THE DIMROTH REARRANGEMENT
OF SOME PYRIMIDINE
AND QUINAZOLINE
IMINES

a thesis
submitted to the
Australian National University
for the Degree of
Master of Science
by
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The work described in this thesis was carried out by the candidate at the Australian National University. Where the work of others was employed appropriate references have been included.

B. T. W.
December 1967
Acknowledgements

I express my gratitude to Professor A. Albert (Head of Department of Medical Chemistry) and to Professor A.N. Hambly (Head of Department) and the staff of Department of Chemistry, for enabling me to attend a course of study in the Department of Chemistry while assisting in research in the Department of Medical Chemistry. I am pleased to acknowledge the contribution of many colleagues in this Department by discussion, suggestion and criticism — in particular Drs. W.L.F. Armarego, M.E.C. Biffin and M.N. Paddon-Row.

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B. T. E.

December 1967
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Summary

This thesis contains a study of the Dimroth Rearrangement in two heterocyclic systems, the iminopyrimidines and the iminoquinazolines.

Section A deals with examples of iminopyrimidines in which the rearrangement is reversible. Thus 1-allyl-1,2-dihydro-2-propyliminopyrimidine and its 2-allylimino-1-propyl-isomer each rearranges under appropriate conditions to give quantitatively the same mixture of both pyrimidines. The position of the equilibrium attained is revealed by the p.m.r. spectra of such pairs of isomers. The ratio of isomers at equilibrium is discussed in terms of the electronic and steric characteristics of the alkyl or alkenyl groups. From such considerations it is concluded that the isomer in which the bulkier and/or more electron-withdrawing group is attached to the extracyclic nitrogen will predominate at equilibrium.

The rearrangement of iminopyrimidines bearing an allyl, prop-2-ynyl, or prop-1-ynyl group at position 5 or 1, is discussed in sections B and C. The rate of rearrangement of the 1- and 5-substituted imines depends on the degree of electron withdrawal exerted by each substituent.
Section B also contains details of a base-induced isomerisation of some of the prop-2-ynylpyrimidines. This, a new reaction in this series, resulted in the isolation of allenyl- and prop-1-ynyl-pyrimidines.

In section C the Dimroth Rearrangement of 1-propynyl-iminopyrimidines is compared with that of the allyl and propyl analogues. In addition to the normal rearrangement, the 1-propynyl-pyrimidine undergoes cycloisomerisation to a triazaindene. The two parallel isomerisations of 1,2-dihydro-2-imino-4,6-dimethyl-1-prop-2'-ynylpyrimidine occur at similar rates. Evidence for the structures of each product, and for possible mechanisms in both isomerisation reactions, was provided by p.m.r. spectra.

Few examples of the effect of electron-donating substituents on rearrangement, are known in the pyrimidine series. Such substituents would be expected to retard the rearrangement. This is well supported by the benz-substituted methoxyiminoquinazolines (section D).
Retardation is particularly well defined in the rearrangement of 2,3-dihydro-2-imino-7-methoxy-2-methylquinazoline. Evidence of base-catalysis of these quinazoline rearrangements is also reported.
THE DIMROTH REARRANGEMENT

IN IMINOPYRIMIDINES
INTRODUCTION

The Dimroth Rearrangement - a general statement

The Dimroth rearrangement is an isomerisation in which an alkyl or aryl substituent appears to migrate from a ring nitrogen atom to an extra-cyclic position thus to become part of an α-amino or -imino group.

Previous Studies - an historical outline

Isotopic labelling\(^1\), a kinetic study\(^2,3,5,6\), and a very extensive study of the rearrangement on a more qualitative basis\(^7,8,9,11\), has produced a great deal of data concerning the mechanism of the reaction and the positional and electronic effects of substituents. This data is discussed on subsequent pages; however it is appropriate to include here a brief statement of the possible reaction mechanism as it is currently understood.

Ring-opening by fission of the bond between the \(1\) and \(6\)-position, e.g. in the pyrimidine (III), is believed to follow the formation of a carbinolamine by covalent addition of water. The resulting cyclic intermediate, a guaniding-aldehyde, after rotation about the \(2,3\)-bond, may recyclise to a rearranged pyrimidine.

Present Studies - an outline of the present work
Introduction

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In addition to pyrimidines, the rearrangement is undergone by other heterocyclic compounds, e.g. pteridines, quinazolines, purines, pyrazolo(3,4-d)pyrimidines, pyridines, triazoles, pyrazoles, tetrazoles, thiadiazoles, and triazines.

Although much of the accumulated data concerns rearrangements in basic media, acid induced rearrangements are known, and the reaction has occurred also during decarboxylation and Raney nickel desulphurisation.

Previous Studies - an historical outline

The first example of this rearrangement was reported in 1888 by Rathke who observed an apparent aryl migration in the isomerisation of 4,6-dianilino-1,2-dihydro-2-imino-1-phenyl-1,3,5-triazine (I). In 1909 Dimroth, after whom the reaction was named, observed the rearrangement of a series of 5-amino-1-aryl-1,2,3-triazoles (II). He suggested a mechanism that involved ring fission, rotation and ring closure to the isomeric triazole. This is accepted today as a general statement of the mechanism of the rearrangement.
Brown and Goerdeler and Roth have verified this gross mechanism experimentally using 1,2-dihydro-2-1H-imidazopyrimidine containing an $^{15}$N-labelled group (III). The later rearrangement was demonstrated using an alkali to 2-methylimidazopyrimidine. Subsequent hydrolysis resulted in the collection of methyamine as its picrate, and 2-hydroxypyrimidine. The latter compound showed strong $^{15}$N-enrichment; the methyamine picrate showed no such enrichment. Thus the nitrogens of the imidazopyrimidine had become incorporated into the picrate ring.

Studies of the rearrangement of imidazopyrimidines by Brown and co-workers, began with the examination of the effect of variation of the alkyl group in 1-alkyl-1,2-dihydroimidazopyrimidines. The rate parameter used in comparisons was susceptibility, defined as the reciprocal of the time required for the disappearance of half the initial aline under standardised conditions. This is obtained by observing the change in the ultraviolet spectrum of the alane free base. The plot of the logarithm of optical density against time, is linear.

\[ \begin{align*}
  &\text{NHPh} \\
  &\text{NHPh} \quad \rightarrow \\
  &\text{PhHN} \quad \rightarrow \\
  &\text{PhHN} \\
  &\text{NHPh}
\end{align*} \]
Brown and Goerdeler and Roth have verified this gross mechanism experimentally using 1,2-dihydro-2-imino-1-methylpyrimidine bearing an $^{15}$N-labelled imino group (III). The iminopyrimidine was rearranged in hot alkali to 2-methylaminopyrimidine. Subsequent hydrolysis resulted in the collection of methylamine as its picrate, and 2-hydroxypyrimidine. The latter compound showed strong $^{15}$N-enrichment; the methylamine picrate showed no such enrichment. Thus the nitrogen of the imino group had become incorporated into the pyrimidine ring and the methyl group was attached to the extra-cyclic nitrogen.

Studies of the rearrangement of iminopyrimidines by Brown and co-workers, began with the examination of the effect of variation of the alkyl group in 1-alkyl-1,2-dihydro-2-iminopyrimidines. The rate parameter used in comparisons of susceptibility to rearrangement, is the time required for the disappearance of half the initial imine under standardised conditions. This is obtained by observing the change in the ultraviolet spectrum of the imine free base. The plot of the logarithm of optical density against time, is linear
for at least two half lives. Thus the disappearance of free base is a pseudo-first order reaction. The determination involves use of two relationships in

\[ k = \frac{2.303}{t_i} \log \frac{D_{\infty} - D_0}{D_0 - D_i} \]  

...... a.

\[ t_{1/2} = \frac{\ln 2}{k} \]  

...... b.

which \( k \) is a rate constant; \( D_{\infty} \) represents optical density at "infinite time"; \( D_0 \), initial optical density; \( D_i \), optical density at a time \( i \); \( t_i \) is the time after initiation of the reaction; \( t_{1/2} \) is the half life.

Equation a. is simplified if the determination is made at a wavelength where only the imine absorbs, that is, at which \( D_{\infty} \) is zero. An analysis of a determination is included in the second section of this thesis, on page 26.

Rates of rearrangement of 1-alkyl-iminopyrimidines are shown below

<table>
<thead>
<tr>
<th>alkyl group</th>
<th>( t_{1/2} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>144 min.</td>
</tr>
<tr>
<td>Et</td>
<td>63</td>
</tr>
<tr>
<td>Bu</td>
<td>58</td>
</tr>
<tr>
<td>Hp</td>
<td>57</td>
</tr>
</tbody>
</table>
The difference in rates, particularly between methyl and ethyl compounds, was interpreted as indicating a steric interference with re-formation of the broken 1,6-bond, thus facilitating rearrangement to the alkylamino isomer.

Addition of an electron-releasing group at C-5 caused the slower rearrangement of 5-ethyl 1,2-dihydro-2-imino-1-methylpyrimidine and its 4,6-dimethyl analogue. When the powerfully electron-releasing dimethylamino group was placed at C-4 the rate was lowered to such an extent that hydrolysis became the predominant reaction. Conversely, the rate was increased considerably by substitution at C-5 with an electron-withdrawing Br substituent. Changes in the ultraviolet spectra and pKₐ values were consistent with the electronic properties of the substituents studied.

The half-lives for the alkyl-substituted compounds (above) represent an overall rate, a composite of the ring fission and ring closure reactions. The rates for each of the two consecutive reactions were observed by Perrin in the rearrangement of 5-bromo-1,2-dihydro-2-imino-1-
methylpyrimidine (IV). These rates are $t_{1/2}^a = 0.9$ min. and $t_{1/2}^b = 26$ min. The first is the rate of ring fission. When compared with the values given above, it indicated the degree of electron-withdrawal exerted by the Br substituent. Reclosure rate (26 min.) was reduced because of the increased stability of the acyclic intermediate. Thus the relative rates of fission and recylclisation are reversed in this example.

Preparative evidence for the nature of the intermediate (v.i.) was obtained by Perrin and Pitman. Oxime formation confirmed the aldehyde function and the ready isolation of this derivative as its carbonate indicated the presence of the strongly basic group such as the substituted guanidine. Spectral (ultraviolet and p.m.r.) evidence was consistent with the guanidino-aldehyde structure. It was found also, by Perrin and Pitman, that under certain conditions hydrolytic deamination of 1,2-dihydro-2-imino-1-methylpyrimidine (III) occurred, to give 2-hydroxypyrimidine. Under the same conditions 2-methylaminopyrimidine was not hydrolysed.

Isolation of free guanidino-aldehyde intermediate was achieved recently by Brown and Paddon-Row, during
study of the rearrangement of 5-cyano- and 5-carbanoyl-
iminopyrimidines. The acyclic intermediate, formed by a
ring fission of 5-cyano-1-methyl-2-methyliminopyrimidine (V), was isolated and characterised. While the substitution of a methy group at nuclear and also at extranuclear nitrogen atoms naturally does not permit observation of the formation of the normal rearranged product, it was found possible to obtain an “abnormal” product, 4-amino-5-formyl-2,3-dihydro-3-
methyl-1-methyliminopyrimidine (VI). Ring closure of the intermediate to starting material was achieved in acid. The 5-cyano-1-methyliminopyrimidine (V) was found to undergo “normal” or “abnormal” rearrangement according to the conditions imposed. Here again the acyclic compound was isolated. The formation of an “abnormal” product is the result of internal addition of the amine to the nitrite group, rather than addition to the carbonyl group; the “normal” occurrence.

Unlike this pyrimidine, the homologue bearing methyl groups at C-4 and C-6 underwent only “normal” rearrangement. This difference was attributed to the
study of the rearrangement of 5-cyano- and 5-carbamoyl-iminopyrimidines. The acyclic intermediate, formed by ring fission of 5-cyano-1,2-dihydro-1-methyl-2-methyliminopyrimidine (V), was isolated and characterised. While the substitution of a methyl group at nuclear and also at extranuclear nitrogen atoms naturally does not permit observation of the formation of the normal rearranged product, it was found possible to obtain an "abnormal" product, 4-amino-5-formyl-2,3-dihydro-3-methyl-2-methyliminopyrimidine (VI). Ring closure of the intermediate to starting material was achieved in acid. The lower homologue (5-cyano-1,2-dihydro-2-imino-1-methylpyrimidine) was found to undergo "normal" or "abnormal" rearrangement according to the conditions imposed. Here again the acyclic compound was isolated. The formation of an "abnormal" product is the result of internal addition of the amine to the nitrile group, rather than addition to the carbonyl group which is the "normal" occurrence.

Unlike this pyrimidine, the homologue bearing methyl groups at C-4 and C-6 underwent only normal rearrangement. This difference was attributed to the
less ready hydration of a keto-group. Hydration of the aldehyde group of the intermediate formed from the mono-methyl homologue, results in a preferential recyclisation by intramolecular reaction at the cyano group. Normal rearrangement was also observed in 5-carbamoyl- and 5-halo- substituted imines at rates which reflected the extent of electron-withdrawal by the substituent. A degree of base catalysis was also noted by Brown and Paddon-Row, in this study, together with an unusual degree of retardation by added C-methyl groups. The anomalous effect of such methyl groups was studied further and it was found that rearrangement was much slower in iminopyrimidines bearing a 4-methyl group than in homologues lacking this substitution or having both 4- and 6-methyl substituents. This anomaly has not yet been resolved.

Mechanisms of Rearrangement

The experiments using a labelled imino group have established that the rearrangement occurs by ring fission, rotation and recyclisation, and,
because the rate constants are in the main composite in nature, ample information is available on the effect of substituents. Despite this, there is very little information on which to base a detailed reaction mechanism.

Taylor and Loeffler suggested that ring opening occurred after nucleophilic attack by hydroxyl ions at C-6 of the pyrimidine nucleus; on the other hand Brown and Harper and Perrin, suggested heterolytic fission of the ring followed by solvation of the resulting acyclic compound. The first suggestion may be discounted on the grounds that there is no consistent evidence of pH dependence of the rate, when calculated on the involvement of the free base and not the pyridinium cation, in the rearrangement. The alternative, heterolytic fission mechanism, implying as it does, the formation of a zwitterion prior to solvation, would be expected to show dependence of the rate upon the ionic strength of the medium or the polarity of the solvent. Certainly, as regards acid-base catalysis, this mechanism is consistent with observation. Both mechanisms imply the following scheme

A $\rightleftharpoons$ B $\rightarrow$ C, a reversible
ring-opening of the imine followed by reclosure to rearranged product, C.

An alternative mechanism has been developed by Perrin and Pitman \(^{2,3,6}\), which appears to overcome the difficulties of those described. In its simplest form the mechanism is represented as

\[
\begin{array}{c}
A \\
\downarrow \\
A.H_2O
\end{array} \rightleftharpoons B \longrightarrow C + H_2O.
\]

An equilibrium is attained, in solution, between the neutral molecule of the imine, and a small amount of its water adduct, \(A.H_2O\). It is this adduct which undergoes ring fission to an acyclic intermediate B. In this simplest case, B recyclises to the rearranged material, C, which because of its hetero-aromatic structure, is not hydrated. Thus \(B \longrightarrow C\) is irreversible in this example. Evidence for the nature of the hydrated imine is based on the ready formation of adducts with bisulphite and ethanol \(^6\). There is not the direct evidence of the covalent hydrate that exists in the case of quinazolines \(^{30,31}\) and pteridines \(^{32}\). However, using
An apparatus designed for studying very rapid reactions, presumptive spectral evidence was obtained for covalent addition of water to 3-bromo-iminopyrimidines. Further evidence for attachment of water in the rearrangement via elimination of the basic proton was obtained. The rate in solvents such as tetrahydrofuran, acetone, dioxane and ether, was increased from no reaction to a rate which was dependent on the amount of added water.

The structure of this adduct is that of a carbinolamine (VII), analogous to the hydrocyclic pseudo-bases described by Heidelberger. Cyclisation reactions are analogous to those postulated for the pseudo-bases and the carbinolamines. The latter are the intermediates in reactions of Schiff bases as suggested by Cordes and Jencks.

The present study focuses on the aspects of the Diels-Alder rearrangement of iminopyrimidines which are described here and are divided into three sections. Section one concerns the measurement of equilibria.
an apparatus designed for studying very rapid reactions, presumptive spectral evidence was obtained for covalent addition of water to 5-bromo-iminopyrimidines\textsuperscript{6}. Further evidence for the participation of water in the rearrangement, was obtained in the observation that the rate in solvents such as tetrahydrofuran, acetone, dioxan and ether, was increased from no reaction to a rate which was dependent on the amount of added water\textsuperscript{6}.

The structure of this adduct is that of a carbinolamine (VII), analogous to the heterocyclic pseudo-base described by Beke\textsuperscript{33}. Ring-opening and cyclisation reactions are analogous to those postulated for the pseudo-bases and the carbinolamines. The latter are the intermediates in reactions of Schiff bases as suggested by Cordes and Jencks\textsuperscript{34}.

**The Present Studies**

The aspects of the Dimroth rearrangement in iminopyrimidines which are reported here, are discussed in three sections. Section A concerns the measurement of equilibria by
a p.m.r. spectral technique, and involves examples of iminopyrimidines in which the total rearrangement is reversible. The factors controlling the position of this equilibrium are discussed. This work was carried out in collaboration with J.S. Harper. The discussion presented must of course cover all the results obtained; however experimental details presented (i.e. preparation of compounds, measurement of ionisation constants and spectra, and the determination of equilibrium ratios) are those for which the writer alone is responsible. This work is reported in the publication "The Dimroth Rearrangement. Part VI. Measurement of Equilibria in Reversible Examples from the Pyrimidine Series." D.J. Brown, B.T. England and J.S. Harper, J. Chem. Soc., (C) 1966, 1165.

Section B of this study concerns the rearrangement of 1-methyliminopyrimidines which are substituted at position-5 by an unsaturated alkyl group. This site is remote from that of ring fission and the rates of rearrangement may be correlated readily with the degree of electron-withdrawal exerted by the substituent.
Base induced prototropic rearrangement produced the first allenylpyrimidine to be reported. This work has recently appeared in a paper which also reports on the rearrangements contained in Section C: "The Dimroth Rearrangement. Part IX. The Formation and Isomerisations of Propynyl (and related)-iminopyrimidines."

D.J. Brown and B.T. England, *J. Chem. Soc. (C)*, 1967, 1922. Reactions of iminopyrimidines substituted at a ring nitrogen by the propynyl group are reported in Section C. In addition to an examination of the Dimroth rearrangement, the formation of a bicyclic product is also reported.
The Reversible Rearrangement of 1-alkyl-2-alkyliminopyrimidines

The rearrangement of 1-alkyl-1,2-dihydro-2-iminopyrimidines is activated by the instability of a system in which an imino group is adjacent to a tertiary nitrogen; it proceeds to completion, because the for- matic product is stable to ring fission. Where the incentive of stability of product does not obtain, it might be expected that equilibrium would be set up between alkyldihydropyrimidines and alkyldihydropyrimidines. The composition of the isomeric mixture must be governed by steric as well as electronic factors. Equilibrium must be attained from either direction, i.e. when either the imine (II) or its isomer (III) is subjected to rearrangement conditions.

The Rearrangement of 1-1-dihydropyrimidine (IV; R=Me), and of the corresponding 1-butyl compound (IV; R=Bu), proceeds to completion. The rate of the reaction, $t_{1/2} = 114$ min. and 50 min. respectively, reflecting the difference in "size" of
The Reversible Rearrangement of $1$-alkyl-$2$-alkyliminopyrimidines

see Fig. A-1

The rearrangement of $1$-alkyl-$1,2$-dihydro-$2$-iminopyrimidines is activated by the instability of a system in which an imino group is adjacent to a tertiary nitrogen; it proceeds to completion, because the formally aromatic product is stable to ring fission. Where the incentive of stability of product does not obtain, it might be expected that an equilibrium would be set up between (I) and (III) (fig. A-1). The composition of the isomeric mixture must be governed by steric as well as electronic factors. Equilibrium must be attained from either direction, i.e. when either the imine (I) or its isomer (III) is subjected to rearrangement conditions.

The rearrangement of $1,2$-dihydro-$2$-imino-$1$-methylpyrimidine (IV; R=Me), and of the corresponding $1$-butyl compound (IV; R=Bu), proceeds to completion. The rate of the reaction, $t_{1/2} = 114$ min. and 58 min. respectively, reflecting the difference in "size" of
the alkyl groups.

A similar situation arises in 1-alkyl-2-alkyliminopyrimidines where the alkyl substituents are markedly different. Digestion at 114 min. is completely observed, whereas no digestion of 1-benzyl-1,2-dihydro-2-methyliminopyrimidine. The equilibrium (III) \( \rightarrow \) (I) is not observed. Thus the larger group is accommodated on the extra-cyclic nitrogen, as is so for 1-alkyl-1,2-dihydro-2-iminopyrimidines.

When the alkyl groups are the same, e.g., 1,2-dihydro-1-ethyl-2-methyliminopyrimidine (I), \( R' = R = \text{Me} \), an equilibrium derivative (IV) is observable. The equilibrium (I) \( \equiv \) (II) is established.

In examples where the alkyl groups are homologous, the technique previously employed of observing the change in ultraviolet spectrum as the equilibrium proceeds, can not be applied. The spectra of the alkyl-imino-pyrimidines differ distinctly. A method involving p.m.r. spectroscopy was developed to determine the isomeric ratios at the equilibrium established in

![Fig. A-1](image-url)
the alkyl groups.

A similar situation arises in 1-alkyl-2-alkyliminopyrimidines where the alkyl substituents are markedly different. Rearrangement appears to be entirely of one direction, \((I) \rightarrow (III)\), in the case of 1-benzyl-1,2-dihydro-2-methyliminopyrimidine. The reaction, \((III) \rightarrow (I)\) is not observed. Thus the larger group is accommodated on the extra-cyclic nitrogen, as is so for 1-alkyl-1,2-dihydro-2-iminopyrimidines.

When the alkyl groups are the same, e.g. 1,2-dihydro-1-methyl-2-methyliminopyrimidine \((I; R'=R=Me)\), and its 5-bromo derivative, no rearrangement is observable. The equilibrium \((I) \rightleftharpoons (II)\) is established\(^6\).

In examples where the alkyl groups are homologues, the technique previously established, of observing the change in ultraviolet spectrum as the rearrangement proceeds, can not be applied. The spectra of the alkylimino-pyrimidines differ only slightly. A method involving p.m.r. spectroscopy was developed to determine the isomeric ratio at the equilibrium established in
P.m.r. spectrum of

a. 1-butyl-2-methyliminopyrimidine,
b. 2-butylimino-1-methylpyrimidine.
P.m.r. spectrum of

a. 2-allylimino-1-propylypyrimidine,

b. 1-allyl-2-propyliminopyrimidine.
such examples. The results of these determinations indicate that relative electron-withdrawal or -release characteristics of the substituent groups, in addition to relative size and shape, influence the equilibrium ratio. Details of the method are contained in the Experimental Section of this thesis. However, the spectra of 2-butylimino-1,2-dihydro-1-methylpyrimidine and of 1-butyl-1,2-dihydro-2-methyliminopyrimidine, are reproduced here.

Rearrangement of 2-butylimino-1,2-dihydro-1-methylpyrimidine may be followed in the disappearance of the peak at 6.17 \text{T} - due to the N-1-methyl protons, and in the appearance of the peak at 6.82 \text{T} - due to the protons of the methylimino substituent. Peak intensity is measured in terms of the aromatic protons in the region 1 to 3 \text{T}.

The spectrum of 1-allyl-1,2-dihydro-2-propyliminopyrimidine and of its isomer, is also reproduced. Analysis of the spectra appears in the table.

The position of equilibrium in the benzyl methyl
imines (I and III; R=PhCH₂, R'=Me) is displaced very obviously toward the imine in which the bulkier group is attached to the extra-cyclic nitrogen (see table of ratios). A similar observation may be made of the equilibrium ratios of butyl methyl imines, although here the effect is not as marked. The preference for the ethylimino compound over the corresponding methylimino isomer is still less obvious; however the trend is apparent, the equilibrium ratio being 6:4 in favour of the former isomer. This rearrangement (I to III; R=Et, R'=Me) was followed for about 48 hr. At this time, although equilibrium had not been attained, the complexity of the spectra prevented further measurements. Such complexity may arise from the several reactions e.g. hydrolysis of each imine and of the acyclic intermediate, which become important during a relatively slow rearrangement.

From these observations it might be concluded that relative steric bulk of the alkyl group is the factor which determines the equilibrium isomer ratio. Such a conclusion is modified when consideration is given to the structure of the ring-opened intermediate.
(e.g. II; R=PhCH₂, R'=Me). The benzylated amino group, while sterically demanding, is also electron depleted compared with the neighbouring methylated amino group. Both steric and electronic factors, then, may be operative in determining the recyclisation of an intermediate such as that of the benzyl methyl imines.

In the case of the isopropyl benzyl imines the greater steric hindrance is expected of the isopropyl group yet it is found that the isomer predominating at equilibrium is that having this group attached to the ring nitrogen. This observation suggests the greater importance of the electronic character of the substituent.

It is proposed that for the allyl propyl imines the difference in spatial requirements of the alkyl groups is reduced, and any preference observed in the isomeric ratio at equilibrium will reflect a difference in electron availability. The pKₐ values of selected compounds support a mildly electron-withdrawing character for the allyl group, and an electron-releasing character for the propyl group:
allylamine (9.5)  \[\text{aniline (4.6)}\]
propylamine (10.7)  \[\text{N-allylaniline (4.2)}\]
\[\text{N-propylaniline (5.1)}\]

It is observed that the rearrangement \((I; R=\text{allyl}, R'=\text{propyl}) \xrightarrow{\text{\(\sim\)}} (III; R=\text{propyl}, R'=\text{allyl})\) starting from either isomer, proceeds to an equilibrium ratio of 3:1 in favour of the allylimino (electron withdrawing) isomer.

Hence "in 1-alkyl-2-alkylimino-1,2-dihydropyrimidines, the equilibrium in alkaline solution will favour the isomer bearing the bulkier and/or more electron-withdrawing alkyl group attached to the extra-cyclic nitrogen" \(^{35}\).
Equilibria for the reaction

\[ \text{I} \rightleftharpoons \text{III} \]

<table>
<thead>
<tr>
<th>Imine initially present</th>
<th>Isomeric Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>R R'</td>
<td>[I]</td>
</tr>
<tr>
<td>I Et Me</td>
<td>40</td>
</tr>
<tr>
<td>III Et Me</td>
<td>30</td>
</tr>
<tr>
<td>I or III Bu Me</td>
<td>5 \textsuperscript{b}</td>
</tr>
<tr>
<td>I or III PhCH\textsubscript{2} Me</td>
<td>10 \textsuperscript{c}</td>
</tr>
<tr>
<td>I or III PhCH\textsubscript{2} Pr\textsuperscript{i}</td>
<td>25</td>
</tr>
<tr>
<td>I or III allyl Pr\textsuperscript{i}</td>
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</tr>
</tbody>
</table>

\textsuperscript{a} Equilibrium not attained (see text).

\textsuperscript{b} Confirms ultraviolet spectral evidence in ref. 13.

\textsuperscript{c} Quoted from ref. 13; p.m.r. study impracticable.
## Ionisation and Ultraviolet Spectra

### Section A

<table>
<thead>
<tr>
<th>Compound</th>
<th>$pK_a^a$</th>
<th>$\lambda_{\text{anal.}}$ (mµ)</th>
<th>$\lambda_{\text{max.}}$ (log $\varepsilon$)</th>
<th>pH $^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,2-Dihydropyrimidine</td>
<td></td>
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<tr>
<td>1-allyl-2-propylimino</td>
<td>$12.25\pm0.04$</td>
<td>320</td>
<td>376(3.21), 244(4.22)</td>
<td>14.3</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>320(3.69), 232(4.24)</td>
<td>8.0</td>
</tr>
<tr>
<td>2-allylimino-1-propyl</td>
<td>$11.47\pm0.03$</td>
<td>320</td>
<td>368(3.42), 232(4.24)</td>
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<td>320(3.62), 232(4.08)</td>
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<td>1-ethyl-2-methylimino $^d$</td>
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<tr>
<td>2-ethylimino-1-methyl</td>
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<td>8.0</td>
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<tr>
<td>1-butyl-2-methylimino $^e$</td>
<td>$11.90\pm0.04$</td>
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<td>368(3.4), 242(4.2)</td>
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<td>320(3.7), 230(4.2)</td>
<td>8.0</td>
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<td>2-butylimino-1-methyl</td>
<td>$12.17\pm0.02$</td>
<td>320</td>
<td>368(3.36), 244(4.17)</td>
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<td>318(3.60), 234(4.16)</td>
<td>8.0</td>
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---

$pK_a$, $\lambda_{\text{anal.}}$, $\lambda_{\text{max.}}$, and pH values were determined on a Spectronic spectrophotometer. Absorption spectra were recorded on a Spectronic spectrophotometer. Ionisation constants were measured at $20^\circ$C by the method outlined by A. Albert, J. Phys. Chem., 1962.

Buffer solutions used are described by D.D. Perrin, ref. 25.

*See ref. 13.*

Solution of hydrochloride prepared.
Notes (Section A)

a Measured at 20° C by the method outlined by A. Albert and E.P. Serjeant, "Ionisation Constants of Acids and Bases", Methuen, London, 1962.

b Spectra were recorded on a Spectracord spectrophotometer, or a Shimadzu RS 27 spectrophotometer. Adsorption peaks were determined on an Optica manual instrument.

c Buffers used are described by D.D. Perrin, ref. 25.

d See ref. 13.

e Solution of hydrochloride prepared from picrate; log ε values approximate.
<table>
<thead>
<tr>
<th>Compound</th>
<th>Medium</th>
<th>Proton Magnetic Resonance Spectra</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>τ-Values; J in c./sec.</td>
</tr>
<tr>
<td>1,2-Dihydropyrimidine</td>
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<td></td>
</tr>
<tr>
<td>1-allyl-2-propylimino</td>
<td>0.1N-DCl</td>
<td>γ-CH₃: 9.05 t (Jᵦ,γ = 6.5); β-CH₂(propyl): 8.3m;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>α-CH₂(propyl): 6.38 t (Jₐ,β = 6.5);</td>
</tr>
<tr>
<td></td>
<td></td>
<td>α-CH₂(allyl): 5.2 d (Jₐ,β = 6);</td>
</tr>
<tr>
<td></td>
<td></td>
<td>γ-CH₂(allyl): 4.6 m (Jᵦ,γcis = 12; Jᵦ,γtrans = 16);</td>
</tr>
<tr>
<td></td>
<td></td>
<td>β-CH(allyl): 3.9 m; 5-H: 2.90 q (Jortho = 6);</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6-H: 1.58 q (Jortho = 6; Jmeta = 2); 4-H: 1.10 q</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Jortho = 4; Jmeta = 1.5)</td>
</tr>
<tr>
<td>2-allylimino-1-propyl</td>
<td>0.1N-DCl</td>
<td>γ-CH₃: 8.95 t (Jᵦ,γ = 6.5); β-CH₂(propyl): 8.1m;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>α-CH₂(propyl): 5.75 t (Jₐ,β = 6.5);</td>
</tr>
<tr>
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<td></td>
<td>α-CH₂(allyl): 5.70 d (Jₐ,β = 6);</td>
</tr>
<tr>
<td></td>
<td></td>
<td>γ-CH₂(allyl): 4.75 m (Jᵦ,γcis = 12; Jᵦ,γtrans = 16);</td>
</tr>
</tbody>
</table>
Section A (page 2)

1-butyl-2-methylimino 0.1N-DC1
\[
\begin{align*}
\beta-\text{CH(allyl)}: & \quad 4.0 \text{m}; 5-\text{H}: 2.83 \text{q (J}_{\text{ortho}}=7); \\
6-\text{H}: & \quad 1.48 \text{q (J}_{\text{ortho}}=7; J_{\text{meta}}=2.5); \\
4-\text{H}: & \quad 1.08 \text{q (J}_{\text{ortho}}=4; J_{\text{meta}}=1.5) \\
\end{align*}
\]
\[
\begin{align*}
\beta,\gamma,\delta \text{(butyl)}: & \quad 8 \text{ to } 9 \text{m}; N-\text{CH}_3: 6.82 \text{s}; \\
\alpha-\text{CH}_2 \text{(butyl)}: & \quad 5.80 \text{t (J}_{\alpha,\beta}=6.5); \\
5-\text{H}: & \quad 2.88 \text{q (J}_{\text{ortho}}=6); 6-\text{H}: 1.55 \text{q (J}_{\text{ortho}}=6; \\
& \quad J_{\text{meta}}=2); 4-\text{H}: 1.10 \text{q (J}_{\text{ortho}}=4; J_{\text{meta}}=1.5) \\
\end{align*}
\]

2-butylimino-1-methyl 0.1N-DC1
\[
\begin{align*}
\delta-\text{CH}_3: & \quad 9.10 \text{t (J}_{\gamma,\delta}=6); \beta,\gamma-\text{CH}_2 \text{(butyl)}: 8.2 \text{ to } 8.8 \text{m}; \\
\alpha-\text{CH}_2 \text{(butyl)}: & \quad 6.35 \text{t (J}_{\alpha,\beta}=6.5); N-\text{CH}_3: 6.17 \text{s}; \\
5-\text{H}: & \quad 2.93 \text{q (J}_{\text{ortho}}=6); 6-\text{H}: 1.60 \text{q (J}_{\text{ortho}}=6; \\
& \quad J_{\text{meta}}=2); 4-\text{H}: 1.13 \text{q (J}_{\text{ortho}}=4; J_{\text{meta}}=1.5) \\
\end{align*}
\]

\[s = \text{singlet, d = doublet, t = triplet, q = quartet, m = multiplet.}\]
The Rearrangements of 5-Propynyl (and related)-iminopyrimidines

Preparation of compounds

see Fig. B-1

The aminopyrimidines (I) were prepared by condensation of appropriately substituted acetylacetone with guanidine dimethylpyrimidine (I; R=CH₂.CH₂CH₃). Methyleneation on N=1 gave the required imine (II; R=CH₂.CH₂CH₂). The 5-propyl-iminopyrimidine was prepared similarly. In the preparation of 2-amino-4,6-dimethyl-5-prop-2'-ynylpyrimidine by condensation of guanidine carbonate with propargyl acetylacetone (i.e. 5-prop-2'-ynyl acetylacetone), a mixture of three compounds was obtained. Recrystallisation from boiling ethanol gave the prop-1'-ynyl compound, (I; R=CH(C₆H₄Cl̋). Allenyl, (I; R=CH₂C(CH₃)₂) and prop-2'-ynyl isomers (I; R=CH₂=C(CH₃)) were obtained by elution from an alumina column with ether. (see Experimental section)

SECTION B

The Rearrangement of 5-Propynyl (and related)-iminopyrimidines

Tables of Spectra follow page 31

Experimental Details page 65
The Rearrangements of 5-Propynyl(and related)-iminopyrimidines

Preparation of compounds

see Fig. B-1

The aminopyrimidines (I) were prepared by condensation of appropriately substituted acetylacetone with guanidine. Acetylacetone derivatives were analysed as the copper complex, bis(alkylacetylacetonato)copper II (III). For example 3-allylacetylacetone was condensed with guanidine to give 5-allyl-2-amino-4,6-dimethylpyrimidine (I; R=CH₂·CH:CH₂). Methylation on N-1 gave the required imine (II; R=-CH₂·CH:CH₂). The 5-propyl-iminopyrimidine was prepared similarly. In the preparation of 2-amino-4,6-dimethyl-5-prop-2'-ynylpyrimidine by condensation of guanidine carbonate with propargyl acetylacetone (i.e. 3-prop-2'-ynyl acetylacetone), a mixture of three compounds was obtained. Recrystallisation from boiling ethanol gave the prop-1'-ynyl compound, (I; R=-CH:C·CH₃). Allenyl, (I; R=-CH:C:CH₂) and prop-2'-ynyl isomers (I; R=-CH₂·C:CH) were obtained by elution from an alumina column with ether. (see Experimental section)
These isomers were recognized by features of their p.m.r. spectra; the expected prop-2'-yayl compound having an acetylenic proton (7.9 t) split (J = 3 c./sec.) by long range coupling to the methylene protons (3.4 t). Movement of the triple bond into conjugation with the pyridine rim have caused the prop-1'-yayl isomer to rearrange as observed in the p.m.r. spectrum as a methyl group at 1.9 t. The protons of the third (allenyl) isomer absorb at 3.8 and 4.9 t in the p.m.r. spectrum and have a splitting constant of 7 c./sec.

The allenyl substituent also gives rise to an intense absorption due to an intense absorption which is characteristic of the group -C≡C-O=C which is characteristic of the group.

γ-Methylation was carried out with the triple-bond substituents to give the derivatives (II; R = -CH₂, -CH₃, or -C₆H₄CH₃) but lack of sufficient material prevented the use of the 5-allenylpyrimidine in such a reaction.

Pyrimidines (II; R = Pr, -CH₂-CH₃, or -C₆H₄CH₃) were rearranged on a preparative scale by warming over steam for 10-15 min. in 2N-alkali. Each

Fig. B-1
These isomers were recognised by features of their p.m.r. spectra: the expected prop-2'-ynyl compound having an acetylenic proton (7.9\(\tau\)) split (\(J = 3\text{ c./sec.}\)) by long range coupling to the methylene protons (3.4\(\tau\)). Movement of the triple bond into conjugation with the pyrimidine ring gave the prop-1'-ynyl isomer, such rearrangement is observed in the p.m.r. spectrum as a methyl group at 7.9\(\tau\). The protons of the third (allenyl) isomer absorb at 3.8 and 4.9\(\tau\) in the p.m.r. spectrum and have a splitting constant of 7 c./sec. The allenyl substituent also gives rise to an intense absorption in the infrared region at 1950 cm\(^{-1}\) which is characteristic of the group\(^{36}\).

\(N\)-Methylation was carried out with the triple-bond substituents to give the derivatives (II; \(R=\text{-CH}_2\text{.C\ddot{\text{=}CH}},\text{ or -C\ddot{\text{=}C.CH}_3}\)) but lack of sufficient material prevented the use of the 5-allenylpyrimidine in such a reaction.

The iminopyrimidines (II; \(R=\text{Pr, -CH}_2\text{.CH:CH}_2\), or \(-\text{C\ddot{\text{=}C.CH}_3}\)) were rearranged on a preparative scale by warming over steam for 10-15 min. in 2N-alkali. Each
corresponding methylamino derivative (IV; R'=NHCH₃) was quickly precipitated in > 80% yield. Although the remaining imine was not rearranged on a preparative scale, spectral evidence for the formation of the methylamino derivative was unequivocal. These products of rearrangement were synthesised by an unambiguous method, from the acetylacetone derivatives. Hydroxypyrimidines (IV; R'=OH) were prepared by condensation of the acetylacetone with urea. This reaction was carried out under acid conditions and consequently no prototropic shift in the prop-2'-ynyl group occurred. After treatment with phosphoryl chloride to give corresponding 2-chloropyrimidines (IV; R'=Cl), heating in a sealed reaction tube with methylamine solution gave the required methylamino pyrimidines (IV; R'=NHCH₃, R=Pr, -CH₂.CH:CH₂, or -CH₂.C:CH). Under the basic conditions of this reaction it was found that again a prototropic shift had occurred and the prop-2'-ynyl derivative was accompanied, in equal amount, by an isomer which was identified as the allene (IV; R'=NHCH₃, R=-CH:C:CH₂). The isomers were separated chromatographically and identified by
infrared and p.m.r. spectra. Reduction in the proportion of allene present to 1 part in 10, followed replacement of methylamine (free base) with aqueous methylamine acetate, and hence providing less strongly basic conditions.

4,6-Dimethyl-2-methylamino-5-prop-1'-ynylpyrimidine (IV; R' = NHCH₃; R = C=C·CH₃) was obtained by hydrolysis and isomerisation of the 2-chloro compound, rechlorination, and methylamination. Alternatively, alkaline isomerisation of the hydroxy compound may be carried out.

Isomerisation within the propynyl group

The prototropic shifts apparent in the isomerisation of prop-2'-ynyl to allenyl and prop-1'-ynyl pyrimidine are induced under relatively mild basic conditions. This may be interpreted as reflecting the electron-withdrawing capacity of the attached ring system, and also the gain in stability of the system in which the triple bond is in conjugation with the ring.

Spectra of isomers are markedly different and reflect the structural changes mentioned.

1. A shift is evident in the ultraviolet spectrum of
the allene to longer wavelengths, by 10–20 mµ, compared
with the non-conjugated prop-2'-ynyl isomer. A
bathochromic shift of 20–40 mµ from the prop-2'-ynyl to
prop-1'-ynylpyrimidine indicates a more "complete"
conjugation.

2. The pK_a of the allene is closely similar to that
of the prop-2'-ynyl isomer (4.90, 4.92 for the
methylamino compounds). It is lowered by approx. 1
unit in the prop-1'-ynyl methylaminopyrimidine.

3. A strong absorption at 1950 cm⁻¹ in the infrared
spectrum is characteristic of the allene. C=C
absorptions are not dependable.

4. P.m.r. spectra provide unequivocal evidence of the
isomerisation. Relevant portions of the spectra are
reproduced here and detailed analyses are contained in
the table.

The preparations by Schulte et al. of 4-hydroxy-2,6-dimethyl- and 2,4,6-hydroxy-2'-ynylpyrimidine, were repeated and examined for evidence of isomerisation. No such evidence was found and the postulated structure was confirmed. It is notable that
in these preparations the allene was not isolable.
the allene to longer wavelengths, by 10-20 m\(\mu\), compared with the non-conjugated prop-2'-ynyl isomer. A bathochromic shift of 20-40 m\(\mu\) from the prop-2'-ynyl to prop-1'-ynylpyrimidine, indicates a more "complete" conjugation.

2. The pK\(_a\) of the allene is closely similar to that of the prop-2'-ynyl isomer (4.90, 4.92 for the methylamino compounds). It is lowered by approximately 1 unit in the prop-1'-ynyl methylaminopyrimidine.

3. A strong absorption at 1950 cm\(^{-1}\) in the infrared spectrum is characteristic of the allene. C\(\equiv\)C absorptions are not dependable.

4. P.m.r. spectra provide unequivocal evidence of the isomerisation. Relevant portions of the spectra are reproduced here and detailed analyses are contained in the table.

The preparations by Schulte et al.\(^{36}\), of 4-hydroxy-2,6-dimethyl- and 2,4,6-hydroxy-5-prop-2'-ynylpyrimidine, were repeated and examined for evidence of isomerisation. No such evidence was found and the postulated structure was confirmed. It is notable that in these preparations ethanol was used as solvent\(^{36}\);
however the main factors precluding isomerisation are, perhaps, the mild conditions used in the preparation of the monohydroxypyrimidine, and the decrease in electron-withdrawing capacity of the pyrimidine ring in the trihydroxy derivative.

The Dimroth Rearrangement

a. Method

Although an outline of the method of measurement of the rate of rearrangement of iminopyrimidines, is included in the Introduction to this thesis, it is appropriate to discuss here, a specific example. For this purpose portion of the ultraviolet spectrum of 1,2-dihydro-2-imino-5-propyl-1,4,6-trimethylpyrimidine is reproduced. The change in optical density is shown, in the accompanying diagram, as a plot of the logarithm of optical density against time.

A solution of the imine (4 x 10^{-4} M) was maintained at 25° in the thermostated cell holder of a Shimadzu spectrophotometer. The first spectrum was recorded as soon as possible (ca 30 sec.) after adding to the sample sufficient aqueous potassium hydroxide of known molarity, to give a concentration of 2 x 10^{-4} M
and a pH of 14. Spectra were then recorded at suitable intervals. Several points should be noted:

- Concentration is important only in providing optical density readings of convenient magnitude and spread.
- The initial point is not necessarily observed.
- Interference from simultaneous hydrolysis reactions (dashed line) represents an "infinity" reaction and was usually recorded 24-30 hours after the initiation of the rearrangement. For convenience, a wavelength was chosen at which optical density is essentially zero, and a graph such as that illustrated, was plotted. A rate constant may be read from the graph:

\[ k = \frac{D_0 - D}{D_0 - D_\infty} \text{ log } \frac{D_0}{D} \]

or more simply

\[ k = \frac{2.303}{t} \log \frac{D_0}{D} \text{ when } D_\infty = 0. \]

The half-life \( t_{1/2} \), the rate parameter used in comparisons of rearrangements, is calculated from the equation:

\[ t_{1/2} = \frac{\ln 2}{k} \]

The Rearrangement of 1,2-Dihydro-3-imino-3-propyl-1,4,5-trimethylpyrimidine.
and a pH of 14. Spectra were then recorded at suitable intervals. Several points should be noted:

1. Concentration is important only in providing optical density reading of convenient magnitude and spread,
2. A simple isosbestic point is not necessarily observed because of minor contributions from simultaneous hydrolysis reactions,
3. The final spectrum (broken line) represents an "infinity" reading and was actually recorded 24-30 hours after the initiation of the rearrangement. For convenience, a wavelength was chosen at which optical density at "infinity" is essentially zero, and a graph such as that illustrated, was plotted. A rate constant may be read from the graph or calculated from the relationship

\[ k = \frac{2.303}{t} \log \left( \frac{D_\infty - D_0}{D_\infty - D} \right) \]

or more simply

\[ k = \frac{2.303}{t} \log \left( \frac{D_0}{D} \right) \quad \text{when} \quad D_\infty \approx 0. \]

The half-life \( t_{1/2} \), the rate parameter used in comparisons of rearrangement rates, is calculated from \( t_{1/2} = \frac{\ln 2}{k} \).
It represents the time taken for the disappearance of half the initial imine. In many cases the appearance of the methylaminopyrimidine may be observed to occur at the same rate. Failure of these rates to correspond has been interpreted as accumulation of the acyclic intermediate, or, as is so when the half-life is very long, as hydrolysis of the imine or methylamino compound or of the acyclic compound.

An alternative method involves the setting of the spectrophotometer at a suitable wavelength, thus to obtain directly a recording of the change in optical density with time, at that setting. This method is essential when it is necessary to follow the rearrangement in a region of the spectrum where optical density changes markedly during a slight change in wavelength.

b. Results

Unlike the iminopyrimidines discussed in Section A, rearrangement of the present compounds proceeds toward the more stable hetero-aromatic structure of the 2-methylaminopyrimidines. The unstable iminopyrimidine is rendered even more unstable by electron-withdrawal from the \( \pi \)-electron system already electron deficient.
because of the ring nitrogens. It is assumed that, remote from the site of reaction, the slight steric differences are unimportant and that the four substituents (propyl, allyl, prop-2'-ynyl, prop-1'-ynyl) provide a series in the degree of electron-withdrawal. Though not providing a quantitative measure of the electronic effect of these substituents, the effect is reflected in the $pK_a$ values of propylamine (10.7), allylamine (9.5) and prop-2-ynylamine (8.15); also in the values of the aminopyrimidines (5.5, 5.1, 4.5, 4.0), the methylamino compounds (5.6, 5.4, 4.9, 4.1), basic (4.2, 4.0, 3.6, 2.7), and acidic values (10.8, 10.7, 10.2, 9.4) for the hydroxypyrimidines, and again in the basic strength of the imines themselves. Electron-withdrawal by the prop-1'-ynyl group, having a triple-bond in conjugation with the ring, has a marked effect on the rate (see table). It is probable that the effect is primarily on the ease of ring fission following withdrawal of electrons from the ring. Such withdrawal may result in an increase in the polarity of the 1,6(C-N)-bond thus enhancing hydration of this bond prior to ring fission.
Whatever the mechanistic pathway, it is apparent that within this group of imines the rate of rearrangement depends on the degree of electron-withdrawal by the 5-substituent.

| 5-propyl  | 178 | 345 | 12.21 |
| 5-allyl   | 157 | 346 | 11.99 |
| 5-prop-2'-'ynyl | 109 | 345 | 11.55 |
| 5-prop-1'-'ynyl |  64 | 356 | 10.97 |

a Half-life in minutes
b Wavelength (nm) at which determination of $t_\frac{1}{2}$ was made.
## Rearrangement rates for pyrimidine-imines

<table>
<thead>
<tr>
<th>Compound</th>
<th>$t_{\frac{1}{2}}$</th>
<th>$\lambda^b$</th>
<th>$pK_a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,2-Dihydro-2-imino-1,4,6-trimethylpyrimidine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-propyl</td>
<td>178</td>
<td>345</td>
<td>12.21</td>
</tr>
<tr>
<td>5-allyl</td>
<td>157</td>
<td>346</td>
<td>11.99</td>
</tr>
<tr>
<td>5-prop-2'-ynyl</td>
<td>109</td>
<td>345</td>
<td>11.55</td>
</tr>
<tr>
<td>5-prop-1'-ynyl</td>
<td>64</td>
<td>356</td>
<td>10.97</td>
</tr>
</tbody>
</table>

$^a$ Half-life in minutes

$^b$ Wavelength (m$\mu$) at which determination of $t_{\frac{1}{2}}$ was made.
## Ionisation and Ultraviolet Spectra

### Section B

<table>
<thead>
<tr>
<th>Compound</th>
<th>pK&lt;sub&gt;a&lt;/sub&gt;&lt;sup&gt;a&lt;/sup&gt;</th>
<th>λ&lt;sub&gt;anal. (m)&lt;/sub&gt;</th>
<th>λ&lt;sub&gt;max. (log ε)&lt;/sub&gt;&lt;sup&gt;b&lt;/sup&gt;</th>
<th>pH&lt;sup&gt;c&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td>Pyrimidine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1(3),4-dihydro-2,6-dimethyl-2-oxo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>unsubst.</td>
<td>3.06±0.04</td>
<td>280</td>
<td>253(3.76), 227(3.90)</td>
<td>6.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>229(4.02), 260(3.61)</td>
<td>1.0</td>
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<tr>
<td>unsubst.</td>
<td>9.77±0.05</td>
<td>280</td>
<td>262(3.68), 230(3.98)</td>
<td>12.0</td>
</tr>
<tr>
<td>t-(1-propynyl)</td>
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<tr>
<td>1,2-dihydro-4,6-dimethyl-2-oxo</td>
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<tr>
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<td>3.82±0.02</td>
<td>315</td>
<td>296(3.80)</td>
<td>6.0</td>
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<td>303(3.91)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>unsubst.</td>
<td>10.45±0.05</td>
<td>305</td>
<td>295(3.75), 222(3.93)</td>
<td>13.0</td>
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<td>296(3.80)</td>
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### Section B (page 2)

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## Section B (page 5)

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<th>pK&lt;sub&gt;a&lt;/sub&gt; ± Error</th>
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<td>327 (3.70), 255 (4.33)</td>
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- **Notes** (Section B)
  - Spectra were recorded on a Spectronic 20 spectrophotometer, or a Shimadzu UV-27 spectrophotometer. Absorption peaks were determined on an Optica manual instrument.
  - Buffers used are described by D.D. Perrin, ref. 25.
  - Spectrum at pH 2.0 is recorded. These compounds are unstable in acid, particularly below pH 2.
  - Included for comparison purposes. See ref. 26.
  - Insufficient material was obtained for complete measurement.
Notes (Section B)

a Measured at 20° C by the method outlined by A. Albert and E.P. Serjeant, "Ionisation Constants of Acids and Bases", Methuen, London, 1962.

b Spectra were recorded on a Spectracord spectrophotometer, or a Shimadzu RS 27 spectrophotometer. Absorption peaks were determined on an Optica manual instrument.

c Buffers used are described by D.D. Perrin, ref. 25.

d Spectrum at pH 2.0 is recorded. These compounds are unstable in acid, particularly below pH 2.

e Included for comparison purposes. See ref. 26.

f Insufficient material was obtained, for complete measurement.
Proton Magnetic Resonance Spectra

Section B

Compound | Medium | \( \tau \)-Values; \( J \) in c./sec.
--- | --- | ---
Pyrimidine

1,2-dihydro-4,6-dimethyl-2-oxo

5-propyl | 0.1N-DCl | \( \gamma \)-Me: 8.98t (\( J_{\beta,\gamma} = 7 \)); \( \beta \)-CH\(_2\): 8.4m; 4- and 6-Me: 7.37s; \( \alpha \)-CH\(_2\): 7.2t (\( J_{\alpha,\gamma} = 6.3 \))

5-allyl | 0.1N-DCl | 4- and 6-Me: 7.38s; \( \alpha \)-CH\(_2\): 6.60m (\( J_{\alpha,\beta} = 5 \)); \( \beta \)-CH: 4.1m; \( \gamma \)-CH\(_2\): -

5-(2-propynyl) | 0.1N-DCl | \( \gamma \)-CH: 7.42t; 4- and 6-Me: 7.28s; \( \alpha \)-CH\(_2\): 6.40d (\( J_{\alpha,\gamma} = 3 \))

5-propyl | CDC\(_1\)\(_3\) | \( \gamma \)-CH: 7.56t; 4- and 6-Me: 7.48s; \( \alpha \)-CH\(_2\): 6.65d

5-(1-propynyl) | 0.1N-DCl | \( \gamma \)-Me: 7.83s; 4- and 6-Me: 7.28s

2-chloro-4,6-dimethyl

5-propyl | CDC\(_1\)\(_3\) | \( \gamma \)-Me: 9.02t (\( J_{\beta,\gamma} = 7 \)); \( \beta \)-CH\(_2\): 8.5m; 4- and 6-Me: 7.62s; \( \alpha \)-CH\(_2\): 7.42t (\( J_{\alpha,\beta} = 6.5 \))
Section B (page 2)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Solvent</th>
<th>Spectral Data</th>
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<td>5-allyl</td>
<td>CDCl$_3$</td>
<td>$\gamma$-CH$<em>2$: 5.0 m; $\beta$-CH: 4.1 m ($J</em>{\beta,\gamma trans}=16$; $J_{\beta,\gamma cis}=12$)</td>
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<tr>
<td>5-(2-propynyl)</td>
<td>CDCl$_3$</td>
<td>$\gamma$-CH: 7.90 t; 4- and 6-Me: 7.36 s; $\alpha$-CH$<em>2$: 6.45 d ($J</em>{\alpha,\gamma}=3$)</td>
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<tr>
<td>5-(1-propynyl)</td>
<td>CDCl$_3$</td>
<td>$\gamma$-Me: 7.81 s; 4- and 6-Me: 7.38 s</td>
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<tr>
<td>2-amino-4,6-dimethyl unsubstituted</td>
<td>CDCl$_3$</td>
<td>4- and 6-Me: 7.71 s; NH$_2$: 4.05 s (broad); 5-H: 3.59 s</td>
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<td>5-propyl</td>
<td>CCl$_4$</td>
<td>$\gamma$-Me: 8.95 t ($J_{\beta,\gamma}=7$); $\beta$-CH$_2$: 8.35 m; 4- and 6-Me: 7.73 s; $\alpha$-CH$<em>2$: 7.4 t ($J</em>{\alpha,\beta}=6.3$)</td>
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<td>5-allyl</td>
<td>CCl$_4$</td>
<td>4- and 6-Me: 7.75 s; $\alpha$-CH$<em>2$: 6.78 m ($J</em>{\alpha,\beta}=5$); $\gamma$-CH$<em>2$: 5.0 m; NH$<em>2$: 4.9 s (broad); $\beta$-CH: 4.1 m ($J</em>{\beta,\gamma trans}=16$; $J</em>{\beta,\gamma cis}=12$)</td>
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<td>5-(2-propynyl)</td>
<td>CDCl$_3$</td>
<td>$\gamma$-CH: 7.90 t; 4- and 6-Me: 7.36 s; $\alpha$-CH$<em>2$: 6.45 d ($J</em>{\alpha,\gamma}=3$)</td>
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### Section B (page 3)

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<th>Chemical Shifts and Multiplicities</th>
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<td>CDCl₃</td>
<td>γ-Me: 7.81s; 4- and 6-Me: 7.38s</td>
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<td>5-allenyl</td>
<td>CDCl₃</td>
<td>4- and 6-Me: 7.58s; γ-CH₂: 4.92d; NH: 4.84 s (broad); α-CH: 3.80t (J_{α,γ} =7.1)</td>
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<td>2-methylamino-4,6-dimethyl</td>
<td>CDCl₃</td>
<td>γ-Me: 9.04t (J=7); β-CH₂: 8.53m;</td>
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<td>5-propyl</td>
<td>CDCl₃</td>
<td>4- and 6-Me: 7.65s; α-CH₂: 7.38t (J=6.5); N-Me: 7.0d (J=5.6); NH: 4.9s (broad)</td>
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<td>5-allyl</td>
<td>CDCl₃</td>
<td>4- and 6-Me: 7.66s; N-Me: 9.8d (J=5.6); α-CH₂: 6.72m (J_{α,β} =5); γ-CH₂: 4.96m; NH: 4.4s (broad); β-CH: 4.1m</td>
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<td>5-(2-propynyl)</td>
<td>CDCl₃</td>
<td>γ-CH: 7.98t; 4- and 6-Me: 7.60s; N-Me: 6.96d (J=5.6); α-CH₂: 6.62d (J_{α,γ} =3); NH: 4.9s (broad)</td>
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<td>5-(1-propynyl)</td>
<td>CDCl₃</td>
<td>γ-Me: 7.85s; 4- and 6-Me: 7.53s; N-Me: 6.97d (J=5.6); NH: 4.7s (broad)</td>
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<td>CDCl₃</td>
<td>4- and 6-Me: 7.60s; N-Me: 6.97d (J=5.6); γ-CH₂: 5.0d; α-CH: 4.82t (J_{α,γ} =7.1)</td>
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### Section B (page 4)

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<td>5-propyl</td>
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<td>γ-Me: 9.02t (J⁺,γ=6.5); β-CH₂: 8.35m; 4-Me: 7.48s; 6-Me: 7.43s; α-CH₂: 6.55m; 1-Me: 6.25s; γ-CH₂: 4.83m; β-CH: 4.08m</td>
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<td>4-Me: 7.28s; 6-Me: 7.22s; α-CH₂: 6.30d (Jα,γ=3); 1-Me: 6.12s; γ-CH: -</td>
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<td>5-(2-propynyl)</td>
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<td>γ-Me: 7.81s; 4-Me: 7.37s; 6-Me: 7.20s; 1-Me: 6.21s</td>
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<tr>
<td>4-hydroxy-2,6-dimethyl-5-(2-propynyl)</td>
<td>0.1N-DCl</td>
<td>γ-CH: 7.78t; 6-Me: 7.48s; 2-Me: 7.25s; α-CH₂: 6.50d (J=3)</td>
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<td>2,4,6-trihydroxy-5-(2-propynyl)</td>
<td>Dioxan</td>
<td>γ-CH: 8.90t; α-CH₂: 7.24d (J=3)</td>
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*s* = singlet, *d* = doublet, *t* = triplet, *q* = quartet, *m* = multiplet
The Rearrangement and Cyclisation
of 1-Propynyl-iminopyrimidines

Preparation of compounds

see Fig. Cel

Pyrimidines (I; R=CH₃) bearing at N-1 an alkyl
or a prop-2'-ynyl group, were prepared by reacting
alkyl iodide or propynyl bromide with 2-amino-4,6-
dimethylpyrimidine. Reaction of the aminopyrimidine
with propyl halide was unsuccessful. Treatment of
the iminopyrimidine (I; R=Me, R'=CH₂CH₂CH₃) with aqueous
potassium hydroxide, that is, under conditions designed
to bring about Diels-Alder rearrangement to give an
alkylamino pyrimidine (II; R=Me, R'=CH₂CH₂CH₃), gave
instead a mixture (1:1) of two compounds. The
components were separated and identified as the expected
pyrimidine (II) and a bicyclic triazaindene (III; R=Me).

In ethanolic alkali the triazaindene alone was formed,
in good yield.

This behaviour is analogous to that reported
by Twai and Niranka¹² for the non-methylated compound
(I; R=H, R'=CH₂CH₂CH₃). Under aqueous conditions the
proportion of normal rearranged product was higher (4:1)
that was found for the higher homologue (1:1).
The Rearrangement and Cyclisation of 1-propynyl-iminopyrimidines

Preparation of compounds

see Fig. C-1

Pyrimidines (I; R=CH₃) bearing at N-1 an alkyl or a prop-2'-ynyl group, were prepared by reacting alkyl iodide or propynyl bromide with 2-amino-4,6-dimethylpyrimidine. Reaction of the aminopyrimidine with propyl halide was unsuccessful. Treatment of the iminopyrimidine (I; R=Me, R'=−CH₂·C:CH) with aqueous potassium hydroxide, that is, under conditions designed to bring about Dimroth rearrangement to give an alkylamino pyrimidine (II; R=Me, R'=−CH₂·C:CH), gave instead a mixture (1:1) of two compounds. The components were separated and identified as the expected pyrimidine (II), and a bicyclic triazaindene (III; R=Me). In ethanolic alkali the triazaindene alone was formed, in good yield.

This behaviour is analogous to that reported by Iwai and Hiraoka¹² for the non-methylated compound (I; R=H, R'=−CH₂·C:CH). Under aqueous conditions the proportion of normal rearranged product was higher (4:1) than was found for the higher homologue (1:1).
2-Allylamino- and 2-prop-2'-ynylamino-4,6-dimethylpyrimidine were each prepared by preparative-scale rearrangement of the corresponding imine, and also by replacement of the chloro substituent from the 2-chloro compound with allylamine or propynylamine.

The structures of each 2-methyl-1,3a,7-triaza-3b-indene (III: R=H, Me) was established by comparison of its hydrochloride and dinitrate with those of a compound prepared by an unambiguous method. The method avoids alkaline conditions and thus the possibility of a Dimroth-like rearrangement of a 2-methyl triazaindene to the 2-methyl isomer.

**The Dimroth Rearrangement**

**3. Method**

The rearrangement and cyclization reaction of 1,2-dihydro-2-imino-4,6-dimethyl-1-prop-2'-ynylpyrimidine was followed by p.m.r. spectroscopy, using both deuterated and non-deuterated solvents. Decrease in height (and integral) of the peak at 4.9 T, produced by the methylene protons of the propynyl group, provided a measure of the rate of disappearance of the initial.

**Fig. C-1**
2-Allylamino- and 2-prop-2'-ynylamino-4,6-dimethylpyrimidinide were each prepared by preparative-scale rearrangement of the corresponding imine, and also by replacement of the chloro substituent from the 2-chloro compound with allylamine or propynylamine.

The structure of each 2-methyl-1,3a,7-triazaindene (III; R=H, Me) was verified by comparison of its hydrochloride and picrate with those of a compound prepared by an unambiguous method. The method avoids alkaline conditions and thus the possibility of a Dimroth-like rearrangement of a 3-methyl triazaindene to the 2-methyl isomer. 40

The Dimroth Rearrangement

a. Method

The rearrangement and cyclisation reaction of 1,2-dihydro-2-imino-4,6-dimethyl-1-prop-2'-ynylpyrimidine was followed by p.m.r. spectroscopy, using both deuterated and non-deuterated solvents. Decrease in height (and integral) of the peak at 4.9°, produced by the methylene protons of the propynyl group, provided a measure of the rate of disappearance of the initial
imine. This methylene group appeared in the spectrum of the propynylaminopyrimidine at 5.1τ and in that of the triazaiindene at 2.1τ. However the method is not sufficiently precise to allow the rate of appearance of these peaks to be measured. In deuterated solvents (NaOD, DCl) the protons of the methyl groups underwent hydrogen-deuterium exchange at such a rate as to limit their usefulness as a standard for determination of the composition of the reaction mixture. Hence the single proton at C-5 was used. In spite of the width of the absorption band due to water, the same rate was obtained using non-deuterated solvents (NaOH, HCl) and based upon the non-exchanging methyl absorptions.

Use was made of the absorption of the methylene protons, again at 4.9τ, in the determination of t_{1/2} for 1,2-dihydro-2-imino-1-prop-2'-ynylpyrimidine (I; R=H, R'=-CH₂·C≡CH). The rate of disappearance in this case may be followed with reference to the absorption peaks of the "aromatic" protons at C-4 and C-6 (0.5 to 1.4τ), and C-5 (2.1 to 2.8τ).
b. Results

The half-life of this last-mentioned imine is compared in the table, with that of 1-propyl- and 1-allyl-iminopyrimidine which were measured by Brown and Paddon-Row. As discussed in Section B, the extent of electron-withdrawal is reflected in the $pK_a$ value and also in the rate of rearrangement. This generalisation appears to apply equally well to present examples, in which the substituent alkyl group is not remote from the site of reaction. Thus the half-life of the 1-propynyl-iminopyrimidine is shorter than that of the iminopyrimidines bearing less electron-attracting groups at N-1; the $pK_a$ of the 1-propynyl-iminopyrimidine is lower than the compounds bearing less electron-attracting groups.

In considering the rearrangement of the imines bearing a propynyl group (I; $R=H$, $CH_3$, $R'=-CH_2.C:CH$) the observed half-life is that of the initial imine. Therefore adjustment must be made to allow for the simultaneous reaction which produces the bicyclic triazaindene. The ratio of isomers produced and hence of the rate of formation, allows such an adjustment to
be made. This ratio, rearranged imine to triazaindene, was 4:1 for the lower homologue, and 1:1 for the dimethyl compound. Observed $t_{1/2}$ values were 5 min. and approximately 25 mins. The net $t_{1/2}$ values for Dimroth rearrangement are therefore 6.2 and 50 mins. respectively.

As the table indicates, the rearrangement of the dimethyl-propynyl-iminopyrimidine was repeated using ultraviolet spectroscopy (previously described). Agreement between results obtained by each method is good. Thus comparisons may be made between N-1 alkyl groups and also between iminopyrimidines and those bearing two methyl groups. Electron-donation by the methyl groups is reflected in $pK_a$ values and also in $t_{1/2}$ values. Comparing the 1-allyl compounds for example, the simpler pyrimidine has a $t_{1/2}$ of 33 mins. and a $pK_a$ of 10.5; the dimethylpyrimidine has a $t_{1/2}$ of 133 mins. and a $pK_a$ of 11.2. It is also possible, in addition to the electronic effect, that the methyl group at C-6 increases the half-life by retarding closure of the acyclic intermediate. Such closure involves the (intramolecular) attack of an amine at the carbon atom of a ketone carbonyl - a reaction which is slower than
attack at the carbonyl of an aldehyde portion.

The formation of triazaindenes only, from the imines in ethanolic solution, may be interpreted as further evidence for the Dimroth rearrangement proceeding very slowly in non-aqueous media.

**P.m.r. spectra and reaction mechanisms**

Hydrogen-deuterium exchange, observed in the p.m.r. spectra of the propynyl-iminopyrimidines (I; R=HCH₃) has provided data which may be interpreted in terms of reaction mechanisms. For convenience the discussion is limited to the reactions of the non-methylated pyrimidine (I; R=H). Observations, comments and conclusions apply equally well to the homologue (I; R=CH₃).

Upon the observation that the acetylenic proton does not appear, due to rapid exchange of this acidic proton, and upon the occurrence of a signal due to methylene protons of the propynyl group, the mechanism involving attack of the imine nitrogen at the γ-carbon atom, can be discarded. Deuteration would occur as shown below, to give no signal attributable to the
propynyl group - this is contrary to observation.

assuming an initial formation of a pseudo-base, requires the mechanism:

This is consistent with the observations.
The alternative, Dimroth rearrangement, assuming an initial formation of a pseudo-base, requires the mechanism:

This is consistent with the observations.
Upon the observation that H-D exchange obscures the methyl substituent of the triazaindene, while retaining a proton of the initial methylene portion, are based the following cyclisation mechanisms:

\[
\begin{align*}
&\text{H-CH} & \rightarrow & \text{HC=C} \\
&\uparrow & \downarrow & \downarrow \\
&\text{CD} & \text{CD} & \text{CD}
\end{align*}
\]

Half-life in minutes; net values in parenthesis (see text).
Isomerisation of 1-Alkylpyrimidine-imines

<table>
<thead>
<tr>
<th>Compound</th>
<th>$t_{1/2}^\text{a}$</th>
<th>$\lambda^\text{b}$</th>
<th>$pK_a$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1,2-Dihydro-2-iminopyrimidine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-propyl</td>
<td>55$^\text{c}$</td>
<td>355</td>
<td>10.96</td>
</tr>
<tr>
<td>1-allyl</td>
<td>33$^\text{c}$</td>
<td>355</td>
<td>10.53</td>
</tr>
<tr>
<td>1-prop-2'-ynyl</td>
<td>5 (6.2)</td>
<td>-</td>
<td>10.04</td>
</tr>
<tr>
<td><strong>1,2-Dihydro-4,6-dimethylpyrimidine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-allyl</td>
<td>133</td>
<td>340</td>
<td>11.16</td>
</tr>
<tr>
<td>1-prop-2'-ynyl</td>
<td>22 (44)</td>
<td>360</td>
<td>10.41</td>
</tr>
<tr>
<td></td>
<td>25 (50)</td>
<td>-</td>
<td>10.53</td>
</tr>
</tbody>
</table>

$^\text{a}$ Half-life in minutes; net values in parenthesis (see text).

$^\text{b}$ Wavelength (m$\mu$) at which determination of $t_{1/2}$ was carried out.

$^\text{c}$ From ref. 8.

$^\text{d}$ By p.m.r. spectroscopy.
## Ionisation and Ultraviolet Spectra

### Section C

<table>
<thead>
<tr>
<th>Compound</th>
<th>pK$_a^a$</th>
<th>$\lambda_{\text{anal.}}$ (mµ)</th>
<th>$\lambda_{\text{max.}}$ (log ε)$^b$</th>
<th>pH$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pyrimidine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-propynylamino</td>
<td>2.90±0.02</td>
<td>320</td>
<td>298(3.46), 230(4.21)</td>
<td>6.0</td>
</tr>
<tr>
<td>4,6-dimethyl-2-propynylamino</td>
<td>4.42±0.04</td>
<td>310</td>
<td>292(3.62), 233(4.15)</td>
<td>7.0</td>
</tr>
<tr>
<td>2-allylamino$^d$</td>
<td></td>
<td></td>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td>2-allylamino-4,6-dimethyl</td>
<td>5.02±0.02</td>
<td>310</td>
<td>298(3.60), 237(4.18)</td>
<td>8.0</td>
</tr>
<tr>
<td><strong>1,2-dihydro-2-imino</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1-propyl$^e$</td>
<td>10.96</td>
<td></td>
<td></td>
<td>14.0</td>
</tr>
<tr>
<td>1-allyl$^e$</td>
<td>10.53</td>
<td></td>
<td></td>
<td>8.0</td>
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<tr>
<td>1-allyl-4,6-dimethyl</td>
<td>11.16±0.01</td>
<td>337</td>
<td>337(3.55), 241(4.11)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>298(3.78)</td>
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</table>
# Section C (page 2)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Value</th>
<th>Wavenumber (cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-propynyl</td>
<td>10.04±0.02</td>
<td>345, 345(3.43), 234(4.15)</td>
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<tr>
<td></td>
<td></td>
<td>305(3.62), 222(4.06)</td>
</tr>
<tr>
<td>4,6-dimethyl-1-propynyl</td>
<td>10.41±0.01</td>
<td>347, 347(3.58), 238(4.13)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>298(3.82), 225(3.91)</td>
</tr>
<tr>
<td>1,3a,7-Triazaindene</td>
<td>4.81</td>
<td></td>
</tr>
<tr>
<td>unsubst. f</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-methyl</td>
<td>5.15±0.03</td>
<td>298, 322(3.59), 290(3.46),</td>
</tr>
<tr>
<td></td>
<td></td>
<td>229(4.21)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>295(2.74), 281(3.74),</td>
</tr>
<tr>
<td></td>
<td></td>
<td>235(3.73), 219(4.21)</td>
</tr>
<tr>
<td>4,6-dimethyl f</td>
<td>5.76</td>
<td></td>
</tr>
<tr>
<td>2,4,6-trimethyl</td>
<td>6.12±0.01</td>
<td>330, 310(3.64), 285(3.67),</td>
</tr>
<tr>
<td></td>
<td></td>
<td>275(3.61), 230(4.34)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>294(3.77), 278(3.88)</td>
</tr>
</tbody>
</table>
Notes (Section C)

a Measured at 20°C by the method outlined by A. Albert and E.P. Serjeant, "Ionisation Constants of Acids and Bases", Methuen, London, 1962.

b Spectra were recorded on a Spectracord spectrophotometer, or a Shimadzu RS 27 spectrophotometer. Absorption peaks were determined on an Optica manual instrument.

c Buffers used are described by D.D. Perrin, ref. 25.

d Included for comparison purposes. See ref. 26.

e See ref. 8.

f See ref. 27.
<table>
<thead>
<tr>
<th>Compound</th>
<th>Medium</th>
<th>T-Values; J in c./sec.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrimidine</td>
<td>0.1N-DCl</td>
<td>γ-CH: 6.75t; α-CH₂: 4.90d (J =3); 5-H: 2.78m; 4- and 6-H: 1.19m</td>
</tr>
<tr>
<td>2-propynylamino</td>
<td>CDCl₃</td>
<td>γ-CH: 7.78t; α-CH₂: 5.72q (J α,NH =6; J α,γ =3); NH: 3.8s (broad); 5-H: 3.37t (J=5); 4- and 6-H: 1.58d (J=5)</td>
</tr>
<tr>
<td>4,6-dimethyl-2-propynylamino</td>
<td>CDCl₃</td>
<td>γ-CH: 7.80t; 4- and 6-Me: 7.68s; α-CH₂: 5.68q (J α,NH =6; J α,γ =3); NH: 4.4s (broad); 5-H: 3.57s</td>
</tr>
<tr>
<td>2,4,6-trimethyl</td>
<td>CDCl₃</td>
<td>γ-CH: 7.72s; α-CH₂: 5.83m (J=11); NH: 4.1s (broad); β-CH: 4.05m; 5-H: 3.60s</td>
</tr>
<tr>
<td>1,2-dihydro-2-imino</td>
<td>N-DCl</td>
<td>4-Me: 7.51s; 6-Me: 7.41s; γ-CH₂: 5.15m; β-CH: 4.08m; α-CH₂: -</td>
</tr>
<tr>
<td>Compound</td>
<td>Solvent</td>
<td>ν-CH</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>---------------</td>
<td>-------</td>
</tr>
<tr>
<td>1-propynyl</td>
<td>0.1N-DCl</td>
<td>6.75t</td>
</tr>
<tr>
<td>4,6-dimethyl-1-propynyl</td>
<td>N-DCl</td>
<td></td>
</tr>
<tr>
<td>1,3a,7-Triazaindene</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-Methyl</td>
<td>CDCl₃</td>
<td></td>
</tr>
<tr>
<td>2,4,6-trimethyl</td>
<td>CDCl₃</td>
<td></td>
</tr>
</tbody>
</table>

s = singlet,  d = doublet,  t = triplet,  q = quartet,  m = multiplet.
THE DIMROTH REARRANGEMENT

IN IMINOQUINAZOLINES
INTRODUCTION

Previous Studies - an historical outline

The rearrangement of an iminoquinazoline was reported in 1903 by Wheeler, Johnson, and McFarland. They suggested that an appropriately substituted \( \sigma \)-guanidinobenzoic acid, in sodium hydroxide or hydrochloric acid, gave 2-aminoo-3,4-dihydro-4-oxoquinazoline by rearrangement of the initial product of cyclisation 2-amino-3,4-dihydro-4-oxo-3-phenylquinazoline. However, while rearrangement does appear to have occurred, evidence for this step is not always conclusive.

Grout (1952) reported the rearrangement of 2-aminoo-3,4-dihydro-3-methyl-4-oxoquinazoline to the 2-methyllaminoquinazoline (I \( \rightarrow \) II; \( R=\text{Me} \)). The rearrangement took place during 6-hr. in boiling 10% sodium hydroxide, and was observed in the 3-ethyl, propyl, phenyl, \( \mu \)-methoxyphenyl and \( \mu \)-methoxyphenyl analogues. With the exceptions of the last compound, yields of the rearranged products were excellent. The authors suggested the formation of an \( \sigma \)-guanidinobenzoate intermediate by fission of the 3,4-bond.

Rearrangement was observed by Taylor and
Introduction

Previous Studies

The rearrangement of an iminoquinazoline was reported in 1903 by Wheeler, Johnson, and McFarland. They suggested that an appropriately substituted \( o \)-guanidinobenzoic acid, in sodium hydroxide or hydrochloric acid, gave 2-anilino-3,4-dihydro-4-oxoquinazoline by rearrangement of the initial product of cyclisation, 2-amino-3,4-dihydro-4-oxo-3-phenylquinazoline. However, while rearrangement does appear to have occurred, evidence for the structures involved is ambiguous.

Grout and Partridge (1960) reported the rearrangement of 2-amino-3,4-dihydro-3-methyl-4-oxoquinazoline to the 2-methylaminoquinazoline (I \( \rightarrow \) II; \( R=\text{Me} \)). The rearrangement took place during 8 hr. in boiling 10N sodium hydroxide, and was observed in the 3-ethyl, propyl, phenyl, \( p \)-methoxyphenyl and benzyl analogues. With the exception of the last compound, rearrangement failed to occur in aqueous dimethylformamide or in sodium hydroxide. The yields of the rearranged products were excellent. The authors suggested the formation of an \( o \)-guanidinobenzoate intermediate by fission of the 3,4-bond.

Rearrangement was observed by Taylor and
Ravindranathan\textsuperscript{14} (1962) in a study of the condensation of anthranilonitrile with phenyl isothiocyanate and with phenyl isocyanate.

Anthranilonitrile and phenyl isothiocyanate gave 4-anilino-1,2-dihydro-2-thioquinazoline (IV; \( R=\text{Ph}, \ R'=\text{H}, \ X=S \)) by a process believed to involve rearrangement of the 4-imino-3-phenyl-2-thioquinazoline (III; \( R=\text{Ph}, \ R'=\text{H}, \ X=S \)). This rearrangement took place in the molten state or in aqueous dimethyl formamide. The analogous 2-oxoquinazoline (III; \( R=\text{Ph}, \ R'=\text{H}, \ X=O \)) failed to rearrange in a variety of basic solvent systems. However when anthranilonitrile and phenyl isocyanate were heated together the rearranged product (IV; \( R=\text{Ph}, \ R'=\text{H}, \ X=O \)) was formed.

1,2,3,4-Tetrahydro-4-imino-1-methyl-3-phenyl-2-thioquinazoline (III; \( R=\text{Ph}, \ R'=\text{Me}, \ X=S \)) rearranged to the anilinoquinazoline (IV) in methanolic sodium methoxide. Rearrangement failed to occur in aqueous dimethylformamide or in sodium hydroxide. The preparation of the analogous 2-oxo compound (III; \( R=\text{Ph}, \ R'=\text{Me}, \ X=O \)) in methanolic sodium methoxide was accompanied by the formation of rearranged material (IV).
The present study has been examined in ways similar to those used for the iminopyrimidines. β-Methylation of 4-amino- and 2-amino-quinazolines gave a single product in each case. The first was 1,4-dihydro-4-imino-1-methylquinazoline which was automatically excluded from study. In the second, 2,3-dihydro-2-imino-3-methylquinazoline a methylene group was inserted indicating the possibility of such compounds for study. In view of the rapidity of

The rearrangement of some simple 2-iminoquinazolines

Thus it is known that the Dimroth rearrangement does occur in iminoquinazolines and it appears that 4-iminoquinazolines undergo fission of the 2,3-bond, whereas 2-iminoquinazolines rearrange following fission of the 3,4-bond.

4-Dihydro-4-methylimin-2-methylthiophenylquinazolines in aqueous methanol obtained hydroxide gave α-amino-3,4-dimethyl-4-oxoquinazoline. This elimination is covalent rearrangement involved nucleophilic attack at C-4 by hydroxyl ion and concomitant expulsion of methyl mercaptan.

\[
\begin{align*}
\text{I} & \quad \rightarrow \quad \text{II} \\
\text{III} & \quad \rightarrow \quad \text{IV} \\
\text{V} & \quad \rightarrow \quad \text{VI}
\end{align*}
\]
3,4-Dihydro-4-methylimino-2-methylthio-3-phenylquinazoline with aqueous methanolic sodium hydroxide gave 2-anilino-3,4-dihydro-3-methyl-4-oxoquinazoline. This hydrolytic rearrangement probably involved nucleophilic attack at C-4 by hydroxyl ion and concomitant expulsion of methyl mercaptan. Thus it is known that the Dimroth rearrangement does occur in iminoquinazolines and it appears that 4-iminoquinazolines undergo fission of the 2,3-bond, whereas 2-iminoquinazolines rearrange following fission of the 3,4-bond.

The Present Studies

The rearrangement of some simple 2-iminoquinazolines has been examined in ways similar to those used for the iminopyrimidines. N-Methylation of 4-amino- and 2-amino-quinazoline gave a single product in each case. The first was 1,4-dihydro-4-imino-1-methylquinazoline which was automatically excluded from study. The second, 2,3-dihydro-2-imino-3-methylquinazoline, rearranged to a methylaminoquinazoline indicating the suitability of such compounds for study. In view of the rapidity of
this rearrangement, it was possible to add an electron-donating substituent to pursue an aspect developed but poorly in the pyrimidine series, and at the same time to reduce the rate to a conveniently measurable value. The compounds chosen for study were the benz-substituted methoxyiminoquinazolines; in this way some interesting electronic and positional effects of the substituent could be studied.
The Rearrangement of 2,3-Dihydro-2-imino-5(6,7, or 8)-methoxy-3-methylquinazoline

see Fig. D-1

a. Site of methylation of 2- and 4-aminoquinazoline.

4-Aminoquinazoline$^{50}$, prepared from the chloro-compound$^{51}$, was heated with methyl iodide. Methylation took place at the N-1-position to give the imine (1), in contrast to the N-3-methylation which occurs with quinazoline itself. Merley and Simpson$^{53}$ showed that quaternionisation occurs at N-1 in 4-phenoxoquinazoline, in 4-anilino-6- and 7-nitro- and in 4-acetamido-6- and 7-nitroquinazoline. Similarly, Fry, Kendall, and Morgan$^{52}$ proved N-1-quaternionisation for 4-methylquinazoline and some 4-alkylchinoquinazolines. That N-1 is the site of methylation in 4-aminoquinazoline was shown to a known oxoquinazoline$^{g}$ and to 2-methylenanthranilic acid. The site of methylation was confirmed by comparison of the chemical shift of the methyl protons of selected model compounds:

### Tables of Spectra

follow page 62

Experimental Details page 77
The Rearrangement of 3,4-Dihydro-2-imino-5(6,7, or 8)-methoxy-3-methylquinazoline

see Fig. D-1

a. Site of methylation of 2- and 4-aminquinazoline.

4-Aminquinazoline, prepared from the chloro-compound, was heated with methyl iodide. Methylation took place at the N-1-position to give the imine (I), in contrast to the N-3-methylation which occurs with quinazoline itself. Morley and Simpson showed that quaternisation occurs at N-1 in 4-phenoxyquinazoline, in 4-anilino-6-and 7-nitro- and in 4-acetamido-6-and 7-nitroquinazoline. Similarly, Fry, Kendall, and Morgan proved N-1-quaternisation for 4-methylquinazoline and some 4-alkylthioquinazolines. That N-1 is the site of methylation in 4-aminquinazoline was shown by acid hydrolysis of the product to a known oxoquinazoline; hydrolysis in alkali gave N-methylanthranilic acid. The site of methylation was confirmed by comparison of the chemical shift of the methyl protons of selected model compounds:
2-Aminoquinolone, prepared from 2-aminobenzaldehyde, was heated with methyl isocyanate and the resulting product was shown to be 2,3-dihydro-2-imino-3-methylquinazolinone. Evidence for this structure consisted, in part, of comparison of the pmr spectra of the corresponding quinolinone, prepared for this purpose by methylation of 1,2-dihydro-2-oxoquinazoline.

Dihydroquinazoline CH₃-signal (δ)
in N DCl/D₂O, at δ 5.10
3-methyl-4-oxo 6.10
1-methyl-4-oxo 6.78
1-methyl-3-oxo 6.23, 5.80
1-imino-1-methyl 5.60

Acid hydrolysis proved unsuccessful; the imino-methylquinazoline was unchanged after 12 hr. at

Fig. D-1
2-Aminoquinazoline, prepared from o-aminobenzaldehyde, was heated with methyl iodide and the resulting product was shown to be 2,3-dihydro-2-imino-3-methylquinazoline (II; R=H). Evidence for this structure consisted, in part, of comparison of the p.m.r. spectra of the corresponding oxoquinazoline, prepared for this purpose by methylation of 1,2-dihydro-2-oxoquinazoline.

<table>
<thead>
<tr>
<th>Dihydroquinazoline</th>
<th>CH₃-signal (τ)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>in N DCl/D₂O</td>
<td></td>
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</tr>
<tr>
<td>3-methyl-2-oxo</td>
<td>6.18</td>
<td>55</td>
</tr>
<tr>
<td>2-imino-3-methyl</td>
<td>6.02</td>
<td></td>
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</tbody>
</table>

Acid hydrolysis proved unsuccessful: the imino-methylquinazoline was unchanged after 12 hr. at
100°C in 6N hydrochloric acid. In alkali, rearrangement took place very readily at 25°C to give 2-methylaminoquinazoline (an authentic sample of this quinazoline was prepared for comparison: treatment of 2-chloroquinazoline with methylamine gave the required compound), but in hot alkali o-aminobenzaldehyde was produced. Final proof of the structure of the imino-methylquinazoline was obtained by oxidation in sulphuric acid and hydrogen peroxide, to the known 2-amino-3,4-dihydro-3-methyl-4-oxoquinazoline, which in turn gave a known dioxoquinazoline by diazotisation, as described by Bogert and Scatchard.

The structures of the methylation products (I) and (II; R=H) are therefore established.

b. Preparation of Compounds for Rearrangement Studies.

Iminoquinazolines (II) bearing a methoxy group

* This acid-oxidation reaction was described by Armarego for the oxidation of the covalent hydrate of quinazoline cations. Thus the reaction in this case probably involves the covalent hydrate of the cation (III) as an intermediate.
on the homocyclic ring, were prepared by methylation of the appropriate 2-aminoquinazolines. 2,3-Dihydro-2-imino-5(6, and 7)-methoxy-3-methylquinazolines (II; R=5-MeO, 6-MeO, 7-MeO) were thus obtained; methylation of 2-amino-8-methoxyquinazoline was unsatisfactory.

Preparation of the 2-amino-methoxyquinazolines was achieved by the method Tsuda et al. However, because yields were low, other routes were explored. These routes were less successful in achieving their specific aim but did produce interesting compounds and reactions.

Tsuda et al have described the preparation of 2-amino-methoxyquinazolines from o-amino-methoxybenzaldehydes. These latter compounds, produced by reduction of the appropriate nitro-benzaldehydes, were obtained (in small yields) by a variety of methods. 2-Methoxy- and 3-methoxy-6-nitrobenzaldehyde were reduced in aqueous ethanol with sodium sulphide and sulphur; 3-methoxy-2-nitrobenzaldehyde was reduced in ethanol-water with sodium dithionite and sodium carbonate; 4-methoxy-2-

* The method of Hinkel et al is least unsatisfactory of the published methods to obtain the mono-nitration product.
nitrobenzaldehyde was converted to the bisulphite adduct and then treated with ferrous sulphate and sodium carbonate.

Following reduction, the crude aminobenzaldehyde was heated with guanidine nitrate and sodium carbonate in dekalin. Yields of pure 2-aminomethoxyquinazolines, were barely sufficient to allow N-methylation to be carried out.

N-Methylated products were obtained by heating the aminquinazoline with methyl iodide in a sealed tube at 130°. Lower temperatures were unsatisfactory. That methylation had occurred at the N-3-position, was confirmed by comparison of the p.m.r. spectrum with that of the known 2-imino-3-methylquinazoline, and also by the ready rearrangement in alkali to the 2-methylamino-methoxyquinazoline. Methylation of the 8-methoxyquinazoline was unsatisfactory.

Other methods of reduction were attempted, with 3-methoxy-6-nitrobenzaldehyde as an example. These

* m-Methoxybenzaldehyde was nitrated according to the method Friedlaender and Schenk. The three mono-nitro isomers were readily separated.
included aqueous sodium dithionite, cf. ref. 66; ferrous sulphate and ammonia, cf. ref. 67; tin and hydrochloric acid, cf. ref. 68; zinc and glacial acetic acid, cf. ref. 69. Each gave very small amounts of a thick oil and was less satisfactory than the method mentioned above.

A second route was explored. It was related to the production of quinazolines from 4-chloroquinazolines as reported by Armarego 73. This reaction involved the formation of a 4-(N'-toluene-p-sulphonylhydrazino)quinazoline, and subsequent alkaline hydrolysis to remove this substituent. However all attempts to prepare the required 2-amino-4-chloroquinazoline from the corresponding hydroxy (oxo) compound 85 were unsuccessful.

A third route via quinazoline-N-oxides was more satisfactory. This method was first used by Adachi 70 and subsequently by Armarego 71 in the preparation of benz-substituted quinazoline-N-oxides. The difficulty of reduction of the nitro group was avoided by the prior formation of the nitro-benzaldoxime. Hydrogenation of this (palladium on charcoal) proceeded smoothly and in good yield. Condensation of the product with triethyl orthoformate gave the quinazoline-N-oxide 71, which reacted with hydroxylamine 72 to give 2-amino-quinazoline-3-oxide.
De-oxygenation of 2-amino-6-methoxyquinazoline-3-oxide, with iron/ferrous sulphate, gave the 2-aminoquinazoline which underwent methylation with methyl iodide to give the iminoquinazoline (II; R=MeO). Other de-oxygenation methods were unsatisfactory. (Reduction with iron/ferrous sulphate, of 6-methoxyquinazoline-3-oxide to 6-methoxyquinazoline, and comparison with a sample of the compound prepared by reductive cyclisation of 5-methoxy-2-nitro-bisformamidobenzaldehyde, supported the structure.) The aminoquinazoline so prepared was identical with that prepared from the aminobenzaldehyde and guanidine; however overall yield was improved four fold. During catalytic reduction of the nitrobenzaldoxime two compounds were formed. If the reduction was terminated immediately upon completion of hydrogen uptake these compounds were formed in such proportions as to be separable. Elemental analysis of the mixture indicated that the compounds were isomeric. They are termed, in this thesis, cis- and trans-isomers* of aminobenzaldoxime.

* These terms describe the relative positions of the oxime hydroxyl and the benzene ring.
(IV, V) and were observed in each of the amino-oximes prepared. If the reduction conditions were maintained for a further period, a single isomer was isolated in quantitative yield; again if the mixture of isomers was resubmitted to the conditions of reduction, a single isomer was isolated. The factors influencing assignment of structure to each isomer (separated by elution from an alumina column with chloroform), are listed below:

**Solubility:** the trans-isomer has lower solubility in, and crystallises from, cold benzene.

**Column chromatography:** the trans-form is retained longer on the alumina than the cis.

**Infrared spectra:** the trans-form exhibits a sharp absorption at 3370 cm\(^{-1}\), markedly more intense than bands (3180, 3050 cm\(^{-1}\)). The spectrum in this region is closely similar to that of the known trans-aminobenzaldoxime. The single sharp hydroxyl absorption of trans-nitrobenzaldoxime appears at 3500 cm\(^{-1}\). Two less intense absorptions at 3420 and 3300 cm\(^{-1}\) replace this single absorption, in the cis-isomer. Such an observation is consistent with intra-molecular bond
formation in this isomer.

**p.m.r. spectra**: the chemical shift of the oxime proton in methoxy-o-aminobenzaldoximes is higher in the trans-isomers than in the cis-isomers. Such an observation was used by Kleinspehn et al. to differentiate between the isomers of various aldoximes. Deshielding in the cis-isomer, due to proximity to the "ring-current", was suggested as the reason for the absorption of the oxime proton downfield from the corresponding proton of the trans-oxime. These authors used the parameter $\delta(OH-CH)$, defined as the difference in chemical shift between the oxime proton and the benzyl proton. The difference between this parameter for cis- and trans-isomers, was found to be ca. 0.8\(\tau\). In the present cases the difference is less, being \(\not\approx\) 0.4\(\tau\). The same trend however, is apparent. It was also observed that the methoxyl protons of the cis-form appears about 0.2\(\tau\) downfield from that absorption in the trans-form.

This must be related to the change in electronic character of the ring-system, resulting from bonding between the amino and oxime groups.

**condensation reaction**: perhaps the only direct evidence
of value for structure differentiation is the product of condensation between the oxime and triethyl orthoformate. The trans-isomer gave a quinazoline-N-oxide; the N-oxide was degraded in alkali to the initial oxime. Mixtures of cis- and trans-amino-oximes gave in this way, mixtures of products, one of which was the N-oxide. Only in the unsubstituted amino-oxime did the cis-isomer produce an N-oxide. As this oxime isomerised readily at room temperature in ethanol, it is suggested that condensation took place after isomerisation to the trans-amino-oxime. The addition of a catalytic amount of copper sulphate to the condensation reaction containing mixtures of isomers was found to give excellent yields of the N-oxide alone. Condensation of a trans-amino-oxime with guanidine gives the corresponding aminoquinazoline. The cis-oximes do not undergo this reaction. The structure of the product of condensation of cis-oximes with triethyl orthoformate is still under investigation as a suspected benzoxadiazepine. cf. ref. 76.

Although the action of hydroxylamine on 6-methoxyquinazoline-3-oxide produced 2-amino-6-methoxyquinazoline-3-oxide, a similar reaction with
5, 7, and 8-methoxyquinazoline-3-oxide did not give the required 2-amino compound.

5-methoxy compound: unchanged amino-oxime was recovered (30%).

6-methoxy compound: as discussed above, the required 2-aminoquinazoline was obtained.

7-methoxy compound: treatment with hydroxylamine in alkali gave amino-oxime (30%) together with a compound identified as 4-oxoquinazoline. Alkali alone gave amino-oxime in good yield. Identification of the oxo-compound was made on the basis of melting point, absorption in the infrared at 1710 cm\(^{-1}\) (2-oxo-6-methoxy, 8-methoxy and 2-oxo-quinazoline absorb at 1690 cm\(^{-1}\), 4-oxo-quinazoline absorbs at 1710 cm\(^{-1}\)), and the single proton singlet in the p.m.r. spectrum at 0.68 ~ due to the proton at C-2 (C-4 proton singlet occurs at 0.08 ~).

8-methoxy compound: amino-oxime was recovered (80%). The structure of the N-oxide itself is not beyond doubt as the oxime (initial and recovered) appears to be of the cis-form. This doubt is based upon the criteria discussed above and also upon the difference in ultraviolet spectrum of the N-oxide and the product of cis-oxime-
triethyl orthoformate condensation.

2,3-Dihydro-2-imino-5(6, and 7)-methoxy-3-methylquinazolines were rearranged in alkali at room temperature, and the corresponding 2-methylamino-methoxyquinazolines were isolated by extraction with chloroform. The ultraviolet spectra of the methylamino products are closely similar to the spectra of corresponding aminoquinazolines. P.m.r. spectra confirmed the structures by the shift in position of the absorption of the methyl protons (see table) and also by the splitting of this absorption peak, resulting from coupling to the amino proton adjacent to the methyl group only in the rearranged product. Attempts to prepare 2-methylamino-methoxyquinazolines by alternative means were unsuccessful. The usual route through 2-chloro compounds was abandoned because chlorination of the corresponding oxo-quinazolines under a variety of conditions, gave either tars or starting material. Attempted trans-amination of 2-amino-methoxyquinazolines gave only unchanged starting material. A mechanism for the rearrangement, based on that for the rearrangement of pyrimidines (pages 9-11) may be formulated; see p.60.
The Dimroth Rearrangement

a. Method

The rearrangement of the iminoquinazolines was observed by the spectral technique outlined previously. Thus the rate of disappearance of the imine was followed as the rate of change in optical density. Rates are expressed as the parameter, $t_\frac{1}{2}$.

b. Results

The accompanying table contains details of the rates of rearrangement of the neutral species of the iminoquinazolines (pH 12.5) and also the rates obtained at higher alkalinity (pH 14).

Unlike the rearrangement of iminopyrimidines, the effect of an increase in alkalinity of the reaction medium is marked. This is particularly so for 2,3-dihydro-2-imino-3-methylquinazoline and its 6-methoxy derivative. That substitution of the homocyclic ring by a methoxy group retards the reaction is still, however, obvious. A mechanism for the rearrangement, based on that for the rearrangement of pyrimidines (pages 9 - 11) may be formulated; see p.60.
## Rearrangement Rates for Quinazoline-imines

<table>
<thead>
<tr>
<th>Compound (pK&lt;sub&gt;a&lt;/sub&gt;)</th>
<th>Half-life (mins.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pH 14 ((\lambda^a \text{ m\u})</td>
</tr>
<tr>
<td>1,2-Dihydro-2-imino-3-methylquinazoline</td>
<td></td>
</tr>
<tr>
<td>unsubst. (10.31)</td>
<td>(&lt;0.5)</td>
</tr>
<tr>
<td>5-methoxy (10.28)</td>
<td>4.8 (286)</td>
</tr>
<tr>
<td>6-methoxy (10.68)</td>
<td>5.2 (280)</td>
</tr>
<tr>
<td>7-methoxy (10.56)</td>
<td>264 (370)</td>
</tr>
</tbody>
</table>

\(a\) Wavelength at which rate of disappearance was followed.

\(b\) Correction for presence of cation is negligible.

Rate measurements suggest that the formation of the pseudo-base (I) is base catalysed except in cases where, because of the position of substituent, proximity effects or electronic effects are more important. Thus in the rearrangement of the 3-methoxy-iminoquinazoline, the tendency to rearrange is not influenced markedly by an increase in alkalinity of the reaction medium. Again,
Rate measurements suggest that the formation of the pseudo-base (I) is base catalysed except in cases where, because of the position of substituent, proximity effects or electronic effects are more important. Thus in the rearrangement of the 5-methoxy-iminoquinazoline, the tendency to rearrange is not influenced markedly by an increase in alkalinity of the reaction medium. Again,
the rearrangement of the 7-methoxyiminoquinazoline is relatively slow and base catalysis is only slight. In the former, the proximity effect, and in the latter the electronic effect, of substituent appears to override other factors.

Armarego\(^8\) has shown that the position of the methoxy group has a marked effect on the formation of a pseudo-base (covalent hydrate); electron donation by a 7-methoxy substituent tending to stabilise the anhydrous form. These results may be interpreted in the present context as inhibition of pseudo-base formation in the 7-methoxy compound (below), overriding the effect of an increase in alkalinity of the medium. In the 6-methoxy compound inhibition is lessened, that is, stability of the anhydrous form is not encouraged, and base catalysis becomes marked. The intrinsic instability of the 5-methoxyiminoquinazoline even at low alkalinity became apparent during the determination of the ionisation constant of this compound (see note to table).
### Ionisation and Ultraviolet Spectra

#### Section D

<table>
<thead>
<tr>
<th>Compound</th>
<th>( pK_a ) (^a)</th>
<th>( \lambda_{\text{anal.}} (\mu) )</th>
<th>( \lambda_{\text{max.}} (\log \varepsilon) ) (^b)</th>
<th>pH (^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2-Aminoquinazoline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>unsubst. (^d)</td>
<td>4.86</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-methoxy</td>
<td>4.88±0.04</td>
<td>260</td>
<td>355(3.40), 304(3.80), 260(4.36), 228(4.37)</td>
<td>8</td>
</tr>
<tr>
<td>6-methoxy</td>
<td>4.77±0.04</td>
<td>285</td>
<td>361(3.55), 262(3.70), 236(4.64)</td>
<td>8</td>
</tr>
<tr>
<td>7-methoxy</td>
<td>5.06±0.02</td>
<td>338</td>
<td>333(3.68), 304(3.64), 242(4.65)</td>
<td>8</td>
</tr>
<tr>
<td>8-methoxy</td>
<td>4.63±0.04</td>
<td>258</td>
<td>356(3.36), 257(4.40), 230(4.29)</td>
<td>8</td>
</tr>
<tr>
<td><strong>2-Methylaminoquinazoline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>unsubst. (^d)</td>
<td>5.02</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-methoxy</td>
<td>4.98±0.03</td>
<td>255</td>
<td>382(3.55), 267(4.07), 237(4.60)</td>
<td>8</td>
</tr>
</tbody>
</table>

\(^a\) pK\(_a\) values are for the protonation of the amino group.

\(^b\) UV spectra values are given for the maximum absorption wavelengths.

\(^c\) pH values are for the medium where the spectra were measured.

\(^d\) unsubst.: unsubstituted.
## Section D (page 2)

### 2,3-Dihydro-2-imino-3-methylquinazoline

<table>
<thead>
<tr>
<th>Substituent</th>
</tr>
</thead>
<tbody>
<tr>
<td>unsubst.</td>
</tr>
<tr>
<td>5-methoxy</td>
</tr>
<tr>
<td>6-methoxy</td>
</tr>
<tr>
<td>7-methoxy</td>
</tr>
</tbody>
</table>

### 1,4-Dihydro-4-imino-1-methylquinazoline

<table>
<thead>
<tr>
<th>Substituent</th>
</tr>
</thead>
<tbody>
<tr>
<td>unsubst.</td>
</tr>
</tbody>
</table>
Notes (Section D)

a Measured at 20°C by the method outlined by A. Albert and E. P. Serjeant, "Ionisation Constants of Acids and Bases", Methuen, London, 1962.

b Spectra were recorded on a Unicam SP800 spectrophotometer. Absorption peaks were determined on an Optica manual instrument.

c Buffers used are described by D. D. Perrin, Ref. 25.

d Included for comparison purposes. See ref. 60.

e $pK_a$ determined by D. T. Light using a rapid-reaction apparatus. See ref. 31.
### Proton Magnetic Resonance Spectra

**Section D**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Medium</th>
<th>(J) values; in (\text{c./sec.})</th>
</tr>
</thead>
<tbody>
<tr>
<td>hydroquinazoline</td>
<td>N-DC1/D(_2)O</td>
<td>(N-CH(_3)) 5.90s; 5- to 8-H: 1.6 to 2.1m;</td>
</tr>
<tr>
<td>4-imino-1-methyl</td>
<td>N-DC1/D(_2)O</td>
<td>(N-CH(_3)) 5.78s; 5- to 8-H: 1.5 to 2.1m;</td>
</tr>
<tr>
<td>1-methyl-4-oxo</td>
<td>N-DC1/D(_2)O</td>
<td>(N-CH(_3)) 6.23s; N(_1)-CH(_3)): 5.80s; 5- to 8-H: 1.3 to 2.0m;</td>
</tr>
<tr>
<td>1,3-dimethyl-4-oxo</td>
<td>N-DC1/D(_2)O</td>
<td>(N-CH(_3)) 6.10s; 5- to 8-H: 1.5 to 2.2m;</td>
</tr>
</tbody>
</table>
Section D (page 2)

2-imino-3-methyl
2-aminoguinazoline

unsubst.
5-methoxy
6-methoxy

N-DCl/D_{2}O
C_{6}D_{6}
N-DCl/D_{2}O
N-DCl/D_{2}O

N-CH_{3}: 6.02s;
N-CH_{3}: 6.18s;
N-CH_{3}: 6.03s; NH_{2}: 4.4s (broad);
N-CH_{3}: 6.06s;

5- to 8-H: 1.5 to 2.4m;
5- to 8-H: 1.7 to 2.4m;
6- to 8-H: 2.2 to 3.2m;
5-, 7-, 8-H: 2.4 to 2.9m;

4-H: 0.28s.
4-H: 0.02s.
4-H: 0.6s.
4-H: 0.87s.

O-CH_{3}: 6.03s; NH_{2}: 4.4s (broad);
O-CH_{3}: 6.06s;

5- to 7-H: 2.8 to 3.4m;
5- to 7-H: 2.8 to 3.4m;

4-H: 1.10s.
4-H: 1.10s.
<table>
<thead>
<tr>
<th>Compound</th>
<th>Solvent</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-methoxy CDC\textsubscript{3}</td>
<td>6- &amp; 8-H: 3.25m; 5-H: 2.35s (J&lt;sub&gt;ortho&lt;/sub&gt; =9); 4-H: 1.10s.</td>
<td></td>
</tr>
<tr>
<td>8-methoxy CDC\textsubscript{3}</td>
<td>6-H: 1.9s (J=9); 4-H: 0.66s.</td>
<td></td>
</tr>
<tr>
<td>5-methoxy 2N DC\textsubscript{1}/D\textsubscript{2}O</td>
<td>6-H: 1.9s (J=9); 4-H: 0.66s.</td>
<td></td>
</tr>
</tbody>
</table>

**2,3-dihydro-2-imino-3-methylquinazoline**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Solvent</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>unsubst. 2N DC\textsubscript{1}/D\textsubscript{2}O</td>
<td>N-CH: 6.0s; 4- to 8-H: 1.8 to 2.2m.</td>
<td></td>
</tr>
<tr>
<td>5-methoxy 2N DC\textsubscript{1}/D\textsubscript{2}O</td>
<td>0-CH\textsubscript{3}: 6.18s; N-CH\textsubscript{3}: 5.97s; 4-H: 0.42s.</td>
<td></td>
</tr>
<tr>
<td>6-methoxy 2N DC\textsubscript{1}/D\textsubscript{2}O</td>
<td>0-CH\textsubscript{3}: 6.02s; N-CH\textsubscript{3}: 5.95s; 5-, 7-, 8-H: 2.05 to 2.25m; 4-H: 0.66s.</td>
<td></td>
</tr>
<tr>
<td>7-methoxy 2N DC\textsubscript{1}/D\textsubscript{2}O</td>
<td>0-CH\textsubscript{3}: 6.18s; N-CH\textsubscript{3}: 5.98s; 6-, 8-H: 2.7s (broad); 5-H: 1.9d (J&lt;sub&gt;ortho&lt;/sub&gt; =9); 4-H: 0.66s.</td>
<td></td>
</tr>
</tbody>
</table>
### 2-methylaminoquinazoline

<table>
<thead>
<tr>
<th>Substitution</th>
<th>Compound</th>
<th>Solvent</th>
<th>N-CH₃</th>
<th>O-CH₃</th>
<th>NH</th>
<th>5- to 8-H</th>
<th>4-H</th>
</tr>
</thead>
<tbody>
<tr>
<td>unsubst.</td>
<td>CDCl₃</td>
<td></td>
<td>6.85d (J=5.4);</td>
<td></td>
<td>4.1s (broad);</td>
<td>2.15 to 2.85m;</td>
<td>0.88s.</td>
</tr>
<tr>
<td>5-methoxy</td>
<td>CDCl₃</td>
<td></td>
<td>7.02d (J=5.4);</td>
<td>6.18s</td>
<td>4.5s (broad);</td>
<td>2.4 to 3.0m;</td>
<td>1.18s</td>
</tr>
<tr>
<td>6-methoxy</td>
<td>CDCl₃</td>
<td></td>
<td>6.92d (J=5.4);</td>
<td>6.15s</td>
<td>4.5s (broad);</td>
<td>2.4 to 3.1m;</td>
<td>1.13s</td>
</tr>
<tr>
<td>7-methoxy</td>
<td>CDCl₃</td>
<td></td>
<td>7.06d (J=5.4);</td>
<td>6.13s</td>
<td>4.3s(broad);</td>
<td>2.4 to 3.3m;</td>
<td>1.25s.</td>
</tr>
</tbody>
</table>

s = singlet,  d = doublet,  m = multiplet.
EXPERIMENTAL DETAILS

Micro-analyses were carried out by Dr. J.E. Fildes and the staff of the Microanalysis Section at the John Curtin School of Medical Research.

Sample purity was checked on paper chromatography using as solvents butanol/acetic acid-5N (30:70) and aqueous ammonium chloride (3%).

Chromatographic separations were carried out with aluminium oxide (B.D.H. Laboratory Reagent - for Chromatographic Adsorption Analysis).

P.m.r. spectra were recorded by Mr. S. Brown on a Perkin-Elmer R10 instrument in deuteriochloroform and 33.5°C.

Internal standards used were tetramethylsilane and the sodium salt of 3(trimethylsilyl)-1-propane sulphonylic acid.

Ionisation constants were determined by the spectro-photometric method described by Albert and Serjeant (1962). Ultraviolet spectra were obtained on a Shimadzu Recording Spectrophotometer RS 27, a Spectracord Spectrophotometer and an Optica Manual Spectrophotometer.

A Unicam SP 200 Spectrometer was used to obtain infra-red spectra.

Melting points are uncorrected.
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Sample purity was checked on paper chromatography using as solvents butanol/acetic acid-5N (30:70) and aqueous ammonium chloride (3%).

Chromatographic separations were carried out with aluminium oxide (B.D.H. Laboratory Reagent - for Chromatographic Adsorption Analysis).

P.m.r. spectra were recorded by Mr. S. Brown on a Perkin-Elmer R10 instrument, at 60 Mc/sec. and 33.5°C. Internal standards used were tetramethylsilane and the sodium salt of 3(trimethylsilyl)-1-propane sulphonylic acid.

Ionisation constants were determined by the spectrophotometric method described by Albert and Serjeant (1962). Ultraviolet spectra were obtained on a Shimadzu Recording Spectrophotometer RS 27, a Spectracord Spectrophotometer and an Optica Manual Spectrophotometer.

A Unicam SP 200 Spectrometer was used to obtain infra-red spectra.

Melting points are uncorrected.
Preparation of Compounds

Section A

2- Allylamino-1,2-dihydro-1-propylypyrimidine.- 2-Allylaminopyrimidine\(^\text{20}\) (7.5 g.) was refluxed for 18 hr. with propyl iodide (19.0 g.). The oily residue from evaporation in vacuo was extracted with boiling ethyl acetate (12 x 50 ml.), and refrigeration of the concentrated extracts gave the allylaminopyrimidine hydriodide (42%), m.p. 92\(^\circ\) (from ethyl acetate) (Found: C, 38.9; H, 5.2; N, 13.7. \(\text{C}_{10}\text{H}_{16}\text{IN}\text{3}\) requires C, 39.35; H, 4.95; N, 13.8%). The picrate had m.p. 104\(^\circ\) (from water) (Found: C, 47.3; H, 4.3; N, 20.7. \(\text{C}_{16}\text{H}_{18}\text{N}\text{6O}\text{7}\) requires C, 47.3; H, 4.5; N, 20.7%).

1-Allyl-1,2-dihydro-2-propyliminopyrimidine.- 2-Propylaminopyrimidine\(^4\) (6.8 g.) was refluxed for 18 hr. with allyl bromide (12.2 g.). The resulting solid (14.3 g.) crystallised from hot concentrated ethanolic solution on dilution with hot ethyl acetate and subsequent concentration. The propyliminopyrimidine hydrobromide (89%) had m.p. 115\(^\circ\) (Found: C, 46.2; H, 6.05; N, 16.5. \(\text{C}_{10}\text{H}_{16}\text{BrN}\text{3}\) requires C, 46.5; H, 5.85; N, 16.3%). The picrate had m.p. 93\(^\circ\) (from water) (Found: C, 47.45; H, 4.6; N, 20.6. \(\text{C}_{16}\text{H}_{18}\text{N}\text{6O}\text{7}\) requires C, 47.3; H, 4.5; N, 20.7%).
2-Butylimino-1,2-dihydro-1-methylpyrimidine.—2-Butylaminopyrimidine \(^4\) was treated with methyl iodide as above. The crude product was suspended in boiling ethyl acetate (600 ml.), and ethanol (ca. 6 ml.) was added to complete solution. Concentration and prolonged refrigeration gave the butyliminopyrimidine hydriodide (54%), m.p. 134\(^{\circ}\) (Found: N, 14.4. \(\text{C}_9\text{H}_{16}\text{IN}_3\) requires N, 14.3%). The picrate had m.p. 87\(^{\circ}\) (from water) (Found: C, 45.6; H, 4.8; N, 20.9. \(\text{C}_{15}\text{H}_{18}\text{N}_6\text{O}_7\) requires C, 45.7; H, 4.6; N, 21.3%).

1-Butyl-1,2-dihydro-2-methyliminopyrimidine.—The crude dark oily hydriodide from 2-methylaminopyrimidine \(^21\) (5.4 g.) and butyliodide (18.4 g.) was characterised as the methyliminopyrimidine picrate (4.2 g.), m.p. 139\(^{\circ}\) (from water) (Found: C, 45.6; H, 4.5; N, 21.1. \(\text{C}_{15}\text{H}_{18}\text{N}_6\text{O}_7\) requires C, 45.7; H, 4.6; N, 21.13%).

Section B

3-Propylacetylacetone.—Sodium acetylacetone (0.75 mole) and propyl iodide (0.15 mole) were heated in a sealed tube for 2 hr. at 180\(^{\circ}\). The solid was removed and the liquid fractionated under reduced pressure. The product
(19%) had b.p. 108-110°/30 mm. (Literature: 90%; b.p. 191-2°/745 mm.).

The addition of ammoniacal cupric acetate to a solution of propylacetylaceton in ethanol gave a copper complex, m.p. 213° C (from benzene) (lit. 22 215°) (Found: C, 55.85; H, 7.5. Calc. for C₁₆H₂₆O₄Cu. C, 55.5; H, 7.6%).

3-Allylacetylaceton.- The liquid (61%) prepared by the method of English et al., had b.p. 110-115°/30 mm. (lit. 195-196°). Treatment with ammoniacal cupric acetate gave the copper complex, m.p. 218° (from benzene). (Found: C, 56.2; H, 6.6. C₁₆H₂₂O₄Cu requires C, 56.2; H, 6.5%).

3-(Propynyl)acetylaceton.- The above method gave a liquid fraction (57%) of b.p. 198-112°/17 mm. The yellow-green copper complex m.p. 178° had (from benzene) (Found: C, 56.5; H, 5.5. C₁₆H₁₈O₄Cu requires C, 56.9; H, 5.4%).

2-Amino-4,6-dimethyl-5-propylpyrimidine.- The method of English et al. applied to the reaction of propylacetylacetone and guanidine carbonate gave the aminopyrimidine (59%), m.p. 165-7° (from ethylacetate) (Found: C, 65.2; H, 9.2; N, 25.3. C₉H₁₅N₃ requires C, 65.4; H, 9.15; N, 25.4%).

5-Allyl-2-amino-4,6-dimethylpyrimidine.- This pyrimidine, prepared by the method of English et al. but
not analysed had m.p. 133° (52%) (from ethylacetate)
(lit. 131-134°). (Found: C, 66.3; H, 8.1; N, 26.0.
C₉H₁₃N₃ requires C, 66.2; H, 8.0; N, 25.75%).

2-Amino-4,6-dimethyl-5-(1-propynyl)pyrimidine.-
3-(2-Propynyl)acetylacetone and guanidine carbonate were
treated by the method of English et al. The crude
reaction product was recrystallised from ethanol to give
the propynylpyrimidine (29%), m.p. 214° (Found: C, 66.8;
H, 7.1; N, 26.3. C₉H₁₁N₃ requires C, 67.05; H, 6.9;
N, 26.1%).

2-Amino-4,6-dimethyl-5-(2-propynyl)pyrimidine.-
The crude reaction product from the above preparation,
and the solid obtained by evaporation of the liquours from
recrystallisation, were put onto an alumina column in light
petroleum. Elution with ether gave, as the middle fraction,
the 2-propynylpyrimidine (15%), m.p. 153° (Found: C, 66.3;
H, 7.0; N, 25.1. C₉H₁₁N₃ requires C, 67.05; H, 6.9;
N, 26.1%).

5-Allenyl-2-amino-4,6-dimethylpyrimidine.- The
above separation procedure was repeated several times on
the early fractions, which were enriched in the allenyl-
pyrimidine. The required pyrimidine (m.p. 142°) was
obtained in very small yield. (Found: N, 26.4; \( \text{C}_9\text{H}_{11}\text{N}_3 \)
requires N, 26.1%).

1,2-Dihydro-2-imino-1,4,6-trimethyl-5-propylpyrimidine.

2-Amino-4,6-dimethyl-5-propylpyrimidine (1.0 g.) and methyl
iodide (10 ml.) were heated together under reflux for 18 hr.

Dissolution of the residue from evaporation in a minimum
quantity of ethanol, followed by dilution with ethyl
acetate gave the propyliminopyrimidine hydriodide (64%)

m.p. 191\(^\circ\)C (Found: C, 39.2; H, 5.8; N, 14.0. \( \text{C}_{10}\text{H}_{18}\text{IN}_3 \)
requires C, 39.1; H, 5.9; N, 13.7%). The picrate had

m.p. 197\(^\circ\)C (Found: C, 47.2; H, 5.15; N, 20.8. \( \text{C}_{16}\text{H}_{20}\text{N}_6\text{O}_7 \)
requires C, 47.7; H, 4.9; N, 20.6%). The hydrochloride

had m.p. 243\(^\circ\)C (from ethanol) (Found: C, 55.2; H, 8.15;
N, 19.4. \( \text{C}_{10}\text{H}_{18}\text{ClN}_3 \) requires C, 55.7; H, 8.4; N, 19.5%).

5-Allyl-1,2-dihydro-2-imino-1,4,6-trimethylpyrimidine.

5-Allyl-2-amino-4,6-dimethylpyrimidine (3.2 g.) was heated
at reflux with methyl iodide (25 ml.), for 18 hr. The
mixture was then evaporated to dryness. The allylimino-
pyrimidine hydriodide (58%) had m.p. 203\(^\circ\)C (from ethanol)

(Found: C, 39.7; H, 5.4; N, 13.9. \( \text{C}_{10}\text{H}_{16}\text{IN}_3 \) requires

C, 39.3; H, 5.3; N, 13.8%). The picrate had m.p. 146\(^\circ\)
(from water) (Found: C, 47.2; H, 4.5; N, 20.5. \( \text{C}_{16}\text{H}_{18}\text{N}_6\text{O}_7 \)
requires C, 47.3; H, 4.5; N, 20.7%). The hydrochloride had m.p. 231° (from ethanol) (Found: C, 55.9; H, 7.5; N, 20.1. \[\text{C}_{10}\text{H}_{16}\text{ClN}_3\] requires C, 56.2; H, 7.55; N, 19.7%).

1,2-Dihydro-2-imino-1,4,6-trimethyl-5-(1-propynyl)pyrimidine. - 2-Amino-4,6-dimethyl-5-(1-propynyl)pyrimidine (1.0 g.) and methyl iodide (10 ml.) were heated overnight in a sealed tube, at 100°. Evaporation and recrystallisation gave the iminopyrimidine hydriodide (23%), m.p. 224° (decomp.) (from ethanol). (Found: C, 39.05; H, 4.6; N, 13.5. \[\text{C}_{10}\text{H}_{14}\text{IN}_3\] requires C, 39.6; H, 4.7; N, 13.9%). The hydrochloride had m.p. 257° (Found: C, 56.8; H, 6.4; N, 19.7. \[\text{C}_{10}\text{H}_{14}\text{ClN}_3\] requires C, 57.2; H, 6.7; N, 19.85%).

1,2-Dihydro-2-imino-1,4,6-trimethyl-5-(2-propynyl)pyrimidine. - 2-Amino-4,6-dimethyl-5-(2-propynyl)pyrimidine (1.0 g.) and methyl iodide (10 ml.) were heated in a sealed tube at 100° for 16 hr. Removal of the excess of methyl iodide by evaporation gave the 2-propynylpyrimidine hydriodide (33%), m.p. 195-196° (from ethanol - light petroleum) (Found: C, 39.8; H, 4.6. \[\text{C}_{10}\text{H}_{14}\text{IN}_3\] requires C, 39.6; H, 4.65%).

1,2-Dihydro-4,6-dimethyl-2-oxo-5-propylpyrimidine. - Propylacetylacetone (23 g.) in ethanol (82 ml.) and urea
(9.9 g.) were mixed and hydrochloric acid (10 N; 22 ml.) was added. As in the general method of Matsukawa and Ohta, the mixture was allowed to stand at room temperature for 21 days. The volume was then reduced to approximately \(\frac{1}{4}\) and water was added to give a volume of about 50 ml. Refrigeration of the neutralised solution gave the oxopyrimidine (46%), m.p. 181° (from water) (Found: C, 65.2; H, 8.5; N, 16.7. \(\text{C}_9\text{H}_{14}\text{N}_2\text{O}\) requires C, 65.0; H, 8.5; N, 16.85%).

5- Allyl-1,2-dihydro-4,6-dimethyl-2-oxopyrimidine.- The oxopyrimidine prepared as above (64%) had m.p. 176° (from water) (Found: C, 66.1; H, 7.3; N, 17.0. \(\text{C}_9\text{H}_{12}\text{N}_2\text{O}\) requires C, 65.8; H, 7.4; N, 17.1%).

1,2-Dihydro-4,6-dimethyl-2-oxo-5-(2-propynyl)pyrimidine.- The oxopyrimidine prepared as above (65%) had m.p. 231° (from water) (Found: C, 66.8; H, 6.1; N, 17.1. \(\text{C}_9\text{H}_{10}\text{N}_2\text{O}\) requires C, 66.65; H, 6.2; N, 17.3%).

2-Chloro-4,6-dimethyl-5-propylpyrimidine.- The 2-oxopyrimidine (6.6 g.) was refluxed for 10 hr. with phosphoryl chloride (40 ml.). After removal of the excess of chlorinating agent the mixture was stirred in ice for 20 min. and then made alkaline. Extraction with ether,
followed by removal of solvent gave the chloropyrimidine (73%), m.p. 56-58° (from light petroleum) (Found: C, 58.3; H, 7.0; N, 14.95. C₉H₁₃ClN₂ requires C, 58.5; H, 7.1; N, 15.2%).

5-Allyl-2-chloro-4,6-dimethylpyrimidine.- 5-Allyl-1,2-dihydro-4,6-dimethyl-2-oxopyrimidine was treated as above, with phosphoryl chloride. Final removal of solvent and distillation gave the colourless chloropyrimidine (60%), b.p. 112-118°/4 mm. (Found: C, 59.0; H, 5.8; N, 15.1. C₉H₁₁ClN₂ requires C, 59.2; H, 6.1; N, 15.3%).

2-Chloro-4,6-dimethyl-5-(2-propynyl)pyrimidine.- The chloropyrimidine (46%) prepared as above had m.p. 114° (from light petroleum) (Found: C, 59.8; H, 5.1; N, 15.3. C₉H₉ClN₂ requires C, 59.85; H, 5.0; N, 15.5%).

1,2-Dihydro-4,6-dimethyl-2-oxo-5-(1-propynyl)pyrimidine.- 2-Chloro-4,6-dimethyl-5-(2-propynyl)pyrimidine (1.5 g.) was suspended in N-sodium hydroxide (50 ml.) and heated over steam until apparently no chloro compound remained (ca. 2 hr.). A suspension of the resulting solid in water was adjusted to pH 6. The oxo-1-propynylpyrimidine (55%) had m.p. 257° (from water) (Found: C, 66.1; H, 6.1; N, 16.9. C₉H₁₀N₂O requires C, 66.65; H, 6.2; N, 17.3%).
similar treatment of 1,2-dihydro-4,6-dimethyl-2-oxo-5-
(2-propynyl)pyrimidine gave the same pyrimidine (62%).

2-Chloro-4,6-dimethyl-5-(1-propynyl)pyrimidine.—
Chlorination of the above 2-oxopyrimidine, as outlined
previously, gave the 2-chloropyrimidine (50%) having m.p.
127° (from light petroleum) (Found: C, 60.1; H, 4.8;
N, 15.2. C_9H_9ClN_2 requires C, 59.85; H, 5.0; N, 15.5%).

4,6-Dimethyl-2-methylamino-5-propylpyrimidine.—
2-Chloro-4,6-dimethyl-5-propylpyrimidine (2 g.) was heated
at 100° in a sealed tube with ethanolic methylamine (30%
w/w, 15 ml.) for 1 hr. The solution was poured into
N-hydrochloric acid (100 ml.) and adjusted to pH 7. The
methylaminopyrimidine (72%), obtained from the ether
extraction of this solution, had m.p. 114° (from light
petroleum) (Found: C, 66.9; H, 9.4; N, 23.3. C_{10}H_{17}N_3
requires C, 67.0; H, 9.6; N, 23.4%).

5-Allyl-4,6-dimethyl-2-methylaminopyrimidine.— The
2-chloropyrimidine was treated in the manner above, to give
the methylaminopyrimidine (72%), m.p. 92° (from light
petroleum) (Found: C, 68.1; H, 8.4; N, 23.5. C_{10}H_{15}N_3
requires C, 67.8; H, 8.5; N, 23.7%).

4,6-Dimethyl-2-methylamino-5-(2-propynyl)pyrimidine.—
(a) The 2-chloro-5-(2-propynyl)pyrimidine when treated with methylamine as above, gave a mixture of isomers. As described previously this mixture is composed of approximately equal parts of the isomeric 2-propynyl and alleny1 compounds. Analysis of the mixture (from light petroleum) supports this: (Found: C, 68.9; H, 7.7; N, 23.6. Calc. for C₁₀H₁₃N₃: C, 68.5; H, 7.5; N, 24.0%).

The mixture was placed on an alumina column in light petroleum, and eluted with ether. 4,6-Dimethyl-2-methylamino-5-(2-propynyl)pyrimidine (31%) was obtained from late fractions; it had m.p. 132° (Found: N, 23.6. C₁₀H₁₃N₃ requires C, 24.0%). This product failed to exhibit the n.m.r. and infrared absorptions expected of the alleny1-pyrimidine.

(b) 2-Chloro-4,6-dimethyl-5-(2-propynyl)pyrimidine was heated with aqueous methylamine which had been adjusted to pH 8.5 with acetic acid and diluted with ethanol. After one hour at 100° in a sealed tube, the reaction was treated as before, to give a mixture of isomers estimated by n.m.r. spectra to be composed of 9 parts 2-propynyl isomer and 1 part allene. Elution with ether, from an alumina column gave a compound identical with that described above.
5-Allenyl-4,6-dimethyl-2-methylaminopyrimidine.- When elution of the 1:1 mixture of isomers described above under (a), was carried out with ether at about twice the previous rate, 5-allenyl-4,6-dimethyl-2-methylaminopyrimidine, m.p. 101°, was isolated in small yield. It was identified by infrared and n.m.r. spectra (Found: N, 23.6; \( \text{C}_{10}\text{H}_{13}\text{N}_3 \) requires C, 24.0%).

4,6-Dimethyl-2-methylamino-5-(1-propynyl)pyrimidine.- 2-Chloro-4,6-dimethyl-5-(1-propynyl)pyrimidine (0.45 g.) was heated for 1 hr. at 100° in a sealed tube, with methylamine (4.0 ml.). The methylaminopyrimidine (69%) had m.p. 161° (from light petroleum) (Found: C, 68.55; H, 7.65; N, 23.85. \( \text{C}_{10}\text{H}_{13}\text{N}_3 \) requires C, 68.5; H, 7.5; N, 24.0%).

Section C

1,2-Dihydro-2-imino-1-(2-propynyl)pyrimidine.- Prepared by the method of Iwai and Hiraoka the imino-pyrimidine hydrobromide (59%) had m.p. 192-193° (lit., 195°) (from ethanol). (Found: C, 39.15; H, 3.7; N, 19.25. \( \text{C}_{7}\text{H}_{8}\text{BrN}_3 \) requires C, 39.3; H, 3.8; N, 19.6%).

1,2-Dihydro-2-imino-4,6-dimethyl-1-(2-propynyl)-pyrimidine.- 2-Amino-4,6-dimethylpyrimidine (2.4 g.) and
propynyl bromide were heated together, sealed, for 16 hr. at 100°, in a rocking furnace. The resulting iminopyrimidine hydrobromide (78%) had m.p. 203° (from ethanol) (Found: C, 44.6; H, 5.1; N, 17.4. \( \text{C}_9\text{H}_{12}\text{BrN}_3 \) requires C, 44.65; H, 5.0; N, 17.4%).

2-(2-Propynyl)aminopyrimidine. The above iminopyrimidine hydrobromide (1 g.), in N-potassium hydroxide solution (9 ml.) was allowed to stand at room temperature for one day. The propynylaminopyrimidine which separated (71%) had m.p. 108° (lit. 108-109°) (Found: C, 62.6; H, 5.7; N, 31.2. Calc. for \( \text{C}_7\text{H}_7\text{N}_3 \): C, 63.1; H, 5.3; N, 31.6%).

2-Methyl-1,3a,7-triazaindene. 1,2-Dihydro-2-imino-1-(2-propynyl)pyrimidine hydrobromide (0.5 g.) in ethanol (20 ml.) was treated, as described by Iwai and Hiraoka, with sodium ethoxide to give the triazaindene (67%) having m.p. 89-91° (lit. 89-90°) (from hexane-ethanol). The same triazaindene (16%) was obtained from the aqueous liquors of the preparation of 2-(2-propynyl)aminopyrimidine by evaporation and subsequent extraction with benzene and ether (Found: C, 62.8; H, 5.3; N, 31.2. Calc. for \( \text{C}_7\text{H}_7\text{N}_3 \): C, 63.1; H, 5.3; N, 31.6%).
4,6-Dimethyl-2-(2-propynyl)aminopyrimidine.- 1,2-Dihydro-4,6-dimethyl-2-imino-1-(2-propynyl)pyrimidine hydrobromide was treated with aqueous potassium hydroxide as above. The solid obtained by evaporation of the reaction mixture, was adsorbed on an alumina column. Elution with ether gave the propynylaminopyrimidine, m.p. 119°, after sublimation at 70°/0.05 mm. (Found: C, 66.9; H, 6.8; N, 26.3. \( \text{C}_5\text{H}_{11}\text{N}_3 \) requires C, 67.0; H, 6.9; N, 26.1%).

2,4,6-Trimethyl-1,3a,7-triazaindene.- Treatment of the appropriate iminopyrimidine hydrobromide with sodium ethoxide as outlined previously, gave the trimethyltriazaindene (78%), m.p. 151° (from water) (Found: C, 67.25; H, 6.9; N, 25.7. \( \text{C}_9\text{H}_{11}\text{N}_3 \) requires C, 67.05; H, 6.9; N, 26.1%). An identical product was obtained by eluting from the alumina column (above) with chloroform.

It was found that treatment of 1,2-dihydro-2-imino-4,6-dimethyl-1-(2-propynyl)pyrimidine hydrobromide with potassium hydroxide gave a mixture composed of the triazaindene (53%) and the propynylaminopyrimidine (47%).

1-Allyl-1,2-dihydro-2-imino-4,6-dimethylpyrimidine.- 2-Amino-4,6-dimethylpyrimidine (0.8 g.) was refluxed for 4 hr. with allyl iodide (6 ml.). The residue from evaporation was dissolved in ethanol (30 ml.). Dilution
with ether gave the **iminopyrimidine hydriodide**, m.p. 184-186° (Found: C, 36.7; H, 4.8; N, 14.2. C$_9$H$_{14}$IN$_3$ requires C, 37.1; H, 4.85; N, 14.4%).

2-**Allylamino-4,6-dimethylpyrimidine**.- 2-Chloro-4,6-dimethylpyrimidine (2.0 g.) in ethanol (20 ml.), and allylamine (10 ml.), were heated over steam for 4 hr. Ethanolic sodium ethoxide was added (from 0.5 g. sodium) and the mixture was evaporated to dryness. Extraction with ether and removal of solvent gave the **allylaminopyrimidine** (78%), m.p. 73° (from light petroleum) (Found: C, 66.5; H, 8.0; N, 25.5. C$_9$H$_{13}$N$_3$ requires C, 66.2; H, 8.0; N, 25.75%).

Section D

2-**Amino-methoxybenzaldoximes**.- The nitro-oximes (1.0 g.) were hydrogenated with 5% palladium-charcoal (0.25 g.) in ethanol (100 ml.) at 1 atm. When two products were formed (see text) separation was achieved on an alumina column, eluting with chloroform. Early fractions contained **cis**-compounds, later fractions contained the **trans**-isomers. Each isomer was crystallised from water or ethanol.
Benzaldoxime m.p. (lit.) % Yield Analysis(%) *

<table>
<thead>
<tr>
<th>Compound</th>
<th>M.p. °C</th>
<th>Yield</th>
<th>C</th>
<th>H</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-methoxy (cis)</td>
<td>145°</td>
<td>40</td>
<td>57.5</td>
<td>6.1</td>
<td>16.3</td>
</tr>
<tr>
<td>3-methoxy (trans)</td>
<td>142°(140°)</td>
<td>&lt;5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-methoxy (cis)</td>
<td>62</td>
<td>57.8</td>
<td>6.2</td>
<td>17.0</td>
<td></td>
</tr>
<tr>
<td>4-methoxy (trans)</td>
<td>145°(143°)</td>
<td>62</td>
<td>57.8</td>
<td>6.2</td>
<td>17.0</td>
</tr>
<tr>
<td>5-methoxy (cis)</td>
<td>142°</td>
<td>20</td>
<td>58.1</td>
<td>6.2</td>
<td>17.0</td>
</tr>
<tr>
<td>5-methoxy (trans)</td>
<td>118°(150°)</td>
<td>53</td>
<td>57.8</td>
<td>6.0</td>
<td>16.85</td>
</tr>
<tr>
<td>6-methoxy (cis)</td>
<td>189-91°</td>
<td>&lt;5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-methoxy (trans)</td>
<td>186°(115-16°)</td>
<td>73</td>
<td>58.2</td>
<td>6.3</td>
<td>17.1</td>
</tr>
</tbody>
</table>

*C₈H₁₀N₂O₂ requires C, 57.8; H, 6.1; N, 16.9%.

2-Amino-methoxyquinazolines.—2-Amino-methoxybenzaldehyde (1.0 g.) was refluxed for 30 min. in dekalin (20 ml.) with guanidine nitrate (2.0 g.) and sodium carbonate (0.8 g.). The precipitate from the decanted dekalin was treated as described by Tsuda et al.⁷⁹ Yields 25-35%

<table>
<thead>
<tr>
<th>Aminoquinazoline</th>
<th>Analysis(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
</tr>
<tr>
<td>5-methoxy</td>
<td>61.8</td>
</tr>
<tr>
<td>6-methoxy</td>
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<tr>
<td>7-methoxy</td>
<td>61.2</td>
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<tr>
<td>8-methoxy</td>
<td>60.9</td>
</tr>
<tr>
<td>Calc. for C₉H₉N₃O₂:</td>
<td>61.7</td>
</tr>
</tbody>
</table>
2,3-Dihydro-2-imino-5(6 and 7)-methoxy-3-methylquinazoline.—

Each 2-amino-methoxyquinazoline (0.2 g.) was heated with methyl iodide (5 ml.) for 2 hr. at 130° in a sealed tube. The hydriodide obtained was recrystallised. Yields 30-40%.

<table>
<thead>
<tr>
<th>Derivative</th>
<th>m.p. (solvent)</th>
<th>Analysis(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>C  H  N</td>
</tr>
<tr>
<td>5-methoxy</td>
<td>259-62° (cellosolve)</td>
<td>37.9 3.7 12.6</td>
</tr>
<tr>
<td>6-methoxy</td>
<td>225° (ethanol)</td>
<td>38.1 3.5 13.2</td>
</tr>
<tr>
<td>7-methoxy</td>
<td>278-80° (ethanol)</td>
<td>37.3 3.9 12.6</td>
</tr>
</tbody>
</table>

* C_{10}H_{12}IN_{3}O requires 37.9 3.8 13.2

2-Methylamino-methoxyquinazolines.— The above hydriodide was allowed to stand in 2N-potassium hydroxide for 1 hr. After extraction with chloroform and removal of this solvent, the methylaminoquinazoline was isolated as its picrate.

<table>
<thead>
<tr>
<th>Methylaminoquinazoline (picrate)</th>
<th>m.p. (solvent)</th>
<th>Analysis(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-methoxy</td>
<td>253° (cellosolve)</td>
<td>45.8 3.3 19.8</td>
</tr>
<tr>
<td>6-methoxy</td>
<td>249° (ethanol)</td>
<td>45.8 3.2 20.1</td>
</tr>
<tr>
<td>7-methoxy</td>
<td>245° (ethanol)</td>
<td>45.6 3.2 19.9</td>
</tr>
</tbody>
</table>

* C_{16}H_{14}O_{8}N_{6} requires 45.9 3.4 20.1

6-methoxy (free base) 156° (methanol) 63.3 5.9 22.6

* C_{10}H_{11}ON_{3} requires 63.5 5.9 22.2
2,3-Dihydro-2-imino-3-methylquinazoline.- 2-
Aminoquinazoline (0.5 g.), in ethanol (5 ml.) was
heated, sealed, for 3 hr. at 100°C, with methyl iodide
(5 ml.). The iminoquinazoline hydriodide (47%) had
m.p. 259°C (from ethanol) (Found: C, 37.9; H, 3.6;
N, 14.7. C₉H₈IN₃ requires C, 37.65; H, 3.5;
N, 14.6%).

2-Methylaminoquinazoline.- The product obtained by
treatment of the above iminoquinazoline with 2N-
potassium hydroxide (as described above) was identical
to that prepared by the method of Armarego and Smith⁶⁰.

1,4-Dihydro-4-imino-1-methylquinazoline.- 4-
Aminoquinazoline (0.5 g.) in ethanol (5 ml.) and with
methyl iodide (5 ml.), were heated at 100°C for 3 hr.
in a sealed tube. The iminoquinazoline hydriodide
(34%) had m.p. 252°C (from ethanol) (Found: C, 37.25;
H, 3.4; N, 14.6. C₉H₁₀IN₃ requires C, 37.65; H, 3.5;
N, 14.6%).

2-Amino-6-methoxyquinazoline-3-oxide.- 6-
Methoxyquinazoline-3-oxide (2.0 g.) was heated at
140°C for 30 min. with hydroxylamine hydrochloride
(3.3 g.) in 2.5N-sodium hydroxide (44.5 ml.). The
solid which formed was removed by filtration and 
recrystallised from 20% aqueous acetic acid. The 
2-aminoquinazoline-3-oxide (20%) had m.p. 271°. 
The filtrate, adjusted to pH 6 gave 2-amino-5-
methoxy-trans-benzaldoxime (60%). (Found: C, 56.4; 
H, 4.9; N, 21.8. C₉H₉N₃O₂ requires C, 56.5; H, 4.75; 
N, 22.0%).

2-Amino-6-methoxyquinazoline.— The quinazoline-N-
oxide (0.5 g.) described above, was heated for 8 hr. 
with iron powder (3 g.) and ferrous sulphate (0.15 g.) 
in aqueous ethanol (15 ml. water; 60 ml. ethanol). 
Evaporation of the solvent after filtration, gave a 
solid (93%) which was identical to the 2-amino-6-
methoxyquinazoline prepared by other methods (above).
Determination of Equilibrium Ratios by P.m.r. Spectroscopy

Section A

The 1-alkyl-2-alkylimino-1,2-dihydropyrimidine hydrohalide (1 part) was mixed in each of several tubes, with N-sodium deuteroxide (5 parts). The solutions of free base were kept at 25° with continuous shaking. At intervals of 0 to 48 hr. the contents of a tube were acidified with aqueous 10N-deuterium chloride (1 part) and the p.m.r. spectrum was recorded.

For 1-butyl-1,2-dihydro-2-methyliminopyrimidine and its isomer, the disappearance and appearance, respectively, of the peak at 6.8 ~ due to the methylimino protons, was followed in terms of the three "aromatic" proton multiplets centred at 1.1, 1.7 and 2.9 ~. After 18 hr. background complexity became so marked that further measurement was meaningless.

For 1-allyl-1,2-dihydro-2-propyliminopyrimidine and its isomer, the disappearance and appearance, respectively, of the triplet centred at 6.3 (due to the α-methylene of the propylimino group) was measured in terms of the "aromatic" proton multiplets.
Determination of Half-lives

a. Ultraviolet spectroscopy

Sections B, C and D

The method used for the determination of the rate of rearrangement ($t_{1/2}$) of iminopyrimidines (Sections B and C), and of iminoquinazolines (Section D), by observing the rate of change of optical density, has been described in detail for a specific example in Section B. Values of $t_{1/2}$ and the wavelength at which they were obtained, are contained in the table within each Section.

b. P.m.r. spectroscopy

A solution of the 1-propynyliminopyrimidine hydrobromide (1 part) in deuterium oxide (5 parts) was kept at precisely 25°C. 3N-Sodium deuteroxide (0.2 ml.) was added to a sample (0.5 ml.) of this solution, and the reaction was allowed to proceed at 25°C for a prescribed time. After acidifying with 10N-deuterium chloride (8 drops) the p.m.r. spectrum was recorded.

For 1,2-dihydro-2-imino-1-propynylpyrimidine, the time required for a decrease to half the initial concentration ($t_{1/2}$ or half-life) was determined from
the rate of disappearance of the peak at 4.9\texttau. This peak was assigned to the methylene protons of the propynyl group. Its contribution to the spectrum was measured by comparison with peaks in the region 0.9 to 1.4\texttau (due to the two protons of positions 4 and 6 in the pyrimidine ring), and with the absorption in the region 2.1 to 2.8\texttau, representing the C-5 proton.

For 1,2-dihydro-4,6-dimethyl-2-imino-1-propynlypyrimidine the rearrangement and cyclisation reactions were followed using both deuterated and non-deuterated solvents. In deuterated solvents the disappearance of the methylene absorption at 4.9\texttau was followed in terms of the proton absorption at 2.9\texttau (the C-5 proton). Under these conditions the rapidity of deuterium exchange at the 4 and 6 methyl groups prevents use of absorption due to these groups, as a reference. In non-deuterated solvents, interpretation is complicated by the wide water-band.

The result obtained by the above method was verified by the determination carried out using ultraviolet spectroscopy (see table).
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