the method of Badger and Buttery (1956) but the quantity of iodine employed was 10 times that stated by Badger and Buttery and more in line with that given by Riegel *et. al.* (1946a) for the preparation di-(4-chloro-8-quinolyl) disulphide. The product crystallised from benzene as colourless crystals, m.p. $206-208.5^{\circ}$. Badger and Buttery give m.p. $205-206^{\circ}$.

8-Benzoylmercaptoquinoline was prepared by the action of benzoyl chloride and sodium hydroxide on the tin complex of 8-mercaptoquinoline as described by Edinger (1908). The product had m.p. $109-112^{\circ}$ (from aqueous alcohol). (Edinger gives m.p. 110°).

8-Benzylmercaptoquinoline was prepared as described by Edinger (1908), by the action of benzyl chloride and sodium hydroxide on the tin complex of 8-mercaptoquinoline. The product had m.p. $114-115^{\circ}$ (from ethanol). (Edinger gives m.p. 112°).

8-Mercaptoquinoline. Acid hydrolysis of 8-benzoyl-mercaptoquinoline as described by Edinger (1908) gave 8-mercaptoquinoline as the dihydrate, m.p. 59° . (Edinger gives m.p. $58-59^{\circ}$).

Di-o-nitrophenyl disulphide, was prepared from o-chloronitrobenzene and sodium polysulphide as described by Foster and Reid (1924). The di-o-nitrophenyl disulphide crystallised from benzene as yellow needles (52%), m.p. $196-197.5^{\circ}$. (Elgersma (1929) gives m.p. 195°).

o-Methylmercaptanitrobenzene. Di-o-nitrophenyl disulphide was reduced with sodium hydrogen sulphide to o-mercaptanitrobenzene which was methylated immediately with methyl iodide as described by Foster and Reid (1924). The o-methylmercaptanitrobenzene (78% based on disulphide) crystallised from ethanol as yellow crystals, m.p. 60° . (Foster and Reid give m.p. $59-60^{\circ}$).

o-Methylmercaptoaniline was prepared by reduction of o-methylmercaptanitrobenzene with iron and hydrochloric acid according to Brand and Stallmann (1921). The o-methylmercaptoaniline (39%) was distilled, b.p. $144-146^{\circ}/34$ mm. (Brand and Stallmann give b.p. $133-134^{\circ}/15$ mm.).

8-Methylmercaptoquinoline. o-Methylmercaptoaniline (2.76g.), arsenic pentoxide (2.90g.), glycerol (6.20g.), and 36N-sulphuric acid (5.6g.) were heated under reflux for 1.5 hours. Water (50 ml.) was added to the cold mixture, and it was made alkaline with sodium hydroxide, and

extracted with chloroform. After drying (Na_2SO_4) the solvent was evaporated and the crude 8-methylmercaptoquinoline (1.52g.; 44%) recrystallised both from light petroleum (b.p. 60-80°) and from aqueous alcohol. It had m.p. 85° which was not depressed on admixture with the product obtained by methylation of 8-mercaptoquinoline described below. (Found, for material dried 20°/10 mm: C, 68.5; H, 5.3; N, 7.8. Calculated for $\text{C}_{10}\text{H}_9\text{NS}$: C, 68.5; H, 5.2; N, 8.0%).

Methylation of 8-mercaptoquinoline (a) with methyl iodide and sodium hydroxide. 8-Mercaptoquinoline dihydrate (2.12g.; 0.011 mole) in N-sodium hydroxide (12 ml.) was shaken with methyl iodide (0.69 ml.; 0.011 mole) for 30 minutes. The white 8-methylmercaptoquinoline (1.37g.; 73%) solidified, was filtered off and crystallised from light petroleum (b.p. 60-80°). It had m.p. 84-85.5°, and was not depressed on admixture with a sample of 8-methylmercaptoquinoline prepared by the Skraup reaction on o-methylmercaptoaniline as described above. (Found, for material dried at 20°/10 mm.: C, 68.6; H, 5.1; N, 8.1. Calculated for $\text{C}_{10}\text{H}_9\text{NS}$: C, 68.5; H, 5.2; N, 8.0%). (Taylor (1951) gives m.p. 78-80° for 8-methylmercaptoquinoline). Paper chromatography of the product in aqueous ammonium chloride and butanol+acetic acid gave only one spot in each case. Methylmercaptan was not produced when 8-methylmercaptoquinoline was (i) warmed with 5N-sulphuric acid or (ii) heated at 100° for

2 hours with 10N-sodium hydroxide and the mixture acidified.

(b) with diazomethane. Diazomethane in ether was prepared as described by Arndt (1943a) from nitrosomethylurea (1g.) which had been prepared according to Arndt (1948b). The ethereal diazomethane was added dropwise with stirring to a cold (0°C) solution of 8-mercaptoquinoline (0.3g.) in methanol (30 ml.) and the mixture stirred for 30 minutes and allowed to stand overnight. The solvent was evaporated and the 8-methylmercaptoquinoline (0.25g.; 77%) recrystallised from light petroleum (b.p. 60-80°). It had m.p. 82.5-84°, which was not depressed on admixture with the product prepared in (a).

8-Methylmercaptoquinoline hydriodide. (a) 8-Benzoylmercaptoquinoline (0.2g.; 0.0075 mole), methanol (5 ml.) and methyl iodide (0.1 ml.; 0.0016 mole) were set aside at 20° for 2 days. The solvent was evaporated and 8-methylmercaptoquinoline hydriodide crystallised from ethanol as yellow needles, m.p. 196-197.5°. (Found: C, 39.4; H, 3.3; N, 4.5, 4.6. C₁₀H₁₀NIS requires C, 39.6; H, 3.3; N, 4.6%).

A sample of 8-methylmercaptoquinoline hydriodide in water was made alkaline with sodium hydroxide and the white precipitate of 8-methylmercaptoquinoline collected and crystallised from light petroleum (b.p. 60-80°). It had m.p. 84-85.5°, which was not depressed with 8-methylmercaptoquinoline from the Skraup reaction. Paper chromatography

in aqueous ammonium chloride and butanol+acetic acid indicated the identity of these two samples.

(b) 8-Benzylmercaptoquinoline (1g.; 0.004 mole), methanol (13 ml.) and methyl iodide (0.6 ml.; 0.01 mole) were heated at 100° for 6 hours. The solvent was evaporated and the residue (1.44g.) was extracted with light petroleum (b.p. 60-80°) giving 8-benzylmercaptoquinoline (0.15g.; 15%) and the remainder was crystallised from ethanol as yellow needles of 8-methylmercaptoquinoline hydriodide (0.62g.; 39%). It had m.p. 189-193° which was not depressed when mixed with a sample from (a). (Found: C, 39.7; H, 3.3; N, 4.6. $C_{10}H_{10}NIS$ requires C, 39.6; H, 3.3; N, 4.6%).

Di-8-quinolyl disulphide and methyl iodide in methanol at 100°. Di-8-quinolyl disulphide (0.1g.; 0.0003 mole), methanol (3 ml.) and methyl iodide (0.075 ml.; 0.0012 mole) were heated at 100° for 8 hours. On cooling the dark brown crystals (0.1g.), believed to be di-8-quinolyl disulphide methiodide periodide, were filtered off and recrystallised from methanol. It had m.p. 198°. (Found: C, 31.5; H, 2.0; N, 3.9. $C_{19}H_{15}N_2I_3S_2$ requires C, 31.8; H, 2.1; N, 3.9%). The deep colouration was discharged by sulphurous acid.

Di-8-quinolyl disulphide and methyl iodide at 100°. Di-8-quinolyl disulphide (0.2g.; 0.0062 mole) and methyl iodide (4 ml.) were heated at 100° for 3 hours. The volatile

matter was removed and the residue (0.37g.) extracted with benzene giving 8-methylmercaptoquinoline (0.16g.; 73%) which was sublimed. It had m.p. 82.5-84°, which was not depressed on admixture with 8-methylmercaptoquinoline from methylation of 8-mercaptoquinoline with methyl iodide. Paper chromatography of both these samples in aqueous ammonium chloride and butanol+acetic acid gave identical spots.

The benzene insoluble product believed to be 8-methylmercaptoquinoline methiodide periodide crystallised from ethanol as purple-brown needles (0.11g.; 15%), m.p. 130°. (Found: C, 23.4; H, 2.0; N, 2.3; S, 5.5. $C_{11}H_{12}NI_3S$ requires C, 23.1; H, 2.1; N, 2.45; S, 5.6%). The deep colouration was discharged by sulphurous acid.

Di-8-quinolyl disulphide with dimethyl sulphate in nitrobenzene at 150°. Di-8-quinolyl disulphide (0.38g.) in nitrobenzene (4 ml.) was heated with dimethyl sulphate (0.9 ml.) at 150° for 1.3 hours. After chilling the nitrobenzene was decanted and the crystals washed with ether and crystallised from a mixture of methanol and ethanol giving yellow crystals (0.22g.), m.p. 218-220°. Found: C, 41.9; H, 4.3; N, 4.7, 4.9; S, 21.9%).

8-Chloroquinoline was prepared from o-chloroaniline, glycerol, arsenic pentoxide and sulphuric acid as described by Fourneau, Trefouel, and Wancolle (1930), and the product distilled, b.p. 138-140°/ca. 3-5 mm. (Fourneau, Trefouel, and Wancolle give b.p. 163°/20 mm.).

8-Chloroquinoline methochloride was prepared as described by Claus and Schöller (1893). 8-Chloroquinoline methiodide was obtained by heating 8-chloroquinoline with methyl iodide in methanol at 100°. The product was then shaken with silver chloride giving 8-chloroquinoline methochloride, m.p. 141-142.5° (decomp.). (Claus and Schöller give m.p. 140°).

8-Hydroxyquinoline with diazomethane. "Diazoxine". "Diazoxine" was prepared by the action of diazomethane on 8-hydroxyquinoline as described by Phillips and Keon (1951). "Diazoxine", once crystallised from benzene as red crystals had m.p. 108-112°. (Phillips and Keon give m.p. 119° (decomp.)).

ISOQUINOLINES.

1-Hydroxyisoquinoline was prepared from isoquinoline, hydrogen peroxide and acetic acid through the N-oxide as described by Albert and Phillips (1956). The 1-hydroxyisoquinoline once crystallised from water, had m.p. 202-207°. (Albert and Phillips give m.p. 208°).

1-Mercaptoisoquinoline. A mixture of 1-hydroxy-isoquinoline (lg.; 0.0069 mole) and phosphorus pentasulphide (lg.; 0.0045 mole) was heated at 150-160° for 3.5 hours. After cooling the excess phosphorus pentasulphide was decomposed by warming with water (8 ml.), the solution adjusted to pH 6.8 with sodium carbonate and was extracted with chloroform. After drying (Na_2SO_4) the solvent was removed and the crude 1-mercaptoisoquinoline

(1.00g.; 90%) recrystallised from ethanol, and aqueous ethanol as orange-brown crystals (0.92g.), m.p. 170-171°. (Found: C, 66.6; H, 4.4; S, 19.8. C_9H_7NS requires C, 67.05; H, 4.4; S, 19.9%).

1-Methylmercaptoisoquinolinē. 1-Mercaptoisoquinoline (2.76g.; 0.017 mole) in N-sodium hydroxide (54 ml.) was shaken with methyl iodide (1.2 ml.; 0.019 mole) for 5 minutes. The mixture was extracted with chloroform, the extract was dried (Na_2SO_4) and the solvent removed. The residue was vacuum distilled giving 1-methylmercaptoisoquinoline as a pale yellow oil (2.34g.; 78%), b.p. 100°/0.08 mm.. (Found: C, 68.7; H, 5.3; S, 18.3. $C_{10}H_9NS$ requires C, 68.5; H, 5.2; S, 18.3%). Paper chromatography in aqueous ammonium chloride and butanol + acetic acid revealed no trace of the N-methyl isomer.

2-Methylisoquinol-1-thione. 2-Methylisoquinol-1-one (1g.; 0.0063 mole) prepared as described by Albert and Phillips (1956) and phosphorus pentasulphide (1g.; 0.0045 mole), were heated at 130-140° for 4 hours. After cooling the excess phosphorus pentasulphide was decomposed by warming with water (8 ml), the solution adjusted to pH 7.0 with sodium carbonate and was extracted with chloroform. The extract was dried (Na_2SO_4), the solvent removed and the 2-methylisoquinol-1-thione (1.05g.; 95%) recrystallised from aqueous alcohol as yellow crystals, m.p. 112°. (White and Brooker (1951) give m.p. 118-119° and Peak and Stansfield (1952) give m.p. 110°).

Isoquinoline-3-aldehyde was prepared by the oxidation of 3-methylisoquinoline with selenium dioxide according to Teague and Rowe (1951) and the product distilled. The fraction b.p. 150-170°/12 mm. was employed in the next experiment. (Teague and Rowe give b.p. 150°/10 mm.).

Oxidation of isoquinoline-3-aldehyde. To isoquinoline-3-aldehyde (47.2g.) in acetone (ca. 150 ml.), was added hydrogen peroxide (23 ml.; 30%), and the mixture allowed to stand at 20°. The temperature rose to ca. 50° and after 3.5 hours more hydrogen peroxide (34 ml.; 30%) was added and the mixture allowed to stand overnight at 20°. The solution was evaporated almost to dryness under reduced pressure and the product boiled with water (400 ml.). There remained an insoluble colourless solid (22.38g.) which was filtered off and recrystallised from ethanol, giving isoquinoline-3-carboxylic acid-2-oxide, m.p. 216° (decomp.). (Baumgarten and Dirks (1958) give m.p. 211-211.5° (decomp.)). (Found: C, 63.1; H, 3.7; N, 7.3, 7.4. Calculated for C₁₀H₇O₃N: C, 63.5; H, 3.7; N, 7.4%).

The filtrate when chilled deposited isoquinoline-3-carboxylic acid (24.34g.; 47% based on isoquinoline-3-aldehyde employed) as colourless needles and corresponding to the published description.

Isoquinoline-3-carboxamide (a) Isoquinoline-3-carboxamide was prepared by refluxing isoquinoline-3-carboxylic acid with ethanol and sulphuric acid, and

pouring the ester into aqueous ammonia as described by Case (1952). The crude isoquinoline-3-carboxamide had m.p. 203-205°. (Case gives m.p. 206° for the crude product).

(b) Isoquinoline-3-carboxylic acid-2-oxide was refluxed with phosphorus trichloride in chloroform and the acid chloride mixed with concentrated aqueous ammonia as described by Baumgarten and Dirks (1958). The isoquinoline-3-carboxamide, once crystallised from methanol, had m.p. 207-208.5°. (Teague and Rowe (1951) give m.p. 213°; and Baumgarten and Dirks give m.p. 212-213°).

3-Aminoisoquinoline was prepared from isoquinoline-3-carboxamide by the action of bromine in potassium hydroxide according to Teague and Rowe (1953). The product, once crystallised from benzene, had m.p. 175-178°. (Teague and Rowe give m.p. 178°).

3-Hydroxyisoquinoline was prepared according to Boyer and Wolford (1956). 3-Aminoisoquinoline was converted by the action of freshly prepared isoamyl nitrite (prepared according to Cohen (1949)) in glacial acetic acid to 3-acetoxyisoquinoline which was hydrolysed with aqueous sodium hydroxide to 3-hydroxyisoquinoline. The 3-hydroxyisoquinoline (76% based on 3-aminoisoquinoline) recrystallised from aqueous alcohol as yellow needles, m.p. 198°. (Boyer and Wolford give resinification and charring at ca. 205°).

3-Mercaptoisoquinoline. A mixture of 3-hydroxyisoquinoline (1g.; 0.007 mole), phosphorus pentasulphide (3g.; 0.012 mole) and tetralin (20 ml.) was refluxed with stirring at 180-185° for 4 hours. After chilling overnight the tetralin was decanted and the residue refluxed with benzene, filtered (charcoal), concentrated and chilled. The orange-red crystals (0.21g.; 19%) of 3-mercaptoisoquinoline were recrystallised from benzene, and had m.p. 217°. (Found: C, 66.9; H, 4.4; N, 8.5. C_9H_7NS requires C, 67.05; H, 4.4; N, 8.7%).

3-Methylmercaptoisoquinoline hydrochloride.

3-Mercaptoisoquinoline (0.09g.; 0.0006 mole) in N-sodium hydroxide (1 ml.) was shaken with methyl iodide (0.05 ml.; 0.0008 mole) for a few minutes and extracted with ether. The extract was dried (Na_2SO_4) and dry hydrogen chloride was passed into the ethereal solution. The ether was decanted and the sticky yellow precipitate was boiled with benzene and ethyl acetate, and crystallised from a mixture of ethanol and ethyl acetate. The 3-methylmercaptoisoquinoline hydrochloride sublimed giving light yellow crystals, m.p. 197-199°. (Found: C, 56.7; H, 4.9; N, 6.6; S, 15.0. $C_{10}H_{10}NClS$ requires C, 56.7. H, 4.8; N, 6.6; S, 15.15%).

o-Carboxyphenylacetonitrile was prepared from phthalide* by the action of potassium cyanide according to Price and Rogers (1942). The o-carboxyphenylacetonitrile had m.p.

* lactone of o-hydroxymethylbenzoic acid.

113-115°. (Price and Rogers give m.p. 113-115°).

Homophthalic acid was prepared according to Price (1942). Hydrolysis of o-carboxyphenylacetonitrile with sulphuric acid gave homophthalic acid, m.p. 177-179°. Price notes the variability of m.p. with rate of heating and gives m.p.s of 174-175° and 182-183°.

Homophthalimide was prepared from homophthalic acid by heating the ammonium salt according to Baer and Kates (1945). A sample of homophthalimide was sublimed. It had m.p. 230-233°. (Baer and Kates give m.p. 230-233°).

1:3-Dichloroisoquinoline was prepared by the action of phosphoryl chloride on homophthalimide as described by Gabriel (1886). The 1:3-dichloroisoquinoline, once recrystallised from ethanol, had m.p. 116-118°. (Gabriel gives m.p. 122-123°).

3-Chloroisoquinoline was prepared from 1:3-dichloroiso-quinoline by the action of red phosphorus and hydriodic acid in acetic acid according to Haworth and Robinson (1948). The crude product had m.p. 41-44°. (Haworth and Robinson give m.p. 46.5°-47.5°).

3-Chloroisoquinoline with sodium hydrogen sulphide
Sodium hydrogen sulphide reagent was prepared by saturating a solution of 2.5 N-sodium hydroxide (25 ml.) with hydrogen sulphide until there was no immediate colour change with phenolphthalein.

3-Chloroisoquinoline (0.5g.) and the aqueous sodium hydrogen sulphide were heated at 200-210° for 70 hours.

After chilling, the yellow solid (0.3g.) was filtered off and the unchanged 3-chloroisoquinoline extracted with light petroleum (b.p. 60-80°) leaving only a trace of yellow solid, 3-mercaptoisoquinoline which was sublimed once. It had m.p. 204-207°. (Found: S, 19.7. C_9H_7NS requires S, 19.9%).

The filtrate was shaken with benzoyl chloride (ca. 3 ml.) and sodium hydroxide, and the oil which separated solidified on chilling. Recrystallisation of the product from light petroleum (b.p. 60-80°) gave white needles of 3-benzoylmercaptoisoquinoline (0.32g.; 39%), m.p. 139°. (Found: C, 72.2; H, 4.0; S, 12.2. $C_{16}H_{11}NOS$ requires C, 72.5; H, 4.2; S, 12.1%).

PYRAZINES.

2-Aminopyrazine was prepared from lumazine by the action of 100% sulphuric acid according to the directions of Weijlard, Tishler, and Erickson (1945). The 2-aminopyrazine sublimed as yellow crystals, m.p. 117-120°. (Weijlard, Tishler, and Erickson give m.p. 118-120°).

2-Hydroxypyrazine was prepared from 2-aminopyrazine by treatment with nitrosylsulphuric acid according to Erickson and Spoerri (1946) and the product once crystallised from acetone had m.p. 185-187°. (Erickson and Spoerri give m.p. 187-188°).

2-Mercaptopyrazine. 2-Hydroxypyrazine (1g.; 0.01 mole) and phosphorus pentasulphide (1.5g.; 0.007 mole)

were refluxed in pyridine (8.5 ml.) for 45 minutes and the pyridine evaporated under reduced pressure. Excess phosphorus pentasulphide was decomposed by warming with water (ca. 5 ml.) and the mixture evaporated to dryness under reduced pressure. The residue was dissolved in N-sodium hydroxide (ca. 15 ml.), filtered, and the filtrate adjusted to pH 2 with hydrochloric acid. After chilling the precipitate (1.03g.) was filtered off and crystallised from water (charcoal) giving 2-mercaptopyrazine (0.52g.; 46%) as yellow plates, m.p. 229°. (Roblin and Clapp (1950) give m.p. 215-218°). Found, for material dried at 20°/10 mm.; S, 28.7. Calculated for $C_4H_4N_2S$, S, 28.6%.

2-Methylmercaptopyrazine. 2-Mercaptopyrazine (0.47g.; 0.0042 mole) in N-sodium hydroxide (15 ml.) was shaken with methyl iodide (0.3 ml; 0.0049 mole) for 20 minutes and extracted with ether. The extract was dried (Na_2SO_4) and ether evaporated giving 2-methylmercaptopyrazine (0.36g.; 68%) which was sublimed at 30°/0.1mm. as a pale cream-coloured solid, m.p. 44-47°. (Found: C, 48.2; H, 4.6; N, 22.2, 22.3; S, 25.0. $C_5H_6N_2S$ requires C, 47.6; H, 4.8; N, 22.2; S, 25.4%).

1-Methylpyraz-2-one was prepared from 2-hydroxypyrazine and diazomethane as described by Dutcher (1947) and the product sublimed as reported by Albert and Phillips (1956). The white sublimate had m.p. 74°. (Dutcher gives m.p. 83-84° for pure 1-methylpyraz-2-one).

1-Methylpyraz-2-thione. 1-Methylpyraz-2-one (0.1g.; 0.0009 mole) and phosphorus pentasulphide (0.3g.; 0.0012 mole) were refluxed in pyridine (3 ml.) for 2 hours. The pyridine was evaporated under reduced pressure, the excess phosphorus pentasulphide decomposed by warming with water and the solution adjusted to pH 4.7 with sodium carbonate. The solution was extracted with chloroform, the extract was dried (Na_2SO_4), the solvent evaporated, and the product washed with a little cold light petroleum (b.p. 60-80°). The residue (0.12g.) was crystallised from light petroleum (b.p. 60-80°), giving yellow needles of 1-methylpyraz-2-thione (0.06g.; 53%), m.p. 132°. (Found: C, 47.4; H, 5.0; N, 22.1, 22.3; S, 25.7. $\text{C}_5\text{H}_6\text{N}_2\text{S}$ requires C, 47.6; H, 4.8; N, 22.2; S, 25.4%).

QUINOXALINES.

2-Hydroxyquinoxaline was prepared from o-phenylene diamine and ethyl glyoxylate hemiacetal of Rigby (1950), as described Gowenlock, Newbold, and Spring (1945), who however used ethyl glyoxylate. The crude 2-hydroxyquinoxaline had m.p. 270-273°. (Gowenlock, Newbold, and Spring give m.p. 271°).

2-Chloroquinoxaline was prepared from 2-hydroxyquinoxaline by the action of phosphorus oxychloride according to Gowenlock, Newbold, and Spring (1945). The 2-chloroquinoxaline was distilled, b.p. 96°/1.5mm.; m.p. 49-50.5°. (Gowenlock, Newbold, and Spring give b.p. 80°/

0.5mm., m.p. 46-47°).

2-Mercaptoquinoxaline was prepared from 2-chloroquinoxaline through the isothiuronium salt by the method of Wolf, Wilson, and Tishler (1954). The 2-mercaptoquinoxaline had m.p. 209°. (Wolf, Wilson, and Tishler give m.p. 204-205°). (Found: C, 58.7; H, 3.9; N, 17.1. Calculated for $C_8H_6N_2S$: C, 59.25; H, 3.7; N, 17.3%).

2-Methylmercaptoquinoxaline. 2-Mercaptoquinoxaline (1.86g.; 0.011 mole) in 2N-sodium hydroxide (ca. 15 ml.) was shaken vigorously as dimethyl sulphate (1.7g.; 0.013 mole) was added in small portions. The oily product (1.85g.) which separated, solidified on cooling, was filtered off, and distilled, b.p. 151-154°/13 mm. The 2-methylmercaptoquinoxaline (1.08g.; 53%) crystallised from light petroleum (b.p. 40-60°) as yellow needles, m.p. 46°. (Cheeseman (1957) reports m.p. 46-47° for 2-methylmercaptoquinoxaline). (Found, for material dried at 20°/10 mm: C, 61.4; H, 4.6; N, 15.8. Calculated for $C_9H_8N_2S$: C, 61.3; H, 4.6; N, 15.9%).

1-Methylquinoxal-2-one was prepared by the action of dimethyl sulphate on 2-hydroxyquinoxaline in sodium hydroxide as described by Cheeseman (1955). The product once crystallised from light petroleum (b.p. 80-100°) had m.p. 117-119°. (Cheeseman gives m.p. 120-121°)

1-Methylquinoxal-2-thione. 1-Methylquinoxal-2-one (0.5g.; 0.003 mole) and phosphorus pentasulphide (1g.; 0.009 mole) were refluxed in benzene (10 ml.) for 20

minutes. The benzene was recovered and the residue warmed with 5N-ammonia (10 ml.) to decompose excess phosphorus pentasulphide. The solution was extracted with chloroform, the extract was dried (Na_2SO_4) and the chloroform evaporated. The residue (0.40g.; 73%) was chromatographed in chloroform over a little alumina, and the 1-methylquinoxal-2-thione crystallised from aqueous alcohol as yellow needles, m.p. 123-125°. (Found, for material dried at 20°/10 mm.: C, 61.4; H, 4.5; N, 16.2. $\text{C}_9\text{H}_8\text{N}_2\text{S}$ requires C, 61.3; H, 4.6. N, 15.9%).

PYRIMIDINES.

2-Hydroxypyrimidine was prepared from 2-amino-pyrimidine by the action of 10N-sodium hydroxide according to Brown (1950). The product had m.p. 179-182°. (Brown gives m.p. 178-180°).

1-Methylpyrimid-2-one. (a) 1-Methylpyrimid-2-one was prepared by the action of dry ethereal diazomethane on 2-hydroxypyrimidine as described by Brown, Hoerger, and Mason (1955). The product, once crystallised from benzene, had m.p. 123-125°. (Brown, Hoerger, and Mason give m.p. 127-128°).

(b) Dimethyl sulphate (1.25 ml.; 0.013 mole) was added to a mixture of 2-hydroxypyrimidine (1g.; 0.01 mole) and potassium carbonate (2g.; 0.014 mole) in water (5 ml.), the mixture warmed to 70° for 15 minutes and allowed to stand overnight at 20°. The solution was extracted with

chloroform, the extract was dried (Na_2SO_4), the solvent evaporated and the residue crystallised from benzene (charcoal) giving white needles (0.61g.; 53%), m.p. 129° . (Brown, Hoerger, and Mason give m.p. $127-128^\circ$).

1-Methylpyrimid-2-thione. 10N-Hydrochloric acid (1 ml.) was added to a mixture of malondialdehyde methyltriethylacetal (2g.; 0.01 mole) and N-methylthiourea (1g.; 0.011 mole) in ethanol (20 ml.) and the mixture set aside overnight at 20° . The mixture was evaporated to dryness, the residue dissolved in water (ca. 20 ml.), made alkaline with potassium carbonate and the solution extracted with chloroform. After drying (Na_2SO_4) the solvent was evaporated and the residue (1.35g.) chromatographed in chloroform over alumina and recrystallised from ethanol giving 1-methylpyrimid-2-thione as yellow crystals (0.67g.; 55%), m.p. $189-191.5^\circ$. (Found: C, 47.7; H, 4.9; N, 22.1; S, 25.6; $\text{C}_5\text{H}_6\text{N}_2\text{S}$ requires C, 47.6; H, 4.8; N, 22.2; S, 25.4%).

4-Chloropyrimidine hydrochloride was prepared from 4-hydroxypyrimidine by the action of phosphorus oxychloride as described by Boarland and McOmie (1951). The product which is unstable was used immediately in the next preparation.

4-Mercaptopyrimidine hydrochloride was prepared from 4-chloropyrimidine hydrochloride and thiourea as described by Boarland and McOmie (1951). The 4-mercaptopyrimidine

hydrochloride crystallised from ethanol as yellow needles, m.p. ca. 227° (decomp.) (Boarland and McOmie give m.p. 220°).

4-Methylmercaptopyrimidine. 4-Mercaptopyrimidine hydrochloride (1.22g.; 0.0082 mole) in N-sodium hydroxide (16.4 ml.) was shaken with methyl iodide (0.5 ml; 0.0082 mole) for ca. 15 minutes. The mixture was extracted with chloroform, the extract was dried (Na_2SO_4) and the solvent evaporated. The residue was distilled giving 4-methylmercaptopyrimidine (0.67g.; 65%) as a clear oil, b.p. 86-87°/12 mm. (Found: C, 47.5; H, 4.9; N, 21.9; S, 25.2. $\text{C}_5\text{H}_6\text{N}_2\text{S}$ requires C, 47.6; H, 4.8; N, 22.2; S, 25.4%).

1-Methylpyrimid-6-one was prepared from 4-hydroxypyrimidine and ethereal diazomethane according to Brown, Hoerger, and Mason, (1955). The product, once crystallised from light petroleum (b.p. 60-80°), had m.p. 120-123°. (Brown, Hoerger, and Mason crystallise from chloroform in which it is very soluble and give m.p. 125-126°).

1-Methylpyrimid-6-thione. 1-Methylpyrimid-6-one (0.2g.; 0.0018 mole) and phosphorus pentasulphide (0.6g.; 0.0027 mole) were refluxed in pyridine (6 ml.) for 1.5 hours. The pyridine was evaporated under reduced pressure, the excess phosphorus pentasulphide was decomposed by warming with water and the solution concentrated to 10 ml, adjusted to pH 4 with sodium carbonate and extracted with chloroform. The extract was dried (Na_2SO_4), the solvent

evaporated, and the residue (0.23g.) crystallised from light petroleum (b.p. 60-80°) giving 1-methylpyrimid-6-thione as light cream coloured crystals (0.15g.; 71%), m.p. 97-98.5°. (Found, for material dried at 20°/10 mm: C, 47.4; H, 4.8; N, 22.2; S, 25.5. $C_5H_6N_2S$ requires C, 47.6; H, 4.8; N, 22.2; S, 25.4%).

The N-methyl-2-methylmercaptopyrimidones. 2-Thiouracil was methylated with dimethyl sulphate and sodium hydroxide as described by Brown, Hoerger, and Mason (1955). The 1-methyl-2-methylmercaptopyrimid-6-one had m.p. 126-128°. (Brown, Hoerger, and Mason give m.p. 122-123°). The 1-methyl-2-methylmercaptopyrimid-4-one was best purified by crystallisation from acetone as colourless plates, m.p. 170-172°. (Brown, Hoerger, and Mason give m.p. 168-169°).

1-Methylpyrimid-4-one was prepared by the desulphurisation of 1-methyl-2-methylmercaptopyrimid-4-one with Raney nickel according to Brown, Hoerger, and Mason (1955). The 1-methylpyrimid-4-one had m.p. 159°. (Brown, Hoerger, and Mason give m.p. 155-156°).

1-Methylpyrimid-4-thione. 1-Methylpyrimid-4-one (0.5g.; 0.0045 mole) and phosphorus pentasulphide (1g.; 0.0045 mole) was refluxed in pyridine (10 ml.) for 1 hour and the pyridine evaporated under reduced pressure. The residue was extracted with boiling methanol and the product (0.51g.) crystallised from methanol (charcoal) giving 1-methylpyrimid-4-thione as yellow needles (0.30g.;

53%), m.p. 246° . (Found, for material dried at $20^{\circ}/10$ mm: C, 47.4; H, 4.8; N, 21.9, 22.0; S, 25.3. $C_5H_6N_2S$ requires C, 47.6; H, 4.8; N, 22.2; S, 25.4%.

BENZENE DERIVATIVES.

Mercaptobenzene. The B.D.H. mercaptobenzene was fractionated and the fraction, b.p. $161^{\circ}/710.3$ mm. collected. (Fischer (1915) gives b.p. $168-169^{\circ}/743$ mm.).

Methylmercaptobenzene. Mercaptobenzene was methylated with dimethyl sulphate in sodium hydroxide as described by Vogel (1948). The product was distilled, b.p. $184-185^{\circ}/697.5$ mm. (Vogel gives b.p. $192-192.5^{\circ}/761$ mm. for methylmercaptobenzene).

Methylmercaptan could not be detected when methylmercaptobenzene was heated with 5N-sulphuric acid.

DETERMINATION OF PHYSICAL CONSTANTS.(1) IONIZATION CONSTANTS.

Where possible, ionization constants were determined by potentiometric titration because of its convenience, but the more laborious spectrometric method was adopted in cases where (a) the solubility was too low ($10^{-3}M$ is usually the lower limit of accuracy for potentiometric titration), or (b) the constant was extreme (e.g. potentiometry loses in accuracy when the pK_a is less than the logarithm of the dilution).

(i) POTENTIOMETRIC TITRATIONS.

The dried specimen (0.0005 mole) was dissolved in air-free water and titrated under nitrogen at 20° , a Cambridge pH set being used with glass and calomel electrodes (standardized to pH 4.00 with 0.05 molar potassium hydrogen phthalate and 9.20 with 0.05 molar borax at 20°). When agreement on restandardization of this instrument after a titration was less than ± 0.02 unit, the figures were rejected and a new titration undertaken. Hydrochloric acid or carbonate-free potassium hydroxide (0.9 equivalents) was added in nine equal portions. The nine pK_a values for each pH reading were calculated (for acid regions) from the formula :

$$pK_a = pH - \log \left(\frac{[B] + [H^+]}{[BH^+] - [H^+]} \right) \quad (1)$$

where $[BH^+]$ and $[B]$ are the concentrations of the molecule, protonated and non-protonated respectively if hydrolysis

corrections (taken care of by the rest of the formula) are neglected, and (for alkaline regions) from:

$$pK_a = pH + \log \left(\frac{[AH] + [OH^-]}{[A^-] - [OH^-]} \right) \quad (2)$$

where $[AH]$ and $[A^-]$ are the concentrations of the molecule and anion respectively. Activities were employed in place of concentrations in formula (1) to calculate the pK_a (thermodynamic) in one case when the pK_a (1.30) lay near the limits for accurate determination by titration at the concentration (0.05 molar) employed :

The activity coefficient f was calculated from the expression:

$$-\log f = \left\{ \frac{\sqrt{I}}{1 + \sqrt{I}} - 0.2 I \right\} 0.5. \quad (3)$$

where I is the ionic strength of the protonated molecule. The nine pK_a values were converted into antilogarithms before averaging. The small spreads encountered gave additional confirmation of the purity of the substance. Solutions of the substance were made as concentrated * as solubility permitted to keep the hydrolysis corrections low. The strength of the titrant was 0.1 molar (added from a burette), or 1 molar (from a micrometer syringe) for the more concentrated solutions.

* but not above 0.05 molar to avoid association effects.

(a) Effect of ionic strength on pK'_a values determined by potentiometric titration.

The pK'_a of 4-methylmercaptopyridine was determined at various ionic strengths of potassium chloride by potentiometric titration of a 0.1 molar solution with 1 molar HCl. The results are summarized below.

Molarity KCl	pK'_a
0.00	5.98
0.1225	6.09
0.50	6.20
1.44	6.33
3.0	6.48

(ii) SPECTROMETRIC DETERMINATIONS OF pK'_a . Solutions (usually 0.000025 molar) were made in a series of buffers, standardised with a glass electrode. This series decreased in pH down to values where the change in spectrum, corresponding to the step of ionization under study, ceased; and similarly it increased towards the alkaline direction. Buffers (0.01 molar) of low ultraviolet absorption (ethylamine, borate, phosphate, acetate, formate and dilute hydrochloric acid) were used, and for low values the acidity function solutions

(sulphuric acid) of Hammett and Paul (1934), Hammett (1940), and Michaelis and Granick (1942). Measurements were made in the Hilger "Uvispek" H700/301 Quartz Spectrophotometer using 1 or 4 cm. cells. Buffer solutions of the same strength were used as controls, * at wavelengths selected because of marked differences found between the extinction coefficients of the two species involved in the equilibrium under study. For an equilibrium between a neutral molecule and a protonated form, the extinction coefficients of the neutral molecule (ϵ_M) and the protonated form (ϵ_{MH^+}) and the extinction coefficients of the sum of the two species (ϵ) were measured in solutions of such pH values as were found during the course of the determinations to correspond to the range from 20 to 80% protonation in 7 equal steps. The pK'_a 's were determined from the following formula:

$$pK'_a = pH - \log \left[(\epsilon_{MH^+} - \epsilon) / (\epsilon - \epsilon_M) \right]$$

converted into antilogarithms and averaged. A similar method and formula was used for the equilibrium involving the neutral molecule and anion. No hydrolysis correction is required in this method, but the usual activity corrections apply (Herington (1950)).

* The appropriate amount of iodide ion was included in the control when methiodides were being examined. The iodide ion has an absorption maximum at 228-229 m μ , log 3.88 and its ultraviolet absorption spectrum is shown in Appendix II.

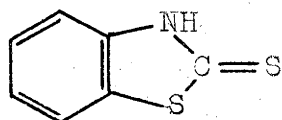
(2) ULTRAVIOLET ABSORPTION SPECTRA of the various species were taken in the Hilger "Uvispek" H700/301 Quartz Spectrophotometer. The solutions were buffered (the same series of buffers as used in spectrophotometric determinations of pK_a), at least 2 pH units away from the previously determined pK_a value, thus ensuring at least 99% of the required species (except when the two pK_a values of a mercapto - compound were less than 4pH units apart when the ultraviolet absorption spectrum of the molecule was taken at a pH mid-way between the two pK_a values). Measurements were taken in 1 and 4 cm. stoppered cells. Decomposition of the compound in solution was found to be negligible in stoppered cells during measurement of the spectrum.

(a) Example of neutralization of solution in sulphuric acid. A 0.0001 molar solution of 1-methylpyrid-4-thione in 4.13 N-sulphuric acid was neutralised under an atmosphere of nitrogen with 10N-sodium hydroxide and the solution diluted to 0.000025 molar at pH 7.0. Ultraviolet spectral reading showed that the molecule of 1-methylpyrid-4-thione was present in solution and the extinction coefficients were almost identical with those found previously for the molecule. This process was carried out to make sure that the sulphuric acid used in the measurement of the spectra of the cation had not destroyed the substance.

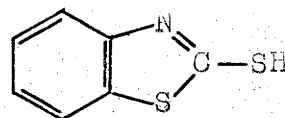
APPENDIX I.HISTORICAL OUTLINE.Mercapto - derivatives of Five - membered Rings.

The possibility of tautomerism in nitrogenous heterocyclic mercapto - compounds in which the heterocyclic nucleus is a five - membered ring is illustrated by the following observations.

(1). Reed, Robertson, and Sexton (1939) found that 2-mercaptobenzothiazole ($I \longleftrightarrow II$) with methyl iodide or dimethyl sulphate and alkali gave mainly the S-methyl derivative, but Sexton and Spinks (1948) found that 2-mercaptobenzothiazole with aqueous or alcoholic formaldehyde gave the N-hydroxymethyl derivative. The structure of this derivative was definitely established by comparison of its ultraviolet absorption spectrum with that of the N- and S-methyl derivatives of 2-mercaptobenzothiazole.

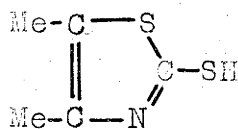


(I)



(II)

(2) Stewart and Mathes (1949) found that reactions involving the sodium salt of 4:5-dimethyl-2-mercaptothiazole (III) and halogenated reagents (e.g. *n*-butyl bromide) usually gave S-substituted derivatives but reaction of the sodium salt with acrylonitrile or of the molecule of (III) with formaldehyde gave the N-substituted derivative. The position of the substituent was established by ultraviolet absorption spectral studies.



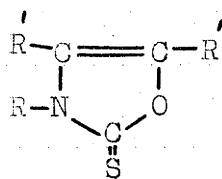
(III)

Evidence of the state of tautomerism at equilibrium in non-aqueous media. The tautomerism of five-membered ring nitrogenous heterocyclic mercapto - compounds has been studied only in non-aqueous media. Infrared, fluorescent and ultraviolet absorption spectral measurements have been made, and in one case dipole moments have been determined.

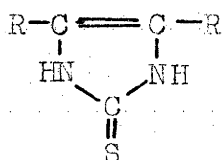
In each case the thioamide structure is favoured at the expense of the thiol structure.

(i) Infrared absorption spectra. A large amount of data has been published on the infrared absorption spectra of five - membered ring nitrogenous heterocyclic

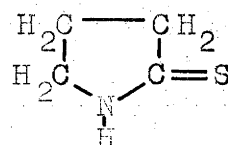
mercapto - compounds in non-aqueous solution. For example Gompper and Herlinger (1956b) have examined 2-mercapto-oxazoles e.g. (IV) and one N-phenyl derivative, and 2-mercapto-iminazoles e.g. (V); Mecke and Mecke (1956) have examined 2-mercaptopyrrolidine (VI), 2-mercapto-oxazoline (VII) and ethylenethiourea (VIII); Fleet (1953) has examined 2-mercaptothiazoline (IX) and its S-methyl derivative; and Ettlinger (1950) has discussed the infrared absorption spectra of 2-mercaptothiazoline (IX), 2-mercapto-oxazoline (VII) and 1-methyl-2-mercaptoiminazole (X).



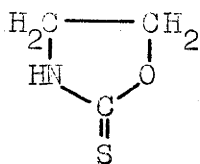
(IV)



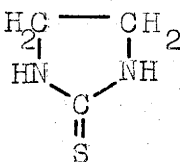
(V)



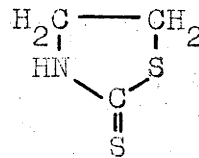
(VI)



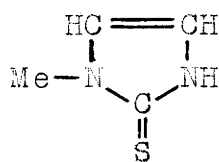
(VII)



(VIII)



(IX)



(X)

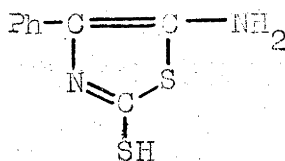
This evidence is considered by the authors to be consistent with a principally thioamide structure for the mercapto - compound. However, in general, comparisons of the mercapto - compound with its N- and S- substituted derivatives have not been made. When such comparisons have been made, they have supported these conclusions. Thus, Gompper and Herlinger showed that the infrared spectrum of 4:5-dipropyl-2-mercapto-oxazole (IV: R = H; R' = Pr) and its N-phenyl derivative were similar, and Fleet has shown that the infrared spectra of 2-mercaptobenzothiazole and its S-methyl derivative were very different.

(ii) Ultraviolet absorption spectra. The ultraviolet absorption spectra of a number of mercapto - compounds of five-membered heterocyclic rings and their N- and S-methyl derivatives have been examined and illustrate the existence of the mercapto - compound mainly in the thioamide form.

(a) Thiazoles. Hasan and Hunter (1936) examined the ultraviolet absorption spectra in methanol of some 6- substituted 2-mercaptobenzothiazoles e.g. 6-methyl-2-mercaptobenzothiazole and their N- and S-methyl derivatives and found that the spectrum of the mercapto - compound was strikingly similar to that of the N-methyl derivative but quite different from that of the S-methyl derivative. The spectrum of the mercapto - compound

underwent a hypsochromic shift when treated with alkali as observed in the present studies of mercapto-derivatives of mono- and diaza-heterocyclic compounds of six-membered rings. Morton and Stubbs (1939) examined the ultraviolet absorption spectra in alcoholic solution of 2-mercaptobenzothiazole and its N- and S-methyl derivatives and found that the spectrum of the mercapto-compound also corresponded to that of the N-methyl derivative but was quite different from that of the S-methyl derivative. Koch (1949) arrived at the same conclusions from ultraviolet absorption spectral studies in ethanol, benzene and chloroform.

Stern (1949) examined the ultraviolet absorption spectra published by Cook et al. (1947, 1948) and has suggested that 2-mercapto-4-phenyl-5-aminothiazole (XI) exists as the thiol form due to conjugation of the benzene ring with the thiol structure.



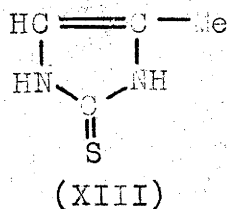
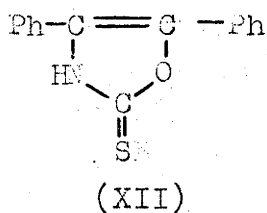
(XI)

He bases his conclusions on the difference of the ultraviolet absorption spectra of the 4-phenyl derivative from 2-mercapto-5-aminothiazole and its 4-n-hexyl and 4-1'-ethyl-n-amyl derivatives, and claims that the long-wavelength absorption band (which lies at shorter

wavelengths in the 4-phenyl derivative) indicates the existence of the thiol form. He mentions the hypsochromic shift in the spectrum of the other mercapto - compounds when they are treated with alkali but 2-mercapto-4-phenyl-5-aminothiazole undergoes a bathochromic shift. However, Stern has compared the spectrum of (XI) in dioxane with the others in alcoholic solution and without regard to pK values. This is not good practice and any conclusions must therefore be suspect.

Oxazoles. Gompper and Herlinger (1956a) have shown by fluorescent and ultraviolet absorption spectral studies in methanol that 4:5-diphenyl-2-mercapto-oxazole (XII) exists mainly as the thioamide because the spectrum resembles that of the N-methyl derivative and not the S-methyl derivative.

Imidazoles. Lawson and Morley (1956) have measured the ultraviolet absorption spectra of 2-mercapto-4-methylimidazole (XIII) in ethanol.



They found it to be similar to that of the N(1)-methyl derivative but quite different to that of the S-methyl derivative.

(iii) Dipole moment measurements. Additional evidence for the dominance of the thioamide structure of 2-mercaptobenzothiazole and its 4- and 6-methyl derivatives in benzene solution has been obtained by Oesper, Lewis, and Smyth (1942) from dipole moment measurements. They have shown that the dipole moment of 2-mercaptobenzothiazole (4.00 D.) is similar to that of its N-methyl derivative (4.30 D.) but quite different to that of its S-methyl derivative (1.42 D.).

APPENDIX II.Ultraviolet Absorption Spectra.

The ultraviolet absorption spectra of the cation, molecule (or zwitterion) and anion (where possible) of each substance * are shown in the following figures.

Fig.	Substance.
9	2-Mercaptopyridine
10	1-Methylpyrid-2-thione
11	2-Methylmercaptopyridine
12	3-Mercaptopyridine
13	N-Methyl derivative of 3-mercaptopyridine
14	3-Methylmercaptopyridine
15	4-Mercaptopyridine
16	1-Methylpyrid-4-thione
17	4-Methylmercaptopyridine
18	2-Mercaptoquinoline
19	1-Methylquinol-2-thione
20	2-Methylmercaptoquinoline
21	3-Mercaptoquinoline
22	N-Methyl derivative of 3-mercaptoquinoline
23	3-Methylmercaptoquinoline
24	4-Mercaptoquinoline
25	1-Methylquinol-4-thione
26	4-Methylmercaptoquinoline
27	5-Mercaptoquinoline
28	N-Methyl derivative of 5-mercaptoquinoline
29	5-Methylmercaptoquinoline
30	6-Mercaptoquinoline
31	N-Methyl derivative of 6-mercaptoquinoline
32	6-Methylmercaptoquinoline
33	8-Mercaptoquinoline
34	8-Methylmercaptoquinoline
35	1-Mercapto <u>iso</u> quinoline
36	2-Methyl <u>iso</u> quinol-1-thione
37	1-Methylmercapto <u>iso</u> quinoline
38	3-Mercapto <u>iso</u> quinoline
39	3-Methylmercapto <u>iso</u> quinoline
40	2-Mercaptopyrazine

* The spectrum of iodide ion is shown in Fig. 50.

41	1-Methylpyraz-2-thione
42	2-Methylmercaptopyrazine
43	2-Mercaptoquinoxaline
44	1-Methylquinoxal-2-thione
45	2-Methylmercaptoquinoxaline
46	1-Methylpyrimid-2-thione
47	1-Methylpyrimid-4-thione
48	1-Methylpyrimid-6-thione
49	4-Methylmercaptopyrimidine
50	Iodide ion

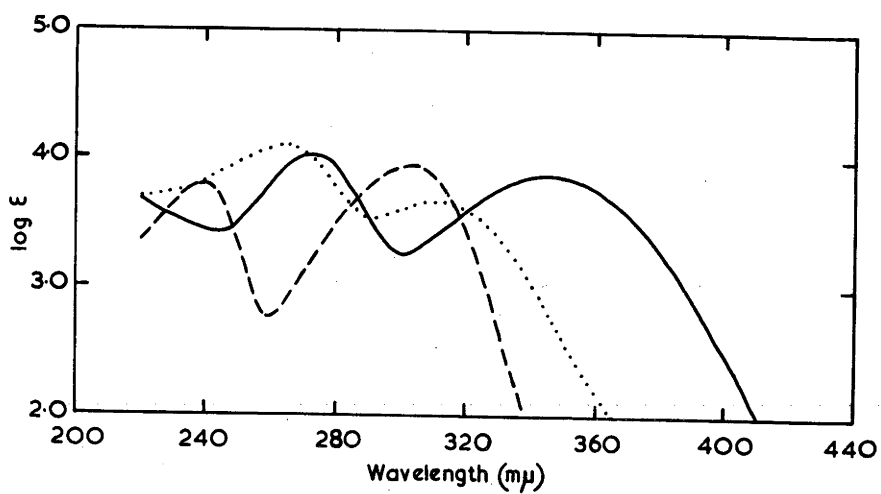


Fig. 9. 2-Mercaptopyridine

— Molecule
 --- Cation
 Anion

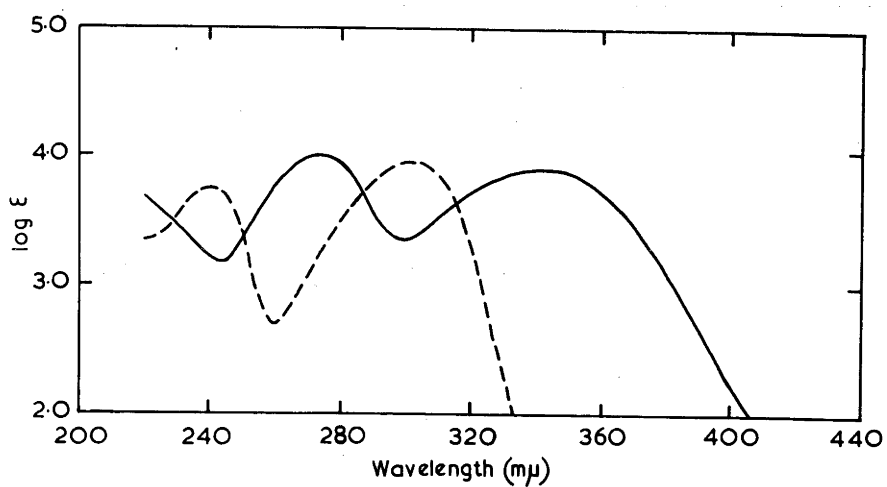


Fig. 10. 1-Methylpyrid-2-thione

— Molecule
 --- Cation

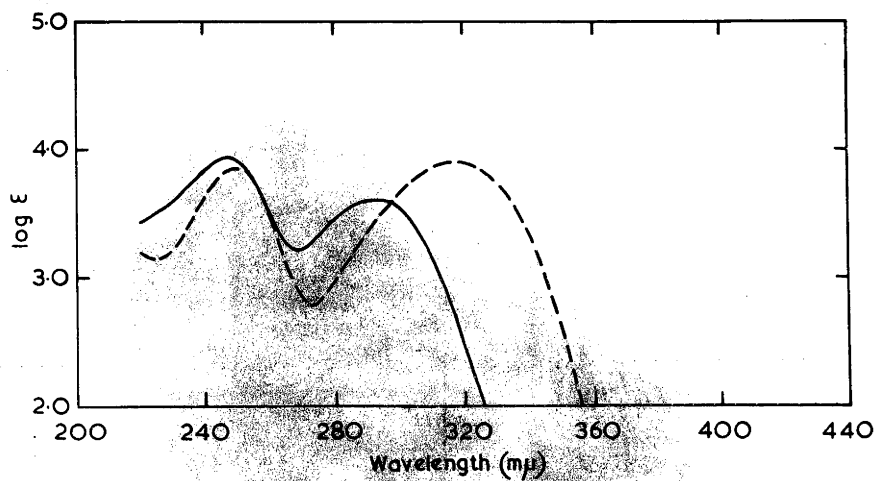


Fig. 11. 2-Methylmercaptopyridine

— Molecule
 - - - Cation

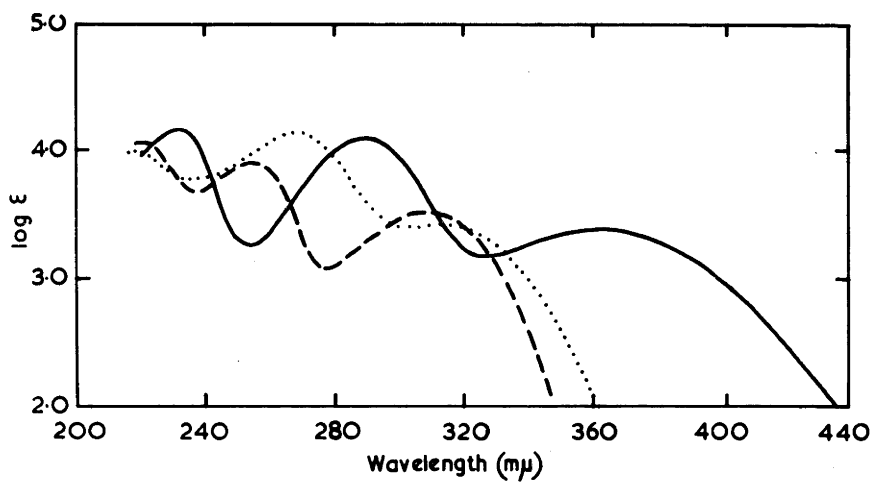


Fig. 12. 3-Mercaptopyridine

— Molecule
 - - - Cation
 Anion

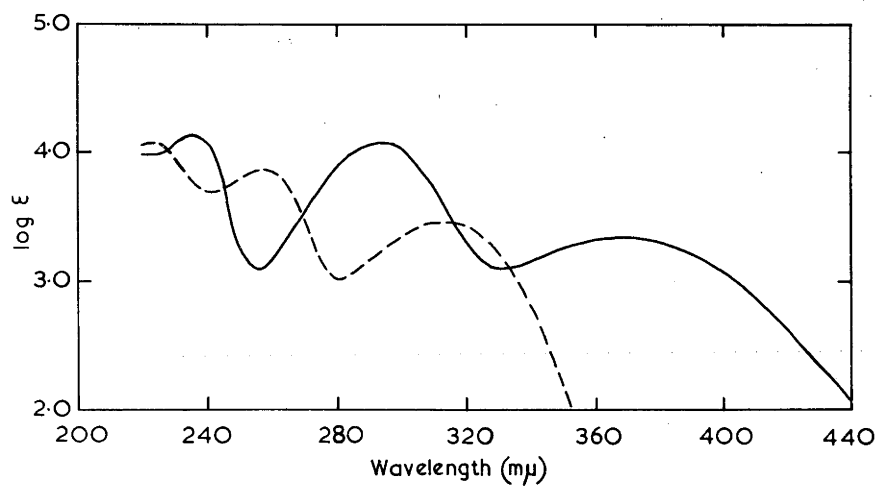


Fig.13. N-Methyl derivative of 3-mercaptopyridine

— Zwitterion
--- Cation

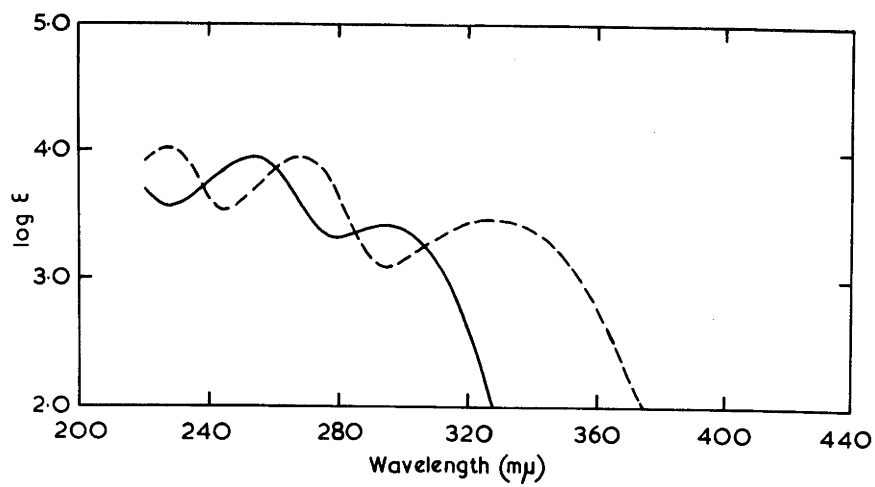


Fig. 14. 3-Methylmercaptopyridine

— Molecule
--- Cation

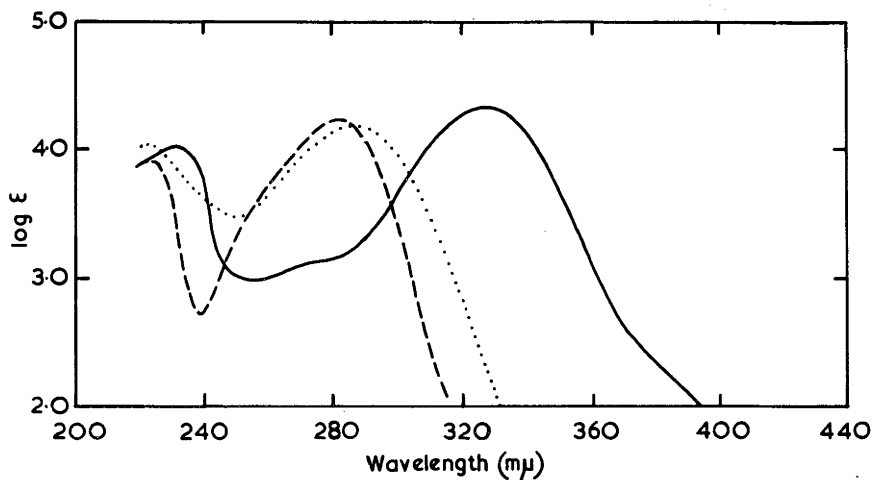


Fig. 15. 4-Mercaptopyridine

— Molecule
- - - Cation
..... Anion

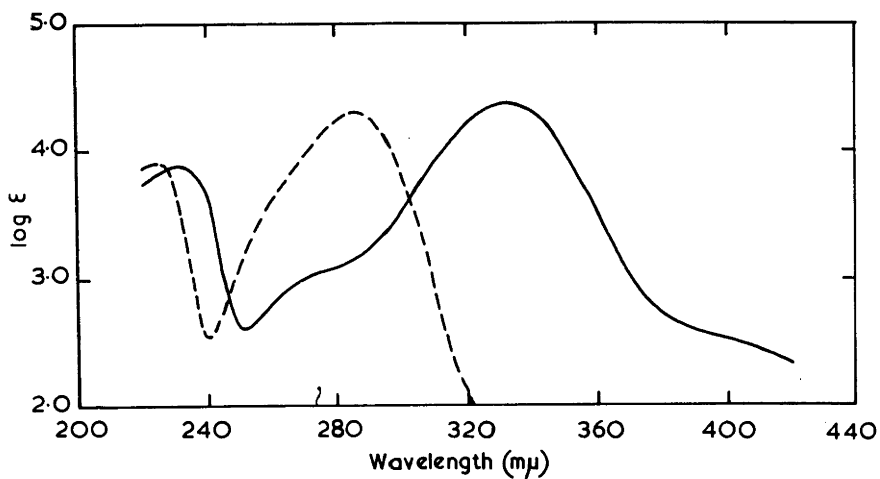


Fig. 16. 1-Methylpyrid-4-thione

— Molecule
- - - Cation

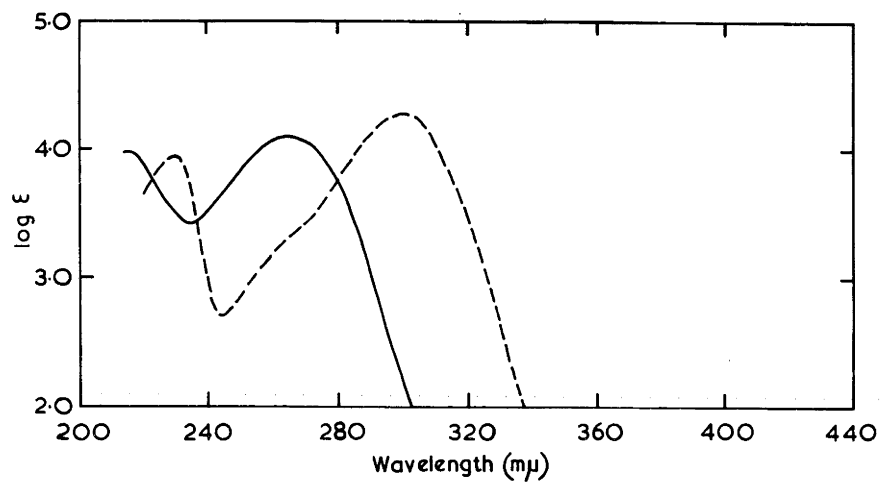


Fig. 17. 4-Methylmercaptopyridine

— Molecule
--- Cation

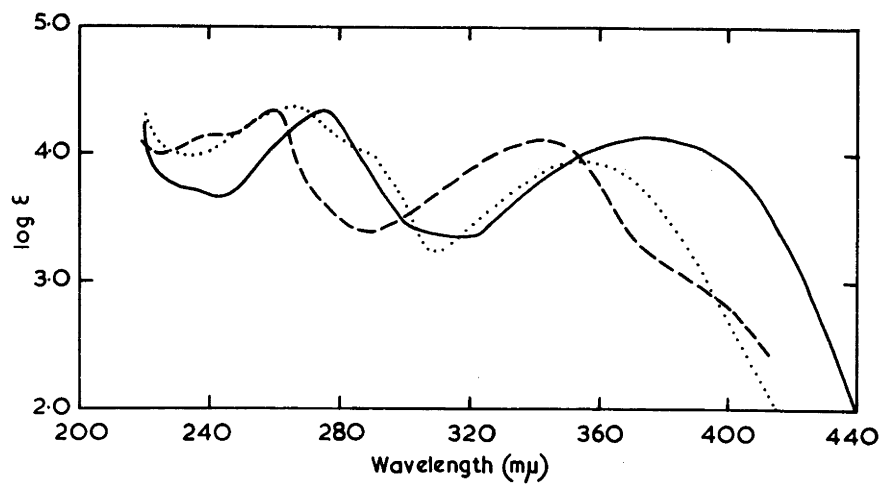


Fig. 18. 2-Mercaptoquinoline

— Molecule
--- Cation
..... Anion

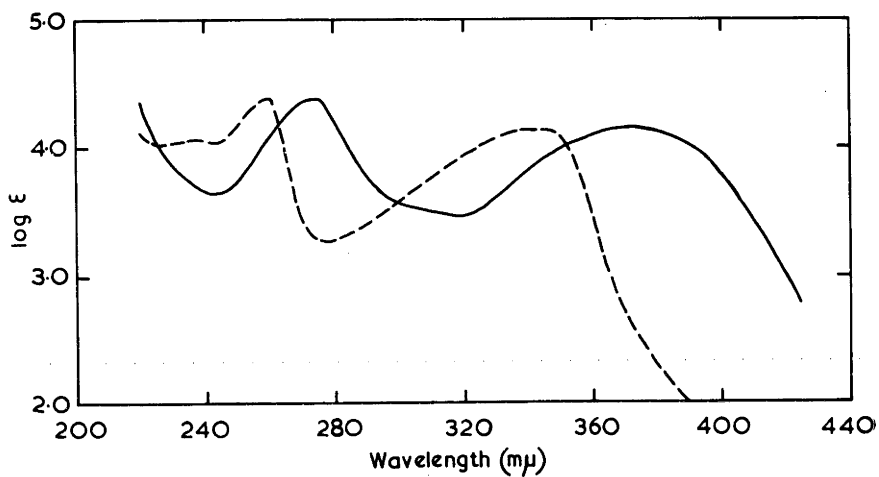


Fig. 19. 1-Methylquinol-2-thione

— Molecule
--- Cation

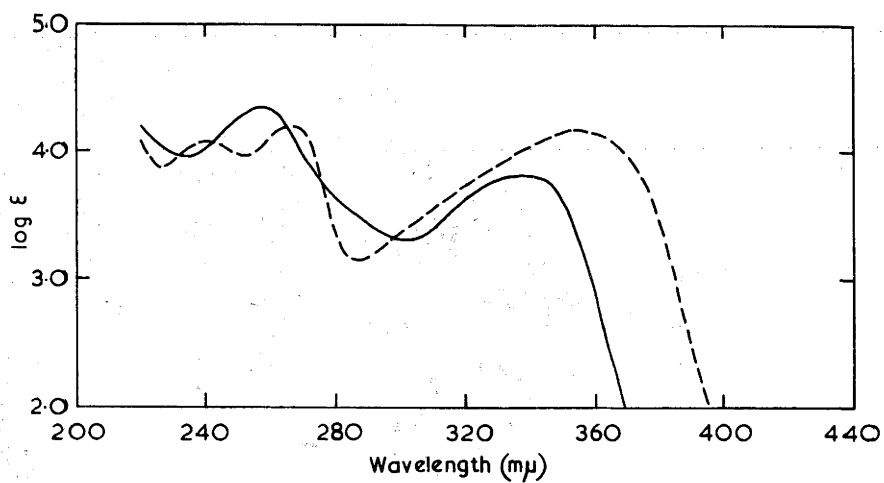


Fig. 20. 2-Methylmercaptoquinoline

— Molecule
--- Cation

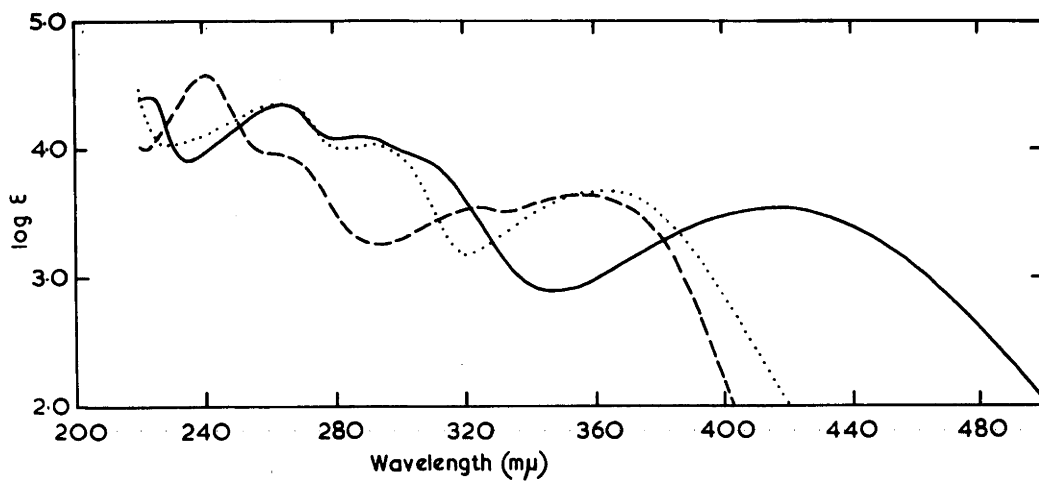


Fig. 21. 3-Mercaptoquinoline

— Molecule
 --- Cation
 Anion

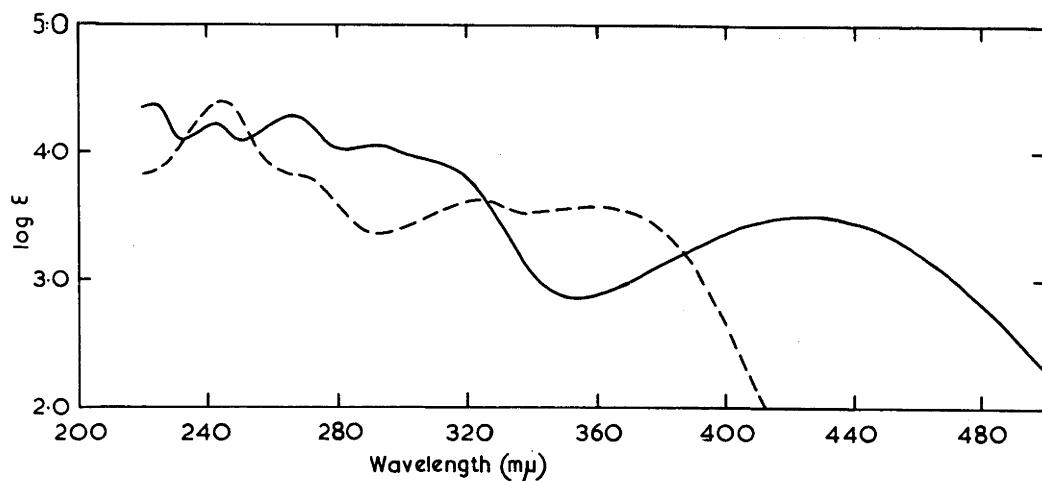


Fig. 22. N-Methyl derivative of 3-mercaptoquinoline

— Zwitterion
 --- Cation

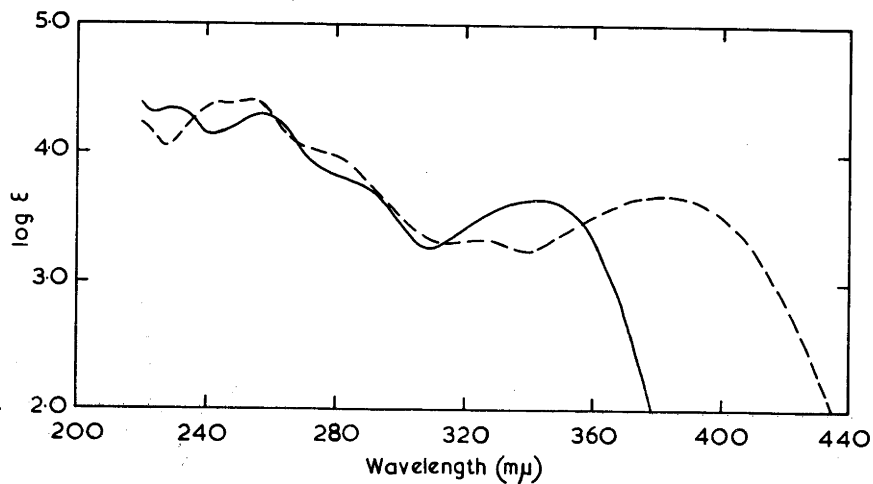


Fig. 23. 3-Methylmercaptoquinoline

— Molecule
 - - - Cation

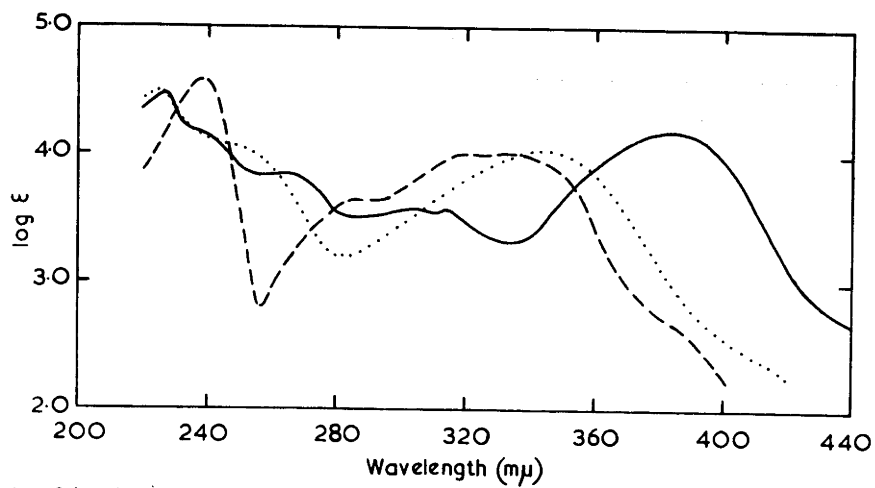


Fig. 24. 4-Mercaptoquinoline

— Molecule
 - - - Cation
 Anion

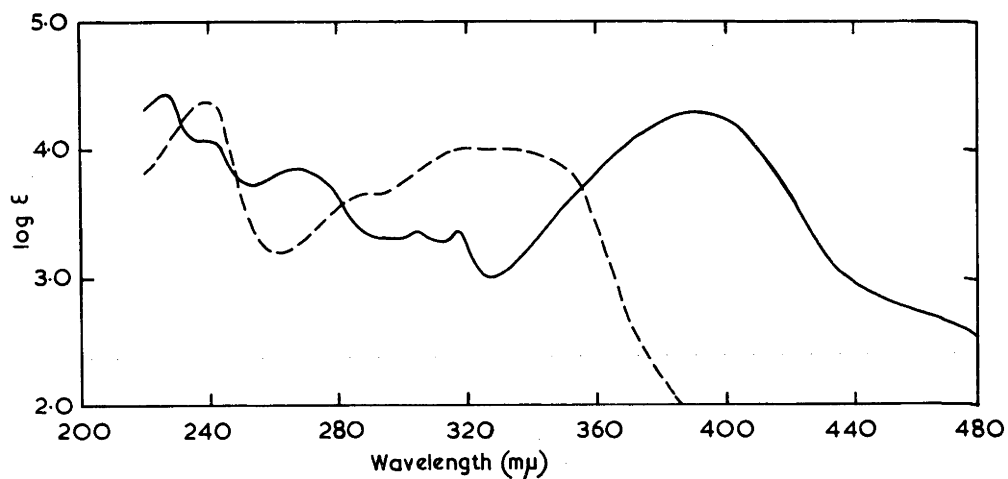


Fig. 25. 1-Methylquinol-4-thione

— Molecule
--- Cation

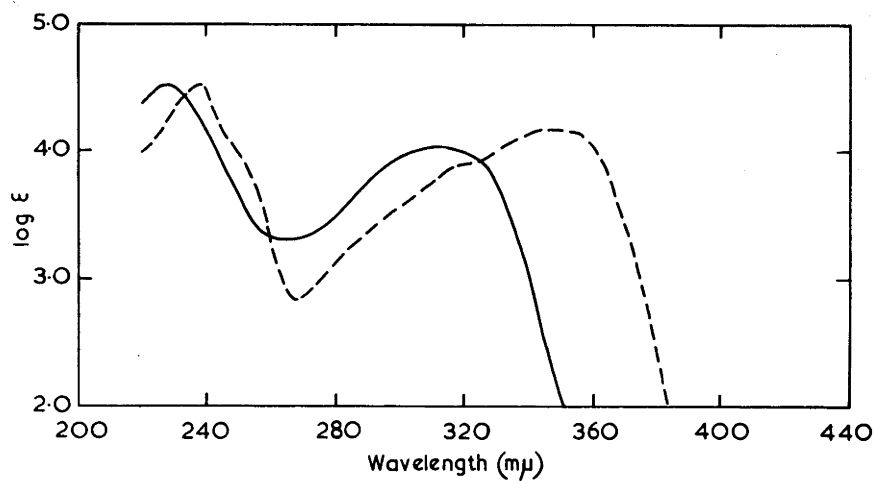
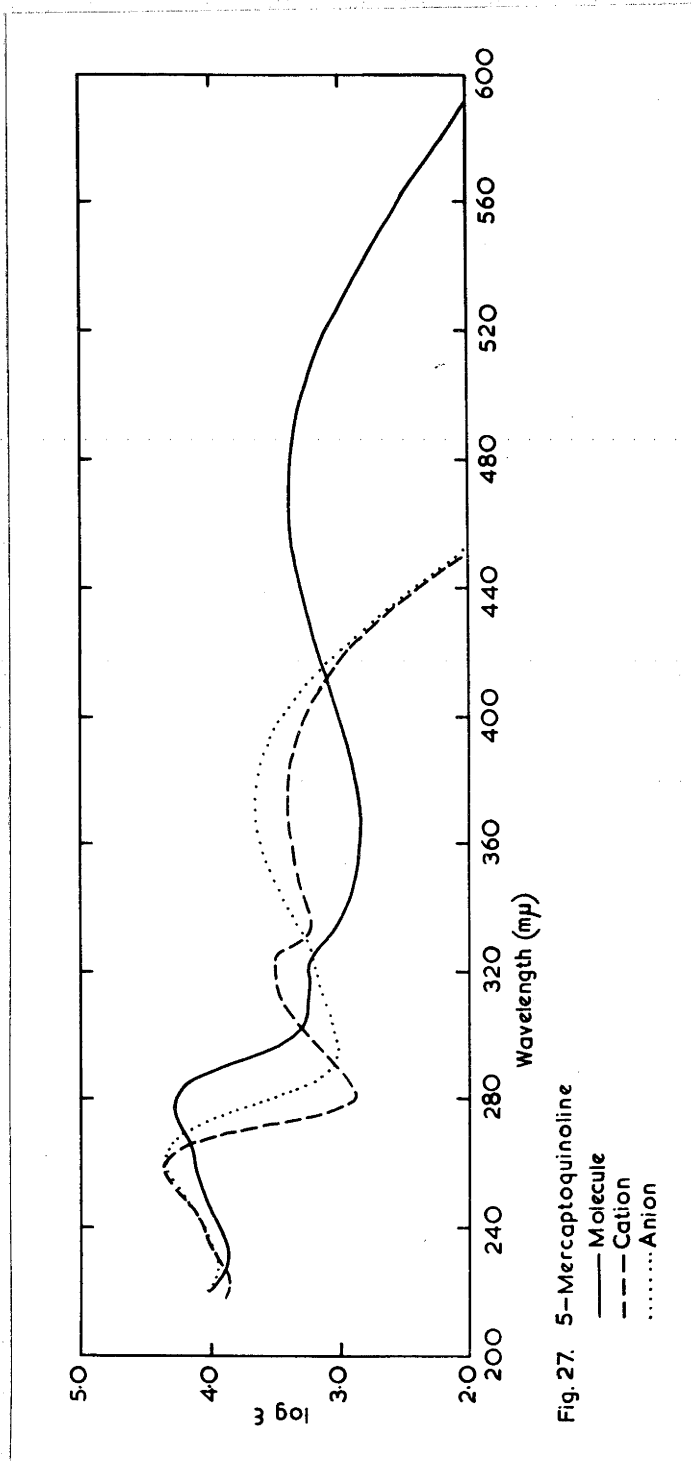


Fig. 26. 4-Methylmercaptoquinoline

— Molecule
--- Cation



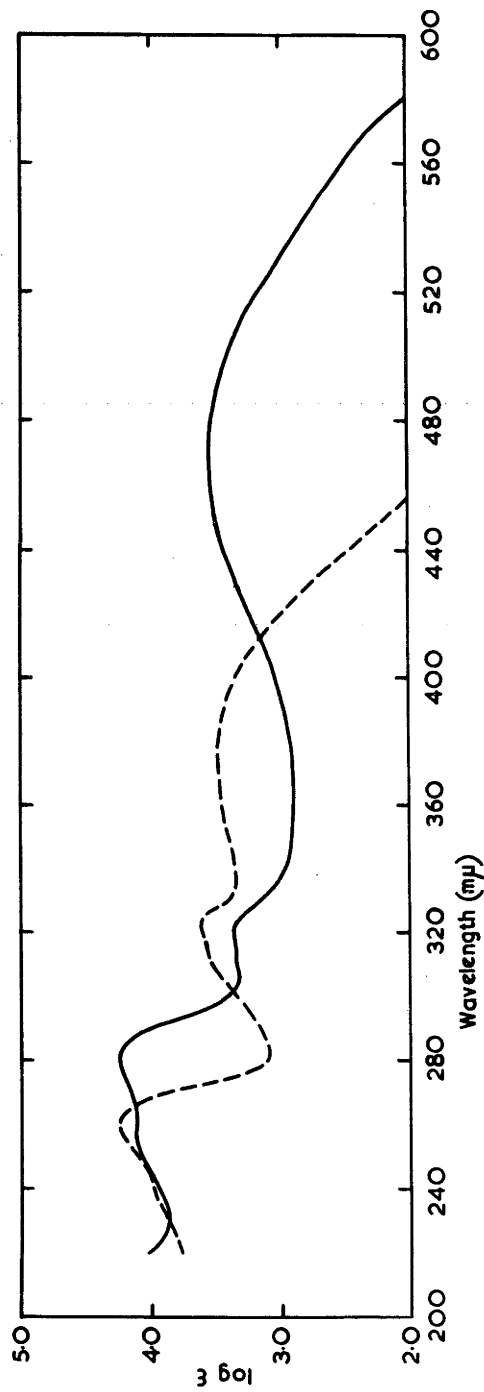


Fig. 28. N-Methyl derivative of 5-mercaptoquinoline

— Zwitterion

- - - Cation

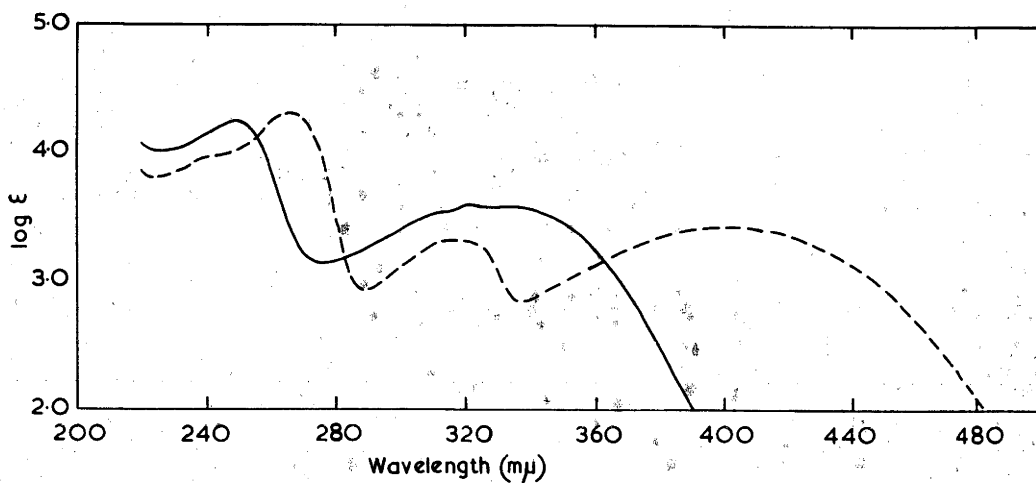


Fig. 29. 5-Methylmercaptoquinoline

— Molecule
 - - - Cation

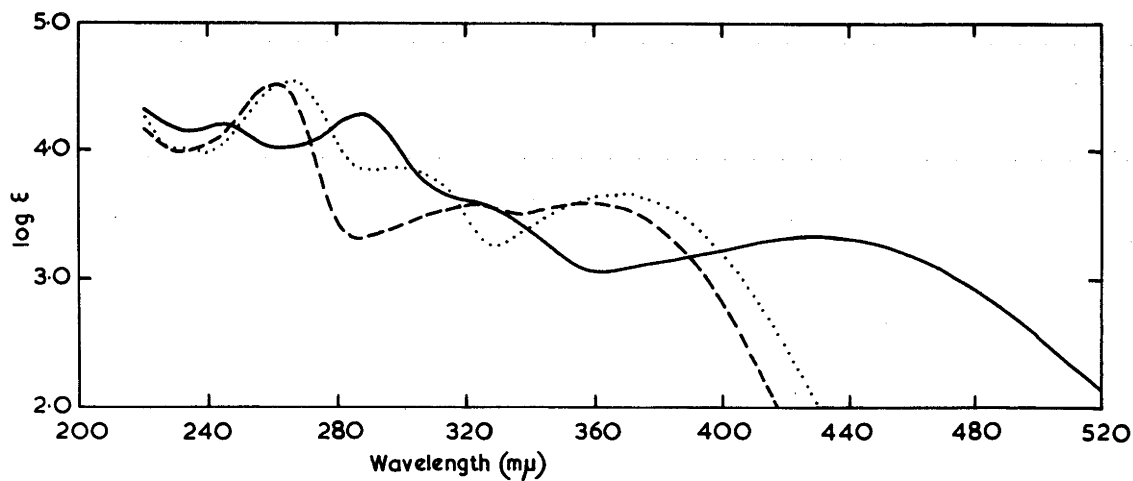
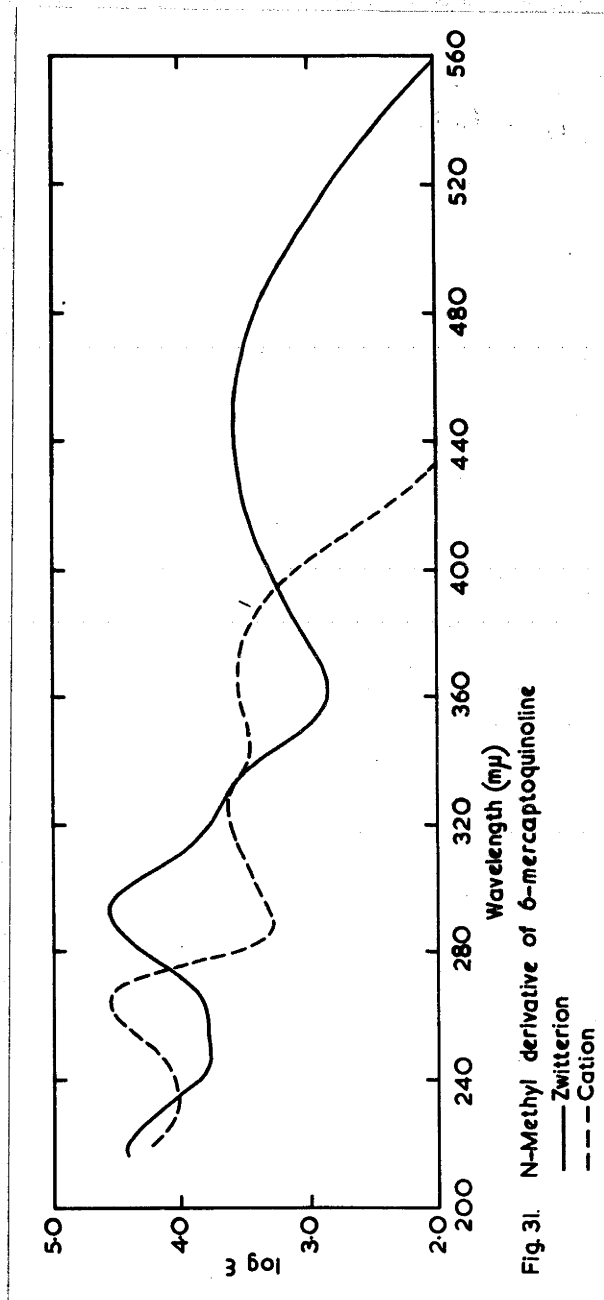


Fig. 30. 6-Mercaptoquinoline

— Molecule
 - - - Cation
 Anion



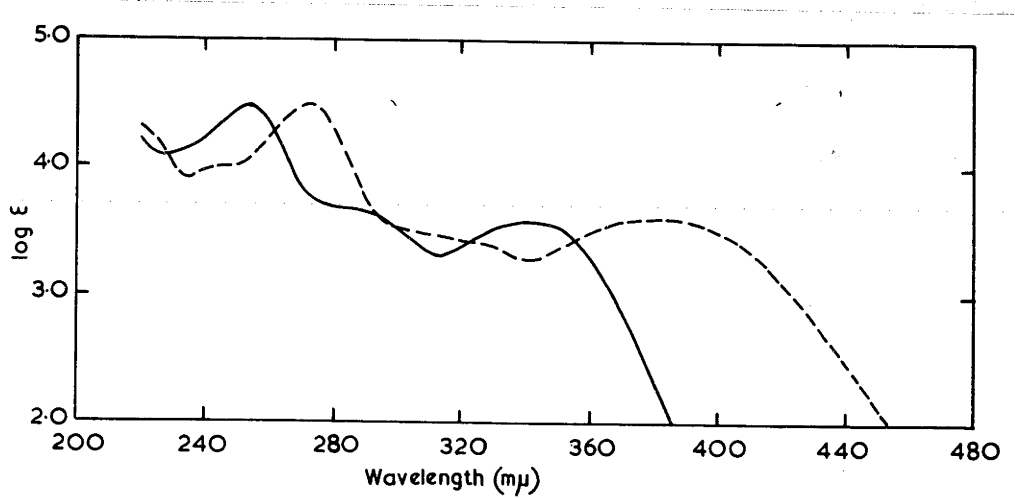


Fig. 32. 6-Methylmercaptoquinoline

— Molecule
--- Cation

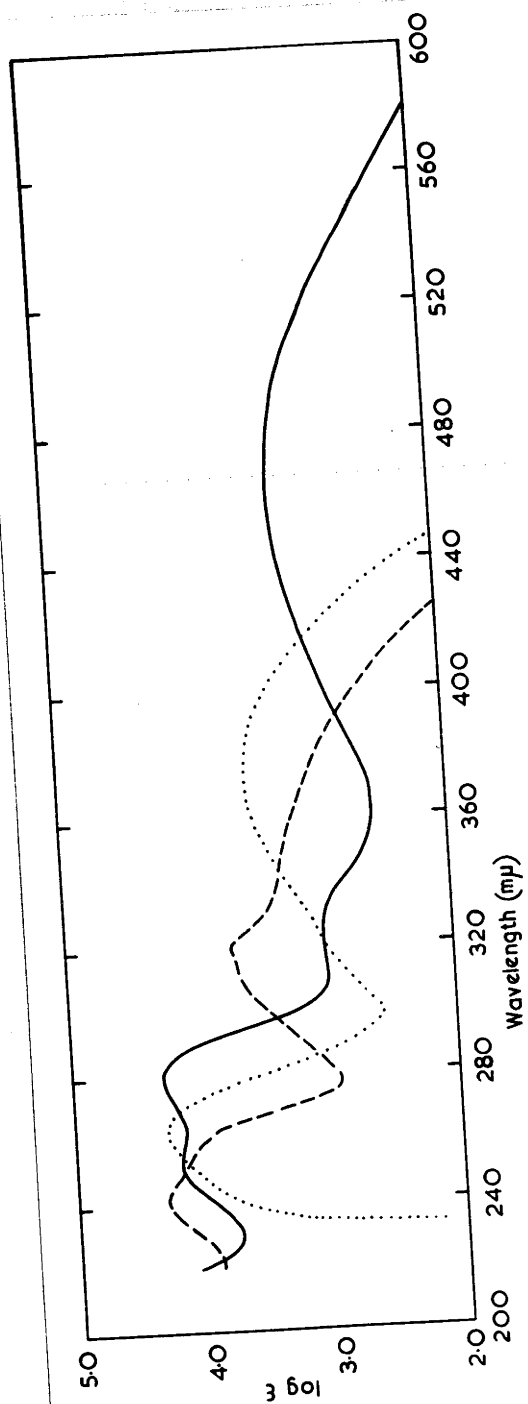


Fig. 33. 8-Mercaptoquinoline

— Molecule
- - - Cation
..... Anion

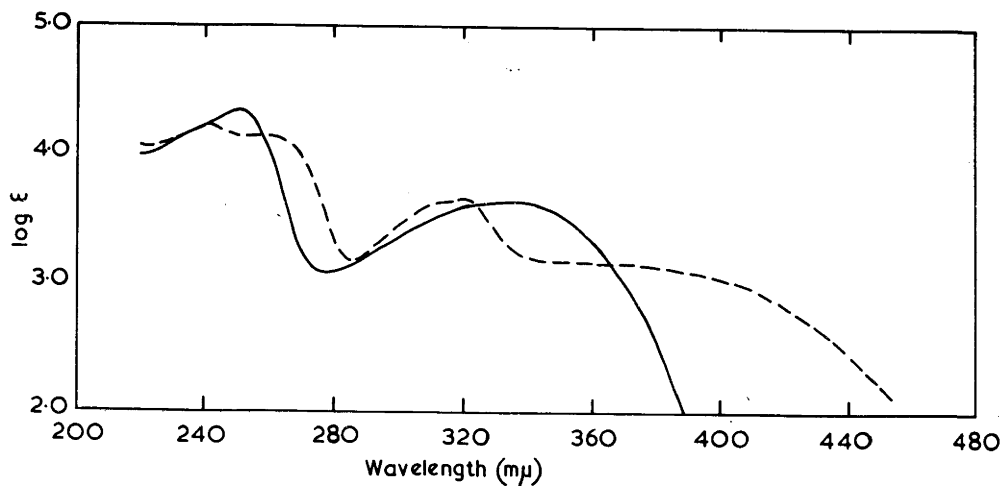


Fig. 34. 8-Methylmercaptoquinoline

— Molecule
 --- Cation

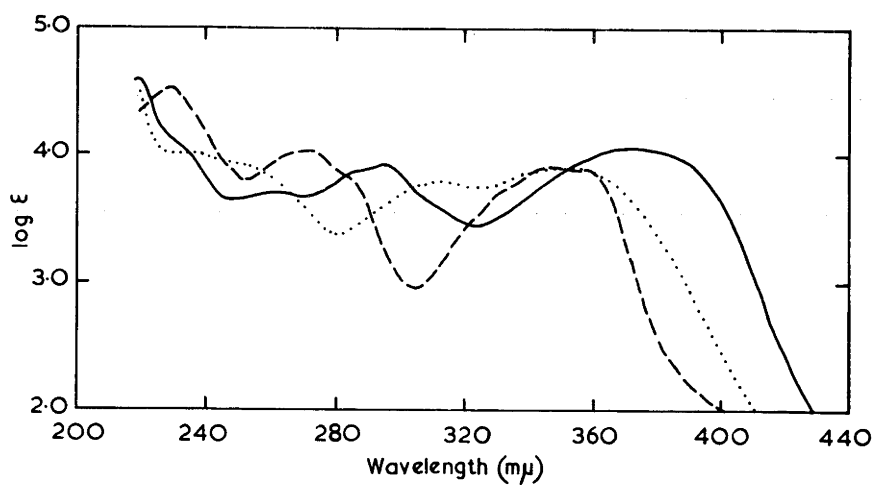


Fig. 35. 1-Mercaptoisoquinoline

— Molecule
 --- Cation
 Anion

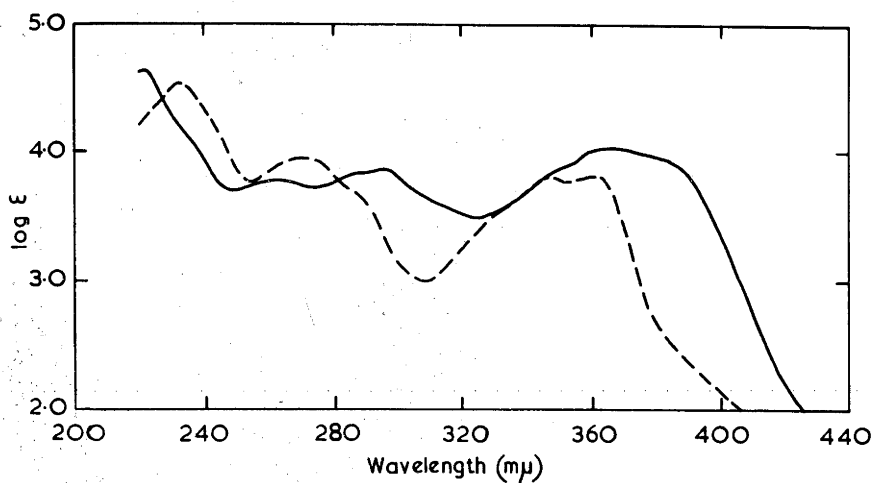


Fig. 36. 2-Methylisoquinolin-1-thione

— Molecule
--- Cation

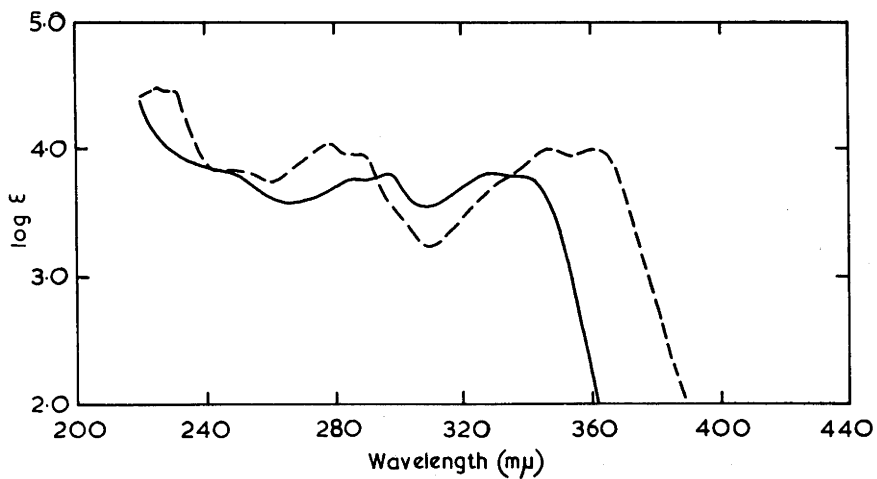


Fig. 37. 1-Methylmercaptoisoquinoline

— Molecule
--- Cation

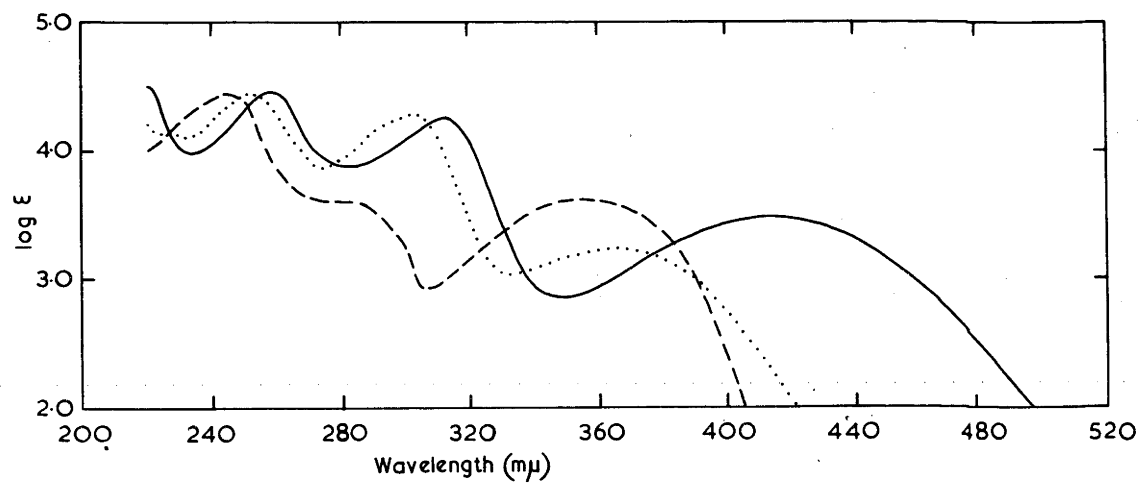


Fig. 38. 3-Mercaptoisoquinoline

— Molecule
 --- Cation
 Anion

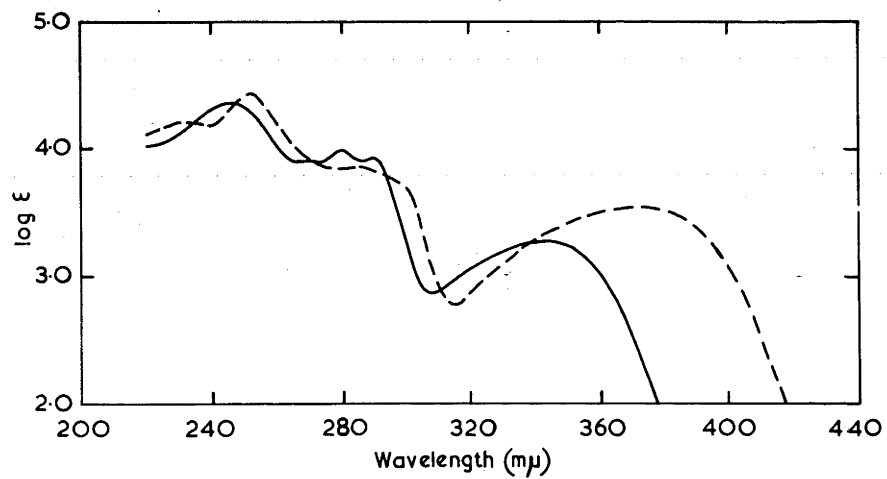


Fig. 39. 3-Methylmercaptoisoquinoline

— Molecule
 --- Cation

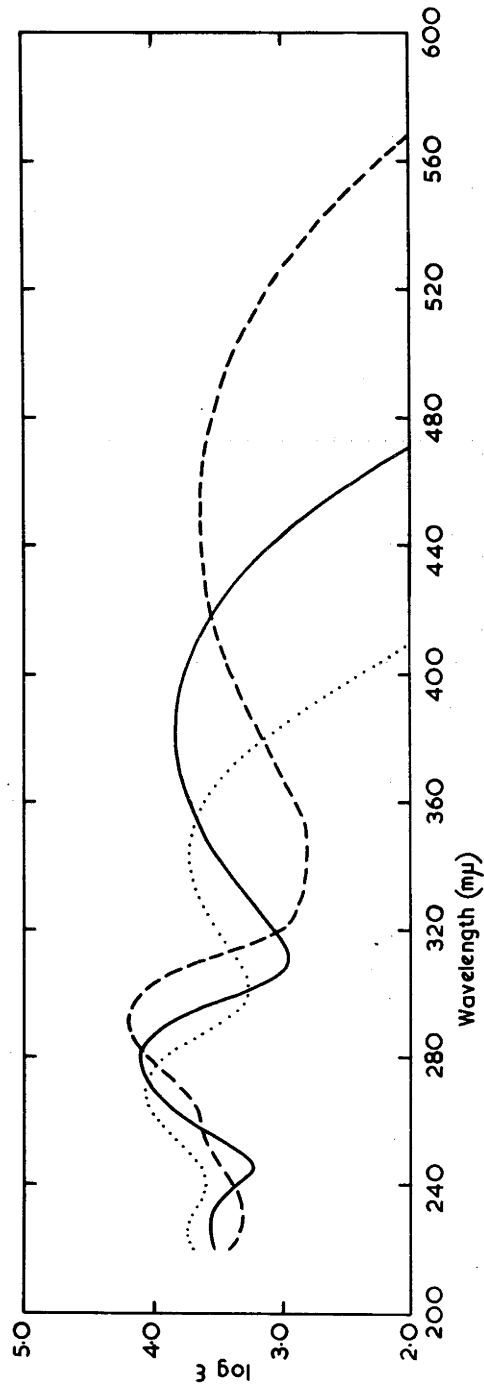


Fig. 4Q 2-Mercaptopyrazine

— Molecule
- - - Cation
..... Anion

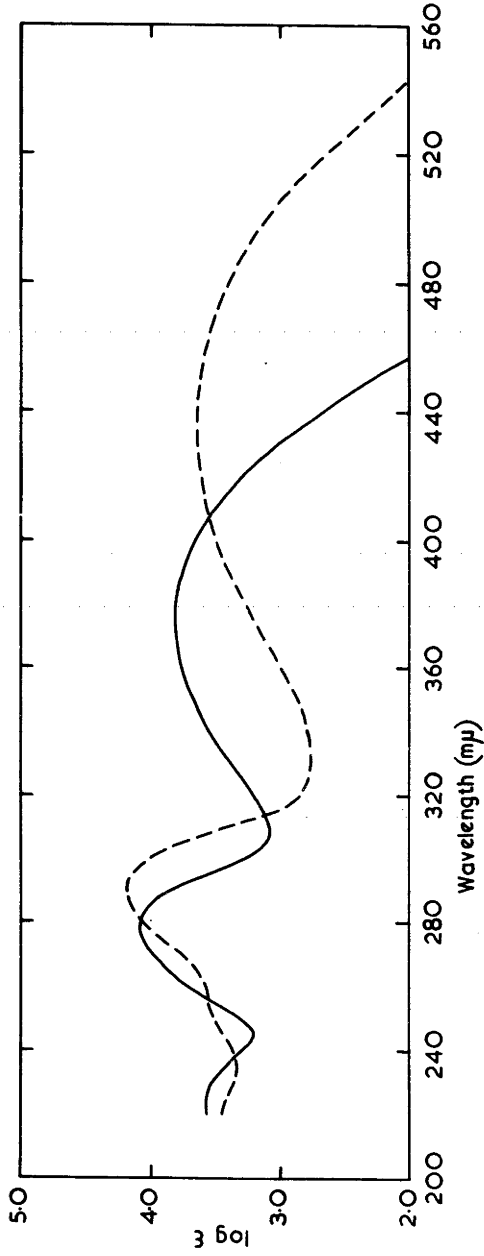


Fig. 41. 1-Methylpyraz-2-thione

— Molecule
- - - Cation

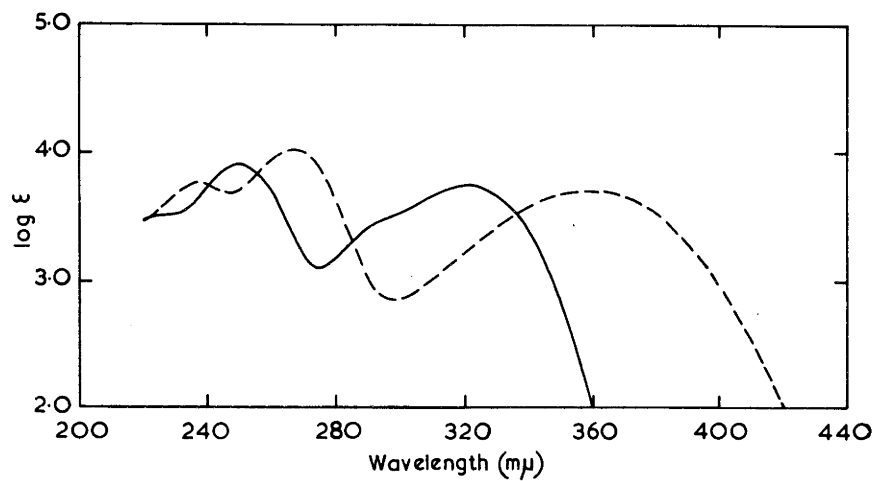


Fig. 42. 2-Methylmercaptopyrazine

— Molecule
--- Cation

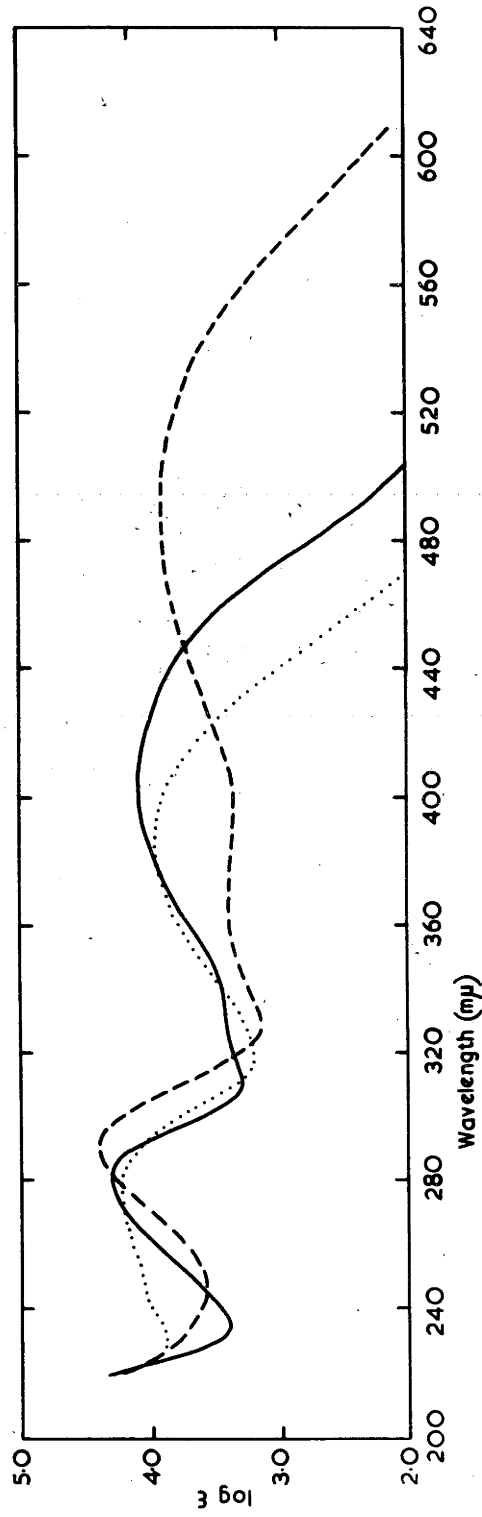


Fig. 43. 2-Mercaptoquinoxaline
— Molecule
- - - Cation
..... Anion

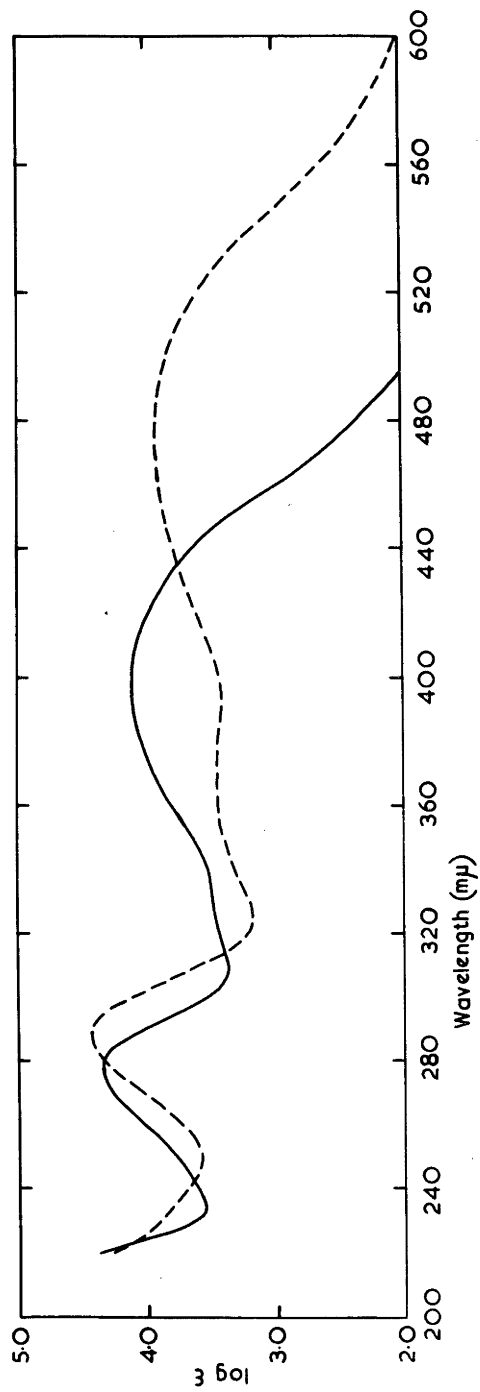


Fig. 4.4. 1-Methylquinoxal-2-thione

— Molecule
-- Cation

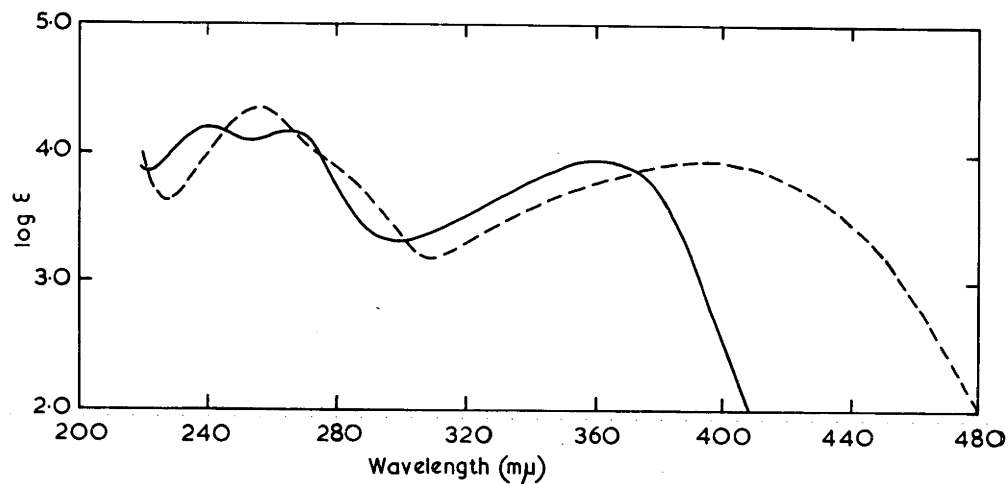


Fig. 45. 2-Methylmercaptoquinoxaline

— Molecule
 --- Cation

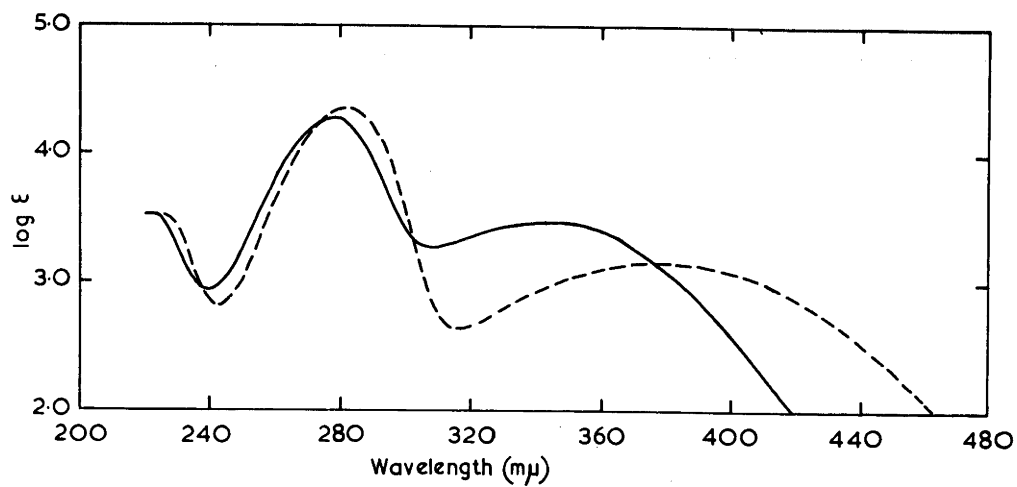


Fig. 46. 1-Methylpyrimid-2-thione

— Molecule
 --- Cation

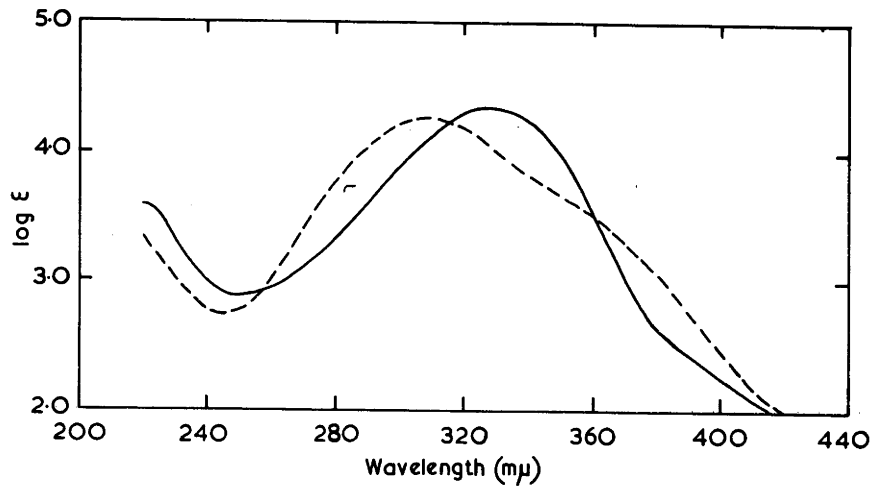


Fig. 47. 1-Methylpyrimid-4-thione
— Molecule
--- Cation

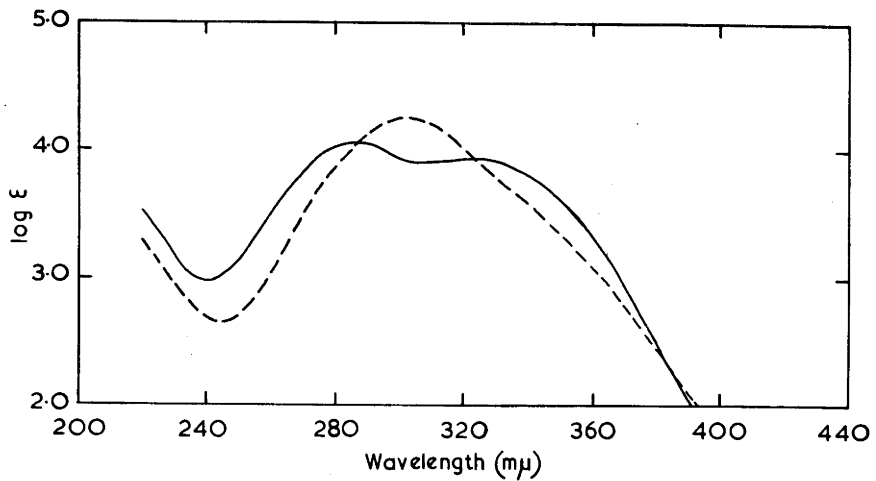


Fig. 48. 1-Methylpyrimid-6-thione
— Molecule
--- Cation

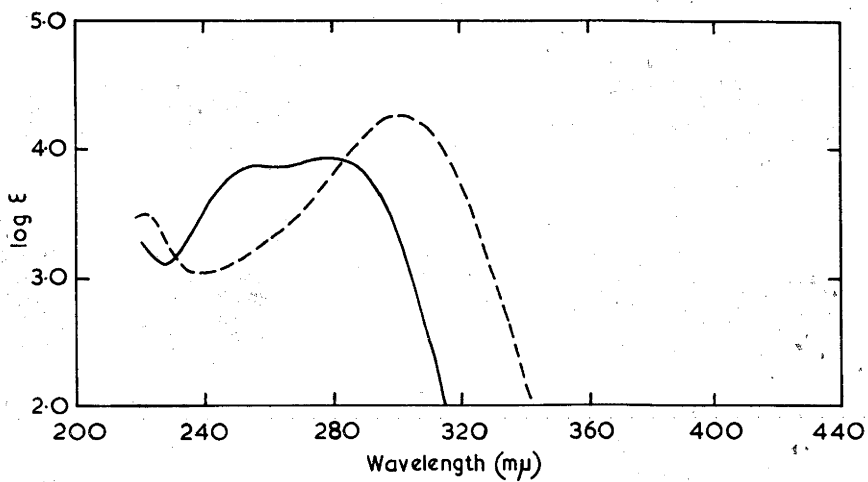


Fig. 49. 4-Methylmercaptopyrimidine.

— Molecule
- - - Cation

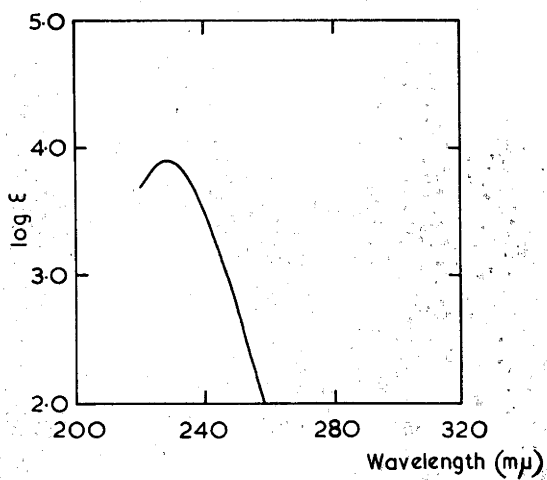


Fig. 50. — Iodide ion

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