Abstract of Thesis.

The use of purine and folic acid antagonists in Cancer Chemotherapy is reviewed and discussed and the syntheses of some potential purine and folic acid antagonists are recorded. Synthetic methods for the preparation of the pyrimido-(4:5,b)-pyrazine (pteridine) ring system are reviewed with particular reference to the unambiguous synthesis of substituted pteridines. The preparation of 7-amino-6-arylpteridines and 7-hydroxy-6-arylpteridines by the condensation of 4-amino-5-nitrosopyrimidines with arylacetonitriles and arylacetyl chlorides respectively is reported; thus, providing a new and unambiguous method for the synthesis of these compounds. Pteridines with an amino group in the pyrazine portion of the nucleus have not previously been described. The structure of these compounds is confirmed by their physical and chemical properties. Some of the 7-amino-6-arylpteridines have been shown to be antagonists of folic acid when tested microbiologically but none of the compounds tested had any chemotherapeutic effect on the Walker Rat Carcinoma. 2:4:7-Triamino-6-phenylpteridine is of interest, however, in that it causes hypertrophy of the kidney.

The second part of the thesis is concerned with the preparation and reactions of quaternary salts from 2-chloro-5-nitropyrimidines. It is shown that 2:4-dichloro-5-nitropyrimidines react with 2-aminopyridines to yield
quaternary salts involving the 2-chloro-group of the pyrimidine ring and the cyclic nitrogen atom of the 2-aminopyridine moiety; the 4-chloro group reacts normally with the amino group of 2-aminopyridine. The formation of this type of quaternary salt is a novel reaction in the pyrimidine series and indicates a difference in reactivity between 2- and 4-chloro groups in 2:4-dichloro-5-nitopyrimidines. Several 2-chloro-5-nitropyrimidines have been shown to form quaternary salts of the above type with 2-aminopyridine and pyridine, but with isoquinoline a different reaction occurs to give 1:2 disubstituted 1:2-dihydro-isoquinolines. The reaction of the quaternary salts formed in the above reaction with ammonia, amines, alcohols and phenols is described and in this way new 2-amino, 2-substituted-amino, alkoxy- and aryloxy-4-(2'-pyridyl)-amino-5-nitro pyrimidines have been prepared. The reaction of these quaternary salts with amines and hydroxy compounds is discussed with a view to elucidating the reaction mechanism.

By reduction of the 5-nitro group of these derived pyrimidines several substituted 5-aminopyrimidines have been prepared and converted to the corresponding pyrimidotriazoles and dihydropteridines. The former, which are potential purine antagonists, have been tested for chemotherapeutic action on the Walker Rat Carcinoma but are inactive.
THESIS
RESEARCHES IN PYRIMIDINE CHEMISTRY
submitted for the degree of
SOME POTENTIAL FURINE AND FOLIC ACID ANTAGONISTS
DOCTOR OF PHILOSOPHY
in the
UNIVERSITY OF LONDON
by
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Institute for Cancer Research,
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RESEARCHES IN PYRIMIDINE CHEMISTRY:

I should like to record my thanks to

SOME POTENTIAL PURINE AND FOLIC ACID ANTAGONISTS

by

Robert Geoffrey William Spickett

1952
I should like to express my thanks to Dr. W.C.J. Ross and also to the late Professor G.A.R. Kon, F.R.S., for many helpful discussions; to Doctors R.N. Beale and E.M.F. Roe for the measurements of the ultraviolet spectra recorded in this work. I should especially like to record my grateful appreciation for the help, criticism and guidance given by my supervisor, Mr. G.M. Timmis, M.Sc.

R.G.W. Spickett
## Errata

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| 76   | 5    | After Barrow and Thorneycroft insert (J. 1939, 769). |
| 78   | 11   | For change read change. |
| 99   | 6    | For dihydropyridinopurine read pyridinopyridinopurine. |
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It has become a well-established principle in chemotherapy that slight modifications in the chemical structure of an essential metabolite of the organism to be attacked may lead to entirely chemotherapeutically effective, the structural analogues (anti-metabolites) usually exhibit these effects by means of deficiency of the metabolites in which they were metabolically involved, and hence show biologically, comparatively, in animals. Many examples of the structural analogues have proved anti-metabolites, and of their action, have been reviewed by Medley (Nature, 1937, p. 307), Medley et al. (J. Biol. Chem., 1940, p. 412), Klenk and Medley (J. Biol. Chem., 1940, p. 412), and Klenk (Proc. Soc. Exp. Biol. and Med., 1941, p. 502).

The close relation of the sulfanilamide group to be assigned a structure was the basis of many patents, which was shown by Angier et al. (J. Biol. Chem., 1933, p. 407) to be I22, \( \text{I22} = \text{NHCONH} - \text{(CONH)}_2 \). The close relation to the sulfanilamide group and properties of the sulfanilamide group and analogues has been adequately reviewed, e.g. by J. E. Ball and R. J. Silver (J. Biol. Chem., 1933, p. 407), J. Biol. Chem., 1940, p. 412, and J. Biol. Chem., 1940, p. 412).
It has become a well established principle in chemotherapy that slight modifications in the chemical structure of an essential metabolite of the organism to be attacked may lead to active chemotherapeutic agents. The structural analogues (anti-metabolites) usually exhibit their effects by signs of deficiency of the metabolite to which they bear structural resemblance when tested microbiologically, enzymatically or in animals. Many examples of the structural changes which produce anti-metabolites, and of their effect, have been reviewed by Woolley (*Physiol. Reviews*, 1947, 27, 308), Woolley et al. (*Ann. N.Y. Acad. Sci.*, 1950, 52, 1197-1378) and Woolley (*A Study of Anti-metabolites*, Wiley, New York, 1952).

The first factor of the folic acid group to be assigned a structure was the liver *L. casei* factor, which was shown by Angier et al. (*Science*, 1946, 103, 667) to be (I, \( R = \text{NHCH}(\text{CO}_2\text{H})\text{CH}_2\text{CH}_2\text{CO}_2\text{H} \)). The literature relating to the isolation, synthesis and properties of the folic acid group and analogues has been adequately reviewed, viz. Jukes and Stokstad (*Physiol. Reviews*, 1949, 28, 51; *Ann. Rev. Biochem.*, 1949, 19, 458), Simpson (*Ann. Reports Chem.*
The study of the relationship between folic acid and its related anti-metabolites in microbiological systems has provided an indication that it is concerned in the production of pyrimidines, purines and nucleic acids; see for example Hitchings et al. (Ann. N.Y. Acad. Sci., 1950, 52, 1318). Purines and pyrimidines are important constituents of nucleic acids and are involved in the biosynthesis of nucleic acids. These biosynthetic processes appear to differ significantly in normal and in malignant tissue and thus compounds which inhibit the utilisation of purines and pyrimidines or inhibit the part that the folic acid complex plays in their utilisation, might conceivably cause greater inhibition of malignant than of normal growth. Drugs which could exert this type of anti-metabolite action have, in fact, shown some effect on malignant tissue (vide infra). The types of compound that have been studied fall into two distinct classes. The first are folic acid analogues and the second, which also comprise more or less complex derivatives of pyrimidine, may have anti-folic activity
or anti-pyrimidine or anti-purine activity or may, in particular cases, show two or more of these effects.

As the full chemical name of the liver L. casei factor (I), viz. \(N-(4-[\{(2\text{-amino-4-hydroxy-6-pteridyl)}\}\text{-methyl\text{-amino\text{-benzoyl\text{-L-glutamico}}}} acid \) is too cumbersome for general use compounds of this type are described as derivatives of pteroyl acid (II), \( (R_1 = \text{OH}; \ R_2 = R_3 = R_4 = \text{H}; \ R_5 = \text{OH}) \). Thus the liver L. casei factor is pteroylglutamic acid (more accurately \(N\text{-pteroyl\text{-L-glutamic acid}}\)).
Analogues of pteroylglutamic acid have been prepared by replacement of one or more substituent groups. For example, the introduction of a methyl group into certain positions of the molecule has been effective in producing inhibitors. Thus, 7-methylpteroylglutamic acid (II, \( R_1 = \text{OH}, R_2 = \text{Me}, R_3 = R_4 = \text{H}, R_5 = \text{NHCH(CO}_2\text{H})\text{CH}_2\text{CH}_2\text{CO}_2\text{H} \)), which is prepared by replacing 2:3-dibromopropionaldehyde by 2:3-dibromobutyraldehyde in the general synthesis of folic acid (see later), is a competitive inhibitor of folic acid both microbiologically and in animals (Martin, Tolman and Moss, Arch. Biochem., 1947, 12, 318; Franklin et al., Proc. Soc. Exp. Biol. Med., 1947, 65, 368; idem, J. Biol. Chem., 1947, 162, 427).

9-Methylpteroylglutamic acid (II, \( R_1 = \text{OH}, R_2 = R_4 = \text{H}, R_3 = \text{Me}, R_5 = \text{NHCH(CO}_2\text{H})\text{CH}_2\text{CH}_2\text{CO}_2\text{H} \)), 10-methylpteroylglutamic acid (II, \( R_1 = \text{OH}, R_2 = R_3 = \text{H}, R_4 = \text{Me}, R_5 = \text{NHCH(CO}_2\text{H})\text{CH}_2\text{CH}_2\text{CO}_2\text{H} \)) and 9:10-dimethylpteroylglutamic acid (II, \( R_1 = \text{OH}, R_2 = \text{H}, R_3 = R_4 = \text{Me}, R_5 = \text{NHCH(CO}_2\text{H})\text{CH}_2\text{CH}_2\text{CO}_2\text{H} \)) have also been found to be antagonists of folic acid (Shrive et al., J. Amer. Chem. Soc., 1949, 71, 3852; Cosulich and Smith, ibid., 1948, 70, 1922;...
Replacement of the glutamic acid residue of pteroylglutamic acid by aspartic acid to give pteroylaspartic acid (I, \( R_1 = \text{CH}, \ R_2 = R_3 = R_4 = \text{H} \), \( R_5 = \text{NHCH(CO}_2\text{H})\text{CH}_2\text{CO}_2\text{H} \)) is effective in producing an antagonist of folic acid. The inhibition produced by this compound is reversed by the addition of pteroylglutamic acid and pteroylgulutamic acid (Hutchings et al., *J. Biol. Chem.*, 1947, 170, 323).

Further analogues of pteroylgulutamic acid have been obtained by replacing the hydroxy- group in the 4-position of the pteridine nucleus by an amino- group, when the "4-aminopteryglutamic acids" were obtained.

4-Aminopteroylglutamic acid (II, \( R_1 = \text{NH}_2 \), \( R_2 = R_3 = R_4 = \text{H} \), \( R_5 = \text{NHCH(CO}_2\text{H})\text{CH}_2\text{CH}_2\text{CO}_2\text{H} \)), obtained by treating 2:4:5:6-tetra-aminopyrimidine with 2:3-dibromopropionaldehyde and L-glutamic acid (Seeger, Smith and Hultquist, *J. Amer. Chem. Soc.*, 1947, 69, 2567), was a potent antagonist of pteroylgulutamic acid and its inhibitory action was only partially reversed by the addition of pteroylgulutamic acid (Franklin, Stokstad and Jukes, *Proc. Soc. Exp. Biol. Med.*, 1948, 67, 399). Other folic acid antagonists have been obtained by replacing the
4-hydroxy-group by an amino-group in the various homologues of folic acid.

Pyrimidine derivatives, which have been found to be folic acid, pyrimidine or purine antagonists, cover several classes of compounds, e.g. simple pyrimidines, purines, pteridines and pyrimidotriazoles.

Simple pyrimidines which have been found to inhibit the growth of L. casei include analogues of thymine (III, \( R = \text{Me} \)) such as 5-amino- (III, \( R = \text{NH}_2 \)), 5-hydroxy- (III, \( R = \text{OH} \)), 5-bromo- (III, \( R = \text{Br} \)) and 5-nitouracil (III, \( R = \text{NO}_2 \)). Of these compounds 5-bromouracil appears to be a thymine antagonist, 5-nitouracil is primarily a folic acid antagonist and the inhibitory action of 5-amino­ uracil may be overcome by either thymine or folic acid (Hitchings et al., Ann. N.Y. Acad. Sci., 1950, 52, 1318). These authors also found that nearly all 2:4-diamino­pyrimidines and their condensed ring derivatives were growth inhibitors of L. casei (Hitchings et al., loc. cit.; J. Biol. Chem., 1948, 174, 765).

Hitchings et al. (loc. cit.) have noted that various derivatives of 2:4-diaminopyrimidine may be classified as antagonists of pteroylglutamic acid or purines.
according to their structures. Thus the growth inhibiting action on L. casei of 2:4-diamino-6:7-dimethylpteridine was reversed by folic acid, whilst 5:7-diaminopyrimidotriazole (IV) and 2:6-diaminopurine (V) were primarily purine antagonists.

Several 2:4-diaminopteridine derivatives were found by Daniel et al. (J. Biol. Chem., 1947, 169, 689) to inhibit the growth of several species of micro-organism; this inhibition was reversed by folic acid. The active compounds were 2:4-diamino-6:7-dimethyl- (VI, $R_1 = R_2 = \text{CH}_3$), 2:4-diamino-6:7-diphenyl- (VI, $R_1 = R_2 = \text{Ph}$) and 2:4-diamino-6:7-dicarboxypteridine (VI, $R_1 = R_2 = \text{CO}_2\text{H}$).
Daniel et al. (J. Biol. Chem., 1948, 173, 123) also showed that 2-amino-4-hydroxy-6:7-diphenylpteridine (VII, \( R_1 = R_2 = \text{Ph} \)) and 2-amino-4-hydroxy-6:7-dimethyl-pteridine (VII, \( R_1 = R_2 = \text{Me} \)) inhibited growth and haemoglobin formation in chicks.

Purine antagonists were obtained by Roblin et al. (J. Amer. Chem. Soc., 1945, 67, 290) by replacing the 8-carbon atom in the ring of the purine nucleus by a nitrogen atom. Thus the guanine analogue, 5-amino-7-hydroxytriazole-(d)-pyrimidine (VIII, \( R_1 = \text{NH}_2 \), \( R_2 = \text{OH} \)) inhibited the growth of E. coli, the inhibition being overcome by purines, guanine being superior to other purines for restoration of growth. Hitchings et al. (Ann. N.Y. Acad. Sci., 1950, 72, 1318) found that similar effects could be obtained when L. casei was the test organism and they further found that corresponding diamino- (VIII, \( R_1 = R_2 = \text{NH}_2 \)) and dihydroxy- (VIII, \( R_1 = R_2 = \text{OH} \)) analogues had little specificity for individual purines.
A large number of pyrimidines, pteridines, purines and folic acid analogues were tested as tumour inhibitors by Burchenal et al. (Proc. Soc. Exp. Biol. Med., 1949, 71, 381). Of the compounds tested only 4-aminopteroylglutamic acid (II, \( R_1 = NH_2, R_2 = R_3 = R_4 = H, R_5 = NHCH(CO_2H)CH_2CH_2CO_2H \)), 4-amino-10-methylpteroylglutamic acid (II, \( R_1 = NH_2, R_2 = R_3 = H, R_4 = Me, R_5 = NHCH(CO_2H)CH_2CH_2CO_2H \)), 9:10-dimethylpteroylglutamic acid (II, \( R_1 = OH, R_2 = H, R_3 = R_4 = Me, R_5 = NHCH(CO_2H)CH_2CH_2CO_2H \)) and 2:6-diaminopurine (IV) were found to have any effect in inhibiting a transplantable mouse leukemia. Stock et al. have studied the effect of these compounds and of 4-aminopteroylaspartic acid (II, \( R_1 = NH_2, R_2 = R_3 = R_4 = H, R_5 = NHCH(CO_2H)CH_2CO_2H \)) on several experimental tumours and have shown that some tumours are markedly inhibited by these compounds, whereas others are not affected. They have also shown that these compounds are very toxic (cf. Philips et al., Ann. N.Y. Acad. Sci., 1950, 52, 1349) and effects on tumours cannot be obtained without these toxic effects becoming apparent in the host.

The triazolopyrimidines (VIII, \( R_1 = NH_2, R_2 = OH \))
was found to inhibit the growth of a transplantable mouse leukemia (Stock et al., Proc. Soc. Exp. Biol. Med., 1949, 72, 565) and a mammary sarcoma (Sugiura et al., Cancer Research, 1950, 10, 178). However, Stock et al. (Proc. Soc. Exp. Biol. Med., 1949, 72, 565) found that the triazolopyrimidines (VIII, $R_1 = \text{NH}_2$, $R_2 = \text{OH}$), (VIII, $R_1 = R_2 = \text{NH}_2$) and (VIII, $R_1 = R_2 = \text{OH}$) were without effect on sarcoma 180 in mice. 4-Aminopteroylglutamic acid, 4-amino-10-methylpteroylglutamic acid and pteroyl-aspartic acid, however, were effective in inhibiting the growth of sarcoma 180 in mice (Moore et al., Proc. Soc. Exp. Biol. Med., 1949, 72, 396, Sugiura et al., Cancer, 1949, 2, 491).

The search for potential folate acid or purine antagonists has been pursued, since the most active antagonists are too toxic to be of practical value (cf. Stock et al., Ann. N.Y. Acad. Sci., 1950, 72, 1360). The compounds described in the first part of this thesis are simple derivatives of pteridine which have been obtained by a novel, unambiguous method. 7-Amino-6-arylpteridines have been prepared from 4-amino-5-nitrosopyrimidines and aryl-acetonitriles, and 7-hydroxy-6-arylpteridines have been
prepared by the action of arylacetyl chlorides on 4-amino-5-nitrosopyrimidines. The 7-amino-6-arylpteridines described herein provide the first examples of pteridines with an amino group in the pyrazine moiety of the nucleus. Several of these compounds were tested microbiologically and some were found to be antagonists of folic acid (Proom, Wellcome Research Laboratories; private communication). The most active compounds of those tested so far were 2:4:7-triamino-6-α-thienylpteridine (IX, $R_1 = \alpha$-thienyl), 2:4:7-triamino-6-p-ethoxyphenylpteridine (IX, $R_1 = \text{EtOC}_6\text{H}_4$), 2:4:7-triamino-6-phenylpteridine (IX, $R = \text{Ph}$) and 2:4:7-triamino-6-p-chlorophenylpteridine (IX, $R_1 = \text{ClC}_6\text{H}_4$). It is of interest that 2:4:7-triamino-p-methoxyphenylpteridine (IX, $R_1 = \text{MeOC}_6\text{H}_4$) and 2:4-diamino-6-phenyl-7-hydroxypteridine (X) are inactive. Thus, changing the 7-hydroxy group in (X) to amino- to give (IX, $R_1 = \text{Ph}$) produces an active compound; this change has a similar effect in the pteroylglutamic series, when the remarkably active "aminofolies" are obtained. These compounds are being tested as purine antagonists.
So far the compounds (IX, $R_1 = \text{Ph}$) and (X) have only been tested as tumour inhibitors on the Walker Rat carcino-sarcoma. The fact that they were inactive is not surprising in view of previous experience with other anti-metabolites (private communication, Prof. Haddow), and their effect on other experimental tumours will be examined. The former, however, possessed the property of inducing hypertrophy of the rat kidney.

New potential folic acid and purine antagonists, i.e. dihydropteridines of the type (XII) and triazoles of the type (XIII), are described at the end of the second part of the thesis, and are being tested as folic acid and purine antagonists and as tumour inhibitors on the Walker rat sarcoma.
Figures XII and XIII
The class of compounds formed by the fusion of a pyridine and pyrazine ring to give the pyridino-pyrazine (I) or pteridines have long been known, although the parent compound was not synthesized until 1946 (Jones, J. Am. Chem. Soc., 1946, 68, 534). The system has been numbered in two different ways, - the first (I), which is used in this thesis, and the second (II), which has been used by the Iranian workers.

**THE SYNTHESIS OF PTERIDINES**

![Chemical Structures](image)

Interest in this class of compound has been stimulated by the recognition that the naturally occurring pterins luteopterin, marnthopterin and components of the folia acid type contain the pyridino-pyrazine ring system. The early work on the synthesis of this class of compounds, on the elucidation of the structure of the pterin pigments of butterfly wings and of folia acid, are reviewed by Sato.
Introduction.

The class of compounds formed by the fusion of a pyrimidine and pyrazine ring to give the pyrimido-(4:5-b)-pyrazines (I) or pteridines have long been known, although the parent compound was not synthesised until 1948 (Jones, Nature, 1948, 162, 524). The system has been numbered in two different ways; the first (I), which is used in America and will be used throughout this thesis, and the latter (II), which has been used by the European workers.

Interest in this class of compound has been stimulated by the recognition that the naturally occurring pterins leucopterin, xanthopterin and compounds of the folic acid type contain the pyrimido-pyrazine ring system. The early work on the synthesis of this class of compounds, on the elucidation of the structure of the pterin pigments of butterfly wings and of folic acid, are reviewed by Gates.
(Chem. Rev., 1947, 41, 63), and in the Annual Reports of
the Chemical Society, 1946, 43, 250; 1948, 45, 226. How­
ever, for the sake of completeness a brief summary will be
included here.

The first synthesis of a pteridine was that of
Kuhling (Ber., 1895, 28, 170), who oxidised "tolualloxaz­
ze (III), presumably via decarboxylation, to 2:4-di­
hydroxypteridine (IV), which was later obtained by Gabriel
and Sohn (Ber., 1907, 40, 4857) by the treatment of pyra­
azine-2:3-dicarboxamide (V) with potassium hypobromite.

The facile condensation of 4:5-diaminopyrimidines (VI)
with 1:2-dicarbonyl compounds, a method of synthesis which
has had wide application, was first examined in detail by
Meyerheim and Sachs (Ber., 1908, 41, 3957), although Isay
(Ber., 1906, 39, 250) had first used the method to character­
ise a 4:5-diaminopyrimidine.
Three pyrimidines were used by Meyerheim and Sachs, namely: 3-methyl-2:6-diketo-4:5-diamino and 1:3-dimethyl-2:6-diketo-4:5-diaminotetrahydropyrimidines and 2:4:5-triamino-6-hydroxypyrimidine, and were condensed with dicarbonyl compounds such as diacetyl, mesoxalic acid and pyruvic acid. Although they recognised the possibility of the formation of isomers from unsymmetrical 1:2-dicarboxyl compounds no attempt was made to assign structures to the products.

Kuhn and Cook (Ber., 1937, 70, 761) and Ganapati (J. Indian. Chem. Soc., 1937, 14, 627) provided many examples of the condensation of 2:6-dihydroxy-4:5-diaminopyrimidine (VI, $R_1 = R_2 = \text{OH}$) with 1:2-dicarboxyl compounds to give pteridines related to the flavines. 2:4-Dihydroxyppteridine IV, for which Kuhn and Cook proposed the name lumazine, was obtained when (VI, $R_1 = R_2 = \text{OH}$) was condensed with glyoxal.
Other dicarboxyl systems, which were condensed with this pyrimidine, included methylglyoxal, diacetyl, phenylglyoxal, benzil, naphthaquinone and phenanthraquinone; these gave rise to substituted lumazines. Again, the structures of the products from unsymmetrical dicarboxyl compounds were not ascertained.

**Xanthopterin, leucopterin and related pterines.**

![](image)

VII  

VIII  

IX

The recognition of the structures of leucopterin (VII), xanthopterin (VIII) and isoxanthopterin (IX) and their inter-relationships provided further impetus to research into the preparation and properties of pteridines. Leucopterin resulted from the fusion of 2:4:5-triamino-6-hydroxypyrimidine with oxalic acid, and further applications of the oxalic acid synthesis and the relationship of
leucopterin to xanthopterin showed that leucopterin was correctly formulated as (VII) (Purman, *Annalen*, 1940, 544, 182, idem, ibid., 1941, 546, 98).

These relationships are best shown as follows:

\[
\begin{align*}
\text{leucopterin} & \xrightarrow{\text{dichloroacetic acid}} \text{Xanthopterin} \\
\text{leucopterin} & \xrightarrow{\text{O}_2/\text{Pt acid solution}} \text{Xanthopterin}
\end{align*}
\]

The condensation of mesoxalic ester with 2:4:5-triamino-6-hydroxypyrimidine to yield xanthopterin and iso-xanthopterin carboxylic acids was of interest as the two compounds were separated and showed marked differences in properties (Purman, *Annalen*, 1941, 548, 284). When the
condensation was carried out in dilute acetic acid solution and the products hydrolysed the major product was isoxanthopterin carboxylic acid (X), together with a small amount of the isomeric xanthopterin carboxylic acid (XI).

In the presence of strong mineral acid, i.e. 2N sulphuric acid, xanthopterin carboxylic acid was the principal product. Furman accounted for the difference in behaviour of the reactants in acetic acid and sulphuric acid by assuming that in acetic acid the 5-amino group reacted first with the keto group of the ester, thus
forming the 7-hydroxy isomer (X): whilst in mineral acid the 5-amino group formed a salt, implying that the keto group of the ester first reacted with the 4-amino group. The fact that some 29% of the 7-hydroxy isomer was obtained in the latter case was accounted for by assuming that the Schiff's base, which was formed as a primary condensation product, was sensitive to acids.

The condensation of $\alpha$-ketoacids and $\alpha$-ketoesters with 4:5-diaminopyrimidines was further studied by Elion and Hitchings ($J$. Amer. Chem. Soc., 1947, 69, 2553) and Elion, Hitchings and Russell (ibid. 1950, 72, 78). By using pyruvic acid, ethyl oxaloacetate and mesoxalic ester as the ketonic components and 2:4:5-triamino-6-hydroxy-(XII, $R = \text{OH}$) and 2:4:5:6-tetraamino-6-hydroxy-(XII, $R = \text{NH}_2$) as the diamine components they found that the direction of the condensation was indeed a function of the acidity of the medium.
The percentage yields of the isomers obtained in the different conditions are shown in the table below, which is reproduced from the paper of Hitchings et al. (J. Amer. Chem. Soc., 1950, 72, 76).

<table>
<thead>
<tr>
<th>Pyrimidine</th>
<th>Reagent</th>
<th>7-OH</th>
<th>6-OH</th>
<th>7-OH</th>
<th>6-OH</th>
</tr>
</thead>
<tbody>
<tr>
<td>XVI, R = OH</td>
<td>Pyruvic acid</td>
<td>10</td>
<td>42</td>
<td>0</td>
<td>76</td>
</tr>
<tr>
<td>-do-</td>
<td>Ethyl oxaloacetate</td>
<td>40</td>
<td>Trace</td>
<td>11</td>
<td>69</td>
</tr>
<tr>
<td>-do-</td>
<td>Ethyl mesoxalate</td>
<td>85</td>
<td>0</td>
<td>29</td>
<td>42</td>
</tr>
<tr>
<td>XVI, R = NH₂</td>
<td>Pyruvic acid</td>
<td>37</td>
<td>13</td>
<td>3</td>
<td>92</td>
</tr>
<tr>
<td>-do-</td>
<td>Ethyl oxaloacetate</td>
<td>66</td>
<td>0</td>
<td>22</td>
<td>49</td>
</tr>
<tr>
<td>-do-</td>
<td>Ethyl mesoxalate</td>
<td>87</td>
<td>0</td>
<td>90</td>
<td>0</td>
</tr>
</tbody>
</table>

Forrest and Walker (J., 1949, 79) had suggested that 4:5-diaminopyrimidines exist as hybrids (XIIa) and (XIIb) in weakly acid solution (ca. pH3 - 7), thus making the 5-amino group the only centre of nucleophilic activity and this enabled Hitchings et al. to account for the formation of the 7-hydroxy isomer in dilute acid solution. Moreover, in agreement with this, as the electrophilic nature of the carbonyl group was increased, the yield of the 7-isomer was also increased. Thus in the series
pyruvic acid, ethyl oxaloacetate and ethyl mesoxalate
the yield of 7-hydroxy isomer increased in the order given.
In strongly acid solution the 5-amino group was assumed to
form a salt, thus depressing the nucleophilic activity of
this group and the direction of the condensation was
reversed to favour the formation of the 6-hydroxy isomer;
an exception was found with ethyl mesoxalate, which still showed a marked tendency to give the 7-isomer. The
increased yields of the 7-isomer when (XII, R = NH$_2$) was
used as the diamine component were attributed to resonance
involving the 4- and 6-amino groups, as shown below, which leaves the 5-amino group relatively stronger as a nucleo-
philic centre by the removal of nucleophilic activity from
the 4- and 6- positions.

The biological importance of xanthopterin (VIII)
has prompted several different syntheses. The first was
by Furrman (Annalen, 1941, 546, 98), who condensed dichloro-
acetic acid with 2:4:5-triamino-6-hydroxy-pyrimidine to give the amide (XIII) which, on treatment of its silver salt with silver carbonate, gave a 10% yield of xanthopterin. Furrman (Annalen, 1941, 548, 284) also obtained xanthopterin from "dihydroxanthopterin" (XIVa) by catalytic oxidation in alkaline solution. This latter preparation involved the use of xanthopterin carboxylic acid, the preparation of which has just been discussed. Xanthopterin carboxylic acid, unlike its isomer, isoxanthopterin carboxylic acid, cannot be decarboxylated. However, if it is first reduced to its dihydroderivative (XV) decarboxylation readily occurs to yield "dihydroxanthopterin". Koschara (Z. Physiol. Chem., 1943, 277, 159) synthesised xanthopterin directly from 2:4:5-triamino-6-hydroxypyrimidine and glyoxylic acid-barium bisulphite by condensation in 78% sulphuric acid. Leucopterin (VII) has provided another, and probably the best, source of xanthopterin since by reduction with sodium amalgam it yields "dihydroxanthopterin", which can be oxidised to xanthopterin with silver nitrate (Totter, J. Biol. Chem., 1944, 154, 105) or alkaline potassium permanganate (Elion, Light and Hitchings, J. Amer.
Chem. Soc., 1949, 71, 741), the method of the latter workers providing the purest specimen, as judged by microbiological activity.

These methods do not, however, provide an unambiguous synthesis of xanthopterin which Boon and Leigh (J., 1951, 1497) have recently claimed to have synthesised.
by an unambiguous method. They condensed 2-amino-4-chloro-5-phenylazo-6-hydroxypyrimidine (XVI) with glycine ethyl ester to give the intermediate α-pyrimidylaminoacetic ester (XVII) which, on reduction with zinc dust in acetic acid gave "dihydroxanthopterin" (XIVA). This, on oxidation with alkaline potassium permanganate by the method of Elion, Light and Hitchings (loc. cit.) gave xanthopterin.

At this stage it should be pointed out that the structure of "dihydroxanthopterin" is at the moment uncertain. It appears from the work of Elion and Hitchings
(J. Amer. Chem. Soc., 1949, 71, 467) that there are two isomeric "dihydroxanthopterins", — the first, α-dihydroxanthopterin (XIVa), obtained by the reduction of xanthopterin (O'Dell, Vandenbelt, Bloom and Pfiffner, J. Amer. Chem. Soc., 1947, 69, 250), the reduction of xanthopterin carboxylic acid (Furrman, Annalen, 1941, 548, 284), or by the reduction of leucopterin (Totter, J. Biol. Chem., 1944, 154, 105; Elion, Light and Hitchings, J. Amer. Chem. Soc., 1949, 71, 741); the second, β-dihydroxanthopterin, was obtained synthetically by the method outlined below. 2:4:5-Triamino-6-hydroxypyrimidine, on heating with chloroacetic acid, gave the chloroacetamide (XVIII) which, on treatment with aqueous sodium bicarbonate at 95°, gave β-dihydroxanthopterin (XIVb).

![Chemical structures](image-url)
Elion and Hitchings found considerable differences between $\alpha$ and $\beta$-dihydroxanthopterins. For instance, the $\alpha$-form may be readily oxidised to xanthopterin under a variety of conditions, whilst the $\beta$-form is unchanged; treatment with aqueous barium hydroxide leads to a barium salt in the case of the $\alpha$-form, whilst ring fission occurs to give the acid (XIX, $R = H$) in the case of the $\beta$-form. This acid can be esterified to (XIX, $R = Me$) and since both acid and ester were readily reconverted to (XIVb) and their ultra-violet absorption spectra indicated a substituted pyrimidine ring with a free 5-amino group, they were assigned the structures (XIX, $R = H$ or Me). This evidence, together with the method of synthesis, seemed to indicate that $\beta$-dihydroxanthopterin was (XIVb).

![Chemical Structure]
Boon and Leigh (loc. cit.) have questioned the structure (XIVb) for β-dihydroxanthopterin since the product (XIVa) obtained from the 5-phenylazopyrimidylacetic ester (XVII) by reduction is identical with α-dihydroxanthopterin, prepared by reduction of leucopterin. They further state that the acid that Hitchings et al. obtained by barium hydroxide treatment of β-dihydroxanthopterin cannot have the structure (XIX, R = H) and they claim that the ethyl ester of an acid of this structure will cyclise to α-dihydroxanthopterin (XIVa). Boon and Leigh did not, however, isolate an ester of the structure (XIX) during the reduction of (XVII), and as Hitchings et al. state that (XIX, R = H or Me) readily cyclised to β-dihydroxanthopterin the question of the structure of this acid still seems to be in doubt. An explanation of these conflicting results may be that α-dihydroxanthopterin has always been obtained under reducing conditions, whereas the β-form has only been formed as a result of the cyclisation of the chloroamide (XVIII). Proof of this could be obtained by treatment of β-dihydroxanthopterin with the reducing agents which give the α-form, when bond migration might possibly give the α-form.
The synthesis of pteridines from 4:5-diamino-pyrimidines and carbonyl compounds was further studied by Polonovski, Vieillefosse and Pesson (Bull. Soc. Chim., 1945, 12, 78) and Polonovski, Pesson and Vieillefosse (ibid., 1945, 12, 924). They found that the 2-thiopteridines obtained from 2-thio-4:5-diamino-6-hydroxypyrimidine (VI, \( R_1 = \text{SH}, R_2 = \text{OH} \)) and various dicarbonyl compounds showed no fluorescence, whereas the hydroxy compounds obtained from them by treatment with hydrogen peroxide and the 2-ethylthiopteridines (prepared by ethylation of the 2-thio compounds or direct synthesis from 2-ethylthio-4:5-diamino-6-hydroxypyrimidine) did fluoresce. Moreover, the thio compounds inhibit the fluorescence of the alkylthio compounds, as does thiourea. To relate the fluorescence with chemical structure they put forward the hypothesis that the 2-thiopteridines (XX) exist as the thiones (XXI), the 2-ethylthiopteridines as (XXII), and the 2:4-dihydroxypteridines as a mixture of the lactim (XXIII) and lactam (XXIV) forms, depending on the pH of the medium.

In the case of the dihydroxy compounds the fluorescence was strong in alkaline solution but in acid solution it was weak, which was assumed to be due to the change from lactim to lactam form. A further point that
emerged from this work was that when the pyrimidine (VI, \( R_1 = \text{SH}, R_2 = \text{OH} \)) was condensed with mesoxalic ester in neutral solution only one compound (XXV) resulted; this, since it could be decarboxylated and was formed in neutral solution, probably had the iso-xanthopterin structure (cf. Purman, Annalen, 1941, 548, 284).

\[
\begin{align*}
\text{XX} & \quad \text{XXI} & \quad \text{XXII} \\
\text{XXIII} & \quad \text{XXIV} \\
\text{XXV}
\end{align*}
\]
The Structure and Synthesis of 'Folic acid' and related compounds.

The isolation and synthesis of the various biologically active factors from liver and fermenting yeast stimulated further research into the pyrimido-(4:5-b)-pyrazine ring system. As a result of combined biological and chemical research Angier et al. (Science, 1945, 102, 227; 1946, 103, 667) identified the liver L. casei factor as N-pteroyl-L-glutamic acid (XXVI), i.e. 'folic acid'.

![Chemical structure of XXVI]

They also showed by anaerobic alkaline hydrolysis that the fermentation L. casei factor lost 2 moles of glutamic acid to yield the liver L. casei factor.

These preliminary results were confirmed in a series of communications by Angier et al. (J. Amer. Chem. Soc., 1948, 70, 1-28). By aerobic alkaline hydrolysis
they degraded the liver L. casei factor to 2-amino-4-hydroxypteridine-6-carboxylic acid (XXVII) and a diazotisable aromatic amine. The structure of the fluorescent pteridine fraction followed from its chemical and physical properties. There were two acidic groups with $pK_a$ values of 3.9 and 7.7. The presence of a carboxylic acid group was shown by decarboxylation, when a monobasic acid $pK_a$ 8.0 was obtained. The presence of a 2-amino group in the pteridine was shown by treatment with chlorine in hydrochloric acid, when guanidine was obtained.

The decarboxylation product was shown to be identical with 2-amino-4-hydroxy-pteridine (XXVIII) obtained by condensing glyoxal with 2:4:5-triamino-6-hydroxypyrimidine.
(XXVII) was then synthesised from isoxanthopterin carboxylic acid (X) by chlorination and reduction, and also directly from 2:4:5-triaminopyrimidine and ethyl-β-bromo-β-β-diethoxypropionate. Thus the positions of the 2-amino and 4-hydroxy groups were established and the position of the carboxyl group was related to the carboxyl group of isoxanthopterin carboxylic acid - probably in the 6-position. The position of the carboxyl group was finally confirmed by degrading 2-amino-4-hydroxy-6-methylpteridine (XXIX) (by the method of Weijlard, Tishler and Erikson, J. Amer. Chem. Soc., 1945, 67, 802) to 2-amino-5-methylpyrazine identical with that obtained from the known 2:5-dimethylpyrazine.

2-Amino-4-hydroxy-6-methylpteridine (XXIX) had itself been obtained from the hydrolysates of the fermentation L. casei factor, and was synthesised by condensing methyl-γ-γ-dimethoxyacetoacetate and 2:4:5-triamino-6-hydroxypyrimidine to 2-amino-4-hydroxypteridine-6-acetic acid (XXX) followed by decarboxylation. The 6-methyl compound and the 6-pteridineacetic acid could be oxidised to the 6-carboxylic acid (XXVII) with potassium permanganate. The preceding transformations of the key pteridines
A further interesting result of the work of Angier et al. was the preparation and characterisation of the isomeric 6-methyl and 7-methyl, and 6-carboxy and
7-carboxy-2-amino-4-hydroxypteridines. The 7-methyl isomer (XXXI) was obtained by the condensation of the diethylacetal of methyl glyoxal with 2:4:5-triamino-6-hydroxypyrimidine in strongly acid solution and was converted to the 7-carboxy compound (XXXII) by oxidation with potassium permanganate.

\[
\text{XXXI} \quad \text{XXXII}
\]

The diazotisable amine fraction from the aerobic alkaline hydrolysis was shown to consist of p-aminobenzoic acid combined as a peptide with L-glutamic acid. That the aromatic amine fraction and pteridine fraction were united by a methylene group attached to the 6- position of the pteridine nucleus followed from sulphurous acid cleavage of the fermentation L-casei factor. Again two fractions were produced, viz. a pteridine and aromatic amine fraction. The former showed the properties of an aldehyde and on
treatment with alkali was claimed to undergo an interesting dismutation to give 2-amino-4-hydroxy-6-methyl-(XXIX) and 6-carboxypteridines (XXVII), (see later).

The synthesis of N-pteroyl-L-glutamic acid requires the condensation of an appropriate three carbon system with 2:4:5-triamino-6-hydroxypyrimidine, and that the resulting 6-substituted pteridine shall be capable of condensation with p-aminobenzoyl-L-glutamic acid. Angier et al. (loc. cit.) prepared the vitamin using several modifications of the above principle. The first method involved the simultaneous condensation of αβ-dibromopropionaldehyde, 2:4:5-triamino-6-hydroxypyrimidine and p-aminobenzoyl-L-glutamic acid (XXXIII), when 30-50% yields of a product containing 10-25% of the active factor were obtained. It was found that the best yields were obtained at pH4. The second method used was to condense the reaction product (XXIV) of pyridine and αβ-dibromopropionaldehyde with 2:4:5-triamino-6-hydroxypyrimidine
to yield the 6-substituted pteridine (XXXV), which was subsequently treated with p-aminobenzoyl-L-glutamic acid in ethylene glycol to yield N-pteroyl-L-glutamic acid (XXVI). The third method involved the bromination of the 2-amino-4-hydroxy-6-methylpteridine to its 6-bromo-6-methyl-analogue, followed by reaction with diethyl p-aminobenzoyl-L-glutamate. The last method utilised reductone (3,5-dihydroxyacrylic aldehyde) which was condensed with p-aminobenzoyl-L-glutamic acid to the intermediate (XXXVI) which was then treated with 2:4:5-triamino-6-hydroxypyrimidine to give (XXVI). The best of these methods is method (i):

\[
\begin{array}{c}
\text{(i)} \\
\text{(H}_{2}\text{N})_2\text{N} \quad \text{CHO} \quad \text{CH}_2\text{Br} \\
\text{CH} \quad \text{Br} \quad \text{CH}_2\text{Br} \\
\text{NH}_2 \quad \text{NH}_2 \\
\text{CH} \quad \text{OH} \\
\end{array}
\]

\[
\text{H}_2\text{N} \quad \text{CONH(CH}_2\text{)}_2\text{CO}_2\text{H} \quad \text{CO}_2\text{H} \rightarrow \text{XXVI}
\]

\[
\begin{array}{c}
\text{(ii)} \\
\text{(H}_{2}\text{N})_2\text{N} \quad \text{CHO} \quad \text{CH}_2\text{Br} \\
\text{CH} \quad \text{Br} \quad \text{CH}_2\text{Br} \\
\text{NH}_2 \quad \text{NH}_2 \\
\text{CH} \quad \text{OH} \\
\end{array}
\]

\[
\text{XXIV} \quad \text{H}_2\text{N} \quad \text{NH} \quad \text{NH}_2 \quad \text{CH}_2\text{Br} \\
\text{CH} \quad \text{OH} \\
\text{XXVI}
\]

\[
\begin{array}{c}
\text{H}_2\text{N} \quad \text{CH}_2\text{Br} \\
\text{XXIV} \quad \text{H}_2\text{N} \quad \text{NH} \quad \text{NH}_2 \quad \text{CH}_2\text{Br} \\
\text{CH} \quad \text{OH} \\
\end{array}
\]

\[
\text{H}_2\text{N} \quad \text{CONH(CH}_2\text{)}_2\text{CO}_2\text{H} \quad \text{CO}_2\text{H} \rightarrow \text{XXVI}
\]

XXXIII

XXXIV

XXXV

XXXVI
Many other variations of these methods have been described in attempts to increase the yield using various three carbon systems and these methods are reviewed in the *Annual Reports of the Chemical Society*, 1948, pg. 236 and 1950, pg. 241. Rydon, *Annual Reports of the Chemical Society*, 1950, pg. 244, suggests that the most satisfactory method of preparing (XXVI) is the condensation of 2:4:5-triamino-6-hydroxypyrimidine and dihydroxyacetone in the presence of hydrazine (see later) to give 2-amino-4-hydroxy-6-hydroxymethylpteridine (XXXVII, \( R = \text{OH} \)) followed by conversion into the 6-chloromethyl compound (XXXVII, \( R = \text{Cl} \)) and condensation with \( p \)-amino
The above methods may be used for the preparation of pteroylglutamic acid (XXXVIII, R = H), (Angier et al., loc. cit.), and analogues of pteroylglutamic acid such as aminopterin (XXXIX, R = H) and A-methopterin (XXXIX, R = Me), (Seager, Smith, Cosulich and Hultquist, J. Amer. Chem. Soc., 1949, 71, 1753).

XXXVII

XXXVIII

XXXIX
The fermentation L. casei factor which was shown to contain two more glutamic acid molecules than the liver L. casei factor, or N)pteroyl-L-glutamic acid, has been shown by synthesis to be the linear peptide (XXXVIII, R = [NHCH(CO₂H)(CH₂)₄CO]₃OH), and is known as teropterin (Angier et al., J. Amer. Chem. Soc., 1949, 71, 2304, idem, ibid., 1950, 72, 74).

During the degradation and synthesis of pteroyl glutamic acid and its analogues the isomeric 6- and 7-carboxy and 6- and 7-methyl-2-amino-4-hydroxypteridines were completely characterised. Thus the direction of many of the condensations of 2,4,5-triamino-6-hydroxypyrimidine can be shown if it is possible to oxidise the product to one of the above acids. These particular pteridine carboxylic acids have been characterised by their characteristic light absorption, (Angier et al., J. Amer. Chem. Soc., 1948, 70, 14) or by paper chromatography, (Weygand, Wacker and Schmied-Kowarz, Experimentia, 1950, 6, 184). Several pteridine-mono- and dicarboxylic acids (XL, R₁ = OH or NH₂, R₂ = OH or NH₂, R₃ and R₄ = CO₂H) have been described by Cain, Mallette and Taylor (J. Amer. Chem. Soc., 1948, 70, 3026). These authors prepared the acids from the corres-
ponding 6- and 7- and 6:7-dimethyl pteridines by oxidation with alkaline potassium permanganate. Cain et al. showed that the product obtained by condensing methylglyoxal with 2:4:5:6-tetraaminopyrimidine was the 7-methyl isomer by degradation with sodium hydroxide to the known 2-amino-6-methylpyrazine carboxylic acid by the method of Weijlard, Tishler and Erickson (J. Amer. Chem. Soc., 1945, 67, 602), and they confirmed that the methylpteridine prepared from 2:4:5-triamino-6-hydroxy- pyrimidine and methylglyoxal diethylacetal was the 7-isomer (cf. Mowat et al., J. Amer. Chem. Soc., 1948, 70, 14).

Decarboxylation of the 6:7-pteridinedicarboxylic acid (XL, $R_1 = R_2 = \text{OH}$, $R_3 = R_4 = \text{CO}_2\text{H}$) showed that the carboxyl group in the 7-position was more stable than that in the 6-position since the 7-carboxylic acid was
obtained.

The Synthesis of Pteridines from Sugars and related compounds.

The use of sugars in the synthesis of pteridines was first studied by Karrer, Schwyzer, Erden and Siegwart (Helv. Chim. Acta, 1947, 30, 1031). They treated 2:4:5-triamino-6-hydroxypyrimidine (XLI) in dilute acetic acid solution, under an atmosphere of carbon dioxide, with aldoses: e.g. arabinose, xylose, galactose, glucose and glyceraldehyde to obtain 7- and/or 6-hydroxyalkylpteridines (XLII). With fructose they isolated a different pteridine (XLIII, n = 3) than that obtained from d-glucose. They were of the opinion that the aldoses gave the 7-hydroxyalkyl and ketoses the 6-hydroxyalkyl isomers.
Petering and Weisblat (J. Amer. Chem. Soc., 1947, 69, 2566) showed that under the conditions used by Karrer et al. the 7-isomer (XLII, n = 3) was formed with D-glucose, whilst under strongly acidic conditions the 6-isomer (XLII, n = 3) was the major product. The type of isomer was identified by its oxidation to a carboxylic acid (XXVII or XXXII) and by its physical properties. These workers also showed that the 6-isomer could be obtained in better yield by condensation of (XLI) with the osones (XLIII). In this latter condensation, however, the conditions pertaining to isomer formation were reversed, i.e. at pH 5-9 the 6-isomer was the major product and in strongly acid solution the 7-isomer was the major product. This latter observation is in agreement with the findings of Hitchings et al. (J. Amer. Chem. Soc., 1950, 72, 78) on the condensation of L-keto acids and esters with (XLVI).

Karrer and Schwyzzer (Helv. Chim. Acta, 1948, 31, 777) claimed to have synthesised 6-hydroxymethyl-4-hydroxy-2-aminopteridine (XLII, n = 0) by treatment of (XLI) with dihydroxyacetone. They cited as evidence for the existence of this compound the formation of folic acid (15% yield) by reaction with p-aminobenzoyl-L-glutamic acid.
At this stage Angier et al. (J. Amer. Chem. Soc., 1948, 70, 3029) pointed out that the condensation of (XLI) with any three carbon compound which might be expected to produce a halomethyl- or hydroxymethyl-dihydropteridine actually gave the fully aromatised methylpteridine (XLIV or XLV, R = Me) by splitting out hydrogen halide or water. From (XLI) and each of the following substances, 1;3-dichloroacetone, \( \alpha \beta \)-dichloropropionaldehyde, \( \alpha \)-bromotetronic acid and DL-glyceraldehyde, they obtained 2-amino-4-hydroxy-7-methylpteridine. They concluded that the compound obtained by Karrer et al. from DL-glyceraldehyde and (XLI), for which poor analytical results had been obtained, was essentially this compound and not 7- or 6-hydroxymethyl-4-hydroxy-2-aminopteridine (XLIV or XLV, R = CH\(_2\)OH).

The effect of hydrazine on the condensation of sugars with (XLI) was studied by Forrest and Walker, (J. 1949, 79 and 2077). They found that in the presence of hydrazine both glucose and fructose gave the same 2-amino-4-hydroxy-8-D-arabotetrahydroxybutylpteridine (XLIV, \( R = (\text{GHOH})_3\text{CH}_2\text{OH} \)) when condensed with (XLI).
In the absence of hydrazine (cf. Karrer, Schwyzer, Erden and Siegwart, loc. cit.) at pH3, glucose and (XLI) gave the 7-isomer (XLV, R = (CHOH)_3CH_2OH). The structure of these compounds was proved by oxidation to the corresponding acids (XLIV, R = CO_2H and XLV, R = CO_2H) which, as already mentioned, had been completely characterised during the elucidation of the structure of N-pteroyl-L-glutamic acid. In their later publication they discussed the effects of hydrazine on the condensation of (XLI) with α-ketols and related substances. The first substance examined was acetal, which gave 2-amino-4-hydroxy-7-methylpteridine (XLV, R = Me) when condensed with (XLI),
although Karrer and Schwyzzer (Helv. Chim. Acta., 1949, 32, 423) observed no direct condensation between (XLI) and acetal. If acetal and (XLI) were allowed to react in presence of hydrazine the 7-isomer was again obtained but if acetal and hydrazine were allowed to react before the addition of (XLI) a mixture of (XLIV, R = Me) and (XLV, R = Me) was obtained, with the latter predominating. However, this partial reversal was attributed to incompleteness of osazone formation (the formation of (XLV, R = Me) being attributed to the equilibrium between acetal and lactaldehyde). This difficulty was overcome by showing that if methylglyoxal and hydrazine were allowed to react before addition of (XLI) the 6-methyl isomer (XLIV, R = Me) was obtained, whereas direct condensation of methylglyoxal and (XLI) gave the 7-methyl isomer (cf. Mowat et al., J. Amer. Chem. Soc., 1948, 70, 14). When acetal was replaced by dihydroxyacetone 6-hydroxymethyl-4-hydroxy-2-aminopteridine (XLIV, R = CH₂OH) was obtained in the presence of hydrazine, whereas in its absence (XLV, R = Me) was obtained. This latter result is another example of the thesis of Angier et al. (J. Amer. Chem. Soc., 1948, 70, 3029) that halomethyl- or hydroxymethylidihydropyridines
split out hydrogen halide or water rather than lost two atoms of hydrogen, but is at variance with the observations of Karrer and Schwyzer (loc. cit.), who claim that 2-amino-4-hydroxy-6-hydroxymethylpteridine (XLIV, R = CH₂OH) results from the direct condensation of (XLI) and dihydroxyacetone. Forrest and Walker also reported that the direct condensation of p-tolyl-D-iso-glucosamine and (XLI) gives 2-amino-4-hydroxy-7-D-
erythro-2′-3′-4′-trihydroxypropylpteridine (XLVI, R = CH₂(CHOH)₂CH₂OH) instead of the expected D-arabotetra-
hydroxybutyl derivative (XLVI, R = (CHOH)₃CH₂OH).

Whereas in presence of hydrazine the expected 2-amino-4-
hydroxy-6-D-arabotetrahydroxybutyl analogue (XLIV,
R = (CHOH)₃CH₂OH) is obtained. These results are in agreement with the results obtained by Weygand, Wacker and Schmied-Kowarzik (Ber., 1949, 82, 25). Again oxidation to the corresponding characteristic 6- and 7-carboxylic acids was used as a criterion of the direction of the condensation,
Forrest and Walker pointed out that of the mechanisms for the formation of 6-hydroxyalkylpteridines neither of those proposed by Ohle and Hielscher (Ber., 1941, 74, 13) and Weygand (Ber., 1940, 73, 1289) for the formation of 8-tetrahydroxy-α-butylquinoxaline (XLVI) could be correct in view of their experiments. Ohle and Hielscher had rejected Weygand’s suggestion that (XLVI) is formed from α-phenylenediamine and glucose by way of α-aminophenylglucoside, Amadori rearrangement, ring closure and dehydrogenation and proposed that glucosphenylosazone was hydrolysed to glucosone followed by direct condensation with α-phenylenediamine. Karrer, Schwyzzer, Erden and Siegwart (Helv. Chim. Acta, 1947, 30, 1031) proposed a mechanism similar to that proposed by Weygand for the formation of (XLVI) for the production of 7-hydroxyalkylpteridines from glucose and (XLI). Forrest and Walker showed that glucosone and (XLI) give the 6-isomer in presence of hydrazine and the 7-isomer in its absence under comparable conditions of pH, and they pointed out that the hydrazine must form an open chain osazone type of derivative with glucose before interaction with (XLI), for had reaction occurred between the sugar and (XLI)
before the participation of hydrazine in the reaction no influence would have been exerted on the course of the reaction. By their experiments with hydroxycarbonyl compounds (which could not form cyclic structures with hydrazine) such as acetol and methylglyoxal they suggested that the reaction takes the following course and not via the ketoaldehyde (osone) postulated by Ohle and Hilscher, Weygand, and Karrer and Schwyzer.

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{H} \quad \text{N} \quad \text{H} \quad \text{NH}_2 \\
\text{CH} & \quad \text{N} \quad \text{N} \quad \text{OH} \\
\text{N} & \quad \text{N} \quad \text{N} \quad \text{N} \\
\text{OH} & \quad \text{N} \quad \text{N} \quad \text{N} \\
\text{N} & \quad \text{N} \quad \text{N} \quad \text{N}
\end{align*}
\]

The 5-amino group of the pyrimidine (XLI), which is the centre of nucleophilic activity at the pH of the reaction, attacks the 2-position of the substituted

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sugar, thus directing the condensation and producing a 6-substituted pteridine. That the residue in the 2-position will be subject to ejection by a nucleophilic reagent follows from the fact that glucosephenyllosazone is converted to L-aminofructose (isoglucosamine), i.e. the phenylhydrazine residue in the 1-position undergoes hydrogenolysis whilst that in the 2-position is hydrolysed (Fischer, *Ber.*, 1886, 19, 1920; Maurer and Schiedt, *ibid.*, 1935, 69, 2187).

In general Petering and Schmidt (*J. Amer. Chem. Soc.*, 1949, 71, 3977) were in agreement with the findings of Forrest and Walker on the condensation of sugars and (XLI). They were able to show from the absorption spectra that the ratio of $E_{255\,\text{m}}/E_{365\,\text{m}}$ in 0.1 N sodium hydroxide was 3.2 for 6-hydroxyalkylpteridines whilst for 7-hydroxyalkylpteridines this ratio was 2.2 and they used this difference to study isomer formation. They found that the presence of boric acid was unnecessary and that other oxidising agents such as phenylhydrazine, hydrogen peroxide and benzoyl peroxide were of no value, whilst hydroxylamine gave no better yield of pteridine than if no oxidising agent was present. They showed that the conditions for
forming the 6-isomer in the synthesis were broad. In general for the reaction with ketoses the pH had to be kept between 4-7, the temperature above 90° and the volume of aqueous medium should be kept small since the 6-isomer is more soluble than the 7-isomer. When aldoses were used similar reaction conditions had to be used in order to direct the reaction to give the 6-isomer, but with the difference that the ratio of reactants, i.e. \( \frac{[\text{sugar}] \times [\text{hydrazine}]}{[\text{pyrimidine}]} \) should not exceed 8, otherwise the yield of pteridine was lowered.

The difference between aldoses and ketoses in the reaction is shown in the diagram (Petering and Schmidt, J. Amer. Chem. Soc., 1949, 71, 3979). Thus the effect of increasing the ratio \( \frac{[\text{sugar}] \times [\text{hydrazine}]}{[\text{pyrimidine}]} \) in the case when a ketose is used is to increase the yield of pteridine, whilst when an aldose is used the yield decreases when this ratio is greater than 8.

From the foregoing discussion it is clear that hydrazine effects the direction of the condensation to a marked extent and this effect has been put to good
Yield of pteridine.

\[ A = D(+)\text{-glucose}, \quad B = L(-)\text{-sorbose} \]

reaction time 45 mins., temp. 95°.

Thus Weygand, Wacker and Schmied-Kowarzik (Ber., 1949, 82, 25) utilised the effect to prepare \(N\)-pteroyl-\(L\)-glutamic acid. \(2\)-amino-4-hydroxy-6-\(D\)-arabotetrahydroxybutyl-

pteridine was oxidised with sodium periodate to \(2\)-amino-4-hydroxypteridine-6-aldehyde (XLVII), which was then condensed with \(p\)-aminobenzoyl-\(L\)-glutamic acid by a reductive method in formic acid.
This aldehyde (XLVII) is itself of interest biologically since it inhibits the activity of xanthine oxidase (cf. Kalekar et al., J. Biol. Chem., 1948, 174, 771). An aldehyde of this structure was first reported by Hutchings et al., (J. Amer. Chem. Soc., 1948, 70, 10), to have been obtained by the sulphurous acid cleavage of fermentation L. casei factor and, as already mentioned, this aldehyde was said to undergo a Canizzaro type dismutation to give 2-amino-4-hydroxy-6-methyl and 6-carboxypteridines. However, Weygand, Wacker and Schmied-Kowarzik pointed out that the sulphurous acid cleavage product was probably the dihydroaldehyde (XLVIII) and they accounted for the formation of the 6-methyl- and 6-carboxypteridines as follows:

\[ \text{H}_2\text{N} \]
\[ \text{N} \]
\[ \text{CH}_2\text{NH} \] 
\[ \text{OH} \] 
\[ \text{R} \]
\[ \rightarrow \]
\[ \text{H}_2\text{N} \]
\[ \text{N} \]
\[ \text{N} \]
\[ \text{CH} = \text{N} \]
\[ \text{H} \]
\[ \text{OH} \]
\[ \text{R} \]
\[ \text{H}_2\text{N} \]
\[ \text{N} \]
\[ \text{N} \]
\[ \text{CH}_2\text{OH} \]
\[ \text{R} \]
\[ \rightarrow \]
\[ \text{H}_2\text{N} \]
\[ \text{N} \]
\[ \text{N} \]
\[ \text{CH}_3 \]
\[ \text{R} \]
\[ \rightarrow \]
\[ \text{H}_2\text{N} \]
\[ \text{N} \]
\[ \text{N} \]
\[ \text{CH}_3 \]
\[ \text{CO}_2\text{H} \]
\[ \text{R} \]
\[ \rightarrow \]
\[ \text{H}_2\text{N} \]
\[ \text{N} \]
\[ \text{N} \]
\[ \text{CH}_3 \]
\[ \text{CO}_2\text{H} \]
\[ \text{R} \]
This provides another example of the preferential splitting out of water from a dihydropteridine (cf. Angier et al., *J. Amer. Chem. Soc.*, 1948, 70, 3029).

Angier et al. (*J. Amer. Chem. Soc.*, 1950, 72, 4630) have prepared (XLVII) from N-pteroyl-L-glutamic acid and from 2-amino-4-hydroxy-6-methylpteridine. It was obtained from the former by sulphurous acid cleavage, followed by oxidation with a slight excess of iodine and from the latter by bromination to the dibromomethyl compound (XLIX), followed by hydrolysis.

![Diagram](image-url)
The 6-pteridinealdehyde (XLVII), on treatment with 5N sodium hydroxide, was converted to a mixture of 2-amino-4-hydroxy-6-hydroxymethylpteridine (L) and the acid (XXVII), thus confirming the observation of Weygand et al. (Ber., 1949, 82, 25) that these compounds were produced from (XLVII) on treatment with 5N sodium hydroxide. Angier et al. showed that (L) could be acetylated to a diacetyl compound and that (XXIX) was acetylated to a monoacetyl compound. The ultraviolet absorption spectra of both of these acetyl compounds showed a ratio of 3.1 for $\frac{E_{\text{max}}}{E_{\text{max}}}$ of the shorter wavelength/ $E_{\text{max}}$ of the longer wavelength (cf. Petering and Schmidt, J. Amer. Chem. Soc., 1949, 71, 3977), whereas the spectra of these compounds as prepared by Karrer et al. (Helv. Chim. Acta., 1949, 32, 423) did not show this ratio. Further, the melting points of the diacetyl derivative of (L) and monoacetyl derivative of (XXIX), as prepared by Karrer et al., were lower than those prepared by Angier et al.

The possible significance of reductone (2:3-dihydroxyacrylic aldehyde, (LI)) in the biosynthesis of pteroylglutamic acid was discussed by Forrest and Walker
Reductone had been used as one of the 3-carbon systems in the synthesis of N-pteroyl-L-glutamic acid by Angier et al. (J. Amer. Chem. Soc., 1948, 70, 25). Forrest and Walker showed that reductone and p-aminobenzoic acid in the ratio of 1:2 gave a condensation product (LII), which when allowed to react with (XLI) gave the 7-substituted pteridine (proved by oxidation to 2-amin-4-hydroxy-7-pteridinescarboxylic acid). The 7-substituted product was also obtained if one mole each of reductone, (XLI) and p-aminobenzoic acid were allowed to react together; the intermediate (LIII) was assumed to be formed.

\[
\begin{align*}
\text{CHO} 
& \begin{array}{c}
\text{C} \\
\text{(OH)}
\end{array}
& \begin{array}{c}
\text{CH} \\
\text{(OH)}
\end{array}
\end{align*}
\]

\[
\begin{align*}
\text{H}_2\text{N} 
& \begin{array}{c}
\text{N} \\
\text{H}_2\text{N}
\end{array}
& \begin{array}{c}
\text{C} \\
\text{(OH)}
\end{array}
& \begin{array}{c}
\text{OHNH} \\
\text{N = CH}
\end{array}
& \begin{array}{c}
\text{N = CH} \\
\text{CO}_2\text{H}
\end{array}
\end{align*}
\]

LII

In agreement with the work of Angier et al. (loc. cit.) Forrest and Walker found that if one mole of
methyl-p-aminobenzoic acid were allowed to react before addition of (XLI), then the product was pteroid acid. Since the condensation of (XLI) with the product (LIV) of methyl-p-aminobenzoate and reductone must be initiated by nucleophilic attack of the 5-amino group on an electrophilic centre they postulate that (LIV) is in equilibrium with (LV).

\[ HO-CH=O(OR)CH=\text{N} \quad \text{LIV} \]

\[ HOCH_2COCH=\text{N} \quad \text{LV} \]

They also point out that the ketoaldehyde (LVI), suggested by Angier et al. as an intermediate, would probably react with (XLI) to give the 7-isomeride of pteroid acid in the same way that methylglyoxal and (XLI) yield 2-amino-4-hydroxy-7-methylpteridine.

\[ \text{CHO-CO-CH-NH} \quad \text{LVI} \]

As a result of the work on the condensation of (XLI) with sugars and related compounds, the following conclusions may be drawn.
1) The direct condensation of \(\alpha\)-ketols and related products with (XLI) at \(\text{pH} 4 \approx 7\) gives a mixture of \(6\)- and \(7\)-substituted pteridines with the latter predominating. In strongly acid solution variable amounts of \(6\)-substituted and \(7\)-substituted pteridines are obtained. If, however, the primary condensation product is an \(\alpha\)-halomethyl- or \(\alpha\)-hydroxymethyldihydropteridine, hydrogen halide or water are split out to give the fully aromatised methylpteridine.

2) Hydrazine directs the condensation of \(\alpha\)-ketols and (XLI) at \(\text{pH} 4 \approx 7\) to the \(6\)-substituted pteridine in most cases. Hydrazine acts as an oxidising agent under these conditions and dihydropteridines produced as intermediates are oxidised to the aromatic structure (i.e., \(6\)-hydroxymethyl or \(6\)-halomethyl pteridines can be isolated).

3) 2-Amino-4-hydroxypteridine-6-aldehyde (XLVII), first claimed to be obtained by treatment of the fermentation L. casei factor with sulphurous acid and later by the oxidation of the 6-hydroxyalkylpteridines (XLIV, \(R = \text{CH}_2\text{CH}_2\) and \((\text{CHOH})_n\text{CH}_2\text{CH}_2\)), was probably contaminated by the dihydroaldehyde (XLVIII) in the first case and the 6-pteridine-acetaldehyde (LVII) in the latter. 2-Amino-4-hydroxy-6-
pteridineacetaldehyde (LVII) has been shown to be formed by the oxidation of 2-amino-4-hydroxy-6-D-erythro-6-trihydroxybutylpteridine (LVIII), (Weygand, Wacker and Schmidt-Kowarz, Ber., 1949, 82, 25), which may occur as an impurity in the 6-hydroxyalkylpteridines. The best methods known to the author of preparing the aldehyde (XLVII) are those given by Angier et al. (J. Amer. Chem. Soc., 1950, 72, 4630).

\[
\begin{align*}
& \text{H}_2\text{N} & & \text{H}_2\text{N} \\
& \text{N} & & \text{N} \\
& \text{OH} & & \text{OH} \\
& \text{CH}_2\text{CHO} & & \text{CH}_2\text{(CHOH)}_2\text{CH}_2\text{OH}
\end{align*}
\]

LVII LVIII

Other Syntheses of Pteridines.

Due to the formation of isomers in the 'standard' synthesis of pteridines attempts have been made to produce pteridines by unambiguous methods. The first of these methods was that of Timmis (Nature, 1949, 164, 139), who condensed, for example, 2:4:6-triamino-5-nitrosopyrimidine with compounds containing the keto-methylene group such as
deoxybenzoin or its unsymmetrical analogues in acetic acid solution.

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{N} \quad \text{NH}_2 \\
\text{N} & \quad \text{N} \quad \text{NH}_2 \\
\text{N} & \quad \text{N} \quad \text{NO} \\
\text{NH}_2 & \quad \text{N} \quad \text{NH}_2
\end{align*}
\]

More recently Boon, Ramage and Jones (J., 1951, 96; B.P. 619, 915), Boon and Jones (J., 1951, 591; B.P. 635, 583), Polonovski and Jerome (Compt. rend., 1950, 230, 592) and Polonovski, Pesson and Puister (Compt. rend., 1950, 230, 2205) have utilised methods involving the cyclisation of substituted pyrimidines. Thus, from the condensation product (LIX) of 2,4-dichloro-5-nitro-6-methylpyrimidine and ethyl-α-aminoacetate Polonovski and Jerome (loc. cit.) prepared 2-amino-4-methyl-6-hydroxydihydropteroine (LX)

\[
\begin{align*}
\text{Cl} & \quad \text{N} \quad \text{NH}_2 \\
\text{Me} & \quad \text{N} \quad \text{NO}_2 \\
\text{Me} & \quad \text{N} \quad \text{NO}_2
\end{align*}
\]

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{N} \quad \text{NH}_2 \\
\text{Me} & \quad \text{N} \quad \text{NH}_2 \\
\text{Me} & \quad \text{N} \quad \text{NH}_2
\end{align*}
\]

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{N} \quad \text{NH}_2 \\
\text{Me} & \quad \text{N} \quad \text{NH}_2 \\
\text{Me} & \quad \text{N} \quad \text{NH}_2
\end{align*}
\]
Boon, Ramage and Jones (loc. cit.) studied the condensation of \( \alpha \)-amino acid esters with 4-chloro-5-nitropyrimidines more fully. Several 4-chloro-5-nitropyrimidines were condensed with ethyl \( \alpha \)-aminoacetate and the products (LXI) reduced with Raney nickel to give, in most cases, the dihydropteridines (LXII). In two cases, however, the intermediate 5-aminopyrimidine (LXIII, \( R_1 = Cl, R_2 = H, R_3 = Me \), and \( R_1 = Cl, R_2 = H, R_3 = Et \)) was obtained, which could be converted to the corresponding dihydropteridine by boiling with water.

\[ \text{LXI} \]

\[ \text{LXII} \]

\[ \text{LXIII} \]

\( \alpha \)-Amino acid esters may be replaced by \( \alpha \)-amino-ketones in this reaction; Polonovski, Pesson and Puister (loc. cit.), Boon and Jones (loc. cit.) Polonovski et al. prepared 2-ethoxy-7:8-dihydro-4-methyl-6:7-diphenyl-pteridine (LXV, \( R_1 = OEt, R_2 = Me, R_3 = R_4 = Ph \)) by this route and Boon and Jones studied the condensation of \( \alpha \)-amino-
acetone and α-aminodesoxybenzoin with several 4-chloro-5-nitropyrimidines. The latter workers showed that the product obtained by oxidation of 4-diethylamino-7:8-di-hydro-6:7-diphenylpteridine (LXV, R₁ = H, R₂ = NH₂Et, R₃ = R₄ = Ph) was identical with 4-diethylamino-6:7-diphenylpteridine (LXVI, R₁ = H, R₂ = NH₂Et, R₃ = R₄ = Ph) obtained from 5:6-diamino-4-diethylaminopyrimidine and benzil.
Boon and Leigh, (J. 1951, 1497), later developed the above method to include the condensation of a 4-chloro-5-phenylazopyrimidine (LXVII, \( R_1 = \text{NH}_2, \ R_2 = \text{OH} \)) with ethyl \( \alpha \)-aminoacetate and \( \alpha \)-aminoacetone, followed by reduction of the products (LXVIII) to the dihydropteridines (LXIIIa, \( R_1 = \text{NH}_2, \ R_2 = \text{OH}, \ R_3 = \text{OH} \) or Me). In this way they obtained xanthopterin (LXIX, \( R_1 = \text{NH}_2, \ R_2 = \text{OH}, \ R_3 = \text{OH} \)) and 2-amino-4-hydroxy-6-methylpteridine (LXIX, \( R_1 = \text{NH}_2, \ R_2 = \text{OH}, \ R_3 = \text{Me} \)) identical with the products obtained by the normal methods.
Synthesis of pteridines from pyrazine intermediates has had little application. Apart from the early synthesis of 2:4-dihydroxypteridine from pyrazine-2:3-dicarboxamide by Gabriel and Sohn (Ber., 1907, 40, 4857) the method has only been used by Albert, Brown and Cheeseman (J., 1951, 474). The latter authors found that 4-hydroxy (LIX, X = 0) and 4-mercaptoperideridines (LIX, X = S) could be prepared from 2-aminopyrazine-3-carboxamide and 2-aminopyrazine-3-carboxythioamide respectively by treatment with ethyl orthoformate.

The methods of synthesis of pteridines used to date may be summarised as follows:—

1) By the condensation of 4:5-diaminopyrimidines with appropriate carbonyl compounds and their derivatives. This method has been used more extensively than any other method but has the drawback that in a given reaction
isomers may be produced and if a well characterised reference compound is lacking the structure of the pteridine produced is doubtful. Further, when isomeric pteridines are produced they may be difficult to separate. As has been shown earlier, some progress has been made in directing the reaction to give either one isomer or the major proportion of one isomer.

2) From pyrazine intermediates. The method has had little use, due mainly, no doubt, to the difficulty in obtaining the pyrazine intermediates.

3) By the ring closure of appropriately substituted pyrimidines. The method was first used by Furman (Annalen, 1941, 546, 98) to synthesise xanthopterin from the substituted dichloroacetamide (LXXI). Later Boon, Ramage and Jones (J., 1951, 96), Boon and Jones (J., 1951, 591), Boon and Leigh (J., 1951, 1497) and Polonovski et al. (Compt. rend., 1950, 230, 392 and 2205) developed methods of synthesising pteridines of known structure by reduction of y-(5-nitro-4-pyrimidylamino)-acetic acid esters (LXXII, R = OEt) and y-(5-nitro-4-pyrimidyl)-aminoketones (LXXII, R = alkyl or aryl).
4) From 4-amino-5-nitrosopyrimidines and ketomethylene systems (Timmis, Nature, 1949, 164, 139). This method, although giving pteridines of known structure, has the drawback that only few 5-nitrosopyrimidines can be readily prepared (Lythgoe, Todd and Topham, J., 1944, 315).

The subject of the present thesis is an extension of method (4). The method involves the condensation of 4-amino-5-nitrosopyrimidine with an aryl-acetonitrile as shown below. Thus pteridines substituted in the pyrazine portion of the nucleus with an amino group become available for the first time.
The Preparation of 7-amino and 7-hydroxy-6-arylpteridines.

The 5-nitroso-4-aminopyrimidines required for condensation with arylacetonitriles have all been prepared by the conventional method. The preparation of these compounds from appropriately substituted pyrimidines and nitrous acid is described in the experimental section. Lythgoe, Todd and Topham (J., 1944, 315) have shown that in general only pyrimidines in which both 4- and 6- positions of the ring are occupied by such groups as NH₂ and OH can be nitrosated. The number of 4-amino-5-nitrosopyrimidines available by this method is, therefore, limited. However, it has been shown that the nitroso group may be introduced into the pyrimidine ring during the synthesis of the ring, (Bayer and Co., D.R.P., 206, 453, Zentralblatt, 1909, I, 806). This patent described the condensation of isonitroso-cyanacetic ester with guanidine, diylndiamide and N-methyl-N-acetylurea in presence of potassium methoxide or sodamide to give the corresponding 5-nitrosopyrimidines. Provided the appropriate nitroso compounds can be obtained there is no reason why this method should not also give those 5-nitrosopyrimidines which are unobtainable by the nitrosation of pyrimidines.
The other components of the reaction, i.e. the arylacetonitriles have been prepared by known methods. Attention is drawn, however, to the Ziegler bromination of toluene and substituted toluenes (Ziegler et al., Annalen, 1942, 551, 80; Schmidt and Karrer, Helv. Chim. Acta., 1946, 29, 573). This method is very suitable for the small scale preparation of certain substituted benzyl bromides in good yield and details are given in the experimental section. The alkoxyarylacetonitriles could not be prepared by this method, however, and were prepared from the corresponding aldehyde by the elegant method of Buck et al. (J. Amer. Chem. Soc., 1938, 60, 1789). The alkoxyaldehyde was converted to the azlactone, which on hydrolysis with sodium hydroxide solution was converted to the corresponding alkoxypyruvic acid. The oximes of these acids, on treatment with acetic anhydride, split out water and carbon dioxide to give the corresponding alkoxyacetonitriles.

Attempts to prepare 2:4:7-triamino-6-arylpteridines (III, R₁ = R₂ = NH₂, R₃ = Ar) from 2:4:6-triamino-5-nitrosopyrimidine (I, R₁ = R₂ = NH₂) and arylacetonitriles (II) in acetic acid in the presence of sodium acetate (Timmis, Nature, 1949, 164, 139) met with little
success. Only from p-nitrophenylacetonitrile (II, $R = p$-NO$_2$) was the corresponding pteridine (III, $R_1 = R_2 = NH_2$, $R_3 = p$-NO$_2$C$_6$H$_4$) obtained. From phenylacetonitrile and p-methoxyphenylacetonitrile faintly fluorescent solutions were obtained from which no pteridines could be isolated.

Of the three arylacetonitriles used in the above reaction p-nitrophenylacetonitrile will have the most activated methylene group by virtue of the strong electron attracting powers of the p-nitrophenyl group. In the presence of the weakly basic acetate anion this will be the compound most likely to condense if the reaction proceeds by way of the arylacetonitrile anion, as postulated later. It therefore seemed reasonable to attempt the reaction of phenylacetonitrile and 2:4:6-triamino-5-nitrosopyrimidine (I, $R = R_2 = NH_2$) in the presence of a stronger basic catalyst. For this purpose
the alkoxide ion was chosen and the reaction was carried out in β-ethoxyethanol in presence of 1 mole of sodium, when a 55% yield of the corresponding pteridine (III, R₁ = R₂ = NH₂, R₃ = Ph) was obtained. 2:4:6-Triamino-5-nitrosopyrimidine has been condensed with substituted arylacetonitriles in this media, when yields of 50% or better of the required pteridine were obtained. The group R in the arylacetonitriles (II) has been varied to include chloro-, ethoxy-, methoxy- and nitro- and the 2:4:7-triaminopteridines (III, R₃ = α-thienyl, R₃ = α-naphthyl) have also been prepared from α-thienylacetonitrile and α-naphthylacetonitrile respectively.

When p-chlorophenylacetonitrile was condensed with (I, R₁ = R₂ = NH₂) in boiling β-ethoxyethanol containing sodium β-ethoxyethoxide the reaction was complete in one hour, whereas the same condensation with p-chlorophenylacetonitrile required four to five hours. This effect, which has also been noted with p-methoxyphenylacetonitrile, may be attributed to the steric effect of the p-substituent. p-Nitrophenylacetonitrile could not be condensed with (I, R₁ = R₂ = NH₂) either in β-ethoxy-
ethanol containing sodium or in acetic acid containing sodium acetate.

2:4-Diamino-6-hydroxy-5-nitrosopyrimidine
(I, $R_1 = \text{NH}_2$, $R_2 = \text{OH}$) could not be condensed with phenylacetonitrile in $\beta$-ethoxyethanol containing sodium due to the extreme insolubility of the material in this medium. However, small yields (ca. 20%) of the required pteridine (III, $R_1 = \text{NH}_2$, $R_2 = \text{OH}$, $R_3 = \text{Ph}$) were obtained if the reaction was carried out in boiling ethylene glycol containing sodium. The yields in this reaction were low because considerable decomposition of the starting materials occurred in this medium and the product was difficult to purify. Similarly 2-hydroxy-4:6-diamino-5-nitrosopyrimidine (I, $R_1 = \text{OH}$, $R_2 = \text{NH}_2$) had to be condensed with phenylacetonitrile in ethylene glycol and again poor yields of the required pteridine (III, $R_1 = \text{OH}$, $R_2 = \text{NH}_2$, $R_3 = \text{Ph}$) were obtained.

2-Methylthio (I, $R_1 = \text{MeS}$, $R_2 = \text{NH}_2$) and 2-ethylthio-4:6-diamino-5-nitrosopyrimidine (I, $R_1 = \text{EtS}$, $R = \text{NH}_2$) may be condensed with phenylacetonitrile in ethanol containing 1 mole of sodium. Under these conditions there is some decomposition and methyl or ethylthiol
is evolved during the reaction. Nevertheless, the required methyl- and ethylthiopteridines (III, 
\[ R_1 = \text{MeS}, \quad R_2 = \text{NH}_2, \quad R_3 = \text{Ph} \quad \text{and} \quad R_1 = \text{EtS}, \quad R_2 = \text{NH}_2, \]
\[ R_3 = \text{Ph} \]) were obtained in good yield. From the reaction of 2-thio-4:6-diamino-5-nitrosopyrimidine (I, \[ R_1 = \text{SH}, \quad R_2 = \text{NH}_2 \]) and phenylacetonitrile in ethanol containing sodium two products were obtained. The first was the expected 2-thio-4:7-diamino-6-phenylpteridine (III, 
\[ R_1 = \text{SH}, \quad R_2 = \text{NH}_2, \quad R_3 = \text{Ph} \]) the other was alkali insoluble, had a sky-blue fluorescence in dilute acid solution and contained no sulphur. The fluorescence of this material was reminiscent of 2-methylthio-2-hydroxy- and 2-amino-4:7-diamino-6-phenylpteridines but different from 2-thio-4:7-diamino-6-phenylpteridine, which has a deep blue fluorescence. Analysis of this compound indicates that it may be 2-ethoxy-4:7-diaminopteridine (III, 
\[ R_1 = \text{OEt}, \quad R_2 = \text{NH}_2, \quad R_3 = \text{Ph} \]). Its ultra-violet absorption spectrum in 5% formic acid closely resembles the absorption spectra of 2:4:7-triamino-6-phenylpteridine and 2-hydroxy-4:7-diamino-6-phenylpteridine in the same solvent. Two explanations can be put forward for the formation of this alkali insoluble product. It could be
formed from an impurity in 2-thio-4:6-diamino-5-nitrosopyrimidine (perhaps 2-hydroxy-4:6-diamino-5-nitrosopyrimidine arising from oxidation of the 2-thio group with nitrous acid during its preparation from 2-thio-4:6-diaminopyrimidine) or it could be formed during the reaction of the nitroso compound with phenylacetonitrile in presence of sodium ethoxide in ethanol. Since 2-hydroxy-4:6-diamino-5-nitrosopyrimidine was not alkylated under similar conditions (i.e. in ethylene glycol containing sodium) it is unlikely that this was the impurity in 2-thio-4:6-diamino-5-nitrosopyrimidine. Therefore it seems likely that the alkali insoluble, non-sulphur-containing material is produced by an exchange reaction involving the sodium alkoxide during the reaction of the 2-thiopyrimidine and phenylacetonitrile (or from di-(4:6-diamino-5-nitrosopyrimidyl)-disulphide, which may be present as an impurity in the 2-thiopyrimidine). Volatile sulphur-containing materials are, in fact, evolved during the reaction.

Other pyrimidines which have been condensed with phenylacetonitrile in $\beta$-ethoxyethanol containing sodium are 2-phenyl-4-amino-6-hydroxy-5-nitrosopyrimidine
(I, $R_1 = \text{Ph}$, $R_2 = \text{OH}$), 2-methyl-4-amino-6-hydroxy-5-nitrosopyrimidine (I, $R_1 = \text{CH}_3$, $R_2 = \text{OH}$), 2-methylthio-4-amino-6-hydroxy-5-nitrosopyrimidine (I, $R_1 = \text{MeS}$, $R_2 = \text{OH}$), 4:6-diamino-5-nitrosopyrimidine (I, $R_1 = \text{H}$, $R_2 = \text{NH}_2$) and 4-amino-6-hydroxy-5-nitrosopyrimidine (I, $R_1 = \text{H}$, $R_2 = \text{OH}$). Thus by varying the groups $R_1$ and $R_2$ in I and R in II the generality of the reaction has been established.

The 2:4:7-triamino-6-arylppteridines may be characterised by their triacetyl derivatives, which were formed when the triamines are boiled with acetic anhydride. 2-Methylthio- and 2-ethylthio-4:7-diamino-6-phenylpteridines gave diacetyl derivatives under these conditions. The 7-amino-6-arylppteridines were further characterised by their ultra-violet absorption spectra in acid and in alkaline solution where possible. These spectra will be discussed later.

The facile condensation of 4-amino-5-nitrosopyrimidines with arylacetonitriles in the presence of basic catalysts could be explained by assuming that the reaction is initiated by the arylacetonitrile anion. Those sub-
stituents which facilitate anion formation (e.g., p-nitro) also favour the reaction. Thus, in the presence of the weakly basic acetate ion the presence of the p-nitro-group is necessary for reaction to take place with 2:4:6-triamino-5-nitrosopyrimidine. The condensation of the arylacetonitrile anion with a nitroso compound could proceed by a mechanism such as

\[
\begin{align*}
\text{R}_1 & \quad \text{R}_2 \quad \text{N} = \text{N} & + & \quad \text{R} \quad \text{CHCN} \\
\text{N} & \quad \text{C} = \text{N} \quad \text{R}_1 \quad \text{N} & \quad \text{R}_3 \quad \text{N} \quad \text{N} \quad \text{R}_1 \quad \text{R}_2 & \quad \text{R}_3 \quad \text{N} \quad \text{N} \quad \text{N} \quad \text{NH}_2
\end{align*}
\]

The condensation of nitroso compounds with phenylacetonitriles in alkaline solution had been shown
to occur by Erlich and Sachs (Ber., 1899, 32, 2541), who found that p-nitrosodimethylaniline and nitrosobenzene condensed with phenylacetonitrile and p-nitrophenylacetoni-
trile to give the corresponding azomethines (VII).

Later Barrow and Thornycroft showed that besides the
azomethine (VII, \( R_1 = H, \ R_2 = N(CH_3)_2 \)) the nitrone (VIII)
was also produced during the reaction of p-nitrosodimethyl-
aniline and phenylacetonitrile in alkaline solution.

An intermediate of the type (V) may well be the
first product of the condensation of arylnitroso compounds
with active methylene groups. This type of intermediate
can then lose a hydroxyl ion to give the azomethine or be
oxidised by excess of the nitroso- compound to the nitrone,
according to the nature of the substituents about the new C-N
bond. Barrow and Thornycroft have postulated a similar
intermediate for the production of azomethines or nitrones
from aryl-nitroso compounds and arylacetonitriles. They suggest that an arylhydroxylamine (IX) is first formed, which may then lose water to give the amino-
methane or be oxidised by excess of the nitroso com-
 pound to the nitron. It appears that in the reaction 
of 4-amino-5-nitrosopyrimidines with arylacetonitriles 
intermediates of the type (V) eliminate a hydroxyl ion 
preferentially for in all cases the major product iso-
 lated was the pteridine (VI). Pteridine N-oxides (X) 
may be formed in small amounts during the reaction by 
oxidation of the intermediate (V) but in no case were 
they formed in amounts sufficient to be isolated.

A polarisation of the nitroso group, similar 
to that postulated above, has been suggested by Remick 
(Electronic Interpretations of Organic Chemistry, 1943,
pg. 130) to explain the reaction of α-picoline methiodide with p-nitrosodimethylaniline. (When α-picoline replaces the methiodide no reaction occurs with p-nitrosodimethylaniline).

\[ \text{H} \text{Me}^* \text{C-H} \text{Me}^* \text{H} \text{Me}^* \text{O} = \text{N} \text{Me}_2 \]

Remick suggested that the positive pole produced at the nitroso nitrogen atom is partially annulled by the conjugative relay of electrons from the Me₂N⁻ group. Thus the reaction will only occur when the nucleophilic activity of the -CH₃ group in picoline has been increased by increasing the inductive effect of the ring nitrogen atom in picoline through salt formation. Similarly the positive change on the nitrogen atom of the nitroso group in the 5-nitrosopyrimidines can be partially annulled by the following electronic effects.
Despite these effects, which tend to decrease the electrophilic character of the nitrogen atom of the nitroso group, it is still sufficiently electrophilic to react with the arylacetonitrile anions under suitable conditions.

7-Hydroxy-6-alkylpteridines and 6-hydroxy-7-alkylpteridines have been obtained from 4:5-diaminopyrimidines and α-keto acids and esters (Elion, Hitchings and Russell, J. Amer. Chem. Soc., 1950, 72, 78), but as yet no 7-hydroxy-6-arylppteridines or 6-hydroxy-7-arylppteridines have been reported. 7-Hydroxy-6-arylppteridines (XII) have now been obtained by the condensation of 4-amino-5-nitrosopyrimidines (I) with arylacetylochlorides (XI). Thus phenylacetyl chloride and 2:4:6-triamino-5-nitroso-
pyrimidine (I, \( R_1 = R_2 = \text{NH}_2 \)) condense at 140° to give 2:4-diamino-7-hydroxy-6-phenylpteridine (XII, \( R_1 = R_2 = \text{NH}_2, \text{Ar} = \text{Ph} \)), a substance which in glacial acetic acid solution has a sky-blue fluorescence. This substance has been obtained as the major product of condensation of phenylglyoxylic acid with a salt of 2:4:5:6-tetraaminopyrimidine in aqueous solution at pH5. If the reaction was carried out in 2N hydrochloric acid solution about 60% of the total product was the 7-hydroxy isomer and 40% was the 6-hydroxy isomer. These two compounds differ considerably in several respects. The latter is readily soluble in dilute ammonia solution, whereas the former is not, indicating that a hydroxyl group in the 6-position is more acidic than that in the 7-position. The fluorescence of the 6-hydroxy isomer in alkaline solution is green, whereas
that of the 7-hydroxy isomer is sky-blue, and the ultra-violet absorption spectra of the two compounds are markedly different. Elion, Hitchings and Russel (loc. cit.) have studied the condensation of α-keto acids with 4:5-diaminopyrimidines and have found that generally the 7-hydroxy isomer is the major product when the reaction is carried out at pH 5, whilst the 6-hydroxy isomer is the major product if the reaction is carried out in strong acid solution.

p-Nitrophenylacetyl chloride and p-methoxyacetyl chloride also condense with 2:4:6-triamino-5-nitrosopyrimidine to give 2:4-diamino-6-p-nitrophenyl-7-hydroxypteridine (XII, \( R_1 = R_2 = \text{OH}, \text{Ar} = p-\text{NO}_2\text{C}_6\text{H}_4 \)) and 2:4-diamino-6-p-methoxyphenyl-7-hydroxypteridine (XII, \( R_1 = R_2 = \text{NH}_2, \text{Ar} = p-\text{MeOC}_6\text{H}_4 \)) respectively. Of these two compounds the former has only a weak fluorescence in alkaline solution, whilst the latter, like the 6-phenyl analogue, has a strong sky-blue fluorescence in ultra-violet light. A probably related effect is that 2:4:7-triamino-6-p-nitropheryl-pteridine has a weak fluorescence compared with that of the 6-phenyl analogue.
The condensation of 6-hydroxy-4-amino-5-nitrosopyrimidines with arylacetyl chlorides could lead to a mixture of a pteridine and the related pyrimido-oxazine (XIII) system. In an attempted condensation of 2:4-diamino-6-hydroxy-5-nitrosopyrimidine (I, \(R_1 = \text{NH}_2\), \(R_2 = \text{OH}\)) with phenylacetyl chloride the temperature had to be raised to 175°F before any reaction occurred, and although the product had a strong fluorescence no pure products could be isolated. When an attempt was made to condense 2-methylthio-4:6-diamino-5-nitrosopyrimidine with phenylacetyl chloride at 130°F methylthiol was evolved and inseparable mixtures were obtained.

![Chemical Structure](attachment:image.png)

As the scope of this reaction appears to be limited by the drastic reaction conditions required and the formation of by-products, attempts were made to condense ethyl phenylacetate and phenylacetamide with 2:4:6-
triamino-5-nitrosopyrimidine, but in no case was the required 2:4-diamino-6-phenyl-7-hydroxypteridine obtained. The condensation of arylacetyl chlorides with 4-amino-5-nitrosopyrimidines may occur by a similar mechanism to that postulated for the condensation of arylacetonitriles with these compounds. It seems equally likely, however, that the reaction could proceed by the direct dehydration of the 4-arylacetamidopyrimidine (XIV), as shown below, and the conditions of the reaction, i.e. high temperature and excess of reagent, would tend to favour such a mechanism.

\[ \text{XIV} \]
An attempt has been made to ascertain the nature of the amino groups in different positions of the pteridine nucleus by hydrolysis with hydrochloric acid and by treatment with nitrous acid. It has been found that 2:4:7-triamino-6-phenylpteridine (XV) is converted to a mixture of 2:7-diamino-4-hydroxy-6-phenylpteridine (XVI) and 2:4-diamino-7-hydroxy-6-phenylpteridine (XVII) on boiling for one hour with 5N hydrochloric acid, but is recovered unchanged on boiling for several hours with more dilute acid, e.g., 2N hydrochloric acid.

The presence of (XVI) and (XVII) together in the reaction product indicates that both the 4- and 7-amino groups are capable of existence in the corresponding imino-forms (XVIII) and (XIX).
That the 4-amino group in the 4-aminopteridines (XX) is capable of existence in the imino form (XXI) has been demonstrated by Taylor and Cain (J. Amer. Chem. Soc., 1949, 71, 2538). These authors have shown that in common with the 2- and 4-aminopyrimidines and the 2- and 4-aminopurines there is a difference in reactivity in the amino groups in the 2- and 4- positions of the pteridine nucleus. Thus an amino group in the 2-position is stable to hydrolysis with 6N hydrochloric acid (although on prolonged hydrolysis it may be replaced by a hydroxy group), whilst it is replaced by a hydroxyl group on treatment with nitrous acid in strong acid solution; however, an amino group in the 4-position is hydrolysed by strong acid and is stable to nitrous acid. On the basis of the reaction of aminopteridines with nitrous acid
and mineral acid Taylor and Cain suggest that they exist in a single tautomeric form in acid solution involving a 2-amino group, removable by nitrous acid, and a 4-imino group, which is hydrolysed by mineral acid.

Another consideration put forward by Taylor and Cain is that whereas an amino group in the 2-position is part of a guanidine structure, an amino group in the 4-position is part of an amidine structure. They point out that guanidine is more stable to acid hydrolysis than an amidine and, therefore, it is to be expected that a 2-amino group will be more stable to acid hydrolysis than a 4-amino group. Since the 7-amino group in the pteridine nucleus is also part of an amidine structure this consideration will apply to an amino group in this position.
Taylor and Cain also observed that the amino groups in 2:4-diaminopteridines were unaffected by nitrous acid regardless of the substituents in the pyrazine portion of the nucleus. This has now been found to be true in the case of 2:4:7-triamino-6-phenylpteridine, which was recovered unchanged after treatment with nitrous acid. Taylor and Cain attributed this to the presence of an electron attracting group in the 4- position of the ring. In the case of the 2-amino-4-hydroxypteridines both of the ring nitrogen atoms will become positively charged in strong acid solution and the presence of an amino group in the 4- position will introduce another salt forming group, thus decreasing the ease of reaction of the 2-amino group with nitrous acid. They note as a parallel the decrease in the ease of diazotisation of aniline with the introduction of nitro groups (Saunders, The Aromatic Diazo Compounds, pgs. 3 - 16).

The formation of 2:4-diamino-7-hydroxy-6-phenylpteridine (XVII) on hydrolysis of 2:4:7-triamino-6-phenylpteridine rather than 2-amino-4:7-dihydroxy-6-phenylpteridine (XVIII) suggests that the 4- and 7-amino groups are
both hydrolysing together but that once one of them is hydrolysed hydrolysis of the other becomes more difficult. This suggests a further method of attack on the nature of the amino groups in different positions in the pteridine nucleus and on the influence of other substituent groups.

2-Hydroxypteridines have now been obtained by the removal of the methylthio- group of 2-methylthiopteridines by mild acid hydrolysis. Thus, by boiling 2-methylthio-4:7-diamino-6-phenylpteridine and 2-methylthio-4-hydroxy-6-phenyl-7-aminopteridine with 2N hydrochloric acid 2-hydroxy-4:7-diamino-6-phenylpteridine and 2:4-dihydroxy-6-phenyl-7-aminopteridine were obtained respectively. The former is also produced by the oxidation of 2-thio-4:7-diamino-6-phenylpteridine with hydrogen peroxide and in small yield by the direct condensation of 2-hydroxy-4:6-diamino-5-nitrosopyrimidine and phenylacetonitrile. Comparison of the ultra-violet absorption spectra of the products of these reactions showed them to be identical.

The conversion of 2-methylthiopyrimidines into the corresponding 2-hydroxy compounds by hydrolysis with
mineral acids is well known (Lythgoe, Quarterly Reviews, 1949, 2, 197-9; Johnson and Hahn, Chem. Reviews, 1933, 13, 193). Thus 2-methylthio-5-methylaminopyrimidine has been converted to 2-hydroxy-5-methylaminopyrimidine by boiling with concentrated hydrochloric acid for eight hours (Case and Hill, J. Amer. Chem. Soc., 1929, 51, 1950) and 4:5-dimethylcytosine has been obtained from 2-ethylthio-6-amino-4:5-dimethylpyrimidine by boiling with 48% hydrobromic acid (Chi and Kao, J. Amer. Chem. Soc., 1936, 58, 772). The replacement of the 2-methylthio- group by a 2-hydroxy- group in 2-methylthio-4:7-diamino-6-phenylpteridine and 2-methylthio-4-hydroxy-7-amino-6-phenylpteridine, however, provide the first demonstration that 2-alkylthiopteridines undergo this reaction. This method provides the best route to 2-hydroxypteridines since the condensation of 4-amino-5-nitrosopyrimidines with arylacetonitriles does not occur readily when a hydroxy group is present in the 2- or 4- position of the pyrimidine ring.

The oxidation of 2-thiopteridines was first observed by Polonovski, Vieillefosse and Pesson (Bull. Soc. Chim., 1945, 12, 78). These authors showed that
2-thio-4-hydroxypteridine and 2-thio-4-hydroxy-6:7-diphenylpteridine were oxidised by hydrogen peroxide in alkaline solution to the corresponding 2-hydroxy compounds. They further found that these compounds were converted to the corresponding 2-ethylthio compounds on treatment with ethyl bromide in alkaline alcoholic solution. Similarly it has now been shown that 2-thio-4:7-diamino-6-phenylpteridine is transformed into the corresponding 2-ethylthio compound when it is boiled with ethyl bromide in sodium ethoxide solution. The compound formed by this method is identical with that obtained by the direct condensation of 2-ethylthio-4:6-diamino-5-nitrosopyrimidine and phenylacetonitrile.
The ultraviolet absorption spectra of certain 6-aryl-7-amino- and 6-aryl-7-hydroxypteridines.

The spectra of these pteridines, which have been determined (where possible) in acid and alkaline solution, are shown in Figs. 1 - 15. Due to the insolubility of most of the compounds in dilute hydrochloric acid the spectra in acid solution have been determined in 4.5% formic acid. Solutions in this solvent were prepared by dissolving the substance in 90% formic acid and diluting to the requisite concentration.

Fig. 1 shows the spectra of the isomeric 2:4-diamino-6-phenyl-7-hydroxypteridine and 2:4-diamino-6-hydroxy-7-phenylpteridine in both acid and alkaline solution. These spectra resemble those of 2:4-diamino-6-methyl-7-hydroxypteridine and 2:4-diamino-6-hydroxy-7-methylpteridine (Elion, Hitchings and Russell, J.A.C.S., 1950, 72, 78). The presence of the phenyl group in the 5- or 7- position has, as expected (because of the extra conjugation of the aryl-group with the pteridine nucleus), increased the intensity of the bands, which are also shifted to a longer wavelength. A further analogy between the spectra of the methyl isomers and phenyl
isomers is the change in spectra brought about in changing from acid to alkaline media. In the case of both the 7-methyl-6-hydroxy and 7-phenyl-6-hydroxy isomers the change from acid to alkaline media causes a drop in intensity and a shift of the long wavelength band to a longer wavelength, whereas in the case of both the corresponding 6-methyl-7-hydroxy- and 6-phenyl-7-hydroxy- compounds the long wavelength band remains practically at the same wavelength and unchanged in intensity.

<table>
<thead>
<tr>
<th>2:4-Diaminopteridine</th>
<th>N/10 Acid solution</th>
<th>N/10 Alkali solution</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( m \mu )</td>
<td>( \mu )</td>
</tr>
<tr>
<td>6-methyl-7-hydroxy-</td>
<td>333</td>
<td>15,000</td>
</tr>
<tr>
<td>6-phenyl-7-hydroxy-</td>
<td>362</td>
<td>19,300</td>
</tr>
<tr>
<td>7-methyl-6-hydroxy-</td>
<td>350</td>
<td>7,100</td>
</tr>
<tr>
<td>7-phenyl-6-hydroxy-</td>
<td>380</td>
<td>17,400</td>
</tr>
</tbody>
</table>

The above table shows the pertinent relationships of the long wavelength band of the above compounds. These relationships provide confirmatory evidence that the product from the condensation of phenylacetyl chloride and 2:4:6-triamino-5-nitrosopyrimidine is the 6-phenyl-7-hydroxy isomer. Further, since 2:4:7-triamino-6-phenylpteridine (obtained by
the condensation of phenylacetonitrile and 2:4:6-triamino-5-nitrosopyrimidine gives the above 2:4-diamino-6-phenyl-7-hydroxypteridine on hydrolysis this triamine is also correctly formulated. Thus, both the method of preparation and the properties of these compounds are in accord with the formulation of these compounds as 6-aryl-7-hydroxy- and 6-aryl-7-aminopteridines.

The spectra (Figs. 2-8) are arranged so that the effect of changing substituents in the 2- position and 6- position of the pteridine nucleus can be observed. The long wavelength band in each series undergoes relatively little change with change of substituent but the introduction of a hydroxyl- or thio- group into the 2- position causes a marked change in the shorter wavelength band (Figs. 2 and 8). Figs. 9, 10, 11 and 13 show the spectra of certain thio- and hydroxypteridines in acid and alkaline solution and again it is the low wavelength band which is affected most by the change in solvent. In each case the long wavelength band is shifted to longer wavelengths in passing from acid to alkaline solution. The spectra of the three monohydroxy-diamino-6-phenylpteridines in 4.5% formic acid are shown in Fig. 12.
Fig. 15 shows the spectrum of the alkali insoluble material from the condensation of 2-thio-4:6-diaminopyrimidine and phenylacetonitrile, which more closely resembles the spectra of 4:7-diamino-6-phenylpteridines with amino-, hydrogen- or methylthio- groups in the 2- position than those with hydroxyl- or thio- groups in this position. Combined with the analytical figures of this compound the spectral data indicate that this compound could be 2-ethoxy-4:7-diamino-6-phenylpteridine. These relationships are shown in the table below:

**Ultraviolet absorption spectra of some 4:7-diamino-6-phenylpteridines**

<table>
<thead>
<tr>
<th></th>
<th>Maxima</th>
<th>Minima</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \lambda )</td>
<td>( E )</td>
</tr>
<tr>
<td>Unsubstituted</td>
<td>356 16,200</td>
<td>309 3,850</td>
</tr>
<tr>
<td></td>
<td>281 5,100 (shoulder)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>261 16,800</td>
<td></td>
</tr>
<tr>
<td>2-Amino-</td>
<td>356 20,000</td>
<td>307 2,900</td>
</tr>
<tr>
<td></td>
<td>282 6,600 (shoulder)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>255 14,500</td>
<td></td>
</tr>
<tr>
<td>2-Methylthio-</td>
<td>364 22,900</td>
<td>311 3,400</td>
</tr>
<tr>
<td></td>
<td>287 21,500</td>
<td></td>
</tr>
</tbody>
</table>
These spectra provide general confirmatory evidence of the structure of this series of compounds. All the spectra investigated have an intense high wavelength band the maximum of which lies in the region 350–380 μ for both acid and alkaline media. This band undoubtedly arises from light absorption by the whole chromophore, including the pteridine and phenyl nuclei.
FIG. 2

IN 4.5% FORMIC ACID.

R = NH₂
R = OH
R = H
R = SH
R = CH₃S

λ (mμ)
FIG. 3

IN 4.5% FORMIC ACID

$\epsilon \times 10^{-3}$

$\lambda (\text{m} \mu)$
FIG. 4

\[ R \quad \text{OH} \quad \text{N}^+ \text{O} \quad \text{OH} \quad \text{R} \quad \text{CH}_3 \quad \text{R} \quad \text{CH}_3S \]

\[ \text{IN} \quad \text{NaOH} \]

\( \lambda \) (m\( \mu \))

\[ \epsilon \times 10^{-3} \]

- \( R = \text{OH} \), ....
- \( R = \text{CH}_3 \),
- \( R = \text{NH}_2 \),
- \( R = \text{H} \),
- \( R = \text{CH}_3S \),
FIG. 6

IN 4.5% FORMIC ACID
R= p-Cl, 
R= O-Cl, 

$\epsilon \times 10^{-3}$

$\lambda$ (m$\mu$)
FIG. 8

![Graph showing absorption spectra for different R groups in 4.5% formic acid.](image)

- **R = OH** (dotted line)
- **R = H** (solid line)
- **R = NH₂** (dashed line)

The graph illustrates the absorption spectra of a compound with varying R groups in a 4.5% formic acid solution.
FIG. 9

\[ \text{IN } \frac{N}{10} \text{ NaOH} \]

\[ \text{IN } 4.5\% \text{ FORMIC ACID} \]

\[ \text{IN } \frac{N}{10} \text{ NaOH} \]

\[ \text{IN } 4.5\% \text{ FORMIC ACID} \]

\[ \varepsilon \times 10^3 \]

\[ \lambda (\text{m\mu}) \]
FIG. 10

[Graph showing absorption spectra of a molecule in different conditions: 4.5% formic acid and NaOH.]
FIG. 12

For the given compounds, the absorption maximum wavelengths ($\lambda$) are measured in the range from 210 to 410 nm. The figures show the variation of absorbance ($\epsilon \times 10^{-3}$) with wavelength ($\lambda$). The compounds are studied in 4-5% formic acid solution.
FIG. 14

IN 4.5\% FORMIC ACID.

$\epsilon \times 10^{-3}$

$\lambda \text{ (m\AA)}$
FIG. 15

ALKALI INSOLUBLE PRODUCT FROM THE CONDENSATION OF
2-thio-4,6-diamino-5-nitropyrimidine and phenylacetonitrile
IN 4-5% FORMIC ACID

PROBABLY:

\[ \text{EtO} \]

\[ \text{N} \]

\[ \text{N} \]

\[ \text{NH}_2 \]

\[ \text{NH}_2 \]

\[ \epsilon \times 10^{-3} \]

\(\lambda \text{ (mµ)}\)
Quaternary salts from 2-chloro-5-nitropyrimidines and their reactions.

I.e., the chloride of the above compound would be: $\text{R}^+ \cdot \text{N}^+ \cdot \text{N}^+ \cdot \text{N}^+ \cdot \text{pyridinium}^+ \cdot \text{pyridinium}^+ \cdot \text{pyridinium}^+ \cdot \text{pyridinium}^+ \cdot \text{pyridinium}^+ \cdot \text{pyridinium}^+ \cdot \text{pyridinium}^+$.
Nomenclature

The compounds described in this section are numbered in the following ways.

1) Pyrimidine derivatives:

\[
\begin{align*}
\text{N} & \rightarrow \text{H} \rightarrow \text{S} \rightarrow \text{t} \rightarrow \text{4} \rightarrow \text{pyridyl} \rightarrow \text{a} \rightarrow \text{m} \rightarrow \text{pyrimidyl} \\
& \rightarrow \text{pyridinim chloride.}
\end{align*}
\]

2) Quaternary salts:

\[
\begin{align*}
\left\{ \begin{array}{c}
5 \quad 6 \\
4 \quad 3 \quad 2 \quad 1' \quad 5' \\
3' \quad 4' \quad 3'' \quad 4'' \quad 6'' \quad 6'''
\end{array} \right\}^+
\end{align*}
\]

i.e. The chloride of the above compound would be:

\[
N=\{2'=[4'-(2''-pyridyl)-aminopyrimidyl]}-pyridinium chloride.
\]
3) Pyrimidotriazoles:

For convenience these compounds were numbered as shown in Fig. I when the experimental work was carried out and they are numbered as such in the experimental section. In the introduction, however, the current American method of numbering is used (Fig. II).

4) Derivatives of isoquinoline and 1:2-dihydroisoquinoline.
Purine antagonists such as 2:6-diaminopurine and 8-azaguanine have been shown to have some activity in retarding tumour growth. The former was shown by Hitchings et al. (J. Biol. Chem., 1948, 174, 765; Annals of the New York Academy of Sciences, 1950, 52, 1318) to be an inhibitor of adenine and Burchenal et al. (Cancer, 1949, 2, 119) has reported the activity of this inhibitor against leukemia. 8-Azaguanine was shown by studies on E. coli (Roblin et al., J. Amer. Chem. Soc., 1945, 67, 290) and on L. casei (Hitchings et al., Annals of the New York Academy of Sciences, 1950, 52, 1318) to be a more or less specific guanine antagonist and Kidder et al. (Science, 1949, 109, 511) have demonstrated the inhibition of mouse leukemia with this compound.

Gordon (J. Amer. Chem. Soc., 1951, 73, 984) has prepared, as potential purine antagonists, compounds in which the 7- and 9- positions of the purine nucleus would be blocked to riboside formation by the inclusion of another fused ring. He used the thiazoline ring to block these positions and prepared some thiazoline derivatives of 2:6-diaminopurine (I). These derivatives were, however, found to be inactive when screened as cancer
inhibiting agents (Gordon, Siri and Campbell, *Science*, 1951, **113**, 61).

At the commencement of this work it was hoped to prepare potential purine antagonists similar to those prepared by Gordon, but with the thiazoline ring replaced with a pyridine ring, i.e. the dihydropyridinopurine ring system (II). Morgan and Stewart (J., 1938, 1292; J., 1939, 1057) have shown that 2-(2':4'-dinitrophenyl)-aminopyridine and 2-(2':4':6'-trinitrophenyl)-aminopyridine lose nitrous acid on heating to give the 1:3-diazalines (III) (R = H or NO₂) respectively. It was expected that appropriately substituted 4-(2'-pyridyl)amino-5-nitropyrimidines (IV) could be similarly ring closed with loss of nitrous acid to give the ring system (II). However, this has not proved to be the case and the investigations were therefore diverted towards the reactions of 2-chloro-5-nitropyrimidines
with pyridines, aminopyridines and related bases, to yield quaternary salts.

\[
\begin{array}{c}
\text{IV} \\
\begin{array}{c}
\text{R}_1 \\
\text{N} \\
\text{NH} \\
\text{NO}_2 \\
\text{R}_1 \\
\end{array}
\end{array}
\quad \xrightarrow{\text{-HNO}_2} \quad
\begin{array}{c}
\text{II} \\
\begin{array}{c}
\text{R}_1 \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{R}_1 \\
\end{array}
\end{array}
\]

It has long been known that 2:4-dichloro-5-nitropyrimidine (\(V, \text{R}_1 = \text{R}_2 = \text{Cl}, \text{R}_3 = \text{H}\)) and 2:4-dichloro-5-nitro-6-methylpyrimidine (\(V, \text{R}_1 = \text{R}_2 = \text{Cl}, \text{R}_3 = \text{Me}\)) react with ammonia in the cold to give the corresponding 2-chloro-4-amino compounds (\(V, \text{R}_1 = \text{Cl}, \text{R}_2 = \text{NH}_2, \text{R}_3 = \text{H or Me}\)), and under more vigorous conditions to give the diaminopyrimidines (\(V, \text{R}_1 = \text{R}_2 = \text{NH}_2, \text{R}_3 = \text{H or Me}\)), (Gabriel and Coleman, Ber., 1901, 34, 1244, and Isay, ibid., 1906, 39, 250). Similarly (\(V, \text{R}_1 = \text{R}_2 = \text{Cl}, \text{R}_3 = \text{H or Me}\)).
\( R_3 = \text{H or Me} \) can be condensed with \( \alpha \)-amino acid esters and \( \alpha \)-aminoketones to yield the \( \alpha \)-(5-nitropyrimidylamino)-acid esters (V, \( R_1 = \text{Cl} \), \( R_2 = \text{NHCH}_2\text{CO}_2\text{Et} \), \( R_3 = \text{H or Me} \)) and \( \alpha \)-(5-nitro-4-pyrimidylamino)-ketones (V, \( R_1 = \text{Cl} \), \( R_2 = \text{NHCH}_2\text{CO}_2\text{CH}_3 \), \( R_3 = \text{H or Me} \)), together with some of the disubstituted compounds (V, \( R_1 = R_2 = \text{NHCH}_2\text{CO}_2\text{Et} \) or \( \text{NHCH}_2\text{CO}_2\text{CH}_3 \), \( R_3 = \text{H or Me} \)), (Boon, Ramage and Jones, J., 1951, 98; Boon and Jones, ibid, 1951, 591; Polonovski and Jerome, Compt. rend., 1950, 230, 392).

The condensation of 2-aminopyridine with 2:4-dichloro-5-nitropyrimidine is, however, more complicated than the reactions described above. When these two compounds were brought together in ice cold methanol the expected 2-chloro-4-(2\(^{\prime}\)-pyridyl)-amino-5-nitropyrimidine (IV, \( R_1 = \text{Cl} \), \( R_2 = \text{H} \)) formed only a minor proportion of the reaction product. The major product of the reaction was a yellow water-soluble material, which contained ionic chlorine.

\[
\begin{align*}
\text{V} & \quad \text{IV} \\
\text{VI}
\end{align*}
\]
The ionic chlorine in this material may be replaced, in aqueous solution, by ionic bromine or iodine and since the compound may also be obtained by treating either a boiling solution of (IV, \( R_1 = Cl, R_2 = H \)) in methanol with a further mole of 2-aminopyridine or by treating a hot methanolic solution of (V, \( R_1 = R_2 = Cl, R_3 = H \)) with three moles of 2-aminopyridine, it has, therefore, been formulated as the quaternary salt (VI, \( R_1 = H \)). (IV, \( R_1 = Cl, R_2 = Me \)) is the only product of the reaction.

When 2-aminopyridine was replaced in this reaction by the homologous 3- and 4-methyl-2-aminopyridines only the quaternary salts (VII) and (VIII) were obtained under a variety of conditions. Likewise 2:4-dichloro-5-nitro-6-methylpyrimidine (V, \( R_1 = R_2 = Cl, R_3 = Me \)) when treated with 2-aminopyridine gave only the quaternary salt (VI, \( R_1 = Me \)). If, however, the dichloro compounds (V, \( R_1 = R_2 = Cl, R_3 = H \) or \( Me \)) were treated with 6-methyl-2-aminopyridine only the chloro group in the 4 position of the pyrimidine nucleus was replaced by the 6-methyl-2-aminopyridyl residue under mild conditions to give the compounds (IX, \( R_1 = Cl, R_2 = H \) or \( Me \)) and under more vigorous conditions both of the chloro groups were replaced to give
the compounds (IX, $R_1 = 2'-(6'-methylpyridyl)$-amino, $R_2 = \text{H or Me}$). The non-formation of quaternary salts from 6-methyl-2-aminopyridine can be attributed to the steric effect of the substituents on both $\alpha$-carbon atoms of the pyridine nucleus.

When 2:4-dichloro-5-nitro-6-aminopyrimidine ($V$, $R_1 = R_2 = \text{Cl}$, $R_3 = \text{NH}_2$) is treated with two moles of 2-aminopyridine at 0° in ethanol solution the monochloro-compound (IV, $R_1 = \text{Cl}$, $R_2 = \text{NH}_2$) is the only product of the reaction. In acetone solution at room temperature, however, one mole of the dichloro-compound and three moles of 2-aminopyridine gave a mixture of the quaternary salt (VI, $R_1 = \text{NH}_2$) and the monochloro-compound (IV, $R_1 = \text{Cl}$, $R_2 = \text{NH}_2$) after long standing. From the foregoing observations it seems that the presence of a methyl group in either the pyrimidine or pyridine moieties facilitates the formation of a quaternary salt whilst an amino group in the 6-position of the pyrimidine nucleus has the opposite effect.

The 2-chloro-group of several 2-chloro-5-nitopyrimidines has been shown to undergo quaternary salt
formation with 2-aminopyridine and also with pyridine. The following pyrimidines react with 2-aminopyridine in either acetone or benzene solution to give the corresponding 2-aminopyridinium salts (XI): 2-chloro-4-[2'-{(6'-methylpyridyl)}-amino]-5-nitropyrimidine (XI, R₁ = 2'-{(6'-methylpyridyl)}-amino, R₂ = H), 2-chloro-4-anilino-5-nitropyrimidine (XI, R₁ = NH₉H₅, R₂ = H), 2-chloro-4-aminopyridine (XI, R₁ = H, R₂ = H).
The formation of quaternary salts from pyridine and reactive chloro-compounds has been shown to occur by Zinke et al. (Annalen, 1904, 358; 1905, 361; 1905, 362; 1914, 493; 1914, 363).

These authors treated pyridine with 2:4-dinitrochlorobenzene and 2:4-dinitrochloronaphthalene and obtained the benzenes and 2:4-dinitrochloromorpholine and obtained the following pyrimidines: 2-chloro-5-nitropyrimidine (X, $R_1 = \text{Me}$, $R_2 = \text{H}$), 2-chloro-4-[(2'-pyridyl)-amino]-5-nitropyrimidine (X, $R_1 = \text{Me}$, $R_2 = \text{H}$), and 2-chloro-4-anilino-5-nitropyrimidine (X, $R_1 = \text{Me}$, $R_2 = \text{H}$).

The pyrimidines also react with pyridine to give the pyridinium salts (XII) as do the following pyrimidines: 2-chloro-4-[(2'-pyridyl)-amino]-5-nitropyrimidine (X, $R_1 = \text{Me}$, $R_2 = \text{H}$), 2-chloro-4-[(2'-pyridyl)-amino]-5-nitropyrimidine (X, $R_1 = \text{Me}$, $R_2 = \text{H}$), and 2-chloro-4-anilino-5-nitropyrimidine (X, $R_1 = \text{Me}$, $R_2 = \text{H}$).

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The pyrimidines also react with pyridine to give the pyridinium salts (XII) as do the following pyrimidines: 2-chloro-4-[(2'-pyridyl)-amino]-5-nitropyrimidine (X, $R_1 = \text{Me}$, $R_2 = \text{H}$), 2-chloro-4-[(2'-pyridyl)-amino]-5-nitropyrimidine (X, $R_1 = \text{Me}$, $R_2 = \text{H}$), and 2-chloro-4-anilino-5-nitropyrimidine (X, $R_1 = \text{Me}$, $R_2 = \text{H}$).
The reaction of aminopyridines with 2:4-
dinitrochlorobenzene was studied by Vompe and Turitsyna
1951, 45, 3846), who showed that whilst 3- and 4-amino-
pyridines gave the corresponding quaternary salts (XV)
and (XVI) 2-aminopyridine gave 2-(2',4'-dinitrophenyl)-
aminopyridine (XVII). Vompe and Turitsyna have attributed
the non-formation of a quaternary salt from 2-aminopyridine
and 2:4-dinitrochlorobenzene to steric factors but the
results reported here show that with a sufficiently reactive
cloro- compound the effect of steric factors in the 2-aminopy-
ridine moiety may be overcome. It must be pointed out,
however, that an o-nitro- group in 2:4-dinitrochlorobenzene
will probably have a greater steric effect than will the
ring nitrogen atoms of 2-chloro-5-nitropyrimidines and it is noted that salt formation only occurs with the 2-chloro-group of 2:4-dichloro-5-nitropyrimidine when 2-aminopyridine is used as the quaternising agent, and not with the 4-chloro-group, which is hindered by the 5-nitro-group.

Evidence that the 2-chloro-group is involved in the quaternisation process has been obtained as follows. 2-Amino-4-chloro-5-nitro-6-methylpyrididine (XX) has been obtained by the chlorination of the hydroxy compound (XIX) with phosphoryl chloride (Boon, Ramage and Jones, J., 1951, 96) and since this hydroxy compound (XIX) has been obtained by the nitration of the product (XVIII) of the condensation of guanidine and ethyl acetoacetate, the amino-group must
be in the 2- position of the pyrimidine nucleus. The mono- chloro- compound (XX) on treatment with 2- amino- pyridine gives the same product (XXI) as is obtained by heating the quaternary salt (VI, \( R_1 = \text{Me} \)) with methanolic ammonia in a sealed tube. The action of aniline and ammonia on the quaternary salt (VI, \( R_1 = \text{H} \)) provides further evidence that the 2- chloro- group is involved in quaternary salt formation. Treatment of the salt (VI, \( R_1 = \text{H} \)) with a 10% ethanolic solution of aniline gives 2-anilino-4-(2'-pyridyl)-amino-5-nitropyrimidine (XXII) and with methanolic ammonia 2-amino-4-(2'-pyridyl)-amino-5-nitropyrimidine (XXIII). These two compounds are different from their isomers (XXIV) and (XXV), which are obtained treating 2-chloro-4-anilino-5-nitropyrimidine and 2-chloro-4-amino-5-nitropyrimidine respectively with 2-aminopyridine.
reaction of the 8-substituted salts from a variety of aliphatic, alicyclic, aromatic primary and secondary amines to give 2-unsubstituted and 2-substituted-amine-pyridines. The products of the reaction, with ammonia, to give 2-amino-8-(2'-pyridyl)-amine-pyridine, were identified with the product obtained from 2-amino-8-(2'-pyridyl)-amine-pyridine with p-toluenesulfonic acid. Similarly, the 2-pyridyl compound (XVI, R₂ = C₆H₅), (XV, R₂ = H) can be obtained either from the salt (XVII, R₀ = C₆H₅), (XVII, R₀ = H) or from 8-chloro-2-(2'-pyridyl)amine-pyridine by treatment with 10% ethanolic ammonia. This salt was also heated with p-toluenesulfonic acid, with the alicyclic amines, piperazine, 2-piperazine and 2-piperazinylamine, with the prostaglandin amines, aminocinnoline, tetrahydroquinoline, and 1,4-dihydropyridine and with sodium cyanide. In all cases the 2-substituted-amine-pyridine was obtained.
The reaction of the quaternary salts from 2-chloro-5-nitropyrimidines with amines.

Salts of the type (XI) and (XII) react with ammonia and a variety of aliphatic, alicyclic and aromatic primary and secondary amines to give 2-amino- and 2-substituted-aminopyrimidines. The salt (XI, R = 2'-pyridylamino, R₂ = H) reacts, in ethanol solution, with ammonia to give 2-amino-4-(2'-pyridyl)-amino-5-nitropyrimidine (XIII), which is identical with the product obtained by boiling 2-chloro-4-(2'-pyridyl)-amino-5-nitropyrimidine with methanolic ammonia. Similarly the 2-piperidino-compound (IV, R₁ = C₅H₁₀N, R₂ = H) can be obtained either from the salt (XI, R₁ = 2'-pyridylamino, R₂ = H) or from 2-chloro-4-(2'-pyridyl)-amino-5-nitropyrimidine by treatment with 10% ethanolic piperidine. This salt has also been treated, in ethanol solution, with the aliphatic amines, methylamine, ethylamine, diethylamine and dimethylamine; with the aromatic amines aniline, anisidine, p-chloroaniline, N-methylaniline and β-naphthylamine and also with morpholine, benzylamine and phenylhydrazine, and in all cases the 2-substituted-aminopyrimidine was obtained.
For the reaction with aromatic amines it was found that aqueous acetone was a better solvent.

The salts (VII), (VIII), (VI, R = Me), (VI, R = NH₂) and (XI, R₁ = 2'-(6'-methylpyridyl)-amino, R = H) also react with many of the above amines to give 2-substituted-aminopyrimidines. Thus it has been shown that 2-aminopyridinium salts of the type (XI) react with amines in such a way that the salt forming linkage is broken.

The quaternary pyridinium salt (XII, R₁ = 2'-pyridylamino, R = H) also reacts with aniline, phenylhydrazine and benzylamine in this way to give 2-anilino-4-(2'-pyridyl)-amino-5-nitropyrimidine, 2-phenylhydrazino-4-(2'-pyridyl)-amino-5-nitropyrimidine and 2-benzylamino-4-(2'-pyridyl)-amino-5-nitropyrimidine respectively. When this salt was treated in alcohol solution with piperidine, however, two products were obtained in approximately equal amounts; the first was the expected 2-piperidino-4-(2'-pyridyl)-amino-5-nitropyrimidine and the second was 2-amino-4-(2'-pyridyl)-amino-5-nitropyrimidine. The formation of the latter product can only be explained by
assuming that the pyridine ring undergoes fission.

The quaternary salt (XII, $R_1 = 2'(6'-\text{methylpyridyl})\text{-amino}$, $R_2 = \text{H}$) reacts with piperidine in a similar manner to give

2-piperidino-4-$[2'-\text{(6'-methylpyridyl})\text{-amino}]$-5-nitropyrimidine and 2-amino-4-$[2'-\text{(6'-methylpyridyl})\text{-amino}]$-5-nitropyrimidine.

These results indicate that there are two routes by which salts of the type (XI) and (XII) react with amines.

The first, or type A, is that generally followed and involves fission of the extra cyclic C-N bond; the second, or type B, which only occurs when the salt is of the type (XII) and the attacking reagent is piperidine, involves the fission of the pyridine ring.

\[ \text{FIG. 1} \]

\[ \text{XI} \]

\[ \text{XII} \]
Other workers have also provided evidence of the two types of reaction of amines with quaternary pyridinium salts. Zinde et al. (Annalen, 1904, 330, 361; ibid., 1905, 338, 107) showed that the pyridinium salt (XV) reacted with amines to give dinitroaniline (XXVI) and a derivative of glutaric aldehyde (XXVII). Thus by boiling the salt (XV) with an ethanolic solution of aniline Zinde et al. were able to isolate 2,4-dinitroaniline and the dianilide of glutaric aldehyde (XXVII, R = C₆H₅NH₂).

Later Vompe and Turitsyna (Doklady Akad. Nauk. S.S.S.R., 1949, 54, 541; C.A., 1949, 43, 4671) showed...
that the quaternary salts (XXVIII) derived from substituted pyridines and 2,4-dinitrochlorobenzene could react with amines in different ways depending upon the nature of the substituent in the pyridine portion of the molecule and on the temperature. The cyclic C-N bonds of the pyridine nucleus underwent fission on treatment with an ethanolic solution of aniline at $0-10^\circ$, when the groups in the 3-position of the pyridine ring were methyl, methoxy or acetamido, i.e. a type B reaction occurred (see Fig. 2); the yield of ring fission products was less than when the unsubstituted salt (XV) was treated in this way. Heating the quaternary salts with aniline in ethanol leads to dissociation of the extracyclic C-N bond, when the substituents in the 3-position are methyl, methoxy, hydroxy, acetamido or dimethylamino (XXVIII, $R_1 = Me, OH, OMe$, NHAc or $NM_2$, $R_2 = H$) and in the 4-position are acetamido or anilino (XXVIII, $R_1 = H$, $R_2 = NHAc$ or NHPh). This reaction leads to dinitrodiphenylamine and proceeds by route A (Fig. 2.). In a later communication Vompe and Turitsyna (Doklady Akad. Nauk. S.S.S.R., 1950, 74, 509; C.A., 1951, 45, 3846) showed that the quaternary salts
derived from 3- and 4-aminopyridines, underwent reaction with aniline to give 2:4-dinitrodiphenylamine, i.e. a type A reaction occurred.

To summarise, results of the nucleophilic attack of amines on the 2:4-dinitrophenyl and substituted-5-nitropyrimidyl salts of pyridine and substituted pyridines indicate that there are two points of attack:

1) The cyclic C-N bond of the pyridine nucleus when ring fission products are obtained, and

2) The extra cyclic C-N bond when substituted-diphenylamines or 2-substituted-aminopyridines are obtained.
Vompe and Turitsyna (Doklady Akad. Nauk. S.S.S.R., 1949, 64, 341; C.A., 1949, 43, 4671, only the abstract available) explain the variable nature of the nucleophilic attack of amines on salts of the type (XXVIII) on the basis that there is a variation of positive change of the \(\alpha-\alpha^+\) carbon atoms of the pyridine nucleus due to the presence of substituent groups, i.e. the electrophilic nature of these atoms is decreased, thus leading to stabilisation of the cyclic C-N bond. Later (Doklady Akad. Nauk. S.S.S.R., 1950, 74, 509) they pointed out that C-N bonds of the pyridine nucleus in the 3- and 4-aminopyridinium salts (XXIX) and (XXX) will be stabilised by the increased electronic concentration at the \(\alpha-\alpha^+\) carbon atoms and at the annular nitrogen atom under the influence of the 3- and 4-amino- groups and that the extra cyclic C-N bond will be weakened by the polarisation of the 2:4-dinitrophenyl-residue. These two effects (shown diagrammatically below) lead to the fission of the extra cyclic C-N bond in the salts (XXIX) and (XXX) to give a 2:4-dinitrodiphenylamine.

\[
\begin{align*}
\text{(XXIX)} & \quad + \text{Cl}^- \\
\text{(XXX)} & \quad + \text{Cl}^-
\end{align*}
\]
Comparison of the 2:4-dinitrophenyl salt of pyridine (XV) and the substituted-5-nitropyrimidyl salts of pyridine (XI, \(R_1 = 2'-\text{pyridylamino}, R_2 = \text{H}\)) and (XI, \(R_1 = 2'-\text{(6'-methylpyridyl)-amino, } R_2 = \text{H}\)) shows that whilst the former reacts with amines entirely by route B (Fig. 2), i.e., it undergoes ring fission, the latter undergo reaction at the extra cyclic C-N bond (except on treatment with piperidine, when apparently some ring fission occurs).

Thus, when the pyridine ring is unsubstituted the effect of changing the quaternising group from 2:4-dinitrophenyl- to substituted-5-nitropyrimidyl- is to change the point of attack of amines from the cyclic C-N bond to the extra cyclic C-N bond. If, as Vompe and Turitsyna (Doklady Akad. Nauk. S.S.S.R., 1950, 74, 509) postulate, the rate of reaction of \(N\)-(2:4-dinitrophenyl)-pyridinium chloride and its derivatives with amines is determined by the concentration of positive charge on the \(\alpha\)-carbon atoms of the pyridine ring as a result of the attraction of electrons by the 2:4-dinitrophenyl- residue, then the substituted-5-nitropyrimidyl- group in the salts...
(XII, R₁ = 2'-pyridylamino, R₂ = H) and (XII, R₁ = 2'-(6'-methylpyridyl)-amino, R₂ = H) will attract electrons less than the 2:4-dinitrophenyl- group, i.e. in the salts of the type (XIII) the concentration of positive change at the α-α⁺ carbon atoms is less than in the salts of the type (XXVIII). Assuming that two different factors (which may each be the resultant of a number of effects) are responsible for fission at the cyclic C=N bond or at the extra cyclic C=N bond, it will be clear that only a slight preponderance of one factor over the other could bring about fission in one way only. Thus it can be understood how by changing the dinitrophenyl- group for a substituted-5-nitropyrimidyl- group or by introducing substituents in the pyridine ring fission could occur at the extra cyclic C=N bond instead of at the cyclic bond. Until more information is available the relative effects of substituent groups on the point of attack of amines on the above types of pyridine quaternary salt cannot be ascertained.

The present work on the reaction of amines of quaternary salts of pyridine with a substituted-5-nitro-
pyrimidyl- group attached to the pyridine nitrogen atom has, however, provided a new method for the preparation of 2-amino- and 2-substituted-aminopyrimidines (XXXI). The groups (NX₂) in the 2- position of the pyrimidine nucleus (XXXI) have been varied to include representatives of the aliphatic aromatic and alicyclic series of amines; the group (R₁) in the 4- position was the 2'-aminopyridyl or substituted 2'-aminopyridyl and the group (R₂) in the 6- position has included hydrogen, methyl- and amino-.

Another interesting effect was noted when the salt (XI, R₁ = 2'-pyridylamino, R₂ = Me) was treated with methanolic ammonia. If the concentration of ammonia was kept high by performing the reaction in a sealed tube then the expected 2-amino-4-(2'-pyridyl)-amino-5-nitro-
6-methylpyrimidine was obtained. If, however, the salt was boiled with methanolic ammonia under reflux none of this 2-aminopyrimidine was obtained; instead, 2-methoxy-4-(2'-pyridyl)-amino-5-nitro-6-methylpyrimidine was obtained. This provides an example of the ease with which quaternary salts of this type can react with alcohols in the presence of bases.

The salt (VII) gave a mixture of 2-amino-4-(2'(3'-methylpyridyl))-amino-5-nitropyrimidine and 2-methoxy-4-(2'(3'-methylpyridyl))-amino-5-nitropyrimidine when treated with methanolic ammonia. Another case in which the quaternary salt was found to react with the solvent as well as the amine arose when the salt (XI, \( R_1 = \))
2'-pyridylemino, $R_2 = \text{NH}_2$) was treated with methanolic piperidines. From this reaction a mixture of 2-methoxy- and 2-piperidino-4-[(2'-pyridyl)-amino-5-nitro-6-amino-
pyrimidines was obtained. In these cases the amine and
the solvent competed for reaction with the quaternary salt,
solved, and on cooling the mixture 2-methoxy-6-[(2'-pyridyl)-
amino-5-nitropyrimidine (XXXI, $X = \text{CH}_3$, $R_1 = 2'$-pyridyl-
amino, $R_2 = \text{H}$) separated. This compound was also obtained
by treating 2-chloro-6-[(2'-pyridyl)-amino-5-nitropyrimidine
with sodium methoxide in methanol, or by boiling the salt
(XXX, $X = \text{H}$) with sodium methoxide in methanol.

![XXXI]

Similarly by treating 2,4-dichloro-5-nitro-
pyrimidine with 4 moles of 2- and 4-methoxy-2-aminopyrimidine
in boiling methanol solution the 2-methoxy-aminopyrimidines
(XXXII, $X = \text{CH}_3$, $R_1 = 2'$-[(2'-methylpyridyl)-amino, $R_2 = \text{H}$)
The reaction of quaternary salts from 2-chloro-5-nitropyrimidines with alcohols and phenols.

When 2:4-dichloro-5-nitropyrimidine was treated in boiling methanol with 2-aminopyridine (4 moles) the quaternary salt (VI, R = H) was precipitated at first, but if the mixture was boiled for some time the salt dissolved, and on cooling the mixture 2-methoxy-4-(2'-pyridyl)-amino-5-nitropyrimidine (XXXII, $X = Me$, $R_1 = 2'$-pyridyl- amino, $R_2 = H$) separated. This compound was also obtained by treating 2-chloro-4-(2'-pyridyl)-amino-5-nitropyrimidine with sodium methoxide in methanol, or by boiling the salt (VI, R = H) with 2-aminopyridine in methanol.

Similarly by treating 2:4-dichloro-5-nitropyrimidine with 4 moles of 3- and 4-methyl-2-aminopyridine in boiling methanol solution the 2-methoxypyrimidines (XXXII, $X = Me$, $R_1 = 2'$-(3'-methylpyridyl)-amino, $R_2 = H$)
and (XXXI, \( X = \text{Me}, \ R_1 = 2\text{'-}(4\text{'}\text{-methylpyridyl})\text{-amino}, \ R_2 = \text{H} \)) were obtained respectively; 2,4-dichloro-5-nitro-6-methylpyrimidine gives the corresponding 2-methoxy compound (XXXI, \( X = \text{Me}, \ R_1 = 2\text{'}\text{-pyridylamino}, \ R_2 = \text{Me} \)) when treated with 4 moles of 2-aminopyridine in methanol solution. If the solvent was ethanol in the above cases the corresponding 2-ethoxy compounds (XXXI, \( X = \text{Et}, \ R_1 \) and \( R_2 \) as before) were obtained.

It has also been found that the quaternary salt (VI, \( R = \text{H} \)) was converted into 2-methoxy-4-(2\text{'}\text{-pyridyl})-amino-5-nitropyridine (XXXI, \( X = \text{Me}, \ R_1 = 2\text{'}\text{-pyridylamino}, \ R_2 = \text{H} \)) in boiling methanol, in the presence of tertiary bases other than 2-aminopyridine. Tertiary bases that were effective were triethylamine, pyridine and dimethylaniline. An equivalent amount of sodium hydroxide solution was also effective in bringing about the replacement of the 2-(2\text{'}-aminopyridinium)-group by the methoxy- group. The quaternary salt (VI, \( R = \text{H} \)) was recovered unchanged from boiling methanol in the absence of a tertiary base or sodium hydroxide solution.

The salt (VI, \( R = \text{H} \)) reacts with ethanol, \( \text{H}-\text{propanol}, \text{H}-\text{butanol}, \text{allyl alcohol}, \text{benzyl alcohol}, \text{phenol} \)}
and p-methoxyphenol in the presence of a slight excess of triethylamine to give the corresponding alkoxy- or aryloxypyrimidine. The replacement of the 2-substituted-aminopyridinium group in the salts (VII) and (VIII) by an alkoxy- or aryloxy- group has also been shown to occur when they are treated with the appropriate alcohol or phenol in presence of triethylamine. Similarly the salt (VI, R = Me) reacts with alcohols and phenol to give the corresponding alkoxy- and phenoxypyrimidines. This salt, on treatment with a tertiary base in an alkanol, gave rise to unidentified deep red bi-products from which the required alkoxy compounds could be separated by chromatography. The formation of these red bi-products is probably due to a secondary reaction at the reactive methyl group in the 6-position of the pyrimidine nucleus. It is of interest to note that the amount of red bi-product increased as the boiling point of the alkanol used was increased (i.e. very little in the case of methanol and a large amount in the case of butanol) but when the salt was treated with phenol and triethylamine no red bi-product appeared to be formed.

The amount of tertiary base (triethylamine) necessary to bring about the replacement of the 2'-{(2-amino-
pyridinium) radical of the salt (VI, \( R = H \)) by a methoxyl group was next determined. It was found that if the reaction was carried out in 50% aqueous methanol (this was an effective solvent for the salt) then 100% yields of 2-methoxy-4-(2'-pyridyl)-amino-5-nitropyrimidine were obtained if the amount of tertiary base present was greater than half an equivalent; with less than half an equivalent of triethylamine decreased yields of 2-methoxy-compound were obtained. With only a catalytic quantity of triethylamine present the quaternary salt was recovered unchanged. The salt was substantially unchanged if one equivalent of the salt, twenty equivalents of methanol and one equivalent of triethylamine were refluxed together in benzene. The overall reaction of the salt (VI, \( R = H \)) with methanol in the presence of a tertiary base is shown below.

\[
\begin{align*}
\left\{ \begin{array}{c}
\text{Cl}^+ + \text{MeOH} \\
\text{MeOH} + \text{NR}_3
\end{array} \right\} & \quad \text{NR}_3 \quad \text{MeOH} \\
\text{HNO}_2 & \quad \text{NH}_2
\end{align*}
\]
Since the 2-chloro group of 2:4-dichloro-5-nitropyrimidine was easily converted into a methoxy group on treatment with 2-aminopyridine in methanol it seemed likely that the 2-chloro group of substituted 5-nitropyrimidines could be replaced by methoxyl on treatment with a tertiary base. Accordingly 2-chloro-4-\([2\text{'}-(6\text{''}-\text{methylpyridyl})]^-\text{amino-5-nitropyrimidine}\) (which was obtained by treating 2:4-dichloro-5-nitropyrimidine with 2-aminopyridine) was refluxed in methanol with 2-aminopyridine (2 moles) for three hours, when on cooling 2-methoxy-4-\([2\text{'}-(6\text{''}-\text{methylpyridyl})]^-\text{amino-5-nitropyrimidine}\) was obtained. 2-Aminopyridine could be replaced in this reaction by any of the following bases: pyridine, \(\gamma\)-picoline, dimethyl aniline or triethylamine, but not by \(\alpha\)-chloropyridine, quinoline or isoquinoline. The conversion of the 2-chloro group into a 2-methoxyl group in the presence of the above bases in methanol may proceed by way of the intermediate quaternary salt. The intermediate quaternary salts have been obtained from 2-chloro-4-\([2\text{'}-(6\text{''}-\text{methylpyridyl})]^-\text{amino-5-nitropyrimidine}\) and 2-aminopyridine and pyridine, and have been shown to form 2-methoxy-4-\([2\text{'}-(6\text{''}-\text{methylpyridyl})]^-\text{amino-5-nitropyrimidine}\).
amino-5-nitropyrimidine when treated in methanol solution with a tertiary base. The non-formation of a quaternary salt, due perhaps to steric hindrance, could account for the failure of 2-chloropyridine and quinoline to effect the conversion of the chloro-group into the methoxy-group. In the case of isoquinoline a different type of product was formed and the reaction of isoquinoline and 2-chloro-4-[[6'-methylpyridyl]amino]-5-nitropyrimidine will be discussed later. The reaction of 2-chloro-5-nitropyrimidines with tertiary bases in methanol to give 2-methoxypyrimidines can, therefore, take place as follows:

They showed that pyridine was the most effective base for the above conversion but that other bases, e.g., dimethylamine and triethylamine, permitted the isolation of the chloro-amine. Since the reaction was not restricted to the use of the tertiary amines derived from the tetrahydro methyl ethers of chloropyrimidine, the results
A similar reaction has been described by Borrows et al. (J., 1949, S 190), who found that the p-toluene sulphonates of 2:6-dinitrophenols (XXXIII) react with phenols in presence of pyridine to give the corresponding diphenylethers (XXXV) via the quaternary pyridinium salts (XXXIV).

They showed that pyridine was the most effective base for the above conversion but that other bases, e.g., dimethylaniline and triethylamine, permitted the isolation of diphenylethers. Further, the reaction was not restricted to the use of the quaternary salts derived from the toluene sulphonyl esters of dinitrophenols, the salts
derived from benzene sulphonyl esters and dinitrohalogenobenzenes being just as effective.

The reaction of the salt (VI, \( R = H \)) with sodium hydroxide solution and sodium acetate solution has provided further interesting results. As described earlier, treatment of the salt (VI, \( R = H \)) with sodium hydroxide in boiling methanol led to the formation of 2-methoxy-4-(2'-pyridyl)-aminopyrimidine, but if this salt was treated in aqueous solution at room temperature with sodium hydroxide solution a yellow compound was precipitated. This compound (anhydro-base R in the experimental section) could not be crystallised but a carefully prepared specimen gave good analytical results for an anhydro-base. This anhydro-base has been tentatively ascribed the structure (XXXVI). Vompe and Turitsyna (Doklady Akad. Nauk. S.S.S.R., 1950, 74, 509) have assigned a similar structure (XXXVII) to the product obtained by treating 4-amino-N-(2:4-dinitrophenyl)pyridinium chloride (XXX) with sodium hydroxide.

XXXVI

XXXVII
On treatment with dilute hydrochloric acid the anhydro-base was reconverted to the quaternary salt (VI, R = H). On boiling with methanol and ethanol the anhydro-base was converted to 2-methoxy- and 2-ethoxy-4-(2'-pyridyl)-amino-5-nitropyrimidine respectively and on treatment with an ethanolic solution of piperidine the anhydro-base gave 2-piperidino-4-(2'-pyridyl)-amino-5-nitropyrimidine. Thus the anhydro-base undergoes similar reactions to the salt (VI, R = H), the extra cyclic C=N bond being the point of attack during reaction with amines and alkanols.

When a solution of the salt (VI, R = H) was treated with sodium acetate solution at room temperature an orange-red solid of unknown constitution was obtained. This solid contained no chlorine and on treatment with sodium hydroxide solution was converted to the anhydro-base (XXXVI) and on trituration with dilute hydrochloric acid the quaternary salt (VI, R = H) was regenerated.

If this red base was boiled with alcoholic piperidine 2-piperidino-4-(2'-pyridyl)-amino-5-nitropyrimidine was obtained. When the salt (VI, R = H) was boiled with sodium acetate solution the red base first formed slowly dissolved and on cooling the resultant yellow solution

XXXVI and (XXX) with alcoholic and piperidone in the presence of

130
2-hydroxy-4-(2'-pyridyl)-amino-5-nitropyrimidine was obtained. It has also been shown that the quaternary salt (XI, \( R_1 = 2'-(6'-\text{methylpyridyl})\)-amino, \( R_2 = H \)) may be converted into 2-hydroxy-4-[2'-(6'-\text{methylpyridyl})]-amino-5-nitropyrimidine on hydrolysis with aqueous sodium acetate. Similarly 2:4-dinitrophenylpyridinium chloride (XV) was shown by Zincke (Annalen, 1904, 333, 298) to be converted into 2:4-dinitrophenol on heating at 150° with aqueous sodium acetate.

The salt (VI, \( R = H \)), the anhydro-base (XXVI) and the pyridinium salt (XII, \( R_1 = 2'\text{pyridylamino}, \) \( R_2 = H \)) were all converted into 2:4-dihydroxy-5-nitropyrimidine on boiling with 5N hydrochloric acid. Thus, both the residue in the 2- position and the 2'-pyridylamino-group in the 4'-position are hydrolysed under these conditions. The hydrolysis of the substituted amino-group in the 4- position of the pyrimidine nucleus with 5N hydrochloric acid is not surprising since it is well known that 4-aminopyrimidines are hydrolysed to 4-hydroxypyrimidine under these conditions. The above reactions are summarised in the diagram.

The reactions of the quaternary salts of the type (XI) and (XII) with alkanols and phenols in the presence of
bases has provided a new method for the synthesis of 2-alkoxy- and 2-aryloxypyrmidines. Experiments indicate that at least half a mole of base is necessary to bring about this replacement. It has further been observed that the quaternary salt is probably an intermediate stage in the reaction of substituted-2-chloro-
5-nitropyrimidines with alkanols in the presence of a tertiary base, and that substituted-2-chloro-5-nitropyrimidines may be converted into the corresponding 2-alkoxy compounds by boiling with the appropriate alkanol in the presence of a tertiary base. Some preliminary experiments on the effect of sodium hydroxide and sodium acetate on salts of the type (XI) have indicated that anhydro-bases are produced under certain conditions and that 2-alkoxy- and 2-hydroxypyrimidines are produced under other conditions.

Some preliminary experiments on the effect of sodium hydroxide and sodium acetate on salts of the type (XI) have indicated that anhydro-bases are produced under certain conditions and that 2-alkoxy- and 2-hydroxypyrimidines are produced under other conditions.
When a solution of 2-chloro-4-[2'-{(6'-methylpyridyl)}-amino-5-nitropyrimidine (XXXVIII) in hot methanol was treated with isoquinoline a bright yellow solid was rapidly precipitated. This solid, m.p. 165°, which did not contain chlorine, could be crystallised from methanol unchanged, but crystallisation from ethanol converted it into an orange compound, m.p. 169-70°. (A mixture of these compounds melted at 164-6°). The orange solid, m.p. 169-70°, could be crystallised from ethanol unchanged or could be obtained by treating (XXXVIII) with isoquinoline in ethanol. Analysis of these two compounds indicated that they were formed from the starting materials by the loss of one mole of hydrochloric acid and the addition of one mole of methanol or ethanol, i.e.:

\[
\text{C}_{10}H_{8}O_{2}N_{5}Cl + C_9H_7N + CH_3OH \rightarrow \text{C}_{19}H_{15}O_2N_6(OCH_3) + HCl
\]

Cryst\ from EtOH

\[
\text{C}_{10}H_{8}O_{2}N_{5}Cl + C_9H_7N + C_2H_5OH \rightarrow \text{C}_{19}H_{15}O_2N_6(OCH_2CH_3) + HCl
\]

These two compounds were readily soluble in dilute hydrochloric acid but could not be recovered from the acid solution on neutralisation with alkali; instead
a compound, m.p. 175°, (from aqueous dioxane) was obtained. Analysis of this compound indicated that it had the empirical formula C_{19}H_{15}O_2N_6(OH). This latter compound could be converted into the compounds m.p. 185° and m.p. 169-70° by crystallisation from methanol or ethanol respectively. These results indicate that the compounds m.p. 185° and m.p. 169-70° may be the methyl and ethyl ethers of the hydroxy-compound, m.p. 175°.

XXXVIII

Treatment of a slightly acid solution of the compound m.p. 185° or of the compound 169-70° with potassium iodide gives rise to the formation of an unstable quaternary iodide. This salt could not be crystallised from water or ethanol, the bright red crystals of the salt being converted into insoluble yellow materials on treatment with these solvents. The yellow material obtained on treatment of the salt with the latter solvent gave the "ethyl ether", m.p. 169-70°, on crystallisation from ethanol.
Analysis of a carefully prepared specimen of the quaternary iodide indicated that it had the empirical formula $C_{19}H_{14}O_3N_6I$, i.e. that it was the iodide of a quaternary salt made up from one mole of (XXXVIII) and one mole of isoquinoline; it has, therefore, been assigned the structure (XXXIX).

The "methyl ether", m.p. 185°, and the "ethyl ether", m.p. 169-70°, were readily converted into a deep red "phenylhydrazone" on treatment with phenylhydrazine in ethanol. Under similar conditions the hydroxycompound, m.p. 175°, forms the same phenylhydrazone more slowly.

The above results indicate that the hydroxycompound, m.p. 175°, formed by the ready hydrolysis of the "methyl ether", m.p. 185°, and the "ethyl ether", m.p. 169-70°, could have the carbinol base structure (XL). The ease with which the quaternary salt is formed in slightly acid solution indicates that this carbinol base is in equilibrium with the quaternary ammonium hydroxide (XLI). (In hydrochloric acid solution the quaternary chloride probably exists in solution). The formation of the deep red "phenylhydrazone" from the hydroxycompound, m.p. 175°, indicates that a third form (the alde-
hyde form (XLIII) exists under certain conditions. Thus under the appropriate conditions the hydroxylan; compound, m.p. 175°, can exist in the three forms (XL), (XLI, A = OH) and (XLII).

\[
\{ \begin{array}{c}
\text{N} \\
\text{N}
\end{array} \}^+ \quad \text{I}^-
\]

It is of interest to note that three similar structures have been put forward to account for the properties of the alkaloid berberine (Henry, The Plant Alkaloids, J. & A. Churchill Ltd., 1949, p51, 332-4).
The structures put forward for berberine are shown below:

1. Ammonium form of berberine
2. Aldehyde form of berberine
3. Carbinol base form of berberine

These compounds are described as the methyl and ethyl ethers of the ammonium and aldehyde forms, respectively, in the experimental section.
The compounds m.p. 185° and 169-70° could be the methyl (XLIII, R₁ = OMe) and ethyl ethers (XLIII, R₁ = OEt) of the carbinol base (XL) but their ease of hydrolysis, in acid solution, into the carbinol base (XL), (or the quaternary ammonium chloride corresponding to (XLI)), and the ready formation of the "phenylhydrazone" (XLIV) seems to indicate that these compounds could be derivatives (possibly the semi-acetals) of the aldehyde (XLII). These compounds are described as the methyl and ethyl ethers of the carbinol base (XL) in the experimental section.

Zincke and Weisspfennig (Annalen, 1915, 596, 103) have postulated a similar structure (XLIV) for the carbinol base obtained by treating 2:4-dinitrophenylisoquinolinium chloride (XLVI) with alkalies. They also showed that this carbinol base was converted into its
methyl and ethyl ethers on boiling with methanol and ethanol respectively. These authors preferred the carbinol base structure (XLV) rather than the aldehyde structure (XLII, \( R = (\text{NO}_2)_2\text{C}_6\text{H}_5 \)) for the compound obtained by treating (XLVI) with alkalies because of the indifference of this compound to phenylhydrazine.

Zinove and Weisspfennig showed that the quaternary salt (XLVI) was split on treatment with phenylhydrazine to give the phenylhydrazone (XLIV, \( R = (\text{NO}_2)_2\text{C}_6\text{H}_5 \)) of the aldehyde (XLII, \( R = (\text{NO}_2)_2\text{C}_6\text{H}_5 \)).

They further showed that treatment of the salt (XLVI) with amines gave a new isoquinolinium salt and dinitroaniline. Thus when 2-(2,4-dinitrophenyl)-isoquinolinium chloride (XLVI) was treated with aniline, phenylisoquinolinium chloride and 2,4-dinitroaniline were obtained.
It has now been shown that when the quaternary iodide (XXXIX) is treated with phenylhydrazine in methanol the phenylhydrazone (XLIV) is obtained. But treatment of the salt (XXXIX) with aniline in ethanol gave only the ethyl ether (XLIII, \( R_1 = \text{OEt} \)). This compound was also obtained when the quaternary salt (XXXIX) was treated in ethanol with diethylamine and ammonia. When, however, quaternary iodide (XXXIX) was triturated with ethanolic piperidine, methyamine or the ethylamine, three new compounds were obtained. These compounds were yellow or orange in colour and analysis indicated that they could be derivatives of the carbinol base (XL). They have been tenta-
tively assigned the structures:

\[
\begin{align*}
\text{NHMe} & \quad \text{H} \\
\text{NHMe} & \quad \text{H} \\
\text{NHMe} & \quad \text{H} \\
\text{NH} & \quad \text{R} \\
\text{NH} & \quad \text{R} \\
\end{align*}
\]

It appears, therefore, that the quaternary salt can undergo reaction with the amine provided the amine is a strong enough base; otherwise it undergoes reaction with the solvent. But in no case could a new quaternary salt (cf. Zincke and Weisspfennig loc. cit.) be obtained.

When the chloro- compound (XXXVIII) was treated with isoquinoline in acetone solution a new compound, m.p. 175°, was obtained. This compound differed from the methyl and ethyl ethers (XLIII, \( R_1 = \text{OMe and } R_1 = \text{OEt} \)) in that it was sparingly soluble in cold dilute acid. On warming with dilute hydrochloric acid for a short while it was hydrolysed to give the carbinol base (XL), i.e. from a slightly acid solution
of the hydrolysate, the quaternary iodide (XXXIX) could be isolated on addition of potassium iodide; complete neutralisation of the hydrolysate gave the carbinol base (XL). The new compound m.p. 175°C could be crystallised from ethanol unchanged and did not give the bright red phenylhydrazone on treatment with phenylhydrazine. Analysis of the new compound indicates that it is made up of one mole each of (XXVIII), isoquinoline and acetone, with the elimination of hydrochloric acid. For convenience this compound has been assigned the structure (XLVII) and is described accordingly in the experimental section. However, there is at present insufficient experimental data to assign a definite structure to this compound.
Pyrimidotriazoles and dihydropteridines derived from 4-(2'-pyridyl)-amino-5-aminopyrimidines.

Since pyrimidotriazoles of the type (XLVIII) have been shown to be purine antagonists (Hitchings et al., Ann. N.Y. Acad. Sci., 1950, 52, 1312; Roblin et al., J. Amer. Chem. Soc., 1945, 67, 290) the corresponding triazoles (XLIX) have been prepared from certain 4-(2'-pyridyl)-amino-5-aminopyrimidines (L).

\[
\text{XLVIII} \quad \text{XLIX} \quad \text{L}
\]

The 4-(2'-pyridyl)-amino-5-aminopyrimidines (L) were prepared by reduction of the corresponding 5-nitro-compounds which, as shown earlier, can be prepared by treatment of quaternary salts of the type (XI) and (XII) with amines, alcohols and phenols. It has been found that these 5-nitro-compounds can be readily reduced to the corresponding 5-amino-compounds (L) with stannous chloride in hydrochloric acid solution. Reduction of the more
soluble nitro compounds can be carried out by addition of a solution of stannous chloride in concentrated hydrochloric acid to a warm solution of the nitro compound in ethanol; the stannichloride of the amino compound separated and could be decomposed in the usual way to give the required 5-aminopyrimidine. The 5-nitro compounds which were insoluble in ethanol were reduced in concentrated hydrochloric acid solution with stannous chloride. The 4-(2'-pyridyl)-amino-5-aminopyrimidines so produced were then treated with sodium nitrite in 50% acetic acid solution (cf. Roblin et al., J. Amer. Chem. Soc., 1945, 67, 290) to give the pyrimidotriazoles (XLIX).

2-Piperidino-4-(2'-pyridyl)-amino-5-amino-pyrimidine ($L$, $R_1 = C_5H_{10}N$, $R_2 = H$) was converted into the corresponding dihydropteridines (LI) and (LII) on treatment with diethyl oxalate and benzoin respectively (cf. Todd et al., J., 1951, 5).
Summary

The treatment of substituted-2-chloro-5-nitropyrimidines with 2-aminopyridine and pyridine has been shown to give quaternary salts of the type (XI) and (XII). These salts have been found to react with amines, alkanols and phenols to give several new 2-amino-, 2-substituted-amino-, 2-alkoxy- and 2-aryloxy-5-nitropyrimidines. Thus, in the reaction of salts of the type (XI) and (XII) with amines and hydroxy compounds the bond joining the annular nitrogen atom of the pyridine nucleus to the carbon atom in the 2-position of the pyrimidine nucleus is the point of attack. Several of the 2-substituted-4-(2′-pyridyl)-amino-5-nitropyrimidines obtained in this way have been reduced to the corresponding 5-aminopyrimidines and the latter have been converted into pyrimidotriazoles of the type (XLIX), which are potential purine antagonists. It has also been shown that 4-(2′-pyridyl)-amino-5-aminopyrimidines of the type (L) may be converted into dihydropteridines.

Preliminary experiments on the reaction of 2-chloro-4-[2′-(6′-methylpyridyl)]-amino-5-nitropyrimidine with isoquinoline have indicated that a quaternary salt derived from these two compounds is unstable and breaks down in presence of alco-
hols to give compounds which may be derivatives of 1-hydroxy-1,2-dihydroisouquinoline (XLIII).
EXPERIMENTAL
A-Nitroso-6:8:6-triaminopyrididine

6:8:6-Triaminopyrididine was prepared from guanidine and malononitrile (Organic Syntheses, Vol. 28, pg. 45) by the method of Traube, (Ber., 1898, 31, 2543) and isolated as the sulphate. It was nitro-
ated by the following modification of Traube's method:

11.08 g. of 6:8:6-triaminopyrididine sulphate
were suspended in water (130 c.c.) and 20 sodium hydrox-
ide (50 c.c.) was added, followed on warming to 40°, a
clear solution was obtained. 38 cc. of nitric acid (50 cc.) was added, followed by sodium nitrite (5.45 g.) dis-
solved in water, and a bright red solution resulted, from which the nitroso compound separated on cooling.
After standing at 0° for two hours the carmine nitroso
compound (4.0 g.) was filtered and washed with water
and ether, and dried at 80°.

6:8:6-Triaminopyridine bisulphite.

This was prepared from the above nitroso
compound by reduction with sodium thiosulphate by the
Soc., 1947, 69, 1032). The bisulphate of this
base was prepared by reprecipitation of the bisulphate.

2:4:6-Triaminopyrimidine was prepared from guanidine and malondinitrile (Organic Syntheses, Vol. 25, pg. 63) by the method of Traube, (Ber., 1904, 37, 4545) and isolated as the sulphate. It was nitrosated by the following modification of Traube's method:-

11.05 g. of 2:4:6-triaminopyrimidine sulphate were suspended in water (150 ccs.) and 2N sodium hydroxide (55 ccs.) was added, when, on warming to 40°, a clear solution was obtained. 2N acetic acid (50 ccs.) was added, followed by sodium nitrite (3.45 g.) dissolved in water, and a bright red solution resulted, from which the nitroso compound separated on cooling. After standing at 0° for two hours the carmine nitroso compound (7.5 g.) was filtered and washed with water and methanol and dried at 90°.

2:4:5:6-Tetraaminopyrimidine bisulphite.

This was prepared from the above nitroso compound by reduction with sodium hydrosulphite by the method of Cain, Mallette and Taylor, (J. Amer. Chem. Soc., 1947, 69, 1814). The hydrochloride of this base was prepared by crystallisation of the bisulphite
from 2N hydrochloric acid, followed by recrystallisation from water.

2-Thio-4:6-diamino-5-nitrosopyrimidine.

This compound was obtained by the treatment of 2-thio-4:6-diaminopyrimidine (Traube, Annalen, 1904, 531, 80; Bendich, Tinker and Brown, J. Amer. Chem. Soc., 1948, 70, 3109) with sodium nitrite in dilute acetic acid solution at 0°, when it separated as a sea-green solid.

2-Methylthio-4:6-diamino-5-nitrosopyrimidine.

2-Thio-4:6-diaminopyrimidine was methylated with dimethyl sulphate in sodium hydroxide solution, following the directions of Pesson (Bull. Soc. Chim. France, 1948, 967) for the ethylation of this thio-pyrimidine. 2-Methylthio-4:6-diaminopyrimidine crystallised from water, m.p. 286-7°. The nitroso compound was prepared by treatment of the above base with sodium nitrite in dilute acetic acid solution (Pesson loc. cit.), when it was obtained as a light blue micro-crystalline solid.

2-Ethylthio-4:6-diamino-5-nitrosopyrimidine.

2-Thio-4:6-diaminopyrimidine was alkylated
The 2-ethylthio compound crystallised from water in colourless needles, m.p. 136-7°, (Fesson gives m.p. 142-4°), and was nitrosated in dilute acid solution to give the 5-nitroso derivative as a friable blue powder.

2-Methylthio-4-amino-6-hydroxy-5-nitrosopyrimidine.

2-Methylthio-4-amino-6-hydroxy-5-nitrosopyrimidine was prepared by the method of Johns and Baumann (J. Biol. Chem., 1913, 14, 384), from 2-thio-4-amino-6-hydroxy-pyrimidine (Traube, Annalen, 1904, 331, 71) and dimethyl sulphate in alkaline solution. It crystallised from alcohol in yellow plates, m.p. 259°. (Johns and Baumann give m.p. 267°). Further crystallisation from water, however, raised the m.p. to 266-7°. Nitrosation of this compound in dilute acid solution gave the nitroso compound as a blue powder.

2:4-Diamino-5-nitroso-6-hydroxy-pyrimidine.

This compound was prepared according to the directions described by Mallette et al (J. Amer. Chem. Soc., 1946, 68, 1998). It was purified by dissolution in N sodium hydroxide, followed by acidification with
N acetic acid, when it separated as a bright red powder.

4-Amino-5-nitroso-6-hydroxypyrimidine.

4-Amino-6-hydroxypyrimidine was obtained by the desulphurisation of the corresponding 2-thio- pyrimidine (Cavalieri and Bendich, J. Amer. Chem. Soc., 1950, 72, 2593). By using a larger volume of water as solvent than was used by Cavalieri and Bendich the yield of the product was increased from 16% to 40%. Nitrosation of this compound in dilute hydrochloric acid gave the nitroso derivative as a pale blue powder.

4,6-Diamino-5-nitrosopyrimidine.

4,6-Diaminopyrimidine was similarly prepared by desulphurisation of the corresponding 2-thio compound. Again, by increasing the volume of water the yield was increased to 40%. Cavalieri and Bendich (loc. cit.) claimed a yield of 24%. The nitrosation of this compound must be carried out in dilute hydrochloric acid in which the nitroso derivative is soluble. The nitroso derivative is precipitated from the blue acid solution by neutralisation with sodium carbonate solution, when it is obtained as a light blue powder.
4:6-Diamino-2-hydroxy-5-nitrosopyrimidine.

4:6-Diamino-2-hydroxypyrimidine was conveniently obtained by boiling an aqueous solution of the corresponding 2-thiopyrimidine with chloroacetic acid. It was isolated as the sulphate, which crystallised from water in colourless prisms. (Bendich, Tinker and Brown, J. Amer. Chem. Soc., 1946, 70, 3109).

The diamine was nitrosated by the method of Wieland and Liebig (Annalen, 1944, 555, 146), when the nitroso compound was obtained as a friable red-violet powder.

2-Phenyl-4-amino-5-nitroso-6-hydroxypyrimidine.

This compound was obtained by nitrosation of 2-phenyl-4-amino-6-hydroxypyrimidine (Traube and Herrman, Ber., 1904, 37, 2268) and formed a greenish-blue powder.

2-Methyl-4-amino-5-nitroso-6-hydroxypyrimidine.

2-Methyl-4-amino-6-hydroxypyrimidine was obtained by the method of Traube (D.R.P., 135, 371; Centralblatt, 1902, II, 1229) from acetamidine and ethyl cyanocacetate in presence of sodium ethoxide. It crystallised from hot water in colourless prisms, m.p. 298-300°. (Traube gives m.p. 300°). The nitroso derivative was obtained as a green solid by treatment of the base with
sodium nitrite in dilute hydrochloric acid.

2:4-Dichloro-5-nitropyrimidine.

Uracil was nitrated with fuming nitric acid, as described by Johnson and Matsuo (J. Amer. Chem. Soc., 1919, 41, 783) and the product converted to the dichloro compound by treatment with phosphoryl chloride and dimethyl aniline, (Whittaker, J., 1951, 1566). The dichloro compound distilled at 124-8°/10 mm. to yield a pale yellow oil, which solidified on standing to a crystalline solid, m.p. 30-2°. (Whittaker gives b.p. 138-9°/14 mm., m.p. 29-30°).

2:4-Dichloro-5-nitro-6-methylpyrimidine.

This compound was prepared by the chlorination of 2:4-dihydroxy-5-nitro-6-methylpyrimidine (Gabriel and Coleman, Ber., 1901, 34, 1248) with phosphoryl chloride and dimethylaniline, as described by Bitterli and Erlenmeyer (Helv. Chim. Acta., 1951, 34, 835). It distilled at 122-4°/12 mm. and on cooling the distillate a yellow crystalline solid, m.p. 52°, was obtained.

2-Amino-4-chloro-5-nitro-6-methylpyrimidine.

This compound was prepared according to the directions of Boon, James and Ramage, (J., 1951, 93), by
chlorination of the corresponding hydroxy compound with phosphoryl chloride. It sublimed in vacuo to give yellow prisms, m.p. 220°, (lit. m.p. 225°). The maximum yield of chloro- compound obtained under these conditions was 30%. The above authors do not state the yield that they obtained.

2:4-Dichloro-5-nitro-6-aminopyrimidine.

2:4-Dihydroxy-6-aminopyrimidine was nitrated and then chlorinated by the method of Bitterli and Erlenmeyer (Helv. Chim. Acta., 1951, 34, 837). The dichloro- compound crystallised from benzene-petroleum ether (b.p. 60-80°) in yellow prisms, m.p. 153-5°. (Bitterli and Erlenmeyer give m.p. 155°.)

The solution was then diluted with an equal volume of water, filtered, and the filtrate saturated with sulphur dioxide, to precipitate the benzoic acid formed in the reaction. The precipitated benzoic acid was removed by filtration and the filtrate was extracted with ether to remove any benzoic acid remaining in solution. The resultant aqueous solution was treated with charcoal, filtered, and the filtrate evaporated to small bulk. At this stage the alkyloxypridine acid usually separated as a
Alkoxyarylacetonitriles.

These compounds were prepared by the following modification of the method of Buck et al., (J. Amer. Chem. Soc., 1938, 60, 1789):

The alkoxybenzaldehyde ($\frac{3}{4}$ mole.), hippuric acid ($\frac{3}{4}$ mole.) anhydrous sodium acetate ($\frac{3}{2}$ mole.) and acetic anhydride (150 gms.) were heated on a steam bath for two hours. 50% ethanol was then added to the hot mixture to decompose excess acetic anhydride and after cooling the precipitated azlactone was filtered and air dried.

The crude azlactone was refluxed with five times its weight of 2N sodium hydroxide for twenty hours. The solution was then diluted with an equal volume of water, filtered and the filtrate saturated with sulphur dioxide, to precipitate the benzoic acid formed in the reaction. The precipitated benzoic acid was removed by filtration and the filtrate was extracted with ether to remove any benzoic acid remaining in solution. The resultant aqueous solution was treated with charcoal, filtered, and the filtrate evaporated to small bulk. At this stage the alkoxypyruvic acid usually separated as a
crystalline solid. If, however, an oil separated it was extracted with ether, the ether solution was dried and the solvent removed on a steam bath to leave the acid as a crystalline solid.

The alkoxypruvic acid was dissolved in excess 2N sodium hydroxide and treated with a slight excess (1.2 moles.) of hydroxylamine hydrochloride dissolved in water. The solution was warmed to 50°; if an oil separated at this stage more sodium hydroxide solution was added until a clear solution was obtained. After standing at room temperature overnight the solution was neutralised with acetic acid and any amorphous solid that separated was removed by filtration. The filtrate was then made strongly acid, when the oxime always separated as a crystalline solid and was filtered and dried over P₂O₅ in vacuo.

The crude dry oxime was added in small portions to an equal weight of acetic anhydride at 100°, when a vigorous reaction occurred. After the addition was complete the solution was heated on a steam bath for one hour. The excess acetic anhydride was decomposed with water and the nitrile extracted with benzene. The benzene extract was washed with sodium bicarbonate solution until the washings were no longer acid, and finally with water.
The benzene solution was dried over anhydrous sodium sulphate and percolated through a column of alumina. After removing the benzene from the percolate the residue was either distilled or crystallised. Overall yields of 20-40% based on the alkoxyaldehyde were obtained.

2-methoxyphenylacetonitrile m.p. 69-70° (benzene - light petroleum).

3-methoxyphenylacetonitrile b.p. 153-5°/15 mm.

2-ethoxyphenylacetonitrile b.p. 140-2°/16 mm.

3-ethoxyphenylacetonitrile b.p. 128-50°/4 mm.

4-ethoxyphenylacetonitrile m.p. 49-50° (benzene - light petroleum).

The alkoxybenzaldehydes were prepared by the method of Werner (Ber., 1895, 28, 2001). The corresponding hydroxy aldehyde (71 g.) was added to a solution of potassium hydroxide in ethanol (600 ccs.) followed by the requisite alkyl iodide (100 g.). After the addition of the alkyl iodide was complete the solution was refluxed for six hours. The precipitated sodium iodide was removed and the solvent evaporated on a steam bath. Distillation of the residue in vacuo gave the alkoxy aldehyde.
o-methoxybenzaldehyde b.p. 120-5°/20 mm.
methoxybenzaldehyde b.p. 120°/20 mm.
o-ethoxybenzaldehyde b.p. 100-4°/3 mm.
m-ethoxybenzaldehyde b.p. 100-4°/5 mm.
p-ethoxybenzaldehyde b.p. 115-20°/6 mm.

This compound was more conveniently prepared from p-methoxybenzylalcohol by the method of Lee, Ziering, Berger and Heineman, (Emil Barrell Jubilee Volume, pg. 299). The alcohol was converted to the chloride by treatment with hydrogen chloride in ether solution and thence to the nitrile, b.p. 146-50°/16 mm., with potassium cyanide in aqueous acetone.

Chlorophenylacetonitriles.

o-, m-, and p-chlorophenylacetonitriles were prepared by the action of potassium cyanide on an aqueous-ethanolic solution of the corresponding bromide or chloride.

- o-chlorophenylacetonitrile b.p. 123-30°/20 mm.
- m-chlorophenylacetonitrile b.p. 136-40 /20 mm.
- p-chlorophenylacetonitrile b.p. 140-5°/20 mm.

The chlorobenzylbromides were prepared by Schmidt.
succinimide in dry carbon tetrachloride solution (Ziegler
et al, Annalen, 1942, 551, 80). Schmidt and Karrer
modified the method by using benzoyl peroxide as catalyst.
An example of the method is given below.

p-Chlorotoluene (51.6 g.) was dissolved in dry
carbon tetrachloride (150 ccs.), finely powdered N-bromo-
succinimide (53.5 g.; 1.2 mole.) and benzoyl peroxide
(0.1 g.) added; the mixture was then refluxed for six
hours. The succinimide produced in the reaction was
filtered and washed with a little dry carbon tetrachloride.
The solvent was removed from the combined filtrate and
washings and the residue distilled in vacuo, when p-chloro-
benzylbromide (37.25 g.), b.p. 188-6°/20 mm., was obtained.
m-Chlorobenzylbromide, b.p. 115-9°/20 mm., was
also obtained by this method.

o-Chlorophenylacetonitrile was obtained from
the commercially available o-chlorobenzylchloride.

Nitrophenylacetonitriles

p-Nitrophenylacetonitrile was commercially
available and was crystallised from benzene-light
petroleum, m.p. 114-5°.
m-Nitrophenylacetonitrile, m.p. 60-20, (from ether-light petroleum) was prepared from m-nitrobenzylbromide, m.p. 55°, which was obtained in 50% yield by the action of N-bromosuccinimide on m-nitrotoluene.

o-Nitrophenylacetonitrile, m.p. 82-40, (from ethanol) was prepared by the method of Rousseau and Lindwall (J. Amer. Chem. Soc., 1949, 72, 5049) from o-nitrotoluene and ethyloxalate.

p-Fluorophenylacetonitrile, b.p. 122-40/22 mm., was prepared by the same method as p-chlorophenylacetonitrile, cf. Suter and Wesson, (J. Amer. Chem. Soc., 1941, 63, 502), who give b.p. 122-30/21 mm.

α-Thienylacetonitrile, b.p. 115-20°/22 mm., was obtained by the method of Blöcke and Zienty, (J. Amer. Chem. Soc., 1941, 63, 2945), by the chloromethylation of thiophene, followed by treatment of the product with aqueous alcoholic potassium cyanide. The yield in the last stage of this process did not approach that of the above authors, being about 12%. The major product was a lower boiling product (b.p. 86-90°/22 mm.), apparently α-thienylmethanol, produced by the hydrolysis of the chloride.
\( \alpha \)-Naphthylacetonitrile (Wislicenus and Wren, *Ber.*, 1905, 38, 502), b.p. 192–205°/12 mm., was prepared by the action of aqueous alcoholic potassium cyanide on \( \alpha \)-chloromethylnaphthalene (obtained by the chloromethylation of naphthalene, *Organic Reactions*, Vol. I, pg. 70).

2-Chloro-4-anilino-5-nitropyrimidine.

2:4-Dichloro-5-nitropyrimidine (0.98 g.) was dissolved in ice cold ethanol (15 ccs.) and an ice cold solution of aniline (1 g.) in ethanol (15 ccs.) added dropwise with stirring. During the addition an orange solid separated and after standing at 0° for one hour this solid was filtered and crystallised from ethanol to yield 2-chloro-4-anilino-5-nitropyrimidine (1.4 g.) as bright orange needles, m.p. 170°. (Found: C, 47.6; H, 2.72; N, 22.37; \( \text{C}_{10} \text{H}_7 \text{O}_2 \text{N}_4 \text{Cl} \) requires: C, 47.9; H, 2.62; N, 22.36%).

When this preparation was repeated on a larger scale a small amount of 2:4-dianilino-5-nitropyrimidine was obtained, which crystallised as felted yellow needles from \( n \)-butanol, m.p. 207°. (Found: C, 63.1; H, 4.87; N, 22.61; \( \text{C}_{16} \text{H}_{13} \text{O}_2 \text{N}_5 \) requires: C, 62.55; H, 4.26; N, 22.3%).

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2-Chloro-4-anilino-5-nitro-6-methylpyrimidine.

2:4-Dichloro-5-nitro-6-methylpyrimidine (5 g.) was dissolved in ice cold ethanol (60 ccs.) and a solution of aniline (5 g.) in ethanol (20 ccs.) was slowly added. A yellow solid separated almost immediately and on crystallisation from ethanol glistening yellow plates of 2-chloro-4-anilino-5-nitro-6-methylpyrimidine (6.5 g.), m.p. 131°, were obtained. (Found: C, 50.5; H, 3.99; N, 20.9; C_{12}H_{9}N_2O requires: C, 49.9; H, 3.43; N, 21.3%).

The reaction liquors on standing deposited a small amount of solid which, on crystallisation from ethanol, gave 2:4-diamilino-5-nitro-6-methylpyrimidine as yellow prismatic needles, m.p. 148°. (Found: C, 63.4; H, 4.82; C_{17}H_{15}O_2N requires: C, 65.5; H, 4.7%).

2-Chloro-4-amino-5-nitropyrimidine.

This compound was prepared by treating 2:4-dichloro-5-nitropyrimidine with methanolic ammonia by the method of Isay (Ber., 1906, 30, 250). It darkened at 200°, finally decomposing at 215-7°.

2-Fiperidino-4-anilino-5-nitropyrimidine.

2-Chloro-4-anilino-5-nitropyrimidine (0.5 g.)
and piperidine (1.5 c.c.s.) were heated on a steam bath for half an hour, when a viscous orange solution resulted. The reaction mixture was triturated with 50% ethanol, when an orange solid (0.6 g.) separated. Crystallisation from ethanol gave slender orange needles of 2-piperidino-4-anilino-5-nitropyrimidine, m.p. 148°. (Found: C, 60.4; H, 5.86; N, 22.94; \( \text{C}_{15} \text{H}_{17} \text{O}_2 \text{N}_5 \) requires: C, 60.2; H, 5.73; N, 23.4%).

\[ \text{2-} \left( 2'-\text{pyridyl} \right) \text{-amino-4-anilino-5-nitropyrimidine.} \]

A mixture of 2-chloro-4-anilino-5-nitropyrimidine (0.5 g.) and 2-aminopyridine (1 g.) was heated on a steam bath for half an hour; 50% ethanol was then added and the resultant solid filtered and washed with water. This solid was crystallised from \( \mu \)-butanol, when 2-(2'-pyridyl)-amino-4-anilino-5-nitropyrimidine (0.65 g.) was obtained as fine yellow needles, m.p. 235°. (Found: C, 58.1; H, 4.21; N, 27.9; \( \text{C}_{15} \text{H}_{12} \text{O}_2 \text{N}_6 \) requires: C, 58.4; H, 3.93; N, 27.3%).

\[ \text{2-} \left( 2'-\text{Pyridyl} \right) \text{-amino-4-aminoo-5-nitropyrimidine.} \]

2-Chloro-4-amino-5-nitropyrimidine (0.5 g.) and 2-aminopyridine (1 g.) were heated at 120-30° for one hour. The melt was then triturated with 50% ethanol and the brown
solid filtered. The solid was dissolved in hot N/20 hydrochloric acid, treated with charcoal, filtered, and the filtrate neutralised with ammonia. After cooling the pale yellow solid was filtered and crystallised from aqueous pyridine, when pale yellow needles of \(2-(2'\text{-pyridyl})\text{-amino-4-amino-5-nitropyrimidine}\) separated, m.p. 278°. (Found: N, 36.5; C\textsubscript{9}H\textsubscript{6}O\textsubscript{2}N\textsubscript{6} requires: N, 36.2%).
5-Nitro-6,8-aminopyrididine (9.2 g) was dissolved in dry benzyl alcohol (100 cm³) containing sodium (0.68 g), distilled phenylacetonitrile (2.8 cm³ 1.3 mole) added, and the solution refluxed for 20 hours. The deep brown solution, which exhibited an intense blue fluorescence in ultraviolet light, was evaporated left with a brown hydrochloride precipitated with charcoal and filtered. The yellow filtrate was neutralized with ammonia, allowed to cool, and the yellow base filtered and dried. Several crystallizations from methanol gave 5-nitro-6,8-aminopyrididine (2 g, 32% yield) as shining yellow plates, m.p. 316°C. (Found: C, 39.2; H, 4.0; N, 59.9. Calc.: C, 39.0; H, 4.4; N, 60.7. Dried at 110°C in vacuo).

The 6-hydroxy derivative, prepared by refluxing the base with alcoholic hydroxide, crystallized from glacial acetic acid to prisms or lemon-yellow needles, m.p. 239°C. (Found: C, 54.6; H, 6.0; N, 58.1. Calc.: C, 54.2; H, 5.7; N, 57.8. Dried at 120°C in vacuo).
6-Phenyl-2:4:7-triaminopteridine.

5-Nitroso-2:4:6-triaminopyrimidine (2.25 g.) was dissolved in dry β-ethoxyethanol (180 cc.) containing sodium (0.45 g.), redistilled phenylacetonitrile (2.1 g., 1.2 moles) added and the solution refluxed for two hours. The dark brown solution, which exhibited an intense blue fluorescence in ultraviolet light, was evaporated to dryness in vacuo and the residue dissolved in hot 2N hydrochloric acid, treated with charcoal and filtered. The yellow filtrate was neutralised with 2N ammonia, allowed to cool and the yellow base filtered and dried. Several crystallisations from m-butanol gave 6-phenyl-2:4:7-triaminopteridine (2 g., 55% yield) as shining yellow plates, m.p. 316°. (Found: C, 57.2; H, 4.7; N, 39.5; \( \text{C}_{12}\text{H}_{11}\text{N}_{7} \) requires: C, 56.9; H, 4.4; N, 38.7%. Dried at 170° in vacuo).

The triacetyl derivative, prepared by refluxing the base with acetic anhydride, crystallised from glacial acetic acid in rosettes of lemon-yellow needles, m.p. 282-4°. (Found: C, 56.8; H, 4.84; N, 26.1; \( \text{C}_{18}\text{H}_{17}\text{O}_{5}\text{N}_{7} \) requires: C, 56.8; H, 4.52; N, 25.85%. Dried at 135° in vacuo).

A mixture of 5-nitroso-2:4:6-triaminopyrimidine (0.75 g.), freshly fused sodium acetate (0.5 g.) and p-nitrophenylacetonitrile (0.9 g., 1.2 moles.) were refluxed in glacial acetic acid (40 ccs.) for twenty hours, when the solution showed a pale green fluorescence in ultraviolet light. The solution was filtered hot to remove small amounts of charred material and the filtrate, on cooling, deposited a mixture of solids. This mixture was separated by triturating with 2N hydrochloric acid, when the pink solid dissolved leaving a yellow solid, which was ground with 2N ammonia, allowed to stand overnight and filtered. Crystallisation from 80% formic acid gave 6-p-nitrophenyl-2:4:7-triaminopteridine (0.85 g.) as orange microprisms, m.p. 356-8° decomp. (Found: C, 48.3; H, 3.3; N, 37.2; C₁₈H₁₀O₂N₃ requires: C, 48.3; H, 3.36; N, 37.6%. Dried at 170° in vacuo).

The triacetyl derivative crystallised from dimethylformamide in yellow prismatic needles, which decomposed at 315-6° with much previous charring. (Found: N, 26.6; C₁₈H₁₆O₅N₃ requires: N, 26.4%. Dried at 170° in vacuo).

5-Nitroso-2:4:6-triaminopyrimidine (0.75 g.) and p-methoxyphenylacetonitrile (0.9 g., 1.2 moles.) were added to a solution of sodium (0.15 g.) in dry β-ethoxyethanol (60 ccs.) and the whole refluxed for two hours, during which time a golden-yellow solid slowly crystallised. The mixture was cooled and the solid filtered and washed with methanol. It was then crystallised several times from glacial acetic acid to give small yellow plates of 6-p-methoxyphenyl-2:4:7-triaminopteridine (0.75 g.), m.p. 328° decomp. (Found: C, 55.6; H, 4.9; N, 34.6; C_{13}H_{15}ON_{7} requires: C, 55.1; H, 4.6; N, 34.6%. Dried at 170° in vacuo.)

The triacetyl derivative crystallised from dimethylformamide in rosettes of yellow needles, m.p. 272° decomp. with much previous charring. (Found: N, 24.33; C_{19}H_{19}O_{4}N_{7} requires: N, 23.95%. Dried at 170° in vacuo).

6-p-Ethoxyphenyl-2:4:7-triaminopteridine.

This compound was prepared in β-ethoxyethanol by the above method and crystallised from glacial acetic acid in fine yellow needles, m.p. 348-50° decomp. (Found: C, 56.4; H, 4.94; N, 32.65; C_{14}H_{16}ON_{7} requires: C, 56.6;
6-p-ethoxyphenyl-2:4:7-triaminopteridine

When a mixture of 5-nitroso-2:4:6-triaminopyrimidine (0.78 g.) and m-methoxyphenylacetonitrile (0.9 g.) were refluxed in 3-ethoxyethanol containing sodium (0.1 g.) the above compound separated and was crystallised from glacial acetic acid in pale yellow micro plates, m.p. 228-30° decomp. These crystals were difficult to filter and it was found better to crystallise the compound from aqueous formic acid, when it separated in clusters of yellow needles, m.p. 330° decomp. (Found: C, 55.4; H, 5.0; N, 35.1; \( \text{C}_15\text{H}_{15}\text{N}_7 \) requires: C, 55.1; H, 4.6; N, 34.6%. Dried at 170° in vacuo).

6-m-Methoxyphenyl-2:4:7-triaminopteridine.

The above compound was prepared from 5-nitroso-2:4:6-triaminopyrimidine and m-methoxyphenylacetonitrile and crystallised from glacial acetic acid in small yellow needles, m.p. 310-12 decomp. (Found: C, 56.3; H, 4.87;
To a solution of 5-nitroso-2:4:6-triaminopyrimidine in β-ethoxyethanol (60 ccs.) containing sodium (0.15 g.) was added p-methoxyphenylacetonitrile (0.9 g.) and the mixture refluxed for four hours. The cooled solution was filtered, evaporated to small bulk in vacuo, water added and the solid that separated filtered. 6-o-Methoxyphenyl-2:4:7-triaminopteridine crystallised in orange-yellow rods when a hot solution of the solid in N/10 hydrochloric acid was neutralised with 2N ammonia solution, m.p. 334° decmp. (Found: C, 54.4; H, 4.27; N, 36.0; C_{13}H_{15}ON_{7} requires: C, 55.1; H, 4.6; N, 34.6%. Dried at 135° in vacuo).

6-p-Chlorophenyl-2:4:7-triaminopteridine.

When a solution of 5-nitroso-2:4:6-triaminopyrimidine and p-chlorophenylacetonitrile in β-ethoxyethanol was refluxed for two hours the above compound separated and was crystallised from glacial acetic acid in lemon yellow prisms, m.p. 378-80° decmp. (Found: C, 50.2; H, 3.49; N, 34.0; C_{12}H_{10}N_{7}Cl requires;
C, 50.5; H, 3.5; N, 34.1%. Dried at 170° in vacuo).

The triacetyl derivative derivative crystallised from dimethylformamide in lemon yellow prisms which decomposed above 350° C. (Found: N, 23.97; C_{15}H_{16}N_{7}O_{3}Cl requires: N, 23.7%. Dried at 135° in vacuo).

6-p-Fluorophenyl-2:4:7-triaminopteridine.

This compound crystallised from glacial acetic acid in clumps of yellow prismatic needles, m.p. 362° decomp. (Found: C, 53.2; H, 4.5; N, 34.9; C_{12}H_{10}N_{7}F requires: C, 53.1; H, 3.72; N, 36.2%. Dried at 170° in vacuo).

6-α-Thienyl-2:4:7-triaminopteridine.

α-Thienylacetoneitrile (0.8 g.) and 5-nitroso-2:4:6-triaminopyrimidine (0.75 g.) were refluxed together in β-ethoxyethanol (60 ccs.) containing sodium (0.15 g.) to give 6-α-thienyl-2:4:7-triaminopteridine (0.95 g.).

The product crystallised from glacial acetic acid in small deep yellow prisms, m.p. 356-6° decomp. (Found: C, 46.7; H, 3.79; N, 37.82; C_{10}H_{9}N_{7}S requires: C, 46.3; H, 3.5; N, 37.8%. Dried at 170° in vacuo). Solutions of this substance in glacial acetic acid or dilute hydrochloric acid had a deep sea green fluorescence.
4:7-Diamino-2-methylthio-6-phenylpteridine.

4:6-Diamino-2-methylthio-5-nitrosopyrimidine (0.5 g.) and phenylacetonitrile (0.35 g.) were added to a solution of sodium (0.1 g.) in dry ethanol (60 cc.) and the resultant solution refluxed for one hour. After a short time a yellow crystalline solid began to separate, the separation being complete at the end of one hour. The mixture was cooled and the crystals separated, dissolved in cold N hydrochloric acid, the yellow solution treated with charcoal and filtered. The filtrate was then neutralised with ammonia and after standing overnight the granular yellow solid was filtered and dried. Several crystallisations from n-butanol gave pale yellow plates of 4:7-diamino-2-methylthio-6-phenylpteridine, m.p. 306°. (Needles were obtained if the solution was allowed to cool slowly). (Found: C, 55.2; H, 4.16; N, 29.6; C15H12N6S requires: C, 55.0; H, 4.23; N, 29.5%. Dried at 135° in vacuo).

The diacetyl derivative crystallised from ethanol in slender yellow needles, m.p. 230°. (Found: N, 22.7; C17H16N6O2S requires: N, 22.8%. Dried at 135° in vacuo).
4:7-Diamino-2-ethylthio-6-phenylpteridine.

4:6-Diamino-2-ethylthio-5-nitrosopyrimidine

(0.5 g.) and phenylacetonitrile were condensed in alcohol as above, and the product, after purification by dissolution in N hydrochloric acid and precipitation with ammonia, was crystallised from n-butanol in lemon-yellow plates (0.4 g.), m.p. 272-4°. (Found: C, 56.7; H, 4.82; N, 27.85; C_{14}H_{14}N_{6}S requires: C, 56.4; H, 4.7; N, 28.2%. Dried at 135° in vacuo).

The diacetyl derivative crystallised from ethanol in pale yellow needles, m.p. 209-10°. (Found: N, 21.2; C_{18}H_{18}O_{2}N_{6}S requires: N, 22.0%. Dried at 135° in vacuo).

2:7-Diamino-4-hydroxy-6-phenylpteridine.

To a solution of sodium (0.3 g.) in dry ethylene glycol (45 cc.) was added 2:4-diamino-6-hydroxy-5-nitrosopyrimidine (0.75 g.) and phenylacetonitrile (0.7 g., 1.2 moles.) and the solution refluxed for seven hours. The solvent was removed and the residue dissolved in hot water, treated with charcoal and neutralised with acetic acid, when a brown amorphous solid was precipitated. This solid was allowed to granulate, filtered and crystall-
ised from 2N hydrochloric acid (charcoal) as the hydrochloride (0.3 g.) in buff needles. Two further crystallisations from 0.5N hydrochloric acid gave an analytically pure specimen as light buff needles. (Found: C, 49.3; H, 4.35; N, 29.0; C\textsubscript{12}H\textsubscript{10}ON\textsubscript{6}.HCl requires: C, 49.6; H, 3.82; N, 29.0%. Dried at 170° in vacuo).

The base was prepared by treating the pure hydrochloride with hot ammonia and was purified by dissolving in hot N/10 caustic soda solution and precipitating from the hot solution with the theoretical amount of N acetic acid as a buff solid, which did not melt but decomposed above 350°. (Found: C, 53.5; H, 5.1; N, 31.0; C\textsubscript{12}H\textsubscript{10}ON\textsubscript{6}.H\textsubscript{2}O requires: C, 52.9; H, 4.45; N, 30.8%. Dried at 170° in vacuo for three hours. Longer drying gave analytical results indicating between 0 and 1 mole of water of crystallisation).

7-Amino-4-hydroxy-2-methyl-6-phenylpteridine.

When 4-amino-6-hydroxy-2-methyl-5-nitrosopyrimidine and phenylacetonitrile were condensed in \(\beta\)-ethoxyethanol containing sodium a colourless solid was obtained, which crystallised from 0.5N hydrochloric acid as long slender needles of the hydrochloride of 7-amino-
4-hydroxy-2-methyl-6-phenylpteridine. (Found: C, 53.3; H, 4.4; N, 23.9; C_{13}H_{11}N_{5}O.HCl requires: C, 53.9; H, 4.18; N, 24.2%. Dried at 100° in vacuo).

The free base was prepared by dissolving the hydrochloride in hot N/10 sodium hydroxide solution and adding the theoretical amount of N acetic acid to the hot solution, when it separated in colourless plates, which did not melt but decomposed above 320°. (Found: C, 61.6; H, 4.36; N, 27.9; C_{13}H_{11}O_{5}N_{5} requires: C, 61.6; H, 4.38; N, 27.7%. Dried at 135° in vacuo).

6-β-Chlorophenyl-2:4:7-triaminopteridine.

5-Nitroso-2:4:6-triaminopyrimidine (0.75 g.) and β-chlorophenylacetonitrile (1 g.) were added to a solution of sodium (0.15 g.) in β-ethoxyethanol (60 ccs.) and the mixture refluxed for four hours. The solution was filtered hot to remove charred material and evaporated to small bulk in vacuo, when, on addition of water, a pale yellow solid separated (0.65 g.). This solid was purified by crystallisation from aqueous dimethylformamide, when the required compound separated as pale yellow rods, m.p. 342° decomp. (Found: C, 50.1; H, 4.3; N, 34.1; C_{12}H_{10}N_{7}Cl requires: C, 50.1; H, 5.5; N, 34.1%. Dried
at 170° in vacuo).

4:7-Diamino-6-Phenylpteridine.

4:6-Diamino-5-nitrosopyrimidine (0.35 g.) was dissolved in β-ethoxyethanol (30 cc.) containing sodium (0.1 g.) and to the hot solution was added phenylacetonitrile (0.35 g.) and the whole refluxed for four hours. The solution was cooled and the yellow solid that separated was filtered. This was dissolved in hot 2N hydrochloric acid and the solution treated with charcoal and filtered. The hot, colourless filtrate was neutralised with ammonia and, after cooling, the resultant solid (0.4 g.) was filtered and crystallised from m-butanol as pale yellow prisms, m.p. 540° decom. (Found: C, 60.5; H, 4.23; N, 35.27%. Dried at 135° in vacuo).

6-m-Nitrophenyl-2:4:7-triaminopteridine.

To a solution of sodium (0.15 g.) in β-ethoxyethanol (60 cc.) was added 5-nitroso-2:4:6-triaminopyrimidine (0.75 g.) and m-nitrophenylacetonitrile (0.9 g.) and the dark red mixture was refluxed for three hours. After cooling the orange-yellow solid was filtered from the dark brown liquor and dissolved in 100% formic acid;
the solution was then diluted to 60% with hot water, treated with charcoal and filtered. The pale yellow filtrate was neutralised with dilute ammonia solution, cooled, and the buff solid filtered. This solid was crystallised from aqueous formic acid as rosettes of needles, which decomposed above 360°. (Found: C, 48.52; H, 5.0; N, 57.75; \( \text{C}_{12}\text{H}_{10}\text{O}_{2}\text{N}_{8} \) requires: C, 48.3; H, 3.38; N, 57.6%. Dried at 135° in vacuo).

**7-Amino-4-hydroxy-6-phenylpteridine.**

This compound resulted from the reaction of 4-amino-6-hydroxy-5-nitrosopyrimidine and phenylacetonitrile in β-ethoxyethanol solution and was purified by dissolving in N/10 sodium hydroxide solution and adding the theoretical amount of N/10 acetic acid to the boiling solution, when 7-amino-4-hydroxy-6-phenylpteridine separated as buff plates, which decomposed without melting above 350°. (Found: C, 60.2; H, 4.09; N, 30.4; \( \text{C}_{12}\text{H}_{9}\text{ON}_{5} \) requires: C, 60.2; H, 3.79; N, 29.3%. Dried at 170° in vacuo).

**6-O-Ethoxyphenyl-2:4:7-triaminopteridine.**

5-Nitroso-2:4:6-triaminopyrimidine (0.75 g.) and o-ethoxyphenylacetonitrile (0.95 g.) were added to
a solution of sodium (0.15 g.) in β-ethoxyethanol
(60 ccs.) and the mixture refluxed for four hours.
After cooling the mixture was filtered to remove any
charred material and the filtrate evaporated to small
bulk in vacuo, when, on the addition of water, a solid
separated. 6-β-Ethoxyphenyl-2:4:7-triaminopteridine
(0.8 g.) crystallised in yellow prisms when a hot solu-
tion of this solid in N/10 hydrochloric acid was neutrali-
sed with ammonia solution; m.p. 308° decomp. (Found:
C, 56.69; H, 5.31; N, 33.8; C₁₄H₁₅O₇N₇ requires:
C, 56.6; H, 5.09; N, 33.0%; Dried at 135° in vacuo
over P₂O₅).

7-Aminoo-2:6-diphenyl-4-hydroxypteridine.

A mixture of 4-amino-6-hydroxy-5-nitroso-2-
phenylpyrimidine (0.54 g.) and phenylacetonitrile was
refluxed in β-ethoxyethanol (60 ccs.) containing sodium
(0.15 g.) for two hours. The resultant mixture was
evaporated to dryness in vacuo, the residue triturated
with dilute acetic acid and the solid (0.35 g.) filtered.
Purification of this solid was affected by dissolving it
in 200 ccs. of 5% potassium hydroxide solution and neutrali-
sing the hot solution with dilute acetic acid, when 7-
amino-2:6-diphenyl-4-hydroxypteridine separated as a
micro-crystalline solid, which rapidly decomposed above 400°. (Found: C, 67.2; H, 4.25; N, 22.1;
C₁₆H₁₃NO₅ requires: C, 67.3; H, 4.08; N, 21.8%.
Dried at 170° in vacuo over P₂O₅).

2:4:7-Triamino-6-m-chlorophenylpteridine.

To a solution of sodium (0.13 g.) in β-ethoxyethanol (60 ccs.) was added 5-nitroso-2:4:6-triamino-
pyrimidine (0.75 g.) and m-chlorophenylacetonitrile (1 g.) and the mixture refluxed for two hours. During this period a yellow crystalline solid separated and after cooling this solid was filtered. Crystallisation from glacial acetic acid gave 2:4:7-triamino-6-m-chlorophenylpteridine (0.75 g.) as clusters of yellow prisms, m.p. 353° decomp. (Found: C, 50.3; H, 4.1; N, 34.3;
C₁₂H₁₀N₇Cl requires: C, 50.5; H, 3.5; N, 34.1%. Dried at 170° in vacuo).

2:4:7-Triamino-6-α-naphthylpteridine.

5-Nitroso-2:4:6-triaminopyrimidine (0.75 g.) and α-naphthylacetonitrile (1.1 g.) were added to a solution of sodium (0.15 g.) in β-ethoxyethanol (60 ccs.) and the mixture refluxed for three hours. After cooling the almost colourless solid was filtered and purified as follows. The solid (0.9 g.) was dissolved in 15 ccs.
of hot 100% formic acid, diluted with 100 ccs. of hot water and the solution treated with charcoal and filtered; the hot filtrate was brought to pH4 with ammonia solution and the yellow solid that separated filtered from the hot solution. Crystallisation of this solid from glacial acetic acid gave 2:4:7-triamino-6-α-naphthylpteridine as fine, pale yellow needles, m.p. 584° decmp. with much previous decomposition. (Found: C, 63.7; H, 4.54; N, 32.0; C₁₆H₁₃N₇ requires: C, 63.4; H, 4.5; N, 32.3%. Dried at 170° in vacuo).

2:4-Diamino-7-hydroxy-6-phenylpteridine.

5-Nitroso-2:4:6-triaminopyrimidine (1 g.) was ground with phenylacetychloride (10 ccs.) and gradually heated to 140° in an oil bath, reaction being complete when no more hydrogen chloride was evolved (about 10 mins.). The dark brown solution was cooled and triturated with ether, when a light brown solid separated. This was filtered and washed with more ether to remove unchanged phenylacetychloride. The solid was ground with hot 2N ammonia solution to liberate the free base, which was filtered and dried in vacuo over P₂O₅. Several crystallisations from glacial acetic acid gave small yellow prisms of 2:4-diamino-
7-hydroxy-6-phenylpteridine (1 g.), m.p. 406-8° decomp. (Found: C, 56.5; H, 3.83; N, 33.2; \( \text{C}_{12}\text{H}_{10}\text{ON}_6 \) requires: C, 56.7; H, 3.96; N, 33.8%). Dried at 170° in vacuo over \( \text{P}_2\text{O}_5 \). This substance had an intense sky-blue fluorescence under ultraviolet light in both acid and alkaline solution.

2:4-Diamino-7-hydroxy-6-p-nitrophenylpteridine.

5-Nitroso-2:4:6-triaminopyrimidine (1 g.) was intimately ground with \( p \)-nitrophenylacetyl chloride (5 g.) and slowly heated to 140° as above. After trituration with ether and ammonia the base (1.3 g.) was obtained as an orange-brown solid. To obtain an analytical specimen the solid was repeatedly extracted with hot 2N ammonia solution, when it nearly all dissolved to give a deep orange solution, which was evaporated to small bulk in vacuo and the orange solid filtered. On crystallisation from 80% formic acid 2:4-diamino-7-hydroxy-6-p-nitrophenylpteridine separated as orange yellow needles, which turned deep red on drying at 170° in vacuo. The substance did not melt but slowly decomposed on heating above 400°. (Found: C, 47.9; H, 3.4; N, 32.5; \( \text{C}_{12}\text{H}_{9}\text{O}_3\text{N}_7 \) requires: C, 48.2; H, 3.61; N, 32.8%). Solutions of the substance
had only a very weak green fluorescence in ultraviolet light.

2:4-Diamino-7-hydroxy-6-p-methoxyphenylpteridine.

Reaction of 5-nitroso-2:4:6-triaminopyrimidine (1 g.) and p-methoxyphenylacetylchloride (7 ccs.) at 140° gave 1.3 g. of crude product. This was purified by extraction of the crude material with 1000 ccs. of 10% potassium hydroxide solution, acidification of the extract with glacial acetic acid, followed by crystallisation of the resultant solid from dimethyl formamide. The pure material separated in yellow prisms, which did not melt but decomposed above 350°. (Found: C, 55.3; H, 4.7; N, 29.4; C_{13}H_{12}O_{2}N_{6} requires: C, 54.9; H, 4.26; N, 29.6%. Dried at 170° in vacuo).

2-Thio-4:7-diamino-6-phenylpteridine.

4:6-Diamino-5-nitroso-2-thiopyrimidine (0.84 g.) was dissolved in ethanol (150 ccs.) containing sodium (0.23 g.) and phenylacetonitrile (0.7 g.) added. The resulting solution was refluxed for four hours and then evaporated to small bulk when, on diluting with an equal volume of water and cooling, an alkali insoluble product A (200 mg.) separated. The filtrate was warmed, treated with charcoal
and filtered and the hot filtrate neutralised with 2N acetic acid, when a yellow solid separated. This solid was dissolved in hot N/5 sodium hydroxide solution, filtered from any insoluble material and the hot filtrate neutralised with the theoretical amount of 2N acetic acid. After cooling the yellow solid was filtered and dissolved in hot 2N hydrochloric acid; it was then neutralised with the theoretical quantity of 2N ammonia solution, when 2-thio-4:7-diamino-6-phenylpteridine (0.65 g.) separated in deep yellow microprisms. The material did not melt but decomposed above 310°. (Found: C, 53.5; H, 4.03; N, 31.07; C_{12}H_{10}N_{5}S requires: C, 53.3; H, 3.7; N, 31.1%. Dried at 135° in vacuo over P_{2}O_{5}). This substance has a dull blue fluorescence in alkaline and acid solution under ultraviolet light.

The alkali insoluble material A was purified by dissolving in hot 2N hydrochloric acid solution, treating with charcoal and neutralising the hot filtrate with ammonia, followed by crystallisation from n-butanol, from which it crystallised in pale yellow prisms, m.p. 290° dec. (Found: C, 59.93; H, 4.61; N, 30.2; 2-ethoxy-4:7-diamino-6-phenylpteridine, C_{14}H_{13}NO_{6} requires: C, 59.8; H, 4.66; N, 29.9%. Dried at 135° in vacuo). Solutions
of this substance have a sky-blue fluorescence in ultra-
violet light.

Hydrolysis of 2-methylthio-4:7-diamino-6-phenylpteridine.

The 2-methylthio compound (0.1 g.) was refluxed
with 15 ccs. of 2N hydrochloric acid until all the methyl-
thiol had been evolved. The solution was cooled and the
yellow solid filtered, dissolved in hot N sodium hydroxide
solution and the resultant solution treated with charcoal
and filtered. The pale yellow filtrate was heated to
boiling and carefully neutralised with the theoretical
amount of N acetic acid, when 2-hydroxy-4:7-diamino-6-
phenylpteridine (80 mg.) separated as a pale yellow micro-
crystalline powder, which did not melt but decomposed above
320°. (Found: C, 56.5; H, 4.4; N, 32.5; \( \text{C}_{12}\text{H}_{10}\text{O}_{6}\text{N}_{6} \)
requires: C, 56.7; H, 3.97; N, 33.1%. Dried at 170°
in vacuum over P_{2}O_{5}).

Hydrolysis with 5N hydrochloric acid led to an
impure product, which was essentially the compound obtained
above. The ultraviolet absorption spectra of this com-
pound showed that the impurity was not the expected 2:4-
dihydroxy-7-amino-6-phenylpteridine.

Hydrolysis of 2-methylthio-7-amino-4-hydroxy-6-phenyl-
pteridine.

2-Methylthio-7-amino-4-hydroxy-6-phenylpteridine
(100 mg.) was boiled with 15 ccs. of 2N hydrochloric acid until all the methylthiol was evolved (about two hours). The mixture was cooled and the solid filtered, dissolved in 20 ccs. of hot N/2 sodium hydroxide solution and the solution treated with charcoal and filtered. The filtrate was heated to boiling and neutralised with 20 ccs. of N/2 acetic acid, when, after a short while, pale yellow rhombs of 2:4-dihydroxy-7-amino-6-phenylpteridine separated, which did not melt but decomposed above 330°. (Found: C, 56.6; H, 3.0; N, 26.2; C₁₂H₉O₂N₅ requires: C, 56.5; H, 2.8; N, 27.4%. Dried at 170° in vacuo over P₂O₅).

2-Hydroxy-4:7-diamino-6-phenylpteridine.

To a solution of sodium (0.23 g.) in ethylene glycol was added 2-hydroxy-4:6-diamino-5-nitrosopyrimidine (0.75 g.) and phenylacetonitrile (0.7 g.) and the solution was refluxed for one hour; the solvent was then removed in vacuo. The residue in the flask was dissolved in hot N/10 sodium hydroxide solution and the dark coloured solution treated with charcoal and filtered. The filtrate was heated to 90° and neutralised with dilute acetic acid, allowed to cool and the dark orange solid filtered. This solid was dissolved in a little hot 100% formic acid,
diluted to 50% with water, treated with charcoal and filtered; the hot filtrate was then neutralised with dilute ammonia solution, when a yellow solid separated. This solid was further purified by dissolution in N/10 sodium hydroxide solution and re-precipitation with the theoretical quantity of acetic acid, when it was obtained as a yellow solid, which was dried over P₂O₅ at 170° in vacuo. (Found: N, 32.4; C₁₂H₁₀O₆N₆ requires: N, 33.1%). The ultraviolet absorption spectrum of this compound showed it to be identical with the compound obtained by the dilute acid hydrolysis of 2-methylthio-4:7-diamino-6-phenylpteridine.


(a) The triamine (0.2 g.) was refluxed with 5N hydrochloric acid (30 cc.) for one hour. The solid A that had separated over this period was filtered from the hot solution and the filtrate allowed to cool, when another solid B separated.

Solid B was dissolved in hot N/10 sodium hydroxide and the solution treated with charcoal and filtered. The filtrate was neutralised with dilute acetic acid and the solid that separated was filtered and extracted with boiling 2N hydrochloric acid, when
it nearly all dissolved. The hydrochloric acid extract was allowed to cool to 30° and the amorphous solid that had separated was filtered. The filtrate was treated with charcoal, the charcoal removed, and the resulting colourless solution was allowed to stand at room temperature for several hours, when slender needles of 4-hydroxy-2:7-diamino-6-phenylpteridine hydrochloride (130 mg.) separated. The ultraviolet absorption spectrum of this compound in N/10 sodium hydroxide was identical with that of the compound obtained by direct synthesis.

The solid A was dissolved in hot N/10 sodium hydroxide and the solution treated with charcoal and filtered. The hot filtrate was neutralised with the theoretical amount of N acetic acid and after cooling the bright yellow solid that had separated was filtered. This procedure was repeated twice and the resultant amorphous yellow solid was dried at 170° in vacuo over P₂O₅. (Found: N, 33.1; calc. for 2:4-diamino-6-phenyl-7-hydroxypteridine, C₁₂H₁₀O₅N₆, N, 33.8%). Comparison of the ultraviolet spectrum of this compound in N/10 sodium hydroxide and that of 2:4-diamino-6-phenyl-7-hydroxypteridine in the same solvent showed that they were identical.
(b) When the triamine (0.2 g.) is boiled for three hours with 2N hydrochloric acid 180-190 mg. of the starting material was recovered. No evidence of alkali soluble material could be obtained.

The ethylation of 2-thio-4,7-diamino-6-phenylpteridine.

To a solution of sodium (0.05 g.) in ethanol (25 ccs.) was added 2-thio-4,7-diamino-6-phenylpteridine (0.1 g.) followed by ethyl bromide (0.1 cc.). The clear yellow solution was refluxed for two hours, when the original dull blue fluorescence in ultraviolet light had changed to a brilliant sky-blue fluorescence. The solvent was removed in vacuo and the residue dissolved in cold 2N acetic acid, the solution treated with charcoal, filtered and neutralised with ammonia, when an amorphous yellow solid separated. Crystallisation from n-butanol gave yellow plates of 2-ethylthio-4,7-diamino-6-phenylpteridine, m.p. 272°, undepressed by admixture with the compound prepared from 2-ethylthio-4,6-diamino-5-nitrosopyrimidine and phenylacetonitrile. Comparison of the ultraviolet absorption spectrum of this compound with that of an authentic specimen showed that they were identical.
The oxidation of 2-thio-4:7-diamino-6-phenylpteridine to 2-hydroxy-4:7-diamino-6-phenylpteridine.

A solution of the 2-thio compound (0.1 g.) was dissolved in N/10 sodium hydroxide, and the solution treated with hydrogen peroxide (5 ccs. of 20 volumes), when an orange colour developed. After standing at room temperature overnight a pale yellow solution remained which had a brilliant blue fluorescence in ultra-violet light. This solution was acidified with N acetic acid and the precipitate collected, dissolved in hot N/10 sodium hydroxide and re-precipitated from the hot solution with N acetic acid. The resultant yellow micro-crystalline solid was dried at 170° in vacuo. Comparison of its ultra-violet absorption spectrum with that of an authentic specimen of 2-hydroxy-4:7-diamino-6-phenylpteridine, prepared from 2-hydroxy-4:6-diamino-5-nitrosopyrimidine and phenylacetanitrile, showed these two compounds to be identical.

The attempted reaction of 2-methylthio-4:7-diaminopyrimidine and aniline.

(a) The 2-methylthio compound (0.1 g.) was refluxed for twenty-four hours with aniline (1 cc.) in ethanol (10 ccs.) No methylthiol was evolved, however, and the starting material was recovered unchanged.
(b) The starting material was again recovered unchanged when the 2-methylthio compound (0.1 g.) was refluxed with aniline (1 cc.) for several hours.

Condensation of 2:4:5:6-tetraaminopyrimidine hydrochloride with phenylglyoxylic acid.

a) At pH 5.

A mixture of 2:4:5:6-tetraaminopyrimidine (190 mg.), sodium acetate (450 mg.) and phenylglyoxylic acid (150 mg.) were dissolved in warm water (10 cc.s) and refluxed for ten minutes. The yellow solid that separated was filtered and on crystallisation from glacial acetic acid gave yellow microprisms of 2:4-diamino-7-hydroxy-6-phenylpteridine (180 mg.), m.p. 406-8° alone or admixed with the pure compound obtained by the condensation of 5-nitroso-2:4:6-triaminopyrimidine and phenylacetyl chloride. The ultraviolet absorption spectra of the two compounds showed that they were identical.

b) In acid solution.

A solution of 2:4:5:6-tetraaminopyrimidine hydrochloride (0.9 g.) and phenylglyoxylic acid (0.7 g.) in 2N hydrochloric acid (25 cc.s) and ethanol (15 cc.s) was refluxed for one hour. The solid was filtered and the filtrate evaporated to dryness; the combined solids
(1.25 g.) were then extracted with hot 2N ammonia 
(3 x 75 ccs.) to leave a pale yellow solid A (0.65 g.). 
The ammonia solution, on evaporation to small bulk, left 
a deep orange solid (0.5 g.) which, in contrast to solid 
A, which had a sky-blue fluorescence in ultraviolet 
light, had a deep green fluorescence. 

Solid A crystallised from glacial acetic acid in yellow microprisms, m.p. 406-8° decomp., alone or 
admixed with the pure compound obtained by the condensa-
tion of 5-nitroso-2:4:6-triaminopyrimidine and phenyl-
acetylchloride.

The second solid crystallised from water in golden needles of 2:4-diamino-6-hydroxy-7-phenylpteridine, 
which did not melt but decomposed above 310°. (Found: 
C, 56.96; H, 4.18; N, 32.7; \( C_{12}H_{10}ON_{6} \) requires: 
C, 56.7; H, 3.96; N, 33.1%. Dried at 170° in vacuo 
over \( \text{P}_2\text{O}_5 \)).
The Reaction of 4-Chloro-4-(2'-pyridyl)-3-nitropyridine with 2-Chloropyrimidine.

a) With 8 molar of 2-Chloropyrimidine.

To an ice cold solution of 4-Chloro-4-(2'-pyridyl)-3-nitropyridine (4.0 g.) in methanol (50 cc.) was added an ice cold solution of 2-Chloropyrimidine (8.1 g.) in methanol (20 cc.). A yellow solid rapidly separated and after standing for hours in an ice bath the crystalline solid was filtered and washed with methanol. This solid (4.8 g.) was separated by hot water into the insoluble 2-Chloro-4-(2'-pyridyl)-3-nitropyridine and the water soluble quaternary salt 2-Chloro-3-(2'-[2,4-(2'-pyridyl)-3-nitropyridine] pyridinium chloride.

2-Chloro-4-(2'-pyridyl)-3-nitropyridine (0.7 g.) crystallised from ethanol in yellow needle-shaped prisms, m.p. 156°. Found: C, 45.6; H, 3.48; N, 27.8; C_{12}H_{11}ClN requires: C, 45.8; H, 3.48; N, 27.8%.

The quaternary chloride (10.3 g.) crystallised from water, or better, ethyl acetate, as a yellow needle-like salt, or lustrous yellow polycrystalline needles, m.p. ca. 120°.
The Reaction of 2:4-dichloro-5-nitropyrimidine with 2-aminopyridine.

a) With 2 moles of 2-aminopyridine.

To an ice cold solution of 2:4-dichloro-5-nitropyrimidine (4.2 g.) in methanol (25 ccs.) was added an ice cold solution of 2-aminopyridine (4.1 g.) in methanol (25 ccs.). A yellow solid rapidly separated and after standing two hours in an ice bath the crystalline solid was filtered and washed with methanol. This solid (4.8 g.) was separated by hot water into the insoluble 2-chloro-4-(2'-pyridyl)-amino-5-nitropyrimidine and the water soluble quaternary salt 2-amino-N-[2'-[4'-(2''-pyridyl)-amino-5-nitropyrimidyil]-pyridinium chloride.

2-Chloro-4-(2'-pyridyl)-amino-5-nitropyrimidine (0.9 g.) crystallised from ethanol in yellow sword-shaped prisms, m.p. 156°. (Found: C, 43.4; H, 2.63; N, 27.2; C₉H₆O₂N₅Cl requires: C, 43.0; H, 2.4; N, 27.8%).

The quaternary chloride (3.6 g.) crystallised from water, or better dilute hydrochloric acid, as lustrous yellow prismatic needles, m.p. 249° decomp.
2-Amino-N-\{2'-[4'-\(2''\)-pyridyl]-amino-5'-nitropyrimidyl\} -pyridinium bromide, - obtained by treating an aqueous solution of the above quaternary chloride with aqueous sodium bromide, crystallised from water in felted yellow needles, m.p. 262° decom. (Found: C, 42.8; H, 3.9; N, 23.95; C\(_{14}H_{12}O_2N_7\)Br requires: C, 45.2; H, 2.85; N, 25.1%).

2-Amino-N-\{2'-[4'-\(2''\)-pyridyl]-amino-5'-nitropyrimidyl\} -pyridinium iodide, - crystallised from water in rosettes of orange needles, m.p. 252° decom. (Found: C, 38.5; H, 3.2; N, 21.1; C\(_{14}H_{12}O_2N_7\)I requires: C, 38.55; H, 2.54; N, 22.4%).

b) With 3 moles of 2-aminopyridine.

When a solution of 2:4-dichloro-5-nitropyrimidine (0.5 g.) in boiling methanol (25 cc.) was treated with 2-aminopyridine (1 g.) the quaternary chloride separated quantitatively, m.p. 249° decom.

Likewise, when a solution of 2-chloro-4-
(2'-pyridyl)-amino-5-nitropyrimidine (0.2 g.) in methanol (15 ccs.) was treated with 2-aminopyridine (0.4 g.) the quaternary chloride separated immediately, m.p. 249° decomp.

c) With 4 moles of 2-aminopyridine in methanol.

To a hot solution of 2:4-dichloro-5-nitropyrimidine (0.98 g.) in methanol (25 ccs.) was added 2-aminopyridine (1.9 g.), when the quaternary chloride described previously separated. Continued boiling, however, gave a clear solution after two hours, which, on cooling, deposited a pale yellow solid. Crystallisation of this solid from ethanol gave 2-methoxy-4-(2'-pyridyl)-amino-5-nitropyrimidine, m.p. 148°, alone and admixed with the compound prepared below.

2-Methoxy-4-(2'-pyridyl)-amino-5-nitropyrimidine.

2-Chloro-4-(2'-pyridyl)-amino-5-nitropyrimidine (0.5 g.) was dissolved in methanol (15 ccs.) and treated with a solution of sodium (0.5 g.) in methanol (100 ccs.). A deep orange-red solution was obtained, which was refluxed for two hours. The solution was acidified with dilute acetic acid, cooled and the yellow crystalline solid filtered and washed with water. Crystallisation from ethanol gave
2-methoxy-4-(2'-pyridyl)-amino-5-nitropyrimidine as yellow plates, m.p. 148°. (Found: C, 48.5; H, 3.93; N, 28.6; \( \text{C}_5\text{H}_3\text{O}_3\text{N}_5 \) requires: C, 48.6; H, 3.67; N, 28.3%).

2-Ethoxy-4-(2'-pyridyl)-amino-5-nitropyrimidine.

(a) 2-Chloro-4-(2'-pyridyl)-amino-5-nitropyrimidine (0.25 g.) was treated with a solution of sodium in ethanol (0.25 g. in 20 ccs.). After refluxing for two hours the solution was evaporated, the residue dissolved in water and acidified, when a pale yellow crystalline solid separated. This was filtered and crystallised from ethanol in clusters of pale yellow needles, m.p. 181°. (Found: O, 51.0; H, 4.95; C, 27.5; \( \text{C}_1\text{H}_{11}\text{O}_3\text{N}_5 \) requires: C, 50.6; H, 4.25; N, 26.8%).

(b) When 2-amino-N-[2'-[4'-(2''-pyridyl)-amino-5'-nitropyrimidyl]]-pyridinium chloride (0.5 g.) was refluxed in methanol solution with 2-aminopyridine (0.5 g.) until a clear solution was obtained, 2-ethoxy-4-(2'-pyridyl)-amino-5-nitropyrimidine separated on cooling, m.p. 131°, alone or admixed with the compound prepared by the above method.

The Reaction of 2:4-dichloro-5-nitropyrimidine with 2-amino-6-methylpyridine.

a) With 2 moles of 2-amino-6-methylpyridine.

An ice cold solution of 2-amino-6-methylpyridine
(2.1 g.) in methanol (20 ccs.) was added to a solution of 2:4-dichloro-5-nitropyrimidine (2 g.) in methanol (20 ccs.), which was stirred and ice cooled during the addition. The mixture was allowed to stand at 0° for one hour, the yellow solid that had separated was filtered and crystallised from ethanol to yield 2-chloro-4-[2'-(6'-methylpyridyl)]-amino-5-nitropyrimidine (2 g.) as fine yellow needles, m.p. 144°. (Found: C, 45.2; H, 3.35; N, 25.74; C10H8O2N5Cl requires: C, 45.2; H, 3.04; N, 26.36%).

b) With 4 moles of 2-amino-6-methylpyrididine.

When 2-amino-6-methylpyridine (2.1 g.) was added to a boiling solution of 2:4-dichloro-5-nitropyrimidine (1 g.) in methanol (25 ccs.) a clear solution was obtained. On continued boiling a yellow solid was gradually deposited, which did not re-dissolve on long boiling. The mixture was cooled, the solid filtered and crystallised from glacial acetic acid to give 2:4-di-[2'- (6'-methylpyridyl)-amino]-5-nitropyrimidine as yellow prismatic needles, m.p. 318-9° decomp. (Found: C, 56.9; H, 4.51; N, 28.79; C15H15O2N7 requires: C, 57.0; H, 4.48; N, 29.08%).
The Reaction of 2:4-dichloro-5-nitropyrimidine with 2-amino-3-methylpyridine.

a) With 3 moles of 2-amino-6-methylpyridine.

An ice cold solution of the 2:4-dichloro-5-nitropyrimidine (2.2 g.) in methanol (20 ccs.) was treated with an ice cold solution of 2-amino-3-methylpyridine (3.5 g.) in methanol (15 ccs.). After standing at 0°C for two hours the resultant solid was filtered. It was completely soluble in hot water and on cooling 2-amino-3-methyl-N-[2'-[4'-(2'-3'-methylpyridyl)]-amino 5'-nitropyrimidyl]-pyridinium chloride (1.8 g.) separated in yellow prisms, m.p. 250°C decomp. (Found: C, 51.4; H, 4.52; N, 26.6; C₁₆H₁₆O₂N₇ requires: C, 51.4; H, 4.32; N, 26.4%).

b) With 2 moles of 2-amino-3-methylpyridine.

The only compound isolated from this experiment was the quaternary salt described above.

c) With 4 moles of 2-amino-3-methylpyridine.

To a solution of 2:4-dichloro-5-nitropyrimidine (1 g.) in methanol (25 ccs.) was added 2-amino-3-methylpyridine (2.3 g.) and the solution was refluxed for two
hours. The solvent was then removed, the residue dissolved in hot water, treated with charcoal and filtered. The filtrate, on cooling, gave 2-methoxy-4-[2'-[3'-methylpyridyl]}-amino-5-nitropyrimidine (1 g.) as pale yellow elongated prisms, which were recrystallised from water, or better petroleum ether (b.p. 40-60°), m.p. 110°. (Found: C, 50.4; H, 4.46; N, 26.9; \( \text{C}_{11}\text{H}_{11}\text{O}_3\text{N}_5 \) requires: C, 50.58; H, 4.24; N, 26.83%).

The Reaction of 2:4-dichloro-5-nitropyrimidine with 2-amino-4-methylpyrididine.

a) With 3 moles of 2-amino-4-methylpyridine.

A solution of 2:4-dichloro-5-nitropyrimidine (2.2 g.) in methanol (20 ccs.) was cooled and an ice cold solution of 2-amino-4-methylpyridine (3.5 g.) in methanol (25 ccs.) was added. After standing at 0° for two hours the precipitated yellow solid was filtered. The solid was completely soluble in hot water and on cooling 2-amino-4-methyl \( \text{N}\left\{2'-[4'-\{2''-[4''-\text{methylpyridyl}]\}-\text{amino-5'}-\text{nitropyrimidyl}\}\right\} \text{pyridinium chloride} \) (2.0 g.) separated as deep yellow needles, m.p. 237-8° decomp. (Found: C, 51.7; H, 4.64; N, 26.05; \( \text{C}_{16}\text{H}_{16}\text{O}_2\text{N}_7 \) requires: C, 51.4; H, 4.52; N, 26.24%).
When the condensation was carried out with 2 moles of 2-amino-4-methylpyridine the only product isolated was the above quaternary chloride.

b) With 4 moles of 2-amino-4-methylpyridine.

A solution of 2,4-dichloro-5-nitropyrimidine (1 g.) and 2-amino-4-methylpyridine (2.5 g.) in methanol (25 ccs.) was refluxed for two hours and the solution cooled. The dark brown solid was filtered and crystallised from n-butanol to give 2-methoxy-4-N-[3'-(4'-methylpyridyl)]-amino-5-nitropyrimidine (1 g.) as yellow prisms, m.p. 180°. (Found: C, 50.65; H, 4.35; N, 27.3; C₁₁H₁₀N₅ requires: C, 50.58; H, 4.24; N, 26.83%).

The Reaction of 2,4-dichloro-6-methyl-5-nitropyrimidine and 2-aminopyridine.

a) With 2 moles of 2-aminopyridine.

To an ice cold solution of 2,4-dichloro-6-methyl-5-nitropyrimidine (2.08 g.) in ether (25 ccs.) was added an ice cold solution of 2-aminopyridine (1.9 g.) in methanol (25 ccs.). The mixture was allowed to stand overnight and the orange solid (2 g.) filtered. Crystallisation from water containing a few drops of dilute hydrochloric acid gave yellow needles of 2-amino-N-[2'-(4'-(2'-
pyridyl)-amino-5'-nitro-6'-methylpyrimidyl]-pyridinium chloride, m.p. 215° decomp. (Found: C, 49.5; H, 3.98; N, 26.75; C_{15}H_{14}O_{2}N_{5}Cl requires: C, 50.0; H, 3.92; N, 27.2%).

b) With 4 moles of 2-aminopyridine in methanol.

2:4-Dichloro-6-methyl-5-nitropyrimidine (1 g.) and 2-aminopyridine (1.9 g.) were refluxed together in methanol (25 ccs.) for two hours. A bright red solution was obtained which, on cooling, deposited red prisms. Several crystallisations from ethanol (charcoal) gave 2-methoxy-4-[(2'-pyridyl)-amino-5-nitro-6-methylpyrimidyl] (0.85 g.) as yellow prisms, m.p. 137°. (Found: C, 50.7; H, 5.01; N, 26.53; C_{11}H_{11}O_{3}N_{5} requires: C, 50.6; H, 4.25; N, 26.8%).

c) With 4 moles of 2-aminopyridine in ethanol.

2:4-Dichloro-5-nitro-6-methylpyrimidyl (1 g.) and 2-aminopyridine (1.9 g.) were refluxed together in ethanol (25 ccs.) for two hours when a deep red solution (almost black) was obtained. A small amount of dark residue was filtered and the filtrate evaporated to dryness. The residue was extracted several times with hot benzene and the cooled extracts filtered through a column.
of alumina. The mixture was separated on the column into a yellow band, which was eluted rapidly on washing the column with benzene, and a deep red band, which was held more firmly. The yellow eluate was evaporated to dryness and the solid crystallised from ethanol to yield slender yellow needles of 2-ethoxy-4-(2'-pyridyl)-amino-5-nitro-6-methylpyrimidine (0.5 g.), m.p. 113-4°.

(Found: C, 53.2; H, 4.83; N, 26.39; C12H13O3N3 requires: C, 52.4; H, 4.76; N, 25.5%).

**The Reaction of 2,4-dichloro-5-nitro-6-methylpyrimidine with 2-amino-6-methylpyridine.**

a) **With 2 moles of 2-amino-6-methylpyridine.**

2,4-Dichloro-5-nitro-6-methylpyrimidine (2.08 g.) was dissolved in ether (30 ccs.) and 6-methyl-2-aminopyridine (2.16 g.) dissolved in methanol (30 ccs.) added. After standing for one hour at 0° the ether was removed in vacuo and water was added, when a yellow solid precipitated. The solid was crystallised twice from ethanol to yield 2-chloro-4-[2'-6-methylpyridyl] -amino-5-nitro-6-methylpyrimidine (2 g.) as felted yellow needles, m.p. 120°.

(Found: C, 46.8; H, 3.85; N, 24.0; C11H10O2N3 requires: C, 47.2; H, 3.6; N, 25.05%).
b) **With 4 moles of 2-amino-6-methylpyridine.**

The reactants were refluxed for two hours in methanol solution. The orange solution was cooled and the crystalline solid that separated was filtered and crystallised from ethanol, when 2:4-di[2'-(6'-methylpyridyl)]-amino-5-nitro-6-methylpyrimidine separated in yellow felted needles, m.p. 180°. (Found: C, 58.2; H, 5.05; \(\text{C}_{17}\text{H}_{17}\text{O}_{2}\text{N}_{7}\) requires: C, 58.1; H, 4.88%).

The Reaction of 2-chloro-4-[2'-(6'-methylpyridyl)]-amino-5-nitro-6-methylpyrimidine with tertiary bases in methanol.

a) **With 2-aminopyridine.**

To a solution of 2-chloro-4-[2'-(6'-methylpyridyl)]-amino-5-nitro-6-methylpyrimidine (0.5 g.) in methanol (20 ccs.) was added 2-aminopyridine (0.5 g.) and the resultant solution was refluxed for three hours. After cooling the pale yellow crystals were filtered and crystallised from ethanol to give 2-methoxy-4-[2'-(6'-methylpyridyl)]-amino-5-nitro-6-methylpyrimidine as pale yellow needles, m.p. 160°. (Found: C, 52.7; H, 5.01; \(\text{C}_{12}\text{H}_{15}\text{O}_{2}\text{N}_{5}\) requires: C, 52.35; H, 4.76%).

b) **With pyridine.**

When the above chloro-compound was treated with
pyridine in methanol as in the preceding experiment
3-methoxy-4-\(2'-(6'-methylpyridyl)\)-amino-5-nitropyrimidinidine was isolated, m.p. and mixed m.p. 160°.

c) With triethylamine.

The corresponding 3-methoxy-compound was again isolated, m.p. and mixed m.p. 160°.

\(\textit{N} \{2'-(4'-(2'-pyridyl)-amino-5'-nitropyrimidyl)\}\) pyridinium chloride.

3-Chloro-4-(3'-pyridyl)-amino-5-nitropyrimidinidine (0.5 g.) was dissolved in hot benzene (25 ccs.).

To this solution was added pyridine (0.7 ccs.) when, after a short while, the solution became cloudy and on cooling the salt (0.8 g.) separated as a yellow semi-crystalline solid. This solid was very soluble in water and could be crystallised from ethanol-ether in small yellow prisms, m.p. 230° decomp. (m.p. dependent on rate of heating). (Found: C, 51.2; H, 3.35; N, 25.1; \(\text{C}_9\text{H}_{11}\text{O}_2\text{N}_4\text{Cl}\) requires: C, 50.8; H, 3.35; N, 25.4%). After standing for several months the specimen had m.p. 201-4° decomp. and smelt strongly of pyridine.
N-[2'-{(4'-anilino-5'-nitropyrimidyl)]-pyridinium iodide.

To a solution of 2-chloro-4-anilino-5-nitropyrimidine (0.3 g.) in hot benzene (20 ccs.) was added pyridine (0.5 ccs.). The solution became turbid and an orange solid rapidly separated. After cooling the orange solid was filtered and dissolved in hot water and the aqueous solution treated with excess sodium iodide, when the required iodide separated. The iodide (0.2 g.) crystallised from water in glistening orange plates, m.p. 215° decom. (Found: C, 42.2; H, 3.22; N, 17.0; \( \text{Cl}_{15}\text{H}_{12}\text{O}_{2}\text{N}_{5}\text{I} \) requires: C, 42.88; H, 2.88; N, 16.67%).

N-[2'-{(4'-{6'-methylpyridyl})-amino-5'-nitropyrimidyl)]-pyridinium chloride.

2-Chloro-4-[2'-{(6'-methylpyridyl)]-amino-5-nitropyrimidine (0.3 g.) was dissolved in hot benzene (30 ccs.) and to this solution was added pyridine (1 ccc.). The solution rapidly became cloudy and on cooling a yellow solid separated. The solid (0.3 g.) was very soluble in cold water but crystallised from ethanol-ether in rosettes of needles, m.p. 200-2° decom. (Found: C, 52.4; H, 4.2; N, 24.4; \( \text{Cl}_{15}\text{H}_{13}\text{O}_{2}\text{N}_{5}\text{Cl} \) requires: C, 52.24; H, 3.3; N, 24.4%).

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N-(2'-[4'-[2''-(6''-methylpyridyl)]-amino-5'-nitro-6'-methylpyrimidinyl]-pyridinium iodide.

2-Chloro-4-[2''-(6''-methylpyridyl)]-amino-5-nitro-6-methylpyrimidin (1 g.) was dissolved in hot benzene (30 ccs.) and pyridine (1 cc.) was added to the hot solution. On cooling a dark precipitate separated, which was filtered and extracted with warm water. The aqueous extract was treated with charcoal, filtered and to the resultant deep yellow solution was added sodium iodide, when the iodide separated as a red precipitate. This salt (0.4 g.) crystallised from water in scarlet needles, m.p. 224° decomp. (Found: C, 42.9; H, 4.5; N, 19.06; C\textsubscript{16}H\textsubscript{15}O\textsubscript{2}N\textsubscript{2}I requires: C, 42.7; H, 3.4; N, 13.7%)

N-(2'-[4'-amino-5'-nitropyrimidinyl]-pyridinium chloride.

2-Chloro-4-amino-5-nitropyrimidine (1 g.) was dissolved in hot acetone (40 ccs.) and to the hot solution was added pyridine (1 cc.). On cooling an almost colourless solid separated, which was very soluble in water and alcohol. The salt (0.8 g.) crystallised from ethanol-ether in rosettes of buff needles, m.p. 255-6° decomp. (Found: C, 42.02; H, 3.54; N, 27.45; C\textsubscript{9}H\textsubscript{8}O\textsubscript{2}N\textsubscript{2}Cl requires: C, 42.6; H, 3.18; N, 27.6%).
2-Amino-N-[2'-(4'-amino-5'-nitropyrimidyl)]-pyridinium chloride.

2-Aminopyridine (1.25 g.) was added to a hot solution of 2-chloro-4-amino-5-nitropyrimidine (1 g.) in acetone (40 cc.) and after warming for a few minutes the salt (1.2 g.) rapidly separated. It crystallised from water in pale orange-yellow rods, m.p. 273-4° decomp. (Found: C, 40.7; H, 3.46; N, 31.1; \( \text{C}_{9}\text{H}_{8}\text{O}_{2}\text{N}_{3}\text{C}_{1} \) requires: C, 40.2; H, 3.3; N, 31.3%).

2-Amino-N-[2'-(4'-aniline-5'-nitropyrimidyl)]-pyridinium chloride.

This salt (0.75 g.) was obtained by the reaction of 2-chloro-4-aniline-5-nitropyrimidine (1 g.) and pyridine (1 cc.) in hot acetone (40 cc.) and crystallised from ethanol-ether in small prisms, m.p. 200-2° decomp. (Found: C, 51.8; H, 4.23; N, 23.9; \( \text{C}_{15}\text{H}_{13}\text{O}_{2}\text{N}_{1} \) requires: C, 52.2; H, 3.8; N, 24.4%).

The iodide crystallised from water in bright orange rods, m.p. 213-4° decomp. (Found: C, 41.35; H, 2.7; N, 19.9; \( \text{C}_{15}\text{H}_{13}\text{O}_{2}\text{N}_{1} \) requires: C, 41.3; H, 3.0; N, 19.3%).

2-Amino-N-[2'-(4'-(6'-methylpyridyl)]-amino-5'-nitropyrimidyl]-pyridinium chloride.

The corresponding 2-chloro-compound (1 g.) was
dissolved in hot acetone (40 ccs.) and the resultant solution treated with 2-aminopyridine (1.25 g.), when the required salt (1.3 g.) separated. It crystallised from ethanol-ether in yellow prisms, m.p. 222-3° decomp. (Found: C, 49.8; H, 4.31; N, 27.7; C_{15}H_{14}O_{2}N_{7}Cl requires: C, 50.1; H, 3.9; N, 27.3%).

The iodide crystallised from water in orange needles, m.p. 252° decomp. (Found: C, 39.6; H, 2.3; N, 21.1; C_{15}H_{14}O_{2}N_{7}I requires: C, 39.9; H, 3.1; N, 21.7%).

**Reaction of 2:4-dichloro-5-nitro-6-aminopyrimidine with 2-aminopyridine.**

a) With 3 moles of 2-aminopyridine.

To a solution of 2:4-dichloro-5-nitro-6-aminopyridine (1 g.) in warm acetone (30 ccs.) was added 2-aminopyridine (1.4 g.) and the resultant solution was allowed to stand at room temperature for several days. The acetone had by this time evaporated and the residual solid was extracted with 40 ccs. of hot water to leave a residue A (0.3 g.). The hot aqueous filtrate was treated with charcoal, filtered and the filtrate allowed to cool, when another solid B (1 g.) separated.
Solid A was crystallised from n-butanol, when 2-chloro-4-(2'-pyridyl)-amino-5-nitro-6-aminopyrimidine separated in slender yellow needles, m.p. 239°. (Found: C, 40.8; H, 2.83; N, 31.8; C$_9$H$_7$O$_2$N$_6$Cl requires: C, 40.5; H, 2.65; N, 31.5%).

Solid B was crystallised from ethanol-ether, when 2-amino-6-[4'- (2''-pyridyl)-amino-5''-nitro-6'-amino-pyrimidyl]-pyridinium chloride separated in clusters of yellow prisms, m.p. 271° decomp. (Found: C, 46.3; H, 3.74; N, 30.4; C$_{14}$H$_{15}$O$_2$N$_8$Cl requires: C, 46.6; H, 3.63; N, 31.1%).

The iodide crystallised from water in orange prisms, m.p. 265° dec. (Found: C, 37.3; H, 3.26; N, 25.04; C$_{14}$H$_{13}$O$_2$N$_8$I requires: C, 37.2; H, 2.9; N, 24.8%).

b) With 2 moles of 2-aminopyridine.

To an ice cold ethanolic solution of 2:4-di-chloro-5-nitro-6-aminopyrimidine (0.8 g. in 25 ccs.) was added a solution of 2-aminopyridine (0.75 g.) in 5 ccs. of ethanol and the resultant mixture allowed to stand at 0° for three days. The solid that had separated was filtered and crystallised from ethanol, when 2-chloro-4-
(2'-pyridyl)-amino-5-nitro-6-aminopyrimidine (1 g.)
separated in yellow needles, m.p. and mixed m.p. 238-9°.
2-Piperidino-4-(2'-pyridyl)-amino-5-nitropyrimidine.

(a) The quaternary salt A (0.25 g.) was added to a solution of piperidine (2 cc.) in boiling methanol (10 cc.), when a deep red solution was first obtained which, on standing for one hour, became pale yellow. On cooling the piperidino-4-(2'-pyridyl)-amino-5-nitropyrimidine (0.2 g.) separated as pale yellow prisms, which crystallized rapidly, or in a crystal cake after standing for a day, m.p. 170°. There was no depression of m.p. when the compound was mixed with the compound prepared by the following method.

(b) 2-Chloro-4-(2'-pyridyl)-amino-5-nitropyrimidine (0.25 g.) was added to a solution of piperidine (2 cc.) in methanol (35 cc.) and the resultant solution refluxed for one hour. On cooling the yellow crystals were filtered and crystallized from ethanol to give 2-piperidino-4-(2'-pyridyl)-amino-5-nitropyrimidine (0.23 g.) as pale yellow prisms, m.p.175°. (Found: N, 56.1; H, 4.38; C, 67.9; C₄H₁₀N₂O₂N₂ requires: N, 57.0; H, 4.47; C, 67.5%). It showed the same crystallization characteristics as the compound prepared from the quaternary salt A.

2-Morpholino-4-(2'-pyridyl)-amino-5-nitropyrimidine.

The quaternary salt A (2 g.) was suspended in
2-Piperidino-4-(2'-pyridyl)-amino-5-nitropyrimidine.

(a) The quaternary salt A (0.25 g.) was added to a solution of piperidine (1 cc.) in boiling methanol (10 ccs.), when a deep red solution was first obtained which, on refluxing for one hour, became pale yellow. On cooling 2-piperidino-4-(2'-pyridyl)-amino-5-nitropyrimidine (0.2 g.) separated as pale yellow prisms, which crystallised from ethanol either in yellow prisms if cooled rapidly, or as deep yellow rhombs if cooled slowly, m.p. 174°. There was no depression of m.p. when the compound was mixed with the compound prepared by the following method.

(b) 2-Chloro-4-(2'-pyridyl)-amino-5-nitropyrimidine (0.25 g.) was added to a solution of piperidine (1 cc.) in methanol (35 ccs.) and the resultant solution refluxed for one hour. On cooling the yellow crystals were filtered and crystallised from ethanol to give 2-piperidino-4-(2'-pyridyl)-amino-5-nitropyrimidine (0.25 g.) as pale yellow prisms, m.p. 174°. (Found: C, 56.1; H, 4.35; N, 27.9; C₁₄H₁₆O₂N₆ requires: C, 56.0; H, 5.37; N, 28.0%). It showed the same crystallisation characteristics as the compound prepared from the quaternary salt A.

2-Morpholino-4-(2'-pyridyl)-amino-5-nitropyrimidine.

The quaternary salt A (2 g.) was suspended in
boiling ethanol (50 ccs.) and morpholine (5 ccs.) was added, when a deep red solution resulted, which was refluxed until it had turned orange (two hours). After cooling the crystals were separated and crystallised from ethanol in feathery yellow needles, m.p. 224°. (Found: C, 51.3; H, 5.28; N, 27.44; \( \text{C}_{13}\text{H}_{14}\text{O}_{3}\text{N}_{6} \) requires: C, 51.66; H, 5.0; N, 27.3%).

2-Amino-4-(2'-pyridyl)-amino-5-nitropyrimidine.

(a) 2-Chloro-4-(2'-pyridyl)-amino-5-nitropyrimidine (0.5 g.) was refluxed for two hours with a solution of ammonia in methanol (15 ccs. of a saturated solution of ammonia in methanol and 15 ccs of methanol). The bright yellow solid that had separated was collected and crystallised from n-butanol in yellow plates, m.p. 251-2°. (Found: C, 46.3; H, 3.9; N, 36.0; \( \text{C}_{9}\text{H}_{8}\text{O}_{2}\text{N}_{6} \) requires: C, 46.54; H, 3.47; N, 36.2%).

(b) A suspension of the quaternary salt A (0.5 g.) in methanol (20 ccs.) was treated with concentrated aqueous ammonia (3 ccs.), when a deep red solution was obtained. After refluxing for two hours the solution had become pale yellow and on cooling yellow plates of 2-amino-4-(2'-pyridyl)-amino-5-nitropyrimidine (0.3 g.) separated, m.p. 251-2°,
alone or admixed with a sample prepared by the above method.

2-Diethylamino-4-(2'-pyridyl)-amino-5-nitropyrimidine.

The quaternary salt A (0.25 g.) was boiled with a solution of diethylamine in ethanol (1 cc. in 10 ccs.) and the product, which separated on cooling, crystallised from ethanol, when the required compound was obtained as yellow plates, m.p. 154°. (Found: C, 54.0; H, 5.66; N, 29.3; \( \text{C}_{13}\text{H}_{16}\text{O}_2\text{N}_6 \) requires: C, 54.15; H, 5.6; N, 29.15%)

2-\( \beta \)-Hydroxyethylamino-4-(2'-pyridyl)-amino-5-nitropyrimidine

To a boiling suspension of the quaternary salt A (1 g.) in ethanol (40 ccs.) was added ethanolamine (3 ccs.) and the orange solution refluxed for two hours. After cooling the crystals were filtered and crystallised from \( \pi \)-butanol in yellow rhombs, m.p. 239-40°. (Found: C, 47.4; H, 4.7; N, 29.8; \( \text{C}_{11}\text{H}_{12}\text{O}_3\text{N}_6 \) requires: C, 47.8; H, 4.4; N, 30.4%).

2-Benzylamino-4-(2'-pyridyl)-amino-5-nitropyrimidine.

To a suspension of the quaternary salt A (0.5 g.) in hot ethanol (25 ccs.) was added benzylamine (2.5 ccs.)
when a red solution was formed, which rapidly turned yellow and deposited yellow crystals. The mixture was refluxed for three-quarters of an hour, cooled and the solid filtered, when crystallisation from n-butanol gave 2-benzylamino-4-(2'-pyridyl)-amino-5-nitropyrimidine as yellow prisms, m.p. 211-2°. (Found: C, 59.3; H, 4.58; N, 26.2; C₁₆H₁₄O₂N₆ requires: C, 59.6; H, 4.4; N, 26.0%).

2-Anilino-4-(2'-pyridyl)-amino-5-nitropyrimidine.

The quaternary salt (0.5 g.) was suspended in ethanol (20 cc.) containing aniline (2 cc.), and refluxed for two hours. The solid slowly dissolved at first and then feathery needles of the anilino compound began to separate. The mixture was then cooled and the solid filtered and crystallised from ethanol in yellow felted needles, m.p. 218°. (Found: C, 59.6; H, 4.8; N, 25.74; C₁₆H₁₄O₂N₆ requires: C, 59.6; H, 4.38; N, 26.1%). A better solvent for this reaction was 50% aqueous acetone.

This compound could also be obtained by shaking the quaternary salt with ethanol and aniline at room temperature for two hours, or by heating the quaternary salt with aniline at 125° for ten minutes.
2-p-Chloranilino-4-(2'-pyridyl)-amino-5-nitropyrimidine.

The quaternary salt A (2 g.) was refluxed with a solution of p-chloraniline (2 g.) in 50% aqueous acetone (100 cc.) for two hours. The product was filtered and crystallised from benzene in glistening yellow plates, m.p. 220-90°. (Found: C, 52.9; H, 3.4; N, 24.2; C₁₅H₁₁O₂N₆Cl requires: C, 52.55; H, 3.23; N, 24.5%).

2-p-Anisidino-4-(2'-pyridyl)-amino-5-nitropyrimidine.

The compound was prepared by reacting the quaternary salt A (1 g.) with anisidine (1 g.) in 50% aqueous acetone (50 cc.) and crystallising from benzene in golden needles, m.p. 196°. (Found: C, 57.0; H, 4.67; N, 24.9; C₁₆H₁₄O₃N₆ requires: C, 56.8; H, 4.17; N, 24.3%).

2-β-Naphthylamino-4-(2'-pyridyl)-amino-5-nitropyrimidine.

By refluxing the quaternary salt A (1 g.) with a solution of β-naphthylamine (1 g.) in 50% aqueous acetone for two hours this compound was obtained; it was then crystallised from n-butanol in felted orange needles, m.p. 244°. (Found: C, 63.3; H, 4.5; N, 23.8; C₁₉H₁₄O₂N₆ requires: C, 63.7; H, 3.94; N, 23.45%).

2-N-Methylanilino-4-(2'-pyridyl)-amino-5-nitropyrimidine.

The quaternary salt A (0.5 g.) was suspended in
ethanol (25 ccs.) and methylaniline (2.5 ccs.) was added and the mixture refluxed for one hour. As some quaternary salt remained unreacted a further 2.5 ccs. of methylaniline was added and refluxing continued until a clear solution was obtained (four hours). Water was added until the solution became cloudy and the solution was then neutralised with acetic acid. After cooling the solid was filtered and crystallised from ethanol in yellow prismatic needles, m.p. 161°C. (Found: C, 59.6; H, 4.73; N, 26.6; $C_{16}H_{14}O_2N_6$ requires: C, 59.6; H, 4.38; N, 26.1%).

The same compound was obtained by heating a mixture of methylaniline (3 ccs.) and the quaternary salt A (0.5 g.) at 170°C until a clear solution was obtained.

2-Dimethylamino-4-(2'-pyridyl)-amino-5-nitropyrimidine.

The quaternary salt A (1 g.) was suspended in hot methanol (50 ccs.) and 30% aqueous dimethylamine (1 cc.) was added; the mixture was then refluxed for two hours. After cooling the solid was filtered and crystallised from ethanol in yellow needles, m.p. 217°C. (Found: C, 51.32; H, 4.4; N, 32.7; $C_{11}H_{12}O_2N_6$ requires: C, 50.75; H, 4.65; N, 32.3%).
2-Ethylamino-4-(2'-pyridyl)-amino-5-nitropyrimidine.

This compound resulted when the quaternary salt A (1 g.) was refluxed with a solution of ethylamine in ethanol (prepared by adding 2.5 ccs. of 25% aqueous ethylamine to 30 ccs. of ethanol) and crystallised from n-butanol in yellow rhombs, m.p. 250°. (Found: C, 51.7; H, 5.1; N, 32.75; C₁₁H₁₂O₂N₆ requires: C, 50.75; H, 4.65; N, 32.4%).

2-Methylamino-4-(2'-pyridyl)-amino-5-nitropyrimidine.

This compound was prepared by refluxing the quaternary salt A (1 g.) with an ethanolic solution of methylamine (prepared by adding 2.5 ccs. of 40% aqueous methylamine to 30 ccs. of ethanol) for two hours and crystallised from n-butanol in fine yellow needles, m.p. 244°. (Found: C, 49.3; H, 4.35; N, 34.4; C₁₀H₁₀O₂N₆ requires: C, 48.8; H, 4.1; N, 34.1%).

2-Phenylhydrazino-4-(2'-pyridyl)-amino-5-nitropyrimidine.

When a suspension of the quaternary salt A (0.3 g.) in ethanol (20 ccs.) was treated with phenylhydrazine (1 cc.) and boiled for two hours, the required compound separated on cooling and was crystallised from butanol in orange-yellow plates, m.p. 212° decom.
This compound has been prepared, as shown above, by the action of 4 moles of 2-aminopyridine on 2,4-dichloro-5-nitropyrimidine and by the action of a methanolic solution of sodium methoxide on 2-chloro-4-(2'-pyridyl)-amino-5-nitropyrimidine. It may also be prepared by treatment of the quaternary salt A in methanol solution with one molar proportion of 2-aminopyridine.

Thus the quaternary salt A (0.34 g.) was suspended in hot methanol (15 cc.) and 2-aminopyridine (0.1 g.) was added. After refluxing for two hours a clear solution was obtained, which on cooling deposited the 2-methoxy compound, m.p. 148°, alone or admixed with a pure specimen.

2-Aminopyridine could be replaced by one molar proportion of triethylamine, pyridine or dimethylaniline, when yields of 80% and upwards of the 2-methoxy compound were obtained. If a catalytic quantity of triethylamine was used in the reaction 80% of the starting material was recovered, together with a small amount of the 2-methoxy
compound. When the reaction was carried out using one molar proportion of triethylamine and ten molar proportions of methanol in benzene solution the quaternary salt did not dissolve even after eight hours boiling and no 2-methoxy compound was isolated.

The following experiments were carried out to determine the molar proportion of tertiary amine required to convert the salt into the 2-methoxy compound.

A series of solutions of the quaternary salt A (0.35 g. 1/100 mole) were prepared in boiling 50% aqueous methanol. To the solutions were added -

a) 0.14 cc. (1/100 mole) of triethylamine,  
b) 0.07 cc. (1/200 mole) of triethylamine,  
c) 0.035 cc. (1/400 mole) of triethylamine,  
d) 1 drop of a 10% methanolic triethylamine solution,

and the resultant solutions were allowed to stand overnight. From experiments (a) and (b) 0.24 g. (100% yield) of 2-methoxy-1-(2'-pyridyl)-amino-5-nitropyrimidine was obtained. From experiment (d) the quaternary salt was recovered unchanged and from experiment (c) 0.1 g. of 2-methoxy compound was obtained.
The above 2-methoxy compound was also obtained, when a solution of the quaternary salt in methanol was treated with 1 mole of aqueous sodium hydroxide.

2-Butyloxy-4-(2'-pyridyl)-amine-5-nitropyridimidine.

The quaternary salt (0.5 g.) was treated in boiling butanol (10 cc.) with 0.5 cc. triethylamine and the resultant solution refluxed for one hour. The 2-butyloxy compound crystallised from ethanol as orange-yellow plates, m.p. 105°. (Found: C, 53.5; H, 5.7; N, 24.7; C_{13}H_{15}O_{3}N_{5} requires: C, 54.0; H, 5.2; N, 24.2%).

2-Propyloxy-4-(2'-pyridyl)-amine-5-nitropyridimidine.

This compound crystallised from ethanol in yellow hexagonal plates, m.p. 121°. (Found: C, 52.3; H, 4.79; N, 25.2; C_{12}H_{15}O_{3}N_{5} requires: C, 52.35; H, 4.76; N, 25.45%).

2-Benzylxoy-4-(2'-pyridyl)-amine-5-nitropyridimidine.

The quaternary salt A (0.5 g.), benzyl alcohol (10 cc.) and triethylamine (0.5 cc.) were heated on an oil bath at 150° for half an hour. The solution was evaporated to dryness in vacuo and the residue treated with ethanol, when a crystalline solid was obtained which
crystallised from ethanol in rectangular yellow plates, m.p. 164°. (Found: C, 59.6; H, 4.5; N, 20.9; C_{16}H_{13}O_{3}N_{5} requires: C, 59.4; H, 4.1; N, 21.4%).

2-Allyloxy-4-(2'-pyridyl)-amino-5-nitropyrimidine.

This compound was prepared by treatment of the quaternary salt A with triethylamine in allyl alcohol and was crystallised from ethanol in yellow plates, m.p. 119°. (Rapid cooling gives flattened needles). (Found: C, 52.9; H, 4.5; N, 25.9; C_{12}H_{11}O_{3}N_{5} requires: C, 52.7; H, 4.1; N, 25.6%).

2-Phenoxy-4-(2'-pyridyl)-amino-5-nitropyrimidine.

The quaternary salt A (1 g.) and phenol (1.5 g.) were warmed on a steam bath, when a clear yellow solution was obtained. To this solution was added triethylamine (0.5 cc.), when a transient red colour resulted and the mixture solidified to a yellow crystalline mass. This crystalline mixture was triturated with a 2N solution of sodium hydroxide (30 cc.) and the insoluble pale yellow solid removed by filtration. This solid was then crystallised from ethanol to give 2-phenoxy-4-(2'-pyridyl)-amino-5-nitropyrimidine as pale yellow needles, m.p. 164°. (Found: C, 58.3; H, 4.0; N, 22.56; C_{15}H_{11}O_{3}N_{5} requires: 219
This compound was prepared from the quaternary salt A and p-methoxyphenol by the method described above for the 2-phenoxy compound. It crystallised from ethanol in yellow prisms, m.p. 200°. (Found: C, 56.8; H, 4.12; N, 20.2; C₁₆H₁₅O₄N₅ requires: C, 56.6; H, 3.9; N, 20.6%).

Treatment of the quaternary salt A with sodium hydroxide solution.

a) In methanol.

The quaternary salt A (0.25 g.) was suspended in methanol (20 ccs.) and three drops of 40% sodium hydroxide solution were added. The clear solution that resulted was refluxed for two hours and on cooling 2-methoxy-4-(2'-pyridyl)-amino-5-nitropyrimidine separated, m.p. 148°, alone or admixed with an authentic specimen.

b) In aqueous solution.

When a cold aqueous solution of the quaternary salt (1 g. in 50 ccs. water) was treated with sodium hydroxide solution (3 ccs. of 2N) an orange-yellow solid separated. After standing in an ice bath for one hour the
solid was filtered, washed with water, methanol and ether and dried over $\text{P}_2\text{O}_5$ in vacuo, m.p. 140-2° with previous softening. [Found: C, 54.3; H, 3.7; N, 30.8; the anhydro base R, $C_{14}H_{11}O_7N_7$, requires: C, 54.4; H, 3.6; N, 31.7%].

This anhydro base R, on boiling with the appropriate alcohol, was converted to the corresponding $2$-alkoxy compound. Thus with methanol 2-methoxy-4-$(2'$-pyridyl)-amino-5-nitropyrimidine, m.p. 145°, and with ethanol 2-ethoxy-4-$(2'$-pyridyl)-amino-5-nitropyrimidine, m.p. 151°, were obtained.

On treatment with piperidine in ethanol (10% solution) 2-piperidino-4-$(2'$-pyridyl)-amino-5-nitropyrimidine, m.p. 174°, alone or admixed with an authentic specimen, was obtained.

When the anhydro base R was stirred with cold 2N hydrochloric acid the quaternary chloride A was regenerated, m.p. 249° decomp., alone or admixed with a pure specimen. If the anhydro base R was boiled for two hours with 5N hydrochloric acid 2:4-dihydroxy-5-nitropyrimidine separated from the solution on cooling.

This latter compound resulted when the quaternary salt A was boiled for two hours with 5N.
hydrochloric acid and also when \( \text{N} \cdot \left[ \text{2' -} \left( \text{4' -} \left( \text{2'' -} \text{pyridyl} \right) \text{amino -5 -nitropyrimidyl} \right) \text{pyridinium} \right] \) chloride was boiled with \(5\text{N} \) hydrochloric acid.

**Reaction of the quaternary salt A with sodium acetate solution.**

If a cold solution of the salt was treated with a saturated solution of sodium acetate a bright red amorphous solid separated. This solid contained no chlorine and on treatment with sodium hydroxide solution was converted to the anhydro base E. Trituration with hydrochloric acid regenerated the quaternary salt.

The red base, on treatment with alcoholic piperidine, gave 2-piperidino-4-(2'-pyridyl)-amino-5-nitropyrimidine, m.p. 174°, alone or admixed with an authentic specimen.

When a solution of the salt was boiled with aqueous sodium acetate for one hour crude 2-hydroxy-4-(2'-pyridyl)-amino-5-nitropyrimidine separated, which crystallised from glacial acetic acid in clusters of pale yellow feathery needles, m.p. 233° decompo. (Found: C, 46.4; H, 3.26; \( \text{C}_9\text{H}_7\text{O}_3\text{N}_5 \) requires: C, 46.3; H, 3.03%).
The quaternary salt B (0.35 g.) was refluxed for two hours with a 10% ethanolic solution of piperidine (15 cc.) when, on cooling, a yellow solid was obtained, which crystallized from ethanol in yellow prisms, m.p. 102°, with previous softening. (Found: C, 57.7; H, 6.9; N, 26.7). The reactions of 2-amino-3-methyl-N-{2'-[4'-(2''-(3''-methylpyridyl)]-amino-5'-nitropyrimidyl]} pyridinium chloride (B)

The quaternary salt B (0.35 g.) was suspended in ethanol (15 cc.), amyl alcohol (11.3 cc.) was added, and the reddish brown mixture refluxed for two hours. On cooling a yellow solid separated, which was filtered and crystallized from ethanol in pale yellow needles, m.p. 180°. (Found: C, 53.8; H, 3.6; N, 36.05; C\textsubscript{15}H\textsubscript{16}N\textsubscript{3}O\textsubscript{4} required: C, 53.5; H, 3.1; N, 36.4%).

2-amino-N-[2''-(3''-methylpyridyl)]-amino-5''-nitropyrimidinium.

To a suspension of the quaternary salt B (0.5 g.) in ethanol (20 cc.) was added amyl alcohol (11.3 cc.) and the mixture refluxed for two hours, when a clear solution was obtained. After cooling and diluting with water the solid was filtered and crystallized from ethanol in yellow prisms, m.p. 200°. (Found: C, 56.9; H, 4.6; N, 25.7; C\textsubscript{16}H\textsubscript{16}N\textsubscript{3}O\textsubscript{4}
2-Piperidino-4-[2′-(3′-methylpyridyl)]-amino-5-nitropyrimidinone.

The quaternary salt B (0.35 g.) was refluxed for two hours with a 10% ethanolic solution of piperidine (15 ccs.) when, on cooling, a yellow solid was obtained, which crystallised from ethanol in yellow rhombs, m.p. 162°, with previous softening. (Found: C, 57.7; H, 5.9; N, 27.05; \( \text{C}_{15}\text{H}_{18}\text{O}_2\text{N}_6 \) requires: C, 57.3; H, 5.77; N, 26.7%).

2-Morpholino-4-[2′-(3′-methylpyridyl)]-amino-5-nitropyrimidinone.

The quaternary salt B (0.35 g.) was suspended in ethanol (15 ccs.), morpholine (1.5 ccs.) was added, and the resultant mixture refluxed for two hours. On cooling a yellow solid separated, which was filtered and crystallised from ethanol as pale yellow needles, m.p. 165°. (Found: C, 53.4; H, 5.4; N, 25.93; \( \text{C}_{14}\text{H}_{16}\text{O}_3\text{N}_6 \) requires: C, 53.2; H, 5.1; N, 26.6%).

2-Anilino-4-[2′-(3′-methylpyridyl)]-amino-5-nitropyrimidinone.

To a suspension of the quaternary salt B (0.5 g.) in ethanol (30 ccs.) was added aniline (1.5 ccs.) and the mixture refluxed for two hours, when a clear solution was obtained. After cooling and diluting with water the solid was filtered and crystallised from ethanol in yellow prisms, m.p. 230°. (Found: C, 59.3; H, 4.5; N, 25.7; \( \text{C}_{16}\text{H}_{14}\text{O}_2\text{N}_6 \))
The quaternary salt B (0.5 g.) was refluxed for one hour with methanolic ammonia (20 ccs.). Most of the solvent was then removed and an equal volume of water was added to the residual solution. After standing at 0°C for some time a pale yellow solid (0.1 g.) separated, which crystallised from ethanol in small yellow prisms, m.p. 207°C. (Found: N, 34.5; C₁₀H₁₀O₂N₆ requires: N, 34.1%).

The combined mother liquors were evaporated to dryness and the residue was extracted with ether. The ethereal solution was washed with water and dried over sodium sulphate. The ether was then removed and the residue crystallised from petroleum ether (60-80°C), when 2-methoxy-4-[2′-(3′-methylpyridyl)]-amino-5-nitropyrimidine (0.2 g.) separated in pale yellow needles, m.p. and mixed m.p. 110°C.

2-Dimethylamino-4-[2′-(3′-methylpyridyl)]-amino-5-nitropyrimidine.

The quaternary salt B (0.5 g.) was suspended in methanol (15 ccs.) and 25% aqueous dimethylamine (0.5 ccs.) was added and the resulting solution refluxed for one hour.
Most of the solvent was removed and an equal volume of water was added to the solution, when a solid separated. This solid was dried and crystallised from benzene-petroleum ether in yellow rods, m.p. 145°. (Found: C, 52.55; H, 5.43; C₁₂H₁₄O₂N₆ requires: C, 52.5; H, 5.1%).

2-Methoxy-4-[2'-{(3'-methylpyridyl)]-amino-5-nitropyrimidine.

The compound, m.p. 110°, obtained by treatment of the quaternary salt B with triethylamine in methanol was identical with that obtained by reaction of excess 2-amino-3-methylpyridine and 2,4-dichloro-5-nitropyrimidine. The mixed m.p. of these two compounds was 110°.

2-Ethoxy-4-[2'-{(3'-methylpyridyl)]-amino-5-nitropyrimidine.

The quaternary salt B (0.5 g.), triethylamine (0.5 cc.) and ethanol (ccs.) were refluxed together for one hour. The solvent was then removed and the residue dissolved in ether; the ethereal solution was then washed with water and dried over sodium sulphate. The ether was removed to leave an oil, which solidified on standing to a pale yellow solid and this solid crystallised from petroleum ether (60-80°) in pale yellow needles, m.p. 86°. (Found: C, 52.4; H, 4.9; C₁₂H₁₃O₃N₅ requires: C, 52.35;
2-Butyloxy-4-[3'-(3'-methylpyridyl)]-amino-5-nitropyrimidine.

This compound was prepared by boiling a mixture of butyl alcohol (10 cc.), the quaternary salt B (0.5 g.) and triethylamine for one hour. It crystallized from petroleum ether (60-80\(^\circ\)) in clusters of yellow needles, m.p. 105\(^\circ\). (Found: C, 55.2; H, 5.73; N, 23.5; \(C_{14}H_{17}NO_{3}\) requires: C, 55.48; H, 5.65; N, 23.1%).
A suspension of the quaternary salt (0.35 g.) in ethanol (15 c.c.) was refluxed for two hours with morpholine (1.5 c.c.), when a yellow solid was obtained, which crystallised from d-butanol in feathery yellow needles, m.p. 78°C. (Found: C, 53.5; H, 5.8; N, 26.3; \( \text{C}_{16}^\text{H}_{24}^\text{N}_2 \text{O}_3 \text{H} \) requires: C, 53.5; H, 5.8; N, 26.3).

Recrystallisation from d-butanol gave yellow prisms, m.p. 77°C. (Found: C, 53.8; H, 5.55; N, 26.4; \( \text{C}_{16}^\text{H}_{24}^\text{N}_2 \text{O}_3 \text{H} \) requires: C, 53.5; H, 5.8; N, 26.3; E, 4.4) N, 26.16%)

When the quaternary salt C (0.35 g.) was refluxed with 10% ethanolic piperidine (15 c.c.) the required compound was obtained as a pale yellow solid, which crystallised from ethanol in pale yellow felted needles, m.p. 160°C. (Found: C, 97.6; H, 6.3; N, 25.7; \( \text{C}_{16}^\text{H}_{24}^\text{N}_2 \text{O}_3 \text{H} \) requires: C, 97.6; H, 6.3).

The reactions of 2-amino-4-methyl-N\{2'\-[4',-\{2''\-[4''-METHYL-PYRIDYL]\}-AMINO-5'-NITROPYRIMIDYL\}\}-PYRIDINUM CHLORIDE (C)
When the quaternary salt \(0 (0.35 \text{ g.})\) was refluxed with 10% ethanolic piperidine (15 ccs.) the required compound was obtained as a pale yellow solid, which crystallised from ethanol in pale yellow felted needles, m.p. 160°. (Found: C, 57.0; H, 5.8; N, 26.7; \(\text{C}_{15}\text{H}_{18}\text{O}_{2}\text{N}_{6}\) requires: C, 57.3; H, 5.77; N, 26.7%).

\[\text{2-Piperidino-4-}[2'-(4'-methylpyridyl)] -\text{amino-5-nitropyrimidine}.
\]

A suspension of the quaternary salt (0.35 g.) in ethanol (15 ccs.) was refluxed for two hours with morpholine (1.5 ccs.), when a yellow solid was obtained, which crystallised from \(\mu\)-butanol in feathery yellow needles, m.p. 210°. (Found: C, 53.3; H, 5.6; N, 26.9; \(\text{C}_{14}\text{H}_{16}\text{O}_{3}\text{N}_{6}\) requires: C, 53.2; H, 5.1; N, 26.6%).

\[\text{2-Morpholino-4-}[2'-(4'-methylpyridyl)] -\text{amino-5-nitropyrimidine}.
\]

This compound crystallised from the solution obtained by refluxing the quaternary salt \(0 (0.5 \text{ g.})\) with aniline (1.5 ccs.) in ethanol (30 ccs.). Recrystallisation from \(\mu\)-butanol gave yellow prisms, m.p. 271°. (Found: C, 59.2; H, 4.53; N, 26.4; \(\text{C}_{16}\text{H}_{14}\text{O}_{2}\text{N}_{6}\) requires: C, 59.6; H, 4.4; N, 26.1%).

\[\text{2-Anilino-4-}[2'-(4'-methylpyridyl)] -\text{amino-5-nitropyrimidine}.
\]
2-Amino-4-[2':(4'-methylpyridyl)]-amino-5-nitropyrimidine.

The quaternary salt C (0.5 g.) and saturated methanolic ammonia (15 ccs.) were refluxed together for one hour. The clear orange solution was then cooled, when an orange-yellow crystalline solid separated, which crystallised from butanol in small yellow prisms, m.p. 258° decomp. (Found: C, 49.1; H, 4.42; C₁₀H₁₀O₂N₆ requires: C, 48.8; H, 4.1%).

2-Dimethylamino-4-[2':(4'-methylpyridyl)]-amino-5-nitropyrimidine.

To a suspension of the quaternary salt C (0.5 g.) in methanol (15 ccs.) was added 25% aqueous dimethylamine (0.5 cc.) and the mixture refluxed for one hour. The solid that separated on cooling was filtered and crystallised from benzene in pale yellow feathery needles, m.p. 218°. (Found: C, 52.7; H, 5.46; C₁₂H₁₅O₂N₆ requires: C, 52.35; H, 5.5%).

2-Methoxy-4-[2':(4'-methylpyridyl)]-amino-5-nitropyrimidine.

This compound was obtained by refluxing the quaternary salt C with a methanolic solution of triethylamine (5%). It crystallised from m-butanol, m.p. 180°.

A mixture of phenol (2 g.), the quaternary salt C.
excess 2-amino-4-methylpyridine on 2:4-dichloro-5-nitropyrimidine in methanol solution.

2-Ethoxy-4-[2'-(4'-methylpyridyl)]-amino-5-nitropyrimidine.

The quaternary salt C (0.5 g.) was refluxed with a solution of triethylamine (0.5 cc.) in ethanol (10 cc.) for one hour. After cooling the solution was neutralised with dilute acetic acid and the solid that separated filtered. It crystallised from benzene-petroleum ether in yellow prisms, m.p. 139°C. (Found: C, 52.8; H, 5.04; C_{12}H_{13}O_{3}N_{5} requires: C, 52.35; H, 4.76%)

2-Butyloxy-4-[2'-(4'-methylpyridyl)]-amino-5-nitropyrimidine.

This compound was prepared by refluxing a mixture of the quaternary salt C (0.5 g.), triethylamine (0.5 cc.) and butanol (10 cc.) for half an hour. The solvent was then removed and the residue dissolved in benzene; the benzene solution was then washed with water and dried over sodium sulphate. After removing the solvent the residue was crystallised from petroleum ether (60-80°C), containing a few drops of benzene, in yellow prisms, m.p. 121°C. (Found: N, 22.94; C_{14}H_{17}O_{3}N_{5} requires: N, 23.1%)

2-Phenoxy-4-[2'-(4'-methylpyridyl)]-amino-5-nitropyrimidine.

A mixture of phenol (1 g.), the quaternary salt C
(0.5 g.) and triethylamine (0.5 cc.) were warmed on a steam bath. A clear solution was first obtained but after a few minutes the whole mass solidified. The solid was triturated with 2N sodium hydroxide (30 cc.), and the resultant solid filtered. Crystallisation from ethanol gave the required phenoxy compound as fine yellow needles, m.p. 224°. (Found: C, 59.6; H, 4.23; N, 21.2; \( \text{C}_{16}\text{H}_{13}\text{O}_3\text{N}_5 \) requires: C, 59.44; H, 4.05; N, 21.67%).
THE REACTIONS OF 2-AMINO-N-{2'-[4'-(2''-PYRIDYL)]-AMINO-5'-NITRO-6'-METHYLMETHYLDECYL} -PYRIDINIUM CHLORIDE (D)

(a) The compound salt D (1 g.) was suspended in saturated ethanolic ammonia (25 cc.) and heated at 100° in a sealed tube for one hour. The solution was cooled and the solid filtered and crystallized from p-benzanol in hard yellow prisms, m.p. 200°, close to obtained with the compound prepared by the method below.

(b) 2-AMINO-N-{2''-METHYLMETHYLDECYL} -PYRIDINIUM CHLORIDE (5 g.) were heated at 100° for half an hour. The salt was suspended in alcohol and the solid filtered and crystallized from p-benzanol in.
2-Piperidino-4-(2'-pyridyl)-amino-5-nitro-6-methylpyrimidine.

The quaternary salt D (0.5 g.) was suspended in ethanol (20 cc.) and piperidine added, when a bright red solution resulted. This solution was refluxed for one and a half hours, when the colour had faded to orange. On cooling an orange solid (0.3 g.) was obtained, which, on crystallisation from ethanol, gave slender golden needles, m.p. 177°. (Found: C, 57.3; H, 6.23; N, 27.1; C_{15}H_{18}O_{2}N_{6} requires: C, 57.3; H, 5.77; N, 26.74%).

2-Amino-4-(2'-pyridyl)-amino-5-nitro-6-methylpyrimidine.

(a) The quaternary salt D (1 g.) was suspended in saturated methanolic ammonia (25 cc.) and heated at 100° in a sealed tube for one hour. The solution was cooled and the solid filtered and crystallised from n-butanol in hard yellow prisms, m.p. 230°, alone or admixed with the compound prepared by the method below.

(b) 2-Amino-4-chloro-5-nitro-6-methylpyrimidine (2 g.) and 2-aminopyridine (4 g.) were heated at 125° for half an hour. The melt was triturated with ethanol and the solid filtered and crystallised from n-butanol in
hard yellow prisms, m.p. 230°. (Found: C, 49.0; H, 4.5; N, 33.9; C_{10}H_{10}O_{2}N_{6} requires: C, 49.8; H, 4.1; N, 34.1%).

2-Anilino-4-(2'-pyridyl)-amino-5-nitro-6-methylpyrimidine.

The quaternary salt D (0.4 g.) was boiled with ethanol (15 cc.) containing aniline (1 cc.) for one and a half hours. On cooling an orange-yellow solid (0.3 g.) separated and was crystallised from ethanol as orange-yellow needles, m.p. 169°. (Found: C, 59.6; H, 4.8; N, 25.74; C_{16}H_{14}O_{2}N_{6} requires: C, 59.6; H, 4.36; N, 26.1%).

2-Morpholino-4-(2'-pyridyl)-amino-5-nitro-6-methylpyrimidine.

To a suspension of the quaternary salt D (0.5 g.) in methanol (15 cc.) was added morpholine (1 cc.) and the solution was refluxed for one hour. After cooling the solid was filtered and crystallised from ethanol in yellow needles, m.p. 153°. (Found: C, 55.5; H, 5.8; N, 26.1; C_{14}H_{16}O_{2}N_{6} requires: C, 55.2; H, 5.1; N, 26.6%).

2-Methoxy-4-(2'-pyridyl)-amino-5-nitro-6-methylpyrimidine.

This compound has been prepared by the action of excess 2-aminopyrimidine on 2:4-dichloro-5-nitro-6-methylpyrimidine in methanol. It may also be prepared by reflux-
ing the quaternary salt D with methanolic triethylamine (5%). The product was worked up as described previously, m.p. 1370, alone or admixed with a pure specimen.

2-Ethoxy-4-(2'-pyridyl)-amino-5-nitro-6-methylpyrimidine.

When the quaternary salt D is refluxed for half an hour with an ethanolic solution of triethylamine (5%) 2-ethoxy-4-(2'-pyridyl)-amino-5-nitro-6-methylpyrimidine is obtained, m.p. 115-40. This compound is identical with that obtained by the action of excess 2-aminopyridine on 2:4-dichloro-5-nitro-6-methylpyrimidine in ethanol.

2-Ethoxy-4-(2'-pyridyl)-amino-5-nitro-6-methylpyrimidine.

The quaternary salt D (0.5 g.) was refluxed for a quarter of an hour with a solution of triethylamine (0.5 g.) in butanol (10 ees.) and the resultant deep red solution evaporated to dryness. The residue was extracted with hot benzene and the extract percolated through a column of alumina. A yellow band could be eluted with benzene, leaving a deep red band at the top of the column. The eluate was evaporated to dryness and the residue crystallised from petroleum ether (b.p. 40-60°), when the required compound (100 mg.) separated in hexagonal yellow plates, m.p. 88-40. (Found: C, 54.8; H, 5.6; N, 22.9; C\textsubscript{18}H\textsubscript{17}O\textsubscript{5}N\textsubscript{5} requires: C, 55.4; H, 5.66; N, 23.1%).
2-Phenoxy-4-(2'-pyridyl)-amino-5-nitro-6-methylpyrimidine.

The quaternary salt D (0.5 g.) and phenol (1 g.) were warmed on a steam bath and triethylamine (0.5 cc.) added, when a clear solution was obtained. After warming for a few minutes the solution solidified to a pale yellow crystalline mass. The mixture was triturated with 30 ccs. of 2N sodium hydroxide and the solid filtered and washed with water. Crystallisation from ethanol gave the required compound as yellow needles, m.p. 193°. (Found: C, 59.3; H, 4.26; N, 21.46; C_{16}H_{13}O_{5}N_{5} requires: C, 59.44; H, 4.05; N, 21.67%).
The quaternary salt X (0.3 g.) was suspended in hot ethanol (15 ccm.) and piperidine (0.3 g.) added. The deep orange-red solution was refluxed for two hours, and the resultant solution, which was still deep orange, deposited a crop (0.1 g.) of yellow-orange plates I. These were separated out the residue was neutralized with 4N hydrochloric acid. The anhydride III was evaporated to dryness, The solid I crystallized from ethanol in yellow needles, m.p. 176-178°, alone or admixed with a pure specimen of 3'-12'-amino-5'-nitro-pyrimidine prepared from 6-chloro-3'-[2"-pyridyl] amino-5'-nitropyrimidine and ammonia.

The solid II crystallized from ethanol in yellow prisms, m.p. 178-179°, alone or admixed with a pure specimen of 3'-12'-amino-5'-nitro-pyrimidine, m.p. 179°.

The residue of the silicate III was at some loss from the oven, some which in pure aqueous amide be ligated.

**THE REACTIONS OF N-[3'-[2'-PYRIDYL]-AMINO-5'-NITRO-
PYRIMIDYL]--PYRIDINIUM CHLORIDE (E)**

*with ninhydrin*

When the quaternary salt X was shaken with ether
With piperidine.

The quaternary salt \( B \) (0.3 g.) was suspended in hot methanol (15 ccs.) and piperidine (0.3 g.) added. The deep orange-red solution was refluxed for two hours, and the resultant solution, which was still deep orange, deposited a crop (0.1 g.) of yellow-orange plates I. These were separated and the filtrate was neutralised with 2N acetic acid and then diluted with an equal volume of water, when a further crop of crystals II (0.1 g.) was obtained. The filtrate III was evaporated to dryness.

The solid I crystallised from \( n \)-butanol in shining yellow plates, m.p. 251-2°, alone or admixed with a pure specimen of 2-amino-4(2'-pyridyl)-amino-5-nitropyrimidine prepared from 2-chloro-4-(2'-pyridyl)-amino-5-nitropyrimidine and ammonia.

The solid II crystallised from ethanol in yellow prisms, m.p. 172-3°, alone or admixed with a pure specimen of 2-piperidino-4-(2'-pyridyl)-amino-5-nitropyrimidine, m.p. 174°).

The residue of the filtrate III was an orange-brown tar, from which no pure compound could be isolated.

With aniline.

When the quaternary salt \( B \) was shaken with either
a cold or hot solution of aniline in methanol (2% solution) \(2\text{-anilino-4-(2'\text{-pyridyl})-amino-5-nitropyrimidine}\) separated, m.p. 218\(^\circ\), alone or admixed with a pure specimen.

**With benzylamine.**

Treatment of the quaternary salt \(E\) with a hot methanolic solution of benzylamine (2% solution) gave \(2\text{-benzylamino-4-(2'\text{-pyridyl})-amino-5-nitropyrimidine}\), m.p. 211-2\(^\circ\), alone or admixed with a pure specimen.

**With methyl alcohol in presence of triethylamine.**

The quaternary salt \(E\) (0.1 g.) was refluxed, in methanol (10 ccs.), with triethylamine (0.1 cc.) for two hours. On cooling the orange solution \(2\text{-methoxy-4-(2'\text{-pyridyl})-amino-5-nitropyrimidine}\) separated, m.p. 148\(^\circ\), alone or admixed with a sample of the pure material.

**With phenylhydrazine.**

The quaternary salt \(E\) (0.1 g.) was refluxed with phenylhydrazine (0.1 cc.) in ethanol (10 ccs.) for one hour. The only product isolated from the reaction was \(2\text{-phenylhydrazino-4-(2'\text{-pyridyl})-amino-5-nitropyrimidine}\), m.p. 212\(^\circ\), alone or admixed with a pure specimen.
REACTIONS OF 2-AMINO-N-{2'-[4'-{(2''-(6''-METHYLPYRIDYL)]-AMINO-5''-NITROPYRIMIDYL}]-PYRIDINIUM CHLORIDE (F)

(a) 2-Chloro-6-[5''-(6''-ethylypyridyl)]-amino-5''-nitropyrimidine (6.4 g.) and pyridine (3 cc.) were warmed on a steam bath for half an hour. The melt was then triturated with alcohol and the resultant solid filtered and crystallized from ethanol, when 6-piperidino-4-[5''-(6''-methylypyridyl)]-amino-5''-nitropyrimidine was obtained.

(b) The piperidino salt 7 (0.8 g.) was boiled with methanolic piperidine (0.5 cc. in 20 cc.) for two hours and the resultant yellow solution cooled, when the above piperidino compound separated, m.p. 170°, alone or admixed with a sample of the above material.

(c) Pachyclor-6-[5''-(6''-methylypyridyl)]-amino-5''-nitropyrimidine (0.35 g.) was softened with methanolic ammonia (10 cc.) for forty-five minutes. The solution was cooled and the yellow solid that had separated was filtered and crystallized from pyridine. In yellow prismatic
2-Piperidino-4-\([2'-(6'-methylpyridyl)]\)-amino-5-nitropyrimidine.

(a) 2-Chloro-4-\([2'-(6'-methylpyridyl)]\)-amino-5-nitropyrimidine (0.4 g.) and piperidine (1 cc.) were warmed on a steam bath for half an hour. The melt was then triturated with ethanol and the resultant solid filtered and crystallised from ethanol, when 2-piperidino-4-\([2'-(6'-methylpyridyl)]\)-amino-5-nitropyrimidine separated in slender yellow needles, m.p. 170°. (Found: C, 57.5; H, 5.72; N, 26.84; C\(_{15}\)H\(_{18}\)O\(_2\)N\(_6\) requires: C, 57.3; H, 5.77; N, 26.74%).

(b) The quaternary salt F (0.5 g.) was boiled with methanolic piperidine (0.5 cc. in 20 cc's.) for two hours and the resultant yellow solution cooled, when the above piperidino compound separated, m.p. 170°, alone or admixed with a sample of the above material.

2-Amino-4-\([2'-(6'-methylpyridyl)]\)-amino-5-nitropyrimidine.

(a) 2-Chloro-4-\([2'-(6'-methylpyridyl)]\)-amino-5-nitropyrimidine (0.25 g.) was refluxed with methanolic ammonia (15 cc's.) for forty-five minutes. The solution was cooled and the yellow solid that had separated was filtered and crystallised from n-butanol in yellow prismatic...
needles, m.p. 225°. (Found: C, 48.9; H, 4.2;
C_{10}H_{10}O_{5}N_{6} requires: C, 48.8; H, 4.1%).

(b) The same compound was obtained when the quaternary salt F was refluxed with methanolic ammonia, m.p. and mixed m.p. 225°.

2-Phenyldrazino-4-[2'-(6'-methylpyridyl)]-amino-5-nitropyrimidine.

The quaternary salt F (0.5 g.) was refluxed with ethanolic phenylhydrazine (0.5 cc. in 25 cc.s) for one hour, when, on cooling, the required compound separated. It crystallised from ethanol in stout orange prisms, m.p. 213° dec. (Found: C, 57.3; H, 4.56;
C_{16}H_{15}O_{5}N_{7} requires: C, 57.0; H, 4.5%).

2-Methoxy-4-[2'-(6'-methylpyridyl)]-amino-5-nitropyrimidine.

(a) To a solution of sodium (0.25 g.) in methanol (15 cc.s) was added 2-chloro-4-[2'-(6'-methylpyridyl)]-amino-5-nitropyrimidine (0.25 g.) and the resultant red solution refluxed for two hours, during which time it turned yellow. An equal volume of water was then added, when 2-methoxy-4-[2'-(6'-methylpyridyl)]-amino-5-nitropyrimidine separated. It crystallised from ethanol in
yellow rods, m.p. 170°. (Found: C, 50.3; H, 4.22; 
C₁₁H₁₁O₃N₅ requires: C, 50.6; H, 4.25%).

(b) The above compound was also obtained when the 
quaternary salt F (0.25 g.) was refluxed with methanol 
(15 ccs.) containing triethylamine (0.25 ccs.).

(c) This methoxypyrimidine was also obtained by 
the action of a variety of organic tertiary bases on 
2-chloro-4-[2'-{(6'-methylpyridyl)}]-amino-5-nitropyrimidine 
in methanol solution. The following example illustrates 
the method.

The 2-chloro- compound (0.25 g.) was dissolved 
in warm methanol (20 ccs.) and pyridine (0.25 cc.) was 
added. The solution was then refluxed for three hours, 
when on cooling the 2-methoxy compound separated, m.p. 
170°, alone or admixed with a pure specimen.

The following bases converted 2-chloro-4-[2'- 
(6'-methylpyridyl)]-amino-5-nitropyrimidine into the 
above methoxy compound:

triethylamine  
2-aminopyridine  
γ-picoline

When 2-chloropyridine replaced the above tertiary bases 
2-chloro-4-[2'-{(6'-methylpyridyl)}]-amino-5-nitropyrimidine
was recovered unchanged. Neither the starting material nor the 2-methoxy compound were obtained when quinoline and isoquinoline were used as bases for the above conversion. The reaction product from the quinoline was an amorphous yellow solid, which contained no chlorine and could not be crystallised. It was, therefore, not examined further. The reaction product from the isoquinoline reaction had several interesting properties and the reaction of isoquinoline with the above chloro compound will be described later.
THE REACTIONS OF \( \text{N}-\{2^\circ-\{4^\circ-\{2^\circ-(6^\circ-\text{METHYLPYRIDYL})\}-\text{AMINO-5'-NITROPYRIMIDYL}\}\}-\text{PYRIDINIUM CHLORIDE (G)} \)

The quaternary salt C (0.5 g.) was dissolved in hot anhydrous toluene and pyridine (0.5 cc.) was added, when a deep red solution was obtained. This solution was refluxed for two hours when, on cooling, a crop of crystals I separated. These crystals were filtered and the filtrate neutralized with 3N acetic

with trichloroacetic acid.

The quaternary salt C (0.25 g.) was refluxed
With piperidine.

The quaternary salt G (0.3 g.) was dissolved in hot methanol (10 ccs.) and piperidine (0.3 c.c.) was added, when a deep red solution was obtained. This solution was refluxed for two hours when, on cooling, a crop of crystals I separated. These crystals were filtered and the filtrate neutralised with 2N acetic acid and diluted with an equal volume of water, when a further crop of crystals II was obtained.

The first crop of crystals was recrystallised from ethanol, when 2-piperidino-4-[2'-(6'-methylpyridyl)]-amino-5-nitropyrimidine (50 mg.) separated, m.p. 170°, alone or admixed with a pure specimen.

The second crop of crystals was sparingly soluble in ethanol but crystallised from a large volume of this solvent to give 2-amino-4-[2'-(6'-methylpyridyl)]-amino-5-nitropyrimidine, m.p. 222°, alone or admixed with a pure specimen. The mother liquors on concentration gave a further crop of the 2-amino compound (total 100 mg.).

With triethylamine in methanol.

The quaternary salt G (0.25 g.) was refluxed
with a solution of triethylamine in methanol (0.25 cc. in 10 cc.s.) for one hour. On cooling the orange reaction mixture 2-methoxy-4-[2'-(6'-methylpyridyl)]-amino-5-nitropyrimidine separated, m.p. 170°, alone or admixed with an authentic specimen.

With phenylhydrazine.

When an ethanolic solution of the quaternary salt G was treated with phenylhydrazine 2-phenylhydrazino-4-[2'-(6'-methylpyridyl)]-amino-5-nitropyrimidine, m.p. 211-3°, separated.
The quaternary salt (9.85 g.) was suspended in hot methanol (50 cc.) and piperidine (9.25 cc.) was added, when a bright red solution was obtained. The solution was refluxed for one hour. at the end of which time it had become yellow, and on cooling a crop of yellow crystals I (90 mg.) separated. The filtrate gave a further crop of yellow crystals II (30 mg.) on standing for two days. The solution was concentrated by evaporation and the residue recrystallized on addition of a small volume of water.

The solid I was crystallized from a large volume of alcohol, when 2-amino-N-\left[4'-(2'-pyridyl)\right]-amino-5'-nitro-6'-aminopyrimidyl]pyridinium chloride (H) separated, m.p. 205°, alone or admixed with a pure specimen.

The solid II crystallized from ethanol in yellow rectangular prisms, m.p. 156-7°, alone or admixed with a pure specimen of 2-chloro-4-(2'-pyridyl)-amino-5-nitro-6-amino-pyrimidin in, prepared by the method given below.

2-Chloro-4-(2'-pyridyl)-amino-5-nitro-6-amino-pyrimidin in (0.1 g.) and piperidine (9.2 cc.) were heated on a steam bath for half an hour. The resultant melt was triturated with a mixture of dilute acetic acid and
With piperidine.

The quaternary salt (0.25 g.) was suspended in hot methanol (20 cc.) and piperidine (0.25 cc.) was added, when a bright red solution was obtained. The solution was refluxed for one hour, at the end of which time it had become yellow, and on cooling a crop of yellow crystals I (50 mg.) separated. The filtrate gave a further crop of crystals II (100 mg.) on neutralisation with dilute acetic acid and the addition of an equal volume of water.

The solid I was crystallised from a large volume of alcohol, when 2-methoxy-4-(2'-pyridyl)-amino-5-nitro-6-aminopyrimidine separated, m.p. 205°, alone or admixed with a pure specimen.

The solid II crystallised from ethanol in yellow rectangular prisms, m.p. 206-7°, alone or admixed with a pure specimen of 2-piperidino-4-(2'-pyridyl)-amino-5-nitro-6-aminopyrimidine prepared by the method given below.

2-Chloro-4-(2'-pyridyl)-amino-5-nitro-6-aminopyrimidine (0.1 g.) and piperidine (0.5 cc.) were heated on a steam bath for half an hour. The resultant melt was tritured with a mixture of dilute acetic acid and
methanol (5 cc, of each) and the solid that separated was filtered. Crystallisation from ethanol gave yellow rectangular plates of 2-piperidino-4-(2'-pyridyl)-amino-5-nitro-6-aminopyrimidine, m.p. 206-7°C. (Found: C, 53.5; H, 5.39; N, 30.6; C₁₄H₁₇O₂N₇ requires: C, 53.34; H, 5.44; N, 31.1%).

With triethylamine in methanol.

The quaternary salt (0.28 g) was suspended in hot methanol (20 cc) and triethylamine (0.25 g) was added. The resultant solution was refluxed for one hour, when, on cooling, 2-methoxy-4-(2'-pyridyl)-amino-5-nitro-6-aminopyrimidine separated, m.p. 263-5°C, alone or admixed with a specimen prepared by the method described below.

2-Chloro-4-(2'-pyridyl)-amino-5-nitro-6-aminopyrimidine (0.1 g) was added to a solution of sodium (0.25 g) in methanol (10 cc). After boiling for three hours the solution was diluted with an equal volume of water and allowed to cool. The solid that separated was filtered and on crystallisation from 9-butanol yellow prisms of 2-methoxy-4-(2'-pyridyl)-amino-5-nitro-
Pyrimidine, m.p. 265°, were obtained. (Found: C, 46.2; H, 3.95; N, 32.1; $\text{C}_7\text{H}_{10}\text{O}_3\text{N}_6$ requires: C, 45.8; H, 3.8; N, 32.1%).
In methanol.

The chloro-compound (1 g.) was dissolved in hot methanol (40 cc.) and isoquinoline (1 cc.) was added when, after a short while, a bright yellow solid began to separate. The mixture was cooled and the crude material (2 g.) was filtered.

Crystallisation from methanol gave leucooxazonine.

The reaction of 2-chloro-4-[2'-{6'-methylpyridyl}]-1:1:2-dihydroisoquinoline (I) as yellow prisms, m.p. 155°. Amino-5-nitropyrimidine with isoquinoline

Found: C, 61.8; H, 4.9; N, 26.3. 

The same compound is obtained when the chloro-compound is treated with the theoretical quantity of isoquinoline.

If the crude material was crystallised from ethanol leucooxazonine is obtained. 2-chloro-4-[2'-{6'-methylpyridyl}]-1:1:2-dihydroisoquinoline (II) separated as flattened orange prisms, m.p. 159-160°. 

Found: C, 63.7; H, 5.6; N, 20.9; C_{13}H_{12}O_{2}N_{4} requires: C, 63.5; H, 4.9; N, 20.7%

The mixed m.p. of the methyl and ethyl ethers is 184-186°.

Both compounds react with phenylhydrazine to
In methanol.

The chloro-compound (1 g.) was dissolved in hot methanol (40 ccs.) and isoquinoline (1 cc.) was added when, after a short while, a bright yellow solid began to separate. The mixture was cooled and the crude material (2 g.) was filtered.

Crystallisation from methanol gave 1-methoxy-2-\{2'-4'-2"-(6'-methylpyridyl)\}-amino-5-nitropyrimidyl]-1:2-dihydroisoquinoline (I) as yellow prisms, m.p. 185°.

(Found: C, 61.9; H, 5.0; N, 21.9; C_{20}H_{18}O_{3}N_{6} requires: C, 61.53; H, 4.64; N, 21.53%).

The same compound is obtained when the chloro-compound is treated with the theoretical quantity of isoquinoline.

If the crude material was crystallised from ethanol 1-ethoxy-2-\{2'-4'-2"-(6'-methylpyridyl)\}-amino-5-nitropyrimidyl]-1:2-dihydroisoquinoline (II) separated as flattened orange prisms, m.p. 169-70°. (Found: C, 62.7; H, 5.0; N, 20.98; C_{21}H_{20}O_{3}N_{6} requires: C, 62.37; H, 4.99; N, 20.78%). The mixed m.p. of the methyl and ethyl ethers is 164-6°.

Both compounds react with phenylhydrazine to...
give a crimson phenylhydrazone. For example, the methyl ether (0.25 g.) was dissolved in hot ethanol (25 ccs.) and phenylhydrazine (0.5 cc.) added, when a crimson precipitate separated immediately. After cooling the phenylhydrazone (0.2 g.) was collected and crystallised from aqueous dioxane, when it separated in crimson prisms, m.p. 167-8° decomp. (Found: C, 64.03; H, 4.88; N, 23.4; C_{25}H_{22}O_{2}N_{8} requires: C, 64.36; H, 4.75; N, 24.03%).

Both the methyl and ethyl ethers give 

\[ 2':4':6'-(5'-methylpyridyl) \text{-isoquinolinium iodide} \]

by the following procedure.

The ether (0.5 g.) was dissolved in hot 2N hydrochloric acid (10 ccs.) and the solution treated with charcoal and filtered. The filtrate was almost neutralised with ammonia solution and then heated to 80-90°. To the resultant solution a saturated solution of potassium iodide was added (15 ccs.) when, on cooling, the quaternary salt separated in shining crimson rods. The salt was filtered, when the temperature of the solution was 25°, as on longer standing a yellow solid also began to separate. This quaternary salt was unstable and attempts to crystallise it from water or potassium iodide solution led
to the formation of a yellow solid. The quaternary salt prepared by this method decomposed at 212°C. (Found: C, 47.4; H, 3.45; N, 16.1; C_{19}H_{14}O_{3}N_{6}I requires: C, 46.92; H, 3.11; N, 17.3%).

Both the ethers (I) and (II) were converted to the parent hydroxy compound 1-hydroxy-2-\{2'-4'-2''-(6''-methylpyridyl)-amino-5-nitropyrimidyl\}-1:2-dihydroisoquinoline by the following procedure.

The ether (0.2 g.) was dissolved in 2N hydrochloric acid (10 ccs.) and then brought to pH 8.5 with sodium hydroxide solution, when an orange amorphous product (0.16 g.) separated. This was crystallised from aqueous dioxane as orange-yellow prisms, m.p. 175°C. (Found: C, 60.9; H, 4.37; N, 22.5; C_{19}H_{16}O_{3}N_{6} requires: C, 60.7; H, 4.3; N, 22.3%).

This hydroxy compound depressed the m.p. of the methyl ether (I), (m.p. 185°C), to 165-6°C and the ethyl ether (II), (m.p. 169-70°C), to 149-53°C. On crystallisation from ethanol the ethyl ether was obtained, m.p. 167-8°C, alone or admixed with a pure specimen. The hydroxy compound reacted with phenylhydrazine more slowly than did the ethers, but the same phenylhydrazone, m.p. 167-8°C decomp., was obtained.
b) In acetone.

2-Chloro-4-[2'-(6'-methylpyridyl)]-amino-5-nitropyrimidine (0.5 g.) was dissolved in hot acetone (25 ccs.) and isoquinoline (0.5 cc.) was added. The deep orange solution so obtained was allowed to cool, when orange-yellow crystals separated. After standing at room temperature overnight the crystals were filtered and recrystallised from aqueous acetone, when 1-acetonyl-

2-[2'-(4'-2''-(6'-methylpyridyl)]-amino-5-nitropyrimidiny]-

1:2-dihydroisoquinoline separated as shining yellow prisms, m.p. 175°. (Found: C, 63.8; H, 5.0; N, 20.2; C_{22}H_{20}O_{5}N_{6}

requires: C, 63.5; H, 4.84; N, 20.3%).

This compound crystallised from ethanol unchanged, did not give a phenylhydrazone and was more sparingly soluble in dilute hydrochloric acid than the methyl and ethyl ethers. It could be dissolved in hot dilute hydrochloric acid, giving a dark brown solution which, on longer boiling (5 mins.), became pale yellow. This yellow solution, on partial neutralisation and addition of potassium iodide, gave the quaternary iodide described above, m.p. and mixed m.p. 210-2° decomps. The yellow solution, on complete neutralisation, precipitated 1-hydroxy-2-[2'-(4'-2''-(6'-methylpyridyl)]-amino-5-nitro-

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pyrimidyl]-1,2-dihydroisoquinoline, which, on crystallisation from aqueous dioxane, had m.p. 175°; there was no depression of m.p. on mixing with an authentic specimen. Crystallisation of the hydroxy compound obtained in this way from ethanol gave the ethyl ether (II), m.p. and mixed m.p. 168-9°.

Reactions of the quaternary iodide with amines.

(1) With aniline.

The quaternary iodide (0.1 g.) was suspended in ethanol (5 cc.) and aniline (0.2 cc.) was added. On stirring the quaternary salt partially dissolved and an orange solid began to appear. After stirring until all the quaternary salt had reacted the solid was filtered and crystallised from ethanol, when the ethyl ether (II) was obtained, m.p. and mixed m.p. 167-8°.

(2) With diethyldiamine.

The ethyl ether (II) was again obtained when the quaternary iodide was triturated with cold 5% ethano- 
ol diethyldiamine.

(3) With ammonia.

Trituration of the quaternary salt with cold...
5% ethanolic ammonia gave the ethyl ether (II), m.p. and mixed m.p. 166-8°.

(4) With piperidine.

When the quaternary salt was treated with cold 5% alcoholic piperidine a bright yellow compound (A) was obtained, which crystallised from ethanol in yellow needles, m.p. 154°. The mixed m.p. with the ethyl ether (II) was 125-8°. (Found: C, 64.8; H, 5.56; N, 22.9; \( \text{C}_{24}\text{H}_{25}\text{O}_2\text{N}_7 \) requires: C, 65.0; H, 5.66; N, 22.1%).

(5) With methylamine.

A compound (B) was obtained in a similar manner, and crystallised from ethanol as orange prisms, m.p. 175°. Mixed m.p. with the ethyl ether (II) was 149-53°. (Found: C, 61.7; H, 5.11; \( \text{C}_{20}\text{H}_{19}\text{O}_2\text{N}_7 \) requires: C, 61.7; H, 4.92%).

(6) With ethylamine.

A compound (C) was obtained, which crystallised from ethanol in yellow needles, m.p. 144-5°. The mixed m.p. with the ethyl ether (II) was 136-40°. (Found: C, 63.0; H, 5.68; N, 24.2; \( \text{C}_{21}\text{H}_{20}\text{O}_2\text{N}_7 \) requires: C, 62.53; H, 5.56%).
H, 5.25; N, 24.3%)

The compounds (A), (B) and (C) depressed the melting points of each other; the mixed m.p's are given below:

(A) with (B) m.p. 130-5°.
(A) with (C) m.p. 115-20°.
(B) with (C) m.p. 130-5°.
8-Piperidino-4-(2'-pyridyl)-amino-5-amino-pyrimidines (2.0 g.) was dissolved in hot ethanol (100 cc.) and a solution of stannous chloride in hot concentrated hydrochloric acid added (3 cc. in 15 cc.) - a vigorous reaction occurred and the stannous chloride of the amines separated immediately. The stannous chloride was decomposed by treatment with all sodium hydroxide and the liberated ethylene dichloride was distilled off. The other products were washed with aqueous sodium carbonate and sodium carbonate solution then removed and the residue crystallized from benzene-petroleum ether, then the amines (0.3 g.) separated as slender pink needles, m.p. 118°. (Found: C, 68.1; H, 6.61; N, 33.3; 0.1098 g. requires: C, 68.3; H, 6.71; N, 33.1).  

8-Butylamino-4-(2'-pyridyl)-amino-pyrimidines (2.0 g.) in ethanol (25 cc.) was reacted with stannous chloride (2.0 g.) in hot concentrated hydrochloric acid (5 cc.) as described above. The amines (0.3 g.) crystallized from benzene in almost colourless plates, m.p. 105°. (Found: C, 68.7; H, 6.5; N, 33.6; 0.1098 g. requires: C, 68.3; H, 6.1; N, 33.6).
2-Piperidino-4-(2'-pyridyl)-amino-5-aminopyrimidine.

2-Piperidino-4-(2'-pyridyl)-amino-5-nitropyrimidine (1.2 g.) was dissolved in hot ethanol (125 ccs.) and a solution of stannous chloride in hot concentrated hydrochloric acid added (5 g. in 15 ccs.). A vigorous reaction occurred and the stannichloride of the amine separated immediately. The stannichloride was decomposed by treatment with 4N sodium hydroxide and the liberated amine was extracted with ether. The ethereal solution was washed with water and dried over sodium sulphate and charcoal. The ether was then removed and the residue crystallised from benzene-petroleum ether, when the amine (0.9 g.) separated as slender pink needles, m.p. 118°. (Found: C, 62.1; H, 6.61; N, 32.0; \( \text{C}_{14}\text{H}_{16}\text{N}_{\alpha} \) requires: C, 62.2; H, 6.71; N, 31.1%).

2-Methoxy-4-(2'-pyridyl)-amino-5-aminopyrimidine.

2-Methoxy-4-(2'-pyridyl)-amino-5-nitropyrimidine (0.5 g.) in ethanol (25 ccs.) was reduced with stannous chloride (1.5 g.) in hot concentrated hydrochloric acid (5 ccs.) as described above. The amine (0.3 g.) crystallised from benzene in almost colourless plates, m.p. 156°. (Found: C, 55.7; H, 5.5; N, 32.6; \( \text{C}_{10}\text{H}_{11}\text{ON}_{\alpha} \) requires: C, 55.3; H, 5.1; N, 32.3%).

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The reduction of the nitro compound (0.6 g.) was carried out with stannous chloride (2 g.), as described in the foregoing experiment. The amine (0.3 g.) crystallized from benzene-petroleum ether in colourless felted needles, m.p. 135°. (Found: C, 56.8; H, 5.7; N, 30.0; \(\text{C}_{11}\text{H}_{13}\text{O}_{3}\text{N}_{5}\) requires: C, 57.1; H, 5.66; N, 30.3%).

2-Morpholino-4-(2'-pyridyl)-amino-5-aminopyrimidine.

The reduction of the corresponding 5-nitro compound (1.7 g.) was carried out with stannous chloride (6 g.) by the above method, when the amine (1 g.) was obtained. It crystallized from benzene-petroleum ether in colourless needles, m.p. 145°. (Found: C, 56.8; H, 6.2; N, 31.2; \(\text{C}_{15}\text{H}_{18}\text{O}_{6}\text{N}_{6}\) requires: C, 57.3; H, 5.92; N, 30.9%).

2-Piperidino-4-(2'-pyridyl)-amino-5-aminopyrimidine.

2-Piperidino-4-(2'-pyridyl)-amino-5-nitro-6-methylpyrimidine (1.5 g.) was dissolved in hot ethanol (150 ccs.) and a solution of stannous chloride (5 g.) in hot concentrated acid (15 ccs.) added. The stannichloride that separated was filtered and decomposed with sodium hydroxide. The free amine crystallized from benzene-petroleum ether in
slender pink needles, m.p. 154°. (Found: C, 63.4; 
H, 7.08; N, 30.1; C_{15}H_{20}N_{6} requires: C, 63.3; H, 7.09; 
N, 29.6%).

2:5-Diamino-4-(3'-pyridyl)-aminopyrimidine.

The corresponding 5-nitro compound (0.6 g.) was 
dissolved in hot concentrated hydrochloric acid (10 ccs.) 
and a solution of stannous chloride (2.5 g.) slowly added. 
A pale yellow solution was obtained, which, on dilution 
with ethanol (30 ccs.), precipitated the stannichloride of 
the amine. Treatment of this stannichloride with 4N sodium 
hydroxide gave the amine (0.45 g.), which crystallised from 
benzene in buff plates, m.p. 142°. (Found: C, 53.37; 
H, 5.2; N, 41.6; C_{9}H_{10}N_{6} requires: C, 53.46; H, 5.0; 
N, 41.57%).

2-Anilino-4-(2'-pyridyl)-amino-5-aminopyrimidine.

This compound (0.35 g.) was obtained by reduction 
of the corresponding nitro compound (0.5 g.) with stannous 
chloride (2 g.) in concentrated hydrochloric acid by the 
method used in the preceding experiment. It crystallised 
from ethanol in buff plates, m.p. 216° decomp. (Found: 
C, 64.5; H, 5.5; N, 29.5; C_{15}H_{14}N_{6} requires: C, 64.7;
2-p-Anisidino-4-(2'-pyridyl)-amino-5-aminopyrimidine.

The corresponding 5-nitro compound (1.2 g.) was dissolved in warm concentrated hydrochloric acid (15 ccs.) and stannous chloride (3 g.) was added. A vigorous reaction occurred and the stannichloride began to separate. At this point ethanol (30 ccs.) was added and the reaction mixture allowed to stand overnight. The stannichloride (3 g.) was filtered and decomposed with 5N sodium hydroxide to give 1 g. of crude amine; crystallisation from ethanol gave 2-p-anisidino-4-(2'-pyridyl)-amino-5-nitropyrimidine as yellow needles, m.p. 215°. (Found: C, 62.5; H, 5.46; C_{16}H_{16}ON_{6} requires: C, 62.3; H, 5.2%).

2-Methoxy-4-(2',4'-methylpyridyl)-amino-5-aminopyrimidine.

This compound resulted when the corresponding nitro compound was reduced with stannous chloride in concentrated hydrochloric acid and it crystallised from benzene in pale yellow plates, m.p. 153°. (Found: C, 56.94; H, 5.46; N, 29.9; C_{11}H_{13}ON_{5} requires: C, 57.2; H, 5.63; N, 30.3%).
2-Anilino-9-(2′-pyridyl)-pyrimidotriazole.

To a solution of 2-anilino-4-(2′-pyridyl)-amino-5-aminopyrimidine (0.25 g.) in 50% acetic acid (5 ccs.) was added a solution of sodium nitrite (0.1 g.) in water. After standing at room temperature for two hours the product was filtered and crystallised from water, when the triazole (0.2 g.) separated in colourless needles, m.p. 220°. (Found: C, 62.25; H, 3.95; N, 33.4; C₁₅H₁₁N₇ requires: C, 62.3; H, 3.81; N, 33.9%).

2-Morpholino-9-(2′-pyridyl)-pyrimidotriazole.

2-Morpholino-4-(2′-pyridyl)-amino-5-aminopyrimidine was treated with sodium nitrite in acetic acid as described above. The triazole crystallised from ethanol in colourless felted needles, m.p. 137°. (Found: N, 34.6; C₁₅H₁₃N₇ requires: N, 34.6%).

2-Methoxy-4-methyl-9-(2′-pyridyl)-pyrimidotriazole.

This compound was prepared from 2-methoxy-4-(2′-pyridyl)-amino-5-amino-6-methylpyrimidine by the above method. It crystallised from ethanol in yellow prismatic needles, m.p. 230° decom. (Found: N, 34.3; C₁₁H₁₀O₂N₂ requires: N, 34.7%).
2-Piperidino-9-(2'-pyridyl)-pyrimidotriazole.

2-Piperidino-4-(2'-pyridyl)-amino-5-amino-pyrimidine (0.54 g.) was dissolved in 50% acetic acid (10 ccs.) and a solution of sodium nitrite (0.15 g.) in water added. After stirring for a short while the mixture was allowed to stand for one hour at room temperature, when a colourless solid separated. This solid was filtered and crystallised from 50% ethanol, when the triazole separated in colourless needles, m.p. 131°.

(Found: N, 31.15; C₁₄H₁₅N₇ requires: N, 31.44%).

2-Piperidino-5-7-diketo-8-(2'-pyridyl)-tetrahydropteridine.

To a solution of sodium (0.05 g.) in ethanol (10 ccs.) was added 2-piperidino-4-(2'-pyridyl)-amino-5aminopyrimidine (0.27 g.) and diethyl oxalate (0.15 cc.). The solution was refluxed for three hours, and then evaporated to dryness. The residue was treated with water to give a gummy solid, which on trituration with ether became completely solid. This solid was dissolved in N sodium hydroxide (10 ccs.), treated with charcoal, filtered and neutralised with N acetic acid, when an almost colourless solid separated. Crystallisation from water gave almost colourless prisms of the tetrahydropteridine, m.p. 220-1°.
2-Piperidino-6,7-diphenyl-9-(2'-pyridyl)-dihydropteridine.

Benzoin (0.23 g,) and 2-piperidino-4-(2'-pyridyl)-amino-5-aminopyrimidine (0.27 g,) were dissolved in a mixture of ethanol (5 ces,) and glacial acetic acid (5 ces,) and refluxed for five hours. The resultant solution was evaporated to dryness in vacuo and the residue dissolved in a little ethanol. Enough water was then added to precipitate a yellow solid (0.3 g). The solid was dissolved in hot dilute hydrochloric acid, treated with charcoal, filtered and the filtrate neutralised with ammonia and cooled. The yellow solid that separated was crystallised from ethanol, when the dihydropteridine separated in yellow prisms, m.p. 170°. (Found: C, 74.7; H, 6.16; N, 13.5; C₁₆H₁₆O₂N₆ requires: C, 75.3; H, 5.9; N, 18.8%).

2-Amino-9-(2'-pyridyl)-pyrimidotriazole.

This compound was prepared by treating a solution of 2:5-diamino-4-(2'-pyridyl)-aminopyrimidine in 50% acetic acid with an aqueous solution of sodium nitrite and crystallised from 10% acetic acid in colourless plates, m.p. 204-5°. (Found: C, 50.8; H, 3.53; N, 46.05; C₆H₇N₇ requires: C, 50.7; H, 3.3; N, 46.0%).

1- and 2-Propenylnaphthalene were required as reference substances for the comparison of their absorption spectra with those of certain metabolites obtained from anthracene and phenanthrene. The 1-compound, usually obtained by the isomerisation of 1-allylnaphthalene, has been synthesised by Zalkind and Zonis (J. Gen. Chem. Russia, 1936, 6, 988) by the dehydration of 1-1'-naphthylpropan-1-ol, obtained from 1-naphthylmagnesium bromide and propionaldehyde; we have prepared the carbinol from ethylmagnesium bromide and 1-naphthaldehyde. In the same way 1-2'-naphthylpropan-1-ol was prepared and dehydrated to the solid 2-propenylnaphthalene, which was oxidised by permanganate to 2-naphthoic acid to establish the position of the double bond. The absorption spectra of the propenylnaphthalenes will be described elsewhere.

1-Propenylnaphthalene.—1-Naphthaldehyde (Badger, J., 1941, 535) (15 g.) in 75 c.c. of ether was gradually added to a stirred ice-cold solution of ethylmagnesium bromide (from 15 c.c. of ethyl bromide) in 50 c.c. of ether. The mixture was heated under reflux for 2 hours, kept overnight, and decomposed with ice and dilute sulphuric acid. The dried ethereal layer gave on distillation 12 g. of carbinol as a pale yellow oil, b. p. 130°/1-5 mm. The carbinol in 200 c.c. of light petroleum-benzene (4:1) was boiled for 10 minutes with 15 g. of phosphoric oxide, and the supernatant liquid cooled and percolated through a column of alumina, which was further eluted with light petroleum (b. p. 60—80°). The oil recovered by evaporation of the solvent was converted into the picrate, m. p. 109—111° (4 g.), from which the pure hydrocarbon could be regenerated by chromatography. It was isolated by evaporation and dried in vacuo, but not distilled (to avoid polymerisation).

2-Propenylnaphthalene.—1-2'-Naphthylpropan-1-ol (12 g.), obtained from 2-naphthaldehyde (11 g.) as described above, distilled at 135—140°/1-5 mm. as an almost colourless oil (Found: C, 83-5; H, 7-6. C13H14O requires C, 83-9; H, 7-6%). Dehydration with phosphoric oxide, followed by repeated chromatography, gave 2-propenylnaphthalene as an oil which solidified; it had m. p. 28° (Found: C, 92-5; H, 7-6. C13H12 requires C, 92-8; H, 7-2%). It did not form a picrate, but a trinitrobenzene complex, yellow needles (from light petroleum-benzene), m. p. 108°, was obtained (Found: N, 10-9. C13H12C6H4O6N3 requires N, 11-1%).

The hydrocarbon (100 mg.) in 10 c.c. of pure acetone was shaken overnight with 140 mg. of finely powdered potassium permanganate. The manganese dioxide sludge was washed with acetone, suspended in water, and brought into solution with sulphur dioxide, whereupon a colourless precipitate was obtained. This was twice crystallised from light petroleum (b. p. 80—100°) and identified as 2-naphthoic acid, m. p. and mixed m. p. 185°.

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2-, 3-, and 4-Methoxy stilbenes were required in connection with some spectrographic studies on compounds of the stilbene series. The 2-methoxy-compound had previously been prepared by Funk and Kostanecki (Annalen, 1915, 409, 33), the cis-form as an oil obtained by the irradiation of the trans-form, m.p. 138°. It has now been prepared by pyrolysis of 4-methoxy-a-phenylcinnamic acid; measurements of the ultra-violet absorption suggest that Stoermer and Frigge’s liquid irradiation product is an equilibrium mixture of the two forms.

Experimental—2-Phenyl-1-o-methoxyphenylethanol. o-Methoxybenzaldehyde (13.6 g.) in ether (50 c.c.) was slowly dropped into a stirred, cold solution of Grignard reagent prepared from benzyl chloride (11.5 c.c.) and magnesium (2.4 g.) in ether (100 c.c.). The mixture was warmed for an hour and then decomposed with ice and dilute sulphuric acid. The product (12 g.) obtained after evaporation of the dried ethereal solution distilled at 205—215°/15 mm. It solidified and crystallised from light petroleum, had m. p. 59° after repeated crystallisation from petroleum (b.p. 40—60°) and finally methyl petroleum, had m. p. 67—68° (Found : C, 78.8; H, 7.1% requires C, 78.9; H, 7.0%).

trans-2-Methoxy stilbene. The carbinal (1 g.) in 15 c.c. of benzene—light petroleum (1 : 1) was boiled under reflux for 15 minutes with 1 g. of phosphoric oxide. The fluorescent solution was decanted, the phosphoric oxide washed with more light petroleum, and the combined solutions were passed through a column of alumina, which was eluted with light petroleum. From the percolate 0.8 g. of solid stilbene was recovered, m. p. 59° after repeated crystallisation from petroleum (b.p. 40—60°) and finally methyl petroleum. From the cis-form as an oil obtained by the irradiation of the cis-form, m. p. and mixed m. p. 136°. The cis-form of the compound has now been prepared by the pyrolysis of 2-methoxy-a-phenylcinnamic acid and is a liquid.

Both the 3-methoxy stilbenes are new and have been obtained by methods similar to those described above.

cis- and trans-4-Methoxy stilbenes have been prepared by Stoermer and Frigge (Annalen, 1915, 409, 33), the cis-form as an oil obtained by the irradiation of the trans-form, m.p. 138°. It has now been prepared by pyrolysis of 4-methoxy-a-phenylcinnamic acid; measurements of the ultra-violet absorption suggest that Stoermer and Frigge’s liquid irradiation product is an equilibrium mixture of the two forms.

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QUATERNARY SALTS FROM 2-CHLORO-5-NITRO-PYRIMIDINES, AND THEIR REACTIONS

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2: 4-Dichloro-5-nitropyrimidine (I; \( R_1 = R_2 = Cl, R_g = H \)) and 2: 4-dichloro-6-methyl-5-nitropyrimidine (I; \( R_1 = R_2 = Cl, R_g = Me \)) have been shown to react with ammonia in the cold to give the corresponding 2-chloro-4-amino-compounds (I; \( R_1 = Cl, R_2 = NH_2, R_g = H \) or Me), and under more vigorous conditions to give the 2: 4-diaminopyrimidines (I; \( R_1 = R_2 = NH, R_g = H \) or Me). Similarly, I; \( R_1 = R_2 = Cl \), or Rg = H or Me can be condensed with \( \alpha \)-amino acid esters and \( \alpha \)-amino-ketones under mild conditions to yield the 2(\( \alpha \)-5-nitro-4-pyrimidylamino)-acid esters (I; \( R_1 = Cl, R_2 = NHCH_2COCH_2, R_g = H \) or Me) and 2(\( \alpha \)-5-nitro-4-pyrimidylamino)-ketones (I; \( R_1 = Cl, R_2 = NHCH_2COEt, R_g = H \) or Me), together with some of the disubstituted compounds (I; \( R_1 = NHCH_2COEt, R_g = H \) or Me) (2).

We have now shown that I; \( R_1 = R_2 = Cl, R_g = H \) condenses with 2-aminopyridine in ice cold methanol to yield a small amount of the expected product 2-chloro-4(2'-pyridyl)-amino-5-nitropyrimidine (II; \( R_1 = Cl, R_2 = H \)) m.p. 148° (found: C, 49.1; H, 3.2; N, 28.2; Cl, 10.4; \( C_{5}H_{7}NO_{2}N^+Cl^- \) requires C, 49.8; H, 3.2; N, 28.4; Cl, 10.3%).

This quaternary salt is also obtained by treating either a boiling methanolic solution of II; \( R_1 = Cl, R_2 = H \) with a further mole. of 2-aminopyridine or a hot methanolic solution of I; \( R_1 = R_2 = Cl, R_g = H \) with three moles of 2-amino-pyridine. Evidence that it is a quaternary salt follows from its water solubility and the presence of ionic chlorine, which may be replaced by ionic bromine or iodine in aqueous solution to yield II; \( R_1 = Cl, R_2 = Br \) or II; \( R_1 = Cl, R_2 = I \), the bromine and iodine compounds being more readily soluble and more stable than the corresponding chloride.

Thus, III; \( R_1 = H \) reacts with boiling methanolic ammonia to give II; \( R_1 = NH_2, R_2 = H \), m.p. 240–2°, with 10% ethanoic diethyamine to give, II; \( R_1 = NEt_3, R_2 = H \), m.p. 133–4°, with 10% ethanoic piperidine to give, II; \( R_1 = C_2H_5N_2, R_2 = H \), m.p. 164° and with 10% ethanoic aniline to give, II; \( R_1 = NHPh, R_2 = H \), m.p. 207–8°. When the quaternary salt (III; \( R_1 = Me \)) is treated with boiling methanoic ammonia it gives the 2-methoxy-compound (II; \( R_1 = OMe, R_2 = Me \)), although the 2-aminocompound (II; \( R_1 = NH_2, R_2 = Me \)) may be obtained if the concentration of ammonia is kept high by performing the reaction in a sealed tube.

Similar reactions occur when 2-aminopyridine is replaced by the homologous 3- and 4-methyl-2-aminopyridines. However, when 2- amino-6-methylpyridine is used only the monochloro compound (VI; \( R_1 = Cl, R_2 = H \)) is obtained, and on more vigorous treatment with pyridine to form the quaternary pyridine salts

The 2-chloro group in II; \( R_1 = Cl, R_2 = H \) and VI; \( R_1 = Cl, R_2 = H \) or Me can take part in quaternary salt formation with pyridine to form the quaternary pyridine salts

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other hand, the quaternary chlorides, (III; \( R_1 = H \) and \( R_1 = Me \)) can also react with ammonia, and a variety of primary and secondary aliphatic, allicyclic and aromatic amines to give the corresponding 2-amino- or 2-substituted-aminopyrimidines. Thus, III; \( R_1 = H \) reacts with boiling methanolic ammonia to give II; \( R_1 = NH_2, R_2 = H \), m.p. 240–2°, with 10% ethanoic diethyamine to give, II; \( R_1 = NEt_3, R_2 = H \), m.p. 133–4°, with 10% ethanoic piperidine to give, II; \( R_1 = C_2H_5N_2, R_2 = H \), m.p. 164° and with 10% ethanoic aniline to give, II; \( R_1 = NHPh, R_2 = H \), m.p. 207–8°. When the quaternary salt (III; \( R_1 = Me \)) is treated with boiling methanoic ammonia it gives the 2-methoxy-compound (II; \( R_1 = OMe, R_2 = Me \)), although the 2-aminocompound (II; \( R_1 = NH_2, R_2 = Me \)) may be obtained if the concentration of ammonia is kept high by performing the reaction in a sealed tube.

Further work on this aspect is being carried out.

Vompe and Turitsyna have reacted 2-aminopyridine with 2: 4-dinitrochlorobenzene and have shown that no quaternary salt formation occurs. The only product isolated was (2–(2'-4'-dinitrophenyl)-2-amino-pyridine. Since 3-amino- and 4-aminopyridine give quaternary salts on the nuclear nitrogen they have attributed the non-formation of a quaternary salt in the case of the 2-amino analogue to steric factors. Our results show that with a sufficiently reactive reagent the effect of such steric factors in 2-aminopyridines may be overcome. These authors have also shown that the quaternary salts from 2: 4-dinitrochlorobenzene and 3- and 4-aminopyridine react with aniline to give 2: 4-dinitrodiphenylamine and that the 2: 4-dinitrophenyl quaternary salts of certain 3-substituted pyridines, VII, react with aniline to give 2: 4-dinitrodiphenylamine.

Treatment of the quaternary salt, III; \( R_1 = H \), with alkali gives a yellow product m.p. 135 – 40° decom., which is
sparingly soluble in water and most solvents, and regenerates
the original salt on trituration with dilute hydrochloric acid.
Analysis of this compound indicates that it may be the anhydro-
base, VIII. Vompe and Turitsyna\(^a\) have postulated an
anhydro-base, IX, of this type for the product obtained by
treating 4-amino-N-(2':4'-dinitrophenyl)-pyridinium chloride
with alkali. Further work on the action of alkali on these
quaternary salts is being carried out in order to confirm the
formation of the anhydro-base, and to investigate the possibility
of fission of the pyridine ring with alkali in a manner similar
to that described by Zincke\(^b, c\) for N-(2:4-dinitrophenyl)-
pyridinium chloride. The possible fission of the pyrimidine
ring under these conditions will also be investigated.

These compounds and certain dihydropteridines, purines and
triazoles derived from them are being tested biologically. Full
details of these investigations will be published elsewhere.

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