SYNTHESIS AND REACTIVITY OF NITROGEN HETEROCYCLIC QUATERNARY AMMONIUM SALTS

(such as quinol-2-yltrimethylammonium iodide and 2-dimethylamino-1-methylquinolinium iodide)

a thesis

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

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NOMENCLATURE

The structures and numbering of the heterocyclic ring systems discussed in this thesis are given below.

Trimethylammonio-derivatives of tetrapyridine, pyridazine, pyridazine, quinoline, isoquinoline, cinnoline, phthalazine and quinoxaline give only the corresponding dimethylaminio-compounds.

Trimethylammonio-compounds were also obtained by the quaternization of 2-dimethylaminopyridine with trimethylamine but in a weaker quaternary base than in the quaternary ammonium compounds with aqueous sodium hydroxide measured and the results are recorded and discussed.

The effects of the term "tetra-membered" and "pentamembered" were used as being more reactive (700 to 800 times) than the chloromethylpyridines.

1. Pyridine
2. Pyrazine
3. Pyridazine
4. Pyrimidine
5. Quinoline
6. Isoquinoline
7. Cinnoline
8. Phthalazine
9. Quinoxaline
10. Purine
SUMMARY

Trimethylammonio-derivatives of nitropyridine, pyrimidine, nitropyrimidine, quinazoline and purine were prepared by the reaction of the corresponding chloro-heterocycle with trimethylamine. A similar process using chloro-pyridine, pyrazine, pyridazine, quinoline, isoquinoline, cinnoline, phthalazine and quinoxaline gave only the corresponding dimethylamino-compounds.

Trimethylammonio-compounds were also obtained by the quaternisation of 2-dimethylamino-pyridine and quinoline with iodomethane but in all other quaternisations studied, methylation took place at the ring nitrogen atom. The structures of these nuclear $N$-methyl derivatives were usually determined by hydrolysis to the oxo-compounds.

The kinetics of the reactions of the trimethylammonio-compounds with aqueous sodium hydroxide were measured and the results are recorded and discussed. The trimethylammonio-compounds were found to be slightly less reactive (5 to 8 times) than the corresponding methylsulphonyl-compounds but were considerably more reactive (700 to 1600 times) than the chloro-analogues. The effects of activation by aza-groups, nitro-groups and annelation are discussed and were found to be in

* The term "aza-group" has been used frequently in this thesis instead of "ring nitrogen atom" and refers to the grouping $-\text{N}=\text{-}$ between carbon atoms.
qualitative agreement with the results obtained in comparable studies of the reactions of chloro- and methylsulphonyl-compounds with charged nucleophiles.

The physical properties of trimethylammonio- and nuclear N-methyl compounds, e.g. ionization constants, ultraviolet spectra and n.m.r. spectra, were recorded and are discussed. The ionization constants illustrate the powerful electron withdrawal by the positive charge associated with the trimethylammonio- or nuclear N-methyl group.

Some qualitative reactions of the ammonio-compounds with a variety of nucleophiles, namely, n-propylamine, hydrazine hydrate, ammoniacal ammonium hydroxide, sodium alkoxides, potassium hydrogen difluoride and sodium hydrogen sulphide, were examined and found to proceed smoothly to give a good yield of the expected product.

The preparation of the previously unknown N-1-methyl derivatives of 3-hydroxy- and 3-mercaptopyridazine and the N-2-methyl derivative of 4-mercaptopyridazine is described and the tautomerism in 3- and 4-hydroxy- and 3- and 4-mercapto-pyridazine is discussed in detail by reference to the ionization constants and ultraviolet spectra of methylated models for the possible tautomeric forms.
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The work described in this thesis was directed towards the preparation of trimethylammonio-derivatives of nitrogen heterocycles and a comparison of their reactivity with that of analogous chloro- and methylsulphonyl-compounds.

This introductory chapter begins with a description of the previous work on the preparation and reactions of nitrogen heterocyclic trimethylammonio-compounds. It is followed by an outline of the results of earlier work on the displacement of the chloro-substituent from the relevant ring systems by charged nucleophiles and a description of the main theories of such displacements.

1 Previous work on the preparation of trimethylammonio-heterocyclic-derivatives

Trimethylammonio-derivatives of nitrogen heterocycles have been prepared by:

(a) the reaction of a chloro-heterocycle with a trialkylanine (usually trimethylamine) or

(b) the quaternization of a dimethylammonio-compound with isopropylamine.

The first method has been used in the preparation of trimethylammonio-derivatives of pyrididine, quinoline and purine. Thus Klotzer (1956a) was able to prepare 4,6-dimethylpyrimidin-2-yltrimethylammonium chloride (10).
CHAPTER 1

INTRODUCTION

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I Previous work on the preparation of nitrogen heterocyclic trimethylammonio-compounds

Trialkylammonio-derivatives of nitrogen heterocycles have been prepared by:

(a) the reaction of a chloro-heterocycle with a trialkylamine (usually trimethylamine) or
(b) the quaternisation of a dimethylamino-compound with iodomethane.

The first method has been used in the preparation of trimethylammonio-derivatives of pyrimidine, quinoline and purine. Thus Klötzer (1956a) was able to prepare 4,6-dimethylpyrimidin-2-yltrimethylammonium chloride (1A),
2,6-dimethylpyrimidin-4-yltrimethylammonium chloride and 2,6-dimethoxypyrimidin-4-yltrimethylammonium chloride. Similarly, Klötzer and Schantl (1963) prepared 5-chloro-4-methoxypyrimidin-2-yltrimethylammonium chloride (1B).

Shepherd and co-workers (1961) reported the preparation of 4-methoxypyrimidin-6-yltrimethylammonium chloride (1E) by two methods, both utilising the reaction of a chloro-heterocycle with trimethylamine. The first method involved the reaction of 4,6-dichloropyrimidine (1C) with trimethylamine and subsequent replacement of the remaining chloro-substituent in 1D by methoxide ion. The second method reversed the order of the two steps, i.e. reaction of 4,6-dichloropyrimidine with sodium methoxide to give the chloro-methoxypyrimidine (1F) and subsequent reaction of this intermediate with trimethylamine to give the required product (1E).

The preparation of a sulphanilamido-pyrimidinyltrimethylammonium salt (1G) has been effected by this method (Clarkson and Martin, 1961). 2-Methylthiopyrimidin-4-yltrimethylammonium chloride (1I) was prepared likewise from the corresponding chloro-heterocycle and trimethylamine by Brown and Lyall (1962). It was used as a 'fixed tautomeric form' in their study of the tautomerism of cytosine.

Reese (1958) reported the preparation of quinol-2-yltrimethylammonium iodide by the reaction of trimethylamine on 2-chloroquinoline and subsequently
precipitated from a tertiary compound as the perchlorate.

This observation has also proved useful for purines where the use of trimethylammonio-derivatives have been proposed. They all contained the trimethylammonio-group in the position, but had a variety of substituents in the 6-position, such as hydrogen (Horwitz and associates, 1962, 1961). The interest had been focused mainly towards the use of the 6-phenylpurin-9-yltrimethylammonium compounds (11, R = H) has been found to inhibit the growth of a transplanted neuroblastoma, an epidermoid carcinoma (860), and adenocarcinoma 785 in mice (Horwitz and associates, 1962). In humans, objective tumor regressions have been observed with this compound (Vatta-Keitcr, Reed, Fox and Talley, 1963; Vatta-Keitcr, 1964).

The second stage in the reaction of a dimethylammonio-compound with some pyridine derivatives (2- or 4-dimethylammonio-pyridine-4-yltrimethylammonium iodide, and derivatives) (1965) have good inductive evidence for the preparation of 2-dimethylamino-pyridine-4-yltrimethylammonium iodide by this reaction. The former compound was prepared by Schultze and Schultze (1936) and its use was extended by Vatta-Keitcr, Schultze and Schultze (1946).
precipitated the quaternary compound as the iodide.

This method of preparation has also proved effective for purines where a number of trimethylammonio-derivatives have been prepared. They all contained the trimethylammonio-group at the 6-position, but had a variety of substituents in the 9-position [1H: \( R = \) hydrogen (Horwitz, 1968); \( R = \beta\)-D-ribofuranosyl (Kiburis and Lister, 1969); \( R = \) tetrahydrofuryl (Lewis, Schneider and Robins, 1961)]. The interest in these trimethylammonio-purines had been directed towards their possible medical importance. Purin-6-yltrimethylammonium chloride (1H; \( R = \) H) has been found to inhibit Ehrlich ascites tumor, an epidermoid carcinoma (DC-5), and adenocarcinoma 755 in mice (Horwitz and Vaitkevicius, 1966; 1961). In humans, objective tumor regressions have been observed with this compound (Vaitkevicius, Reed, Fox and Talley, 1963; Vaitkevicius and Reed, 1966).

The second method, i.e. the reaction of a dimethylamino-compound with iodomethane, yielded pyrid-2-yltrimethylammonium iodide, and Brown and Teitei (1965) have good inductive evidence for the preparation of 4-dimethylaminopyrimidin-6-yltrimethylammonium iodide by this reaction. The former compound was prepared by Tschitschibabin and Konowalowa (1926) and its identity was established by Gol'dfarb, Setkina and Danyushevskiy (1948).
II Previous work on the displacement of the trimethylammonio-group from nitrogen heterocycles

Although the trimethylammonio-group has been displaced from heterocyclic ring systems by a variety of nucleophiles, no quantitative measurements have been made. However, in the benzene series, Bolto and Miller (1956) have obtained some data for the displacement of the trimethylammonio-group by methoxide ion from para-substituted nitrobenzenes and have found that this group was replaced 7.5 times more readily than the chloro-substituent.

In this section therefore a summary of the qualitative aspects of the displacement of the trimethylammonio-group from nitrogen heterocycles will be given. The trimethylammonio-group has been displaced readily from pyrimidines by hydroxide (Klotzer, 1957c; Brown and Lyall, 1962), alkoxide (Klotzer, 1956c), cyanide (Klotzer, 1956a, b and c; Klotzer and Schantl, 1963), dinitrophenoxide (Klotzer, 1956c) and sulphonamide ions (Klotzer, 1956a; Klotzer and Bretschneider, 1956; Klotzer and Schantl, 1963; Shepherd, Taft and Krazinskii, 1961). However, iodide, phthalimide, and malonate ester ions were found to demethylate the quaternary salts (Klotzer, 1956c), presumably by preferential aliphatic $S_N2$ attack at the methyl carbon atom of the trimethylammonio-group. [Meerwein, Wunderlich and Zenner (1962) found that the trimethylammonio-group in the diazonium
salt formed from 4-amino-3,5-dichlorophenyltrimethylammonium chloride (1J) was replaced by chloride ion to give 1,3,5-trichlorobenzene (1K).]

In the purine series, the trimethylammonio-group has been replaced by fluoride (Kiburis and Lister, 1969; Horwitz and Tomson, 1961), azide (Horwitz and Tomson, 1961) and hydroxide (Walsh and Wolfenden, 1967), while Reese (1958) found the trimethylammonio-group in quinoline to be replaceable by hydroxide ion.

The use of the quaternary salts (1L and 10) has permitted the preparation of the corresponding cyanopyrimidines (1M and 1P) by reaction with potassium or copper(I) cyanide (Klotzer, 1956a, b and c; Klotzer and Schantl, 1963) whereas these cyanopyrimidines could not be prepared from the corresponding chloropyrimidines (1N and 1Q) by reaction with potassium or copper(I) cyanide.

The ammonio-group in the 4-position of 6-methoxypyrimidin-4-yltrimethylammonium chloride (Shepherd, Taft and Krasinskii, 1961) and 2,6-dimethoxypyrimidin-4-yltrimethylammonium chloride (Klotzer, 1956a; Klotzer and Bretschneider, 1956) was found to be more reactive than a chloro-substituent even towards a bulky nucleophile such as the sulphonamide ion. An explanation of the higher reactivity of the trimethylammonio-compound has been proposed by Shepherd and co-workers (1961). These authors suggested that the higher reactivity of the
trimethylammonio-substituent relative to the sterically
more favoured chlorine-substituent was due to its
favourable electronic attraction of the anion
(sulphonanide anion-ammonium cation).

Stabilisation of the resultant intermediate complex by
electrostatic interaction of the contiguous negative
ring nitrogen and the positive ammonium nitrogen atoms.

Also, since trimethylamine is a weaker leaving group and
since the sulphonamide anion can nucleophilise due to
trimethylamine, the reversibility of the reaction is
effectively prevented.

III. Previous Kinetic Work on Heteroaromatic
Substitution

Heteroaromatic rings such as pyridine and pyrimidine,
methylsulphonyl- (and methylsulphinyl-) and methylsulpho-
substituents have been concentrated mainly
the replacement of halogen (principally chlorine),
methylsulphonyl- (and methylsulphinyl-) and methylsulpho-
substituents. Much of the work on these compounds
involved the use of anions such as fluoride ion as
nucleophiles. The studies on sulphur-containing
substituents, however, employed the methanolate ion as
nucleophile except in the pyridine and purine series
where the hydroxide ion was used extensively.

1O

1P

1Q

1M

1N

1K
trimethylammonio-substituent relative to the sterically more favoured chloro-substituent was due to (a) the favourable electrostatic attraction of the reagent ions (sulphonamide anion and ammonio-cation) and (b) the stabilisation of the resultant intermediate complex by electrostatic interaction of the contiguous negative ring nitrogen and the positive ammonium nitrogen atoms. Also, since trimethylamine is a better leaving group and since the sulphonamide anion can donate a proton to trimethylamine, the reversability of the reaction is effectively prevented.

III Previous kinetic work on nucleophilic heteroaromatic substitution

Previous kinetic studies of displacements from nitrogen heterocycles have been concentrated mainly on the replacement of halo-(principally chloro-), methylsulphonyl-(and methylsulphinyl-) and methylthio-substituents. Much of the work on chloro-compounds involved the use of amines and alkoxide ions as nucleophiles. The studies on sulphur-containing substituents, however, employed the methoxide ion as nucleophile except in the pyrimidine and purine series where the hydroxide ion was used. Kinetic studies of nucleophilic substitution by methoxide ion have been made on 2-, 3- and 4-chloropyridines (Liveris and Miller, 1963; Kato, Hayashi and
Anzai, 1967), 2- and 4-chloroquinolines (Illuminati and Marino, 1958; Belli, Illuminati and Marino, 1963), 2-chloroquinoxaline and 4-chlorocinnoline (Illuminati, 1964). Chapman and Russell-Hill (1956) have studied the reactions of most of the above compounds plus the chloropyrimidines and some of the remaining chloro-azanaphthalenes with sodium ethoxide in ethanol. Chan and Miller (1967) have studied the reactions of chloro-substituted monocyclic diazines with p-nitrophenoxide ion in methanol. The kinetics of replacement of the chloro-substituent from some chloro-nitro-compounds by ethoxide ion in ethanol have been studied by Bevan (1951) and by Chapman and Russell-Hill (1956).

The displacement of the methylsulphonyl-, methylsulphinyl- and methylthio-substituents by methoxide ion from a substituted pyrazine, isoquinoline, cinnoline, phthalazine and quinoxaline and from a number of substituted pyridines, pyridazines and quinolines has been studied kinetically by Barlin and Brown (1967a and b, 1968). Nucleophilic displacement of the methylsulphonyl-group by hydroxide ion from substituted pyrimidine has been studied by Ford (1968) and from substituted purines by Brown and Ford (1969). The conclusions arising from the kinetic work with the sulphur-containing substituents are compatible with those from the earlier studies with the chloro-substituent.
Because the range of heterocyclic nuclei in the chloro-compounds used by past workers corresponds more closely to the range of nuclei studied as trimethylammonio-compounds in this thesis, the kinetic results from the chloro-heterocycles have been chosen as the basis for the discussion which follows.

a) Activation by ring nitrogen atoms

The insertion of an aza-group in place of the -CH= group in an aromatic system increases the reactivity of that system to nucleophilic attack. This has been attributed to a reduction in the energy of repulsion between the nucleophile and the \( \pi \) electrons of the aromatic system and to the stabilisation of the negative charge donated to the heteroaromatic ring by the nucleophile. This effect is greatest when the aza-group is placed \( \alpha \) or \( \gamma \) to the leaving group, but is still appreciable when placed \( \beta \).

A measure of this effect on reactivity is well illustrated by the work of Chapman and Russell-Hill (1956) on chloro-azanaphthalenes and related compounds. Insertion of an aza-group in 2-chloronaphthalene to give either 2-chloroquinoline or 3-chloroisooquinoline caused an increase in the rate of replacement of the chloro-substituent by ethoxide ion. Thus for 2-chloroquinoline, the rate constant for replacement by ethoxide ion at 20\(^\circ\) was \( 6.9 \times 10^9 \) times greater than that for 2-chloronaphthalene; and 3-chloroisooquinoline was \( 1.3 \times 10^5 \) times more reactive than 2-chloronaphthalene at 20\(^\circ\).
The effect of introducing a second aza-group is also well illustrated by the same workers. Insertion of an aza-group in 4-chloroquinoline to give 4-chlorocinnoline resulted in an increase by a factor of 7300 in the rate constant for the displacement of the chloro-substituent by ethoxide ion at 20°C.

Similar increases were observed in the monocyclic azines and diazines by Chan and Miller (1967) where it was concluded that "to a reasonable degree of approximation the reactivity is that expected from independent contributions of each nitrogen atom".

b) Nitro- versus aza-group activation

The relative activation of the nitro- and aza-groups when situated para to the reacting centre will be discussed in this section because this is the only situation relevant to the present work. A number of examples have been reported in the literature (Chapman and Russell-Hill, 1956; Bevan, 1951) and have been reviewed (Illuminati, 1964). The ratio of reactivity for NO₂/aza activation varied from 6 to 15 in these studies. The consistently higher reactivity of the nitro-compounds (i.e. ratio NO₂/aza >1) with charged nucleophiles may indicate a somewhat higher capacity of the nitro-group to accommodate the electronic charge in the transition state (Illuminati, 1964). The conflicting behaviour at the para position (and also at the ortho position) towards neutral nucleophiles could, in
Illuminati's view (1964), result from a combination of solvent and hydrogen bonding effects which obscure the fundamental differences between the activating species.

c) Alpha versus gamma activation by ring nitrogen atoms

It has been observed that the aza-group, which may be α, β or γ to the reacting centre, has a different activating influence on the various positions of an aromatic substrate towards nucleophilic attack. Thus Liveris and Miller (1963) found that at 100°C 4-chloropyridine reacted 12 times faster than 2-chloropyridine with methanolic sodium methoxide. Likewise, Chapman and Russell-Hill (1956) found 4-chloropyridine to be more reactive than 2-chloropyridine towards sodium ethoxide.

Electron density calculations, despite their variability, have been used as an indication of relative positional reactivity in heterocyclic ring systems. Such calculations indicated that in the ground state the α-position in pyridine and pyrimidine is more electron deficient than the γ-position (Shepherd and Fedrick, 1965). The greater reactivity of the γ-position, exhibited in synthesis and kinetic studies, suggests therefore that the ground state of the substrate (and hence the calculations based on the ground state) is not a good model for predictions concerning the transition state.
A number of explanations have been proposed to account for the higher reactivity of the \( \gamma \)-position relative to the \( \alpha \)-position and these are as follows:

i. The greater stability of the para-quinonoid type transition state (1R) compared with the ortho-quinonoid form (1S) (Chapman and Rees, 1954).

ii. Electronic repulsion between the lone pair of electrons of the nucleophile and the lone pair orbitals of the ring nitrogens would be greater when attack is at the \( \alpha \)-position (Edwards and Pearson, 1962).

iii. The localisation energy (Barnes, 1959) required to produce an intermediate of the type (1T) or some form approaching it will be lower when the nitrogen atom is at the centre of such a resonating anionic pentadienoid system than when it is situated at the end of such a system (Shepherd and Fedrick, 1965).

d) **Annelation effects**

The structural changes involved in the fusion of a benzene ring to another ring can be treated as arising from the insertion of a bidentate ligand, \((\text{CH})_4\), and this has been referred to as annelation. This results in a change in the aromaticity of the ring system. Generally, annelation is accompanied by a fairly large increase in reactivity. This can be attributed to the expanded area available for delocalisation of the charge in the transition state resulting in a reduction in the activation energy. Thus 2-chloroquinoline is 290 times
more reactive than 2-chloropyridine towards ethoxide ion at 20° (Chapman and Russell-Hill, 1956).

However, in reaction with ethoxide ion at 20°, 3-chloroisoquinoline is 0.0055 times as reactive as 2-chloropyridine (Chapman and Russell-Hill, 1956). The low reactivity in this fused system has been attributed to a reduction in the activating influence of the nitrogen atom by partial bond fixation in the 2:3 position. It is probable that the comparatively low reactivity of 2-chloroquinazoline relative to 2-chloropyrimidine towards ethoxide ion at 20° (Chapman and Russell-Hill, 1956) is also due to the reduction in the activating influence of N-3 by bond fixation. This may partially offset any increase in reactivity due to the larger area available for the distribution of the charge in the transition state.

e) Theoretical calculations

Many calculations have been performed in an attempt to predict relative reactivities of different sites within a ring and among different ring systems. The two main methods have been summarised by Shepherd and Fedrick (1965). The first, which was mentioned earlier, involved the calculation of electron densities at different ring positions in the ground state. This method generally failed to predict the higher reactivity of the 4-position in heteroaromatics. The other method involved the calculation of the "atom localisation energies" (or activation energies) required to develop a
positive charge at the different positions in the heteroaromatic ring and the negative charge on the ring nitrogen atom (Longuet-Higgins, 1950a and b; Barnes, 1959). These estimated localisation energies ($\Delta U - \Delta U^0$) should correlate with the experimentally determined heats of activation ($\Delta H^\ddagger$). This has been found to be qualitatively so for a restricted range of chloroazanaphthalenes with piperidine (Chapman and Russell-Hill, 1956).

One of the main shortcomings of the localisation energy approach is that it assumes a completely localised transition state ($1U$) in all cases. This is probably invalid as wide variation would be expected depending on the character of the nucleophile and the substrate undergoing nucleophilic substitution (Chapman and Russell-Hill, 1956). The theory also assumes a constant entropy of activation ($\Delta S^\ddagger$) and hence is not applicable to reactions involving charged nucleophiles. When $\Delta S^\ddagger$ is not constant, Evans and Polanyi (1936) suggested that the activation energies at absolute zero ($\Delta U - \Delta U^0$) are more closely related to the logarithm of the rate constant at ordinary temperatures than to the experimentally determined heats of activation. A few ethoxy-dechlorination rates in the bicyclic azines show a straight-line relationship with the calculated heats of activation (Chapman and Russell-Hill, 1956).

Hence, while the theoretical calculations may sometimes
be correct qualitatively, their quantitative reliability is low. Therefore in this thesis they are treated with some caution.

IV The mechanisms of nucleophilic substitution in heteroaromatic systems

Two main mechanisms have been proposed for nucleophilic aromatic substitution. These are the $S_N^1$ and $S_N^2$ mechanisms.

The salient features of the $S_N^1$ mechanism are that the bond to the leaving group is broken before the new bond is created, and bond breakage is generally the slow and rate determining step. Reactions following such a mechanism are therefore unimolecular and obey first order kinetics. Such reactions proceed through intermediates of somewhat the same nature as a carbonium ion.

Only one type of aromatic substitution has been shown convincingly to operate through the $S_N^1$ mechanism: the decomposition of diazonium ions in acidic polar media (Lewis and Insole, 1964). Klötzer (1956b and c) considered the $S_N^1$ mechanism as a possibility for the reactions of trimethylammonio-heterocycles, but no experimental evidence has been presented to support this postulate. Shepherd and Fedrick (1965) considered that the formation of an electron deficient heterocyclic carbonium ion ($1W$) and a reactive, electron-rich nucleophile ($NR_3$) in close proximity to each other was unlikely with substrates of the type $1V$. 
The mechanism requires as a basic assumption that the incoming group and the leaving group, in the transition state, are in at least partially bonded to the carbon atom undergoing nucleophilic attack. Reactions following such a mechanism are bimolecular and generally show second order kinetics. Within this basic framework two alternative processes have been postulated. Bunnett and Zahler (1951) point out that, on the basis of stereochemical and theoretical considerations, there is no acceptable transition state for aromatic substitution in which the benzenoid mesomerism is maintained. They proposed, therefore, the two stage mechanism which they considered to be acceptable on both stereochemical and theoretical grounds. In this mechanism, the carbon atom undergoing substitution is assumed to change from sp² to sp³ hybridisation. The intermediate complex is assumed to have some stability and this is supported by evidence from certain benzenoid derivatives (Bunnett, 1950; Dickason, Ovill and Pickles, 1965).

Chapman (1958), however, when discussing the mechanism and kinetics of nucleophilic substitution in nitrogen heterocycles, proposed the simpler one stage process (Fig. 2) because he considered the two stage mechanism unnecessary and not consistent with some of the experimental evidence in its favor. Chapman concluded that the transition state tended towards structure 1AA, but the implication that the C-X bond was unaltered or
The $S_N^2$ mechanism requires as a basic assumption that the incoming group and the leaving group, in the transition state, are both at least partially bonded to the carbon atom undergoing nucleophilic attack. Reactions following such a mechanism are bimolecular and generally show second order kinetics. Within this basic framework two alternative processes have been postulated. Bunnett and Zahler (1951) point out that, on the basis of stereochemical and theoretical considerations, there is no acceptable transition state for aromatic substitution in which the benzenoid mesomerism is maintained. They proposed, therefore, the two stage mechanism (FIG. 1) which they considered to be acceptable on both stereochemical and theoretical grounds. In this mechanism, the carbon atom undergoing substitution is assumed to change from $sp^2$ to $sp^3$ hybridisation. The intermediate complex is assumed to have 'some' stability and this is supported by evidence from certain benzenoid derivatives (Bunnett, 1958; Dickeson, Dyall and Pickles, 1968).

Chapman (1955), however, when discussing the mechanism and kinetics of nucleophilic substitution in nitrogen heterocycles, proposed the simpler one stage process (FIG. 2) because he considered the two stage mechanism as "an unnecessary and complicating postulate" in the absence of "critical evidence in its favour". Chapman considered that the transition state tended towards structure (1AA), but the implication that the C-X bond was unaltered or
the C-Y bond was fully formed was not intended.

The mechanism for bimolecular nucleophilic substitution has been extensively reviewed (Bunnett, 1958; Iliuminati, 1964), and the two-step process appears to be favoured. Recent work (Dickason, Dyall and Pickles, 1968; Iliuminati and Stegel, 1969; Biffin, Hiltle, Moritz and Paul, 1970) on the formation and isolation of Iliuminati-type complexes from substituted trinitrobenzenes and dinitrophenolines suggests that these replacements may proceed by the two step process. Kinetic measurements (Iliuminati and Stegel, 1969) showed for the halo-substituted dinitrophenolines with 

stabilized transition state and an increase in the rate of formation of the Iliuminati complex relative to the trinitrobenzene. These authors suggest therefore that this indicated a trend which may have a bearing on the mechanism of nucleophilic heteroaromatic substitution. If the assumption that the two stage mechanism involving a Iliuminati-type compound as the reaction intermediate is correct, then a combination of these effects on the potential energy vs. reaction coordinate diagram may lead to a flattening of the two stage mechanism.

The difference between the two step and one step mechanisms is, according to Iliuminati (1964), actually, but not conceptually, immaterial as long as the transition
that the C-Y bond was fully formed was not intended.

The mechanism for bimolecular nucleophilic substitution has been extensively reviewed (Bunnett, 1958; Illuminati, 1964; Shepherd and Fedrick, 1965) and the two stage mechanism appears to be favoured. Recent work (Dickeson, Dyall and Pickles, 1968; Bemporad, Illuminati and Stegel, 1969; Biffin, Miller, Moritz and Paul, 1970) on the formation and isolation of Meisenheimer-type complexes from substituted trinitrobenzenes and dinitropyridines suggests that these replacements may proceed by the two step process. Kinetic measurements (Bemporad, Illuminati and Stegel, 1969) showed, for the halo-substituted dinitropyridines with alkoxide ion, a decrease in the stability and an increase in the rate of formation of the Meisenheimer complex relative to the trinitrobenzenes. These authors suggest therefore that this indicated a trend which may have a bearing on the mechanism of nucleophilic heteroaromatic substitution. If the assumption that the two stage mechanism involving a Meisenheimer-type compound as a true reaction intermediate is correct, then a combination of these effects on the potential energy vs reaction co-ordinate diagram may lead to a flattening of the two-peak profile and an approach to the one step mechanism.

The difference between the two step and one step mechanisms is, according to Illuminati (1964), actually, but not conceptually, immaterial as long as the transition
state of the rate determining step has a structural similarity closely resembling the $\sigma$-complex (12). Chapman and Russell-Hill (1956) seem prepared to agree with this point.

Reaction parameters, in this thesis, will be discussed in terms of the two stage mechanism and, for simplicity, the $\sigma$-complex will be taken as being equivalent to the transition state.

However this last method with dimethylamino-derivatives of nitrogen heterocycles and methylating reagents frequently gave ring nitrogen methylated products instead.

In all cases the use of $^1$H n.m.r. spectroscopy assisted greatly in the determination of the structure of the products of reaction.

The use of higher alkyl analogues has been avoided because of steric hindrance to their preparation. (Walsh and Wolfenden (1967) found that the rate of
The methods of preparation of trimethylammonio- and ring nitrogen methylated compounds will be discussed in this chapter and evidence for the position of the methyl group in the latter will be presented.

The trimethylammonio-compounds, described in this thesis, were prepared by one of two methods. The desired compound was obtained either by the action of trimethylamine on a reactive chloro-heterocycle, as illustrated by equation 1:

\[ \text{R-Cl + NMe}_3 \rightarrow \text{R-NMe}_3\text{Cl}^- \quad (1) \]

or by the reaction of a dimethylamino-compound with iodomethane (equation 2):

\[ \text{R-NMe}_2 + \text{I-Me} \rightarrow \text{R-NMe}_3\text{I}^- \quad (2) \]

However this last method with dimethylamino-derivatives of nitrogen heterocycles and methylating reagents frequently gave ring nitrogen methylated products instead.

In all cases the use of \(^1\text{H}\) n.m.r. spectroscopy assisted greatly in the determination of the structure of the products of reaction.

The use of higher alkyl analogues has been avoided because of steric hindrance to their preparation.

[Walsh and Wolfenden (1967) found that the rate of
reaction of 6-chloropurine ribonucleoside with trimethylamine at 25°C was 11,000 times greater than that for reaction with triethylamine.

I. By the reaction of a chloro-heterocycle with trimethylamine

The general procedure adopted was to treat a solution of the chloro-heterocycle in benzene (dimethylformamide or acetone were used where the chloro-heterocycle had low solubility in benzene) with a solution of trimethylamine (usually in large excess) in the same solvent at room temperature or below. The quaternary salt, being insoluble in benzene (and similar solvents) was readily isolated as the precipitate. The quaternary salts obtained in this way are listed in Table 1 together with solvent, reaction conditions and yield. The products obtained from this reaction were usually purified by recrystallisation or reprecipitation. However, some of these trimethylammonio-compounds could not be purified in this manner due to high reactivity towards the solvent and/or solubility difficulties. In these cases, purification for characterisation was achieved by conversion to the picrate or trichloromercurate. The compounds for which recrystallisation or reprecipitation was not a satisfactory means of purification were 5-nitopyrimidin-2-yltrimethylammonium chloride (2A), pyrimidin-4-yltrimethylammonium chloride (2B) and quinazolin-2- and 4-yltrimethylammonium chloride (2C and 2D).
It was found that, while most of the salts were sufficiently stable for storage, some of them (2A, 2B and 2D) were both unstable and deliquescent.

The effect of solvent on the course of the reaction of 2-chloro-5-nitropyridine with trimethylamine at 20\degree has been investigated in benzene, chloroform, ethyl acetate, diethyl ether, dimethylformamide and nitromethane. When the first four solvents were employed, the product of the reaction was 5-nitropyrid-2-yltrimethylammonium chloride, but with dimethylformamide or nitromethane, the reaction product was 2-dimethylamino-5-nitropyridine, and no quaternary salt could be detected.

Chloro-heterocycles which were relatively reactive generally gave trimethylammonio-compounds by this method, but exceptions were noted. For example, 8-chloro-9-methylpurine, which, on the basis of its reactivity towards ethoxide ion (Barlin and Chapman, 1965) and, of more relevance, piperidine (Barlin, 1967) relative to the reactivity of its isomers, might be expected to give a quaternary salt, gave instead only 8-dimethylamino-9-methylpurine and no quaternary salt could be detected. The greater steric crowding in the 8-position of 9-methylpurines relative to that in purines may account for this non-isolation of the trimethylammonio-compound by enhancing the rate of its break-down to the dimethylamino-compound.
TABLE 1

Preparation of trimethylammonio-compounds from the chloro-heterocycle and trimethylamine

<table>
<thead>
<tr>
<th>Product</th>
<th>Solvent for reaction</th>
<th>Reaction conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyridine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^{+}\text{2-NMe}_3\text{-5-NO}_2$</td>
<td>benzene</td>
<td>$5^0/2\text{ h}$</td>
<td>72%</td>
</tr>
<tr>
<td>Pyrimidine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^{+}\text{2-NMe}_3$</td>
<td>benzene</td>
<td>$20^0/24\text{ h}$</td>
<td>89%</td>
</tr>
<tr>
<td>$^{+}\text{2-NMe}_3\text{-5-NO}_2$</td>
<td>benzene</td>
<td>$5^0$</td>
<td>82%</td>
</tr>
<tr>
<td>$^{+}\text{4-NMe}_3$</td>
<td>benzene</td>
<td>$5^0/12\text{ h}$</td>
<td>48%</td>
</tr>
<tr>
<td>Quinazoline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^{+}\text{2-NMe}_3$</td>
<td>benzene</td>
<td>$5^0/24\text{ h}$</td>
<td>92%</td>
</tr>
<tr>
<td>$^{+}\text{4-NMe}_3$</td>
<td>benzene</td>
<td>$5^0/5\text{ days}$</td>
<td>98%</td>
</tr>
<tr>
<td>Purine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^{+}\text{2-NMe}_3\text{-9-Me}$</td>
<td>benzene</td>
<td>$50^0/24\text{ h}$</td>
<td>74%</td>
</tr>
<tr>
<td>$^{+}\text{6-NMe}_3\text{-9-Me}$</td>
<td>benzene</td>
<td>$20^0/24\text{ h}$</td>
<td>74%</td>
</tr>
<tr>
<td>$^{+}\text{6-NMe}_3\text{-9-H}$</td>
<td>dimethylformamide</td>
<td>$5^0/12\text{ h}$</td>
<td>85%</td>
</tr>
<tr>
<td>$^{+}\text{8-NMe}_3\text{-9-H}$</td>
<td>acetone</td>
<td>$53^0/24\text{ h}$</td>
<td>72%</td>
</tr>
</tbody>
</table>
Dimethylamino-compounds were also produced from 2- and 4-chloro-3-nitropyridines despite their relatively high reactivity. Steric hindrance towards reaction with trimethylamine by the \( \alpha \)-nitro-group may be the reason for the non-isolation of quaternary salts from these two reactions. It is of interest to note that Bishop, Cavell and Chapman (1952) were able to isolate quaternary salts formed by the reaction of pyridine with these two chloro-nitropyridines. This suggests that quaternary salt formation in these compounds can occur when the nucleophile is less bulky than trimethylamine or where decomposition of the quaternary intermediate is prevented by the absence of labile alkyl groups that can be eliminated as the haloalkane.

Chloro-compounds which were less reactive required more severe conditions to induce reaction with trimethylamine and in these cases only dimethylamino-compounds could be isolated. 2- and 4-Chloropyridine, 2-chloropyrazine, 3-chloropyridazine, 2- and 4-chloroquinoline, 1-chloroisouquinoline, 4-chlorocinnoline, 1-chlorophthalazine, 2-chloroquinoxaline and 2-chloropurine reacted in this way. Even under limiting conditions, with unchanged starting material present, only the dimethylamino-compound was formed and no trimethylammonio-compound could be detected. The effect of more severe conditions on the products is illustrated by the reaction of 2-chloro-9-methylpurine with trimethylamine in benzene.
When the reaction mixture was heated at $50^\circ$ for 24 h, 9-methylpurin-2-yltrimethylammonium chloride was obtained.

However, when the reaction was repeated at $150^\circ$ for 2.5 h, only 2-dimethylamino-9-methylpurine could be detected. This instability to heat probably explains why the less reactive chloro-compounds, when heated under sufficiently severe conditions to induce reaction, gave only dimethylamino-compounds, presumably by decomposition of the trimethylammonio-compound by elimination of chloromethane.

Unlike Reese (1958) I was unable to prepare quinol-2-yltrimethylammonium iodide from 2-chloroquinoline with liquid trimethylamine in a sealed tube at $40^\circ$ for 48 h.

II By quaternisation of a dimethylamino-heterocycle with iodomethane

The alternative method of preparation of trimethylammonium salts (by reaction of the dimethylamino-compound with iodomethane) offered an advantage over the reaction of the chloro-compound with trimethylamine in that quaternisation could be effected under relatively mild conditions. However, it suffered from a major disadvantage: quaternisation often took place at sites other than the dimethylamino-group.

Only two trimethylammonio-compounds, namely pyrid-2- and quinol-2-yltrimethylammonium iodides, were...
prepared by this method. All the other methylations attempted gave nuclear N-methyl derivatives.

Quaternisation of 2-dimethylaminopyridine with iodomethane had been carried out by Tschitschibabin and Konowalowa (1926) but they had been unable to establish the identity of the product. However, Goldfarb, Setkina and Danyushevskii (1948), on the basis of ultraviolet spectral comparison, came to the conclusion that the product was pyrid-2-yltrimethylammonium iodide; and this has been confirmed in the present work by studies of the $^1H$ n.m.r. spectrum (Chapter 4).

The methylation of 2-dimethylaminoquinoline with iodomethane has been reported by Luthy, Bergstrom and Mosher (1949). At $100^\circ$ they obtained only 2-dimethylamino-1-methylquinolinium iodide. This reaction has now been repeated at room temperature and it was found that the major product of the reaction was quinol-2-yltrimethylammonium iodide (2E), contaminated with the isomeric 2-dimethylamino-1-methylquinolinium iodide (2F). The trimethylammonio-compound was purified by selectively hydrolysing the more reactive nuclear N-methyl compound by dissolving the reaction product in 0.2M sodium hydroxide at room temperature, extracting the hydrolysis product 1,2-dihydro-1-methyl-2-oxoquinoline, and subsequently recovering the unchanged quinol-2-yltrimethylammonium iodide.
The methylation of the other dimethylamino-compounds to give nuclear \textit{N}-methyl derivatives will now be discussed. Quaternisation of 4-dimethylaminopyridine with iodomethane at 20^0 gave only 4-dimethylamino-1-methylpyridinium iodide as described by Jerchel, Fischer and Thomas (1956), and the identity of the product and the absence of the trimethylammonio-compound in the crude product was confirmed by examination of the $^1$H n.m.r. spectrum. Two signals in the $^1$H n.m.r. spectrum corresponded to the ring nitrogen methyl protons and the protons of the dimethylamino-group, and the peak intensities were in the ratio 1:2. 4-Dimethylamino-3-nitropyridine likewise gave only 4-dimethylamino-1-methyl-3-nitropyridinium iodide, but 2-dimethylamino-3-nitropyridine failed to react with iodomethane even at 160^0 for 24 h.

Cheeseman (1960) reported that methylation of 2-dimethylaminopyrazine with iodomethane occurred at a ring nitrogen atom and not at the dimethylamino-group but he did not establish the identity of the product. The $^1$H n.m.r. spectrum (Table 9) now shows that methylation has occurred \textit{meta} to the dimethylamino-group to give 3-dimethylamino-1-methylpyrazinium iodide (2G) since the singlet due to H-2 is at lower field than the multiplet due to H-5.

3-Dimethylaminopyridazine in iodomethane at 20^0 gave 3-dimethylamino-1-methylpyridazinium iodide (2H). The position of the methyl group was determined by hydrolysis.
as being N-1 rather than N-2. Thus the methiodide gave, on hydrolysis, not the known 2,3-dihydro-2-methyl-3-oxopyridazine (2K) but the previously unknown anhydro-base of 3-hydroxy-1-methylpyridazinium hydroxide (2I). This base was also obtained when 3-chloro-1-methylpyridazinium iodide (2J) (prepared from 3-chloropyridazine and iodomethane) was treated with sodium hydroxide. The chloro-methiodide and dimethylamine gave the same product as that obtained by methylation of 3-dimethylaminopyridazine: 3-dimethylamino-1-methylpyridazinium iodide (2H). See FIG. 3.

However when 4-dimethylaminopyridazine reacted with iodomethane in benzene at 20° it gave a mixture of the two nuclear N-methyl isomers (2L and 2M) (established by the 1H n.m.r. spectrum) but no trimethylammonio-compound. This isomeric pair could not be separated by recrystallisation or by thin-layer chromatography but, by selectively hydrolysing the more reactive 4-dimethylamino-1-methylpyridazinium iodide (2L), a separable mixture of 1,4-dihydro-1-methyl-4-oxopyridazine (2N) and 5-dimethylamino-1-methylpyridazinium iodide (2M) was obtained. Similarly methylation with dimethyl sulphate in ethanolic sodium ethoxide gave a mixture of the same two nuclear N-methyl compounds. Eichenberger, Rometsch and Druey (1956) reported the preparation of only the anhydro-base of 5-hydroxy-1-methylpyridazinium hydroxide on methylation of 4-hydroxy pyridazine with dimethyl sulphate.
3

In ethanolic sodium ethoxide. An investigation of this reaction in this work revealed that both 1,4-dihydro-1-methyl-4-oxopyridazine and the hydro-base of 4-hydroxy-1-methylpyridinium hydroxide are produced.

Both 4-dimethylaminquinoline and 1-dimethylaminophenazine isoquinolines on methylation with dimethylsulfate in 90% aqueous poly nuclear 2-methyl derivatives and this assignment was supported by their 'H n.m.r. spectra.

Iodometry at 24° for 12 h. 4-dimethylaminquinolinium iodide was established by hydrolysis in the same manner as 4-hydroxy-2-methylquinolinium hydroxide (Kucharsk, 1960) rather than 4-hydroxy-2-methylquinoline. The 'H n.m.r. supports this assignment.

The hydrolysis of 2-dimethylaminophenazine was followed spectrophotometrically as the reaction mixture was monitored free of 2-dimethylaminophenazine. 2-Oxocinoline from 2-quinoloxalone was separated in.

FIG 3

2G

2H

2I

2J

2K

2L

2M

2N
in ethanolic sodium ethoxide. A reinvestigation of this reaction in this work revealed that both 1,4-dihydro-1-methyl-4-oxopyridazaine and the anhydro-base of 5-hydroxy-1-methylpyridazinium hydroxide are produced.]

Both 4-dimethylaminoquinoline and 1-dimethylamino-isoquinoline on methylation with iodomethane at 20° gave only nuclear N-methyl derivatives and this assignment was supported by their 1H n.m.r. spectra.

4-Dimethylaminocinnoline, when allowed to stand with iodomethane at 20° for 12 h, gave 4-dimethylamino-2-methylcinnolinium iodide. The identity of the product was established by hydrolysis to the known anhydro-base of 4-hydroxy-2-methylcinnolinium hydroxide (Ames and Kucharska, 1963), rather than 1,4-dihydro-1-methyl-4-oxocinnoline. The 1H n.m.r. spectrum was consistent with this assignment.

Examination of the 1H n.m.r. spectra of the products obtained from the reactions of 2-dimethylaminoquinoxaline and 1-dimethylaminophthalazine with iodomethane demonstrated quite convincingly that only ring nitrogen methylation had occurred to give one product in each case. The hydrolysis of 2-dimethylaminoquinoxalinium methiodide was followed spectroscopically and the ultraviolet spectrum of the reaction mixture at the end of the reaction differed from those of the starting material, 2-hydroxyquinoxaline (Cheeseman, 1958) and 1,2-dihydro-1-methyl-2-oxoquinoxaline (Cheeseman, 1958). The product
isolated from the reaction mixture analysed for the anhydro-base of 3-hydroxy-1-methylouinoxalinium hydroxide.

Similar hydrolysis of 1-dimethylaminophthalazinium methiodide yielded a solution with an ultraviolet spectrum that was different from those of starting material, 1-hydroxyphthalazine (Albert and Barlin, 1962) and 1,2-dihydro-2-methyl-1-oxophthalazine (Albert and Barlin, 1962). Unfortunately, no product could be isolated from the reaction mixture. The evidence suggests that methylation has occurred meta to the dimethylamino-group. Methylation ortho to the dimethylamino-group cannot be discounted, however, since the hydrolysis of this methiodide need not have resulted in the replacement of the dimethylamino-group.
CHAPTER 3

KINETICS OF REACTION OF TRIMETHYLAMMONIO-HETEROCYCLES WITH AQUEOUS SODIUM HYDROXIDE

Although most of the kinetic studies reported in the literature have used amines or alkoxide ions as nucleophiles in alcohols as solvents, hydroxide ion was chosen as nucleophile throughout this study because certain of the compounds were reactive towards methanol and ethanol alone and because a comparison across a broad series of quaternary salts was desired.

The kinetics of the reactions of trimethylammonio-heterocycles towards hydroxide ion were followed spectroscopically. The ultraviolet wavelength for the examination of the reaction mixture was chosen so that the maximum difference in absorption between the quaternary salt and the hydroxy-heterocycle produced was ensured. The reactions were followed either by the appearance of a peak due to the product or by the disappearance of a peak due to the starting material. FIG 4 gives an example of the type of spectral changes observed.

The conversion of the trimethylammonio-compounds, in all cases except one (purin-8-yltrimethylammonium chloride, discussed below), proceeded smoothly, as indicated by the ultraviolet spectra, to give the hydroxy-compound as the only product (the spectrum
FIG 4

Ultraviolet spectral changes (observed at pH 5) during the reaction of pyrid-2-yltrimethylammonium iodide with aqueous sodium hydroxide to give 2-hydroxypyridine.

(A) 0% reaction  (E) 75.1% reaction
(B) 19.8% reaction  (F) 87.3% reaction
(C) 40.8% reaction  (G) 100% reaction
(D) 57.9% reaction
corresponding to $t_\infty$ was that of the hydroxy-compound). This implies that (a) the reactions were 'clean', i.e. free from any significant by-products and (b) the reversibility of the reaction could be neglected (Chapman, Parker and Soanes, 1954).

Although purin-8-yltrimethylammonium chloride reacted with sodium hydroxide in aqueous solution to give 8-hydroxypurine, some 8-dimethylaminopurine was also produced. The production of 8-dimethylaminopurine was presumably due to $S_N2$ attack by hydroxide ion at one of the methyl carbon atoms of the trimethylammonio-group.

Kinetic runs performed on this quaternary salt showed a decrease in the value of the rate coefficient with time. For these reasons, an approximate value of the rate coefficient at one temperature only was determined for this compound.

Examination of the kinetic runs showed that in all cases (except that of 5-nitropyrimidin-2-yltrimethylammonium chloride, which will be discussed in section II) halving (or doubling) the concentrations of reactants resulted in a doubling (or halving) of the time for 50% reaction, but left the second order rate coefficient unaltered. This demonstrated that the reactions investigated were bimolecular processes and that no appreciable base catalysis was occurring.
I  Order of reaction

As stated above, all the 'clean' reactions of the trimethylammonio-compounds with sodium hydroxide, i.e.

\[
R-NMe_3Cl + NaOH \rightarrow R-OH + NMe_3 + NaCl
\]

(except that of 5-nitropyrimidin-2-yltrimethylammonium chloride), were bimolecular processes and they obeyed second order kinetics. The rate coefficients were calculated using the usual second order kinetic equation:

\[
k = \frac{1}{t(a - b)} \ln \frac{b}{a} \frac{a - x}{b - x}
\]

where \( k \) is the second order rate coefficient, with units \( 1 \text{ mol}^{-1} \text{s}^{-1} \),

\( a \) is the initial concentration of hydroxide ion,

\( b \) is the initial concentration of the trimethylammonio-(or chloro-) compound,

\( x \) is the concentration of hydroxy-compound formed at time \( t \) (s).

Corrections for solvent expansion or contraction were made where necessary.

II  The anomalous behaviour of 5-nitropyrimidin-2-yltrimethylammonium chloride

Unlike the reactions of the trimethylammonio-compounds in general, the reaction of 5-nitropyrimidin-2-yltrimethylammonium chloride with aqueous sodium hydroxide did not obey second order kinetics. The half life for this
reaction was found to be independent of concentration, showing, that for this quaternary salt, first order kinetics applied.

The first order rate coefficients were calculated from the first order equation:

\[
\frac{1}{k} = t \ln \frac{b}{b-x}
\]

where \( k \) is the first order rate coefficient in units \( s^{-1} \),

\( b \) is the concentration of the quaternary salt, and

\( x \) is the concentration of hydroxy-compound formed at time \( t \) (s).

As this compound showed first order kinetics, it implies that the rate determining step (R.D.S.) is unimolecular, but it does not imply that a unimolecular process is operating throughout the whole reaction. This suggests two possible mechanisms which are illustrated in FIGS 5 and 6.

The mechanism proposed in FIG 5 is not favoured because the formation of heterocyclic carbonium ions appears unlikely (Shepherd and Fedrick, 1965). This is especially so for 5-nitropyrimidin-2-yltrimethylammonium chloride from which the carbonium ion (3A) would be formed in close proximity to the electron-rich leaving group (trimethylamine). Also, the C-2 atom is activated to \( S_N^2 \) attack both by the ring nitrogen atoms and the nitro-group. [Miller (1951) considers that carbonium ion formation, and the \( S_N^1 \) mechanism, are more likely in
systems such as 3,4,5-trihydroxyanilinofuorochrome [3] with a weakly basic nucleophile (water) giving 1,2,4,5-

tetramethylbenzene (3B). In the carbon atom deactivation the rate-determining step is the rate-determining step. If this rate determining step involves only the species, 3B, and decomposes by a unimolecular step, then this reaction would indeed exhibit second order kinetics, as would be expected.

III Discussion of the kinetic results

The kinetics of the reactions of trisethylammonio-

derived 4-nitroquinazolines, purine and its 9-methyl derivative with hydroxide ion in water have been measured and the results are presented in Tables 3, 3 and 4.

Table 2 gives the details of some typical experiments for some of the compounds studied and chloro-heteroaromatics. The results show that the rate kinetics were observed between about 10 and 40, when the rate coefficients were calculated from the expressions given above. The standard deviations shown.

3C

\[ \text{NMe}_3^+ \text{O} \text{H} \text{NMe}_3^+ \text{Cl}^- \rightarrow \text{NMe}_3^+ \text{O} \text{H} \text{NMe}_3^+ \text{Cl}^- \]

3D

\[ \text{HO} \text{H} \text{OH} \text{OH} \text{H} \text{OH} \text{OH} \text{OH} \]
systems such as 3,4,5-trihydroxyanilinium chloride (3C) with a weakly basic nucleophile (water) giving 1,3,4,5-tetrahydroxybenzene (3D) since the carbon atom is deactivated towards $S_{N2}$ substitution.

The alternative mechanism, illustrated in FIG 6, could account for the observed kinetics. In this mechanism, it is assumed that the rate of conversion of the starting material to the intermediate (3B) is fast relative to the second stage and that the second stage is the rate determining step. If this rate determining step involves only the species, 3B, and decomposes by a unimolecular step, then this reaction would indeed exhibit first order kinetics, but the overall process would be bimolecular.

III Discussion of the kinetic results

The kinetics of the reactions of trimethylammonio-derivatives of pyridine, pyrimidine, quinoline, quinazoline, purine and its 9-methyl derivative with hydroxide ion in water have been measured and the results are presented in Tables 2, 3 and 4.

Table 2 gives the details of some typical kinetic experiments for the reactions of some trimethylammonio- and chloro-heterocycles. The results show that regular kinetics were observed between about 10% and 80% reaction when the rate coefficients were calculated from the expressions given above. The standard deviation about
### Table 2

#### Reactions of hydroxide ions

**Pyrid-2-yltrimethylammonium iodide at 118.9°C**

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>23</th>
<th>35</th>
<th>52</th>
<th>66</th>
<th>86</th>
<th>110</th>
<th>141</th>
<th>186</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reaction (%)</td>
<td>19.8</td>
<td>29.2</td>
<td>40.8</td>
<td>48.8</td>
<td>57.9</td>
<td>65.8</td>
<td>75.1</td>
<td>83.7</td>
</tr>
<tr>
<td>$10^3 k$ (1 mol$^{-1}$ s$^{-1}$)</td>
<td>1.02</td>
<td>1.04</td>
<td>1.06</td>
<td>1.06</td>
<td>1.05</td>
<td>1.02</td>
<td>1.03</td>
<td>1.02</td>
</tr>
<tr>
<td>Mean $10^3 k = 1.04 ± 0.02$; after correction for solvent expansion, 1.11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**5-Nitropyrid-2-yltrimethylammonium chloride at 10.0°C**

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>12</th>
<th>25</th>
<th>38</th>
<th>54</th>
<th>73</th>
<th>92</th>
<th>123</th>
<th>154</th>
<th>208</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reaction (%)</td>
<td>8.4</td>
<td>15.9</td>
<td>23.2</td>
<td>30.8</td>
<td>39.8</td>
<td>47.1</td>
<td>56.6</td>
<td>65.0</td>
<td>76.1</td>
</tr>
<tr>
<td>$10^3 k$ (1 mol$^{-1}$ s$^{-1}$)</td>
<td>25.0</td>
<td>24.4</td>
<td>24.4</td>
<td>23.9</td>
<td>24.4</td>
<td>24.3</td>
<td>24.0</td>
<td>24.0</td>
<td>24.3</td>
</tr>
<tr>
<td>Mean $10^3 k = 24.3 ± 0.3$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**5-Nitropyrimidin-2-yltrimethylammonium chloride at 4.0°C**

<table>
<thead>
<tr>
<th>Time (s)</th>
<th>1.2</th>
<th>2.2</th>
<th>3.1</th>
<th>4.1</th>
<th>5.8</th>
<th>7.9</th>
<th>9.4</th>
<th>11.5</th>
<th>15.7</th>
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<tbody>
<tr>
<td>Reaction (%)</td>
<td>9.2</td>
<td>16.1</td>
<td>21.6</td>
<td>27.6</td>
<td>36.8</td>
<td>46.4</td>
<td>52.9</td>
<td>59.8</td>
<td>71.3</td>
</tr>
<tr>
<td>$10^3 k$ (s$^{-1}$)</td>
<td>8.04</td>
<td>7.97</td>
<td>7.85</td>
<td>7.87</td>
<td>7.91</td>
<td>7.90</td>
<td>8.00</td>
<td>7.92</td>
<td>7.94</td>
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<tr>
<td>Mean $10^3 k = 7.93 ± 0.06$</td>
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**Quinol-2-yltrimethylammonium iodide at 79.6°C**

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>13</th>
<th>27</th>
<th>39</th>
<th>54</th>
<th>68</th>
<th>90</th>
<th>115</th>
<th>142</th>
<th>204</th>
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<tbody>
<tr>
<td>Reaction (%)</td>
<td>8.6</td>
<td>17.5</td>
<td>24.3</td>
<td>32.2</td>
<td>38.4</td>
<td>46.8</td>
<td>56.8</td>
<td>64.0</td>
<td>75.5</td>
</tr>
<tr>
<td>$10^3 k$ (1 mol$^{-1}$ s$^{-1}$)</td>
<td>2.98</td>
<td>2.96</td>
<td>3.00</td>
<td>2.97</td>
<td>2.95</td>
<td>2.93</td>
<td>3.05</td>
<td>3.00</td>
<td>2.88</td>
</tr>
<tr>
<td>Mean $10^3 k = 2.97 ± 0.05$; after correction for solvent expansion, 3.05</td>
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</tbody>
</table>
### TABLE 2 continued

**Quinazolin-4-yltrimethylammonium chloride at 20.4°C**  
Hydroxide ion 0.00250M, trimethylammonio-compound 0.000032M.

<table>
<thead>
<tr>
<th>Time (s)</th>
<th>12</th>
<th>19</th>
<th>26</th>
<th>33</th>
<th>46</th>
<th>54</th>
<th>67</th>
<th>82</th>
<th>112</th>
<th>137</th>
<th>190</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reaction (%)</td>
<td>12.1</td>
<td>18.2</td>
<td>24.2</td>
<td>30.3</td>
<td>38.6</td>
<td>44.5</td>
<td>51.3</td>
<td>58.6</td>
<td>69.1</td>
<td>76.8</td>
<td>86.5</td>
</tr>
<tr>
<td>$k \cdot 10^3$ (1.mol$^{-1}$ s$^{-1}$)</td>
<td>4.35</td>
<td>4.25</td>
<td>4.21</td>
<td>4.33</td>
<td>4.27</td>
<td>4.39</td>
<td>4.30</td>
<td>4.31</td>
<td>4.23</td>
<td>4.28</td>
<td>4.24</td>
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<tr>
<td>Mean $k \cdot 10^3$</td>
<td>4.29 ± 0.05.</td>
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</table>

**4-Chloroquinazoline at 19.85°C**  
Hydroxide ion 0.0125M, chloro-compound 0.000212M.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>36</th>
<th>55</th>
<th>79</th>
<th>106</th>
<th>137</th>
<th>175</th>
<th>227</th>
<th>332</th>
<th>449</th>
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<tbody>
<tr>
<td>Reaction (%)</td>
<td>14.5</td>
<td>21.0</td>
<td>29.0</td>
<td>37.1</td>
<td>45.2</td>
<td>53.6</td>
<td>62.9</td>
<td>77.8</td>
<td>87.1</td>
</tr>
<tr>
<td>$10^3k \cdot 10^3$ (1.mol$^{-1}$ s$^{-1}$)</td>
<td>5.80</td>
<td>5.67</td>
<td>5.79</td>
<td>5.82</td>
<td>5.86</td>
<td>5.87</td>
<td>5.87</td>
<td>6.10</td>
<td>6.13</td>
</tr>
<tr>
<td>Mean $10^3k \cdot 10^3$</td>
<td>5.88 ± 0.15.</td>
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</tr>
</tbody>
</table>

**9-Methylpurin-6-yltrimethylammonium chloride at -0.05°C**  
Hydroxide ion 0.00151M, trimethylammonio-compound 0.000147M.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>45</th>
<th>67</th>
<th>142</th>
<th>201</th>
<th>264</th>
<th>381</th>
<th>564</th>
<th>657</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reaction (%)</td>
<td>7.1</td>
<td>10.9</td>
<td>22.4</td>
<td>30.3</td>
<td>36.6</td>
<td>48.8</td>
<td>63.1</td>
<td>66.1</td>
</tr>
<tr>
<td>$10^3k \cdot 10^3$ (1.mol$^{-1}$ s$^{-1}$)</td>
<td>18.1</td>
<td>19.2</td>
<td>20.1</td>
<td>19.2</td>
<td>19.1</td>
<td>19.7</td>
<td>18.3</td>
<td></td>
</tr>
<tr>
<td>Mean $10^3k \cdot 10^3$</td>
<td>19.2 ± 0.7; after correction for solvent contraction, 19.1.</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**6-Chloro-9-methylpurine at 59.8°C**  
Hydroxide ion 0.0398M, chloro-compound 0.000386M.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>9</th>
<th>24</th>
<th>48</th>
<th>75</th>
<th>106</th>
<th>154</th>
<th>195</th>
<th>244</th>
<th>361</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reaction (%)</td>
<td>6.3</td>
<td>15.4</td>
<td>28.7</td>
<td>40.6</td>
<td>49.6</td>
<td>63.6</td>
<td>72.7</td>
<td>81.8</td>
<td>91.6</td>
</tr>
<tr>
<td>$10^3k \cdot 10^3$ (1.mol$^{-1}$ s$^{-1}$)</td>
<td>3.01</td>
<td>2.92</td>
<td>2.95</td>
<td>2.90</td>
<td>2.72</td>
<td>2.76</td>
<td>2.80</td>
<td>2.94</td>
<td>2.88</td>
</tr>
<tr>
<td>Mean $10^3k \cdot 10^3$</td>
<td>2.88 ± 0.09; after correction for solvent expansion, 2.93.</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
## TABLE 3
Kinetic results for the reactions of trimethylammonio- and chloro-compounds with hydroxide ions.

<table>
<thead>
<tr>
<th>Temp (<em>°C</em>)</th>
<th>$10^2[\text{OH}^-]$ (M)</th>
<th>$10^4[-\text{N}^+\text{Me}_3]$ (M)</th>
<th>$10^3k_b$</th>
<th>$10^3k_c$</th>
<th>$t_{b_1}d$</th>
<th>$t_{b_1}e$</th>
<th>$t_{b_1}'f$</th>
<th>An.λ (nm)</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>129.8</td>
<td>16.00</td>
<td>14.00</td>
<td>2.62</td>
<td>2.80</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>118.9</td>
<td>16.00</td>
<td>14.00</td>
<td>1.04</td>
<td>1.11</td>
<td></td>
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</tr>
<tr>
<td>109.2</td>
<td>16.00</td>
<td>14.00</td>
<td>0.426</td>
<td>0.447</td>
<td>171</td>
<td></td>
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<tr>
<td>109.2</td>
<td>8.00</td>
<td>6.98</td>
<td>0.422</td>
<td>0.443</td>
<td>342</td>
<td>2.00</td>
<td>2.00</td>
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</tr>
</tbody>
</table>

**Pyrid-2-yltrimethylammonium iodide**

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<tr>
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<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>20.05</td>
<td>0.477</td>
<td>1.37</td>
<td>65.4</td>
<td>65.4</td>
<td>38.5</td>
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</tr>
<tr>
<td>20.05</td>
<td>0.239</td>
<td>0.692</td>
<td>67.9</td>
<td>67.9</td>
<td>76</td>
<td>1.97</td>
<td>2.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10.0</td>
<td>0.477</td>
<td>1.37</td>
<td>24.3</td>
<td>24.3</td>
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</tr>
<tr>
<td>-0.05</td>
<td>0.477</td>
<td>1.37</td>
<td>8.24</td>
<td>8.22</td>
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</tbody>
</table>

**5-Nitropyrid-2-yltrimethylammonium chloride**

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<tr>
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<th></th>
</tr>
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<tbody>
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<td>29.8</td>
<td>0.301</td>
<td>2.90</td>
<td>137.0</td>
<td>137.0</td>
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<td>19.85</td>
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<td>57.3</td>
<td>57.3</td>
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</tr>
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<td>338</td>
<td>1.99</td>
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</table>

**Pyrimidin-2-yltrimethylammonium chloride**

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</thead>
<tbody>
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<td>20.0</td>
<td>0.250</td>
<td>0.547</td>
<td>245.0^2</td>
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<tr>
<td>20.0</td>
<td>0.125</td>
<td>0.273</td>
<td>230.0^2</td>
<td>3.0</td>
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<tr>
<td>11.3</td>
<td>0.250</td>
<td>0.547</td>
<td>127.0^2</td>
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<tr>
<td>4.0</td>
<td>0.250</td>
<td>0.547</td>
<td>79.3^2</td>
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**5-Nitropyrimidin-2-yltrimethylammonium chloride**

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<tbody>
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<td>0.477</td>
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<td>110.0</td>
<td>110.0</td>
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</tr>
<tr>
<td>7.5</td>
<td>0.477</td>
<td>2.04</td>
<td>57.4</td>
<td>57.3</td>
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<td></td>
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</tr>
<tr>
<td>-0.05</td>
<td>0.477</td>
<td>2.03</td>
<td>28.9</td>
<td>28.8</td>
<td>95</td>
<td>1.97</td>
<td>2.00</td>
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<tr>
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<td>0.954</td>
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</table>

**Pyrimidin-4-yltrimethylammonium chloride**

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<td>6.4</td>
<td>6.4</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Quinol-2-yltrimethylammonium iodide</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>99.8 4.00 2.96 14.0 14.6 323 4.8</td>
<td>89.75 4.00 4.04 6.48 6.70 44.5 323 4.8</td>
<td>89.75 2.00 2.02 6.53 6.75 88.5 1.99 2.00 323 4.8</td>
<td>79.6 4.00 2.96 2.97 3.05 323 4.8</td>
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<td></td>
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</tr>
<tr>
<td></td>
<td>Quinazolin-2-yltrimethylammonium chloride</td>
<td>30.05 0.477 1.91 68.0 68.2 241 5.0</td>
<td>20.2 0.477 1.90 28.9 28.9 241 5.0</td>
<td>10.2 0.477 1.91 10.1 10.1 248 2.02 2.00 241 5.0</td>
<td>10.2 0.954 3.81 10.8 10.8 123 241 5.0</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quinazolin-4-yltrimethylammonium chloride</td>
<td>40.0 0.250 0.245 15700 15800 229 5.0</td>
<td>31.5 0.250 0.246 9490 9520 229 5.0</td>
<td>20.4 0.250 0.320 4290 4290 65 229 5.0</td>
<td>20.4 0.125 0.140 4120 4120 135 2.08 2.00 229 5.0</td>
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<tr>
<td></td>
<td>4-Chloroguiazoline</td>
<td>39.65 1.25 2.13 35.0 35.2 263 7.0</td>
<td>29.95 1.25 2.13 16.2 16.2 57 263 7.0</td>
<td>29.95 0.626 1.06 16.1 16.2 114.5 2.01 2.00 263 7.0</td>
<td>19.85 1.25 2.12 5.88 5.88 263 7.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9-Methylpurin-2-yltrimethylammonium chloride</td>
<td>19.8 5.36 5.15 14.5 14.4 315 6.5</td>
<td>9.8 5.36 5.15 5.15 5.14 427 315 6.5</td>
<td>9.8 2.68 2.60 5.04 5.03 851 1.99 1.98 315 6.5</td>
<td>-0.2 5.36 5.14 1.62 1.61 315 6.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
TABLE 3 continued, page 3

| Compound                        | a | b | c | d | e | f | g | h | i | j | k |
|--------------------------------|---|---|---|---|---|---|---|---|---|---|---|---|
| 9-Methylpurin-6-yltrimethylammonium chloride | 19.9 | 0.151 | 1.47 | 118 | 117 | 250 | 6.4 |
| 9.95 | 0.151 | 1.47 | 48.0 | 47.8 | 162 | 250 | 6.4 |
| 9.95 | 0.301 | 2.94 | 43.2 | 43.1 | 91 | 1.79 | 2.00 | 250 | 6.4 |
| -0.05 | 0.151 | 1.47 | 19.2 | 19.1 | 250 | 6.4 |

6-Chloro-9-methylpurine

| Compound                        | a | b | c | d | e | f | g | h | i | j | k |
|--------------------------------|---|---|---|---|---|---|---|---|---|---|---|---|
| 6-Chloro-9-methylpurine         | 69.8 | 3.98 | 3.87 | 6.20 | 6.39 | 49 | 250 | 5.6 |
| 69.8 | 1.99 | 1.94 | 6.01 | 6.18 | 97 | 1.98 | 2.00 | 250 | 5.6 |
| 59.8 | 3.98 | 3.86 | 2.88 | 2.93 | 250 | 5.6 |
| 49.8 | 3.98 | 3.86 | 1.24 | 1.26 | 250 | 5.6 |

Purin-6-yltrimethylammonium chloride

| Compound                        | a | b | c | d | e | f | g | h | i | j | k |
|--------------------------------|---|---|---|---|---|---|---|---|---|---|---|---|
| Purin-6-yltrimethylammonium chloride | 79.6 | 3.86 | 5.98 | 5.69 | 5.91 | 249 | 5.3 |
| 69.1 | 5.02 | 5.96 | 2.47 | 2.54 | 249 | 5.3 |
| 59.3 | 5.02 | 5.97 | 1.21 | 1.24 | 184 | 249 | 5.3 |
| 59.3 | 2.51 | 2.99 | 1.15 | 1.18 | 397 | 2.16 | 2.00 | 249 | 5.3 |

Purin-8-yltrimethylammonium chloride

| Compound                        | a | b | c | d | e | f | g | h | i | j | k |
|--------------------------------|---|---|---|---|---|---|---|---|---|---|---|---|
| Purin-8-yltrimethylammonium chloride | 127.3 | 1.92 | 1.85 | 2.91 | 277 | 5.6 |

a = 0.1.  
b In 1. mol⁻¹ s⁻¹ except for 5-nitropyrimidin-2-yltrimethylammonium chloride which obeyed first order kinetics and the results are in s⁻¹; the standard deviation was usually below 3%.  
c Corrected for solvent expansion or contraction.  
d Time for 50% reaction in min except for 5-nitropyrimidin-2-yltrimethylammonium chloride and quinazolin-4-yltrimethylammonium chloride where the units are s.  
e The ratio of t₁₂ for two experiments at different concentrations.  
f Calculated values from the concentration of reactants employed.  
g Analytical wavelength for determination of percentage reaction.  
h pH of buffer solutions used to stop the reactions and for spectroscopic measurements.  
i The rapid reaction "stopped flow" technique (Perrin, 1965) was used to study these reactions.  
j First order rate coefficient.  
k Approximate value.
### TABLE 4

Rate coefficients and Arrhenius parameters for reactions with hydroxide ions

<table>
<thead>
<tr>
<th>Compound</th>
<th>Temp</th>
<th>$10^3 a$</th>
<th>$E_b$</th>
<th>$\log A^c$</th>
<th>$\Delta H^b$</th>
<th>$\Delta S^d$</th>
<th>$\Delta S^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrid-2-yltrimethylammonium iodide</td>
<td>20.0</td>
<td>0.000008</td>
<td>114</td>
<td>12.3</td>
<td>112</td>
<td>18.0</td>
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<tr>
<td>5-Nitropyrid-2-yltrimethylammonium</td>
<td>20.05</td>
<td>65.4</td>
<td>68.4</td>
<td>11.0</td>
<td>66.0</td>
<td>42.9</td>
<td></td>
</tr>
<tr>
<td>chloride</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Pyrimidin-2-yltrimethylammonium</td>
<td>19.85</td>
<td>57.3</td>
<td>62.7</td>
<td>10.0</td>
<td>60.3</td>
<td>62.1</td>
<td></td>
</tr>
<tr>
<td>chloride</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>2-Chloropyrimidine</td>
<td>20.0</td>
<td>0.079</td>
<td></td>
<td></td>
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<tr>
<td>2-Methylsulphonylpyrimidine</td>
<td>20.0</td>
<td>301</td>
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<td>5-Nitropyrimidin-2-yltrimethylammonium</td>
<td>20.0</td>
<td>230</td>
<td>46.1</td>
<td>7.6</td>
<td>43.7</td>
<td>108.1</td>
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<tr>
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<tr>
<td>Pyrimidin-4-yltrimethylammonium</td>
<td>20.0</td>
<td>162</td>
<td>57.3</td>
<td>9.4</td>
<td>54.9</td>
<td>73.6</td>
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<tr>
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<tr>
<td>Quinol-2-yltrimethylammonium</td>
<td>20.0</td>
<td>0.0086</td>
<td>84.5</td>
<td>10.0</td>
<td>82.1</td>
<td>61.6</td>
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<td>iodide</td>
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<tr>
<td>Quinazolin-2-yltrimethylammonium</td>
<td>20.2</td>
<td>28.9</td>
<td>68.4</td>
<td>10.6</td>
<td>65.9</td>
<td>49.8</td>
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<tr>
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<tr>
<td>Quinazolin-4-yltrimethylammonium</td>
<td>20.4</td>
<td>4290</td>
<td>49.5</td>
<td>9.5</td>
<td>47.1</td>
<td>72.2</td>
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<tr>
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</tr>
<tr>
<td>4-Chloroquinazoline</td>
<td>19.85</td>
<td>5.88</td>
<td>69.4</td>
<td>10.2</td>
<td>67.0</td>
<td>58.6</td>
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<tr>
<td>9-Methylpurin-2-yltrimethylammonium</td>
<td>19.8</td>
<td>1.44</td>
<td>73.2</td>
<td>10.3</td>
<td>70.7</td>
<td>56.5</td>
<td></td>
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<tr>
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<tr>
<td>9-Methyl-2-methylsulphophurine</td>
<td>20.0</td>
<td>8.43</td>
<td></td>
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<tr>
<td>9-Methylpurin-6-yltrimethylammonium</td>
<td>19.9</td>
<td>117</td>
<td>60.7</td>
<td>9.9</td>
<td>58.6</td>
<td>63.2</td>
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<tr>
<td>chloride</td>
<td></td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>6-Chloro-9-nethylpurine</td>
<td>20.0</td>
<td>0.074</td>
<td>74.5</td>
<td>9.2</td>
<td>72.0</td>
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<tr>
<td>9-Methyl-6-methylsulphophurine</td>
<td>20.0</td>
<td>980</td>
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<tr>
<td>Purin-6-yltrimethylammonium chloride</td>
<td>20.0</td>
<td>0.032</td>
<td>72.0</td>
<td>8.4</td>
<td>69.5</td>
<td>93.3</td>
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<tr>
<td>Purin-8-yltrimethylammonium chloride</td>
<td>127.3</td>
<td>2.7</td>
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</tbody>
</table>
In Table 4, the results of all the kinetic experiments for the ammone- and chloro-compounds are listed. The activation parameters ($E$, the energy of activation, and $\ln k$, the Arrhenius factor) and the enthalpy and entropy of activation, $\Delta H^\ddagger$ and $\Delta S^\ddagger$, respectively, which were calculated from the kinetic results. Table 4 also contains some calculated rate coefficients.

The mean value of $k$ was usually 35 or less. Where necessary, the values may have been corrected for solvent expansion (or contraction).

Table 4 gives the results of all the kinetic experiments for the ammone- and chloro-compounds.

### Table 4, page 2

<table>
<thead>
<tr>
<th>Compound</th>
<th>$k$</th>
<th>$\Delta H^\ddagger$</th>
<th>$\Delta S^\ddagger$</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>10</td>
<td>12</td>
<td>40</td>
<td>Accurate to ±1 kJ mol$^{-1}$</td>
</tr>
<tr>
<td>B</td>
<td>5</td>
<td>15</td>
<td>50</td>
<td>Accurate to ±1 unit.</td>
</tr>
<tr>
<td>C</td>
<td>15</td>
<td>20</td>
<td>60</td>
<td>Calculated from experimental results.</td>
</tr>
<tr>
<td>D</td>
<td>20</td>
<td>25</td>
<td>70</td>
<td>Approximate value, uncorrected for solvent expansion.</td>
</tr>
</tbody>
</table>

- **a** In $1 \text{mol}^{-1}\text{s}^{-1}$ except for 5-nitropyrimidin-2-yltrimethylammonium chloride where the results are in $s^{-1}$.
- **b** Accurate to ±1 kJ mol$^{-1}$.
- **c** Accurate to ±0.3 unit.
- **d** Accurate to ±1 unit.
- **e** Calculated from experimental results.
- **f** Ford, 1968.
- **g** Brown and Ford, 1969.
- **h** Approximate value, uncorrected for solvent expansion.

A comparison of the reactivity of these trimethylammonio-compounds, prepared in this work, with the chloro- and methylsulphonyl-analogues is restricted because little information is available in the literature for the reactivity of these compounds with hydroxide ions. Rate coefficients for the reactivity towards hydroxide ion of 2-chloro- and 2-nitropyrimidines, 2-chloromethylsulphonylpyrimidine (Ford, 1968) and 9-methyladenine and 9-methylthiouracil (Brown and Ford, 1969) have been published. Not the Arrhenius parameters have not been given. Kinetic experiments have been performed in certain cases.
the mean value of \( k \) was usually 3% or less. Where necessary the values of \( k \) have been corrected for solvent expansion (or contraction).

Table 3 gives the results of all the kinetic experiments for the ammonio- and chloro-compounds. Table 4 lists the Arrhenius parameters (\( E \), the energy of activation, and \( \log A \), the Arrhenius factor) and the enthalpy and entropy of activation, \( \Delta H^\ddagger \) and \( \Delta S^\ddagger \) respectively, which were calculated from the kinetic results. Table 4 also contains some calculated rate coefficients at 20°C and data from the literature for reactions of chloro- and methylsulphonyl-compounds with hydroxide ion for comparison.

a) Comparative reactivities of trimethylammonio-, chloro- and methylsulphonyl-compounds

A comparison of the reactivity of the trimethylammonio-compounds, prepared in this work, with their chloro- and methylsulphonyl-analogues is restricted because little information is available in the literature for the reactivity of these compounds with hydroxide ion.

Rate coefficients for the reactivity towards hydroxide ion of 2-chloro- and 2-methylsulphonylpyrimidine (Ford, 1968) and 9-methyl-2- and 6-methylsulphonylpurine (Brown and Ford, 1969) have been published, but the Arrhenius parameters have not been given. Kinetic experiments have been performed in certain cases (4-chloroquinazoline and 6-chloro-9-methylpurine) to
extend this range and the values of the rate coefficients and the Arrhenius parameters are given in Tables 3 and 4.

Examination of the data in Table 5 shows that the trimethylammonio-compounds were slightly less reactive (5 to 8 times) than the corresponding methylsulphonyl-compounds at 20°C, but considerably more reactive (700 to 1600 times) than the corresponding chloro-analogues.

9-Methylpurin-6-yltrimethylammonium chloride was more reactive than the corresponding chloro-compound through a markedly lower value of the activation energy (49.5 kJ mol⁻¹ as compared with 69.4 kJ mol⁻¹), which was reinforced by a higher value of log A for 9-methylpurin-6-yltrimethylammonium chloride (10.3 as opposed to 9.2).

Quinazolin-4-yltrimethylammonium chloride was more reactive than 4-chloroquinazoline and this is consistent with the lower value for the activation energy of the former (60.7 kJ mol⁻¹) than that for the latter (74.5 kJ mol⁻¹). However, this difference is compensated by the higher value of log A for 4-chloroquinazoline.

The higher reactivity of the methylsulphonyl-compounds relative to the trimethylammonio-compounds observed in this work may be due to the greater ability of the methylsulphonyl-group to activate the molecule to nucleophilic attack by electron withdrawal, operating both by the inductive and mesomeric mechanisms (Barlin and Brown 1967a) relative to the trimethylammonio-group.
TABLE 5

Comparison of reactivities of trimethylammonio-, methylsulphonyl- and chloro-compounds with hydroxide ion

<table>
<thead>
<tr>
<th>Compound</th>
<th>Rate at 20$^\circ$ (1.mol$^{-1}$s$^{-1}$)</th>
<th>Ratio of reactivity at 20$^\circ$</th>
<th>Ratio of reactivity at 20$^\circ$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{SO}_2\text{Me}/\text{NMe}_3$</td>
<td>$\text{NMe}_3/\text{Cl}$</td>
<td>$\text{Pyrimidine}$</td>
<td>$\text{Quinazoline}$</td>
</tr>
<tr>
<td>$2-\text{NMe}_3$</td>
<td>$57.3 \times 10^{-3}$</td>
<td>5.25</td>
<td>7.25x10$^2$</td>
</tr>
<tr>
<td>$4-\text{NMe}_3$</td>
<td>$4290 \times 10^{-3}$</td>
<td></td>
<td>7.29x10$^2$</td>
</tr>
<tr>
<td>$2-\text{NMe}_3$</td>
<td>$1.44 \times 10^{-3}$</td>
<td>5.85</td>
<td></td>
</tr>
<tr>
<td>$6-\text{NMe}_3$</td>
<td>$117.4 \times 10^{-3}$</td>
<td>8.35</td>
<td>1.59x10$^3$</td>
</tr>
</tbody>
</table>

Chapman and Kees (1954) from studies on the reactivity of 2- and 4-chloropyrimidine located positional differences in the pyrimidine series which indicated that the isomer with the substituent at the 4-position was the more reactive.

Additional differences in the purine series were noted previously (Darlin and Chapman, 1965; Darlin, 1967) that 6-methylpurin-9-yltrimethylammonium chloride was found to be approximately 60 times more reactive than 9-methylpurin-2-yltrimethylammonium chloride towards hydroxide ion.

Although only one value of $k$ is available for the order expected when compared with the observed reactivities of 6- and 8-chloropurines towards hydroxide ion (Darlin, 1967) which show the 8-isomer to be much less reactive.
which operates solely through the inductive mechanism.

b) Positional effects

The kinetic results for the reactions of pyrimidin-2- and 4-yltrimethylammonium chloride towards hydroxide ion showed that the 4-isomer was ca 3 times more reactive than the 2-isomer at 20°C. The higher reactivity of this isomer was mirrored by its lower energy of activation (difference = 4.5 kJ mol⁻¹), but compensating this was a lower value of the frequency factor (9.4 compared with 10.0).

Chapman and Rees (1954), from studies of the reactivity of 2- and 4-chloropyrimidine towards piperidine, also found that the isomer with the substituent at the 4-position was the more reactive.

Positional differences in the purine series were the same as noted previously (Barlin and Chapman, 1965; Barlin, 1967). Thus 9-methylpurin-6-yltrimethylammonium chloride was found to be approximately 80 times more reactive than 9-methylpurin-2-yltrimethylammonium chloride towards hydroxide ion.

Although only one value of k is available for purin-8-yltrimethylammonium chloride (Table 3), it is of the order expected when compared with the observed reactivities of 6- and 8-chloropurine towards ethoxide ion (Barlin, 1967) which show the 8-isomer to be much less reactive.
c) Effect of activation by nitro-groups

It was noted (Chapter 1, part IIIb) that the effect of a nitro-group on the activation of a ring position towards nucleophilic attack was very similar to the effect of an aza-group; the relative rates of NO₂/aza generally involving factors within one order of magnitude. Both the effect of introduction of a nitro-group into a ring and the effect of replacement of an aza-group by a carbon attached to a nitro-group on the reactivity of the substrate will be discussed in this section.

The effect of the presence of a nitro-group on the susceptibility of a ring position to nucleophilic attack is well illustrated by a comparison of the reactivities of pyrid-2-yltrimethylammonium iodide (3E) and 5-nitropyrid-2-yltrimethylammonium chloride (3F). It can be seen, from the data in Table 4, that the presence of the nitro-group has increased the ease of replacement of the trimethylammonio-group by a factor of $8 \times 10^6$ in the value of $k$. The higher reactivity of 5-nitropyrid-2-yltrimethylammonium chloride, relative to the substrate lacking the nitro-group, is reflected in the large difference in the energy of activation for the two compounds (68.4 kJ mol⁻¹ compared with 114 kJ mol⁻¹). Compensating somewhat for this big difference, however, is the larger frequency factor of pyrid-2-yltrimethylammonium iodide (12.3) while that for 5-nitropyrid-2-yltrimethylammonium chloride is 11.0.
Laidler (1963) has stated that if the formation of the activated complex involves a separation of opposite charges or an approach of like charges, there will be an abnormally low frequency factor.

The transition state (3H) for 5-nitropyrid-2-yltrimethylammonium chloride is likely to involve greater charge separation than that (3G) for pyrid-2-yltrimethylammonium iodide, and this may explain in part the lower value of log A of the former.

The effect of the presence of a nitro-group in the pyrimidine ring is shown by comparing the results obtained from the hydrolysis of pyrimidin-2-yltrimethylammonium chloride (3I) and 5-nitropyrimidin-2-yltrimethylammonium chloride (3J). A direct comparison of the rate coefficients cannot be made as the former obeyed second order kinetics and the latter had first order kinetics. However, interesting differences in the Arrhenius parameters are apparent. There is a large difference of 16.6 kJ mol\(^{-1}\) in the energy of activation (Table 4) which suggested, on the basis of activation energies alone, that the nitro-compound should be more reactive. However, the frequency factor (log A) for the nitro-compound is much less (7.6) than that for pyrimidin-2-yltrimethylammonium chloride (10.0). This implies that a greater separation of charge has occurred in the transition state of the nitro-compound. This difference in log A values for these two reactions tends to offset the large difference in the energies of activation.
However, as these two reactions probably follow different reaction mechanisms, the conclusions drawn from a comparison of the Arrhenius parameters may be invalid since the Arrhenius parameters reflect properties of the transition states which may not be similar for these two reactions.

Inspection of the data in Table 4 shows that pyrimidin-4-yltrimethylammonium chloride (3K), with an activation energy and frequency factor of 57.3 kJ mol$^{-1}$ and 9.4 respectively is more reactive than 5-nitropyrid-2-yltrimethylammonium chloride (3F) where the corresponding values are 68.4 kJ mol$^{-1}$ and 11.0 respectively. This is contrary to previous observations that compounds containing a nitro-group are more activated towards reaction with a charged nucleophile than those containing an aza-substituent when each is present in a neutral substrate. This higher reactivity of the nitro-compound has been attributed to the nitro-group's higher capacity to delocalise the negative charge (relative to its azalogue) in the transition state (3N) derived from the neutral substrate (3M).

However, in the transition state (3H) derived from the cation of 3F, this greater delocalisation of charge in the nitro-compound would result in a greater charge separation in 3H relative to 3L, and a lower reactivity of the nitro-compound may be expected. The log A values for these two compounds (3F, 11.0; 3K, 9.4), however, do not conform to the predictions of Laidler (1963).
d) **Effect of zwitterion formation**

Comparison of the reactivity of purin-8-yltrimethylammonium chloride (30) with that of 9-methylpurin-8-yltrimethylammonium chloride (3P) towards hydroxide ion at 20° shows that the former is 0.00027 times as reactive as the latter. The lower reactivity of 30 is probably due to the approach of an anion to the zwitterion (30) whereas, with the 9-methyl derivative, the approach is to the cation of 3P. These differences in electrostatic inductive effects are illustrated by the energies of activation of 72.5 kcal mol⁻¹ for purin-8-yltrimethylammonium chloride and 60.7 kcal mol⁻¹ for 9-methylpurin-8-yltrimethylammonium chloride. The temperature differential for comparable reaction rates is ca. 100°.

Similar differences in reactivity have been recorded for the chloropurines and their 9-methyl derivatives towards hydroxide ion (Barlina, 1961).

The lower reactivity of 8-methylpurin-8-yltrimethylammonium chloride (3R) towards hydroxide ion and the tendency for it to undergo demethylation are also probably due to zwitterion formation. This effect is likely to be greatest when the trimethylammonium group is in the 8-position because, in this case, the site for attack of the anionic nucleophile is adjacent to the nitrogen atom carrying the negative charge.
d) **Effect of zwitterion formation**

Comparison of the reactivity of purin-6-yltrimethylammonium chloride (30) with that of 9-methylpurin-6-yltrimethylammonium chloride (3P) towards hydroxide ion at $20^\circ$ shows that the former is 0.00027 times as reactive as the latter. The lower reactivity of 30 is probably due to the approach of an anion to the zwitterion (3Q) whereas, with the 9-methyl derivative, the approach is to the cation of 3P. These differences in electrostatic interaction are illustrated by the energies of activation of 72.9 kJ mol$^{-1}$ for purin-6-yltrimethylammonium chloride and 60.7 kJ mol$^{-1}$ for 9-methylpurin-6-yltrimethylammonium chloride. The temperature differential for comparable reaction rates is ca 100$^\circ$.

Similar differences in reactivity have been recorded for the chloropurines and their 9-methyl derivatives towards ethoxide ion (Barlin, 1967).

The low reactivity of purin-8-yltrimethylammonium chloride (3R) towards hydroxide ion and the tendency for it to undergo demethylation are also probably due to zwitterion formation. This effect is likely to be greatest when the trimethylammonio-group is in the 8-position because, in this case, the site for attack of the anionic nucleophile is adjacent to the nitrogen atom carrying the negative charge.
The effects of annelation of a benzene ring to pyrid-2-yldimethylammonium iodide (35) to give quinol-2-yldimethylammonium iodide (3T) resulted in an increase in reactivity by a factor of 1108. This is of the order found for the reactions of the corresponding chlorocompounds with ethoxide ions (Chapman and Russell-Hill, 1956; Anand, methylsulphonyl-compounds with methoxide ion, 1976) (Darling and Brown, 1947). The difference in energy of activation for the two compounds (35, 116 kcal mol⁻¹, 3T, 84.5 kcal mol⁻¹) is large.
e) **Annelation effects**

Two effects of annelation of a benzene ring to a heterocyclic ring have been observed in this work. The first was the general increase in reactivity due to the larger area available for the delocalisation of the charge in the transition state of the annelated compounds, as shown by quinol-2-yltrimethylammonium iodide and quinazolin-4-yltrimethylammonium chloride. The other was a reduction in reactivity as shown by quinazolin-2-yltrimethylammonium chloride, due to bond fixation preventing full participation of all mesomeric forms in the transition state. These comparisons are shown in Table 6.

Previous workers (Chapman and Russell-Hill, 1956; Barlin and Brown, 1967b) generally observed an increase in reactivity on annelation, though Chapman and Russell-Hill (1956) also found that 3-chloroisoquinoline was less reactive towards ethoxide ion than 2-chloropyridine.

Annelation of a benzene ring to pyrid-2-yltrimethylammonium iodide (3S) to give quinol-2-yltrimethylammonium iodide (3T) resulted in an increase in reactivity by a factor of 1100. This is of the order found for the reactions of the corresponding chloro-compounds with ethoxide ion (290) (Chapman and Russell-Hill, 1956) and methylsulphonyl-compounds with methoxide ion (370) (Barlin and Brown, 1967b). The difference in energy of activation for the two compounds (3S, 114 kJ mol⁻¹; 3T, 84.5 kJ mol⁻¹) is large.
Quinazolin-4-yltrimethylammonium chloride is likewise more reactive than pyrimidin-4-yltrimethylammonium chloride, but the ratio of reactivity is relative small in this case. Whereas the frequency factors for the reaction of these two salts are approximately the same, the differences in reactivity are attributable to the energies of activation. It should be noted, however,
that the $^1$H n.m.r. spectrum of quinazolin-4-yltrimethylammonium chloride (which is discussed in Chapter 4) strongly suggests that ca 25% of this compound exists as the hydrated species in aqueous solution.

In contrast to these two examples quinazolin-2-yltrimethylammonium chloride was found to be less reactive than pyrimidin-2-yltrimethylammonium chloride (at 20°, the ratio of reactivity of bicycle/monocycle = 0.5). This is believed to be due to bond fixation which reduces the activating influence of N-3 by hindering its participation in the transition state. Chapman and Russell-Hill (1956) proposed a similar explanation to account for the observed reactivities of 2-chloroquinazoline and 2-chloropyrimidine.

f) Theoretical calculations

Many attempted correlations between reactivities of heterocyclic compounds and calculated electron densities and localisation energies have been made. These have been summarised by Albert (1959), Ridd (1963) and Shepherd and Fedrick (1965).

An attempt has been made in this thesis to see if any correlations exist between the observed order of reactivity of the trimethylammonio-compounds with the theoretically calculated quantities and these are given below. It should be noted however that the calculations are based on the ring system alone and no consideration of the nature of the leaving group or of the nucleophile is made. Because of the limited number of trimethyl-
ammonio-compounds available, the correlations noted may be fortuitous.

i Comparison with calculated electron densities

Many attempts have been made to calculate electron densities in the ring systems under consideration. However, many of these calculations give very different and conflicting values.

The use of variable electronegativity self consistent field method (Black, Brown and Heffernan, 1967) gives rise to the values of the electron densities quoted in Table 7. The values of the electron densities calculated in this way predict the order of reactivity: pyrid-2-yltrimethylammonium iodide < pyrimidin-2-yltrimethylammonium chloride = quinazolin-2-yltrimethylammonium chloride, and pyrimidin-4-yltrimethylammonium chloride < quinazolin-4-yltrimethylammonium chloride. This is essentially the order found experimentally except that, from the experimental measurements, pyrimidin-2-yltrimethylammonium chloride is slightly more reactive than quinazolin-2-yltrimethylammonium chloride.

However, correlations fail completely when different positions within the same ring are compared. Thus electron densities predict that pyrimidin-2-yltrimethylammonium chloride should be more reactive than its 4-isomer, and that quinazolin-2-yltrimethylammonium chloride should be more reactive than quinazolin-4-yltrimethylammonium chloride. This is contrary to the experimental results.


## Table 7

Electron densities and potential energies of activation

<table>
<thead>
<tr>
<th>Heterocycle</th>
<th>Ring position</th>
<th>$q^a$</th>
<th>$\Delta U - \Delta U_0^b$</th>
<th>$\log k^c$</th>
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</thead>
<tbody>
<tr>
<td>Pyridine</td>
<td>2</td>
<td>0.964</td>
<td>8/3</td>
<td>-8.10</td>
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<td>0.928</td>
<td>26/3</td>
<td>-1.24</td>
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<td>0.947</td>
<td>26/3</td>
<td>-0.79</td>
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<td>Quinoline</td>
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<td>0.956</td>
<td>128/24</td>
<td>-5.07</td>
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<td>0.928</td>
<td>158/24</td>
<td>-1.54</td>
</tr>
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<td>Quinazoline</td>
<td>4</td>
<td>0.937</td>
<td>248/33</td>
<td>+0.63</td>
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</tbody>
</table>

---

*a* Obtained from the figures given by Black, Brown and Heffernan (1967).  
*c* Values of $\log k$ at 20° for the reactions of trimethylammonio-compounds with hydroxide ion.
Correlation of reactivity with localisation energies

Attempts to correlate the reactivity of substituted aza-naphthalenes with the potential energies of activation ($\Delta U - \Delta U^0$) calculated by the localisation energy approach of Longuet-Higgins (1950a and b) have been made by Chapman and Russell-Hill (1956) and Brown (1968). As the entropies of activation were not constant, the value of $\log k$ was taken as a better reflection of the heats of activation at absolute zero ($\Delta U - \Delta U^0$) than $\Delta H^+$ (Evans and Polanyi, 1936) and some correlation was noted by these workers.

The values of the heats of activation at absolute zero and the $\log k$ values for reactions of the ammonio-compounds with hydroxide ion are given in Table 7 and show a qualitative correlation. However, due to the small sample size in the present study, this approach has not been pursued further.

Therefore, although theoretical calculations sometimes correctly predict qualitative (but not quantitative) reactivities, they should, as noted by earlier workers, be treated with great caution.
This chapter consists of a discussion of the physical properties, namely ionization constants, ultraviolet spectra and $^1$H n.m.r. spectra, of the nitrogen heterocyclic trimethylammonio- and ring nitrogen methylated compounds studied in this work.

I Ionization constants

The ionization constants of the trimethylammonio- and ring nitrogen methylated compounds (which are ionized throughout the whole pH range) are given in Table 8 together with those of the parent heterocycle and related compounds for comparison.

a) Trimethylammonio-compounds

The powerful electron withdrawal by the positively charged trimethylammonio-group is clearly demonstrated by an inspection of the ionization constants given in Table 8. An example which illustrates this point is the comparison of the basic $pK_a$ values of pyridine and pyrid-2-yltrimethylammonium iodide. In each case, the $pK_a$ measured is for protonation at the ring nitrogen atom. The presence of the positively charged substituent in the ammonio-compound adjacent to the basic centre causes the $pK_a$ value of pyridine (5.23) to be lowered to -4.64, i.e. by >9 logarithmic units.
<table>
<thead>
<tr>
<th>Compound</th>
<th>Charged species involved</th>
<th>pK&lt;sub&gt;a&lt;/sub&gt;</th>
<th>Spectroscopy in water&lt;sup&gt;b&lt;/sup&gt;</th>
<th>λ&lt;sub&gt;max&lt;/sub&gt;,(nm)</th>
<th>log c</th>
<th>pH&lt;sup&gt;c&lt;/sup&gt;</th>
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<tr>
<td>Pyridine</td>
<td>0</td>
<td>5.23&lt;sup&gt;d&lt;/sup&gt;</td>
<td>250.5, 256.5, 263&lt;sup&gt;e&lt;/sup&gt;</td>
<td>3.39, 3.44, 3.26</td>
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<td>+</td>
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<td>250.5, 255.5, 261&lt;sup&gt;e&lt;/sup&gt;</td>
<td>3.66, 3.72, 3.54</td>
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<td>2-Aminopyridine</td>
<td>0</td>
<td>6.86&lt;sup&gt;e&lt;/sup&gt;</td>
<td>229, 287&lt;sup&gt;g&lt;/sup&gt;</td>
<td>3.97, 3.58</td>
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<tr>
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<td>+</td>
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<td>-7.6&lt;sup&gt;f&lt;/sup&gt;</td>
<td>205, 251, 256, 262&lt;sup&gt;h&lt;/sup&gt;</td>
<td>3.40, 3.71, 3.76, 3.60</td>
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<td>Pyrid-2-yltrimethylammonium iodide</td>
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<td>++</td>
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<td>251, 257, 261&lt;sup&gt;k&lt;/sup&gt;</td>
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**TABLE B continued, page 3**
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<th>Formula</th>
<th>Molar Mass</th>
<th>Δε (L mol⁻¹ cm⁻¹)</th>
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<td>203.16</td>
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<td>C14H15N3Cl</td>
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**TABLE 8 continued, page 4**
### TABLE 8 continued, page 5

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<td>** m</td>
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<td></td>
<td>** -1.0&lt;sup&gt;ee&lt;/sup&gt;</td>
<td>248, 266, 269, 361, 435&lt;sup&gt;i&lt;/sup&gt;,&lt;sup&gt;k&lt;/sup&gt;</td>
<td>4.21, 4.29, 4.30, 3.72, 3.78</td>
</tr>
<tr>
<td>Purine</td>
<td>0</td>
<td>&lt;220, 263&lt;sup&gt;99&lt;/sup&gt;</td>
<td>3.48, 3.90</td>
</tr>
<tr>
<td></td>
<td>+ 2.39&lt;sup&gt;ff&lt;/sup&gt;</td>
<td>&lt;220, 260&lt;sup&gt;99&lt;/sup&gt;</td>
<td>4.09, 3.79</td>
</tr>
<tr>
<td></td>
<td>- 8.93&lt;sup&gt;ff&lt;/sup&gt;</td>
<td>219, 271&lt;sup&gt;99&lt;/sup&gt;</td>
<td>3.92, 3.88</td>
</tr>
<tr>
<td>9-Methylpurin-2-yltrimethylammonium chloride</td>
<td>+</td>
<td>264</td>
<td>3.76</td>
</tr>
<tr>
<td></td>
<td>** 0.39&lt;sup&gt;hh&lt;/sup&gt;</td>
<td>260&lt;sup&gt;ff&lt;/sup&gt;</td>
<td>4.00</td>
</tr>
<tr>
<td></td>
<td>m</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>9-Methylpurin-6-yltrimethylammonium chloride</td>
<td>+</td>
<td>267</td>
<td>3.89</td>
</tr>
<tr>
<td></td>
<td>m</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>6-Aminopurine</td>
<td>0</td>
<td>260&lt;sup&gt;99&lt;/sup&gt;</td>
<td>4.13</td>
</tr>
<tr>
<td></td>
<td>+ 4.22&lt;sup&gt;99&lt;/sup&gt;</td>
<td>262&lt;sup&gt;99&lt;/sup&gt;</td>
<td>4.12</td>
</tr>
<tr>
<td></td>
<td>- 9.69&lt;sup&gt;99&lt;/sup&gt;</td>
<td>267&lt;sup&gt;99&lt;/sup&gt;</td>
<td>4.08</td>
</tr>
<tr>
<td>Substance</td>
<td>Value</td>
<td>References</td>
<td></td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-----------</td>
<td>------------</td>
<td></td>
</tr>
<tr>
<td>Purin-6-yltrimethylammonium chloride</td>
<td>6.85±1</td>
<td>6</td>
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<tr>
<td></td>
<td>265±1</td>
<td>7</td>
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<td>209.272</td>
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<tr>
<td>8-Aminopurine</td>
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<td>241.283</td>
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<td>4.6899</td>
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<td></td>
<td>28899</td>
<td>12</td>
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<td></td>
<td>9.3699</td>
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<td>230.29099</td>
<td>14</td>
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<td>Purin-8-yltrimethylammonium chloride</td>
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<td>264</td>
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</tr>
<tr>
<td></td>
<td>203.268</td>
<td>17</td>
<td></td>
</tr>
</tbody>
</table>

a Neutral species; –, anion; +, cation; ++, dication. b Shoulders and inflexions are underlined. Values below 0 have been obtained in solutions of sulphuric acid to which Hammet acidity functions [the H₀ scale of Paul and Long (1957) has been used for convenience] have been assigned. c Albert, Goldacre and Phillips, 1948. d Albert, 1955a. e Mason, 1962. f Osborn, Schofield and Short, 1956.
The pKₐ value of pyrid-2-yltrimethylammonium iodide (4A) is 3 units higher than that governed by deprotonation of 2-aminopyridine. Because the dications (4A and 4E) formed from each would be similar, and so should possess similar energies, the difference in pKₐ values reflects the loss of anomeric stabilisation of 2-aminopyridine monocation (6 = 4D) (Albert, Goldacre and Phillips, 1948) together with any energy differences associated with protonation at an amine-group of a methyl group in the compounds being compared are lost.

It is thought that the positively charged trimethylammonium-group withdraws electrons from a ring system solely by the inductive mechanism (Govan, Evans and Hirst, 1958). Its effect on pKₐ values, therefore, is dependent on the distance separating the interacting centres. Thus, the pKₐ values governing the loss of a proton from 8-9 in purin-6- and 8-yltrimethylammonium chloride are respectively 2.08 and 4.05 in logarithmic units.

**TABLE 8 continued, page 7**

| **aa** The results were within ± 0.08 when the pKₐ was determined spectroscopically on 0.00003M solutions at λ = 365 nm. | **bb** The results were within ± 0.09 when the pKₐ was determined spectroscopically on 0.00002M solutions at λ = 420 nm. | **cc** Albert, Armarego and Spinner, 1961. | **dd** Cheeseman, 1958. | **ee** The results were within ± 0.05 when the pKₐ was determined spectroscopically on 0.0002M solutions at λ = 360 nm. | **ff** Albert and Brown, 1954. | **gg** Mason, 1954. | **hh** The results were within ± 0.03 when the pKₐ was determined spectroscopically on 0.00003M solutions at λ = 275 nm. | **ii** The results were within ± 0.05 when the pKₐ was determined spectroscopically on 0.0001M solutions at λ = 265 nm. | **jj** Reist, Benitez, Goodman, Baker and Lee, 1962, give the ultraviolet spectrum in water and Horwitz, 1968, gives for a solution in 0.1M hydrochloric acid max 265.7 nm (λ 8, 272). | **kk** The results were within ± 0.04 when the pKₐ was determined spectroscopically on 0.0001M solutions at λ = 265 nm. | **ll** The results were within ± 0.03 when the pKₐ was determined spectroscopically on 0.00001M solutions at λ = 270 nm. |
The $pK_a$ value of pyrid-2-yltrimethylammonium iodide (4A) is 3 units higher than that governed by dication formation in 2-aminopyridine. Because the dications (4B and 4E) formed from each would be similar, and so should possess similar energies, the difference in $pK_a$ values reflects the loss of mesomeric stabilisation of 2-aminopyridine monocation (4C $\leftrightarrow$ 4D) (Albert, Goldacre and Phillips, 1948) together with any energy differences associated with protonation at an ammonio-group or a ring nitrogen atom. [The effect of a methyl group on $pK_a$ values is known to be relatively small (Barlin and Perrin, 1966; Clark and Perrin, 1964).]

A similar difference in basic $pK_a$ values (2.94 units) was observed between quinol-2-yltrimethylammonium iodide (4F) and its isomer, 2-dimethylamino-1-methylquinolinium iodide (4G $\leftrightarrow$ 4H), and an explanation comparable with that given above is proposed. In this case, however, differences due to substitution of hydrogen atoms by methyl groups in the compounds being compared are less.

It is thought that the positively charged trimethylammonio-group withdraws electrons from a ring system solely by the inductive mechanism (Bevan, Emokpae and Hirst, 1968). Its effect on $pK_a$ values, therefore, is dependent on the distance separating the interacting centres. Thus, the $pK_a$ values governing the loss of a proton from N-9 in purin-6- and 8-yltrimethylammonium chloride are respectively 2.08 and 4.05 logarithmic units.
lower (i.e., they are stronger acids) than that for the parent
(8.93). Whereas the effect of the trimethylammonium ion on the
basic pK of pyridine is 0.39, the trimethylammonium ion in
9-methylpurine (8.27) is slightly less effective (Brown and
Bendich, 1958). This reduction is much less when less
basic pK occurs when substituted or polar conformation in
pyridine is more stable than that of the dipolar, cyano-
and methyl-sulfonyl substituents. The effect on the
acidic pK of dimethylaminopurine chloride (6.87)
was of the same order found for the cyano substituent. (The
acidic pK of 2-cyano-9-methylpurine is 6.69, Brown and
Bendich, 1958.)

Unfortunately, the trimethylammonium compounds in strong acetic acid cannot be
measured.

B) Methiodides of dimethylamino-heterocyclics

Examination of the data in Table 6 shows
that 2-diethylamino-9-methylamino-9-methyl-
and 2-dimethylamino-9-methylamino-9-methyl-
trimethylammonium iodide have comparable

d The pK of 2-chloropyridine is 0.84 (Kinnell, 1960); of 2-cyanopyridine is 0.28 (Kinnell, 1959a); and of 2-methylsulfonylpyridine is 3.60 (Barlow and Brown, 1957a).
lower (i.e. they are stronger acids) than that for purine (8.93). Likewise, the effect of the ammonio-group on the basic $pK_a$ of 9-methylpyrin-2-yltrimethylammonium chloride (0.39) is to lower its $pK_a$ by 1.88 units relative to 9-methylpurine (2.27, Albert and Brown, 1954). This reduction is much less than that observed with pyrid-2-yltrimethylammonium iodide and suggests that protonation occurs at a position remote from the substituent, i.e. in the imidazole ring.

Whereas the effect of the trimethylammonio-group on basic $pK_a$ values when substituted at the 2-position in pyridine was greater than that of the chloro-, cyano- and methylsulphonyl-substituents*, its effect on the acidic $pK_a$ in purin-6-yltrimethylammonium chloride (6.85) was of the order found for the cyano substituent. (The acidic $pK_a$ of 6-cyanopurine is 6.88, Giner-Sorolla and Bendich, 1958).

Unfortunately, the instability of the remaining trimethylammonio-compounds in strong acid precluded measurement of their basic $pK_a$ values.

b) Methiodides of dimethylamino-heterocycles

Examination of the data in Table 8 shows that 2-dimethylamino-1-methylquinolinium iodide and 1-dimethylamino-2-methylisoquinolinium iodide have comparable

* The $pK_a$ of 2-chloropyridine is 0.49 (Linnell, 1960); of 2-cyanopyridine is -0.26 (Mason, 1959a); and, of 2-methylsulphonylpyridine is -1.50 (Barlin and Brown, 1967a).
basicities but that 4-dimethylamino-1-methylquinolinium iodide is a much stronger base than either of these. The closer proximity of the positively charged ring nitrogen atom in the first two compounds to the basic centre (i.e. the dimethylamino-group) relative to the distribution of charge in 4-dimethylamino-1-methylquinolinium iodide, could account for this basicity relative to that of the 4-dimethylamino-compound.

Of 4-dimethylamino-2-methylcinnolinium iodide (4I), 1-dimethylaminophthalazinium methiodide (probably 4J) and 3-dimethylamino-1-methylquinoxalinium iodide (4K), the quinoxaline is the strongest base. Methylation in all three compounds is believed to have taken place at the ring nitrogen atom meta to the dimethylamino-group. Therefore, protonation of compounds 4I and 4J would involve the addition of a proton adjacent to a ring nitrogen atom already carrying a positive charge; but in 4K, protonation would not be so severely restricted and hence it is the strongest base.

Instability of such monocyclic methiodides in strong acid prevented measurement of their ionization constants.

II Ultraviolet spectra

Table 8 contains the ultraviolet spectra of the trimethylammonio- and ring nitrogen methylated compounds discussed in this thesis. The ultraviolet spectra of the parent heterocycles and related compounds have also been included.
Prima-ethylamino-compounds

The study of the properties of the prima-ethylamino-compounds has been published in a number of works (Weiss, 1967; Weiss, 1969; Weiss et al., 1970; Weiss and Weiss, 1971). It was expected, therefore, that the prima-ethylamino-compounds would have ultraviolet spectra similar to those of the neutral species of compounds lacking this substituent, but different from those of the monocation of the corresponding amino-compounds where protonation is known to occur at the ring nitrogen site. Thus, the spectra of prima-ethylamino-compounds were similar to that of the neutral species, and different from that of 2-aminopyridine. No unusual electronic effects were noted.

The close agreement between the spectra of prima-ethylamino-compounds and the corresponding neutral species of 2-ethylamino-compounds indicated the absence of hydration in the monocationic species of the prima-ethylamino-compounds.
a) Trimethylammonio-compounds

The optical transparency of the ammonio-group has been reported by a number of workers (Wohl, 1939; Bowden and Braude, 1952; Albert, 1960; Barlin and Pfleiderer, 1971). It was expected, therefore, that the trimethylammonio-compounds would have ultraviolet spectra similar to those of the neutral species of compounds lacking this substituent, but different from those of the monocations of the corresponding amino-compounds where protonation is known to occur at the ring nitrogen atom. Thus the spectrum of pyrid-2-yltrimethylammonium iodide was similar to that of the neutral species of pyridine but different from that of 2-aminopyridine monocation. Corresponding similarities were noted for all the other trimethylammonio-compounds prepared in this work except for quinazolin-4-yltrimethylammonium chloride, which is discussed below.

The close agreement between the spectra of 5-nitropyrimidin-2-yltrimethylammonium chloride and the anhydrous neutral species of 5-nitropyrimidine indicated the absence of hydration in the monocaticionic species of the ammonio-compound. [It is known that the cation of 5-nitropyrimidine is hydrated (Biffin, Brown and Lee, 1967).]

Although the spectrum of quinazolin-2-yltrimethylammonium chloride is similar to that of the neutral species of quinazoline, that of the isomeric quinazolin-4-yltrimethylammonium chloride was quite different.
The $^1$H n.m.r. spectrum of this trimethylammonio-compound, which will be discussed later, suggests strongly that hydration has occurred to ca 25%. The presence of hydration adequately explains the lack of similarity in the ultraviolet spectra of quinazolin-4-yltrimethylammonium chloride and the neutral species of quinazoline. [The cationic form of quinazoline is known to hydrate (Albert, Armarego and Spinner, 1961).]

Conversion of pyrid-2-yltrimethylammonium iodide to the dication produced a small bathochromic shift in its spectrum which is consistent with protonation at the ring nitrogen atom (Albert, 1960; Barlin and Pfleiderer, 1971). The resulting spectrum was similar to that of both pyridine monocation and 2-aminopyridine dication.

The conversion of the monocations of purin-6- and 8-yltrimethylammonium chloride to the zwitterions produced, in each case, a small bathochromic shift similar to that observed when the neutral species of purine is converted to its anion.

b) Methiodides of dimethylamino-heterocycles

A comparison of the spectra of the methiodides of 3- and 4-dimethylaminopyridazine with those of the monocations of 3-amino-6-methyl- and 4-amino-pyridazine respectively reveals that they are different. (Although the spectrum of 3-amino-6-methylpyridazine monocation was employed for comparison, because of the unavailability of that of 3-aminopyridazine monocation,
the 6-methyl group was not expected to have any appreciable effect on the ultraviolet spectrum.) This indicates that methylation and protonation have not occurred at the corresponding nitrogen atom in each case. Protonation of 3-amino-6-methyl- and 4-aminopyridazine was expected to involve the N-2 and N-1 nitrogen atoms respectively. Methylation of 3- and 4-dimethylamino- pyridazine is therefore believed to have taken place at the N-1 and N-2 nitrogen atoms respectively, i.e. meta to the dimethylamino-group. (Methylation at the dimethylamino-group can be discounted from considerations of the ultraviolet and 1H n.m.r. spectra.) The structures assigned are also consistent with the chemical evidence discussed in Chapter 2 part II.

Similarly, the spectra of the methiodides of 4-dimethylaminocinnoline and 2-dimethylaminoquinoxaline were different from those of the monocations of the corresponding amino-compounds. This lack of similarity is consistent with methylation occurring at the N-2 and N-4 nitrogen atoms respectively.

The ultraviolet spectra of the monocations of 2-dimethylamino-1-methylquinolinium iodide and quinol-2-yltrimethylammonium iodide were quite different as expected, but the dications of these two compounds, because of the optical transparency of the -NR3 group, were similar, and also similar to that of quinoline monocation. Likewise, the spectrum of the dication of
4-dimethylamino-1-methylquinolinium iodide resembled that of quinoline monocation.

However, the spectrum of the monocation of 4-dimethylamino-1-methyl-3-nitropyridinium iodide differs from that of 4-amino-3-nitropyridine monocation. Also the dication of 1-dimethylamino-2-methylisoquinolinium iodide differs from that of isoquinoline monocation. This is probably due to steric inhibition by the nitro-group in the former case and the peri-proton in the latter to mesomeric interaction of the dimethylamino-group and the ring nitrogen atom (Essery and Schofield, 1963).

III N.m.r. spectra

The $^1$H n.m.r. spectra of the trimethylammonio- and ring nitrogen methylated derivatives of monocyclic azines and bicyclic azines are given in Tables 9 and 10, and those of the trimethylammonio-purines are in Table 11. The $^1$H n.m.r. spectra of some chloro- and methylsulphonyl-compounds are also included in Tables 9 and 11 for reference.

Inspection of the Tables reveals that the signals due to the protons of:

1. the trimethylammonio-group occur in the range 5.92 - 6.34 $\tau$ (except for quinazolin-4-yltrimethylammonium chloride which is discussed below).
<table>
<thead>
<tr>
<th>Compound</th>
<th>Chemical shifts (δ) of protons</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Pyridine</td>
<td></td>
</tr>
<tr>
<td>Unsubst. b</td>
<td>3.26</td>
</tr>
<tr>
<td>2-NMe$_3$</td>
<td>1.65-2.5</td>
</tr>
<tr>
<td>2-Cl</td>
<td>1.9 -2.6</td>
</tr>
<tr>
<td>2-SO$_2$Me$^c$</td>
<td>1.65-2.1</td>
</tr>
<tr>
<td>3-NO$_2$</td>
<td>0.40</td>
</tr>
<tr>
<td>5-NO$_2$-2-NMe$_3$</td>
<td>1.65</td>
</tr>
<tr>
<td>4-NMe$_2$-1-Me$^f$</td>
<td>1.93</td>
</tr>
<tr>
<td>4-NMe$_2$-3-NO$_2$-1-Me$^f$</td>
<td>0.87</td>
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<tr>
<td>Pyrimidine</td>
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</tr>
<tr>
<td>Unsubst. g</td>
<td>0.57</td>
</tr>
<tr>
<td>2-NMe$_3$</td>
<td>0.94</td>
</tr>
<tr>
<td>2-Cl</td>
<td>1.13</td>
</tr>
<tr>
<td>5-NO$_2$</td>
<td>0.53</td>
</tr>
<tr>
<td>5-NO$_2$-2-NMe$_3$</td>
<td>0.12</td>
</tr>
<tr>
<td>2-Cl-5-NO$_2$</td>
<td>0.36</td>
</tr>
<tr>
<td>4-NMe$_3$</td>
<td>0.53</td>
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<tr>
<td>Pyrazine</td>
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<td>3-NMe$_2$-1-Me$^j$</td>
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</tr>
<tr>
<td>4-NMe$_2$-2-Me$^j$</td>
<td>1.22</td>
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</tbody>
</table>

a Spectra were determined in D$_2$O solution with sodium 3-trimethylsilylpropanesulphonate as internal standard. The salts were present as the iodides except where otherwise indicated. b Merry and Goldstein, 1966. c For preparation see Barlin and Brown (1967a). The $^1$H n.m.r. signal due to the protons of the -SO$_2$Me group was at 6.57. d The $^1$H n.m.r. spectrum of the cation in 5M DCl showed peaks at 0.00, 0.31, 1.41 and 0.56; corresponding to H-2, H-4, H-5 and H-6 protons respectively.
TABLE 9 continued

This salt was present as its chloride. f Pyridinium compound. g The $^1$H n.m.r. spectrum of the monocation in 5M DCl showed peaks at 0.04, 0.34, 1.46 and 0.34 ppm corresponding to H-2, H-4, H-5 and H-6 protons respectively. h Biffin, Brown and Lee, 1967. Hydration of the cation of 5-nitropyrimidine did not permit a comparison of its $^1$H n.m.r. spectrum with that of the quaternary salt. i Pyrazinium compound. j Pyridazinium compound.
### TABLE 10

Nuclear magnetic resonance spectra of salts of quinoline, isoquinoline, cinnoline, phthalazine, quinazoline, and quinoxaline

<table>
<thead>
<tr>
<th>Compound</th>
<th>Other Ring protons</th>
<th>( ^{+}\text{-NMe}_3 )</th>
<th>( ^{+}\text{-NMe} )</th>
<th>( ^{+}\text{-NMe}_2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Quinoline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-( ^{+}\text{-NMe}_3 )</td>
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<td>1.30-2.00</td>
<td>6.20</td>
<td></td>
</tr>
<tr>
<td>2-( ^{+}\text{-NMe}_2-1-\text{-Me} )</td>
<td>1.50-2.20</td>
<td>1.50-2.20</td>
<td>5.82</td>
<td>6.50</td>
</tr>
<tr>
<td>4-( ^{+}\text{-NMe}_2-1-\text{-Me} )</td>
<td>1.60-2.30, 3.10-3.20</td>
<td>1.60-2.30, 3.10-3.20</td>
<td>5.95</td>
<td>6.53</td>
</tr>
<tr>
<td><strong>Isoquinoline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-( ^{+}\text{-NMe}_2-2-\text{-Me} )</td>
<td>1.50-2.80</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cinnoline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-( ^{+}\text{-NMe}_2-2-\text{-Me} )</td>
<td>1.15, 1.70-2.00</td>
<td></td>
<td>5.31(^d)</td>
<td>6.31(^d)</td>
</tr>
<tr>
<td><strong>Phthalazine</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-( ^{+}\text{-NMe}_2-7-\text{-Me} )</td>
<td>0.59, 1.50-1.90</td>
<td></td>
<td>5.58</td>
<td>6.58</td>
</tr>
<tr>
<td><strong>Quinazoline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-(+\text{-NMe}_3 )</td>
<td>0.05, 1.60-1.80</td>
<td></td>
<td>6.10</td>
<td></td>
</tr>
<tr>
<td>4-(+\text{-NMe}_3 )</td>
<td>0.51, 2.52</td>
<td></td>
<td>5.92, 7.00</td>
<td></td>
</tr>
<tr>
<td><strong>Quinoxaline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-( ^{+}\text{-NMe}_2-1-\text{-Me} )</td>
<td>0.75, 1.90-2.20</td>
<td></td>
<td>5.32(^d)</td>
<td>6.46(^d)</td>
</tr>
</tbody>
</table>

\(^a\) Spectra were determined in \( ^2\text{H}_2\) solution unless otherwise stated, and at 33.5° with sodium 3-trimethylsilylpropanesulphonate as internal standard. 
\(^b\) This salt was present as its iodide. 
\(^c\) This salt was present as its chloride. 
\(^d\) DCl was added to shift the signal due to \( ^2\text{H}_2\) down field.
TABLE 11

Nuclear magnetic resonance spectra of purines

<table>
<thead>
<tr>
<th>Purine</th>
<th>2</th>
<th>6</th>
<th>8</th>
<th>9-Me</th>
<th>+NMe₃</th>
<th>-SO₂Me</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unsubst. b</td>
<td>1.47</td>
<td>1.34</td>
<td>1.72</td>
<td>0.69</td>
<td>0.49</td>
<td>0.94</td>
</tr>
<tr>
<td>+NMe₃-9-Me d</td>
<td>0.67</td>
<td>1.22</td>
<td>5.92</td>
<td>6.17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-Cl-9-Me</td>
<td>1.10</td>
<td>1.44</td>
<td>6.11</td>
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Chemical shifts (δ) of protons a

---

a Spectra were determined in D₂O solution unless otherwise stated, and at 33.5° with sodium 3-trimethylsilylpropanesulphonate as internal standard. b Matsuura and Goto, 1965. c Spectrum in 1.2M DCI. d This quaternary salt was present as its chloride. e Reist, Benitez, Goodman, Baker and Lee (1962) give 6.17.
ii the nuclear $^+\text{N-Me}$ group occur in the range $5.31 - 6.03\tau$.

iii the dimethylamino-group in the methiodides occur in the range $6.37 - 6.52\tau$.

The signals due to each of these groups were sharp singlets.

a) Monocyclic azines

The effect of electron withdrawal in the monocyclic azines by the trimethylammonio-group resulted in a downfield shift in the signals due to the ring protons (Pyrimidin-2-yltrimethylammonium chloride does not show this effect for the $H-4$ and $H-6$ protons.). This shift was intermediate in magnitude between that due to chloro- and methylsulphonyl-substituents and is consistent with the higher reactivity of the methylsulphonyl-compounds.

The spectra obtained for the methiodides of the dimethylamino-compounds showed the presence of a dimethylamino- and nuclear $\text{N-methyl}$ group and the absence of a trimethylammonio-group in each case.

Although Cheeseman (1960) had reported the methylation of 2-dimethylaminopyrazine by iodomethane to give only one product, he was unable to determine its structure. Inspection of the $^1\text{H}$ n.m.r. spectrum of this compound showed that methylation had occurred meta to the dimethylamino-group to give 3-dimethylamino-1-methylpyrazinium iodide since the singlet due to the $H-2$ proton is at lower field than the multiplet due to the $H-5$ proton.
b) **Bicyclic azines**

Complete analysis of the spectra of the bicyclic azines, by inspection, was not possible because of the complexity of the spectra.

However, the $^1$H n.m.r. spectrum of quinazolin-4-yltrimethylammonium chloride showed peaks at 0.51 and 2.52$\tau$, and at 5.92 and 7.00$\tau$, both pairs in the ratio of 3:1, as well as signals due to the remaining ring protons. Armarego and Willette (1965) have found that the H-2 proton of quinazoline is shifted upfield from 0.49$\tau$ to 1.65$\tau$ in the hydrated quinazoline cation.

Thus, the $^1$H n.m.r. spectrum indicates that quinazolin-4-yltrimethylammonium chloride exists in aqueous solution as a mixture of the hydrated and anhydrous cations (presumably 4L and 4M) in the approximate ratio of 1:3. This interpretation also accounts for the lack of similarity observed in the ultraviolet spectrum of quinazolin-4-yltrimethylammonium chloride and quinazoline.

c) **Purines**

The signals due to the ring protons of the trimethylammonio-purines are seen to be shifted downfield (to lower $\tau$) by the ammonio-group relative to purine. This effect was greater when the substituent was in the pyrimidine ring. This downfield shift, however, was less than that observed on protonation of purine. As noted for the monocyclic series, the signals due to the
ring protons in the trimethylammonio-compounds are at intermediate field between those of the methylsulphonyl- and chloro-compounds (the one exception being 8-chloro-purine).

The relatively high reactivity of heterocyclic trimethylammonio-compounds towards hydroxide ion described in Chapter 3 shows that these compounds could be potentially useful in synthesis. This potential is further heightened by the preparative work of Kötzzer (1956a, b and c) and Kötzzer and Schöns (1958) in which they were able to prepare 2-cyano-4,6-dimethyl- and 4-cyano-2,6-dimethyl-pyrimidine via the corresponding trimethylammonio-compounds but not directly from the chloro-analogues with cyanide ion in acetonitrile. It is true that in some series the chloro-compounds themselves are sufficiently reactive, but trimethylammonio-compounds, as has been shown, can be obtained directly by quaternization of the dimethylamine-compound with iodoethane.

This potential has been explored further by examination of the reactions of the trimethylammonio-compounds with a variety of nucleophiles, namely: a-propylamine, hydrazine hydrate, amines, amides, hydroxide-ammonium chloride, potassium hydroxide trifluoride and sodium hydrogen sulphide. In general, these reactions, which are discussed below, proceeded smoothly to give the expected product in good yield. Full details are given in Chapter 7.
CHAPTER 5

QUALITATIVE REACTIONS WITH NUCLEOPHILES

The relatively high reactivity of heterocyclic trimethylammonio-compounds towards hydroxide ion described in Chapter 3 shows that these compounds could be potentially useful in synthesis. This potential is further heightened by the preparative work of Klötzer (1956a, b and c) and Klötzer and Schantl (1963) in which they were able to prepare 2-cyano-4,6-dimethyl- and 4-cyano-2,6-dimethyl-pyrimidine via the corresponding trimethylammonio-compounds but not directly from the chloro-analogues with cyanide ion in acetamide. It is true that in some series the chloro-compounds themselves are sufficiently reactive, but trimethylammonio-compounds, as has been shown, can be obtained directly by quaternisation of the dimethylamino-compound with iodomethane.

This potential has been explored further by an examination of the reactions of the trimethylammonio-compounds with a variety of nucleophiles, namely: n-propylamine, hydrazine hydrate, alkoxides, ammonium hydroxide-ammonium chloride, potassium hydrogen difluoride and sodium hydrogen sulphide. In general, these reactions, which are discussed below, proceeded smoothly to give the expected product in good yield. Full details are given in Chapter 7.
a) **Reactions with n-propylamine**

The quaternary salts (e.g. 5A) when allowed to react with n-propylamine, generally under mild conditions, e.g. 50°C for 3 h, gave n-propylamino-compounds in high yields (e.g. 5B, 68%). 9-Methyl-2- and 6-n-propylamino-purine, 5-nitro-2-n-propylaminopyridine, 2-n-propylaminopyrimidine, and 2- and 4-n-propylaminoquinazoline were prepared in this way. The products were isolated as the picrates except for 5-nitro-2-n-propylaminopyridine which was isolated as the free base. The compounds were identified by elemental analysis or by comparison with known melting points.

b) **Reactions with hydrazine hydrate**

The trimethylammonio-compounds, likewise, were found to react readily with 98% hydrazine hydrate at 20°C for 15 min to give the hydrazino-compounds (e.g. 5C). The reaction mixtures were generally evaporated to dryness under reduced pressure and the products recrystallised and identified by elemental analysis or by comparison with known melting points. The products were usually obtained in high yields. Five hydrazino-compounds were prepared in this way.

c) **Reactions with alkoxide ion**

Similarly, sodium alkoxides in the corresponding alcohol (methanol or ethanol) were found to react readily with trimethylammonio-compounds to give the alkoxy-compounds (e.g. 5D). The reactions proceeded
smoothly, and the product was isolated by extraction with chloroform, benzene, or ether and identified as the corresponding base or picrate by elemental analysis, melting point or mixed melting point. Five 1,3-dimethylammonio-compounds gave good yields in the alkoxycarbonylation of dimethylacetamide.

d) Reactions with ammonia hydroxide

The 1,3-dimethylammonio-compounds when heated with aqueous anhydrous ammonium chloride gave the ammonio-compound. Ammonium chloride was added to the ammoniohydroxide to reduce the concentration of hydroxide ion as in studies of the reaction of methylolphenyl-heterocycles (H. R. Körner and Arning, 1965). Both 2-aminopurines and 2-aminofluoropyrimidines are obtained by this reaction. 2-Aminopyrimidines were obtained as the picrate, which was recrystallized as the hydrochloride to a new product with picrylamidine as the hydrochloride.

e) Reaction with potassium fluoride in difluoride

5-N-fluoro-5-pyrimidinyltriphenylammonium chloride was readily prepared and 6,8-difluoro-6-methylpurine (5E) by reaction with potassium hydrogen difluoride in ethanol containing 5% of water at 80°C. (R. Z. and C. Lister [1969] reported the conversion of purin-8-y1g-1-nitrophenethylammonium chloride to 6-fluoropurine by this method.)
smoothly and the product was isolated by extraction with chloroform, benzene or ether and identified as the free base or picrate by elemental analysis, melting point or mixed melting point. Five trimethylammonio-compounds gave good yields of the alkoxy-heterocycle.

d) Reactions with ammonium hydroxide - ammonium chloride

The trimethylammonio-compounds when heated with aqueous ammoniacal ammonium chloride gave the amino-compound. Ammonium chloride was added to the ammonium hydroxide to reduce the concentration of hydroxide ion as in studies of the reactions of methylsulphonyl-heterocycles (Barlin and Brown, 1967c). Both 2-amino- and 2-amino-5-nitro-pyrimidine were formed by this reaction. 2-Aminopyrimidine was isolated as the picrate and the nitropyrimidine as the free base.

e) Reaction with potassium hydrogen difluoride

9-Methylpurin-6-yltrimethylammonium chloride was readily converted to 6-fluoro-9-methylpurine (5E) by reaction with potassium hydrogen difluoride in ethanol containing 5% of water at 50°. [Kiburis and Lister (1969) reported the conversion of purin-6-yltrimethylammonium chloride to 6-fluoropurine by this method.]
f) **Reaction with aqueous sodium hydrogen sulphide**

The reaction of 5-nitropyrid-2-yltrimethylammonium chloride (5F) with aqueous sodium hydrogen sulphide (prepared by bubbling hydrogen sulphide through aqueous sodium hydroxide until the solution no longer immediately reddened phenolphthalein) proceeded smoothly at room temperature for 10 min to give the corresponding mercapto-compound (5G).
Tautomerism in Pyridazinones and Pyridazinthiones

Tautomeric equilibria involving hydroxy- and mercapto-derivatives* of nitrogen heterocycles have been widely examined by comparing the ultraviolet spectra and ionization constants of each parent hydroxy- or mercapto-compound with those of its $N$- and $O$-(or $S$-) methyl derivatives. In the hydroxy series, this method has been applied by Marshall and Walker (1951), Albert and Phillips (1956), Mason (1957, 1958) and Barlin and Pfleiderer (1971). Albert and Barlin (1959, 1962) have likewise used this method in the mercapto series. The whole topic has been reviewed by Katritzky and Lagowski (1963).

The application of this technique has been limited in the pyridazine series by the lack of three of the anhydro-bases of the $N$-methyl derivatives. The preparation of these compounds ($6A: R = \text{Me}, X = \text{O}; R = \text{Me}, X = \text{S}; 6B: R = \text{Me}, X = \text{S}$) in this work has removed this limitation.

* Throughout this chapter, such names as "3-hydroxypyridazidine" and "3-mercaptopyridazidine" have been used in their traditional sense, without implying that the tautomer with an -OH or -SH group is necessarily present in more than a trace amount at equilibrium.
Preparing of the N-methyl derivatives

The anhydrobases of 3-hydroxy- and 3-methyl-1-mercapto pyridazinium hydroxide were prepared from 3-chloropyridazine through 3-chloro-1-methylpyridazinium iodide by reaction with sodium hydroxide and sodium hydroxide sulphide respectively.

The position of methylation of 3-chloropyridazine, and hence the identities of 6A (R = Me, X = O; R = Me, X = S), were established by their difference from the known N-methyl isomers (Duffin and Kendall, 1959) (6B: R = Me, Y = O; R = Me, Y = S). The anhydro-base of 6-mercapto-1-methylpyridazinium hydroxide (6C; R = Me, X = Y) was prepared, as the corresponding dianion (Balters, 1965), by heating the 2,2'-dipyridyl analogue (Eichnerberger, Haenicke and Gravy, 1956) with phosphorus pentasulphide in benzene.

The assignment of structures to all these N-methyl derivatives was based originally on the assumption that 3- and 4-hydroxypyridazines had major tautomeric contributors of the type 6D (R = H, Y = O) and 6E (R = H, Y = O). The physical properties (pK and ultraviolet spectra) of 3- and 4-hydroxypyridazine showed similarities to one N-methyl compound in each case and these were designated 2,3-dihydro-3-oxopyridazine (6C; R = Me, Y = O) and 1,4-dihydro-1-methyl-4-oxopyridazine (6D; R = Me, Y = O) respectively. These assignments have never been confirmed by unambiguous...
Preparation of the N-methyl derivatives

The anhydro-bases of 3-hydroxy- and 3-mercapto-1-methylpyridazinium hydroxide were prepared from 3-chloropyridazine through 3-chloro-1-methylpyridazinium iodide by reaction with sodium hydroxide and sodium hydrogen sulphide respectively.

The position of methylation of 3-chloropyridazine, and hence the identities of 6A (R = Me, X = O; R = Me, X = S), were established by their difference from the known N-2-methyl isomers (Duffin and Kendall, 1959) (6C: R = Me, Y = O; R = Me, Y = S). The anhydro-base of 5-mercapto-1-methylpyridazinium hydroxide (6B: R = Me, X = S) was prepared, as for the corresponding cinnoline (Barlin, 1965), by heating the oxygen analogue (Eichenberger, Rometsch and Druey, 1956) with phosphorus pentasulphide in benzene.

The assignment of structures to all these N-methyl derivatives was based originally on the assumption that 3- and 4-hydroxypyridazine had major tautomeric contributors of the type 6C (R = H, Y = O) and 6D (R = H, Y = O). The physical properties (pK\textsubscript{a} and ultraviolet spectra) of 3- and 4-hydroxypyridazine showed similarities to one N-methyl compound in each case and these were designated 2,3-dihydro-2-methyl-3-oxopyridazine (6C: R = Me, Y = O) and 1,4-dihydro-1-methyl-4-oxopyridazine (6D: R = Me, Y = O) respectively. These assignments have never been confirmed by unambiguous
synthesis despite the preparations described by Overend, Turton and Wiggins (1950) which do not necessarily differentiate between N-1 and N-2-methyl derivatives of 3-hydroxypyridazine. However, the assigned orientations are considered correct since, in each series, the parent hydroxy-compound shows a marked similarity to one N-methyl derivative and differs from the other. This is quite different from that of the N-methyl derivatives of 4-hydroxycinnoline which both have similar spectra, and whose assigned structures have recently required reversal (Ames and Kucharska, 1963).

II Ultraviolet spectra

The spectra of all the ionic species of the compounds discussed in this chapter are given in Table 12 together with published data for the reference compounds. Detailed spectra of 3-mercaptopyridazine and its methyl derivatives as neutral species and cations are given in FIGS 7 and 8 to facilitate comparison.

Examination of the spectra of the neutral species of 3-mercaptopyridazine and its methyl derivatives (FIG 7) shows a close similarity between the parent mercaptopyridazine and its N-2-methyl derivative and major differences from the N-1- and S-methyl compounds. Similarly, 3-hydroxypyridazine is different in spectrum from its N-1- and O-methyl derivatives. These observations are consistent with the parent compound
TABLE 12

Physical properties (pKₐ and spectra)

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</tbody>
</table>

a Neutral species; +, cation; -, anion. b Shoulders and inflexions are underlined. c Values below zero have been obtained in solutions of sulphuric acid to which Hammett acidity functions [the H_o scale of Paul and Long (1957) has been used for convenience] have been assigned. d Albert and Phillips, 1956. e Mason, 1957. f Mason, 1959. g The results were within ±0.05 units when the pK_a was determined spectroscopically on 0.00002M solutions at λ = 310 nm. h Determined on the chloroplastinate and the reference cell compensated with chloroplatinic acid. i Albert and Barlin, 1962. j Eichenberger, Rometsch, and Druey, 1956. k The results were within ±0.05 units when the pK_a was determined spectroscopically on 0.00003M solutions at λ = 295 nm. l The results were within ±0.05 units when the pK_a was determined spectroscopically on 0.00004M solutions at λ = 310 nm.

pyridazineum hydroxide at pH 3.0;
(D) 3-methylthiopryridazine at pH 8.1.
Ultraviolet spectra in water at \( \sim 20^\circ \), of the neutral species of

(A) 3-mercaptopyridazine at pH 4.98;
(B) 1,6-dihydro-1-methyl-6-thiopyridazine at pH 7.0;
(C) anhydro-base of 3-mercapto-1-methylpyridazinium hydroxide at pH 3.0;
(D) 3-methylthiopyridazine at pH 6.1.
Ultraviolet spectra in water at ~20°, of the monocations of

(E) 3-mercaptopyridazine at $\mathrm{pH} = 4.20$;
(F) 1,6-dihydro-1-methyl-6-thiopyridazine at $\mathrm{pH} = 4.20$;
(G) anhydro-base of 3-mercapto-1-methyl-pyridazinium hydroxide at $\mathrm{pH} = 2.60$;
(H) 3-methylthiopyridazine at $\mathrm{pH} = 1.68$.
existing predominantly in the form 6C (R = H, Y = 0 or S).
Likewise, 4-mercapto- and 4-hydroxy-pyridazine (Mason, 1957) are thought to exist predominantly in the form 6D (R = H, Y = 0 or S).

Although 4-hydroxypyridazine exists mainly in the form 6D (R = H, Y = 0), it, like 4-hydroxycinnoline (Ames and Kucharska, 1963), methylates to give principally the N-2-methyl isomer together with a little 1,4-dihydro-1-methyl-4-oxopyridazine (which had previously been prepared by another route).

3-Hydroxypyridazine, on protonation, gives a cation analogous with those of its O- and N-2-methyl derivatives. These are different from that of the N-1-methyl derivative. This is in keeping with 3-hydroxypyridazine monocation having a structure like 6E. Likewise, 4-hydroxy- and 4-mercapto-pyridazine have been found to give cations of the type 6F (R = H, X = 0 or S) which are analogous with those of the O- (or S-) and N-1-methyl derivatives.

However, the cation of 3-mercaptopyridazine shows more individuality: its spectrum lies almost midway between that of the N-1- and N-2-methyl derivatives (FIG 8). This probably indicates that the cation is composed of at least two forms. As the cations of 3-methylthiopyridazine and the anhydro-base of 3-mercapto-1-methylpyridazinium hydroxide show differences comparable with those observed between the cations of
2-mercapto- and 2-methylthio-pyridine (Albert and Barlin, 1959), a significant contributor to this cation may have the structure 6G (R = R' = H).

III Ionization constants

Whereas the basic $pK_a$ values of the hydroxy- (or mercapto-) compounds closely resemble those of the $N$-methyl derivative of the predominant tautomer, the isomeric $N$-methyl compounds in each case showed a higher basic strength. This stronger basicity is consistent with the addition of a proton to a zwitterion, like 6A. The $pK_a$ differences between such pairs of $N$-methyl isomers are seen to be greater in the derivatives of hydroxy-compounds and also when the substituent is in the 3-position.

The relative electronic effects of a mercapto- and methylthio-group, and hence their likely influences on the structure of the cation when each was situated adjacent to the basic centre, were checked by comparing the $pK_a$ values of 2-methylthioaniline (3.45) and 2-mercaptoaniline (2.91). They did not differ appreciably.

In summary, hydroxy- and mercapto-pyridazines have been shown to exist predominantly in the pyridazin-one and -thione forms.
CHAPTER 7

EXPERIMENTAL

Analyses were by Dr Fildes and her staff in the Department of Medical Chemistry, Australian National University, Canberra. Solids for analysis were dried at 20°/20mm. unless otherwise stated. Melting points were taken in 'Pyrex' capillaries and are uncorrected.

All compounds were examined for the presence of impurities and isomers by paper chromatography on Whatman No 1 paper with (a) 3% aqueous ammonium chloride, and (b) butan-2-ol - 5M-acetic acid (7:3) as solvent and were recrystallised where possible to constant melting point. All trimethylammonio-compounds and nuclear N-methyl compounds were also examined for the presence of possible isomers by $^1$H n.m.r. spectroscopy.

All new compounds are underlined at their first mention in the body of the text of this experimental section. (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.)
Reaction of 2-chloropyridine with trimethylamine.

2-Chloropyridine (0.20 g), trimethylamine (1 g) and benzene (6 ml) were heated in a sealed tube at 100° for 3 days. A sample of the reaction mixture on thin-layer chromatography (alumina, benzene) showed under 254 nm ultraviolet light a little 2-dimethylaminopyridine (identical with an authentic sample prepared as described by Cumper and Singleton, 1967) and unchanged 2-chloropyridine. The reaction mixture was filtered to remove tetramethylammonium chloride (which showed no significant ultraviolet absorption). The filtrate was evaporated to dryness and ethanolic picric acid was added to give 2-dimethylaminopyridine picrate (0.019 g), m.p. 180-181° (from ethanol), undepressed on admixture with an authentic specimen (Pentimalli, 1964: 181-181.5°).

Pyrid-2-yltrimethylammonium iodide.—Pyrid-2-yltrimethylammonium iodide was prepared by heating 2-dimethylaminopyridine (Cumper and Singleton, 1967) with iodomethane at 100° for 2 h (Tschitschibabin and Konowalowa, 1926; Gol'dfarb, Setkina and Danyushevskii, 1948). The product, after recrystallisation from ethanol, had m.p. 194° (Tschitschibabin and Konowalowa, 1926, give 184°) (Found: C, 36.0; H, 5.1; N, 10.4. Calc. for C₈H₁₃I N₂: C, 36.4; H, 5.0; N, 10.6%). The picrate,
prepared in aqueous solution and recrystallised from ethanol, had m.p. 112-113° (Tschitschibabin and Konowalowa, 1926, give 113°).

2-Hydroxypyridine.—Pyrid-2-yltrimethylammonium iodide (0.10 g) and sodium hydroxide (10 ml; 4M) were heated in a sealed tube at 110° for 5 h. The reaction mixture was then adjusted to pH 5 and evaporated to dryness. The residue was extracted with benzene and the product crystallised from benzene-light petroleum (b.p. 60-80°) to give 2-hydroxypyridine (0.026 g), m.p. and mixed m.p. 104-106° (Koenigs and Koerner, 1883, give 106°).

2-Methoxypyridine.—Pyrid-2-yltrimethylammonium iodide (0.020 g) and methanolic sodium methoxide (2 ml; 2M) were heated at 100° for 12 h. The reaction mixture was chilled, diluted with water, adjusted to pH 7, and extracted with chloroform. The extract was dried (Na₂SO₄), the solvent removed, and the residual oil treated with ethanolic picric acid to give 2-methoxypyridine picrate (0.013 g), m.p. 159-160° not depressed on admixture with an authentic sample (Barlin and Brown, 1967a: 159-160°).

Reaction of 2-chloro-3-nitropyridine with trimethylamine.—A mixture of 2-chloro-3-nitropyridine (0.5 g; Bishop, Cavell and Chapman, 1952) and
trimethylamine (1.0 g) in benzene (5 ml) was heated in a sealed tube at 60° for 24 h and then evaporated to dryness under reduced pressure. The residue, subjected to thin-layer chromatography (alumina, ether), gave unchanged 2-chloro-3-nitropyridine (0.2 g) and 2-dimethylamino-3-nitropyridine (0.2 g), characterised as the picrate, m.p. 101° (from ethanol) (Smalley, 1966, gives 101°).

2-Chloro-5-nitropyridine was prepared as described by Phillips, 1941, from 2-aminopyridine through 2-hydroxy-5-nitropyridine (Caldwell and Kornfeld, 1942).

5-Nitropyrid-2-yltrimethylammonium chloride.—Trimethylamine (1.8 g) was added to a cold solution of 2-chloro-5-nitropyridine (0.5 g) in benzene (26 ml) and the mixture allowed to stand at 4° for 2 h. A white precipitate formed quickly. The product (0.5 g) was filtered off and purified by reprecipitation from warm methanol by addition of diethyl ether to give 5-nitropyrid-2-yltrimethylammonium chloride, m.p. 165.5° (Found, for material dried at 100°/1 h: N, 19.4. C₆H₁₂ClN₃O₂ requires N, 19.4%). The picrate, prepared in and recrystallised from ethanol, had m.p. 131° (Found, for material dried at 100°/1 h: C, 41.0; H, 3.4; N, 20.5. C₁₄H₁₄N₆O₃ requires C, 40.95; H, 3.5; N, 20.5%).
5-Nitropyrid-2-ylpyridinium picrate.—Pyridine (1.0 ml) was added to a solution of 2-chloro-5-nitropyridine (0.1 g) in benzene (3 ml) and the mixture refluxed for 1 h. After cooling, the reaction mixture was decanted from the oil which had separated. This oil was treated with ethanolic picric acid and gave a yellow precipitate of 5-nitropyrid-2-ylpyridinium picrate (0.009 g) which after recrystallisation from ethanol had m.p. 179-180° (Bishop, Cavell and Chapman, 1952: 181.5°) (Found, for material dried at 100°/1 h: C, 44.7; H, 2.4; N, 19.4. Calc. for C$_{16}$H$_{10}$N$_6$O: C, 44.6; H, 2.3; N, 19.5%).

2-Hydroxy-5-nitropyridine.—A mixture of 5-nitropyrid-2-yltrimethylammonium chloride (0.050 g) and sodium hydroxide (5 ml; M) was allowed to stand at 20° for 10 min, then adjusted to pH 5 and evaporated to dryness. The residue was extracted with cold propan-2-ol which, after concentration, deposited 2-hydroxy-5-nitropyridine (0.010 g) m.p. and mixed m.p. 184° (Fanta and Stein, 1955, give 182.5 - 184.5°).

2-Hydrazino-5-nitropyridine.—Hydrazine hydrate (1 ml) was added to a solution of 5-nitropyrid-2-yltrimethylammonium chloride (0.1 g) in water (1 ml) and the mixture allowed to stand at 20° for 15 min. The solution turned dark red in colour and was evaporated to dryness.
under reduced pressure. The residue was crystallised from ethanol (charcoal) and gave yellow, 2-hydrazino-5-nitropyridine (0.052 g), m.p. 207° (Mangini and Frenguelli, 1939, give 205-206°) (Found, for material dried at 100°/1 h: C, 39.1; H, 4.2; N, 36.4. Calc. for C₅H₆N₄O₂: C, 39.0; H, 3.9; N, 36.4%).

2-Mercapto-5-nitropyridine.—A solution of 5-nitropyrid-2-yltrimethylammonium chloride (0.10 g) in aqueous sodium hydrogen sulphide (5 ml; 1M) (prepared by bubbling hydrogen sulphide through sodium hydroxide solution until the solution no longer immediately reddened phenolphthalein) was allowed to stand at 20° for 10 min. The solution was acidified and chilled. The precipitate (0.05 g) was filtered off and crystallised from aqueous methanol to give 2-mercapto-5-nitropyridine (0.037 g), m.p. 165-168° (decomp.) [Binz and Rath, 1931, give 168° (decomp.); Takahashi, Ueda and Iwai, 1958, report two forms with m.p. 185° and 190° respectively].

2-Methoxy-5-nitropyridine.—A solution of 5-nitropyrid-2-yltrimethylammonium chloride (0.1 g) in methanol (1 ml) was added to methanolic sodium methoxide (5 ml; 0.8M) and the mixture allowed to stand at 20° for 10 min. The reaction mixture was evaporated to dryness and the residue extracted with chloroform. Evaporation of the
chloroform gave 2-methoxy-5-nitropyridine (0.07 g), which, after crystallisation from light petroleum (b.p. 60-80°) (charcoal), had m.p. 106-108°, undepressed on admixture with an authentic specimen (Gruber, 1953: 109-110°).

5-Nitro-2-n-propylanaminopyridine.— A mixture of 5-nitropyrid-2-yltrimethylammonium chloride (0.10 g) and n-propylamine (1 ml) were heated together in a sealed tube at 50° for 3 h. The reaction mixture was evaporated to dryness and the residue extracted with cyclohexane. The cyclohexane solution was concentrated and gave 2-n-propylamino-5-nitropyridine (0.05 g), m.p. 91-92° (Found: C, 53.4; H, 6.4; N, 23.1. \( \text{C}_8\text{H}_{11}\text{N}_3\text{O}_2 \) requires: C, 53.0; H, 6.1; N, 23.2%).

Reaction of 4-chloropyridine with trimethylamine.— A mixture of 4-chloropyridine (0.5 g; obtained from commercial 4-chloropyridine hydrochloride by adjusting a cold aqueous solution to pH 6 with sodium carbonate and isolating the product by the method of Leis and Curran, 1945), trimethylamine (1.0 g) and benzene (5 ml) was heated in a sealed tube at 100° for 42 h. Tetramethylammonium chloride (which showed no significant ultraviolet absorption) was filtered off and the filtrate was examined by thin-layer chromatography on alumina in benzene, chloroform and diethyl ether. Unchanged
4-chloropyridine and a trace of 4-dimethylaminopyridine, identical with an authentic sample (Wibaut and Broekman, 1961) of m.p. 113° (lit., 110-112°), were found to be present.

4-Dimethylamino-1-methylpyridinium iodide. — This compound was prepared from 4-dimethylaminopyridine (Wibaut and Broekman, 1961) and iodomethane as described by Jerchel, Fischer and Thomas (1956). It had m.p. 240° (lit., 140°) (Found, for material dried at 100°/1 h: C, 36.2; H, 5.15; N, 10.5. Calc. for C₈H₁₃IN₂: C, 36.4; H, 5.0; N, 10.6%).

Reaction of 4-chloro-3-nitropyridine with trimethylamine. — 4-Chloro-3-nitropyridine (0.6 g; Albert and Barlin, 1963) was added to a solution of trimethylamine (1 g) in benzene (10 ml) and the mixture allowed to stand at 20° for 2 days. The reaction mixture was evaporated to dryness at 20° under reduced pressure and the residue subjected to thin-layer chromatography (alumina, ether). It gave 4-dimethylamino-3-nitropyridine (0.015 g), identified as its picrate, m.p. 192° (from ethanol) (Smalley, 1966, gives 192°) and unchanged 4-chloro-3-nitropyridine (0.5 g), characterised as 4-amino-3-nitropyridine, m.p. 201° (from ethanol) (Clark-Lewis and Singh, 1962, give 204°) by reaction with aqueous ammonia at room temperature (Clark-Lewis and Singh, 1962).
4-Dimethylamino-1-methyl-3-nitropyridinium iodide.—
A solution of 4-dimethylamino-3-nitropyridine (0.050 g; Smalley, 1966) in iodomethane (1 ml) was allowed to stand at room temperature for 20 h. The precipitate (0.091 g) was filtered off and recrystallised from ethanol (charcoal) to give 4-dimethylamino-1-methyl-3-nitropyridinium iodide (0.041 g), m.p. 200-201°C (Found: C, 31.1; H, 4.1; N, 13.6. C₁₈H₁₂IN₃O₂ requires C, 31.1; H, 3.9; N, 13.6%).

3-Nitropyridine.—3-Aminopyridine was diazotised as described by Schickh, Binz and Schulz (1936) except that the diazonium chloride was converted to the fluoroborate and this was decomposed over copper powder. The product, after recrystallisation from light petroleum (b.p. 60°C-80°C), gave 3-nitropyridine, m.p. 39°C (Friedl, 1912, gives 41°C).

PYRAZINES

Reaction of 2-chloropyrazine with trimethylamine.—
A mixture of 2-chloropyrazine (0.1 g; commercial) and trimethylamine (0.5 g) in benzene (4 ml) was heated in a sealed tube at 100°C for 23 h. The reaction mixture was filtered to remove tetramethylammonium chloride, and the filtrate concentrated. The residue, with ethanolic picric acid, gave 2-dimethylaminopyrazine.
picrate (0.1 g), m.p. 158-159°, not depressed on admixture with an authentic sample (Cheeseman, 1960: 158-160°).

When the reaction was repeated at 100° for 3 h, mostly 2-chloropyrazine remained and no trimethylammonio-compound could be detected.

3-Dimethylamino-1-methylpyrazinium iodide. — Methylation of 2-dimethylaminopyrazine (Cheeseman, 1960) with iodomethane in methanol as described by Cheeseman (1960) gave 3-dimethylamino-1-methylpyrazinium iodide, m.p. 133-134° (lit., 136-137°) (Found: C, 31.7; H, 4.8; N, 15.9. Calc. for C₇H₁₂IN₃: C, 31.7; H, 4.6; N, 15.9%). The ¹H n.m.r. spectrum of this compound allowed the determination of its structure.

PYRIDAZINES

3-Chloropyridazine was prepared as described by Evans and Wiselogle, 1945, from 3-hydroxypyridazine (Homer, Gregory, Overend and Wiggins, 1948).

Reaction of 3-chloropyridazine with trimethylamine. — 3-Chloropyridazine (0.10 g) and trimethylamine (0.4 g) in benzene (4 ml) were heated in a sealed tube at 100° for 24 h. The precipitate of tetramethylammonium chloride was filtered off, the filtrate concentrated
and ethanolic picric acid added to the residue. The product (0.10 g) was recrystallised from ethanol to give 3-dimethylaminopyridazinone picrate, m.p. 184.5-185°, not depressed on admixture with the sample prepared below (Crossland and Kofod, 1967, give 178-179°) (Found, for material dried at 100°/1 h: C, 41.0; H, 3.4; N, 23.7. Calc. for C₁₂H₁₅N₆O₇: C, 40.9; H, 3.4; N, 23.9%).

When the reaction was repeated at 100° for 3 h, mostly unchanged chloro-compound remained; a little 3-dimethylaminopyridazine but no trimethylammonio-compound could be detected.

3-Dimethylaminopyridazine.—A mixture of 3-chloropyridazine (0.1 g), ethanol (4 ml), and ethanolic dimethylamine (1 ml; 33%) was heated in a sealed tube at 100° for 6 h. Sodium hydroxide (1 ml; 1M) was added, the mixture evaporated to dryness and the oily residue extracted in chloroform. The picrate (0.19 g), prepared in and recrystallised from ethanol (charcoal), had m.p. 184-185°.

3-Chloro-1-methylpyridazinium iodide.—Iodomethane (2 ml) was added to a solution of 3-chloropyridazine (0.7 g) in ethanol (4 ml) and the mixture allowed to stand at room temperature for 4 days. The precipitate (1.15 g) was filtered off, washed with benzene and air dried.
It was recrystallised from propan-2-ol (charcoal) to give 3-chloro-1-methylpyridazinium iodide (0.95 g), m.p. 150-151° (Found: C, 23.2; H, 2.1; I, 49.3; N, 10.7. C_5H_6ClIN_2 requires C, 23.4; H, 2.4; I, 49.5; N, 10.9%).

3-Dimethylamino-1-methylpyridazinium iodide and picrate.

(a) A solution of 3-dimethylaminopyridazine (0.10 g) in iodomethane (1 ml) was allowed to stand at 20° for 1 h. The precipitate (0.18 g) was filtered off and recrystallised from chloroform-benzene to give 3-dimethylamino-1-methylpyridazinium iodide, m.p. 195-197° (Found: C, 31.8; H, 4.8; N, 15.9. C_7H_12IN_3 requires C, 31.7; H, 4.6; N, 15.9%). The picrate, prepared from the iodide and aqueous picric acid, was recrystallised from water. It had m.p. 142° (Found: C, 42.9; H, 3.9; N, 22.9. C_13H_14N_6O_7 requires C, 42.6; H, 3.9; N, 23.0%).

(b) A mixture of 3-chloro-1-methylpyridazinium iodide (0.050 g) and ethanolic dimethylamine (6 ml; 16%) was allowed to stand at room temperature for 5 min. The reaction mixture was evaporated to dryness under reduced pressure at 25° and the residue extracted with chloroform. The solvent was evaporated and aqueous picric acid added to the residue to give 3-dimethylamino-1-methylpyridazinium picrate (0.030 g), m.p. 142°, undepressed on admixture with a sample prepared in (a).
3-Hydroxy-1-methylpyridazinium hexachloroplatinate.—A solution of 3-chloro-1-methylpyridazinium iodide (0.05 g) in aqueous sodium hydroxide (5 ml; 0.1 M) was allowed to stand at 20°C for 30 min, adjusted to pH 7, and extracted with chloroform (5 x 10 ml) to remove impurities. The aqueous solution was then evaporated to dryness at 20°C under reduced pressure, the residue dried thoroughly, and then extracted with cold methanol. The methanolic solution was concentrated at 20°C under reduced pressure to ca 1.5 ml and a solution of hexachloroplatinic acid (0.1 g) in methanol (0.5 ml) added with swirling and the mixture chilled for 30 min. The solid (0.028 g) which separated was filtered off and recrystallised from propan-2-ol to give yellow 3-hydroxy-1-methylpyridazinium hexachloroplatinate (0.016 g), m.p. 186-188°C (Found: C, 19.3; H, 2.6; N, 8.8%. C_{10}H_{14}Cl_{6}N_{4}O_{2}Pt requires C, 19.1; H, 2.2; N, 8.8%).

Anhydro-base of 3-hydroxy-1-methylpyridazinium hydroxide.—3-Dimethylamino-1-methylpyridazinium iodide (0.010 g) and sodium hydroxide (10 ml; M) were refluxed for 33 h. A portion (2 ml) of the reaction mixture was buffered to pH 4, diluted to 50 ml and afforded an ultraviolet spectrum identical with that of the hexachloroplatinate above after compensation with chloroplatinic acid.
Anhydro-base of 3-mercapto-1-methylpyridazinium hydroxide.—A solution of 3-chloro-1-methylpyridazinium iodide (0.15 g) and sodium hydrosulphide monohydrate (0.22 g) in water (5 ml) was allowed to stand at 20° for 30 min, adjusted to pH 7, and evaporated to dryness. The residue was extracted with propan-2-ol and the product recrystallised from propan-2-ol (charcoal) to give the anhydro-base of 3-mercapto-1-methylpyridazinium hydroxide (0.05 g), m.p. 216–217° (decomp.) (Found: C, 47.6; H, 4.7; N, 21.8. C₅H₆N₂S requires C, 47.6; H, 4.8; N, 22.2%).

4-Dimethylaminopyridazine.—3,4-Dichloro-5-dimethylaminopyridazine (Crossland and Kofod, 1967) was prepared from furfural through mucochloric acid (Chan and Miller, 1967), 4,5-dichloro-2,3-dihydro-3-oxopyridazine (Kuraishi, 1956) and 3,4,5-trichloropyridazine (Kuraishi, 1956). It was dechlorinated as described below rather than by the less satisfactory method of Crossland and Kofod (1967).

A mixture of 3,4-dichloro-5-dimethylaminopyridazine (1.0 g), magnesium oxide (2.0 g), 10% palladium-charcoal (0.5 g) and ethanol (20 ml) was shaken with hydrogen at 200/710 mm until uptake ceased. The reaction mixture was filtered and the filtrate concentrated and chromatographed over alumina (10 in x 2 in diam.). The product was recrystallised from benzene-light petroleum
(b.p. 60-80°) to give 4-dimethylaminopyridazine (0.42 g), m.p. 45° (Crossland and Kofod, 1967, give 47-48°).

The crystals which separated gave, after repeated recrystallisation from propan-2-ol, 4-dimethylamino-1- and -2-methylpyridazinium iodides.

---A solution of 4-dimethylaminopyridazine (0.27 g) and iodomethane (2 ml) in benzene (15 ml) was allowed to stand at room temperature for 7 days. The precipitate (0.53 g) was filtered off and recrystallised from propan-2-ol to give a mixture of the above methiodides. It had m.p. 176-178° (Found: C, 31.9; H, 4.6; N, 15.8. C₇H₁₂IN₃ requires C, 31.7; H, 4.6; N, 15.9%). (The ¹H n.m.r. spectrum showed peaks at 5.59, 6.82, 5.88, and 6.68, both pairs in the ratio 1:2, as well as peaks due to ring protons.)

This product (0.1 g) and sodium hydroxide (10 ml; 0.1M) were allowed to stand at room temperature for 6 days, and the reaction mixture extracted with chloroform. The chloroform extract, after evaporation and recrystallisation of the residue from light petroleum (b.p. 60-80°), gave 1,4-dihydro-1-methyl-4-oxopyridazine (0.005 g), m.p. 97°, not depressed on admixture with an authentic specimen (Eichenberger, Rometsch and Druey, 1956, give 98-99°) (Found: C, 54.7; H, 5.6; N, 25.6. Calc. for C₅H₆N₂O: C, 54.6; H, 5.5; N, 25.4%).

The aqueous solution, after chloroform extraction, was adjusted to pH 6 and evaporated to dryness under reduced pressure at 20°. The residue was extracted
with warm propan-2-ol and the product (0.016 g) was
treated with 46% hydroiodic acid in propan-2-ol (50% v/v).
The crystals which separated gave, after repeated
recrystallisations from propan-2-ol, 4-dimethylamino-2-
methylypyridazinium iodide (0.011 g), m.p. 223° (Found:
C, 31.6; H, 4.5; N, 15.7. C7H12IN3 requires
C, 31.7; H, 4.6; N, 15.9%).

Methylation of 4-Hydroxypyridazine.—4-Hydroxy-
pyridazine (1.92 g; Eichenberger, Rometsch and Druey,
1956) was methylated with dimethylsulphate and sodium
ethoxide as described by Eichenberger et al., 1956.
The crude hydrochloride (1.51 g) after recrystallis-
ation from ethanol gave 1-methyl-5-hydroxypyridazinium
chloride (0.75 g), m.p. 239-240° (decomp.) [lit., 234°
(decomp.)] from which the free base (Eichenberger
et al., 1956) was obtained.
The filtrates from the collection of the crude
hydrochloride and from its recrystallisations were
combined and evaporated to dryness. The residue was
dissolved in a little water, made alkaline with potassium
carbonate and extracted with chloroform to give an oil.
This oil was subjected to thin-layer chromatography
(alumina, chloroform) and gave 1,4-dihydro-1-methyl-4-
oxopyridazine (0.27 g), identical with another specimen
prepared by catalytic dechlorination of 3,6-dichloro-
1,4-dihydro-1-methyl-4-oxopyridazine (Eichenberger,
et al., 1956).
Anhydro-base of 1-methyl-5-mercaptopyridazinium hydroxide.—The anhydro-base of 1-methyl-5-hydroxy-pyridazinium hydroxide (0.150 g) and phosphorus pentasulphide (0.50 g) in benzene (20 ml) were refluxed for 3 h. The solvent was evaporated, water added, and the mixture warmed to decompose excess phosphorus pentasulphide. This mixture was extracted with chloroform, the extract dried (Na$_2$SO$_4$), the solvent evaporated and the product recrystallised from benzene to give orange needles of the anhydro-base of 1-methyl-5-mercaptopyridazinium hydroxide (0.050 g), m.p. 143-144° (Found, for material dried at 100°/1 h: C, 47.9; H, 5.1; N, 21.8; S, 25.2. C$_5$H$_6$N$_2$S requires C, 47.6; H, 4.8; N, 22.2; S, 25.4.%).

PYRIMIDINES

Pyrimidin-2-yltrimethylammonium chloride.—Pyrimidin-2-yltrimethylammonium chloride was prepared from 2-chloropyrimidine (Kogon, Minin and Overberger, 1955) and trimethylamine in benzene as described by Goya, Takahashi and Okano (1966), but purified by recrystallisation from propan-2-ol. It had m.p. 204-205° (lit., 215°) (Found, for material dried at 100°/1 h: C, 48.5; H, 7.2; Cl, 20.4; N, 24.4. Calc. for C$_7$H$_12$ClN$_3$: C, 48.4; H, 7.0; Cl, 20.4; N, 24.2%). The picrate, prepared in and recrystallised from ethanol,
had m.p. 175-176° (Found: C, 42.7; H, 4.1; N, 23.1. 
\( \text{C}_{13}\text{H}_{14}\text{N}_{6}\text{O}_{7} \) requires C, 42.6; H, 3.9; N, 22.9%).

2-Hydroxypyrimidine.—A solution of pyrimidin-2-
yltrimethylammonium chloride (0.05 g) in sodium hydroxide 
(10 ml; 0.035M) was heated at 100° for 10 min. The 
solution was adjusted to pH 5, evaporated to dryness and 
the residue extracted with boiling ethyl acetate (2 x 25 ml). 
Concentration of the extracts gave crystals of 2-hydroxy-
pyrimidine (0.01 g), m.p. 176° (Brown, 1950a, gives 
178-180°). It proved identical with an authentic sample 
(Brown, 1950a) on paper chromatography.

2-Aminopyrimidine.—Pyrimidin-2-yltrimethylammonium 
chloride (0.097 g), ammonium hydroxide (3 ml; d 0.91) 
and ammonium chloride (0.32 g) were heated in a sealed 
tube at 100° for 1 h. The tube was opened, and the 
reaction mixture was boiled to remove ammonia and 
aqueous picric acid added to give 2-aminopyrimidine 
picrate (0.074 g), m.p. 235-237° (Buttner, 1903, gives 
237-238°).

2-Hydrazinopyrimidine.—Hydrazine hydrate (0.5 ml) 
was added to pyrimidin-2-yltrimethylammonium chloride 
(0.020 g) in water (1 ml) and the mixture allowed to 
stand at 20° for 15 min. The reaction mixture was 
evaporated to dryness under reduced pressure and the
residue crystallised from benzene to give 2-hydrazinopyrimidine (0.010 g), m.p. 108° (Chesterfield, McOmie and Sayer, 1955, give 108-110°).

2-n-Propylaminopyrimidine.—A mixture of pyrimidin-2-yltrimethylammonium chloride (0.022 g) and n-propylamine (1 ml) were heated in a sealed tube at 100° for 1 h.

The reaction mixture was evaporated to dryness and the residue extracted with benzene. The benzene was removed and the oil treated with ethanolic picric acid to give 2-n-propylaminopyrimidine picrate (0.015 g), m.p. 150-151° (Brown and Harper, 1963, give m.p. 151-152°).

2-Chloro-5-nitropyrimidine was prepared as described by Roblin, Winnek and English, 1942, from 2-hydroxy-5-nitropyrimidine (Stempel, 1968; Wempen, Blank and Fox, 1969).

5-Nitropyrimidin-2-yltrimethylammonium chloride.—A cold solution of trimethylamine (0.37 g) in benzene (10 ml) was added to 2-chloro-5-nitropyrimidine (0.100 g) in cold benzene (20 ml) and the precipitate of 5-nitropyrimidin-2-yltrimethylammonium chloride (0.113 g) was filtered off and washed with cold benzene. This product had m.p. 204° (decomp.) (Found: N, 25.3. \( \text{C}_7\text{H}_{11}\text{ClN}_4\text{O}_2 \) requires N, 25.6%), and could not be further purified by recrystallisation.
Aqueous lithium picrate [prepared from saturated aqueous picric acid (1.2 ml) by addition of lithium carbonate] was added to this salt (0.011 g) dissolved in the minimum of cold water. The precipitate was filtered off and washed with cold water. The picrate (0.002 g) had m.p. 132-133\(^\circ\) (Found: C, 36.3; H, 3.3; N, 22.5. \(\text{C}_{13}\text{H}_{13}\text{N}_{7}\text{O}_{9}\cdot\text{H}_{2}\text{O}\) requires C, 36.3; H, 3.3; N, 22.8%).

2-Hydroxy-5-nitropyrimidine. —5-Nitropyrimidin-2-yltrimethylammonium chloride (0.23 g) was dissolved in sodium hydroxide (7 ml; 1M), the mixture allowed to stand at 20\(^\circ\) for 5 min, and then adjusted to pH 4. This solution, concentrated under reduced pressure to 2 ml, gave crystals of 2-hydroxy-5-nitropyrimidine (0.013 g), m.p. and mixed m.p. 199-200\(^\circ\) (from water) (Stempel, 1968, gives 199-201\(^\circ\); Wempen, Blank and Fox, 1969, give 202-203\(^\circ\)).

2-Amino-5-nitropyrimidine. —A mixture of 5-nitropyrimidin-2-yltrimethylammonium chloride (0.018 g), aqueous ammonia (1 ml; d 0.91) and ammonium chloride (0.11 g) were heated in a sealed tube at 50\(^\circ\) for 15 min. The tube was opened and the reaction mixture was evaporated to dryness and the residue was repeatedly extracted with benzene. The benzene was removed and
the product crystallised from propan-2-ol to give
2-amino-5-nitropyrimidine (0.006 g), m.p. 235° (Hale
and Brill, 1912, give 236°).

4-Chloropyrimidine hydrochloride was prepared as
described by Boarland and McOmie, 1951, from
4-hydroxypyrimidine (Brown, 1950b).

Pyrimidin-4-yltrimethylammonium chloride.—4-Chloro-
pyrimidine hydrochloride (0.90 g) was added to a
solution of sodium hydrogen carbonate (0.5 g) in water
(6 ml) and the mixture extracted with benzene (4 x 20 ml).
The combined extracts were dried (Na₂SO₄), the solution
concentrated to ca 20 ml, and cooled to 5°. A cold
solution of trimethylamine (1.0 g) in benzene (5 ml) was
then added and the mixture allowed to stand at 5° for
12 h. The precipitate was filtered off and washed with
benzene to give pyrimidin-4-yltrimethylammonium chloride
(0.50 g), m.p. 138° (decomp.) (Found, for material dried
at 100°/1 h: Cl, 20.3; N, 23.9. C₇H₁₂ClN₃ requires
Cl, 20.4; N, 24.3%).

The picrate, prepared in and recrystallised from
ethanol, had m.p. 159-160° (Found: C, 42.6; H, 3.8;
N, 23.0. C₁₃H₁₄N₆O₇ requires C, 42.6; H, 3.9;
N, 22.9%).
4-Hydroxypyrimidine.—A solution of pyrimidin-4-yltrimethylammonium chloride (0.050 g) in sodium hydroxide (5 ml; 0.1M) was allowed to stand at 20°C for 5 min. The solution was then adjusted to pH 6 and evaporated to dryness. The residue was extracted with chloroform; the product, crystallised from ethanol-light petroleum (b.p. 60-80°C), gave 4-hydroxypyrimidine (0.004 g), m.p. and mixed m.p. 164°C (Brown, 1950b, gives 163-165°C).

QUINOLINES

Reaction of 2-chloroquinoline with trimethylamine.—The reaction of liquid trimethylamine with 2-chloroquinoline in a sealed tube according to the method of Reese (1958) gave only 2-dimethylaminoquinoline and no trimethylammonio-compound.

Quinol-2-yltrimethylammonium iodide.—A solution of 2-dimethylaminoquinoline (1.20 g; Gilman, Crounse, Massie, Benkeser and Spatz, 1945) in iodomethane (6 ml) was allowed to stand at 20°C for 30 days. The precipitate (2.10 g; containing quinol-2-yltrimethylammonium iodide and 2-dimethylamino-1-methylquinolinium iodide) was filtered off and recrystallised from water. It had m.p. 166-167°C (Found: C, 45.7; H, 5.0; N, 8.9. Calc. for C_{12}H_{15}IN_2: C, 45.9; H, 4.8; N, 8.9%). This product (0.5 g) was dissolved in sodium hydroxide
(35 ml; 0.2M) and allowed to stand at 20° for 3.5 h. The reaction mixture was extracted with ether, the extracts dried (Na₂SO₄) and the solvent removed to give 1,2-dihydro-1-methyl-2-oxoquinoline (0.100 g) m.p. 72° [from light petroleum (b.p. 60-80°)] (Perkin and Robinson, 1913, give 74°).

The aqueous solution was adjusted to pH 6, evaporated to dryness at 20° and the residue extracted with warm propan-2-ol. The product was recrystallised from a small volume of water with addition of potassium iodide to give quinol-2-yltrimethylammonium iodide (0.22 g), m.p. 171° (Reese, 1958, gives 168°) (Found: C, 45.7; H, 4.9; N, 8.8%).

2-Hydroxyquinoline. — A solution of quinol-2-yltrimethylammonium iodide (0.100 g) in sodium hydroxide (5 ml; 3M) was heated in a sealed tube at 100° for 20 min. The reaction mixture was adjusted to pH 7, and chilled. The precipitate was collected and recrystallised from ethanol to give 2-hydroxyquinoline (0.040 g), m.p. and mixed m.p. 198° (Friedländer and Ostermaier, 1881, give 198-199°).

Reaction of 4-chloroquinoline with trimethylamine. — A mixture of 4-chloroquinoline (0.1 g; Riegel, Lappin, Adelson, Jackson, Albisetti, Dodson and Baker, 1946) and trimethylamine (0.35 g) in benzene (5 ml) was heated
in a sealed tube at 195° for 19 h. The reaction mixture, on thin-layer chromatography (alumina, benzene), gave 4-dimethylaminoquinoline (0.04 g), identified as the picrate, m.p. 189-192° (from ethanol) (Suzuki, 1961, gives 192°) (Found, for material dried at 100°/1 h: C, 50.9; H, 3.7; N, 17.4. Calc. for C₁₂H₁₅N₂O₂: C, 50.9; H, 3.7; N, 17.5%), and unchanged 4-chloroquinoline (0.05 g).

No reaction was observed when the reactants were heated at 53° for 4 days.

4-Dimethylamino-1-methylquinolinium iodide.—A solution of 4-dimethylaminoquinoline (0.1 g; Steck and Ewing, 1948) and iodomethane (2 ml) was allowed to stand at 20° for 14 h. The precipitate was filtered off and recrystallised from ethanol-ethyl acetate to give 4-dimethylamino-1-methylquinolinium iodide (0.1 g), m.p. 216-218° (Found: C, 45.7; H, 4.8; N, 8.8. C₁₂H₁₅IN₂ requires C, 45.9; H, 4.8; N, 8.9%).

ISOQUINOLINES

Reaction of 1-chloroisooquinoline with trimethylamine.—1-Chloroisooquinoline (Gabriel and Colman, 1900) in excess trimethylamine at 35° for 30 days gave, as described by Reese (1958), tetramethylammonium chloride, and 1-dimethylaminoisooquinoline.
1-Dimethylaminoisoguinoline.—1-Chloroisoguinoline (1.2 g) and ethanolic dimethylamine (10 ml; 16%) were heated in a sealed tube at 155° for 16 h. The reaction mixture was concentrated, made alkaline and extracted with chloroform to give 1-dimethylaminoisoguinoline (75%), b.p. 101-102°/2 mm (Tanida, 1958, gives 124-125°/5 mm). The picrate, prepared in and recrystallised from benzene, had m.p. 165° (lit., 165-166°).

1-Dimethylamino-2-methylisoguinolinium iodide.—A solution of 1-dimethylaminoisoguinoline (0.50 g) in iodomethane (5 ml) was allowed to stand at 20° for 19 days. The precipitate (0.49 g) was collected and recrystallised from ethanol to give 1-dimethylamino-2-methylisoguinolinium iodide (0.30 g), m.p. 189-190° (Found, for material dried at 100°/1 h: C, 45.8; H, 5.0; N, 8.7. C₁₂H₁₅IN₂ requires C, 45.9; H, 4.8; N, 8.9%).

CINNOLINES

4-Chlorocinnoline was prepared from 4-hydroxycinnoline as described by Leonard and Boyd (1946b) from o-nitrobenzoyl chloride through o-nitro- (Reynolds and Hauser, 1950) and o-aminoacetophenone (Leonard and Boyd, 1946a).
Reaction of 4-chlorocinnoline with trimethylamine.—

4-Chlorocinnoline (0.30 g) and trimethylamine (1.00 g) in benzene (6 ml) were heated in a sealed tube at 145 °C for 7.5 h. Tetramethylammonium chloride was filtered off and the filtrate subjected to thin-layer chromatography (alumina, benzene) to give unchanged 4-chlorocinnoline (0.17 g) and 4-dimethylaminocinnoline (0.10 g), characterised as the picrate, m.p. 202-204 °C (from ethanol) undepressed on admixture with an authentic sample prepared as described below.

4-Dimethylaminocinnoline.—4-Chlorocinnoline (0.20 g) and ethanolic dimethylamine (3 ml; 33%) were heated in a sealed tube at 100 °C for 24 h. The solvent was evaporated and the product subjected to thin-layer chromatography (alumina, chloroform) to give 4-dimethylaminocinnoline (0.20 g). The picrate, prepared in and recrystallised from ethanol, had m.p. 205-207 °C (Found, for material dried at 100 °C/1 h: C, 48.3; H, 3.5; N, 20.8. C\textsubscript{16}H\textsubscript{14}N\textsubscript{6}O\textsubscript{7} requires C, 47.8; H, 3.5; N, 20.9%).

4-Dimethylamino-2-methylcinnolinium iodide.—A solution of 4-dimethylaminocinnoline (0.15 g) in iodomethane (1 ml) was allowed to stand at 20 °C for 12 h. The precipitate (0.28 g) was recrystallised from water to give 4-dimethylamino-2-methylcinnolinium iodide.
Anhydro-base of 4-hydroxy-2-methylcinnolinium hydroxide.—4-Dimethylamino-2-methylcinnolinium iodide (0.010 g) and sodium hydroxide (5 ml; 0.1M) were refluxed for 1 h. The mixture was extracted with chloroform, the extract dried (Na₂SO₄) and the solvent evaporated. The product was recrystallised from benzene to give the anhydro-base of 4-hydroxy-2-methylcinnolinium hydroxide (0.002 g), m.p. 163-164° (Ames and Kucharska, 1963, give 163-165°), identical with an authentic specimen (Ames and Kucharska, 1963) on paper chromatography. The ultraviolet spectrum was identical with that previously recorded (Barlin, 1965).

**PHTHALAZINES**

1-Chlorophthalazine was prepared as described by Brasyunas and Podzhyunas, 1959, from 1-hydroxyphthalazine (Gabriel and Neumann, 1893).

1-Dimethylaminophthalazine.—A mixture of 1-chlorophthalazine (3.9 g) and ethanolic dimethylamine (42 ml; 33%) was heated at 150° for 7 h. The solvent was evaporated, the residue made alkaline and extracted
with benzene. The oil so obtained was chromatographed in chloroform over alumina (10 in by 2.5 in diam.) to give 1-dimethylaminophthalazine (2.9 g). The picrate, prepared in and recrystallised from ethanol, had m.p. 175-176\(^\circ\) (Found: C, 47.4; H, 3.6; N, 20.7. \(\text{C}_{16}\text{H}_{14}\text{N}_{6}\text{O}_{7}\) requires C, 47.8; H, 3.5; N, 20.9%).

**Reaction of 1-chlorophthalazine with trimethylamine.**—
1-Chlorophthalazine (0.2 g) and trimethylamine (0.3 g) in benzene (4 ml) were heated in a sealed tube at 150\(^\circ\) for 12 h. The precipitate, which showed no significant u.v. absorption and contained no trimethylammonium compound, was filtered off and the filtrate concentrated. The residue was subjected to thin-layer chromatography (alumina, ether) and yielded unchanged 1-chlorophthalazine (0.09 g) and 1-dimethylaminophthalazine (0.10 g), which was characterised as the picrate, m.p. 175-176\(^\circ\) (from ethanol) undepressed on admixture with an authentic sample prepared as described above.

**1-Dimethylaminophthalazinium methiodide.**—A solution of 1-dimethylaminophthalazine (2.0 g) in iodomethane (8 ml) was allowed to stand at 20\(^\circ\) for 3 days. The precipitate was filtered off and recrystallised from ethanol to give 1-dimethylaminophthalazinium methiodide (2.38 g), m.p. 217-218\(^\circ\) (Found: C, 42.3; H, 4.7; N, 13.2. \(\text{C}_{11}\text{H}_{14}\text{IN}_{3}\) requires C, 41.9; H, 4.5; N, 13.3%).
Hydrolysis of 1-dimethylaminophthalazinium methiodide.

—1-Dimethylaminophthalazinium methiodide (0.002 g) and sodium hydroxide (50 ml; 0.02M) were refluxed for 1 h. A portion (10 ml) of the reaction mixture was buffered to pH 7 and diluted to 50 ml and afforded an ultraviolet spectrum that was different from that of starting material, 1-hydroxyphthalazine and 1,2-dihydro-2-methyl-1-oxophthalazine (Albert and Barlin, 1962).

QUINOXALINES

Reaction of 2-chloroquinoxaline with trimethylamine.—

2-Chloroquinoxaline (0.100 g; Gowenlock, Newbold and Spring, 1945) and trimethylamine (0.8 g) in benzene (6 ml) were heated in a sealed tube at 150° for 3.5 h. Tetramethylammonium chloride was filtered off and the filtrate subjected to thin-layer chromatography (alumina, 1:1 cyclohexane-benzene) to give unchanged 2-chloroquinoxaline (0.040 g) and 2-dimethylaminoquinoxaline (0.052 g), m.p. 94° (from chloroform) (Cheeseman, 1957, gives 94-95°) (Found, for material dried at 80°/1 h: C, 69.3; H, 6.4; N, 24.7. Calc. for C_{10}H_{11}N_{3}: C, 69.3; H, 6.4; N, 24.3%).

3-Dimethylamino-1-methylquinoxalinium iodide.—A mixture of 2-dimethylaminoquinoxaline (0.1 g; Cheeseman, 1957) and iodomethane (2 ml) was allowed to stand at
20° for 12 days. The precipitate was filtered off and recrystallised from ethanol-light petroleum (b.p. 60-80°) to give 3-dimethylamino-1-methylquinoxalinium iodide (0.150 g), m.p. 245-246° (Found: C, 42.0; H, 4.9; N, 13.2. C₁₁H₁₄I₃N₃ requires C, 41.9; H, 4.5; N, 13.3%).

Anhydro-base of 3-hydroxy-1-methylquinoxalinium hydroxide.— 3-Dimethylamino-1-methylquinoxalinium iodide (0.1 g) and sodium hydroxide (40 ml; 0.1M) were refluxed for 1.5 h, cooled and extracted with chloroform. The extract was dried (Na₂SO₄), the solvent evaporated off and the product subjected to thin-layer chromatography (alumina, chloroform) to give the product (0.020 g) which after recrystallisation from light petroleum (b.p. 60-80°) gave a white solid (0.007 g), m.p. 249-250° (Found: N, 17.8%). The ultraviolet spectrum of this compound was different from that of 2-hydroxyquinoxaline and 1,2-dihydro-1-methyl-2-oxo-quinoxaline (Cheeseman, 1958). The product is believed to be the anhydro-base of 3-hydroxy-1-methylquinoxalinium hydroxide (C₉H₈N₂O requires N, 17.5%).
QUINAZOLINES

2-Chloroquinazoline was prepared as described by Albert and Barlin, 1962, from o-aminobenzaldehyde (Smith and Opie, 1948) through 2-hydroxyquinazoline (Gabriel and Stelzner, 1896; Gabriel and Posner, 1895).

Quinazolin-2-yltrimethylammonium chloride.—Trimethylamine (0.7 g) was added to a cold solution of 2-chloroquinazoline (0.20 g) in benzene (10 ml) and the mixture allowed to stand at 50 for 24 h. The quinazolin-2-yltrimethylammonium chloride (0.25 g) was filtered off, washed with benzene and dried. It had m.p. 160-1610 (Found, for material dried at 1000/1 h: N, 18.8. C11H11ClN3 requires N, 18.8%).

Aqueous lithium picrate was added to a solution of the above salt (0.002 g) in water (1 ml) and the precipitate of quinazolin-2-yltrimethylammonium picrate (0.001 g) collected and washed with cold water. It had m.p. 179-1800 (Found: C, 48.9; H, 4.1; N, 19.9. C17H16N6O7 requires C, 49.0; H, 3.9; N, 20.2%).

2-Hydroxyquinazoline.—A solution of quinazolin-2-yltrimethylammonium chloride (0.05 g) and sodium hydroxide (5 ml; 0.4M) was allowed to stand at 200 for 1 h. The mixture was adjusted to pH 5, chilled, and 2-hydroxyquinazoline (0.02 g) collected. It was
identical on paper chromatography with an authentic specimen (Gabriel and Posner, 1895).

2-Hydrazinoquinazoline.—Hydrazine hydrate (0.5 ml) was added to quinazolin-2-yltrimethylammonium chloride (0.020 g) and the mixture allowed to stand at 20° for 15 min. The reaction mixture was evaporated to dryness under reduced pressure and the residue crystallised from propan-2-ol to give 2-hydrazinoquinazoline (0.009 g), m.p. 130-131° (Claesen and Vanderhaeghe, 1959, give 132-133°) (Found, for material dried at 100°/1 h: C, 60.2; H, 5.4. Calc. for C8H8N4: C, 60.0; H, 5.0%).

2-Methoxyquinazoline.—A solution of quinazolin-2-yltrimethylammonium chloride (0.10 g) and sodium methoxide (from 0.15 g sodium) in methanol (5 ml) was refluxed for 10 min. The reaction mixture was evaporated to dryness and the residue extracted with boiling chloroform. The product obtained from the extract was dissolved in the minimum of water and aqueous picric acid added to give 2-methoxyquinazoline picrate (0.098 g) which, after crystallisation from ethanol, had m.p. 135-136° (Adachi, 1955, gives 137-138°) (Found, for material dried at 100°/1 h: C, 46.3; H, 2.8; N, 17.8. Calc. for C15H11N5O8: C, 46.3; H, 2.9; N, 18.0%).
2-n-Propylaminoquinazoline.—Quinazolin-2-yltrimethylammonium chloride (0.020 g) and n-propylamine (1 ml) were heated together at 50° for 3 h. The reaction mixture was evaporated to dryness and the residue extracted with benzene. The benzene was removed and ethanolic picric acid added to give 2-n-propylaminoquinazoline picrate (0.025 g), m.p. 187° (Found, for material dried at 100°/1 h: C, 49.0; H, 4.1; N, 20.1. C_{17}H_{16}N_{6}O_{7} requires: C, 49.0; H, 3.9; N, 20.2%).

Quinazolin-4-yltrimethylammonium chloride.—A solution of 4-chloroquinazoline (1.5 g; Armarego, 1961) and trimethylamine (3.0 g) in benzene (45 ml) was allowed to stand at 4° for 5 days. The precipitate of quinazolin-4-yltrimethylammonium chloride (2.0 g) was filtered off, washed with benzene and dried. It had m.p. 98-99° (decomp.) (Found: Cl, 15.7. C_{11}H_{14}ClN_{3} requires Cl, 15.9%).

This salt (0.050 g) with aqueous lithium picrate gave the picrate (0.067 g), m.p. 178-180° (decomp.) (Found, for material dried at 100°/1 h: C, 49.1; H, 4.0; N, 20.2. C_{17}H_{16}N_{6}O_{7} requires C, 49.0; H, 3.9; N, 20.2%).

Mercuric chloride (0.120 g) dissolved in methanol (5 ml) was added to a solution of quinazolin-4-yltrimethylammonium chloride (0.050 g) in methanol at 20° for 15 min. The precipitate was filtered off.
(2 ml) and the precipitate of quinazolin-4-yltrimethylammonium trichloromercurate (0.089 g) was filtered off. It had m.p. 170-172° (Found, for material dried at 100°/1 h: C, 26.8; H, 2.9; N, 8.4. C₁₁H₁₄Cl₃HgN₃ requires C, 26.7; H, 2.9; N, 8.5%).

4-Hydroxyquinazoline.—(a) Quinazolin-4-yltrimethylammonium chloride (0.050 g) was dissolved in sodium hydroxide (5 ml; 1M) and after 5 min at 20° the reaction mixture was adjusted to pH 7 and evaporated to dryness. The residue was extracted with ethyl acetate (50 ml) and the product recrystallised from ethanol to give 4-hydroxyquinazoline (0.022 g), m.p. 215° (Armarego, 1961, gives 215-216°), undepressed on admixture with an authentic sample (Armarego, 1961). (b) 4-Chloroquinazoline (0.100 g) was shaken with sodium hydroxide (5 ml; 3M) until dissolution was complete (ca 10 min). The reaction mixture was then adjusted to pH 7 and evaporated to dryness. The product was extracted with boiling ethyl acetate, and recrystallised from ethanol to give 4-hydroxyquinazoline (0.070 g), m.p. and mixed m.p. 215°.

4-Hydrazinoquinazoline.—A mixture of hydrazine hydrate (1 ml) and quinazolin-4-yltrimethylammonium chloride (0.1 g) in water (1 ml) was allowed to stand at 20° for 15 min. The precipitate was filtered off
and crystallised from propan-2-ol to give 4-hydrazinoquinazoline (0.044 g), m.p. 187° (Dewar, 1944, gives 186°) (Found: C, 60.2; H, 5.1; N, 35.1. Calc. for C₈H₈N₄: C, 60.0; H, 5.0; N, 35.0%).

4-Methoxyquinazoline.—A solution of quinazolin-4-yltrimethylammonium chloride (0.10 g) and sodium methoxide (from 0.1 g sodium and 5 ml methanol) was allowed to stand at 20° for 5 min. The reaction mixture was evaporated to dryness and the residue extracted with ether. The ether was removed and the residue treated with ethanolic picric acid to give 4-methoxyquinazoline picrate (0.17 g). It was recrystallised from ethanol and had m.p. 174-175° undepressed on admixture with an authentic sample (Adachi, 1955: 174-175°).

4-n-Propylaminoquinazoline.—Quinazolin-4-yltrimethylammonium chloride (0.020 g) and n-propylamine (1 ml) were heated in a sealed tube at 50° for 3 h. The reaction mixture was evaporated to dryness and the residue extracted with benzene. The benzene was removed and ethanolic picric acid added to give 4-n-propylaminoquinazoline picrate (0.025 g), which, after crystallisation from ethanol had m.p. 205-206° (Found, for material dried at 100°/1 h: C, 47.4; H, 3.9; N, 19.2. C₁₇H₁₆N₆O₇.H₂O requires: C, 47.0; H, 4.2; N, 19.4%).
2-Chloro-9-methylpurine was prepared as described by Barlin (1967) from 2,4-dichloro-5-nitropyrimidine (Brown, 1957) through 2-chloro-4-methylamino-5-nitro- and 5-amino-2-chloro-4-methylaminopyrimidine.

9-Methylpurin-2-yltrimethylammonium chloride.— Trimethylamine (0.5 g) and 2-chloro-9-methylpurine (0.1 g) in benzene (4 ml) were heated in a sealed tube at 50° for 24 h. The precipitate (0.1 g), filtered off, washed with benzene, and recrystallised from ethanol-light petroleum (b.p. 60-80°) gave white crystals of 9-methylpurin-2-yltrimethylammonium chloride, m.p. 179-180° (Found: C, 43.8; H, 6.8; N, 28.65. \( \text{C}_9\text{H}_{14}\text{ClN}_5\cdot\text{H}_2\text{O} \) requires C, 44.0; H, 6.6; N, 28.5%).

Reaction of 2-chloro-9-methylpurine with trimethylamine at 150°.—2-Chloro-9-methylpurine (0.036 g) and trimethylamine (0.1 g) in benzene (2.5 ml) were heated in a sealed tube at 150° for 2.5 h. The precipitate of tetramethylammonium chloride was filtered off, the filtrate evaporated to dryness and the residue sublimed (50°/1.5 mm) to give the colourless 2-dimethylamino-9-methylpurine (0.019 g), identical on paper chromatography with an authentic sample prepared below.
2-Dimethylamino-9-methylpurine.—2-Chloro-9-methylpurine (0.1 g) in ethanol (2.5 ml) was added to ethanolic dimethylamine (2 ml; 33%) and the mixture heated at 100° for 2.5 hr. The mixture was evaporated to dryness and the residue (0.133 g) was purified by thin-layer chromatography in benzene and chloroform over alumina, and recrystallised from light petroleum (b.p. 60-80°) to give 2-dimethylamino-9-methylpurine (0.033 g), m.p. 89-90° (Found, for material dried at 75°/1 h: C, 54.4; H, 6.2; N, 39.3. C₈H₁₁N₅ requires C, 54.2; H, 6.3; N, 39.5%).

The picrate, prepared in and recrystallised from benzene, had m.p. 201-203° (Chaman and Golovchinskaya, 1963, give 198-199°) (Found, for material dried at 100°/1 h: C, 41.5; H, 3.75; N, 27.2. Calc. for C₁₄H₁₂N₈O₇: C, 41.4; H, 3.5; N, 27.6%).

2-Hydroxy-9-methylpurine.—9-Methylpurin-2-yltrimethylammonium chloride (0.05 g) and sodium hydroxide (5 ml; 0.4M) were heated at 100° for 5 min and then adjusted to pH 6. Paper chromatographic examination (three solvent systems) of the reaction mixture showed that 2-hydroxy-9-methylpurine was produced and was identical with an authentic specimen (Johns, 1911).
9-Methyl-2-n-propylaminopurine.—A mixture of 9-methylpurin-2-yltrimethylammonium chloride (0.020 g) and n-propylamine (1 ml) was heated at 100°C for 6 h. The reaction mixture was evaporated to dryness and the residue extracted with benzene. The benzene was removed and ethanolic picric acid added to the residue to give 9-methyl-2-n-propylaminopurine picrate (0.022 g), which, after recrystallisation from ethanol, had m.p. 226°C (Found, for material dried at 100°C/1 h: C, 42.65; H, 4.1. C_{15}H_{16}N_{8}O_{7} requires: C, 42.9; H, 3.8%).

2-Chloropurine was prepared as described by Montgomery (1956) from 2-chloro-4,5-diaminopyrimidine (Albert, Brown and Cheeseman, 1951).

Reaction of 2-chloropurine with trimethylamine.—2-Chloropurine (0.1 g), acetone (10 ml) and trimethylamine (0.4 g) were heated in a sealed tube at 100°C for 4.5 h. The tetramethylammonium chloride was filtered off, the filtrate evaporated to dryness and the solid (0.105 g), recrystallised from water (charcoal), gave 2-dimethylaminopurine, m.p. 219-222°C (Albert and Brown, 1954, give 222-223°C) whose ultraviolet spectrum was identical with published data (Mason, 1954).

When the reaction was repeated at 50°C for 72 h, 2-dimethylaminopurine and 2-chloropurine were obtained, but no trimethylammonio-compound could be detected.
6-Chloro-9-methylpurine was prepared as described by Barlin and Chapman (1965) from 5-amino-4,6-dichloropyrimidine through 5-amino-4-chloro-6-methylamino-pyrimidine (Brown, 1954).

9-Methylpurin-6-yltrimethylammonium chloride.—Trimethylamine (0.2 g) and 6-chloro-9-methylpurine (0.05 g) in dry benzene were allowed to stand at 25°C for 24 h, the precipitate (0.05 g) was filtered off, washed with benzene, dried and recrystallised from propan-2-ol to give 9-methylpurin-6-yltrimethylammonium chloride, m.p. 161-162°C (Found: C, 42.6; H, 6.7; Cl, 14.2; N, 27.4. \( \text{C}_{9}\text{H}_{14}\text{ClN}_{5}.1.5\text{H}_{2}\text{O} \) requires C, 42.4; H, 6.7; Cl, 13.9; N, 27.5%).

6-Dimethylamino-9-methylpurine.—6-Chloro-9-methylpurine (0.1 g) and ethanolic dimethylamine (1 ml; 33%) in ethanol (4 ml) were allowed to stand at 20°C for 7 h, and then evaporated to dryness under reduced pressure. The residue, recrystallised from light petroleum (b.p. 60-80°C), gave 6-dimethylamino-9-methylpurine (0.071 g), m.p. 118-119°C (Baker, Schaub and Joseph, 1954, give 114-115°C) (Found: C, 54.1; H, 6.6; N, 39.2. Calc. for \( \text{C}_{8}\text{H}_{11}\text{N}_{5} \): C, 54.2; H, 6.3; N, 39.5%).
6-Hydroxy-9-methylpurine.—(a) 9-Methylpurin-6-yltrimethylammonium chloride (0.050 g) and sodium hydroxide (1 ml; 0.035M) were warmed gently, and then adjusted to pH 5. A solid separated and it was recrystallised from water to give 6-hydroxy-9-methylpurine (0.006 g), m.p. 360°, which was identical on paper chromatography with an authentic specimen (Brown and Mason, 1957).

(b) 6-Chloro-9-methylpurine (0.10 g) and sodium hydroxide (2 ml; 2.5M) were heated at 100° for 5 min. The solution was adjusted to pH 5, boiled, and sufficient water added to dissolve the solid at 100°. After cooling, the crystalline solid (0.07 g) was filtered off and shown to be identical to the product obtained from (a) by paper chromatographic comparison.

6-Ethoxy-9-methylpurine.—A solution of 9-methylpurin-6-yltrimethylammonium chloride (0.02 g) and sodium ethoxide (from 0.02 g sodium and 5 ml ethanol) was refluxed for 15 min. The solution was evaporated to dryness and the product extracted with boiling benzene. The benzene was removed and the residue crystallised from light petroleum (b.p. 60-80°) to give 6-ethoxy-9-methylpurine (0.01 g), m.p. 115-116°, undepressed on admixture with an authentic sample (Barlin, 1967: 107-108°) (Found, for material dried at 70°/1 h:
C, 53.6; H, 5.8. Calc. for C$_8$H$_{10}$N$_4$O: C, 53.9; H, 5.7%). It was identical on paper chromatography with an authentic sample (Barlin, 1967).

6-Fluoro-9-methylpurine —9-Methylpurin-6-yltrimethylammonium chloride (0.020 g) and potassium hydrogen difluoride (0.070 g) in ethanol (2 ml) were heated at 50$^\circ$ for 2 h. The reaction mixture was diluted with water and adjusted to pH 7 by addition of aqueous sodium hydrogen carbonate. This solution was extracted with chloroform, the extracts dried (Na$_2$SO$_4$) and the chloroform distilled off. The residue was crystallised from hexane to give 6-fluoro-9-methylpurine (0.006 g), m.p. 130-131$^\circ$ (Beaman and Robins, 1963, give 125-127$^\circ$).

6-Hydrazino-9-methylpurine.—A mixture of hydrazine hydrate (0.5 ml) and 9-methylpurin-6-yltrimethylammonium chloride (0.021 g) in water (0.5 ml) was allowed to stand at 20$^\circ$ for 15 min. The reaction mixture was evaporated to dryness and the residue crystallised from methanol to give 6-hydrazino-9-methylpurine (0.005 g), m.p. 211-212$^\circ$ (Robins and Lin, 1957, give 210-211$^\circ$).

9-Methyl-6-n-propylaminopurine.—A mixture of 9-methylpurin-6-yltrimethylammonium chloride (0.020 g) and n-propylamine (1 ml) was heated at 50$^\circ$ for 3 h.
The reaction mixture was evaporated to dryness and the residue extracted with benzene. The benzene was removed and ethanolic picric acid added to give 9-methyl-6-n-propylaminopurine picrate (0.025 g), which, after recrystallisation from ethanol, had m.p. 223-225° (Found, for material dried at 100°/1 h: C, 42.6; H, 4.1. C₁₅H₁₆N₈O₇ requires: C, 42.9; H, 3.8%).

9-Methyl-6-methylsulphonylpurine.--The following method was found preferable to that described by Brown and Ford, 1969. Potassium permanganate (0.053 g) dissolved in water (2 ml) was added to a solution of 9-methyl-6-methylthiopurine (0.030 g; Brown and Ford, 1969) in 50% aqueous acetic acid (2 ml) at 20° during 15 min. The reaction mixture was cooled in ice, decolourised by passing sulphur dioxide, and adjusted, by addition of aqueous sodium carbonate, to pH 7. It was extracted immediately with chloroform, the extracts dried (Na₂SO₄), the solvent removed under reduced pressure at 20° and the product recrystallised from methanol to give 9-methyl-6-methylsulphonylpurine (0.022 g), m.p. 211° (decomp.) (lit., 210-212°).

6-Chloropurine was prepared from 4,5-diamino-6-chloropyrimidine (Albert, Brown and Cheeseman, 1952) as described by Goldman, Marsico and Gazzola (1956).
Purin-6-yltrimethylammonium chloride was prepared from 6-chloropurine (Barlin 1967) and trimethylamine in dimethylformamide at 20° as described by Horwitz, 1968. It was purified by reprecipitation from aqueous solution by addition of acetone and had m.p. 187-189° (lit., 189-191°) (Found: C, 45.1; H, 5.9; Cl, 16.6; N, 32.9. Calc. for $C_8H_{12}ClN_5$: C, 44.9; H, 5.65; Cl, 16.6; N, 32.75%).

6-Hydroxypurine. ---Purin-6-yltrimethylammonium chloride (0.05 g) and sodium hydroxide (4 ml; 0.07M) were heated on a steam bath for 5 min; the reaction mixture was neutralised and then evaporated to dryness. The residue was extracted with boiling ethyl acetate and the solution, after concentration, gave 6-hydroxypurine (0.025 g), identical with an authentic specimen when examined on paper chromatography.

6-Methoxypurine. ---Purin-6-yltrimethylammonium chloride (0.1 g) and methanolic sodium methoxide (10 ml; 0.1M) were heated on a steam bath for 5 min. The solution was evaporated to dryness, the residue dissolved in water (1 ml), and the solution adjusted to pH 7. 6-Methoxypurine (0.064 g) separated out and was crystallised from chloroform-acetone. It had m.p. 194-195° (Huber, 1957, gives m.p. 194-195°).
8-Chloro-9-methylpurine was prepared from 4,5-diaminopyrimidine (Brown, 1952) through 8-mercaptopurine (Barlin and Chapman, 1965), 8-methylthiopurine (Albert and Brown, 1954) and 8-chloropurine (Beaman and Robins, 1962) as described by Barlin and Chapman (1965).

Reaction of 8-chloro-9-methylpurine with trimethylamine.

—8-Chloro-9-methylpurine (0.02 g) in benzene (2 ml) with trimethylamine (0.1 g) was allowed to stand at room temperature for 10 days. Examination of the reaction mixture on paper chromatography showed the presence of 8-dimethylamino-9-methylpurine by comparison with an authentic specimen (see below) and also unchanged 8-chloro-9-methylpurine. No quaternary purine salt could be detected.

8-Dimethylamino-9-methylpurine.—Ethanolic dimethylamine (1 ml; 33%) and 8-chloro-9-methylpurine (0.01 g) in ethanol (0.5 ml) were heated in a sealed tube at 100°C for 30 min. This mixture was taken to dryness and the residue recrystallised from light petroleum (b.p. 60-80°C) to give 8-dimethylamino-9-methylpurine (0.003 g), m.p. 91°C (Found: C, 54.2; H, 6.5; N, 39.9. C₈H₁₁N₅ requires C, 54.2; H, 6.3; N, 39.5%).
Purin-8-yltrimethyl ammonium chloride.—Trimethylamine (0.5 g) and 8-chloropurine (0.1 g; Beaman and Robins, 1962) in acetone (12 ml) were heated in a sealed tube at 53 °C for 24 h. The precipitate (0.09 g), was filtered off, washed with acetone and recrystallised from ethanol (charcoal) to give purin-8-yltrimethyl ammonium chloride, m.p. 179-180 °C (Found: C, 45.1; H, 5.6; N, 32.7. C₈H₁₂ClN₅ requires: C, 44.9; H, 5.65; N, 32.75%).

8-Dimethylaminopurine.—8-Chloropurine (0.05 g), ethanol (2 ml) and ethanolic dimethylamine (2 ml; 33%) were heated in a sealed tube at 100 °C for 3 h. The ethanol was distilled off and the residue recrystallised from water to give 8-dimethylaminopurine (0.02 g), m.p. 292 °C (decomp.) undepressed on admixture with an authentic sample [Albert and Brown, 1954: 292 °C (decomp.)].

8-Hydroxypurine.—Purin-8-yltrimethyl ammonium chloride (0.005 g) and sodium hydroxide (1 ml; 0.2M) were heated in a sealed tube at 150 °C for 5 h. The reaction mixture was adjusted to pH 6, and then examined on paper chromatography (two solvent systems) and by ultraviolet spectroscopy. It was shown to contain mostly 8-hydroxypurine, by comparison with an authentic specimen (Albert and Brown, 1954; Mason, 1954), together with some 8-dimethylaminopurine.
2-Mercaptoaniline.—This compound (Caucuil and Casadevall, 1955) was prepared from o-chloronitrobenzene through o,o’-dinitrodiphenyldisulphide (Wohlfahrt, 1902; Foster and Reid, 1924). The hydrochloride had m.p. 214° (decomp.) (lit., 217°). Potentiometric titration in 0.005M solutions gave $pK_a$ values of 2.91 ± 0.07 and 6.22 ± 0.03 (Danehy and Noel, 1960, give $pK_a$ values 3.00 and 6.59).

2-Methylthioaniline.—Hydrochloric acid (140 ml; 10M) was added slowly to a mixture of o-nitromethylthio-benzene (10 g; Hodgson and Handley, 1927), granular tin (35 g), and aqueous ethanol (200 ml; 1:1) which was refluxed on a steam bath. When decolourisation was complete, the mixture was cooled, made strongly alkaline with sodium hydroxide, steam distilled, and the product extracted from the aqueous distillate with ether and distilled. It gave 2-methylthioaniline (4.1 g), b.p. 135-137°/20mm (Zincke and Siebert, 1915, give 133-134°/15mm). Potentiometric titration in 0.005M solutions gave $pK_a = 3.45 ± 0.05$.

Sodium hydroxide solutions.—Carbon dioxide-free sodium hydroxide solutions were prepared from carbon dioxide-free distilled water and B.D.H. concentrated volumetric solutions. The concentrations were determined by titration with standardised acid and the solutions were stored under an atmosphere of nitrogen.
Ionization constants. These were determined as a rule spectrophotometrically as described by Albert and Serjeant (1962). Solutions above pH 2.5 were made in aqueous buffers (Perrin, 1963) and standardised with a glass electrode. Dilute solutions of hydrochloric acid of known pH were used for the range pH 1 to 2.5, and at greater acidity, standard solutions of sulphuric acid, to which Hammett acidity functions had been assigned [the $H_0$ scale of Paul and Long (1957) has been used for convenience] were employed. The $pK_a$ values were determined by measuring the ultraviolet absorption ($\varepsilon$) at constant concentrations of the compound at a chosen wavelength. These measurements were made at intervals of 0.2 units, spanning approximately ±0.8 units from the estimated $pK_a$. The extinction coefficients of the pure species, e.g. $\varepsilon_{M^+}$ and $\varepsilon_{MH^{++}}$, were measured in solutions of pH at least 2 units away from the estimated $pK_a$, hence ensuring the presence of a single species. The $pK_a$ was calculated from the expression:

$$pK_a = pH - \log \frac{(\varepsilon_{MH^{++}} - \varepsilon)}{(\varepsilon - \varepsilon_{M^+})}$$

The values for the ionization constants given in the Tables are the mean of about 9 such $pK_a$ terms. The stability of the dications in solutions of strong acid was checked by neutralisation.
Ultraviolet spectra were recorded on a Unicam S.P.800 recording spectrophotometer, and the $\lambda_{\text{max}}$ and $\varepsilon$ values were checked on an 'Optica' CF4 manual instrument. (The 'Optica' was also used for measuring the ultraviolet absorptions of the solutions used for measuring the ionization constants and rate coefficients.) The solutions were in aqueous buffer or standard acid and were at least 2 pH units away from the measured $pK_a$ value.

N.m.r. spectra were recorded at 60 MHz/s and 33.5° on a Perkin-Elmer R10 spectrometer. Chemical shifts are given on the $\tau$ scale; sodium trimethylsilylpropane sulphonate was used as internal reference unless otherwise stated. Where required, portions of the spectra were expanded.

Kinetic procedure. At temperature greater than ca 80°C, solutions were heated in sealed tubes in a thermostat. The tubes were chilled briefly and their contents diluted with buffer to 50 ml.

At temperatures less than ca 80°C, solutions were heated in stoppered tubes in a thermostat. At specified times, their contents were quenched in buffer solution and diluted to 50 ml.

The ultraviolet absorption of each sample was then measured at a fixed wavelength. Each run consisted of about 9 samples, covering at least 10% - 70% reaction.
Absorptions corresponding to 't₀' and 't∞' (>ca 40 times the half life of the reaction and corresponding to 98% - 100% reaction) were also measured.

When the half life of the reaction was too short to permit the use of these conventional sampling techniques (i.e. with 5-nitropyrimidin-2-yltrimethylammonium chloride and quinazolin-4-yltrimethylammonium chloride) the rapid reaction stopped-flow technique was used (a complete description of both the method and the apparatus used is given by Perrin, 1965).

The rate coefficients were calculated from the expressions given in Chapter 3 by means of a P.D.P S/I computer, running 7 user focal. An example of the computer print-out is given in FIG 9, which is explained below.

A is the initial concentration of sodium hydroxide.
B is the initial concentration of substrate.
DINIT is the initial optical density reading.
DINIF is the final optical density reading.
NO OF PTS is the number of data pairs.

Pairs of values for time (T) in seconds and the observed optical density (DOBS) at time (T) are then entered. The computer responds by calculating the value of the rate coefficient (K) and the percentage reaction (%REACT) corresponding to such a data pair. When all the data pairs have been entered, the computer responds by calculating:
### FIG 9

**G**

A: 0.0025 B: 0.000032 DINIT: 0.990 DINF: 0.495 NO OF PTS: 11

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**AV. VALUE OF K** 0.428829E+01  
**STD. DEVN.** 0.545478E-01  
(1.127%)  
**TIME FOR 50% REACT.** 64.65
i the average value of the rate coefficient (AV. VALUE OF K)

ii the standard deviation (STD. DEVN.)

iii the standard deviation expressed as a percentage of the rate coefficient.

iv the time for 50% reaction in seconds.

Wherever necessary, the value of the rate coefficient has been corrected for solvent expansion or contraction.

Each reaction was studied at three temperatures covering a 20° range and log k plotted against 1/T (T = temperature °A). The slope of the straight line gave the energy of activation (E = -2.303R x slope).

The frequency factor (log A) and the transition state parameters, $\Delta H^\ddagger$ and $\Delta S^\ddagger$, were calculated from the expressions:

$$\log A = \log k - \frac{E}{2.303RT}$$

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

$$\Delta S^\ddagger = 2.303R(\log A - \log T) - 205.7$$

($R$, the universal gas constant, = 8.314 J.deg.$^{-1}$mol.$^{-1}$.)
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<th>Compounds</th>
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<td>4-Bromobenzylidene and picrate</td>
<td>Wibaut and Broekman, 1961.</td>
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<td>C&lt;sub&gt;9&lt;/sub&gt;H&lt;sub&gt;11&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;6&lt;/sub&gt;Pt</td>
</tr>
<tr>
<td>Anhydro-base of 3-mercapto-1-methylpyridazinium hydroxide</td>
<td>C&lt;sub&gt;9&lt;/sub&gt;H&lt;sub&gt;11&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;Cl</td>
</tr>
<tr>
<td>5-Dimethylamino-1-methylpyridazinium iodide</td>
<td>C&lt;sub&gt;9&lt;/sub&gt;H&lt;sub&gt;13&lt;/sub&gt;N&lt;sub&gt;4&lt;/sub&gt;I</td>
</tr>
<tr>
<td>Anhydro-base of 5-mercapto-1-methylpyridazinium hydroxide</td>
<td>C&lt;sub&gt;9&lt;/sub&gt;H&lt;sub&gt;11&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;Cl</td>
</tr>
<tr>
<td>Pyrimidin-2-yltrimethylammonium picrate</td>
<td>C&lt;sub&gt;10&lt;/sub&gt;H&lt;sub&gt;13&lt;/sub&gt;N&lt;sub&gt;4&lt;/sub&gt;NO&lt;sub&gt;3&lt;/sub&gt;</td>
</tr>
<tr>
<td>5-Nitopyrimidin-2-yltrimethylammonium chloride and picrate</td>
<td>C&lt;sub&gt;10&lt;/sub&gt;H&lt;sub&gt;13&lt;/sub&gt;N&lt;sub&gt;4&lt;/sub&gt;NO&lt;sub&gt;3&lt;/sub&gt;</td>
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<tr>
<td>Pyrimidin-4-yltrimethylammonium chloride and picrate</td>
<td>C&lt;sub&gt;10&lt;/sub&gt;H&lt;sub&gt;13&lt;/sub&gt;N&lt;sub&gt;4&lt;/sub&gt;NO&lt;sub&gt;3&lt;/sub&gt;</td>
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<tr>
<td>4-Dimethylamino-1-methylquinolinium iodide</td>
<td>C&lt;sub&gt;10&lt;/sub&gt;H&lt;sub&gt;13&lt;/sub&gt;N&lt;sub&gt;4&lt;/sub&gt;NO&lt;sub&gt;3&lt;/sub&gt;</td>
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<td>1-Dimethylamino-2-methylisoquinolinium iodide</td>
<td>C&lt;sub&gt;10&lt;/sub&gt;H&lt;sub&gt;13&lt;/sub&gt;N&lt;sub&gt;4&lt;/sub&gt;NO&lt;sub&gt;3&lt;/sub&gt;</td>
</tr>
<tr>
<td>4-Dimethylaminocinnoline picrate</td>
<td>C&lt;sub&gt;10&lt;/sub&gt;H&lt;sub&gt;13&lt;/sub&gt;N&lt;sub&gt;4&lt;/sub&gt;NO&lt;sub&gt;3&lt;/sub&gt;</td>
</tr>
<tr>
<td>4-Dimethylamino-2-methylcinnolinium iodide</td>
<td>C&lt;sub&gt;10&lt;/sub&gt;H&lt;sub&gt;13&lt;/sub&gt;N&lt;sub&gt;4&lt;/sub&gt;NO&lt;sub&gt;3&lt;/sub&gt;</td>
</tr>
<tr>
<td>1-Dimethylaminophthalazine picrate</td>
<td>C&lt;sub&gt;10&lt;/sub&gt;H&lt;sub&gt;13&lt;/sub&gt;N&lt;sub&gt;4&lt;/sub&gt;NO&lt;sub&gt;3&lt;/sub&gt;</td>
</tr>
<tr>
<td>1-Dimethylaminophthalazinium methiodide</td>
<td>C&lt;sub&gt;10&lt;/sub&gt;H&lt;sub&gt;13&lt;/sub&gt;N&lt;sub&gt;4&lt;/sub&gt;NO&lt;sub&gt;3&lt;/sub&gt;</td>
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<tr>
<td>3-Dimethylamino-1-methylquinoxalinium iodide</td>
<td>C&lt;sub&gt;10&lt;/sub&gt;H&lt;sub&gt;13&lt;/sub&gt;N&lt;sub&gt;4&lt;/sub&gt;NO&lt;sub&gt;3&lt;/sub&gt;</td>
</tr>
<tr>
<td>Anhydro-base of 3-hydroxy-1-methylquinoxalinium hydroxide</td>
<td>C&lt;sub&gt;10&lt;/sub&gt;H&lt;sub&gt;13&lt;/sub&gt;N&lt;sub&gt;4&lt;/sub&gt;NO&lt;sub&gt;3&lt;/sub&gt;</td>
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<td>Quinazolin-2-yltrimethylammonium chloride and picrate</td>
<td>C&lt;sub&gt;10&lt;/sub&gt;H&lt;sub&gt;13&lt;/sub&gt;N&lt;sub&gt;4&lt;/sub&gt;NO&lt;sub&gt;3&lt;/sub&gt;</td>
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<tr>
<td>2-n-Propylquinazoline picrate</td>
<td>C&lt;sub&gt;10&lt;/sub&gt;H&lt;sub&gt;13&lt;/sub&gt;N&lt;sub&gt;4&lt;/sub&gt;NO&lt;sub&gt;3&lt;/sub&gt;</td>
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Quinazolin-4-yltrimethylammonium chloride, picrate and trichloromercurate
4-n-Propylaminoquinazoline picrate
9-Methylpurin-2-yltrimethylammonium chloride
2-Dimethylamino-9-methylpurine
9-Methyl-2-n-propylaminopurine picrate
9-Methylpurin-6-yltrimethylammonium chloride
9-Methyl-6-n-propylaminopurine picrate
8-Dimethylamino-9-methylpurine
Purin-8-yltrimethylammonium chloride

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PUBLICATIONS


The Tautomerism of N-Heterocycles. Pyridazinones and Pyridazinthiones.


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