"Experiments Relating to the Synthesis of Lysergic Acid."

THESIS

submitted by

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HISTORICAL.

As a result of the combined efforts of chemists and biologists, numerous fungi have, in the last few years, been brought to the forefront of scientific interest. From these low forms of life, extremely valuable therapeutic agents have been derived. These are the so-called "antibiotics" which are among the most powerful weapons available in the fight against infectious diseases. That fungi can produce useful remedies is, however, no new discovery. The fungus *Claviceps purpurea*, which produces the ergots seen in the ears of infected rye, has been employed on a purely empirical basis in medicine for several hundred years and has claimed the interest of numerous research workers for many decades. An excellent account of the interesting history of ergot is given in George Barger's monograph *Ergot and Ergotism* (1).

Although the first crystalline alkaloid of ergot was isolated as long ago as 1875 by Tanret (2), the idea that the active principles of ergot are alkaloids only began to find general acceptance about twenty-five years ago. Since then, the ergot alkaloids and the derivatives prepared from them have become valuable and, in some cases, indispensable remedies in the most varied fields of medicine.

The natural alkaloids of ergot which have so far been isolated are shown in table I. Their classification into three groups - the ergotamine group, the ergotoxine group, and the ergometrine group - is based upon differences in their chemical structure. As the table shows, the ergot alkaloids occur in pairs. The two alkaloids of a pair are stereoisomers and each readily undergoes rearrangement to the other. This isomerism is due to the isomerism between lysergic and *iso*lysergic acids, the parent compounds from which all the alkaloids of ergot are derived. Whether existing independently or forming part of the alkaloid molecule, lysergic acid readily undergoes rearrangement to the isomeric *iso*lysergic acid and *vice versa*.

TABLE I.

Group name	Derived from lysergic acid	Derived from *iso*lysergic acid	Formula
Ergotamine	Ergotamine	Ergotaminine	$C_{33}H_{35}O_5N_5$
	Ergosine	Ergosinine	$C_{30}H_{37}O_5N_5$
Ergotoxine	Ergocristine	Ergocristinine	$C_{35}H_{39}O_5N_5$
	Ergokryptine	Ergokryptinine	$C_{32}H_{41}O_5N_5$
	Ergocornine	Ergocorninine	$C_{31}H_{39}O_5N_5$
Ergometrine	Ergometrine	Ergometrinine	$C_{19}H_{23}O_2N_3$

The first important evidence regarding the structure of the ergot alkaloids came from a study of the products obtained by alkaline hydrolysis. By hydrolysing certain alkaloid preparations with alcoholic potassium hydroxide, Smith and Timmis (3),(4) obtained a substance ergine ($C_{16}H_{17}ON_3$) which could be converted into the isomeric *iso*ergine and *vice versa* (5). Ergine and *iso*ergine were shown to be the amides of *iso*lysergic acid and lysergic acid ($C_{16}H_{16}O_2N_2$) respectively which were later obtained by Jacobs and Craig (6) who used more energetic hydrolytic conditions.

All the alkaloids of ergot contain either lysergic acid or *iso*lysergic acid as the principal and characteristic constituent of the molecule. The alkaloids of the ergotamine and ergotoxine groups are polypeptides, the lysergic acid or *iso*lysergic acid being joined to other amino acids. The last pair of alkaloids shown in table I, ergometrine-ergometrinine, has a simpler structure, lysergic acid or *iso*lysergic acid being combined merely with (+)-2-aminopropanol. Shortly after Jacobs and Craig (7) had established the composition of ergometrine, its partial synthesis, the first to be achieved in the field of ergot chemistry, was accomplished by Stoll and Hofmann (8).

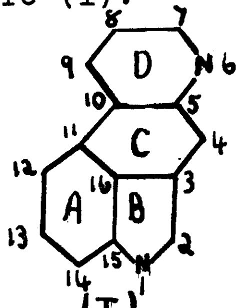
While all the details regarding the structure of the peptide portions in the ergotamine and ergotoxine

TABLE II.

Ergotamine group	Ergotamine Ergotaminine ($C_{33}H_{35}O_5N_5$)	(-)-phenylalanine	pyruvic acid	(+)-proline ammonia	(+)-Lysergic acid (+)-isoLysergic acid ($C_{16}H_{16}O_2N_2$)
	Ergosine Ergosinine ($C_{30}H_{37}O_5N_5$)	(-)-leucine			
Ergotoxine group	Ergocristine Ergocristinine ($C_{35}H_{39}O_5N_5$)	(-)-phenylalanine	dimethylpyruvic acid		
	Ergokryptine Ergokryptinine ($C_{32}H_{41}O_5N_5$)	(-)-leucine			
	Ergooornine Ergocorninine ($C_{31}H_{39}O_5N_5$)	(-)-valine			
Ergometrine group	Ergometrine Ergometrinine ($C_{19}H_{23}O_2N_3$)	(+)-2-aminopropanol			

groups have not been established with certainty, the constituent amino acids have been isolated and characterised. These results which have shown the chemical relationship of the ergot alkaloids are summarised in table II.

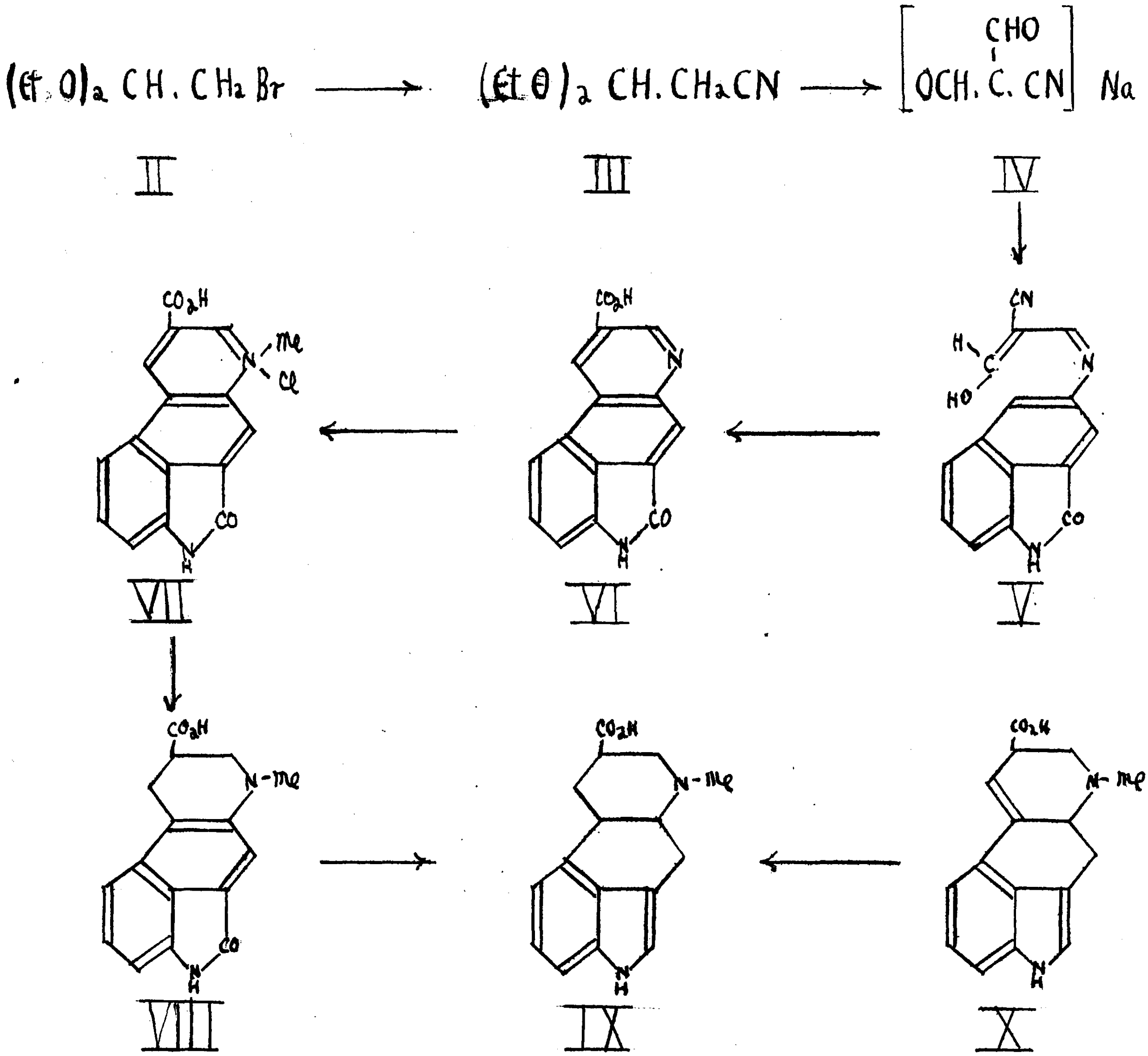
Fundamental knowledge regarding the structures of lysergic and _iso_lysergic acids is due to the investigations carried out by Jacobs and his collaborators. Thus from cleavage products such as quinoline (9),(10), 1-methyl-5-aminonaphthalene (9),(10) and 3:4-dimethylindole (11),(12),(13) obtained by the action of energetic reagents it was possible to deduce the presence of a tetracyclic structure (I).



(I)

In this formula the following groups may be clearly recognised: an indole system (rings A and B), a naphthalene system (rings A and C) and a quinoline system (rings C and D).

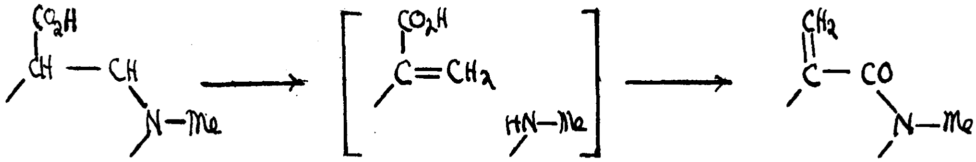
Further evidence regarding the structures of lysergic and _iso_lysergic acids was provided by the synthesis of dihydrolysergic acid by Uhle and Jacobs (14).



The starting material for this synthesis was bromoacetal (II), which was converted by means of potassium cyanide into cyanoacetal (III). This was subsequently treated with ethyl formate and sodium to give the sodium salt of cyanomalondialdehyde (IV), which Uhle and Jacobs then reacted with 3-aminonaphthostyril. In this way they obtained 3-(2-cyano-2-formylethylideneamino) naphthostyril (V). On treatment with zinc chloride and hydrochloric acid, this compound yielded 3'-amino-5:6-benzoquinoline-3:7-dicarboxylic acid lactam (VI), which was converted into the corresponding methochloride (VII) by means of methyl iodide and silver chloride. By catalytic hydrogenation of this methochloride, Uhle and Jacobs were able to obtain 3'-amino-N-methyl-1:2:3:4-tetrahydro-5:6-benzquinoline-3:7-dicarboxylic acid lactam (VIII) which, on treatment with sodium in boiling butanol, gave a very small yield of (±)-dihydrolysergic acid (IX). The totally synthetic preparation obtained in this way proved to be identical with the product prepared by catalytic hydrogenation of (±)-lysergic acid of natural origin.

The ring system of lysergic acid and the nature and position of the substituents having been established, there remained two further questions of importance regarding the fine structure of lysergic acid still to be settled: (a) the position of the readily reducible double bond and (b) the mechanism of the reaction by which lysergic acid isomerises to *iso*lysergic acid and *vice versa*.

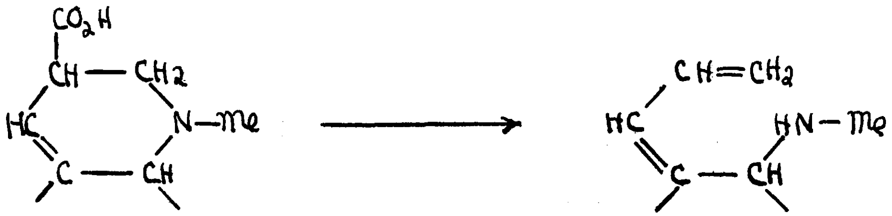
The results of recent investigations by Stoll, Hofmann and Troxler (15) furnished proof that the double bond is in the 9:10-position in both acids. Accordingly lysergic acid and *iso*lysergic acid can both be represented by formula X. The main basis for the deductions was the finding that both lysergic acid and *iso*lysergic acid react like β-aminocarboxylic acids on heating with acetic anhydride, *i.e.*, with opening of ring D, and subsequent lactam formation taking place between the secondary amino group and the carboxyl group:



Lysergic acid or *iso*lysergic acid

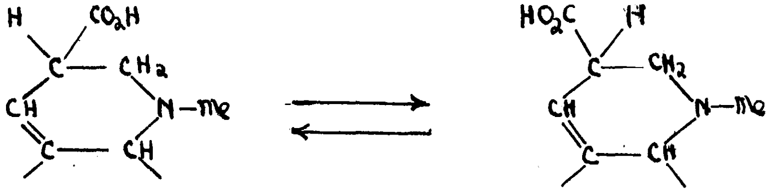
"Lactam"

In these degradation experiments it was found that both lysergic acid and *iso*lysergic acid gave rise to the same lactam. The position of the readily reducible double bond must therefore be the same in both acids. This conclusion is also in agreement with the results of decarboxylation experiments on lysergic acid and *iso*-lysergic acid, both compounds yielding the same product, as shown in the following scheme:



During this decarboxylation not only is the carboxyl group split off, but the linkage between nitrogen atom 6 and carbon atom 7 is also broken. The ultraviolet absorption spectrum of the decarboxylated product indicates clearly that the newly formed double bond between C-7 and C-8 is conjugated with the double bond already present, which must therefore be between carbon atoms 9 and 10. The chromophore system of this decarboxylation product is similar to that of the lactam just discussed, a fact which was confirmed by the agreement between the absorption spectra of the two compounds.

On the assumption that a double bond is present between carbon atoms 9 and 10, lysergic acid must have two asymetric centres, one at C-5 and the other at C-8. That both lysergic acid and *iso*lysergic acid possess a second asymetric centre in addition to that at C-8 was proved by the fact that the lactam previously discussed is optically active, although the asymetric centre at C-8 is no longer present. These facts also indicate that lysergic acid and *iso*lysergic acid have the same configuration at C-5 and, since the double bond in ring D is situated in the same position, $\Delta^{9,10}$, in both acids, the only difference between them must be in the spatial arrangement of the substituents at C-8. Available evidence indicates that in lysergic acid the carboxyl group is nearer nitrogen atom 6 than it is in <u>iso</u>lysergic acid. The following formulae illustrate these relationships:



Lysergic acid   <u>iso</u>Lysergic acid

As already mentioned, natural (+)-lysergic acid and natural (+)-<u>iso</u>lysergic acid have an identical configuration at C-5 and differ only in their configuration at C-8. Theoretically, however, either the D- or the L-configuration may be present at each of the two asymetric carbon atoms 5 and 8. This may be represented schematically as follows:

C - 5		C - 8	
D_5	L_5	D_8	L_8

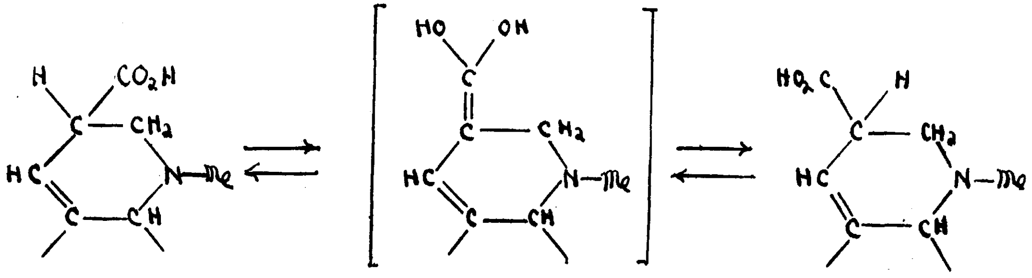
By combining these four possibilities, the following four optically active isomers are obtained:

D_5D_8	D_5L_8	L_5L_8	L_5D_8
A	B	C	D

A and C are optical antipodes and so are B and D. On the other hand, A and B are diastereoisomers and the same relationship applies to C and D. As can be gathered from this schematic representation, A and B and also C and D agree in the configuration at C-5 and differ only in the configuration at C-8. Thus, either A and C are the two optical antipodes of lysergic acid while B and D are the optical antipodes of *iso*lysergic acid, or *vice versa*. Both possibilities must be taken into consideration, since the absolute configuration is not known either at C-5 or at C-8.

Practical experience with lysergic acid and *iso*lysergic acid is in complete agreement with these theoretical considerations. Both natural (+)-lysergic acid and its optical antipode (-)-lysergic acid are known, as well as (+)-*iso*lysergic acid and (-)-*iso*lysergic acid. The two corresponding racemates have likewise been prepared.

These steric relationships having been elucidated, a simple explanation is available for the conversion of lysergic acid into *iso*lysergic acid and *vice versa*.

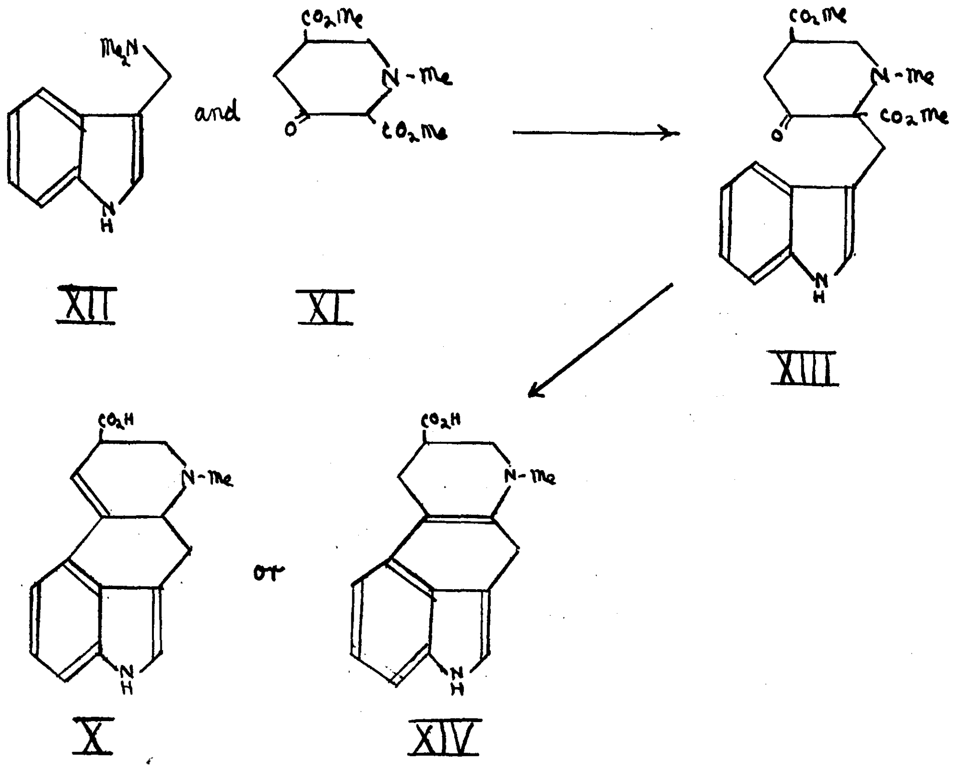


Lysergic acid "Enolic form" *iso*Lysergic acid

Enolisation of the carboxyl group at position 8 leads to the intermediate formation of an acid enolate which subsequently rearranges once more to the acid form, with the result that an alteration may take place in the configuration of the substituents at C-8.

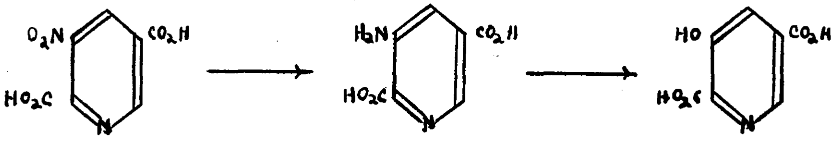
INTRODUCTION.

Since ring D is the most complicated ring in lysergic acid, containing as it does a carboxy group, an N-methyl group, a double bond and two asymetric carbon atoms, it was decided to attempt a synthesis of ring D apart from the rest of the molecule. A suitable form of ring D would be dimethyl 3-keto-1-methylpiperidine-2:5-dicarboxylate (XI). This compound contains the required carboxy and N-methyl groups; it also has two active centres - an active hydrogen at C-2 and the 3-keto group - required to link it with a suitable indole derivative (rings A and B) such as gramine (XII) and consequently to form ring C.



Under Mannich Base reaction conditions, dimethyl 3-keto-1-methylpiperidine-2:5-dicarboxylate (XI) and gramine (XII) should condense to give the compound XIII which on hydrolysis, decarboxylation and cyclisation should give either (±)-lysergic and (±)-isolysergic acids (X) or an isomer (XIV) with the double bond in the 5:10-position.

Since gramine (XII) is readily obtainable, the immediate problem lay in synthesising dimethyl 3-keto-1-methylpiperidine-2:5-dicarboxylate (XI) from some readily obtainable starting material. Because of the greater stability of aromatic nuclei it was decided to attempt first to synthesise 3-hydroxyisocinchomeronic acid (XV) which would be converted by methylation, reduction and oxidation into the required dimethyl 3-keto-1-methylpiperidine-2:5-dicarboxylate (XI). 3-Hydroxyisocinchomeronic acid (XV) has not been prepared, but it has been found possible to obtain in good yield from pyridine a derivative of 3-nitroisocinchomeronic acid (XVI) which would give 3-hydroxyisocinchomeronic acid (XV) by reduction to 3-aminoisocinchomeronic acid (XVII) followed by diazotisation. The problem of the synthesis of 3-nitroisocinchomeronic acid (XVI), how it was achieved and the proof of its structure is discussed in the following section. Thus the way has been opened to the postulated synthesis of lysergic acid (X) described above.



XVI XVII XV

THEORETICAL.

(A) General Considerations.

The compound requiring to be synthesised was 3-nitro-*iso*cinchomeronic acid (XVI) which contains a 3-nitro group, a 2-carboxy group and a 5-carboxy group. The only method available for the introduction of a 3-nitro group into the pyridine nucleus is by direct nitration. This immediately presents a grave problem in that pyridine can only be nitrated at high temperatures under forcing conditions, and even then only in low yields. However it has been found that, with an activating group such as amino or hydroxy present in a position *ortho* or *para* to that of the entering nitro group, nitration goes smoothly at low temperatures to give good yields of the 3-nitropyridine.

Pyridine carboxylic acids may be obtained by the permanganate oxidation of the corresponding alkylpyridines. Other methods include replacement of amino groups or bromine atoms by nitrile groups followed by hydrolysis, or in some cases the Kolbé reaction.

Each of the groups taken by itself can therefore be introduced with little difficulty, but the problem becomes complicated when all three groups are to be introduced into the pyridine nucleus at specific positions. The following points should be noted:

(a) The two carboxy groups or their precursors should be introduced before the nitro group, since the nitro group being deactivating increases the difficulty of aromatic substitution.

(b) At least one of these precursors should be an activating group to aid the nitration; the activating group should be the one in the 2-position as the 5-position is *meta* to the 3-position.

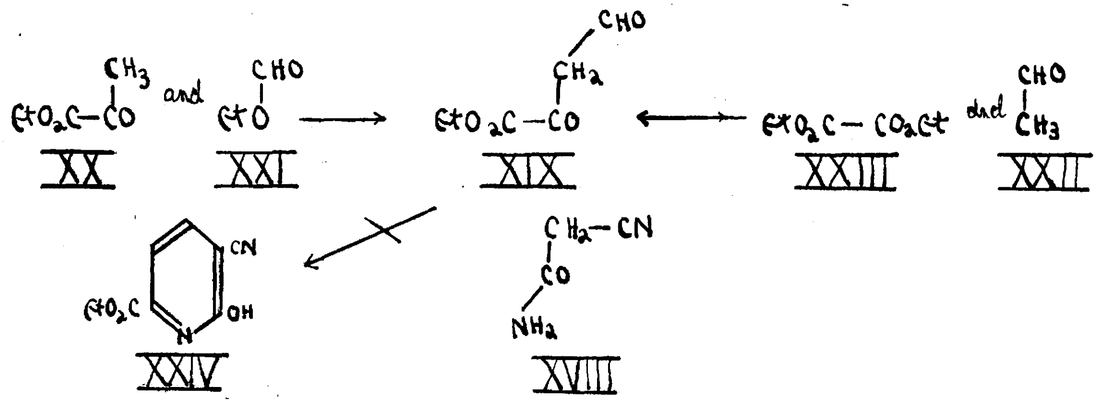
(c) The activating group should be the first substituent in the pyridine nucleus in order to facilitate the entry of the second carboxy group or its precursor.

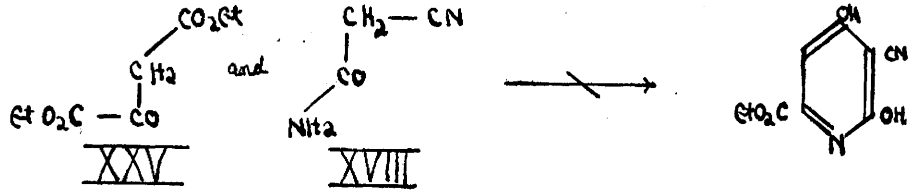
With these general considerations in mind it is possible to construct numerous hypothetical syntheses of 3-nitro*iso*cinchomeronic acid (XVI) which must be tested experimentally.

(B) Preparation of Intermediates from Aliphatic Compounds.

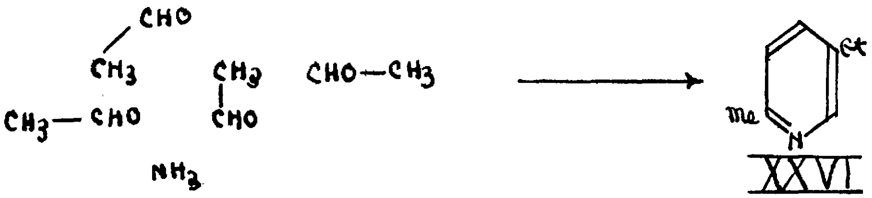
Early experiments were directed towards the condensation of aliphatic compounds with a view to obtaining pyridine derivatives which might be useful intermediates in the synthesis of 3-nitro*iso*cinchomeronic acid (XVI).

Attempts to condense cyanoacetamide (XVIII) with the hitherto unknown ethyl formylpyruvate (XIX), prepared from ethyl pyruvate (XX) and ethyl formate (XXI) and from acetaldehyde (XXII) and ethyl oxalate (XXIII), under catalytic conditions failed to give the required ethyl 5-cyano-6-hydroxypicolinate (XXIV). Similarly, no condensation product was obtained with cyanoacetamide (XVIII) and ethyl oxalylacetate (XXV).





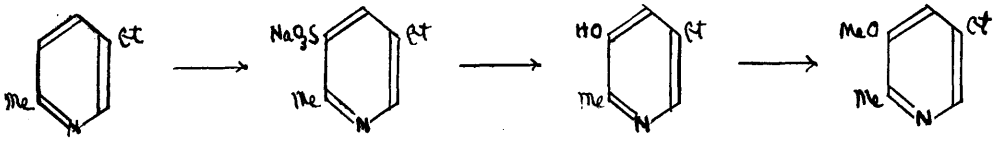
Graf (16) has shown that when acetaldehyde is condensed with ammonia, 5-ethyl-2-methylpyridine (XXVI) is obtained in good yield.



This compound contains two alkyl groups in the correct positions, but it was found that the 2-methyl group did not activate the 3-position to the extent required for easy nitration. Thus on heating 5-ethyl-

2-methylpyridine (XXVI) with a mixture of oleum and potassium nitrate at 100° for five hours, 5-ethyl-2-methylnitropyridine was obtained and characterised as its picrate. The yield of this product was however so low that it was not possible to proceed further.

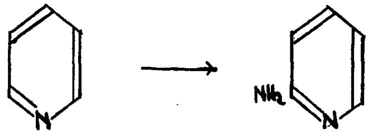
Attention was then turned to the possibility of introducing a hydroxy group into the 3-position by sulphonation followed by fusion with alkali. Sulphonation of 5-ethyl-2-methylpyridine (XXVI) gave the corresponding 3-sulphonic acid as its sodium salt (XXVII) (17). Fusion of this material with potassium hydroxide gave 5-ethyl-2-methyl-3-pyridol (XXVIII). Attempts were made to oxidise this compound with aqueous permanganate, but although the permanganate was decolourised, no product could be isolated from the reaction mixture. As it was conceivable that the molecule had been completely degraded owing to the presence of the 3-hydroxy group, steps were taken to prevent this by protecting the 3-hydroxy group. Methylation of 5-ethyl-2-methyl-3-pyridol (XXVIII) by diazomethane in ether gave 5-ethyl-3-methoxy-2-methylpyridine (XXIX) which was characterised as its mercuric chloride compound. On treating 5-ethyl-3-methoxy-2-methylpyridine (XXIX) with aqueous permanganate, the solution was decolourised but no product could be isolated from the reaction mixture.



XXVI XXVII XXVIII XXIX

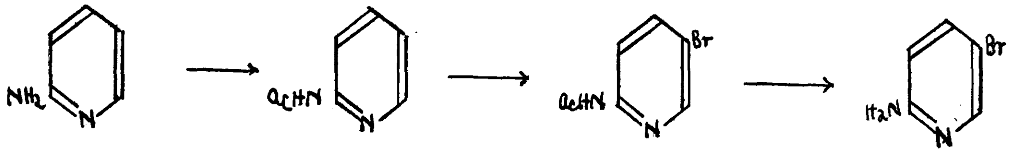
(C) Reactivity of Halogen Atoms in Pyridine Nuclei.

In view of the failures recorded in (B) it was decided to use pyridine itself as the starting material in all future attempts to synthesise 3-nitroisocinchomeronic acid (XVI). An activating group was introduced into the 2-position by heating pyridine (XXX) in toluene with sodamide (18) to give 2-aminopyridine (XXXI). All subsequent work was based on this compound.



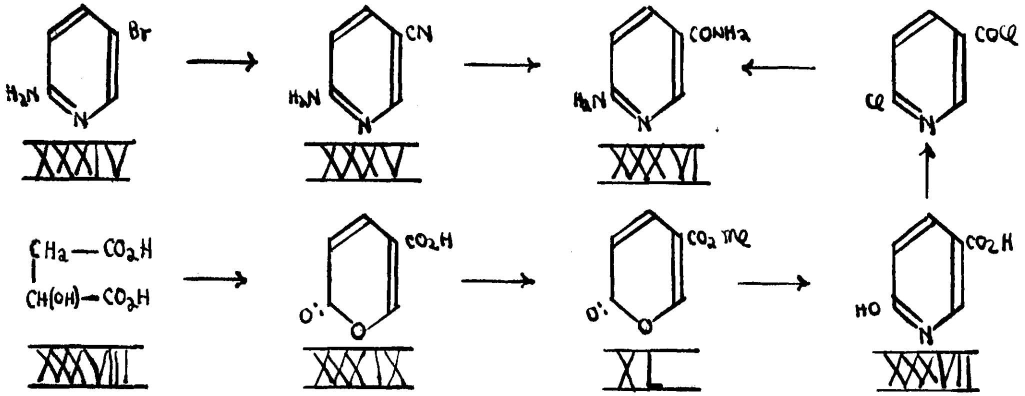
XXX XXXI

The introduction of a carboxy precursor in the 5-position was achieved by brominating 2-acetylaminopyridine (XXXII), prepared from 2-aminopyridine (XXXI), followed by hydrolysis of the 2-acetylamino-5-bromopyridine (XXXIII) so formed to give 2-amino-5-bromopyridine (XXXIV) (19).

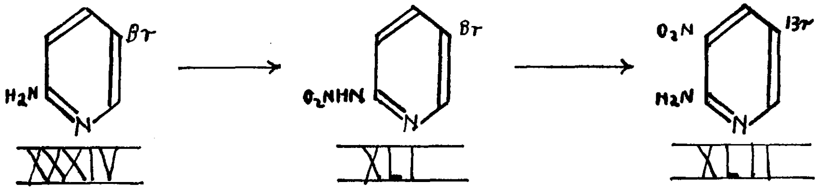


XXXI XXXII XXXIII XXXIV

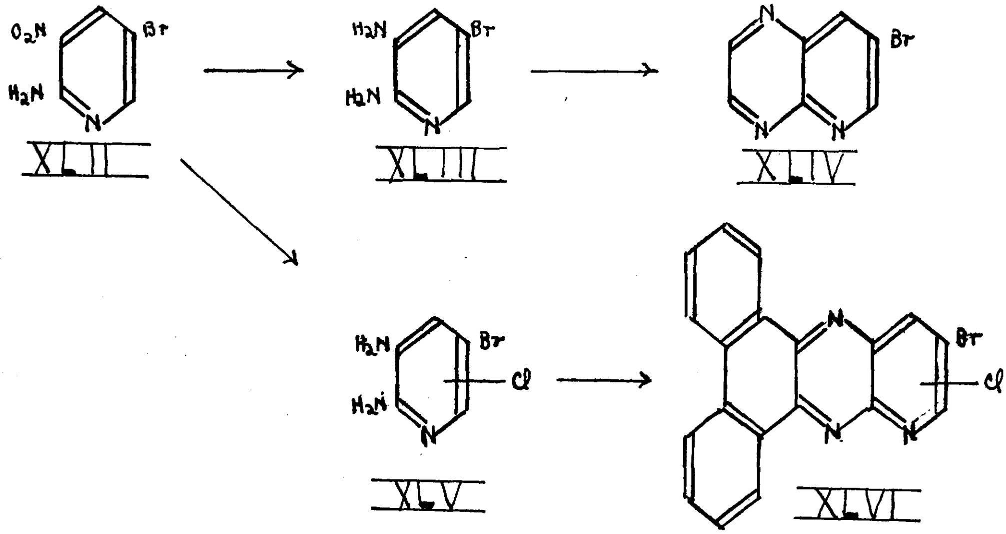
The proof of the position of the 5-bromine atom in 2-amino-5-bromopyridine (XXXIV) rests in its conversion through 6-aminonicotinonitrile (XXXV) to 6-aminonicotinamide (XXXVI) which is identical with the compound obtained by the chlorination of 6-hydroxynicotinic acid (XXXVII) followed by treatment with ammonia (19). The structure assigned to 6-hydroxynicotinic acid (XXXVII) depends upon its preparation from malic acid (XXXVIII) <u>via</u> coumalic acid (XXXIX) and methyl coumalate (XL) (20), (21).



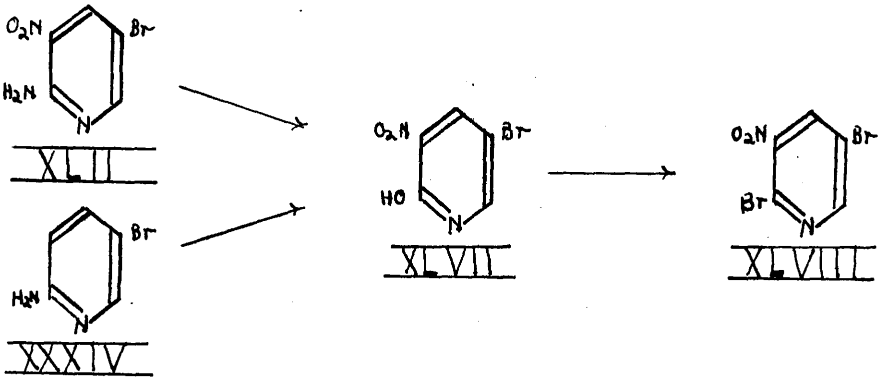
Having introduced two suitable groups in the 2- and 5-positions, there remained the introduction of the 3-nitro group. This was achieved by nitrating 2-amino-5-bromopyridine (XXXIV) in concentrated sulphuric acid to form 5-bromo-2-nitraminopyridine (XLI) (22), which on isomerisation by heating in concentrated sulphuric acid gave the required 2-amino-5-bromo-3-nitropyridine (XLII) (22). 2-Amino-5-bromo-3-nitropyridine (XLII) was also obtained directly from 2-amino-5-bromopyridine (XXXIV) without the isolation of the intermediate 5-bromo-2-nitraminopyridine (XLI).



That the nitro group in 2-amino-5-bromo-3-nitropyridine (XLII) is in fact in the 3-position has been verified by Petrow and Saper (23) by reduction with iron filings and dilute hydrochloric acid to give 2:3-diamino-5-bromopyridine (XLIII) which reacts with glyoxal giving 7-bromo-5-azaquinoxaline (XLIV). Further verification was obtained by the reduction of 2-amino-5-bromo-3-nitropyridine (XLII) with tin and concentrated hydrochloric acid to form 2:3-diamino-5-bromo-4(6)-chloropyridine (XLV) which gave a quinoxaline derivative (XLVI) with phenanthraquinone.

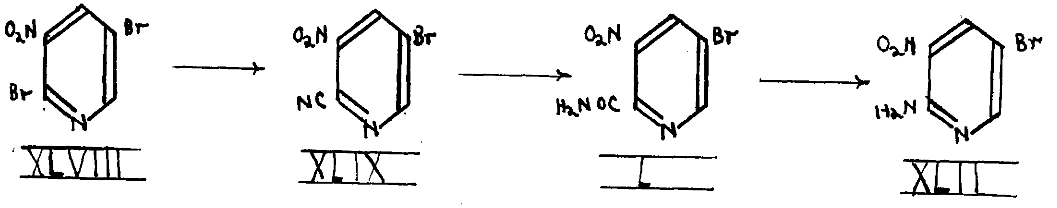


There now remained the final problem of converting the 2-amino group and the 5-bromine atom into carboxy groups. To do this, it was necessary first to convert the 2-amino through 2-hydroxy to 2-bromo. This was achieved by treating a solution of 2-amino-5-bromo-3-nitropyridine (XLII) in sulphuric acid with sodium nitrite to give 5-bromo-3-nitro-2-pyridol (XLVII) which was also obtained directly from 2-amino-5-bromopyridine (XXXIV) without isolation of the intermediates 5-bromo-2-nitraminopyridine (XLI) and 2-amino-5-bromo-3-nitropyridine (XLII). The hydroxy compound reacted with phosphorus tribromide-pentabromide mixture to give the required 2:5-dibromo-3-nitropyridine (XLVIII).



Attempts to replace the two bromine atoms by forming organo-metallic compounds followed by carbonation were entirely without success. Thus 2:5-dibromo-3-nitropyridine (XLVIII) formed a di-Grignard compound with magnesium, but since the product was insoluble it could not be carbonated with solid or liquid carbon dioxide. 2:5-Dibromo-3-nitropyridine (XLVIII) did not react to any appreciable extent with lithium metal even in boiling toluene and could be recovered unchanged after treatment with excess n-butyl lithium followed by carbonation.

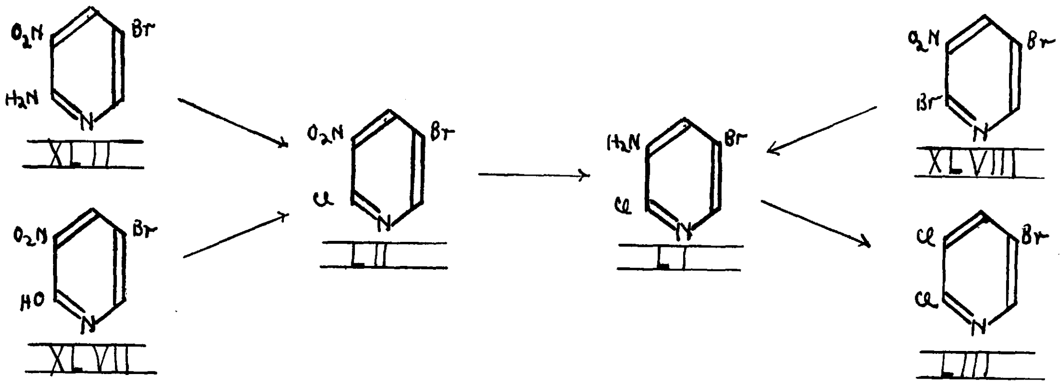
After these failures, recourse had to be taken to treatment with cuprous cyanide in the hope that the bromine atoms might be replaced by nitrile groups. 2:5-Dibromo-3-nitropyridine (XLVIII) was heated with cuprous cyanide; a reaction took place at 180° and from the reaction mixture there was obtained a product, $C_6H_2O_2N_3Br$ in which one of the bromine atoms had been replaced by a nitrile group. The position of the nitrile group was determined by hydrolysis with concentrated sulphuric acid to the amide which was degraded to the amine by the Hofmann reaction. The amine so prepared was identical with 2-amino-5-bromo-3-nitropyridine (XLII) and therefore its two precursors were 5-bromo-3-nitropicolinonitrile (XLIX) and 5-bromo-3-nitropicolinamide (L).



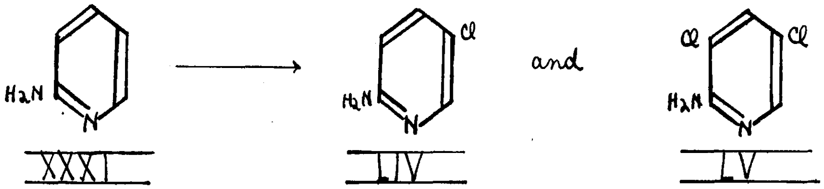
Attempts to replace the second bromine atom by heating 5-bromo-3-nitropicolinonitrile (XLIX) with cuprous cyanide or by refluxing them together in quinoline met with no success.

Having failed to replace the 5-bromine atom, presumably due to its lack of reactivity, it was decided to investigate the reactivity of the bromine atoms in 3-amino-2:5-dibromopyridine towards cuprous cyanide. In order to prepare this compound, 2:5-dibromo-3-nitropyridine (XLVIII) was reduced with tin and hydrochloric acid. The product obtained however analysed for $C_5H_4N_2ClBr$ in which the nitro group had been reduced to amino and one of the bromine atoms replaced by chlorine. This compound was therefore either 3-amino-2-bromo-5-chloropyridine or 3-amino-5-bromo-2-chloropyridine. That it was in fact the latter compound was proved by synthesising both of them by unambiguous methods, and comparing their properties with those of the compound obtained from 2:5-dibromo-3-nitropyridine (XLVIII).

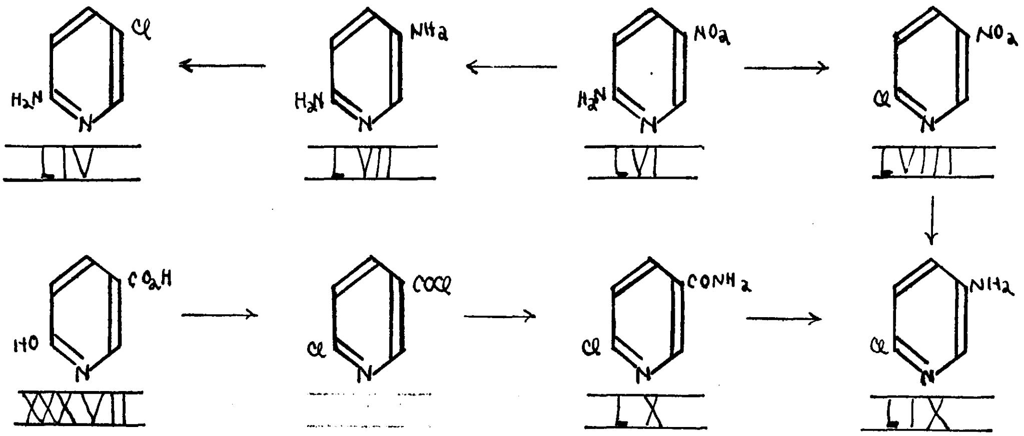
3-Amino-5-bromo-2-chloropyridine (LI) was obtained by the reduction by iron filings and glacial acetic acid of 5-bromo-2-chloro-3-nitropyridine (LII), prepared by the action of phosphoryl chloride-phosphorus pentachloride mixture on 5-bromo-3-nitro-2-pyridol (XLVII) and by the action of nitrous acid in hydrochloric acid on 2-amino-5-bromo-3-nitropyridine (XLII). The 3-amino-5-bromo-2-chloropyridine (LI) thus synthesised was identical with the product obtained by the action of tin and concentrated hydrochloric acid on 2:5-dibromo-3-nitropyridine (XLVIII). It was characterised by diazotisation in concentrated hydrochloric acid in the presence of copper powder to give 5-bromo-2:3-dichloropyridine (LIII).



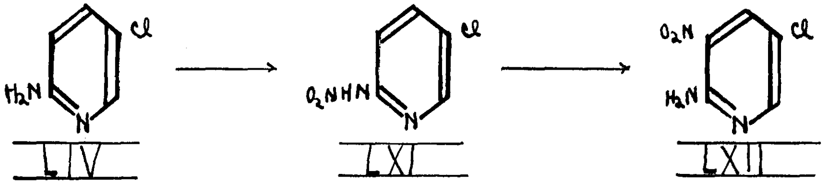
To synthesise 3-amino-2-bromo-5-chloropyridine, 2-aminopyridine (XXXI) was chlorinated in ethanol at 0° (24) to give a mixture of 2-amino-5-chloropyridine (LIV) and a compound claimed to be 2-amino-3:5-dichloropyridine (LV). The two compounds were separated by making use of the relative insolubility of the former in light petroleum.



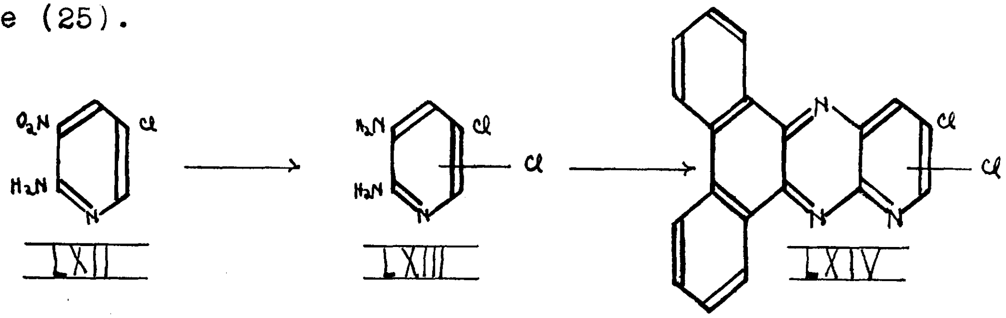
The orientation of the substituents in 2-amino-5-chloropyridine (LIV) can be deduced from its preparation from 2-amino-5-nitropyridine (LVI) through 2:5-diaminopyridine (LVII) (25), and from the conversion of 2-amino-5-nitropyridine (LVI) through 2-chloro-5-nitropyridine (LVIII) (26) into 5-amino-2-chloropyridine (LIX) (27) which is identical with the product obtained by the action of hypohalite on 6-chloronicotinamide (LX) (28) prepared by the chlorination of 6-hydroxynicotinic acid (XXXVII) followed by treatment with amonia (29).



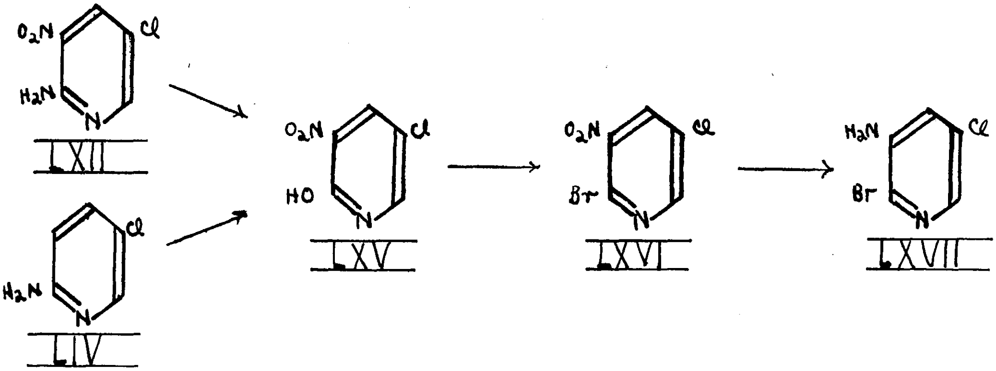
2-Amino-5-chloropyridine (LIV) was then nitrated in concentrated sulphuric acid yielding 5-chloro-2-nitraminopyridine (LXI) (24) which on isomerisation by heating in concentrated sulphuric acid gave 2-amino-5-chloro-3-nitropyridine (LXII) (24). 2-Amino-5-chloro-3-nitropyridine (LXII) was also prepared directly from 2-amino-5-chloropyridine (LIV) without isolation of the intermediate 5-chloro-2-nitraminopyridine (LXI).



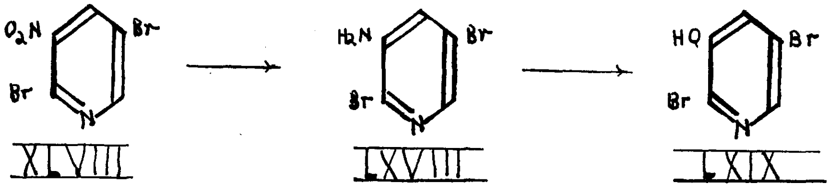
The position of the nitro group in 2-amino-5-chloro-3-nitropyridine (LXII) follows from its reduction with tin and concentrated hydrochloric acid to give 2:3-diamino-4:5- or 5:6-dichloropyridine (LXIII) which forms a quinoxaline derivative (LXIV) with phenanthraquinone (25).



2-Amino-5-chloro-3-nitropyridine (LXII) was treated with nitrous acid in concentrated sulphuric acid to give 5-chloro-3-nitro-2-pyridol (LXV) which was also obtained directly from 2-amino-5-chloropyridine (LIV) without isolation of the intermediates 5-chloro-2-nitraminopyridine (LXI) and 2-amino-5-chloro-3-nitropyridine (LXII). The hydroxy compound reacted with phosphorus tribromide-pentabromide mixture giving 2-bromo-5-chloro-3-nitropyridine (LXVI) which on reduction by iron filings and glacial acetic acid yielded the required 3-amino-2-bromo-5-chloropyridine (LXVII). This compound was distinct from the product obtained by the action of tin and concentrated hydrochloric acid on 2:5-dibromo-3-nitropyridine (XLVIII).

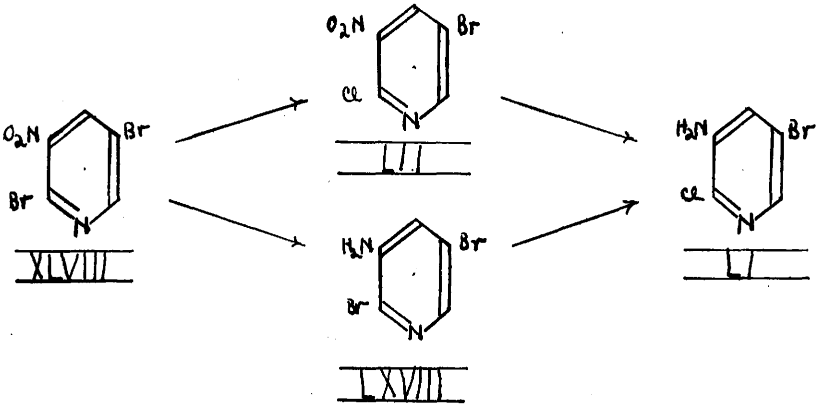


Having determined the structure of this product, it was found that the required 3-amino-2:5-dibromopyridine (LXVIII) could be obtained from 2:5-dibromo-3-nitropyridine (XLVIII) if the reduction were carried out by iron filings and glacial acetic acid. 3-Amino-2:5-dibromopyridine (LXVIII) was characterised by diazotisation

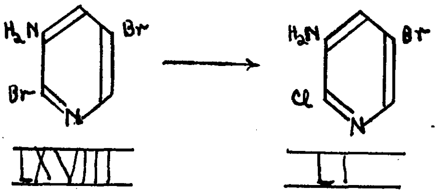


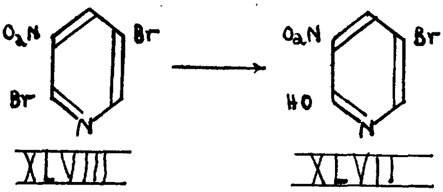
in sulphuric acid yielding 2:5-dibromo-3-pyridol (LXIX).

It was considered desirable to elucidate the mechanism whereby the 2-bromine atom in 2:5-dibromo-3-nitropyridine (XLVIII) was replaced by a 2-chlorine atom, during its reduction with tin and hydrochloric acid. This reaction could conceivably proceed by two different routes:



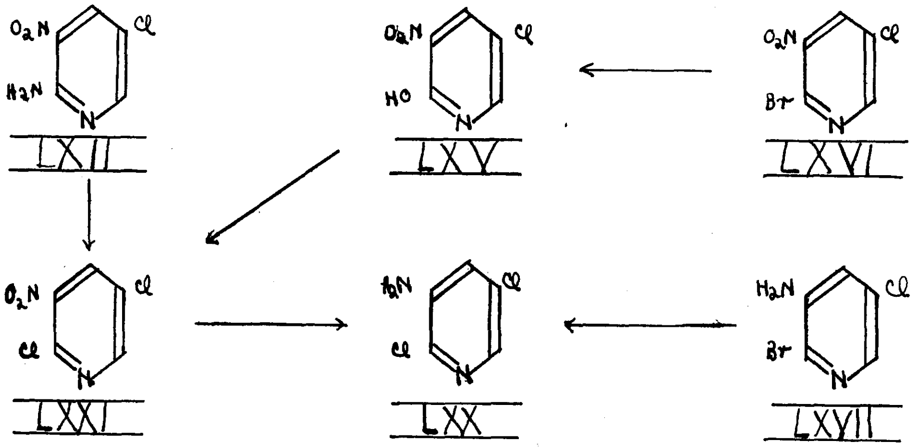
It was found that when 3-amino-2:5-dibromopyridine (LXVIII) was refluxed with concentrated hydrochloric acid, 3-amino-5-bromo-2-chloropyridine (LI) was obtained, whereas under similar reaction conditions 2:5-dibromo-3-nitropyridine (XLVIII) gave rise to 5-bromo-3-nitro-2-pyridol (XLVII).





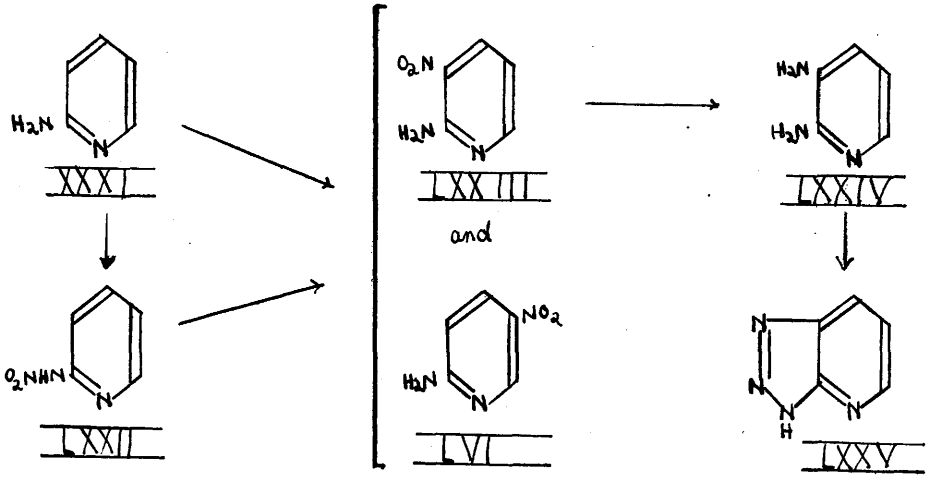
These experiments not only suggested that the mechanism of the reaction was that of reduction to 3-amino-2:5-dibromopyridine (LXVIII) followed by replacement of the 2-bromine atom, but also demonstrated the effect of substituent groups on the reactivity of the 2-bromine atom in the pyridine nucleus.

In order to give this work a broader basis in experimental fact, a series of reactions were carried out on similar compounds. It was found that on refluxing 2-bromo-5-chloro-3-nitropyridine (LXVI) with concentrated hydrochloric acid, 5-chloro-3-nitro-2-pyridol (LXV) was obtained, while under similar conditions 3-amino-2-bromo-5-chloropyridine (LXVII) yielded 3-amino-2:5-dichloropyridine (LXX). This last compound was identical with the product obtained by the reduction by iron filings and glacial acetic acid of 2:5-dichloro-3-nitropyridine (LXXI) prepared by the action of phosphoryl chloride-



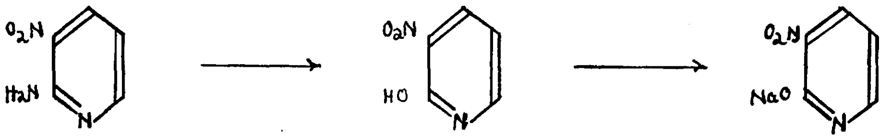
phosphorus pentachloride mixture on 5-chloro-3-nitro-2-pyridol (LXV) and by the action of nitrous acid in concentrated hydrochloric acid on 2-amino-5-chloro-3-nitropyridine (LXII).

Finally it was decided to study the reaction of the parent compounds 2-bromo-3-nitropyridine and 3-amino-2-bromopyridine with concentrated hydrochloric acid. To obtain these two compounds, 2-aminopyridine (XXXI) was first nitrated in concentrated sulphuric acid to give 2-nitraminopyridine (LXXII) (30) which on heating in concentrated sulphuric acid isomerised to form a mixture of 2-amino-3-nitropyridine (LXXIII) and 2-amino-5-nitropyridine (LVI) (30). This same mixture was also obtained directly from 2-aminopyridine (XXXI) without isolation of the intermediate 2-nitraminopyridine (LXXII) (30). Separation of the mixture was achieved by fractional crystallisation from ethanol-acetone mixture.



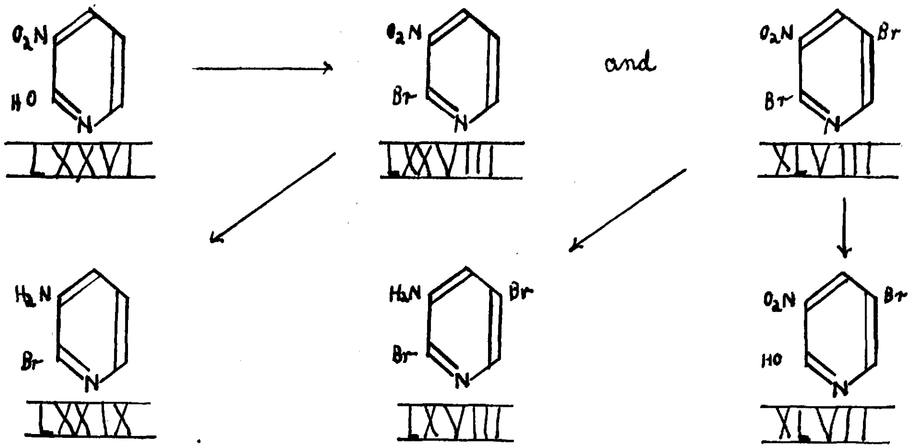
The structure of 2-amino-3-nitropyridine (LXXIII) has been established by reduction to 2:3-diaminopyridine (LXXIV) which with nitrous acid forms a triazine (LXXV) (25).

Treatment of 2-amino-3-nitropyridine (LXXIII) with nitrous acid in sulphuric acid gave 3-nitro-2-pyridol (LXXVI) (27) which was characterised by the formation of its sodium salt (LXXVII).



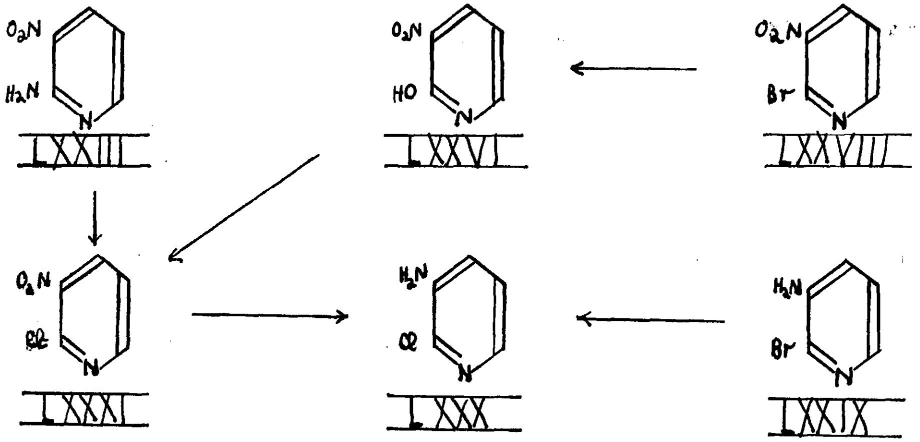
LXXIII LXXVI LXXVII

On treatment with phosphorus tribromide-pentabromide mixture, 3-nitro-2-pyridol (LXXVI) gave rise to two products: one was the required 2-bromo-3-nitropyridine (LXXVIII), the other being a compound, m.p.80°. The second product analysed for a mixture of bromonitropyridine and dibromonitropyridine with the latter predominating. It was not found possible to effect a separation of the constituents of the compound, m.p.80° by crystallisation, however the presence of 2:5-dibromo-3-nitropyridine (XLVIII) was verified by the isolation in good yield of 3-amino-2:5-dibromopyridine (LXVIII) on reduction with iron filings and glacial acetic acid and by refluxing it with concentrated hydrochloric acid to give 5-bromo-3-nitro-2-pyridol (XLVII) also in good yield. The required 3-amino-2-bromopyridine (LXXIX) was obtained by the reduction of 2-bromo-3-nitropyridine (LXXVIII) with iron filings and glacial acetic acid.

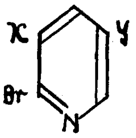


It was found that on refluxing 2-bromo-3-nitropyridine (LXXVIII) with concentrated hydrochloric acid, 3-nitro-2-pyridol (LXXVI) was obtained. In the case of 3-amino-2-bromopyridine (LXXIX), refluxing with concentrated hydrochloric acid gave 3-amino-2-chloropyridine (LXXX), which has the same properties as the compound obtained by the monochlorination of 3-aminopyridine by Schickh, Binz and Schulz (31) and which is identical with the product obtained by the same authors (31) by the reduction of 2-chloro-3-nitropyridine (LXXXI) with iron filings and glacial acetic acid. 2-Chloro-3-nitropyridine (LXXXI) which was obtained by the action of a phosphoryl chloride-phosphorus pentachloride mixture on 3-nitro-2-pyridol

(LXXVI) is identical with the product obtained by Tschitschibabin and Bylinkin (27) by the treatment of 2-amino-3-nitropyridine (LXXIII) with nitrous acid in concentrated hydrochloric acid.



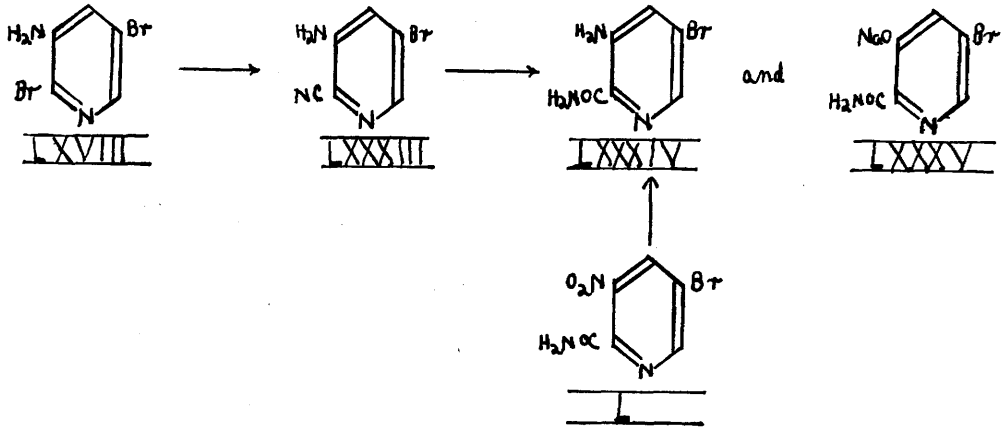
These results may be summarised in the following way:


LXXXII.

In the general formula LXXXII, where Y may be hydrogen, chlorine or bromine, when X is nitro the 2-bromine atom will be replaced by hydroxy on refluxing with concentrated hydrochloric acid, whereas when X is amino under similar conditions the 2-bromine atom will be replaced by chlorine. There can be no reasonable doubt that the different effects of the nitro group and the amino group ortho to the 2-bromine atom are due to the greater-I effect of the nitro group which imparts a more highly ionic character to the bromine-carbon bond. The conditions used being hydrolytic, the 2-bromine atom is replaced by a hydroxy group. Conversely, the effect of the ortho amino group is to strengthen the bromine-carbon bond enough to withstand the hydrolytic conditions, but not enough apparently to withstand replacement of the bromine by chlorine.

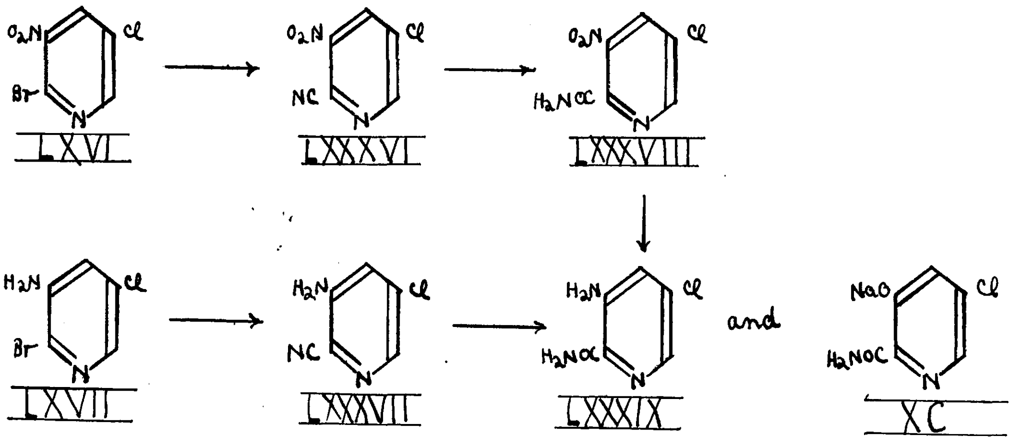
Having investigated these reactions, attention was once again turned to the reactivity of 5-bromine atoms towards cuprous cyanide. On heating 3-amino-2:5-dibromopyridine (LXVIII) with cuprous cyanide, reaction took place at 180°; a product, $C_6H_4N_3Br$ in which one of the bromine atoms had been replaced by a nitrile group was isolated from the reaction mixture. That this compound was 3-amino-5-bromopicolinonitrile (LXXXIII) was proved by hydrolysis with concentrated sulphuric acid. Two products were isolated: the first was 3-amino-5-bromopicolinamide (LXXXIV) identical with the compound obtained by reducing 5-bromo-3-nitropicolinamide (L) with iron filings and glacial acetic acid, thus verifying the structures assigned to 3-amino-5-bromopicolinonitrile (LXXXIII) and 3-amino-5-bromopicolinamide (LXXXIV); the second product analysed for

$C_8H_4O_2N_2BrNa.2H_2O$ in which NH_2 in 3-amino-5-bromopicolinamide (LXXXIV) had been replaced by NaO. Whether the amido or the amino group had been affected was not proved, but that the latter had occurred was considered more probable since under similar conditions the amido group in 5-bromo-3-nitropicolinamide (L) was not hydrolysed; indeed, taking into consideration the previously discussed different effects of the ortho nitro group and the ortho amino group, it would be expected that the amido group be more difficultly hydrolysable in 3-amino-5-bromopicolinamide (LXXXIV) than in 5-bromo-3-nitropicolinamide (L). On this account, it seems not unreasonable to formulate the second product as the dihydrate of the sodium salt (LXXXV) of 5-bromo-3-hydroxypicolinamide.



All attempts to replace the 5-bromine atom by heating 3-amino-5-bromopicolinonitrile (LXXXIII) with cuprous cyanide were unsuccessful.

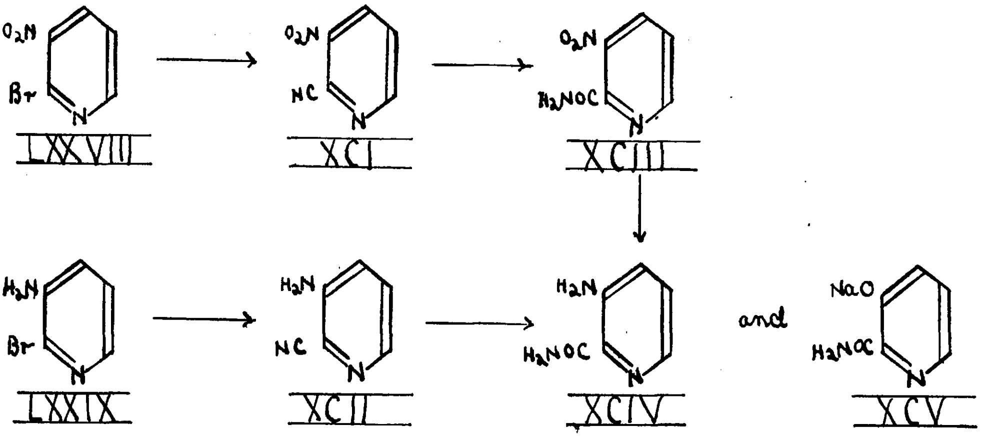
In view of the lack of reactivity of 5-bromine atoms towards cuprous cyanide, it was decided to investigate similar compounds containing 5-chlorine atoms. Thus it was found that both 2-bromo-5-chloro-3-nitropyridine (LXVI) and 3-amino-2-bromo-5-chloropyridine (LXVII) reacted with cuprous cyanide at high temperatures to give 5-chloro-3-nitropicolinonitrile (LXXXVI) and 3-amino-5-chloropicolinonitrile (LXXXVII) respectively. 5-Chloro-3-nitropicolinonitrile (LXXXVI) was characterised by hydrolysing with concentrated sulphuric acid to form 5-chloro-3-nitropicolinamide (LXXXVIII). Under similar conditions, 3-amino-5-chloropicolinonitrile (LXXXVII) gave 3-amino-5-chloropicolinamide (LXXXIX), identical with the product obtained by the reduction of 5-chloro-3-nitropicolinamide (LXXXVIII) with iron filings and glacial acetic acid,



and the sodium salt (XC) of 5-chloro-3-hydroxypicolinamide.

Attempts to replace the 5-chlorine atom by heating 5-chloro-3-nitropicolinonitrile (LXXXVI) or 3-amino-5-chloropicolinonitrile (LXXXVII) with cuprous cyanide or by refluxing them together in quinoline met with no success.

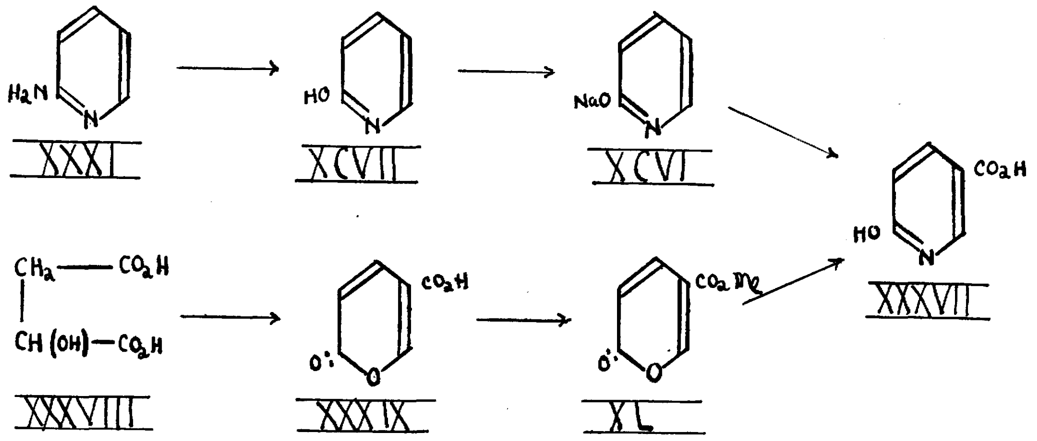
It was found that 2-bromo-3-nitropyridine (LXXVIII) and 3-amino-2-bromopyridine (LXXIX) also reacted with cuprous cyanide to give 3-nitropicolinonitrile (XCI) and 3-aminopicolinonitrile (XCII) respectively. Hydrolysis of 3-nitropicolinonitrile (XCI) with concentrated sulphuric acid gave 3-nitropicolinamide (XCIII), whereas under similar conditions 3-aminopicolinonitrile (XCII) yielded 3-aminopicolinamide (XCIV), identical with the product obtained by the reduction of 3-nitropicolinamide (XCIII) with iron filings and glacial acetic acid, and



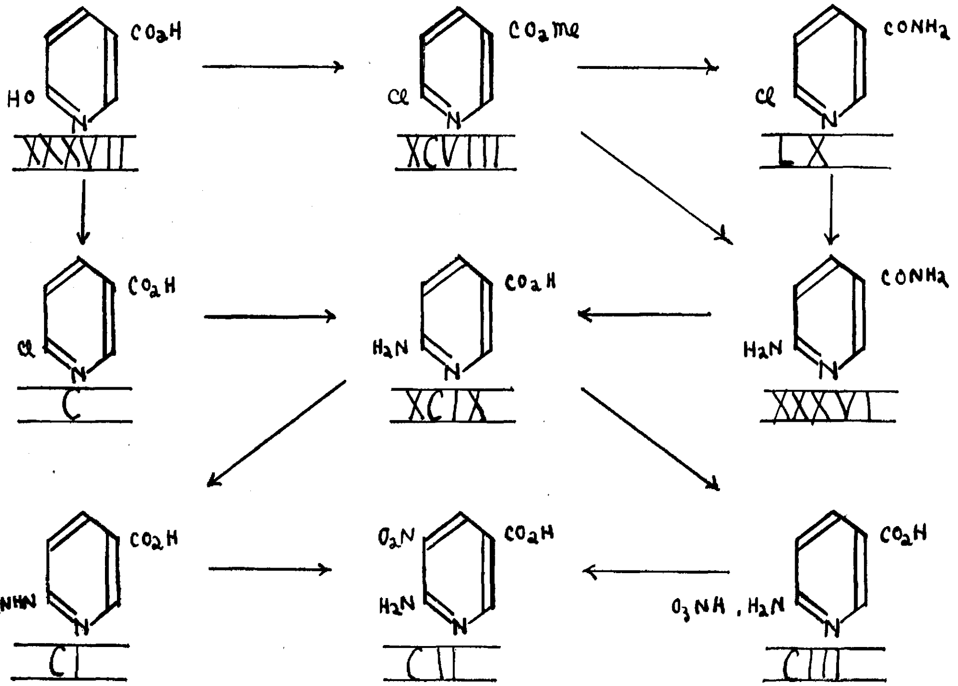
the sodium salt (XCV) of 3-hydroxypicolinamide.

(D) Nitration of 6-Hydroxynicotinic Acid and Related Compounds.

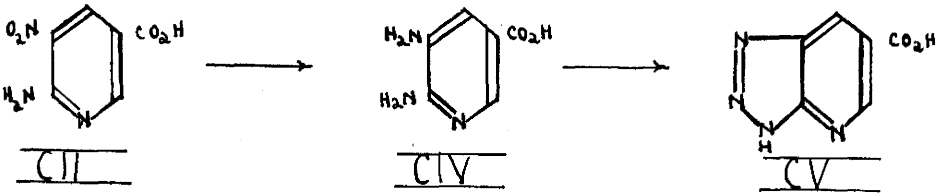
In view of the lack of reactivity of 5-halogen atoms in the pyridine nucleus discussed in (C), alternative methods of introducing 5-carboxy groups were investigated. In 1924 Tschitschibabin and Kirssanow (32) found that sodium 2-pyridolate (XCVI), prepared from 2-aminopyridine (XXXI) by the action of nitrous acid in sulphuric acid to give 2-pyridol (XCVII) (33), (34) followed by treatment with alkali (34), on heating under pressure in an atmosphere of carbon dioxide underwent a Kolbé reaction, and that only the para isomer, 6-hydroxynicotinic acid (XXXVII), was formed. This product is identical with that obtained from malic acid (XXXVIII), through coumalic acid (XXXIX) and methyl coumalate (XL) (20) (21).



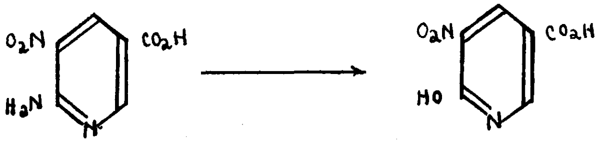
A 5-nitro group can be introduced into 6-hydroxynicotinic acid (XXXVII) by the following tedious method: 6-hydroxynicotinic acid (XXXVII) is heated at 100° with phosphoryl chloride and the product decomposed with methanol to form methyl 6-chloronicotinate (XCVIII) (35), which on treatment with ammonia at room temperature yields 6-chloronicotinamide (LX), identical with the compound obtained by Forrest and Walker (29) by the chlorination of 6-hydroxynicotinic acid (XXXVII) followed by treatment with ammonia. On heating 6-chloronicotinamide (LX) with ammonia there is obtained 6-aminonicotinamide (XXXVI) (19) which can be prepared directly from methyl 6-chloronicotinate (XCVIII) without isolation of the intermediate 6-chloronicotinamide (LX). Hydrolysis of 6-aminonicotinamide (XXXVI) with aqueous sodium hydroxide gives 6-aminonicotinic acid (XCIX) (19) which can also be obtained more directly from 6-hydroxynicotinic acid (XXXVII) by chlorination with phosphoryl chloride-phosphorus pentachloride mixture yielding 6-chloronicotinic acid (C) (21) followed by ammonolysis (36). The 5-nitro group can be introduced by two methods: by nitration of 6-aminonicotinic acid (XCIX) in concentrated sulphuric acid to form 6-nitraminonicotinic acid (CI) followed by isomerisation by heating in concentrated sulphuric acid yielding 6-amino-5-nitronicotinic acid (CII) or by the formation of 6-aminonicotinic acid nitrate (CIII) which on heating in concentrated sulphuric acid also gives 6-amino-5-nitronicotinic acid (CII) (37).



The position of the nitro group in 6-amino-5-nitronicotinic acid (CII) follows from its reduction with tin and concentrated hydrochloric acid to 5:6-diaminonicotinic acid (CIV) (37) which with nitrous acid forms a triazine (CV) (36).

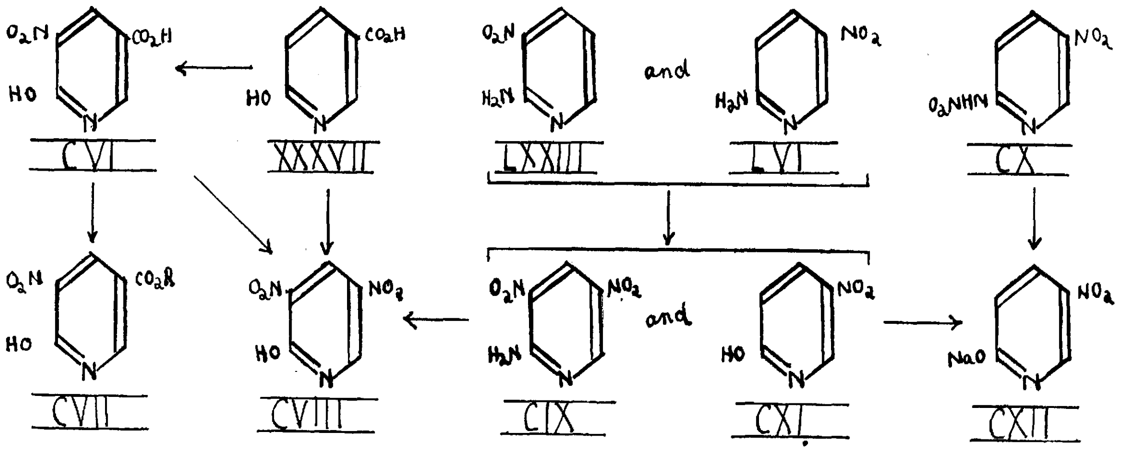


The final stage in the synthesis is achieved by heating 6-amino-5-nitronicotinic acid (CII) with alkali, yielding 6-hydroxy-5-nitronicotinic acid (CVI) (37).



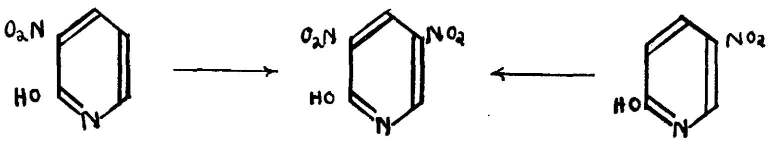
CII CVI

In order to shorten this synthesis, the nitration of 6-hydroxynicotinic acid (XXXVII) under varying conditions was studied. Treatment of 6-hydroxynicotinic acid (XXXVII) with fuming nitric acid at 50° gave 6-hydroxy-5-nitronicotinic acid (CVI) identical in every respect with the compound obtained by Räth and Prange (37). 6-Hydroxy-5-nitronicotinic acid (CVI) was characterised by the formation of its methyl and ethyl esters (CVII, R = Me and Et respectively). When refluxed with fuming nitric acid, 6-hydroxynicotinic acid (XXXVII) gave a dinitropyridol, m.p.175° which was also obtained by similar treatment of 6-hydroxy-5-nitronicotinic acid (CVI). The compound, m.p.175° which was characterised by the formation of its sodium salt was identified as 3:5-dinitro-2-pyridol (CVIII) by the following unambiguous syntheses: 2-amino-3:5-dinitropyridine (CIX) has been prepared (38), (39) by the nitration of either 2-amino-3-nitropyridine (LXXIII) or 2-amino-5-nitropyridine (LVI) in each case by acid-rearrangement of the (different) nitraminonitro intermediates. These facts have been contested by Räth and Prange (40) who have found that on heating 2-nitramino-5-nitropyridine (CX) in concentrated sulphuric acid, there is obtained only 5-nitro-2-pyridol (CXI). In our hands, nitration of a mixture of 2-amino-3-nitropyridine (LXXIII) and 2-amino-5-nitropyridine (LVI) in concentrated sulphuric acid followed by acid-rearrangement yielded a mixture of the required 2-amino-3:5-dinitropyridine (CIX) and 5-nitro-2-pyridol (CXI), identical with the product obtained by the action of nitrous acid in sulphuric acid on the same mixture of 2-amino-3-nitropyridine (LXXIII) and 2-amino-5-nitropyridine (LVI) (30), (cf. Tschitschibabin (26) who uses pure 2-amino-5-nitropyridine (LVI)). 5-Nitro-2-pyridol (CXI) was characterised by the formation of its sodium salt (CXII) which has properties similar to those of the compound obtained by the alkaline hydrolysis



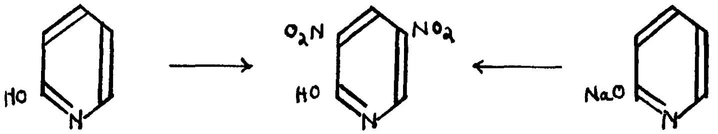
of 2-nitramino-5-nitropyridine (CX) (40). Treatment of 2-amino-3:5-dinitropyridine (CIX) with nitrous acid in sulphuric acid yielded 3:5-dinitro-2-pyridol (CVIII) identical with the specimen obtained by the direct nitration of 6-hydroxynicotinic acid (XXXVII).

Alternatively 3:5-dinitro-2-pyridol (CVIII) was obtained by the nitration of 3-nitro-2-pyridol (LXXVI) in fuming nitric acid or in mixed acid, and of 5-nitro-2-pyridol (CXI) in fuming nitric acid. Nitration of 5-nitro-2-pyridol (CXI) in mixed acid yielded a product, m.p.148-140° which was shown by analysis and light absorption to be a mixture of 5-nitro-2-pyridol (CXI) and 3:5-dinitro-2-pyridol (CVIII) in approximately equal proportions. Crystallisation of 5-nitro-2-pyridol (CXI) and 3:5-dinitro-2-pyridol (CVIII) together from water gave the same product, which was converted into the required 3:5-dinitro-2-pyridol (CVIII) by nitration in fuming nitric acid.



LXXVI CVIII CXI

Finally, the nitration of 2-pyridol (XCVII) was investigated. Nitration in fuming nitric acid yielded a product, m.p.151-152° which was also obtained by a similar nitration of sodium 2-pyridolate (XCVI). The product, m.p.151-152° was shown by analysis and light absorption to be a mixture of 5-nitro-2-pyridol (CXI) and 3:5-dinitro-2-pyridol (CVIII). Attempts to prepare it by the crystallisation of 5-nitro-2-pyridol (CXI) and 3:5-dinitro-2-pyridol (CVIII) or of 3-nitro-2-pyridol (LXXVI) and 3:5-dinitro-2-pyridol (CVIII) together from water were not successful. Further nitration of the compound, m.p.151-152° in fuming nitric acid yielded the required 3:5-dinitro-2-pyridol (CVIII).

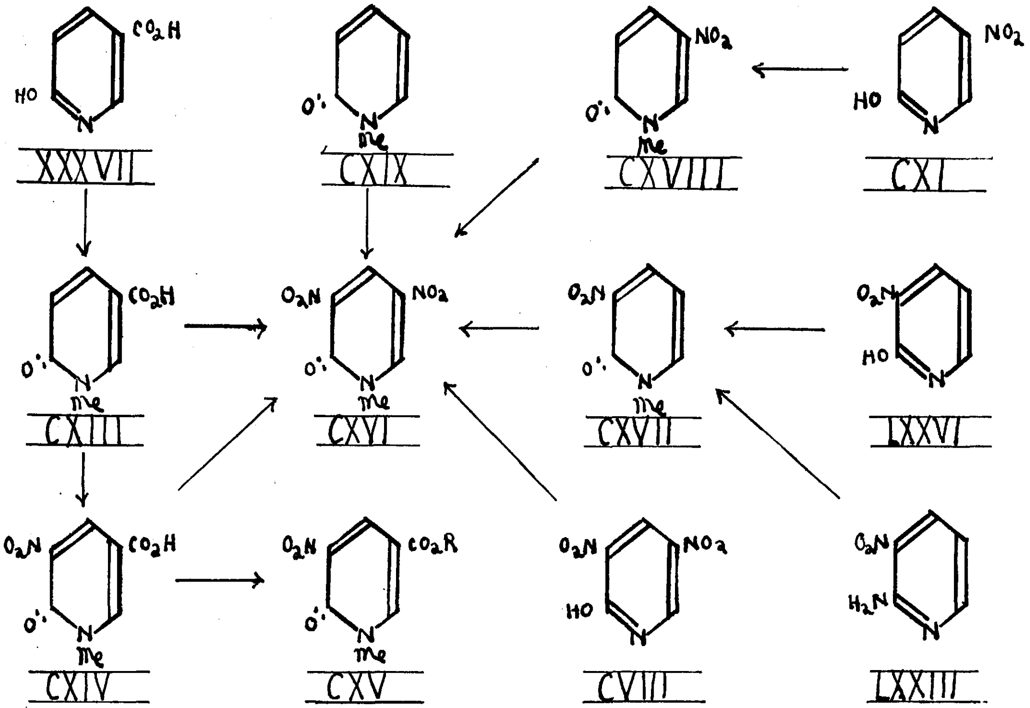


XCVII CVIII XCVI

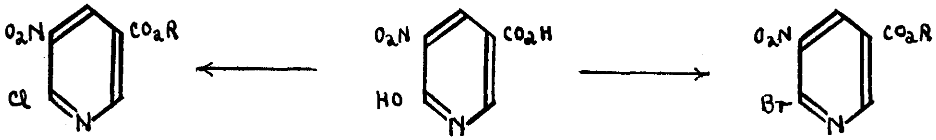
A further proof of the structure ascribed to the dinitration product from 6-hydroxynicotinic acid (XXXVII) was obtained by a study of the nitration of 1:6-dihydro-6-keto-1-methylnicotinic acid (CXIII). The structure of 1:6-dihydro-6-keto-1-methylnicotinic acid (CXIII) has been determined by its formation by the methylation of 6-hydroxynicotinic acid (XXXVII) (41) (cf. (42) in which 1:6-dihydro-6-keto-1-methylnicotinic acid (CXIII) is prepared by the methylation of nicotinic acid followed by oxidation). Treatment of 1:6-dihydro-6-keto-1-

methylnicotinic acid (CXIII) with fuming nitric acid at 55° gave 1:6-dihydro-6-keto-1-methyl-5-nitronicotinic acid (CXIV) characterised by the formation of its methyl and ethyl esters (CXV, R = Me and Et respectively). When however 1:6-dihydro-6-keto-1-methylnicotinic acid (CXIII) was refluxed with fuming nitric acid it gave a dihydromethyldinitropyridone, m.p.178° which was also obtained by similar treatment of 1:6-dihydro-6-keto-1-methyl-5-nitronicotinic acid (CXIV). The compound, m.p.178° was identified as 1:2-dihydro-1-methyl-3:5-dinitro-2-pyridone (CXVI) by its formation from 1:2-dihydro-1-methyl-3-nitro-2-pyridone (CXVII) and 1:2-dihydro-1-methyl-5-nitro-2-pyridone (CXVIII) by nitration. 1:2-Dihydro-1-methyl-3-nitro-2-pyridone (CXVII) was obtained by the methylation of 3-nitro-2-pyridol (LXXVI) and has the same properties as the compound prepared by Tschitschibabin and Konowalowa (43) from 2-amino-3-nitropyridine (LXXIII) by nitration and methylation followed by treatment with alkali. 1:2-Dihydro-1-methyl-5-nitro-2-pyridone (CXVIII) was prepared from 5-nitro-2-pyridol (CXI) by methylation (44). 1:2-Dihydro-1-methyl-3:5-dinitro-2-pyridone (CXVI) has previously been obtained by Fischer and Chur (45) by the nitration of 1:2-dihydro-1-methyl-2-pyridone (CXIX). 1:2-Dihydro-1-methyl-3:5-dinitro-2-pyridone (CXVI) was prepared from 3:5-dinitro-

2-pyridol (CVIII) by methylation, thus proving the structure assigned to the latter compound.



The structure ascribed to 1:6-dihydro-6-keto-1-methyl-5-nitronicotinic acid (CXIV) depends upon its formation from 1:6-dihydro-6-keto-1-methylnicotinic acid (CXIII) and upon its conversion into 1:2-dihydro-1-methyl-3:5-dinitro-2-pyridone (CXVI). Other attempts to correlate it with compounds of established structure were not successful. Thus it was not obtained by the methylation of 6-hydroxy-5-nitronicotinic acid (CVI), and attempts to convert it into the ester of 6-chloro-5-nitronicotinic acid (CXX) by treatment with phosgene in toluene, thionyl chloride or phosphoryl chloride-phosphorus pentachloride mixture followed by decomposition of the product with alcohol, or into the ester of 6-bromo-5-nitronicotinic acid (CXXI) by treatment with phosphorus tribromide-pentabromide mixture followed by decomposition of the product with alcohol were unsuccessful, although methyl and ethyl 6-chloro-5-nitronicotinate (CXX, R = Me and Et respectively) and methyl and ethyl 6-bromo-5-nitronicotinate (CXXI, R = Me and Et respectively) were readily obtained by similar treatment of 6-hydroxy-5-nitronicotinic acid (CVI). Attempts to decarboxylate 1:6-dihydro-6-keto-1-methyl-5-nitronicotinic acid (CXIV) to form 1:2-dihydro-1-methyl-3-nitro-2-pyridone (CXVII) were not successful.

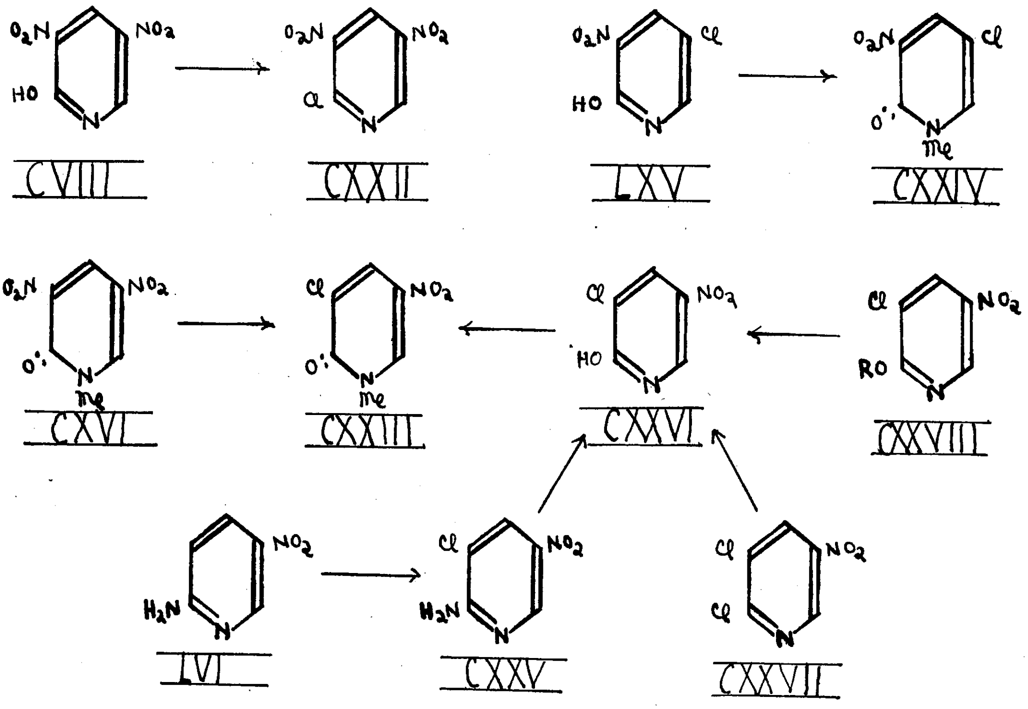


CXX CVI CXXI

An attempt to confirm the structure of 3:5-dinitro-2-pyridol (CVIII) by connecting it with 1:2-dihydro-1-methyl-3:5-dinitro-2-pyridone (CXVI) was not successful. It was proposed to convert both compounds into 2-chloro-3:5-dinitropyridine (CXXII). In the case of 3:5-dinitro-2-pyridol (CVIII), reaction with phosphoryl chloride-phosphorus pentachloride mixture proceeded smoothly to give 2-chloro-3:5-dinitropyridine (CXXII). On the other hand, treatment of 1:2-dihydro-1-methyl-3:5-dinitro-2-pyridone (CXVI) with phosphoryl chloride-phosphorus pentachloride mixture gave a compound, $C_6H_5O_3N_2Cl$ formed by the replacement of a nitro group in 1:2-dihydro-1-methyl-3:5-dinitro-2-pyridone (CXVI) by a chlorine atom, and not the expected 2-chloro-3:5-dinitropyridine (CXXII); the compound could be obtained in better yield by treatment of 1:2-dihydro-1-methyl-3:5-dinitro-2-pyridone (CXVI) with thionyl chloride. This compound was shown by synthesis to be 3-chloro-1:2-dihydro-1-methyl-5-nitro-2-pyridone (CXXIII) and to be different from 5-chloro-1:2-dihydro-1-methyl-3-nitro-2-pyridone (CXXIV).

The last compound was synthesised by the methylation of 5-chloro-3-nitro-2-pyridol (LXV), and is distinct from the product obtained by the chlorination of 1:2-dihydro-1-methyl-3:5-dinitro-2-pyridone (CXVI).

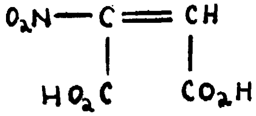
To synthesise 3-chloro-1:2-dihydro-1-methyl-5-nitro-2-pyridone (CXXIII), 2-amino-5-nitropyridine (LVI) was chlorinated in ethanol at 0° to form 2-amino-3-chloro-5-nitropyridine (CXXV) (cf. Bystritskaya and Kirssanow (46) who chlorinate with hypohalite), which on treatment with nitrous acid in sulphuric acid yielded 3-chloro-5-nitro-2-pyridol (CXXVI). (47) describes the formation of 3-chloro-5-nitro-2-pyridol (CXXVI) from 2:3-dichloro-5-nitropyridine (CXXVII) by the action of hydrochloric acid at 150°; no mention of 2:3-dichloro-5-nitropyridine (CXXVII) however occurs in the literature. The formation of 3-chloro-5-nitro-2-pyridol (CXXVI) from 2-alkoxy-3-chloro-5-nitropyridine (CXXVIII) by the action of zinc chloride and hydrogen chloride is claimed in (48) though the starting material is not described in the literature and the constants of the product disagree with (47) and the preparation from 2-amino-3-chloro-5-nitropyridine (CXXV). The final stage of the synthesis was effected by the methylation of 3-chloro-5-nitro-2-pyridol (CXXVI) to form the required 3-chloro-1:2-dihydro-1-methyl-5-nitro-2-pyridone (CXXIII), identical with the product obtained by the chlorination of 1:2-dihydro-1-methyl-3:5-dinitro-2-pyridone (CXVI).



Attempts to obtain more evidence regarding the structure of 3:5-dinitro-2-pyridol (CVIII) by studying the nitration of nicotinic acid N-oxide (49) met with no success.

The detailed proof of the structure of the dinitropyridol obtained from 6-hydroxynicotinic acid (XXXVII) as described above was necessary since Tschitschibabin and Schapiro (33) have claimed that nitration of 2-pyridol (XCVII) gives a product described as 3:5-dinitro-2-pyridol (CVIII) the properties of which are entirely different from those of the 3:5-dinitro-2-pyridol (CVIII) described above. The nitration of 2-pyridol (XCVII) was repeated according to Tschitschibabin and Schapiro giving a product which had the properties of the compound described by these authors; this product was found to be a mixture of sodium-3-nitro-2-pyridolate (LXXVII) and sodium 3:5-dinitro-2-pyridolate. The latter constituent was isolated from the mixture as the free pyridol (CVIII) by crystallisation from dilute hydrochloric acid. The presence of the former constituent was deduced from the analysis and from the light absorption characteristics of the mixture. Nitration of the mixture with fuming nitric acid under reflux gave 3:5-dinitro-2-pyridol (CVIII) in good yield.

Binz and Maier-Bode (50) have also claimed to have prepared by the nitration of 2-pyridol (XCVII) a compound described as 3:5-dinitro-2-pyridol (CVIII) which has entirely different properties from those of the 3:5-dinitro-2-pyridol (CVIII) described above. On repeating the nitration of 2-pyridol (XCVII) according to Binz and Maier-Bode a very small quantity of the compound described by these authors was obtained; the yield was increased slightly by substituting sodium 2-pyridolate (XCVI) for 2-pyridol (XCVII). Other attempts to increase the yield by varying the reaction conditions were not successful. The compound contained sodium and crystallised unchanged from dilute hydrochloric acid. As it exploded when heated above its melting point no reliable carbon and hydrogen analyses were obtained. It did not react with diazomethane in ether, and no product was obtained with dimethyl sulphate and alkali, with fuming nitric acid nor with phosphoryl chloride-phosphorus pentachloride mixture. On refluxing the compound with concentrated hydrochloric acid for two hours a product, m.p. 150-152° (decomp.) was obtained which analysed for $C_4H_3O_6N.4H_2O$. It had no appreciable light absorption in water above 2200Å, and hence did not contain a pyridine nucleus. It titrated for a dibasic acid with strong alkali. The only structures which will account for all the observed facts are those of the tetrahydrates of nitromaleic and nitrofumaric acids (CXXIX); the melting point favours the former compound.



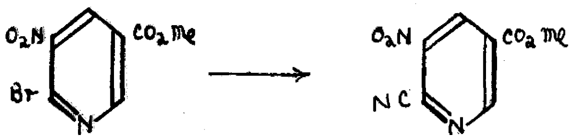
$$\begin{array}{ccc} O_2N-C & = & CH \\ | & & | \\ HO_2C & & CO_2H \end{array}$$

CXXIX

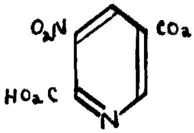
On heating this compound *in vacuo* at 140° over phosphorus pentoxide for five hours, a product, m.p. 211° (decomp.) was obtained which analysed for $C_4H_{12}O_8N_2$. The compound was acidic but there was not enough of it available to determine its titration equivalent.

Owing to the impossibility of obtaining analysis results for the precursor of these two compounds, no structure could be ascribed to it and hence the mechanism whereby the pyridine nucleus had been broken down could not be investigated.

Having proved indubitably the structure assigned to the dinitropyridol, m.p.175° obtained from 6-hydroxy-nicotinic acid (XXXVII) and having disposed of previous claims to have prepared it, attention was once again turned to the synthesis of 3-nitro*iso*cinchomeronic acid (XVI). There now remained to convert the 6-hydroxy group in 6-hydroxy-5-nitronicotinic acid (CVI) into a carboxy group. The first step had already been taken in the preparation of the methyl and ethyl esters of 6-chloro-5-nitronicotinic acid (CXX, R = Me and Et respectively) and of 6-bromo-5-nitronicotinic acid (CXXI, R = Me and Et respectively). It was found that replacement of the 6-chlorine atom by a nitrile group did not take place when methyl or ethyl 6-chloro-5-nitronicotinate (CXX, R = Me or Et respectively) was heated with cuprous cyanide or refluxed with the same reagent in quinoline. However on heating methyl 6-bromo-5-nitronicotinate (CXXX) with cuprous cyanide, reaction took place at 240° and from the mixture was isolated methyl 6-cyano-5-nitronicotinate (CXXXI) which is a derivative of the required 3-nitro<u>iso</u>cinchomeronic acid (XVI).



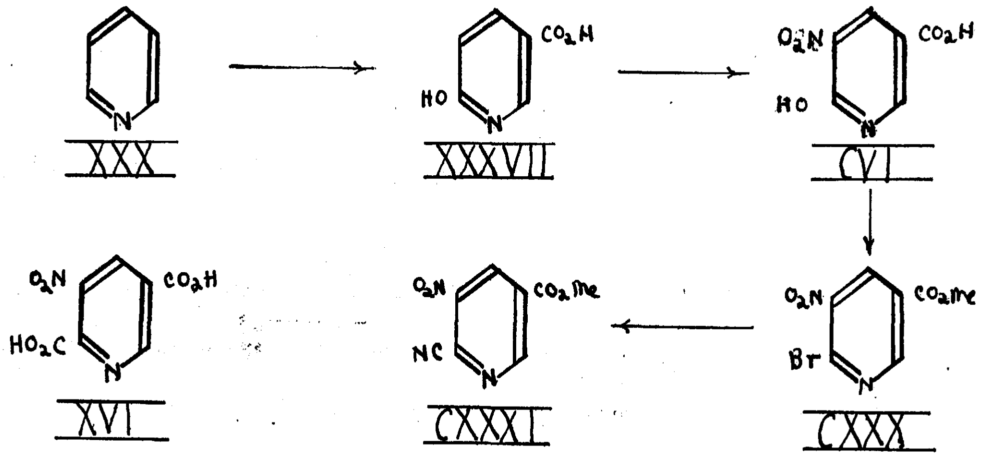
CXXX CXXXI



XVI

(E) Conclusions.

A derivative of 3-nitro<u>iso</u>cinchomeronic acid (XVI), required as an intermediate in a projected synthesis of LysergiThis last compound is converted in four stages (XXX). This last compound is converted in four stages into 6-hydroxynicotinic acid (XXXVII) which on nitration with fuming nitric acid at 50° gives 6-hydroxy-5-nitronicotinic acid (CVI). This compound on treatment with phosphorus tribromide-pentabromide mixture followed by decomposition of the product with methanol yields methyl 6-bromo-5-nitronicotinate (CXXX). The final stage is achieved by heating methyl 6-bromo-5-nitronicotinate (CXXX) with cuprous cyanide to give methyl 6-cyano-5-nitronicotinate (CXXXI) which is a derivative of the required 3-nitro<u>iso</u>cinchomeronic acid (XVI).



EXPERIMENTAL.

All melting points are uncorrected.

Ethyl pyruvate (XX).— A mixture of pyruvic acid (32 g.) (Org.Synth.,4,63), ethanol (250 c.c.) and benzene (100 c.c.) was fractionated in a Fenské until all the water from the reaction had been removed. The residue was distilled to give ethyl pyruvate (22 g.) as a liquid, b.p.64-68°/18-20 mm. (Steude, Annalen,1891,261,25, gives b.p.66°/18-20 mm.).

Sodio ethyl formylpyruvate.— (a) Ethyl formate (7.9 c.c.) was added to a solution of sodium (2.3 g.) in dry ethanol (70 c.c.) followed by ethyl pyruvate (10.7 c.c.) during 10 minutes with stirring. After refluxing for 3 hours, the mixture was cooled and the solid material collected and dried to give sodio ethyl formylpyruvate (13.6 g.) as a yellow powder, m.p.$>$300°.

(b) Sodium (5.6 g.) was added slowly to a cooled mixture of acetaldehyde (14.5 g.), ethyl oxalate (40 g.) and dry ether (500 c.c.) with stirring. When the reaction was complete, the solid material was collected and dried to give sodio ethyl formylpyruvate (31.5 g.) as a yellow powder, m.p.$>$300°.

Ethyl formylpyruvate (XIX).— Sodio ethyl formylpyruvate

(100 g.), water (500 c.c.) and ether (500 c.c.) were stirred and a slight excess of diluted sulphuric acid added. The ether layer was separated, shaken with saturated aqueous sodium bicarbonate (100 c.c.), dried (Na_2SO_4) and the ether removed on the water-bath. The residue was distilled to give <u>ethyl formylpyruvate</u> (14.5 g.) as a liquid, b.p.56°/2.2 mm. n_D 1.4126.

Found: C,50.2; H,6.1%

$C_6H_8O_4$ requires: C,50.0; H,5.6%

<u>Attempted Condensation of Cyanoacetamide with Ethyl formylpyruvate</u>.— (a) Cyanoacetamide (0.84 g.) (<u>Org. Synth</u>.,<u>9</u>,36), ethanol (50 c.c.), ethyl formylpyruvate (1.44 g.) and piperidine (0.5 c.c.) were refluxed together for 24 hours, concentrated to 10 c.c. and cooled. The solid was collected and dried to give needles (0.5 g.), m.p.114-117°, alone or mixed with authentic cyanoacetamide. No crystalline material was obtained from the mother liquor.

(b) Cyanoacetamide (0.84 g.), ethanol (50 c.c.), ethyl formylpyruvate (1.44 g.) and diethylamine (0.4 c.c.) were refluxed together for 24 hours, concentrated to 10 c.c. and cooled. The solid was collected and dried to give needles (0.4 g.), m.p.115-118°, alone or mixed with authentic cyanoacetamide. No crystalline material was obtained from the mother liquor.

Ethyl oxalylacetate (XXV).— (cf. Wislicenus, Ber.,1886, 19,3225). Ethyl acetate (65 c.c.) was added to a stirred mixture of ethyl oxalate (91 c.c.), dry ether (700 c.c.) and sodium wire (15 g.). The mixture was stirred until solid material began to precipitate, stored overnight at 0° and the solid collected, dried and shaken with ether (500 c.c.) and water (1000 c.c.) containing a slight excess of sulphuric acid. The ether layer was separated, dried (Na_2SO_4) and the ether removed on the water-bath. The residue was distilled to give ethyl oxalylacetate (52 g.) as a liquid, b.p.116-118°/ 9-11 mm. (Wislicenus, Annalen,1888,246,318, gives b.p. 131-132°/24 mm.). n_D 1.4500 (Brühl, J.prakt.Chem., 1894,50,140, gives n_D 1.4560).

Attempted Condensation of Cyanoacetamide with Ethyl oxalylacetate.— (a) Cyanoacetamide (1.05 g.), ethanol (50 c.c.), ethyl oxalylacetate (2.35 g.) and diethylamine (0.5 c.c.) were refluxed together for 24 hours, concentrated to 10 c.c. and cooled. The solid was collected and dried to give needles (0.5 g.), m.p.112-116°, alone or when mixed with authentic cyanoacetamide. No crystalline material was obtained from the mother liquor.

(b) Cyanoacetamide (4.2 g.), ethanol (130 c.c.), ethyl oxalylacetate (9.4 g.) and piperidine (0.5 c.c.) were refluxed together for 24 hours, concentrated to 40 c.c. and cooled. The solid was collected and dried to give needles (2.0 g.), m.p.117-118°, alone or mixed with authentic cyanoacetamide. No crystalline material was obtained from the mother liquor.

5-*Ethyl*-2-*methylpyridine* (XXVI).— (cf. Graf, *J.prakt. Chem.*,1932,*133*,19). Paraldehyde (270 g.), glacial acetic acid (60 g.) and aqueous ammonia (120 g.; *d*,0.88) were heated at 180° for 6 hours. The reaction mixture was made strongly alkaline with aqueous sodium hydroxide and steam distilled. The distillate was made strongly alkaline with aqueous sodium hydroxide and the aqueous layer returned for distillation, the process being repeated until the distillate was no longer alkaline. The combined basic layers were dried (NaOH flakes) and fractionated to give paraldehyde (170 g.), b.p.124-126°, an intermediate fraction (5 g.), b.p.126-175° and a base (28 g.), b.p.175-176°. The first two fractions were recycled with paraldehyde (100 g.), glacial acetic acid (60 g.) and aqueous ammonia (120 g.; *d*,0.88). Fractionation of the combined dried basic layers gave paraldehyde (100 g.), b.p.124-126°, an intermediate fraction (4 g.), b.p.126-175° and a base (77 g.), b.p. 175-176°. The two basic fractions were combined to give 5-ethyl-2-methylpyridine (105 g.) as a liquid, b.p. 175° (Fichter and Labhardt, Ber.,1909,42,4714, give b.p.174-176°). The picrate of 5-ethyl-2-methylpyridine was obtained as yellow needles, m.p.162°, from ethanol; Fichter and Labhardt describe it as yellow plates from water, m.p.164°.

5-Ethyl-2-methylnitropyridine.— 5-Ethyl-2-methylpyridine (15 g.) was added slowly to oleum (70 c.c.; 60% free SO_3), heated to 100° and potassium nitrate (30 g.) added during 30 minutes. After heating at 100° for a further 5 hours the solution was cooled, diluted with water, made alkaline with aqueous sodium hydroxide-potassium hydroxide with cooling and extracted with ether. The residue (7 g.) on evaporation of the ether was distilled to give 5-ethyl-2-methylpyridine (6 g.), b.p.175-176°, a higher boiling fraction (0.3 g.), b.p.176-210°, and an undistillable residue from which no useful product was obtained. The higher boiling fraction was redistilled to give a fraction (0.05 g.), b.p.176-200° and 5-ethyl-2-methylnitropyridine (0.15 g.) as a pale yellow liquid, b.p.200-210°/760 mm. The picrate of 5-ethyl-2-methylnitropyridine separated from ethanol as yellow needles, m.p.155-156°.

Found: N,18.0%

$C_{14}H_{14}O_9N_6$ requires: N,17.7%

5-<u>Ethyl</u>-2-<u>methyl</u>-3-<u>pyridol</u> (XXVIII).— (cf. <u>U</u>.<u>S</u>.<u>P</u>.,1,880, 645). 5-Ethyl-2-methylpyridine (47 g.) was added slowly to a mixture of oleum (104 c.c.; 20% free SO_3) and basic mercuric sulphate (1 g.) and heated at 225° for $3\frac{1}{2}$ hours with occasional shaking. The mixture was cooled, poured into ice-water (1000 c.c.) and was treated with calcium carbonate until there was no acid reaction to litmus. The mixture was steam distilled (5-ethyl-2-methylpyridine (35 g.) being recovered from the distillate), filtered and the filtrate heated to boiling and made just alkaline to phenolphthalein by the addition of aqueous sodium carbonate. After hot filtration, the solution was evaporated to give sodium 5-ethyl-2-methylpyridine-3-sulphonate (10 g.) as a light brown solid.

The solid (10 g.) was added slowly to a melt of potassium hydroxide (19 g.) and water (0.5 c.c.) at 160° and the temperature raised to 240° for 15 minutes. On cooling, the mass was dissolved in water (25 c.c.) and concentrated hydrochloric acid added with cooling until the solution was just neutral to phenolphthalein. The mixture was shaken with ethyl acetate (3 x 60 c.c.), the extract evaporated and the residue sublimed at 120/10^{-4}mm. to give 5-ethyl-2-methyl-3-pyridol (2.75 g.) as a crystalline solid, m.p.175-176° (*ibid*. gives prisms, m.p. 175°, from benzene). Light absorption in ethanol: Maximum at 2780Å (ε = 8300) (Stiller, Keresztesy and Stevens, *J.A.C.S.*,1939,*61*,1237, give light absorption in water at pH 2.1: Maximum at 2900Å (ε = 7000), and light absorption in water at pH 10.2: Maxima at 2400 (ε = 5800) and 3050Å (ε = 5900)).

Oxidation of 5-Ethyl-2-methyl-3-pyridol.— To a stirred mixture of 5-ethyl-2-methyl-3-pyridol (2 g.) and water (100 c.c.) at 70° was added potassium permanganate (18.2 g.) in water (200 c.c.) during one hour. The temperature was raised to 85-90° for a further 30 minutes and the mixture filtered hot through a sintered funnel, the manganese dioxide cake being washed with hot water (100c.c.). The filtrate was acidified by dilute hydrochloric acid and evaporated to dryness. No product was obtained from the residue by the action of aqueous barium chloride and ammonia or by the action of methanolic hydrochloric acid.

5-Ethyl-3-methoxy-2-methylpyridine (XXIX).— A solution of excess diazomethane in ether (*Org.Synth.*,*15*,3) was added to 5-ethyl-2-methyl-3-pyridol (2 g.) and the mixture kept at 0° until there was no further evolution of nitrogen. The residue on evaporation consisted of 5-ethyl-3-methoxy-2-methylpyridine (2.2 g.) as a pale yellow oil.

No picrate was obtained by the action of a saturated solution of picric acid in ethanol.

On the addition of an excess of hot saturated aqueous mercuric chloride, a precipitate was obtained which on crystallisation from water gave the mercuric chloride compound of 5-ethyl-3-methoxy-2-methylpyridine (1.5 g.) as small prisms, m.p.150°.

Found: N,3.1%

$C_9H_{13}ONCl_2Hg$ requires: N,3.3%

Oxidation of 5-Ethyl-3-methoxy-2-methylpyridine.— To a stirred mixture of 5-ethyl-3-methoxy-2-methylpyridine (1.1 g.) and water (50 c.c.) at 70° was added potassium permanganate (9.1 g.) in water (100 c.c.) during one hour. The temperature was raised to 85-90° for a further 30 minutes and the mixture filtered hot through a sintered funnel, the manganese dioxide cake being washed with hot water (50 c.c.). The filtrate was acidified with dilute hydrochloric acid and evaporated to dryness. No product was obtained from the residue by the action of aqueous barium chloride and ammonia or by the action of methanolic hydrochloric acid.

2-Aminopyridine (XXXI).— (cf. D.R.P.,362,446). Pyridine (100 g.), toluene (100 g.) and powdered sodamide (100 g.) were refluxed for 10 hours and the residue distilled to give 2-aminopyridine (94 g.) as a white crystalline solid, m.p.58° (Fischer, Ber.,1899,32,1301, gives m.p.56°), b.p.200-210°/760 mm. (Philips, Annalen,1895,288,263, gives b.p.210°/760 mm.).

2-Amino-5-bromopyridine (XXXIV).— (cf. Caldwell, Tyson and Lauer, J.A.C.S.,1944,66,1479). 2-Aminopyridine (47 g.), glacial acetic acid (152 c.c.) and acetic anhydride (52 c.c.) were refluxed for 3 hours, bromine (27 c.c.) added dropwise with stirring at 45-55°, the solution taken to dryness, and the residue diluted with water containing sodium metabisulphite. The solution was made almost alkaline by the addition of hydrated sodium carbonate and the precipitate collected, dried and crystallised from ethanol to give 2-acetylamino-5-bromopyridine (45 g.) as needles, m.p.175° (Palzek and Sucharda, Ber.,1928,61,1813, give needles, m.p.175°, from ethanol).

The product (45 g.) was dissolved in boiling ethanol (150 c.c.), concentrated hydrochloric acid (125 c.c.) added and refluxed for 3 hours. The residue on evaporation was basified by saturated aqueous potassium carbonate, cooled and the residue collected, dried and crystallised from benzene to give 2-amino-5-bromopyridine (30.0 g.) as plates, m.p.136-137° (Tschitschibabin and Tjashelowa, J.Russ.Phys.Chem.Soc.,1920,50,483, give plates, m.p.137°, from benzene).

5-Bromo-2-nitraminopyridine (XLI).— (cf. Tschitschibabin and Tjashelowa, J.Russ.Phys.Chem.Soc.,1920,50,483). 2-Amino-5-bromopyridine (5 g.) was added slowly and with cooling to sulphuric acid (12 c.c.; d,1.84) followed by a mixture of nitric acid (1.95 c.c.; d,1.42) and sulphuric acid (2.1 c.c.; d,1.84) added dropwise with stirring below 20°. After stirring for a further hour at 15° the mixture was poured onto ice (150 g.) and the residue collected, dried and crystallised from ethyl acetate to give 5-bromo-2-nitraminopyridine (3.0 g.) as yellow needles, m.p.188° (decomp.) (Tschitschibabin and Tjashelowa, ibid., give yellow needles, m.p.181°(decomp.), from water or ethanol).

2-Amino-5-bromo-3-nitropyridine (XLII).— (a) (cf. Tschitschibabin and Tjashelowa, J.Russ.Phys.Chem.Soc., 1920,50,483). 5-Bromo-2-nitraminopyridine (3.0 g.) and sulphuric acid (15 c.c.; d,1.84) was heated at 100° for one hour, cooled, poured onto ice (150 g.) and made just alkaline with sodium hydroxide with cooling. The solid was collected, dried and crystallised from ethyl acetate to give 2-amino-5-bromo-3-nitropyridine (1.6 g.) as yellow needles, m.p.205° (Tschitschibabin and Tjashelowa, ibid., give yellow needles, m.p.205°, from ethanol).

(b) 2-Amino-5-bromopyridine (10 g.) was added slowly and with cooling to sulphuric acid (24 c.c.; d,1.84) followed by a mixture of nitric acid (3.9 c.c.; d,1.42) and sulphuric acid (4.2 c.c.; d,1.84) added dropwise with stirring below 20°. After stirring for a further hour at 15° the mixture was heated at 100° for one hour, cooled, poured onto ice (250 g.) and made just alkaline with sodium hydroxide with cooling. The solid was collected, dried and crystallised from ethyl acetate to give 2-amino-5-bromo-3-nitropyridine (6.4 g.) as yellow needles, m.p.205°, alone or mixed with a specimen (a).

2:3-Diamino-5-bromo-4(6)-chloropyridine (XLV).— 2-Amino-5-bromo-3-nitropyridine (2.75 g.), concentrated hydrochloric acid (30 c.c.) and granulated tin (7 g.) were refluxed until all the tin had dissolved. The solution was evaporated and the residue dissolved in hot water (15 c.c.) and filtered. The filtrate was basified by the addition of aqueous sodium hydroxide (30 c.c.; 50%) with cooling, and the solid material collected, dried and extracted with boiling benzene (3 x 100 c.c.). The residue obtained on evaporation was crystallised from water to give 2:3-diamino-5-bromo-4(6)-chloropyridine (0.6 g.) as long needles, m.p.164°.

Found: N,18.7%

$C_5H_5N_3ClBr$ requires: N,18.9%

A filtered solution of 2:3-diamino-5-bromo-4(6)-chloropyridine (0.1 g.) in glacial acetic acid (5 c.c.) was added to a hot filtered solution of phenanthraquinone (0.12 g.) in glacial acetic acid (15 c.c.) and heated at 100° for 15 minutes. On cooling, the crystals were collected, washed with glacial acetic acid (5 c.c.) and dried to give the phenanthraquinone derivative of 2:3-diamino-5-bromo-4(6)-chloropyridine (0.07 g.) as orange needles, m.p.270-272°.

Found: N,11.0%

$C_{19}H_9N_3ClBr$ requires: N,10.6%

5-Bromo-3-nitro-2-pyridol (XLVII).— (a) To a cooled solution of 2-amino-5-bromo-3-nitropyridine (10 g.) in sulphuric acid (25 c.c.; d,1.84) was added a cooled solution of sodium nitrite (6 g.) in water (15 c.c.) slowly and with stirring. After stirring for a further 30 minutes at 0° the solution was diluted with water (150 c.c.) with cooling and the orange precipitate collected, dried and crystallised from ethanol to give 5-bromo-3-nitro-2-pyridol (6.05 g.) as pale yellow needles, m.p.240-241° (decomp.).

Found: C,27.7; H,1.0%

$C_5H_3O_3N_2Br$ requires: C,27.4; H,1.4%

(b) 2-Amino-5-bromopyridine (10 g.) was added slowly and with cooling to sulphuric acid (24 c.c.; d,1.84) followed by a mixture of nitric acid (3.9 c.c.; d,1.42) and sulphuric acid (4.2 c.c.; d,1.84) added dropwise with stirring below 20°. After stirring for a further hour at 15° the mixture was heated at 100° for one hour, cooled and a cooled solution of sodium nitrite (8 g.) in water (20 c.c.) added slowly with stirring. After stirring for a further 30 minutes at 0° the solution was diluted with water (150 c.c.) with cooling and the orange precipitate collected, dried and crystallised from ethanol to give 5-bromo-3-nitro-2-pyridol (6.8 g.) as pale yellow needles, m.p.240-241° (decomp.), alone or mixed with a specimen (a).

2:5-Dibromo-3-nitropyridine (XLVIII).— 5-Bromo-3-nitro-2-pyridol (40 g.) was added to a mixture of phosphorus tribromide (100 g.) and bromine (29.2 g.), heated at 100° for 20 hours, decomposed with methanol (500 c.c.) and evaporated to 200-300 c.c. Water (1000 c.c.) was added and the precipitated solid collected, dried and crystallised from light petroleum (60-80°) to give 2:5-dibromo-3-nitropyridine (41 g.) as stout needles, m.p. 93°.

Found: C,21.4; H,1.0%

$C_5H_2O_2N_2Br_2$ requires: C,21.3; H,0.7%

Reaction of 2:5-Dibromo-3-nitropyridine with Magnesium.— (a) To magnesium shavings (1.215 g.) was added a solution of ethyl bromide (0.2 g.) in dry ether (4 c.c.). After the reaction had begun, a solution of 2:5-dibromo-3-nitropyridine (2.82 g.) and ethyl bromide (1.98 g.) in dry ether (40 c.c.) was added slowly with stirring. As the reaction proceeded, a brown precipitate of the Grignard compound was formed. When the reaction had slackened, the mixture was refluxed for 2 hours, cooled and poured onto dry, powdered, solid carbon dioxide. After evaporation of the carbon dioxide the mixture was shaken with water (100 c.c.) containing concentrated hydrochloric acid (10 c.c.). No product was obtained from the residue on evaporation of the mixture by the action of methanolic hydrochloric acid and no starting material was recovered.

(b) The previous experiment was repeated, except that carbonation was carried out by treatment with liquid carbon dioxide under pressure. No product was obtained nor was any starting material recovered.

Reaction of 2:5-Dibromo-3-nitropyridine with Lithium.— (a) 2:5-Dibromo-3-nitropyridine (2.82 g.), lithium wire (0.30 g.) and dry ether (50 c.c.) were refluxed with stirring for five hours. No reaction took place nor did any take place on storing at 10° for 24 hours. The solution was decanted from the lithium, evaporated and the residue crystallised from light petroleum (40-60°) to give stout needles (2.80 g.), m.p.93°, alone or mixed with authentic 2:5-dibromo-3-nitropyridine.

(b) 2:5-Dibromo-3-nitropyridine (2.82 g.), lithium wire (0.30 g.) and dry toluene (50 c.c.) were refluxed with stirring for 10 hours. No reaction took place nor did any take place on storing at 10° for 24 hours. The solution was decanted from the lithium, evaporated and the residue crystallised from light petroleum (40-60°) to give stout needles (2.60 g.), m.p.93°, alone or mixed with authentic 2:5-dibromo-3-nitropyridine.

Reaction of 2:5-Dibromo-3-nitropyridine with n-Butyl lithium.— *n*-Butyl chloride (1 g.) (Org.Synth.,5,27) in dry ether (10 c.c.) was placed in a flask with a side neck for admitting dry nitrogen, the main neck being fitted with a 3-way adaptor, carrying a dropping funnel, a mercury sealed stirrer and a reflux condenser to the outlet of which was attached an oil bubbling device. Lithium wire (0.6 g.) was added, stirring was commenced and the flow of nitrogen set at about 2 bubbles per second. When the reaction had commenced, a solution of n-butyl chloride (2.7 g.) in dry ether (10 c.c.) was added dropwise, and when the reaction began to slacken, dry ether (10 c.c.) was added and the mixture refluxed for a further 2 hours. The solution was cooled to -35° and to it was added a solution of 2:5-dibromo-3-nitropyridine (4.2 g.) in dry ether (50 c.c.). After standing at -35° for 15 minutes, the solution was carbonated by pouring it onto dry powdered solid carbon dioxide. The carbon dioxide was allowed to evaporate and the mixture acidified by shaking with dilute hydrochloric acid. The ether layer was separated and the aqueous layer and solid material combined and evaporated. No product was obtained from the residue by the action of methanolic hydrochloric acid. The ether layer was evaporated and the residue crystallised from light petroleum (40-60°) to give stout needles (1.0 g.), m.p.93°, alone or mixed with authentic 2:5-dibromo-3-nitropyridine.

5-Bromo-3-nitropicolinonitrile (XLIX).— An intimate mixture of 2:5-dibromo-3-nitropyridine (2.82 g.) and cuprous cyanide (2.7 g.) (Org.Synth.,8,4) was heated on a metal-bath in a flask fitted with an air-cooled reflux condenser plugged at the top with cotton-wool. Reaction took place at 180°, a vacuum was applied and the heat source removed after 15 seconds. On cooling, the vacuum was released and the cotton-wool, apparatus and residue thoroughly washed with acetone. The residue obtained on evaporation of the washings was crystallised from benzene-light petroleum (40-60°) to give 5-bromo-3-nitropicolinonitrile (1.5 g.) as needles, m.p.102°.

Found: C,31.5; H,1.2; N,18.3%

$C_6H_2O_2N_3Br$ requires: C,31.6; H,0.9; N,18.4%

5-Bromo-3-nitropicolinamide (L).— 5-Bromo-3-nitropicolinonitrile (0.5 g.) and sulphuric acid (1 c.c.; d,1.84) were heated for 2 hours at 100°, diluted with water (10 c.c.) with cooling, and the precipitate collected, dried and crystallised from water to give 5-bromo-3-nitropicolinamide (0.3 g.) as needles, m.p.232-233° (decomp.).

Found: C,29.1; H,2.0; N,17.1%

$C_6H_4O_3N_3Br$ requires: C,29.3; H,1.6; N,17.1%

2-Amino-5-bromo-3-nitropyridine (XLII).— 5-Bromo-3-nitropicolinamide (12.1 g.) was added to a solution of bromine (9 g.) in water (500 c.c.) containing potassium hydroxide (35 g.) at 0° and shaken vigorously for 3 hours, warmed to 70° for 30 minutes and stored at 0° for 16 hours. The yellow precipitate was collected, dried and crystallised from ethyl acetate to give 2-amino-5-bromo-3-nitropyridine (7 g.) as yellow needles, m.p.205°, alone or mixed with a specimen prepared from 2-amino-5-bromopyridine.

Reaction of 5-Bromo-3-nitropicolinonitrile with Cuprous Cyanide.— (a) An intimate mixture of 5-bromo-3-nitropicolinonitrile (1.14 g.) and cuprous cyanide (0.9 g.) was heated on a metal-bath in a flask fitted with an air-cooled reflux condenser plugged at the top with cotton-wool. Reaction took place at 240°, a vacuum was applied and the heat source removed after 15 seconds. On cooling, the vacuum was released and the cotton-wool, apparatus and residue thoroughly washed with acetone. The residue obtained on evaporation of the washings was crystallised from benzene-light petroleum (40-60°) to give needles (0.6 g.), m.p.102°, alone or mixed with authentic 5-bromo-3-nitropicolinonitrile. No crystalline product was obtained from the mother liquors.

(b) 5-Bromo-3-nitropicolinonitrile (1.14 g.), cuprous cyanide (0.9 g.) and quinoline (10 c.c.) were refluxed for one hour, cooled, filtered and the residue extracted with ether (2 x 10 c.c.). The combined filtrate and extracts were shaken with water (25 c.c.) containing just enough hydrochloric acid to extract the quinoline from the ether layer. Evaporation of the ether layer gave a residue (0.1 g.) from which no crystalline material was obtained.

5-Bromo-2-chloro-3-nitropyridine (LII).— (a) 5-Bromo-3-nitro-2-pyridol (1.1 g.), phosphorus pentachloride (2 g.) and phosphoryl chloride (1.5 c.c.) were heated at 100° for 2 hours, decomposed with methanol (10 c.c.), water (40 c.c.) added, and the solid material collected, dried and extracted with light petroleum (50 c.c.; 60-80°). The residue obtained on evaporation was crystallised from ethanol (charcoal)-water to give 5-bromo-2-chloro-3-nitropyridine (0.5 g.) as prisms, m.p.68°.

Found: C,25.7; H,0.7%

$C_5H_2O_2N_2ClBr$ requires: C,25.3; H,0.8%

(b) (cf. Pieroni, Atti.accad.Lincei,1926,[6],2,125, who claims to have carried out this reaction but who gives no experimental details and gives neither analyses nor melting point for the product). To a mixture of 2-amino-5-bromo-3-nitropyridine (2.18 g.) and concentrated hydrochloric acid (10 c.c.) at 0° was added sodium nitrite (1.5 g.) in water (4 c.c.) slowly and with cooling and the mixture shaken for a further hour, after which time the solution was almost neutralised by the addition of aqueous sodium hydroxide (30%) with cooling. The solid which separated was collected, dried and crystallised from ethanol (charcoal)-water to give 5-bromo-2-chloro-3-nitropyridine (1.01 g.) as prisms, m.p.68°, alone or mixed with a specimen (a).

Found: C,25.6; H,1.0%

3-Amino-5-bromo-2-chloropyridine (LI).— (a) 5-Bromo-2-chloro-3-nitropyridine (1.7 g.), glacial acetic acid (12 c.c.) and iron filings (2.0 g.) were heated at 100° for 2 hours, diluted with water (15 c.c.) and a solution of sodium hydroxide (4 g.) in water (10 c.c.) added with cooling. The solid material was collected, dried and crystallised from acetone (charcoal)-water to give 3-amino-5-bromo-2-chloropyridine (1.0 g.) as needles, m.p. 131°. Light absorption in ethanol: Maxima at 2510 (ε = 7210) and 3120Å (ε = 4960).

Found: C,28.9; H,1.6; N,13.8%

$C_5H_4N_2ClBr$ requires: C,28.9; H,1.9; N,13.5%

(b) 2:5-Dibromo-3-nitropyridine (2.82 g.), concentrated hydrochloric acid (30 c.c.) and granulated tin (7 g.) were refluxed until all the tin had dissolved, evaporated and the residue dissolved in hot water (15 c.c.) and filtered. Aqueous sodium hydroxide (30 c.c.; 50%) was added with cooling and the precipitate collected, dried and extracted with hot benzene (100 c.c.). The residue on evaporation was crystallised from water (charcoal) to give 3-amino-5-bromo-2-chloropyridine (0.2 g.) as needles, m.p.131°, alone or mixed with a specimen (a). Light absorption in ethanol: Maxima at 2510 (ε = 7250) and 3140Å (ε = 4730).

Found: C,29.1; H,2.1%

5-Bromo-2:3-dichloropyridine (LIII).— 3-Amino-5-bromo-2-chloropyridine (0.3 g.) was dissolved in concentrated hydrochloric acid (10 c.c.), cooled to 0° and sodium nitrite (0.55 g.) in water (1.5 c.c.) added dropwise with good shaking. Copper powder (1.1 g.) was added and the mixture shaken for one hour and almost neutralised by the addition of aqueous sodium hydroxide (30%) with cooling. The solid was collected, dried and extracted with acetone, the residue on evaporation being shaken with light petroleum (5 c.c.; 40-60°) and filtered. The remaining residue (0.1 g.) had m.p.119-125° alone or mixed with authentic 3-amino-5-bromo-2-chloropyridine. The filtrate was evaporated and the residue crystallised from aqueous acetone to give 5-bromo-2:3-dichloropyridine (0.1 g.) as needles, m.p.30-31°.

Found: Cl + Br, 66.0%

$C_5H_2NCl_2Br$ requires: Cl + Br, 66.5%

2-Amino-5-chloropyridine (LIV).— (cf. Tschitschibabin and Jegorow, J.Russ.Phys.Chem.Soc.,1928,60,683). Chlorine was passed into 2-aminopyridine (4.53 g.) in ethanol (150 c.c.) at 0° until 6.7 g. had been absorbed. The ethanol was evaporated and the residue made alkaline with sodium carbonate and steam distilled. The crystals in the distillate were collected and the filtrate was saturated with hydrogen chloride, concentrated to small bulk and basified with aqueous sodium hydroxide (20%). The crystals were collected, combined with those previously obtained and extracted with boiling light petroleum (2 x 50 c.c.; 60-80°) leaving 2-amino-5-chloropyridine (2.6 g.) as a solid, m.p.135-136° (Tschitschibabin and Jegorow, ibid., give m.p.135-136°). The residue obtained on evaporation of the light petroleum extract was crystallised from aqueous ethanol, to give 2-amino-3:5-dichloropyridine (1.0 g.) as prisms, m.p. 80-81° (Tschitschibabin and Jegorow, ibid., give m.p.80-81°).

5-Chloro-2-nitraminopyridine (LXI).— (cf. Tschitschibabin and Jegorow, J.Russ.Phys.Chem.Soc.,1928,60,683). 2-Amino-5-chloropyridine (3.71 g.) was added slowly and with cooling to sulphuric acid (12 c.c.; d,1.84) followed by a mixture of nitric acid (1.95 c.c.; d,1.42) and sulphuric acid (2.1 c.c.; d,1.84) added dropwise with stirring below 20°. After stirring for a further hour at 15° the mixture was poured onto ice (150 g.) and the residue collected, dried and crystallised from ethyl acetate to give 5-chloro-2-nitraminopyridine (3.4 g.) as yellow needles, m.p.165-166° (decomp.) (Tschitschibabin and Jegorow, ibid., give m.p.159-160° (decomp.)).

2-Amino-5-chloro-3-nitropyridine (LXII).— (a) (cf. Tschitschibabin and Jegorow, J.Russ.Phys.Chem.Soc.,1928, 60,683). 5-Chloro-2-nitraminopyridine (1.5 g.) and sulphuric acid (4 c.c.; d,1.84) were heated at 100° for one hour, cooled, poured onto ice (50 g.) and made just alkaline with sodium hydroxide with cooling. The solid was collected, dried and crystallised from ethanol to give 2-amino-5-chloro-3-nitropyridine (0.4 g.) as long flat yellow prisms, m.p.196° (Tschitschibabin and Jegorow, ibid., give m.p.195-196°).

(b) 2-Amino-5-chloropyridine (3.71 g.) was added slowly and with cooling to sulphuric acid (12 c.c.; d,1.84) followed by a mixture of nitric acid (1.95 c.c.; d,1.42) and sulphuric acid (2.1 c.c.; d,1.84) added dropwise with stirring below 20°. After stirring for a further hour at 15° the mixture was heated at 100° for one hour, cooled, poured onto ice (150 g.) and made just alkaline with sodium hydroxide with cooling. The solid was collected, dried and crystallised from ethanol to give 2-amino-5-chloro-3-nitropyridine (2.0 g.) as long flat yellow prisms, m.p.196°, alone or mixed with a specimen (a).

5-Chloro-3-nitro-2-pyridol (LXV).— (a) To a cooled solution of 2-amino-5-chloro-3-nitropyridine (1.25 g.) in sulphuric acid (4 c.c.; d,1.84) and water (2.5 c.c.) was added sodium nitrite (1 g.) slowly and with stirring. After stirring for a further hour at 0° the reaction mixture was diluted with water (30 c.c.) with cooling and the orange precipitate collected, dried, and crystallised from ethanol to give 5-chloro-3-nitro-2-pyridol (1.18 g.) as yellow prisms, m.p.235°.

Found: C,34.7; H,1.5%

$C_5H_3O_3N_2Cl$ requires: C,34.4; H,1.7%

(b) 2-Amino-5-chloropyridine (3.71 g.) was added slowly and with cooling to sulphuric acid (12 c.c.; d,1.84) followed by a mixture of nitric acid (1.95 c.c.; d,1.42) and sulphuric acid (2.1 c.c.; d,1.84) added dropwise with stirring below 20°. After stirring for a further hour at 15° the reaction mixture was heated at 100° for one hour, cooled and water (10 c.c.) added with cooling followed by sodium nitrite (4.0 g.) keeping the temperature below 10°. After stirring for a further hour at 0° the mixture was diluted with water (100 c.c.) with cooling and the orange precipitate collected, dried and crystallised from ethanol to give 5-chloro-3-nitro-2-pyridol (2.0 g.) as yellow prisms, m.p.235°, alone or when mixed with a specimen (a).

2-Bromo-5-chloro-3-nitropyridine (LXVI).— 5-Chloro-3-nitro-2-pyridol (1.75 g.) was added to a mixture of phosphorus tribromide (5 g.) and bromine (1.6 g.) and heated at 100° for 5 hours. The reaction mixture was decomposed with methanol (10 c.c.), water (30 c.c.) added and the precipitate collected, dried and extracted with light petroleum (50 c.c.; 60-80°). The extract was evaporated and the residue crystallised from ethanol (charcoal)-water to give 2-bromo-5-chloro-3-nitropyridine (1.4 g.) as prisms, m.p.75°.

Found: C,25.8; H,0.8; N,11.4%

$C_5H_2O_2N_2ClBr$ requires: C,25.3; H,0.8; N,11.8%

3-Amino-2-bromo-5-chloropyridine (LXVII).— 2-Bromo-5-chloro-3-nitropyridine (1.7 g.), glacial acetic acid (12 c.c.) and iron filings (2 g.) were heated at 100° for 2 hours, diluted with water (15 c.c.) and partially neutralised by the addition of sodium hydroxide (4g.)

in water (10 c.c.) with cooling. The residue was collected, dried and crystallised from acetone (charcoal)-water to give 3-amino-2-bromo-5-chloropyridine (1.2 g.) as needles, m.p.142°. Light absorption in ethanol: Maxima at 2520 ($\mathcal{E}$= 11,500) and 3140Å ($\mathcal{E}$ = 5700).

Found: C,29.6; H,1.8%

$C_5H_4N_2ClBr$ requires: C,28.9; H,1.9%

3-Amino-2:5-dibromopyridine (LXVIII).— 2:5-Dibromo-3-nitropyridine (2 g.), glacial acetic acid (12 c.c.) and iron filings (2 g.) were heated at 100° for 2 hours, water (15 c.c.) was added and the mixture partially neutralised by the addition of a solution of sodium hydroxide (4 g.) in water (10 c.c.) with cooling. The solid material was collected, dried and crystallised from acetone (charcoal)-water to give 3-amino-2:5-dibromopyridine (1.5 g.) as needles, m.p.153°.

Found: C,24.2; H,1.3%

$C_5H_4N_2Br_2$ requires: C,23.8; H,1.6%

2:5-Dibromo-3-pyridol (LXIX).— 3-Amino-2:5-dibromopyridine (1.26 g.) was added to a solution of sodium nitrite (0.35 g.) in sulphuric acid (8 c.c.; d,1.84) at 20°, shaken for 30 minutes and diluted with water (25 c.c.) with cooling. The solution was heated gradually to 100° until no more nitrogen was evolved, cooled and partially neutralised by the addition of a solution of sodium hydroxide (11 g.) in water (20 c.c.) with cooling. The solid was collected, dried and extracted with acetone, the residue on evaporation of the extract being crystallised from aqueous methanol (charcoal) to give 2:5-dibromo-3-pyridol (0.6 g.) as needles, m.p.195-197°.

Found: C,24.1; H,1.2%

$C_5H_3ONBr_2$ requires: C,23.7; H,1.2%

3-Amino-5-bromo-2-chloropyridine (LI).— 3-Amino-2:5-dibromopyridine (0.5 g.) was refluxed with concentrated hydrochloric acid (10 c.c.) for 2 hours, evaporated and the residue crystallised from water (charcoal) to give 3-amino-5-bromo-2-chloropyridine (0.15 g.) as needles, m.p.131°, alone or mixed with a specimen prepared from 5-bromo-2-chloro-3-nitropyridine.

5-Bromo-3-nitro-2-pyridol (XLVII).— 2:5-Dibromo-3-nitropyridine (1 g.), concentrated hydrochloric acid (10 c.c.) and glacial acetic acid (10 c.c.) were refluxed for 3 hours, evaporated and the residue crystallised from ethyl acetate to give 5-bromo-3-nitro-2-pyridol (0.5 g.) as pale yellow needles, m.p.242° (decomp.), alone or mixed with a specimen prepared from 2-amino-5-bromo-3-nitropyridine.

Found: C,27.6; H,1.2%

Calc. for $C_5H_3O_3N_2Br$: C,27.4; H,1.4%

5-Chloro-3-nitro-2-pyridol (LXV).— 2-Bromo-5-chloro-3-nitropyridine (0.25 g.) was refluxed with concentrated hydrochloric acid (2.5 c.c.) and glacial acetic acid (2.5 c.c.) for 3 hours. The residue obtained on evaporation was crystallised from ethanol to give 5-chloro-3-nitro-2-pyridol (0.1 g.) as yellow prisms, m.p. 235°, alone or mixed with a specimen prepared from 2-amino-5-chloro-3-nitropyridine.

2:5-Dichloro-3-nitropyridine (LXXI).— (a) 5-Chloro-3-nitro-2-pyridol (0.87 g.), phosphorus pentachloride (2.0 g.) and phosphoryl chloride (1.5 c.c.) were heated at 100° for 2 hours, decomposed with methanol (10 c.c.), cooled to below 0° and water (40 c.c.) added slowly with shaking. The residue was collected, dried, extracted with light petroleum (50 c.c.; 60-80°) and the extract evaporated. The residue was crystallised from ethanol (charcoal)-water to give 2:5-dichloro-3-nitropyridine (0.5 g.) as prisms, m.p.43°.

Found: N,14.6%

$C_5H_2O_2N_2Cl_2$ requires: N,14.5%

(b) 2-Amino-5-chloro-3-nitropyridine (1.74 g.) was shaken with concentrated hydrochloric acid (20 c.c.) and cooled in ice and salt. A solution of sodium nitrite (1.5 g.) in water (4 c.c.) was added dropwise with good shaking and the mixture shaken for a further hour. The solution was almost neutralised by the addition of aqueous sodium hydroxide (30%) dropwise and with cooling and the precipitate collected, dried and crystallised from ethanol (charcoal)-water to give 2:5-dichloro-3-nitropyridine (1.3 g.) as prisms, m.p.43°, alone or mixed with a specimen (a).

3-Amino-2:5-dichloropyridine (LXX).— (a) 2:5-Dichloro-3-nitropyridine (1.35 g.), glacial acetic acid (12 c.c.) and iron filings (2.0 g.) were heated at 100° for 2 hours, diluted with water (15 c.c.) and partially neutralised by the addition of sodium hydroxide (4 g.) in water (10 c.c.) with cooling. The residue was collected, dried and crystallised from acetone (charcoal)-water to give 3-amino-2:5-dichloropyridine (1.0 g.) as long needles, m.p.128°.

Found: N,17.0%

$C_5H_4N_2Cl_2$ requires: N,17.2%

(b) 3-Amino-2-bromo-5-chloropyridine (0.5 g.) was refluxed with concentrated hydrochloric acid (10 c.c.) for two hours. The residue obtained on evaporation was crystallised from acetone-water to give 3-amino-2:5-dichloropyridine (0.2 g.) as long needles, m.p.129°, alone or mixed with a specimen (a).

2-Nitraminopyridine (LXXII).— (cf. Phillips, *J.*,1941,9). 2-Aminopyridine (54 g.) was added slowly and with cooling to sulphuric acid (240 c.c.; *d*,1.84) followed by a mixture of nitric acid (39 c.c.; *d*,1.42) and sulphuric acid (42 c.c.; *d*,1.84) added dropwise with stirring below 20°. After stirring for a further hour at 15° the mixture was poured onto ice (2500 g.) and the residue collected, dried and crystallised from ethanol to give 2-nitraminopyridine (60 g.) as needles, m.p.190° (decomp.) (Phillips, *ibid.*, gives m.p.190° (decomp.)).

2-Amino-3-nitropyridine (LXXIII) and 2-Amino-5-nitropyridine (LVI).— (cf. Phillips, *J.*,1941,9). (a) 2-Nitraminopyridine (60 g.) and sulphuric acid (200 c.c.; *d*,1.84) were heated gradually to 100° and maintained at this temperature for 30 minutes, cooled, poured onto ice (2000 g.) and made just alkaline with sodium hydroxide with cooling. The solid was collected, dried and crystallised once from acetone-ethanol to give a mixture of aminonitropyridines (48 g.). The mixture (10 g.) was crystallised from acetone-ethanol to give 2-amino-5-nitropyridine (3 g.) as yellow needles, m.p.187-188° (Tschitschibabin, *J.Russ.Phys.Chem.Soc.*,1914,*46*,1236, gives m.p.188°). Concentration of the mother liquor gave a crop (6 g.) from mother liquor A. 3 recrystallisations from acetone-ethanol gave additional 2-amino-5-nitropyridine (2 g.). The combined mother liquors with A, on concentration to 100 c.c. and cooling, gave 2-amino-3-nitropyridine (2 g.) as yellow needles, m.p.163° (Tschitschibabin, ibid., gives m.p.162°).

(b) 2-Aminopyridine (54 g.) was added slowly and with cooling to sulphuric acid (240 c.c.; d,1.84) followed by a mixture of nitric acid (39 c.c.; d,1.42) and sulphuric acid (42 c.c.; d,1.84) added dropwise with stirring below 20°. After stirring for a further hour at 15° the mixture was gradually heated to 100° and maintained at this temperature for 30 minutes, cooled, poured onto ice (2000 g.) and made just alkaline with sodium hydroxide with cooling. The solid was collected, dried and crystallised once from acetone-ethanol to give a mixture of aminonitropyridines (50 g.). The mixture (10 g.) was fractionally crystallised as before to give 2-amino-3-nitropyridine (1.5 g.) as yellow needles, m.p.163°, alone or mixed with a specimen (a), and 2-amino-5-nitropyridine (6 g.) as yellow needles, m.p.187-188°, alone or mixed with a specimen (a).

3-Nitro-2-pyridol (LXXVI).— (cf. Tschitschibabin and Bylinkin, J.Russ.Phys.Chem.Soc.,1920,50,471). To a cooled solution of 2-amino-3-nitropyridine (1.95 g.) in water (20 c.c.) and sulphuric acid (3 c.c.; d,1.84) was added ice (20 g.) followed by sodium nitrite (2 g.) in portions with stirring. After stirring for a further 30 minutes at 0°, the solid was collected, dried and crystallised from methanol to give 3-nitro-2-pyridol (0.7 g.) as yellow needles, m.p.224-225° (Tschitschibabin and Bylinkin, ibid., give m.p.224°). Light absorption in water: Maxima at 2580 ($\varepsilon = 2600$) and 3580Å ($\varepsilon = 7380$).

Found: N,20.4%

Calc. for $C_5H_4O_3N_2$: N,20.0%

Sodium 3-nitro-2-pyridolate (LXXVII).— 3-Nitro-2-pyridol (1.4 g.) was dissolved in hot water (10 c.c.) containing sodium hydroxide (0.5 g.). The solid which separated on cooling was collected, dried and crystallised from aqueous ethanol to give the monohydrate of sodium 3-nitro-2-pyridolate (0.9 g.) as fine yellow needles, m.p.340° (decomp.). Light absorption in water: Maxima at 2580 ($\varepsilon = 2400$) and 3600Å ($\varepsilon = 6600$).

Found: N,15.6%

$C_5H_3O_3N_2Na.H_2O$ requires: N,15.6%

2-Bromo-3-nitropyridine (LXXVIII).— 3-Nitro-2-pyridol (14 g.) was added to a mixture of phosphorus tribromide (50 g.) and bromine (16 g.) and heated at 100° for 5 hours. The reaction mixture was decomposed with methanol (100 c.c.) added dropwise with cooling, water (300 c.c.) added and the precipitate collected, dried and extracted several times with boiling benzene. The residue obtained on evaporation of the benzene was refluxed with light petroleum (2 x 150 c.c.; 60-80°) and filtered hot. The insoluble residue was crystallised from ethanol (charcoal)-water to give 2-bromo-3-nitropyridine (10 g.) as prisms, m.p.125°.

Found: C,30.0; H,1.7%

$C_5H_3O_2N_2Br$ requires: C,29.6; H,1.5%

On evaporation of the combined light petroleum extracts a residue was obtained which was shaken for a few seconds with boiling light petroleum (50 c.c.; 60-80°) and filtered hot. The crystals which separated on cooling were recrystallised several times from light petroleum (60-80°) to give a compound (2 g.) as pale yellow prisms, m.p.80°.

Found: C,23.1; H,1.0; N,10.8%

The compound (2 g.), glacial acetic acid (12 c.c.) and iron filings (2 g.) were heated at 100° for 2 hours, water (15 c.c.) was added and the mixture partially neutralised by the addition of a solution of sodium hydroxide (4 g.) in water (10 c.c.) with cooling. The solid material was collected and crystallised from acetone (charcoal)-water to give needles (1.1 g.), m.p. 153°, alone or when mixed with a specimen of 3-amino-2:5-dibromopyridine obtained from 2:5-dibromo-3-nitropyridine.

The compound (1 g.), concentrated hydrochloric acid (10 c.c.) and glacial acetic acid (10 c.c.) were refluxed for 3 hours, evaporated and the residue crystallised from water to give yellow needles (0.4 g.), m.p.241° (decomp.), alone or when mixed with a specimen of 5-bromo-3-nitro-2-pyridol obtained from 2-amino-5-bromo-3-nitropyridine.

3-Amino-2-bromopyridine (LXXIX).— 2-Bromo-3-nitropyridine (1.45 g.), glacial acetic acid (12 c.c.) and iron filings (2.0 g.) were heated at 100° for 2 hours, diluted with water (15 c.c.) and basified by the addition of 30% aqueous sodium hydroxide with cooling. The mixture was extracted with chloroform (50 c.c.), and the extract filtered and evaporated. Crystallisation of the residue from methanol (charcoal)-water gave 3-amino-2-bromopyridine (0.8 g.) as needles, m.p.79°.

Found: C,34.9; H,3.0%

$C_5H_5N_2Br$ requires: C,34.7; H,2.9%

3-Nitro-2-pyridol (LXXVI).— 2-Bromo-3-nitropyridine (1 g.), concentrated hydrochloric acid (10 c.c.) and glacial acetic acid (10 c.c.) were refluxed for 3 hours and the solution evaporated. The residue was crystallised from methanol to give 3-nitro-2-pyridol (0.5 g.) as pale yellow needles, m.p.224°, alone or mixed with a specimen obtained from 2-amino-3-nitropyridine.

2-Chloro-3-nitropyridine (LXXXI).— (a) 3-Nitro-2-pyridol (0.7 g.), phosphorus pentachloride (2.0 g.) and phosphoryl chloride (1.5 c.c.) were heated at 100° for two hours, decomposed with methanol (10 c.c.) and evaporated to dryness. The residue was shaken with water (10 c.c.) and the remaining residue collected, dried and crystallised from ethanol (charcoal)-water to give 2-chloro-3-nitropyridine (0.2 g.) as prisms, m.p.101°.

(b) (cf. Tschitschibabin and Bylinkin, *J.Russ.Phys.Chem. Soc.*,1920,*50*,471). 2-Amino-3-nitropyridine (1.39 g.) was shaken with concentrated hydrochloric acid (20 c.c.) and cooled in ice and salt. A solution of sodium nitrite (1.5 g.) in water (4 c.c.) was added dropwise with good shaking and the mixture shaken for a further hour. The solution was almost neutralised by the addition of 30% aqueous sodium hydroxide dropwise and with cooling and the precipitate collected, dried and crystallised from ethanol (charcoal)-water to give 2-chloro-3-nitropyridine (0.78 g.) as prisms, m.p.101°, alone or mixed with a specimen (a) (Tschitschibabin and Bylinkin, *ibid.*, give needles, m.p.101-102°, from water).

3-Amino-2-chloropyridine (LXXX).— (a) (cf. Schickh, Binz and Schulz, Ber.,1936,69,2593). 2-Chloro-3-nitropyridine (1.1 g.), glacial acetic acid (12 c.c.) and iron filings (2.0 g.) were heated at 100° for 2 hours, diluted with water (15 c.c.) and basified by the addition of 30% aqueous sodium hydroxide with cooling. The residue was filtered and crystallised from acetone (charcoal)-water to give 3-amino-2-chloropyridine (0.1 g.) as plates, m.p.79-80° (Schickh, Binz and Schulz, ibid., give crystals, m.p.80°, from benzene).

(b) 3-Amino-2-bromopyridine (1 g.) and concentrated hydrochloric acid (10 c.c.) were refluxed for 3 hours and the solution evaporated. The residue was dissolved in the minimum of water and basified by the addition of 30% aqueous sodium hydroxide with cooling. The solid material was collected, dried and crystallised from acetone (charcoal)-water to give 3-amino-2-chloropyridine (0.5 g.) as plates, m.p.78°, alone or when mixed with a specimen (a).

3-Amino-5-bromopicolinonitrile (LXXXIII).— An intimate mixture of 3-amino-2:5-dibromopyridine (2.52 g.) and cuprous cyanide (1.8 g.) was heated on a metal-bath in a flask fitted with an air-cooled reflux condenser plugged at the top with cotton-wool. Reaction took place at 180°;

a vacuum was applied and the heat source removed after 15 seconds. On cooling, the vacuum was released and the cotton-wool, apparatus and residue thoroughly washed with acetone. The residue obtained on evaporation of the washings was crystallised from benzene to give 3-amino-5-brompicolinonitrile (0.5 g.) as needles, m.p.175°.

Found: N,21.3%

$C_6H_4N_3Br$ requires: N,21.2%

3-Amino-5-bromopicolinamide (LXXXIV).— (a) 3-Amino-5-bromopicolinonitrile (0.05 g.) and sulphuric acid (0.1 c.c.; d,1.84) were heated at 100° for 2 hours. Water (0.5 c.c.) was added and the solution basified by the addition of 30% aqueous sodium hydroxide with cooling. The residue was collected, dried and extracted with acetone, the extract being evaporated to dryness and the residue crystallised from water to give 3-amino-5-bromopicolinamide (0.01 g.) as needles, m.p.168°.

Found: N,19.0%

$C_6H_6ON_3Br$ requires: N,19.4%

The acetone insoluble portion consisted of the dihydrate of the sodium salt of 5-bromo-3-hydroxypicolinamide (0.03 g.) as a microcrystalline powder, m.p.> 300°.

Found: C,25.6; H,2.5%

$C_6H_4O_2N_2BrNa.2H_2O$ requires: C,26.2; H,2.9%

(b) 5-Bromo-3-nitropicolinamide (1.75 g.), glacial acetic acid (12 c.c.) and iron filings (2 g.) were heated at 100° for 2 hours, diluted with water (15 c.c.) and partially neutralised by the addition of a solution of sodium hydroxide (4 g.) in water (10 c.c.) with cooling. The residue was collected, dried and extracted with acetone. The residue obtained on evaporation was crystallised from benzene-light petroleum (40-60°) to give 3-amino-5-bromopicolinamide (1.1 g.) as needles, m.p.168°, alone or when mixed with a specimen (a).

Reaction of 3-Amino-5-bromopicolinonitrile with Cuprous Cyanide.— (a) An intimate mixture of 3-amino-5-bromopicolinonitrile (1 g.) and cuprous cyanide (0.9 g.) was heated on a metal-bath in a flask fitted with an air-cooled reflux condenser plugged at the top with cotton-wool. The temperature was maintained at 250° for 5 minutes and on cooling, the residue was thoroughly extracted with acetone and the extract evaporated. The residue so obtained was crystallised from benzene to give needles (0.5 g.), m.p.175°, alone or mixed with authentic 3-amino-5-bromopicolinonitrile. No crystalline material was obtained from the mother liquors.

(b) 3-Amino-5-bromopicolinonitrile (1 g.), cuprous cyanide (0.9 g.) and quinoline (10 c.c.) were refluxed for one hour, cooled, filtered and the residue extracted with ether (2 x 10 c.c.). The combined filtrate and extracts were shaken with water (25 c.c.) containing just enough hydrochloric acid to extract the quinoline from the ether layer. Evaporation of the ether layer gave a residue (0.05 g.) from which no crystalline material was obtained.

5-Chloro-3-nitropicolinonitrile (LXXXVI).— An intimate mixture of 2-bromo-5-chloro-3-nitropyridine (1.2 g.) and cuprous cyanide (0.9 g.) was heated on a metal-bath in a flask fitted with an air-cooled reflux condenser plugged at the top with cotton-wool. Reaction took place at 210°, a vacuum was applied and the heat source removed after 15 seconds. On cooling, the vacuum was released and the cotton-wool, apparatus and residue thoroughly washed with acetone. The residue obtained on evaporation of the washings was crystallised from benzene-light petroleum (60-80°) to give 5-chloro-3-nitropicolinonitrile (0.3 g.) as needles, m.p.98°.

Found: C,39.6; H,0.9; N,23.0%

$C_6H_2O_2N_3Cl$ requires: C,39.3; H,1.1; N,22.9%

3-Amino-5-chloropicolinonitrile (LXXXVII).— An intimate mixture of 3-amino-2-bromo-5-chloropyridine (2.0 g.) and cuprous cyanide (2.0 g.) was heated on a metal-bath in a flask fitted with an air-cooled reflux condenser plugged at the top with cotton-wool. Reaction took place at 170°, a vacuum was applied and the heat source removed after 15 seconds. On cooling the vacuum was released and the cotton-wool, apparatus and residue washed thoroughly with acetone. The residue obtained on evaporation of the washings was crystallised from benzene to give 3-amino-5-chloropicolinonitrile (0.3 g.) as needles, m.p.175°.

Found: C,47.0; H,2.4%

$C_6H_4N_3Cl$ requires: C,46.9; H,2.6%

5-Chloro-3-nitropicolinamide (LXXXVIII).— 5-Chloro-3-nitropicolinonitrile (0.25 g.) and sulphuric acid (0.5 c.c.; d,1.84) were heated at 100° for 2 hours, water (5 c.c.) was added with cooling and the precipitate collected, dried and crystallised from acetone-water to give 5-chloro-3-nitropicolinamide (0.15 g.) as needles, m.p.230°.

Found: C,35.5; H,2.0; N,20.7%

$C_6H_4O_3N_3Cl$ requires: C,35.7; H,2.0; N,20.8%

3-Amino-5-chloropicolinamide (LXXXIX).— (a) 3-Amino-5-chloropicolinonitrile (0.04 g.) and sulphuric acid (0.08 c.c.; d,1.84) were heated at 100° for 2 hours. Water (0.4 c.c.) was added and the solution basified by the addition of 30% aqueous sodium hydroxide with cooling.

The residue was collected, dried and extracted with acetone, the extract being evaporated to dryness and the residue crystallised from water to give 3-amino-5-chloropicolinamide (0.005 g.) as needles, m.p.168°.

Found: C,41.8; H,3.5; N,24.4%

$C_6H_6ON_3Cl$ requires: C,42.0; H,3.5; N,24.5%

The acetone insoluble portion consisted of the dihydrate of the sodium salt of 5-chloro-3-hydroxypicolinamide (0.03 g.) as a microcrystalline powder, m.p. 300°.

Found: C,31.0; H,3.7; N,11.8; Cl,15.6%

$C_6H_4O_2N_2ClNa.2H_2O$

requires: C,31.2; H,3.5; N,12.2; Cl,15.4%

(b) 5-Chloro-3-nitropicolinamide (1.4 g.), glacial acetic acid (12 c.c.) and iron filings (2.0 g.) were heated at 100° for 2 hours, diluted with water (15 c.c.) and partially neutralised by the addition of sodium hydroxide (4 g.) in water (10 c.c.) with cooling. The residue was collected, dried and crystallised from acetone (charcoal)-water to give 3-amino-5-chloropicolinamide (0.8 g.) as needles, m.p.168°, alone or mixed with a specimen (a).

Reaction of 5-Chloro-3-nitropicolinonitrile with Cuprous Cyanide.— (a) An intimate mixture of 5-chloro-3-nitropicolinonitrile (0.9 g.) and cuprous cyanide (0.9 g.) was heated on a metal-bath in a flask fitted with an air-cooled reflux condenser plugged at the top with cotton-wool. The temperature was maintained at 250° for 5 minutes and on cooling, the residue was thoroughly extracted with acetone and the extract evaporated. The residue so obtained was crystallised from benzene-light petroleum (60-80°) to give needles (0.3 g.), m.p.98°, alone or mixed with authentic 5-chloro-3-nitropicolinonitrile. No crystalline material was obtained from the mother liquors.

(b) 5-Chloro-3-nitropicolinonitrile (0.9 g.), cuprous cyanide (0.9 g.) and quinoline (10 c.c.) were refluxed for 1 hour, cooled, filtered and the residue extracted with ether (2 x 10 c.c.). The combined filtrate and extracts were shaken with water (25 c.c.) containing just enough hydrochloric acid to extract the quinoline from the ether layer. Evaporation of the ether layer gave a residue (0.1 g.) from which no crystalline material was obtained.

<u>Reaction of 3-Amino-5-chloropicolinonitrile with Cuprous Cyanide</u>.— (a) An intimate mixture of 3-amino-5-chloropicolinonitrile (0.8 g.) and cuprous cyanide (0.9 g.) was heated on a metal-bath in a flask fitted with an air-

cooled reflux condenser plugged at the top with cotton-wool. The temperature was maintained at 250° for 5 minutes and on cooling, the residue was extracted with acetone and the extract evaporated. The residue so obtained was crystallised from benzene to give needles (0.5 g.), m.p.175°, alone or mixed with authentic 3-amino-5-chloropicolinonitrile. No crystalline material was obtained from the mother liquors.

(b) 3-Amino-5-chloropicolinonitrile (0.8 g.), cuprous cyanide (0.9 g.) and quinoline (10 c.c.) were refluxed for 1 hour, cooled, filtered and the residue extracted with ether (2 x 10 c.c.). The combined filtrate and extracts were shaken with water (25 c.c.) containing just enough hydrochloric acid to extract the quinoline from the ether layer. Evaporation of the ether layer gave a residue (0.05 g.) from which no crystalline material was obtained.

3-<u>Nitropicolinonitrile</u> (XCI).— An intimate mixture of 2-bromo-3-nitropyridine (0.75 g.) and cuprous cyanide (0.7 g.) was heated on a metal-bath in a flask fitted with an air-cooled reflux condenser plugged at the top with cotton-wool. Reaction took place at 150°, a vacuum was applied and the heat source removed after 15 seconds. On cooling, the vacuum was released and the cotton-wool, apparatus and residue thoroughly washed with acetone. The residue obtained on evaporation of the washings was crystallised from benzene-light petroleum (60-80°) to give 3-nitropicolinonitrile (0.3 g.) as prisms, m.p.78°.

Found: C,47.9; H,2.3%

$C_6H_3O_2N_3$ requires: C,48.3; H,2.0%

3-Aminopicolinonitrile (XCII).— An intimate mixture of 3-amino-2-bromopyridine (1.73 g.) and cuprous cyanide (1.8 g.) was heated on a metal-bath in a flask fitted with an air-cooled reflux condenser plugged at the top with cotton-wool. Reaction took place at 160°, a vacuum was applied and the heat source removed after 15 seconds. On cooling, the vacuum was released and the cotton-wool, apparatus and residue thoroughly washed with acetone. The residue obtained on evaporation of the washings was crystallised from benzene to give 3-aminopicolinonitrile (0.3 g.) as needles, m.p.147°. The product was further purified by sublimation at $80°/10^{-4}$mm. to give a sublimate, m.p.149°.

Found: C,60.4; H,4.5%

$C_6H_5N_3$ requires: C,60.5; H,4.2%

3-Nitropicolinamide (XCIII).— 3-Nitropicolinonitrile (0.1 g.) and sulphuric acid (0.2 c.c.; *d*,1.84) were heated at 100° for 2 hours. Water (2 c.c.) was added with cooling and the precipitate was collected, dried and crystallised from acetone-water to give 3-nitropicolinamide (0.05 g.) as needles, m.p.209°. The product was further purified by sublimation at 100°/10^{-5}mm. to give a sublimate, m.p.211°.

Found: C,43.5; H,3.0%

$C_6H_5O_3N_3$ requires: C,43.1; H,3.0%

3-Aminopicolinamide (XCIV).— (a) 3-Aminopicolinonitrile (0.12 g.) and sulphuric acid (0.24 c.c.; d,1.84) were heated at 100° for 2 hours. Water (1 c.c.) was added and the solution basified by the addition of 30% aqueous sodium hydroxide with cooling. The residue was collected, dried and extracted with acetone, the extract being evaporated to dryness and the residue crystallised from water to give 3-aminopicolinamide (0.01 g.) as needles, m.p.175°. The product was further purified by sublimation at 100°/10^{-5}mm. to give a sublimate, m.p.175-177°.

Found: C,52.0; H,5.0%

$C_6H_7ON_3$ requires: C,52.5; H,5.1%

The acetone insoluble portion consisted of the dihydrate of the sodium salt of 3-hydroxypicolinamide (0.03 g.) as a microcrystalline powder, m.p.$>$300°.

Found: C,36.2; H,4.2%

$C_6H_5O_2N_2Na.2H_2O$ requires: C,36.7; H,4.6%

(b) 3-Nitropicolinamide (0.02 g.), glacial acetic acid (0.12 c.c.) and iron filings (0.02 g.) were heated together at 100° for 2 hours. On cooling, the mixture was diluted with water (0.15 c.c.) and partially neutralised by the addition of a solution of sodium hydroxide (0.04 g.) in water (0.10 c.c.), cooled and the solid material collected, dried and extracted with acetone (20 c.c.). The residue obtained on evaporation was crystallised from water to give 3-aminopicolinamide (0.01 g.) as needles, m.p.174-175°, alone or when mixed with a specimen (a).

2-Pyridol (XCVII).— (cf. Tschitschibabin and Schapiro, J.Russ.Phys.Chem.Soc.,1921,53,233). 2-Aminopyridine (16 g.) was dissolved in water (68 c.c.) and sulphuric acid (6.5 c.c.; d,1.84) and sodium nitrite (18 g.) added slowly and with stirring below 0°. After keeping for one hour at 15°, the reaction mixture was boiled for 15 minutes, cooled and taken to pH5 with sodium carbonate. The residue obtained on evaporation was extracted with boiling chloroform (2 x 100 c.c.), the extract evaporated and the residue crystallised from benzene to give 2-pyridol (12 g.) as pale yellow prisms, m.p.106°, which sublimed at 100°/10^{-2}mm. to give a sublimate, m.p.108° (Tschitschibabin and Schapiro, *ibid*., give m.p.106-107°). Light absorption in water: Maxima at 2200 (ε = 7000) and 2940Å (ε = 5700) (Specker and Gawrosch, *Ber*.,1942,*75*,1342, give light absorption in methanol: Maxima at 2270 (ε = 10,000) and 2970Å (ε = 6300)).

Sodium 2-*pyridolate* (XCVI).— (a) 2-Pyridol (1.0 g.) was dissolved in hot water (5 c.c.) containing sodium hydroxide (1.0 g.). The solid which separated on cooling was collected, dried and crystallised from ethanol to give the *monohydrate* of sodium 2-pyridolate (0.5 g.) as plates, m.p.330°. (Tschitschibabin and Szokow, *Ber*.,1925,*56*,2650 claim to have obtained sodium 2-pyridolate as a dihydrate). Light absorption in water: Maxima at 2200 (ε = 5600) and 2940Å (ε = 4700).

Found: N,10.4%

$C_5H_4ONNa.H_2O$: N,10.4%

(b) (cf. Tschitschibabin and Rjasanzew, *J*.*Russ*.*Phys*.*Chem*.*Soc*.,1915,*47*,1571). 2-Aminopyridine (94 g.) was dissolved in water (800 c.c.) and sulphuric acid (110 c.c.; *d*,1.84) and a solution of sodium nitrite (100 g.) in water (250 c.c.) added slowly below the surface with stirring below 5°. After stirring for a further hour at 0° the reaction mixture was basified by the addition of a solution of sodium hydroxide (250 g.) in water (750 c.c.) with cooling, the solid which separated being collected, dried and crystallised from ethanol to give the monohydrate of sodium 2-pyridolate (59 g.) as plates, m.p.330°, alone or mixed with a specimen (a).

Methyl coumalate (XL).— (cf. Pechmann, Ber.,1884,17, 936). Malic acid (40 g.) was added slowly to a mixture of sulphuric acid (60 g.; d,1.84) and oleum (60 g.; 20% free SO_3) and heated at 100° for 4 hours. Methanol (42 g.) was added and the heating continued for 3 hours. The solution was poured onto ice (300 g.), sodium carbonate was added until sodium sulphate began to precipitate and the mixture extracted with ether (4 x 200 c.c.). The extract was dried (Na_2SO_4) and the ether evaporated to give a residue of crude methyl coumalate (13.6 g.) as a yellow solid, m.p.60-70° (Pechmann, ibid., gives m.p.74°).

6-Hydroxynicotinic acid (XXXVII).— (a) (cf. Tschitschibabin and Kirssanow, Ber.,1924,57,1161). Sodium 2-pyridolate (29 g.) (dried to constant weight at 110°) was heated at 200° for 1 hour in carbon dioxide at 20-30 atmospheres, dissolved in hot water (100 c.c.) and the solution acidified with sulphuric acid (50%). The solid which separated on storing at 0° for 24 hours was collected, dried and crystallised from water (charcoal) to give 6-hydroxynicotinic acid (1.5 g.) as a microcrystalline powder, m.p.302-303° (decomp.). (Tschitschibabin and Kirssanow, ibid., give needles, m.p.304° (decomp.), from water).

(b) (cf. Pechmann and Welsh, Ber.,1884,17,2384). Methyl coumalate (12 g.) was added to aqueous ammonia (50 c.c.; 15%) with cooling, shaken for 10 minutes and a solution of sodium hydroxide (15 g.) in water (60 c.c.) added. The mixture was heated to boiling for 10 minutes, cooled and acidified with concentrated hydrochloric acid with cooling. The solid which separated on storing at 0° for 24 hours was collected, dried and crystallised from water (charcoal) to give 6-hydroxynicotinic acid (6.3 g.) as a microcrystalline powder, m.p.302° (decomp.), alone or mixed with a specimen (a). (Pechmann and Welsh, ibid., give needles, m.p.303° (decomp.) from water).

Methyl 6-chloronicotinate (XCVIII).— (cf. Reissert, Ber.,1895,28,119). 6-Hydroxynicotinic acid (3.0 g.) and phosphoryl chloride (5 c.c.) were heated at 100° for $2\frac{1}{2}$ hours, evaporated and the residue decomposed with methanol (20 c.c.). The reaction mixture was refluxed for 10 minutes, cooled and poured into water (50 c.c.), the solid which separated being collected, dried and crystallised once from light petroleum (60-80°) and then from aqueous methanol to give methyl 6-chloronicotinate (2.3 g.) as plates, m.p.83° (Reissert, _ibid_., gives plates, m.p.86-89°, from aqueous ethanol).

Found: C,49.4; H,3.5%

Calc. for $C_7H_6O_2NCl$: C,49.0; H,3.5%

6-_Chloronicotinamide_ (LX).— (a) Methyl 6-chloronicotinate (0.25 g.) and aqueous ammonia (3 c.c.; _d_,0.88) were shaken for 5 hours, diluted with water (12 c.c.) and the solid collected, dried and crystallised from spirit (charcoal) to give 6-chloronicotinamide (0.15 g.) as rectangular plates, m.p.212-213°.

(b) (cf. Forrest and Walker, _J_.,1948,1939). 6-Hydroxynicotinic acid (30 g.) and phosphoryl chloride (50 c.c.) were heated at 100° for $2\frac{1}{2}$ hours, evaporated and the residue dissolved in acetone (50 c.c.) and added to aqueous ammonia (100 c.c.; _d_,0.88) slowly and with cooling. After standing at 0° for 30 minutes, water (300 c.c.) was added and the solid material collected, dried and crystallised from spirit (charcoal) to give 6-chloronicotinamide (20 g.) as rectangular plates, m.p.212-214°, alone or mixed with a specimen (a). (Forrest and Walker, _ibid_., give rectangular plates, m.p.208°, from spirit;

Mills and Widdows, J.,1908,1372 give long needles, m.p, 210-211°, from water for the product obtained by the same method).

6-Aminonicotinamide (XXXVI).— (a) (cf. Caldwell, Tyson and Lauer, J.A.C.S.,1944,66,1479). 6-Chloronicotinamide (0.5 g.), aqueous ammonia (5 c.c.; d,0.88) and sodium iodide (0.05 g.) were heated at 150-160° for 4-5 hours. The solution was evaporated and the residue crystallised from aqueous ethanol to give 6-aminonicotinamide (0.2 g.) as a microcrystalline powder, m.p.200° (Caldwell, Tyson and Lauer, ibid., give a microcrystalline powder, m.p.200°, from aqueous ethanol).

(b) Methyl 6-chloronicotinate (0.5 g.), aqueous ammonia (5 c.c.; d,0.88) and sodium iodide (0.05 g.) were shaken for 5 hours and heated at 150-160° for 4-5 hours. The solution was evaporated and the residue crystallised from aqueous ethanol to give 6-aminonicotinamide (0.25 g.) as a microcrystalline powder, m.p.200°, alone or mixed with a specimen (a).

6-Chloronicotinic acid (C).— (cf. Pechmann and Welsh, Ber.,1884,17,2384). 6-Hydroxynicotinic acid (13.9 g.) and phosphoryl chloride (5 c.c.) were heated to 120-130° and phosphorus pentachloride (60 g.) added during 10 minutes. After heating for a further 5 minutes the mixture was cooled and decomposed with ice (200 g.). The solid was collected, dried and crystallised from water to give 6-chloronicotinic acid (14.5 g.) as prismatic needles, m.p.196-197° (Pechmann and Welsh, *ibid.*, give plates, m.p.199°, from water).

Found: C,46.2; H,2.4%

Calc. for $C_6H_4O_2NCl$: C,45.7; H,2.6%

6-*Aminonicotinic acid* (XCIX).— (a) (cf. Caldwell, Tyson and Lauer, *J.A.C.S.*,1944,*66*,1479). 6-Aminonicotinamide (0.5 g.) and aqueous sodium hydroxide (5 c.c.; 10%) were refluxed until all the solid had dissolved, cooled and acidified with glacial acetic acid to give a precipitate of 6-aminonicotinic acid (0.3 g.) as a microcrystalline powder, m.p.312° (Caldwell, Tyson and Lauer, *ibid.*, give m.p.312°).

(b) (cf. Marckwald, *Ber.*,1894,*27*,1317). 6-Chloronicotinic acid (7.0 g.) and aqueous ammonia (50 c.c.; *d*,0.88) were heated at 170° for 7 hours. The residue obtained on evaporation was dissolved in dilute sodium hydroxide solution, filtered and acidified with glacial acetic acid to give a precipitate of 6-aminonicotinic acid (5.0 g.) as a microcrystalline powder, m.p.309-311°, alone or mixed with a specimen (a). (Marckwald, *ibid.*, gives m.p.> 300°).

6-Amino-5-nitronicotinic acid (CII).— (cf. Räth and Prange, Annalen, 1929, 467, 1). (a) To a stirred solution of 6-aminonicotinic acid (1.0 g.) in sulphuric acid (2.5 c.c.; d, 1.84) was added a mixture of nitric acid (0.5 c.c.; d, 1.42) and sulphuric acid (0.5 c.c.; d, 1.84) dropwise and with cooling. After stirring for 3 hours the solution was poured into water (50 c.c.) and the precipitated solid collected, dried and crystallised from water to give 6-nitraminonicotinic acid (0.8 g.) as small prisms, m.p.233° (decomp.) (Räth and Prange, ibid., give m.p.233° (decomp.)).

The compound (0.5 g.) was dissolved with cooling in sulphuric acid (1.5 c.c.; d, 1.84) and gradually heated to 100° during $1\frac{1}{2}$ hours. The solution was cooled, water (5 c.c.) was added and the filtrate diluted with water (5 c.c.) and almost neutralised with aqueous sodium hydroxide (30%) with cooling. The solid was collected, dried and crystallised from dilute acetic acid to give 6-amino-5-nitronicotinic acid (0.15 g.) as small yellow needles, m.p.297-298° (decomp.) (Räth and Prange, ibid., give needles, m.p.300-301° (decomp.), from water).

(b) To a suspension of 6-aminonicotinic acid (1.0 g.) in water (2 c.c.) containing 2 drops of phenolphthalein was added a slight excess of aqueous sodium hydroxide (10%). Nitric acid (d, 1.42) was added to the filtrate until no further material precipitated. The solid was collected and dried to give 6-aminonicotinic acid nitrate (1.1 g.) as a microcrystalline powder, m.p.242° (decomp.) (Räth and Prange, _ibid_., give m.p.242° (decomp.)).

The compound (1.0 g.) was dissolved in sulphuric acid (2.5 c.c.; _d_,1.84) with cooling and gradually heated to 105° during 2 hours. The solution was cooled, poured onto ice-water (15 g.) and almost neutralised with aqueous sodium hydroxide (30%) with cooling. The solid was collected, dried and crystallised from dilute acetic acid to give 6-amino-5-nitronicotinic acid (0.3 g.) as small yellow needles, m.p.298-299° (decomp.) alone or mixed with a specimen (a) (Räth and Prange, _ibid_., give needles, m.p.296° (decomp.), from water).

5:6-_Diaminonicotinic_ _acid_ (CIV).— (cf. Räth and Prange, _Annalen_,1929,_467_,1). 6-Amino-5-nitronicotinic acid (1.5 g.), concentrated hydrochloric acid (18 g.) and granulated tin (4.4 g.) were refluxed until all the tin had dissolved. The residue obtained on evaporation was dissolved in water (50 c.c.) and the solution detinned electrolytically. The solution was evaporated and the residue dissolved in aqueous ammonia (15%) and acidified with glacial acetic acid with cooling. The precipitate was collected and dried to give the monohydrate of 5:6-

diaminonicotinic acid (0.7 g.) as an amorphous grey powder, m.p.> 310°.

Action of Nitrous Acid on 5:6-Diaminonicotinic acid.— (cf. Marckwald, Ber.,1894,27,1317). To a cooled solution of 5:6-diaminonicotinic acid (0.06 g.) in hydrochloric acid (2.0 c.c.; 15%) was added sodium nitrite with shaking until free nitrous acid was detected. The solution was almost neutralised by aqueous sodium hydroxide (10%) and the precipitate collected and dried at 100° over phosphorus pentoxide in vacuo to give the triazine derivative of 5:6-diaminonicotinic acid (0.01 g.) as needles, m.p.270° (decomp.).

Found: N,34.5%

Calc. for $C_6H_4O_2N_4$: N,34.1%

6-Hydroxy-5-nitronicotinic acid (CVI).— (a) (cf. Räth and Prange, Annalen,1929,467,1). 6-Amino-5-nitronicotinic acid (0.4 g.) and aqueous sodium hydroxide (8 c.c.; 10%) were heated at 100° for 2 hours. The solution was acidified with concentrated hydrochloric acid with cooling and the precipitate collected, dried and crystallised from water (charcoal) to give 6-hydroxy-5-nitronicotinic acid (0.1 g.) as yellow prisms, m.p.279-280° (decomp.) (Räth and Prange, ibid., give needles, m.p.277° (decomp.) from water). Light absorption in water: Maxima at 2110 (ε = 18,300) and 3600Å (ε = 7430).

(b) 6-Hydroxynicotinic acid (50 g.) was dissolved in nitric acid (500 c.c.; d,1.52) with cooling and the solution kept at 45-50° for 4 hours. The mixture was evaporated below 45° and the residue crystallised from water to give 6-hydroxy-5-nitronicotinic acid (20 g.) as yellow needles, m.p.278° (decomp.) alone or mixed with a specimen (a). Light absorption in water: Maxima at 2110 (ε = 19,200) and 3600Å (ε = 7900).

Found: C,39.1; H,2.3; N,15.2%

Calc. for $C_6H_4O_5N_2$: C,39.1; H,2.2; N,15.2%

Methyl 6-hydroxy-5-nitronicotinate (CVII, R = Me).— Dry hydrogen chloride was passed into a solution of 6-hydroxy-5-nitronicotinic acid (1 g.) in methanol (50 c.c.) for 30 minutes and the mixture refluxed for 2 hours, evaporated and the residue crystallised from methanol to give methyl 6-hydroxy-5-nitronicotinate (0.7 g.) as pale yellow needles, m.p.206°.

Found: C,42.5; H,2.8; N,14.1%

$C_7H_6O_5N_2$ requires: C,42.4; H,3.1; N,14.1%

Ethyl 6-hydroxy-5-nitronicotinate (CVII, R = Et).—

(a) 6-Hydroxy-5-nitronicotinic acid (1 g.) and phosphoryl chloride (5 c.c.) were heated at 100° for 3 hours, evaporated and the residue decomposed with ethanol (10 c.c.). The residue on evaporation was crystallised from benzene to give ethyl 6-hydroxy-5-nitronicotinate (0.6 g.) as long pale yellow needles, m.p.165-167°.

Found: C,45.4; H,3.8; N,13.4%

$C_8H_8O_5N_2$ requires: C,45.3; H,3.8; N,13.2%

(b) Dry hydrogen chloride was passed into a solution of 6-hydroxy-5-nitronicotinic acid (1 g.) in ethanol (50 c.c.) for 30 minutes and the mixture refluxed for 2 hours, evaporated and the residue crystallised from benzene to give ethyl 6-hydroxy-5-nitronicotinate (0.8 g.) as long pale yellow needles, m.p.165-167°, alone or mixed with a specimen (a).

5-Nitro-2-pyridol (CXI).— (cf. Phillips, *J.*,1941,9). A mixture of aminonitropyridines (19.6 g.) (*vide supra*) was dissolved in water (200 c.c.) and sulphuric acid (32 c.c.; *d*,1.84) and ice (200 g.) added. Sodium nitrite (20 g.) was added with stirring and the mixture stirred for a further 30 minutes. The precipitate was collected, dried and crystallised from water to give 5-nitro-2-pyridol (12 g.) as prismatic needles, m.p. 190° (Phillips, *ibid*., gives m.p.180°; Tschitschibabin and Schapiro, *J.Russ.Phys.Chem.Soc.*,1921,*53*,233, give m.p.188° for this product obtained by the nitration of 2-pyridol; Räth and Prange, *Ber.*,1925,*58*,1208, give long needles, m.p.191-192°, from water for the compound obtained by the hydrolysis of 2-nitramino-5-nitropyridine with sodium hydroxide and acidification of the sodium salt thus obtained). Light absorption in water: Maxima at 2040 (ε = 12,330) and 3020Å (ε = 10,900).

Found: C,43.2; H,2.5; N,19.7%

Calc. for $C_5H_4O_3N_2$: C,42.9; H,2.9; N,20.0%

Sodium 5-nitro-2-pyridolate (CXII).— 5-Nitro-2-pyridol (1.4 g.) was dissolved in hot water (10 c.c.) containing sodium hydroxide (0.5 g.). The solid which separated on cooling was crystallised from aqueous ethanol to give the trihydrate of sodium 5-nitro-2-pyridolate (0.8 g.) as stout yellow needles, m.p.318° (decomp.)(Räth and Prange, Ber.,1925,58,1208, give yellow needles, m.p.303° (decomp.), from water). Light absorption in water: Maxima at 2060 (ε = 9100) and 3020Å (ε = 10,500).

Found: N,13.2%

Calc. for $C_5H_3O_3N_2Na.3H_2O$: N,13.0%

2-Amino-3:5-dinitropyridine (CIX).— A mixture of aminonitropyridines (8 g.) (vide supra) was added with cooling to sulphuric acid (24 c.c.; d,1.84) followed by a mixture of nitric acid (3.9 c.c.; d,1.42) and sulphuric acid (4.2 c.c.; d,1.84) added with stirring below 10°. After stirring for 1 hour at 15°, the mixture was heated for 1 hour at 65° and finally for 15 minutes at 150°. The cooled solution was poured onto ice (150 g.) and the precipitate collected, dried and crystallised from ethanol to give 2-amino-3:5-dinitropyridine (1.6 g.) as long yellow needles, m.p.189° (Tschitschibabin and Kirssanow, Ber.,1928,61,1223, give yellow needles, m.p.190-191°, from ethanol; Tschitschibabin and Rasorenow, J.Russ.Phys.Chem.Soc.,1915,47,1286, give yellow needles, m.p.191-192°).

Found: C,33.0; H,2.5%

Calc. for $C_5H_4O_4N_4$: C,32.6; H,2.2%

Evaporation of the mother liquors and crystallisation of the residue from water gave 5-nitro-2-pyridol (3.6 g.) as prismatic needles, m.p.187°, alone or when mixed with a specimen prepared from aminonitropyridines by nitrous acid.

3:5-Dinitro-2-pyridol (CVIII).— (a) 6-Hydroxynicotinic acid (2 g.) in nitric acid (20 c.c.; d,1.52) was refluxed for 30 hours. The residue obtained on evaporation was crystallised from water to give 3:5-dinitro-2-pyridol (1.0 g.) as stout yellow needles, m.p.175°. Light absorption in water: Maxima at 2140 (ε = 13,400) and 3260Å (ε = 11,400).

Found: C,32.8; H,1.9; N,22.9%

$C_5H_3O_5N_3$ requires: C,32.4; H,1.6; N,22.7%

(b) 6-Hydroxy-5-nitronicotinic acid (1 g.) in nitric acid (10 c.c.; d,1.52) was refluxed for 30 hours. The residue obtained on evaporation was crystallised from water to give 3:5-dinitro-2-pyridol (0.5 g.) as stout yellow needles, m.p.175°, alone or mixed with a specimen (a).

(c) Dry sodium nitrite (0.7 g.) was slowly added to sulphuric acid (15 c.c.; d,1.84) with shaking and gentle heating to complete solution. The solution was cooled to 30° and treated with 2-amino-3:5-dinitropyridine (0.92 g.) added in portions with stirring. The reaction mixture was then stirred for 2 hours during which time the temperature fell to 10°. The reaction mixture was diluted with water (20 c.c.), kept at 10° for 30 minutes and then treated with a solution of sodium hydroxide (15 g.) in water (30 c.c.). After shaking for 30 minutes at 30° the solid was collected dried and crystallised from water to give 3:5-dinitro-2-pyridol (0.8 g.) as pale yellow needles, m.p.174-175°, alone or mixed with a specimen (a). Light absorption in water: Maxima at 2140 (ε = 12,470) and 3320Å (ε = 11,130).

Found: C,32.7; H,1.6; N,23.0%

(d) 3-Nitro-2-pyridol (1 g.) was refluxed with nitric acid (10 c.c.; d,1.52) for 2 hours. The residue obtained on evaporation was crystallised from water to give 3:5-dinitro-2-pyridol (0.3 g.) as pale yellow prismatic needles, m.p.175°, alone or mixed with a specimen (a). Light absorption in water: Maxima at 2120 (ε = 13,400) and 3300Å (ε = 11,400).

Found: C,32.5; H,1.6%

(e) 3-Nitro-2-pyridol (7 g.) was dissolved in sulphuric acid (9.5 c.c.; d,1.84) and a mixture of nitric acid (5.0 c.c.; d,1.52) and sulphuric acid (4.8 c.c.; d,1.84) added dropwise with shaking. The temperature was raised gradually to 100° and maintained at this temperature for 1 hour. The cooled mixture was poured onto ice (40 g.) and aqueous sodium hydroxide (7 c.c.; 40%) added. The precipitate was collected, dried and crystallised from water to give 3:5-dinitro-2-pyridol (5.3 g.) as pale yellow prismatic needles, m.p.175°, alone or mixed with a specimen (a). Light absorption in water: Maxima at 2110 (ε = 15,600) and 3300Å (ε = 12,500).

Found: C,32.8; H,1.3%

(f) 5-Nitro-2-pyridol (5 g.) was refluxed with nitric acid (50 c.c.; d,1.52) for 2 hours. The residue obtained on evaporation was crystallised from water to give 3:5-dinitro-2-pyridol (2.5 g.) as pale yellow prismatic needles, m.p.175°, alone or mixed with a specimen (a).

Light absorption in water: Maxima at 2120 (ε = 13,000) and 3300Å (ε = 12,300).

Found: C,32.7; H,1.7%

(g) 5-Nitro-2-pyridol (7 g.) was dissolved in sulphuric acid (9.5 c.c.; d,1.84) and a mixture of nitric acid (3.2 c.c.; d,1.52) and sulphuric acid (4.8 c.c.; d,1.84) added dropwise with shaking. The temperature was raised gradually to 100° and maintained at this temperature for 1 hour. The cooled mixture was poured onto ice (40 g.) and aqueous sodium hydroxide (7 c.c.; 40%) added. The precipitate was collected, dried and crystallised from water to give a compound (4.2 g.) as small pale yellow prisms, m.p.148-150°. Light absorption in water: Maxima at 2110 ($E^{1\%}_{1cm.}$ = 650) and 3170Å ($E^{1\%}_{1cm.}$ = 640).

Found: C,36.8; H,1.7%

5-Nitro-2-pyridol (1.0 g.) and 3:5-dinitro-2-pyridol (1.0 g.) were crystallised together from water to give small pale yellow prisms (1 g.), m.p.148-150°, alone or mixed with the compound. Light absorption in water: Maxima at 2080 ($E^{1\%}_{1cm.}$ = 690) and 3170Å ($E^{1\%}_{1cm.}$ = 650).

Found: C,36.6; H,2.0%

The compound (4.2 g.) was refluxed with nitric acid (50 c.c.; d,1.52) for 2 hours. The residue obtained on evaporation was crystallised from water to give 3:5-

dinitro-2-pyridol (3.5 g.) as pale yellow prismatic needles, m.p.175°, alone or mixed with a specimen (a). Light absorption in water: Maxima at 2120 (ε = 14,100) and 3300Å (ε = 11,500).

Found: C,33.0; H,1.4%

(h) 2-Pyridol (2.0 g.) was refluxed with nitric acid (20 c.c.; d,1.52) for 2 hours. The residue on evaporation was crystallised from water to give a compound (0.9 g.) as pale yellow prisms, m.p.151-152°. Light absorption in water: Maxima at 2120 ($E^{1\%}_{1cm.}$ = 660) and 3140Å ($E^{1\%}_{1cm.}$ = 593).

Found: C,35.0; H,1.8%

Sodium 2-pyridolate (2.0 g.) was refluxed with nitric acid (20 c.c.; d,1.52) for 2 hours. The residue on evaporation was crystallised once from dilute hydrochloric acid and then from water to give pale yellow prisms (0.7 g.), m.p.151-152°, alone or mixed with the compound. Light absorption in water: Maxima at 2100 ($E^{1\%}_{1cm.}$= 683) and 3120Å ($E^{1\%}_{1cm.}$= 623).

Found: C,34.6; H,1.7%

5-Nitro-2-pyridol (0.2 g.) and 3:5-dinitro-2-pyridol (0.8 g.) were crystallised together once from water to give pale yellow prisms, m.p.151-154°. Light absorption in water: Maxima at 2100 ($E^{1\%}_{1cm.}$= 670) and

3140Å ($E^{1\%}_{1cm.}$ = 600).

Found: C,33.1; H,1.8%

After two further recrystallisations from water, the material had m.p.161-170°.

3-Nitro-2-pyridol (0.2 g.) and 3:5-dinitro-2-pyridol (0.8 g.) were crystallised together once from water to give pale yellow prisms, m.p.149-151°. Light absorption in water: Maxima at 2100 ($E^{1\%}_{1cm.}$ = 750) and 3380Å ($E^{1\%}_{1cm.}$ = 592).

Found: C,34.4; H,1.7%

After two further recrystallisations from water, the material had m.p.160-165°.

The compound (0.5 g.) was refluxed with nitric acid (5 c.c.; d,1.52) for 2 hours. The residue obtained on evaporation was crystallised from water to give 3:5-dinitro-2-pyridol (0.25 g.) as pale yellow prismatic needles, m.p.175°, alone or mixed with a specimen (a). Light absorption in water: Maxima at 2100 (ε = 13,300) and 3300Å (ε = 10,800).

Found: N,23.1%

Sodium 3:5-dinitro-2-pyridolate.— 3:5-Dinitro-2-pyridol (1.85 g.) was dissolved in hot water (10 c.c.) containing sodium hydroxide (0.5 g.). The solid which separated on cooling was collected, dried and crystallised from aqueous ethanol to give the dihydrate of sodium 3:5-dinitro-2-pyridolate (0.9 g.) as long pale yellow needles, m.p.298° (decomp.). Light absorption in water: Maxima at 2100 (ε = 13,600) and 3260Å (ε = 10,100).

Found: N,17.0%

$C_5H_2O_5N_3Na.2H_2O$ requires: N,17.3%

1:6-Dihydro-6-keto-1-methylnicotinic acid (CXIII).— (cf. D.R.P.,522,060). Nicotinic acid (12.3 g.) (*Org. Synth.*,4,49) and dimethyl sulphate (9.5 c.c.) were heated at 100° for 3 hours. Water (20 c.c.) was added, the mixture cooled in an ice-bath and with stirring treated simultaneously with separate solutions of potassium ferricyanide (65.8 g.) in water (132 c.c.) and sodium hydroxide (16 g.) in water (27 c.c.) added dropwise at such a relative rate that half of the first solution had been added when addition of the second was complete and at such a rate that the temperature of the reaction mixture did not rise above 10°. After standing overnight at 10°, concentrated hydrochloric acid (20 c.c.) was added with cooling and the solid material collected, dried and crystallised from ethanol to give 1:6-dihydro-6-keto-1-methylnicotinic acid (10.2 g.) as needles, m.p.238-239° (Pechmann and Welsh, *Ber.*,1884, *17*,2384, give needles, m.p.237-238°, from water, for the preparation from methyl coumalate and methylamine followed by hydrolysis; Späth and Koller, *Ber.*,1923, *56*,880, give m.p.183° for the isomeric 1:2-dihydro-2-keto-1-methylnicotinic acid).

1:6-*Dihydro*-6-*keto*-1-*methyl*-5-*nitronicotinic* *acid* (CXIV).— 1:6-Dihydro-6-keto-1-methynicotinic acid (30.6 g.) was dissolved in nitric acid (306 c.c.; *d*,1.52) with cooling and the solution kept at 50-55° for five hours. Water (200 c.c.) was added to the residue obtained on evaporation below 50° and the mixture neutralised with solid sodium bicarbonate. A solid (A) was removed by filtration and the filtrate acidified with concentrated hydrochloric acid. The solid material was collected, dried and crystallised from water to give 1:6-*dihydro*-6-*keto*-1-*methyl*-5-*nitronicotinic* *acid* (15.8 g.) as stout yellow needles, m.p.217-222°. Light absorption in water: Maxima at 2180 (ε = 18,100) and 3640Å (ε = 6600).

Found: C,42.6; H,3.0; N,14.2%

$C_7H_6O_5N_2$ requires: C,42.4; H,3.1; N,14.1%

Methyl 1:6-*dihydro*-6-*keto*-1-*methyl*-5-*nitronicotinate* (CXV, R = Me).— 1:6-Dihydro-6-keto-1-methyl-5-nitronicotinic acid (1.98 g.), phosphorus pentachloride (4.2g.)

and phosphoryl chloride (2.0 g.) were refluxed for 1 hour. The residue on evaporation was crystallised from methanol to give *methyl* 1:6-*dihydro*-6-*keto*-1-*methyl*-5-*nitronicotinate* (1.5 g.) as yellow needles, m.p.147-149°.

Found: C,45.2; H,3.7; N,13.3%

$C_8H_8O_5N_2$ requires: C,45.3; H,3.8; N,13.2%

Ethyl 1:6-*dihydro*-6-*keto*-1-*methyl*-5-*nitronicotinate* (CXV, R = Et).— 1:6-Dihydro-6-keto-1-methyl-5-nitronicotinic acid (1.98 g.) and thionyl chloride (10 c.c.) were refluxed for 3 hours. The residue obtained on evaporation was crystallised from ethanol to give *ethyl* 1:6-*dihydro*-6-*keto*-1-*methyl*-5-*nitronicotinate* (1.5 g.) as pale yellow needles, m.p.124°.

Found: C,47.8; H,4.4%

$C_9H_{10}O_5N_2$ requires: C,47.8; H,4.5%

1:2-*Dihydro*-1-*methyl*-3-*nitro*-2-*pyridone* (CXVII).— 3-Nitro-2-pyridol (20 g.) was dissolved in water (163 c.c.) containing potassium hydroxide (16.3 g.), dimethyl sulphate (18.1 g.) added and the mixture refluxed for 4 hours. The cooled solution was filtered from a solid (A) and the filtrate extracted with benzene (2 x 100 c.c.). The dried (Na_2SO_4) benzene extract was evaporated and the residue combined with the solid

(A) and crystallised from ethyl acetate (charcoal) to give 1:2-dihydro-1-methyl-2-pyridone (11.1 g.) as yellow needles, m.p.176° (Tschitschibabin and Konowalowa, *Ber.*, 1925,*58*,1712, give yellow needles, m.p.175-176°, for the product obtained by the action of methyl iodide on 2-nitramino-3-nitropyridine followed by heating with alkali). Light absorption in water: Maxima at 2040 (ε = 14,700) and 3660Å (ε = 7200).

Found: C,47.0; H,4.1%

Calc. for $C_6H_6O_3N_2$: C,46.8; H,3.9%

1:2-*Dihydro*-1-*methyl*-5-*nitro*-2-*pyridone* (CXVIII).— (cf. Räth, *Annalen*,1930,*484*,52). The trihydrate of sodium 5-nitro-2-pyridolate (0.43 g.), ethanol (10 c.c.) and methyl iodide (2 c.c.) was refluxed for 1½ hours. The residue obtained on evaporation was crystallised from water (charcoal) to give 1:2-dihydro-1-methyl-5-nitro-2-pyridone (0.2 g.) as yellow needles, m.p.175° (Räth, *ibid*., gives needles, m.p.175°). Light absorption in water: Maxima at 2180 (ε = 8000) and 3040Å (ε = 9900).

1:2-*Dihydro*-1-*methyl*-3:5-*dinitro*-2-*pyridone* (CXVI).— (a) 1:6-Dihydro-6-keto-1-methylnicotinic acid (3.06 g.) and nitric acid (30.6 c.c.; *d*,1.52) were refluxed for 5 hours. The residue obtained on evaporation was crystallised from water to give 1:2-dihydro-1-methyl-3:5-dinitro-2-pyridone (2.0 g.) as yellow leaflets, m.p.178°. Light absorption in water: Maxima at 2080 (ε = 20,600), 2180 (ε = 19,100) and 3100Å (ε = 12,700).

Found: C,36.5; H,2.4; N,21.1%

Calc. for $C_6H_5O_5N_3$: C,36.2; H,2.5; N,21.1%

(b) The solid (A) obtained during the preparation of 1:6-dihydro-6-keto-1-methyl-5-nitronicotinic acid was crystallised from water to give 1:2-dihydro-1-methyl-3:5-dinitro-2-pyridone (0.2 g.) as pale yellow plates, m.p.178°, alone or mixed with a specimen (a).

(c) 1:6-Dihydro-6-keto-1-methyl-5-nitronicotinic acid (0.25 g.) and nitric acid (5 c.c.; d,1.52) were refluxed for 4 hours. The residue obtained on evaporation was crystallised from water to give 1:2-dihydro-1-methyl-3:5-dinitro-2-pyridone (0.2 g.) as pale yellow leaflets, m.p.177°, alone or mixed with a specimen (a).

(d) 1:2-Dihydro-1-methyl-3-nitro-2-pyridone (0.7 g.) and nitric acid (10 c.c.; d,1.52) were refluxed for 2 hours. The residue obtained on evaporation was crystallised from water to give 1:2-dihydro-1-methyl-3:5-dinitro-2-pyridone (0.3 g.) as yellow leaflets, m.p. 175-177°, alone or mixed with a specimen (a).

(e) 1:2-Dihydro-1-methyl-5-nitro-2-pyridone (0.7 g.)

and nitric acid (10 c.c.; d,1·52) were refluxed for 2 hours. The residue obtained on evaporation was crystallised from water to give 1:2-dihydro-1-methyl-3:5-dinitro-2-pyridone (0·5 g.) as yellow leaflets, m.p. 177°, alone or mixed with a specimen (a). Light absorption in water: Maxima at 2140 (ε = 18,900) and 3070Å (ε = 12,200).

(f) (cf. Fischer and Chur, J.prakt.Chem.,1916,93,363). 1:2-Dihydro-1-methyl-2-pyridone (10·9 g.) (Org.Synth., 15,41) and nitric acid (100 c.c.; d,1·52) were refluxed for 2 hours. The residue obtained on evaporation was crystallised from water to give 1:2-dihydro-1-methyl-3:5-dinitro-2-pyridone (10·3 g.) as yellow leaflets, m.p.178°, alone or mixed with a specimen (a). (Fischer and Chur, ibid., give m.p.178°).

(g) 3:5-Dinitro-2-pyridol (0.93 g.) was dissolved in hot water (10 c.c.) containing potassium hydroxide (0.28 g.). The residue obtained on evaporation was heated with methanol (5 c.c.) and methyl iodide (3 c.c.) at 120° for 3 hours. The residue obtained on evaporation was crystallised from water (charcoal) to give 1:2-dihydro-1-methyl-3:5-dinitro-2-pyridone (0.5 g.) as small yellow plates, m.p.178°, alone or mixed with a specimen (a). Light absorption in water: Maxima at 2080 (ε = 20,600), 2180 (ε = 19,000) and 3080Å (ε = 12,200).

Found: C,36.5; H,2.6; N,21.5%

Methylation of 6-Hydroxy-5-nitronicotinic acid.— (a) 6-Hydroxy-5-nitronicotinic acid (1.84 g.) was dissolved in water (11.4 c.c.) containing potassium hydroxide (1.7 g.), dimethyl sulphate (1.28 g.) added and the mixture refluxed for 4 hours. The solution was acidified with concentrated hydrochloric acid with cooling. The solid material was collected and dried to give a black powder, m.p.150-250° (decomp.), from which no useful material was obtained.

(b) 6-Hydroxy-5-nitronicotinic acid (1.84 g.) was dissolved in water (12 c.c.) containing potassium hydroxide (1.2 g.) and the solution evaporated. The residue was heated with methanol (10 c.c.) and methyl iodide (5 c.c.) at 130-140° for 5 hours. The residue obtained on evaporation was acidified with dilute hydrochloric acid, boiled and filtered hot. No crystalline material was obtained from the filtrate.

Chlorination of 1:6-Dihydro-6-keto-1-methyl-5-nitronicotinic acid.— (a) 1:6-Dihydro-6-keto-1-methyl-5-nitronicotinic acid (2 g.) and a 20% solution of phosgene in toluene (22 c.c.) were heated at 140° for 7 hours. The residue obtained on evaporation was boiled with water (40 c.c.) for 1 minute, filtered hot and the solid which separated on cooling crystallised from water to give yellow needles (1.8 g.), m.p.217-222°, alone or mixed with authentic 1:6-dihydro-6-keto-1-methyl-5-nitronicotinic acid.

(b) 1:6-Dihydro-6-keto-1-methyl-5-nitronicotinic acid (2 g.) and thionyl chloride (10 c.c.) were heated at 120° for 5 hours. The residue obtained on evaporation was boiled with water (40 c.c.) for 1 minute, filtered hot and the solid which separated on cooling crystallised from water to give yellow needles (1.6 g.), m.p.217-222°, alone or mixed with authentic 1:6-dihydro-6-keto-1-methyl-5-nitronicotinic acid.

(c) 1:6-Dihydro-6-keto-1-methyl-5-nitronicotinic acid (1 g.), phosphorus pentachloride (3 g.) and phosphoryl chloride (2 c.c.) were heated at 150° for 5 hours. The residue obtained on evaporation was decomposed with ethanol (10 c.c.), water (30 c.c.) was added and the mixture evaporated to 10 c.c. below 30°. The liquid was decanted and the residual gum extracted with boiling benzene (20 c.c.). Evaporation of the benzene extract gave a gum (0.1 g.) from which no crystalline material was obtained.

Bromination of 1:6-Dihydro-6-keto-1-methyl-5-nitronicotinic acid.— 1:6-Dihydro-6-keto-1-methyl-5-nitronicotinic acid (2.0 g.) was added to a mixture of phosphorus tribromide (20 g.) and bromine (3.2 g.) and heated at 100° for 10 hours. The residue obtained on evaporation was decomposed with methanol (40 c.c.) and filtered hot. No crystalline material was obtained from the filtrate or from the insoluble material.

Methyl 6-chloro-5-nitronicotinate (CXX, R = Me).— A mixture of 6-hydroxy-5-nitronicotinic acid (0.92 g.), phosphorus pentachloride (3 g.) and phosphoryl chloride (5 c.c.) was heated at 100° for 2 hours. To the residue obtained on evaporation was added methanol (10 c.c.) followed by water (40 c.c.), the precipitated solid being collected, dried and crystallised from light petroleum (60-80°) to give methyl 6-chloro-5-nitronicotinate (0.92 g.) as pale yellow leaflets, m.p. 76°.

Found: C,38.9; H,2.3; N,12.8%

$C_7H_5O_4N_2Cl$ requires: C,38.8; H,2.3; N,12.9%

Ethyl 6-chloro-5-nitronicotinate (CXX, R = Et).— A mixture of 6-hydroxy-5-nitronicotinic acid (0.92 g.), phosphorus pentachloride (2.1 g.) and phosphoryl chloride (5 c.c.) was heated at 100° for 2 hours. To the residue obtained on evaporation was added ethanol (10 c.c.) followed by water (20 c.c.) the precipitated solid being collected, dried and crystallised from aqueous ethanol to give ethyl 6-chloro-5-nitronicotinate (0.5 g.) as prisms, m.p.61°.

Found: C,41.6; H,3.3; N,12.5%

$C_8H_7O_4N_2Cl$ requires: C,41.7; H,3.1; N,12.1%

Methyl 6-bromo-5-nitronicotinate (CXXI, R = Me).— 6-Hydroxy-5-nitronicotinic acid (1.84 g.) was added to a mixture of phosphorus tribromide (10 c.c.) and bromine (6.4 g.) and heated at 100° for 20 hours. The residue obtained on evaporation was decomposed with methanol (20 c.c.) and the mixture evaporated, the residue being crystallised from light petroleum (60-80°) to give methyl 6-bromo-5-nitronicotinate (1.6 g.) as pale yellow needles, m.p.98°.

Found: N,10.6%

$C_7H_5O_4N_2Br$ requires: N,10.7%

Ethyl 6-bromo-5-nitronicotinate (CXXI, R = Et).— 6-Hydroxy-5-nitronicotinic acid (1.84 g.) was added to a mixture of phosphorus tribromide (10 c.c.) and bromine (3.2 g.) and heated at 100° for 7 hours. The residue obtained on evaporation was decomposed with ethanol (20 c.c.), water (40 c.c.) was added and the mixture evaporated to 20 c.c. below 30°. The solid was collected, dried and extracted with boiling light petroleum (60-80°), the insoluble fraction being crystallised from benzene to give pale yellow needles (0.6 g.), m.p.165-167°, alone or mixed with a specimen of ethyl 6-hydroxy-5-nitronicotinate, obtained by the esterification of 6-hydroxy-5-nitronicotinic acid.

The light petroleum extract was evaporated and the residue crystallised from light petroleum (60-80°) to give ethyl 6-bromo-5-nitronicotinate (1.1 g.) as stout pale yellow needles, m.p.85°.

Found: C,35.0; H,2.8; N,10.1%

$C_8H_7O_4N_2Br$ requires: C,34.9; H,2.6; N,10.2%

Decarboxylation of 1:6-Dihydro-6-keto-1-methyl-5-nitronicotinic acid.— (a) 1:6-Dihydro-6-keto-1-methyl-5-nitronicotinic acid (0.1 g.) was sublimed at 170°/ 10^{-3}mm. and the sublimate extracted with benzene (5 c.c.). No residue was obtained on evaporation of the extract.

(b) 1:6-Dihydro-6-keto-1-methyl-5-nitronicotinic acid (0.25 g.) was heated at 300° for 30 minutes, cooled and extracted with benzene (5 c.c.). No residue was obtained on evaporation of the extract.

(c) 1:6-Dihydro-6-keto-1-methyl-5-nitronicotinic acid (0.1 g.) and calcium oxide (0.2 g.) were heated at 240° for 5 minutes. The mass was covered with a layer of calcium oxide (0.1 g.) and heated at 170°/

10^{-5}mm. No sublimate was obtained.

(d) 1:6-Dihydro-6-keto-1-methyl-5-nitronicotinic acid (1.0 g.) and calcium oxide (3.0 g.) were heated at 300° for 30 minutes, cooled and extracted with benzene (10 c.c.). No residue was obtained on evaporation of the extract.

(e) 1:6-Dihydro-6-keto-1-methyl-5-nitronicotinic acid (1.0 g.) and quinoline (20 c.c.) were refluxed for 4 hours. The quinoline was removed by steam distillation and the remaining solution evaporated. No solid material was obtained on evaporation of the benzene extract of the residue.

(f) 1:6-Dihydro-6-keto-1-methyl-5-nitronicotinic acid (1.0 g.) and concentrated hydrochloric acid (20 c.c.) were refluxed for 8 hours, the residue obtained on evaporation being extracted with benzene (10 c.c.). No residue was obtained on evaporation of the benzene extract.

2-Chloro-3:5-dinitropyridine (CXXII).— A mixture of 3:5-dinitro-2-pyridol (0.93 g.), phosphorus pentachloride (1.5 g.) and phosphoryl chloride (2 c.c.) was heated at 120° for 2 hours. The residue obtained on evaporation was treated with water (15 c.c.) and basified by the addition of aqueous sodium hydroxide (30%) with cooling. The solid was collected, dried and crystallised from light petroleum (60-80°) to give 2-chloro-3:5-dinitropyridine (0.5 g.) as laminae, m.p.64°.

Found: N,20.5%

$C_5H_2O_4N_3Cl$ requires: N,20.6%

2-Amino-3-chloro-5-nitropyridine (CXXV).— (a) 2-Amino-5-nitropyridine (1.39 g.) in ethanol (100 c.c.) was treated with dry chlorine until 10.0 g. had been absorbed. The residue obtained on evaporation was shaken with water (20 c.c.), collected, dried and crystallised from ethanol (charcoal) to give 2-amino-3-chloro-5-nitropyridine (0.35 g.) as pale yellow needles, m.p.211-213° (Bystritskaya and Kirssanow, J.Gen.Chem.,U.S.S.R.,1940,10,1827, give m.p.205-206°).

Found: N,24.4%

Calc. for $C_5H_4O_2N_3Cl$: N,24.2%

(b) 2-Amino-5-nitropyridine (1.39 g.) was dissolved in ethanol (100 c.c.) and treated with chlorine (0.71 g.) with ice cooling. The residue obtained on evaporation was shaken with water (20 c.c.), collected, dried and crystallised from ethanol (charcoal) to give 2-amino-3-chloro-5-nitropyridine (0.85 g.) as pale yellow needles, m.p.211-213°, alone or mixed with a specimen (a).

3-Chloro-5-nitro-2-pyridol (CXXVI).— 2-Amino-3-chloro-5-nitropyridine (0.35 g.) in sulphuric acid (1.0 c.c.; d,1.84) and water (0.5 c.c.) was cooled below 10° and treated with sodium nitrite (0.3 g.) added in portions with shaking. After shaking for a further hour the reaction mixture was diluted with water (6 c.c.), cooled to 0° and filtered. The dried solid was crystallised from aqueous ethanol to give 3-chloro-5-nitro-2-pyridol (0.2 g.) as pale yellow prisms, m.p.198° (U.S.P., 1,778,784 gives m.p.198°; D.R.P.,597,974 gives m.p.165-167°).

Found: N,16.5%

Calc. for $C_5H_3O_3N_2Cl$: N,16.1%

3-Chloro-1:2-dihydro-1-methyl-5-nitro-2-pyridone (CXXIII).— (a) A solution of 3-chloro-5-nitro-2-pyridol (1.75 g.) in aqueous potassium hydroxide (10 c.c.; 6%) was evaporated and the residue refluxed with ethanol (10 c.c.) and methyl iodide (5 c.c.) for 2 hours. The residue obtained on evaporation was extracted with hot benzene (10 c.c.), the extract being evaporated and the residue sublimed at 110°/10^{-2}mm. The sublimate was crystallised from ethyl acetate-light petroleum (40-60°) to give 3-chloro-1:2-dihydro-1-methyl-5-nitro-2-pyridone (1.5 g.) as prisms, m.p.115°.

Found: C,38.8; H,2.5%

$C_6H_5O_3N_2Cl$ requires: C,38.2; H,2.7%

(b) A mixture of 1:2-dihydro-1-methyl-3:5-dinitro-2-pyridone (1.99 g.), phosphorus pentachloride (3 g.) and phosphoryl chloride (2 c.c.) was heated at 150° for 4 hours. The residue obtained on evaporation was treated with water (15 c.c.) and basified by the addition of aqueous potassium hydroxide (30%) with cooling. The mixture was shaken with cold benzene (20 c.c.), the insoluble 1:2-dihydro-1-methyl-3:5-dinitro-2-pyridone (0.5 g.; m.p.170-174°) separated, and the dried (Na_2SO_4) benzene extract evaporated. The residue was crystallised from ethyl acetate-light petroleum (60-80°) (charcoal) to give 3-chloro-1:2-dihydro-1-methyl-5-nitro-2-pyridone (0.2 g.) as prisms, m.p.115°, alone or mixed with a specimen (a).

(c) 1:2-Dihydro-1-methyl-3:5-dinitro-2-pyridone (1.0 g.) and thionyl chloride (5 c.c.) were heated at 140-150° for 5 hours. The residue obtained on evaporation was shaken with hot benzene (10 c.c.). The mixture was cooled, filtered from 1:2-dihydro-1-methyl-3:5-dinitro-2-pyridone (0.25 g.; m.p.169-172°) and the benzene evaporated, the residue being crystallised from ethyl acetate-light petroleum (60-80°) (charcoal) to give 3-chloro-1:2-dihydro-1-methyl-5-nitro-2-pyridone (0.4 g.)

as prisms, m.p.114-115°, alone or mixed with a specimen (a).

5-Chloro-1:2-dihydro-1-methyl-3-nitro-2-pyridone (CXXIV).— A solution of 5-chloro-3-nitro-2-pyridol (1.75 g.) in aqueous potassium hydroxide (10 c.c.; 6%) was evaporated to dryness and the residue refluxed for 2 hours with ethanol (10 c.c.) and methyl iodide (4.0 g.). The reaction mixture was filtered from solid material which was washed with benzene. The filtrate and washings were evaporated and the residue crystallised from benzene-light petroleum (60-80°) (charcoal) to give 5-chloro-1:2-dihydro-1-methyl-3-nitro-2-pyridone (0.5 g.) as pale yellow prisms, m.p.126°. A mixture with the compound (m.p.115°) obtained by the chlorination of 1:2-dihydro-1-methyl-3:5-dinitro-2-pyridone had m.p.85-95°.

Found: C,38.8; H,2.7%

$C_6H_5O_3N_2Cl$ requires: C,38.2; H,2.7%

Nicotinic acid N-oxide.— (cf. Clemo and Koenig, J.,1949, S231). Nicotinic acid (10 g.), glacial acetic acid (30 g.) and perhydrol (30 g.) were heated at 100° for 3 hours with occasional shaking. The residue obtained on evaporation was crystallised from methanol to give nicotinic acid N-oxide (5.2 g.) as needles, m.p.249° (decomp.) (Clemo and Koenig, ibid., give yellow needles, m.p.249° (decomp.) from methanol).

Nitration of Nicotinic acid N-oxide.— (a) Nicotinic acid *N*-oxide (2 g.) and nitric acid (20 c.c.; *d*,1.42) were taken to dryness in an evaporating basin and the residue crystallised from water to give needles (1.6 g.), m.p.249-251° (decomp.), alone or mixed with authentic nicotinic acid *N*-oxide. On evaporation, the mother liquors gave a gum (0.2 g.) from which no crystalline material was obtained.

(b) Nicotinic acid *N*-oxide (2 g.) and nitric acid (20 c.c.; *d*,1.52) were refluxed for 3 hours, evaporated and the residue crystallised from water to give needles (1.4 g.), m.p.246-249° (decomp.), alone or mixed with authentic nicotinic acid *N*-oxide. On evaporation, the mother liquors gave a gum (0.4 g.) from which no crystalline material was obtained.

(c) Nicotinic acid *N*-oxide (1 g.), glacial acetic acid (5 c.c.) and nitric acid (5 c.c.; *d*,1.52) were refluxed for 3 hours, evaporated and the residue crystallised from water to give needles (0.8 g.), m.p.249-250° (decomp.), alone or mixed with authentic nicotinic acid *N*-oxide. On evaporation, the mother liquors gave a gum (0.1 g.) from which no crystalline material was obtained.

(d) Nicotinic acid N-oxide (1 g.), glacial acetic acid (5 c.c.), nitric acid (5 c.c.; d,1.52) and acetic anhydride (2 c.c.) was gradually heated to 100° and maintained at this temperature for 3 hours. The residue obtained on evaporation was crystallised from water to give needles (0.7 g.), m.p.246-248° (decomp.), alone or mixed with authentic nicotinic acid N-oxide. On evaporation the mother liquors gave a gum (0.1 g.) from which no crystalline material was obtained.

Nitration of 2-Pyridol.— (a) (cf. Tschitschibabin and Schapiro, J.Russ.Phys.Chem.Soc.,1921,53,233). Nitric acid (4.5 c.c.; d,1.52) was added slowly and with cooling to 2-pyridol (5 g.) in oleum (20 c.c.; 20% free SO_3) and the reaction mixture stirred for 2 hours. After decomposition with water (100 c.c.) and almost complete neutralisation with aqueous sodium hydroxide (30%) with cooling, the solid material was collected, dried and extracted with ethanol. Evaporation of the extract gave a yellow crystalline residue (4.0 g.) which was dissolved in oleum (10 c.c.; 20% free SO_3) and nitric acid (1.5 c.c.; d,1.52) added slowly with cooling. The reaction mixture was stirred at 15° for 1 hour, heated at 100° for 3 hours, cooled, decomposed with water (100 c.c.) and almost neutralised with aqueous sodium hydroxide (30%). The residue obtained on evaporation was extracted with ethanol, evaporation of which gave a yellow crystalline residue (3 g.). One crystallisation from aqueous ethanol gave pale yellow needles, m.p.298° (decomp.) (Tschitschibabin and Schapiro, ibid., give m.p.286° (decomp.)). Light absorption in water: Maxima at 2160 ($E^{1\%}_{1cm.}$ = 580) and 3380Å ($E^{1\%}_{1cm.}$ = 585).

Found: N,16.5%

The product was crystallised five times from aqueous ethanol to give pale yellow needles, m.p.298° (decomp.). Light absorption in water: Maxima at 2150 ($E^{1\%}_{1cm.}$ = 610) and 3380Å ($E^{1\%}_{1cm.}$ = 660).

Found: N,16.8%

Recrystallisation of the once crystallised material from dilute hydrochloric acid gave 3:5-dinitro-2-pyridol as long prisms, m.p.175°, alone or mixed with a specimen obtained from 2-amino-3:5-dinitropyridine. Light absorption in water: Maxima at 2120 (ε = 12,200) and 3260Å (ε = 10,500).

Found: N,22.9%

Calc. for $C_5H_3O_5N_3$: N,22.7%

The crude product (1.0 g.) and nitric acid (10 c.c.; d,1.52) were refluxed for 2 hours, the residue on evaporation being crystallised once from dilute hydrochloric acid and then from water to give 3:5-dinitro-2-pyridol (0.7 g.) as pale yellow needles, m.p.175°, alone or mixed with a specimen obtained from 2-amino-3:5-dinitropyridine. Light absorption in water: Maxima at 2130 (ε = 12,400) and 3320Å (ε = 11,200).

Found: N,22.3%

(b) (cf. Binz and Maier-Bode, Angew.Chem.,1936,49,486). 2-Pyridol (24 g.) was dissolved in sulphuric acid (48 c.c.; d,1.84) and a mixture of nitric acid (16 c.c.; d,1.52) and sulphuric acid (24 c.c.; d,1.84) added slowly and with stirring below 40°. The solution was stirred for a further 2 hours below 40°, poured onto ice (210 g.) and partially neutralised by the addition of aqueous sodium hydroxide (35 c.c.; 40%). The solid was collected, dried and extracted with boiling methanol (2 x 200 c.c.). The insoluble material was crystallised from water to give a compound (0.5 g.) as yellow prismatic needles, m.p.286° (decomp.) (Binz and Maier-Bode, ibid., give m.p.280° (decomp.)). Light absorption in water: Maxima at 2410 ($E^{1\%}_{1cm.}$ = 680) and 3500Å ($E^{1\%}_{1cm.}$ = 318).

Found: N,12.8; Na,10.9%

The methanol extract was evaporated to dryness and the residue crystallised from methanol to give 3-nitro-2-pyridol (6 g.) as yellow needles, m.p.224°, alone or mixed with a specimen prepared from 2-amino-3-nitropyridine. (Binz and Maier-Bode, *ibid*., give m.p.224-225°).

(c) Sodium 2-pyridolate (29 g.) was dissolved in sulphuric acid (48 c.c.; *d*,1.84) and a mixture of nitric acid (16 c.c.; *d*,1.52) and sulphuric acid (24 c.c.; *d*,1.84) added slowly and with stirring below 40°. The solution was stirred for a further 2 hours below 40°, poured onto ice (210 g.) and partially neutralised by the addition of aqueous sodium hydroxide (35 c.c.; 40%). The solid was collected, dried and extracted with boiling methanol (2 x 200 c.c.). The insoluble material was crystallised from water to give yellow prismatic needles (2.0 g.), m.p.286° (decomp.), alone or mixed with a specimen (b). Light absorption in water: Maxima at 2400 ($E^{1\%}_{1cm.}$ = 710) and 3500Å ($E^{1\%}_{1cm.}$ = 330).

Found: N,12.9; Na,11.1%

The methanol extract was evaporated to dryness and the residue crystallised from methanol to give 3-nitro-2-pyridol (5.8 g.) as yellow needles, m.p.224°, alone or mixed with a specimen (b).

(d) To sodium 2-pyridolate (1.17 g.) in water (5 c.c.) was added nitric acid (0.7 c.c.; *d*,1.52). No precipitate was obtained on storing at 0°.

(e) A mixture of sulphuric acid (6 c.c.; *d*,1.84), nitric acid (1.3 c.c.; d,1.52) and water (18 c.c.) was partially neutralised by the addition of aqueous sodium hydroxide (4.5 c.c.; 40%). To the cooled mixture was added 2-pyridol (2 g.). No precipitate was obtained on storing at 0°.

(f) A solution of 2-pyridol (2 g.) in sulphuric acid (6 c.c.; d,1.84) was shaken for 2 hours, poured onto ice (18 g.) and nitric acid (1.3 c.c.; d,1.52) added, followed by aqueous sodium hydroxide (4.5 c.c.; 40%). No precipitate was obtained on storing at 0°.

Properties of Compound m.p.286° (decomp.).— (a) The compound contained C, H, N and Na but no S. It exploded above 300°. It crystallised unchanged from dilute hydrochloric acid. It ionised in water. Its solution in water had pH 6.5 and showed a mild buffering action at pH 8-10 with alkali.

(b) The compound did not react with diazomethane in ether.

(c) The compound (2.0 g.) was dissolved in water (11.4 c.c.) containing potassium hydroxide (1.7 g.), dimethyl sulphate (1.28 g.) added and the mixture refluxed for 4 hours. The solution was acidified with concentrated hydrochloric acid and evaporated. No crystalline material was obtained from the residue.

(d) The compound (0.2 g.) and nitric acid (2.0 c.c.; *d*,1.52) were refluxed for 2 hours and evaporated to dryness. The residue was a crystalline inorganic material, m.p.310-320°, alone or mixed with a specimen of sodium nitrate.

(e) The compound (0.4 g.), phosphorus pentachloride (1.0 g.) and phosphoryl chloride (5 c.c.) were heated at 100° for 2 hours. The residue obtained on evaporation was decomposed with methanol (10 c.c.) and the solution cooled and filtered. The dried residue (0.2 g.) was crystallised from water to give yellow prismatic needles, m.p.286° (decomp.) alone or mixed with a specimen of the compound, m.p.286° (decomp.). No crystalline material was obtained from the methanol filtrate.

(f) The compound (0.2 g.) and concentrated hydrochloric acid (2.0 c.c.) were refluxed for 2 hours and evaporated to dryness. The residue was crystallised from water and dried at 80-100° to give a *compound* (0.05 g.) as prismatic needles, m.p.150-152° (decomp.). Light absorption in water: no maxima above 2000Å (Light absorption of pyridine in water: Maxima at 2510 (ε = 2720), 2570 (ε = 3020) and 2620Å (ε = 2000)).

Found: C,20.7; H,4.8; N,6.0%

$C_4H_3O_6N.4H_2O$ requires: C,20.6; H,4.8; N,6.0%

The compound m.p.150-152° (decomp.) contained no Cl or Na. Its solution in water had pH 3.5 and it had a titration equivalent of 110.

The compound m.p.150-152° (decomp.) was heated *in vacuo* over phosphorus pentoxide at 140° for 5 hours to give a *compound* m.p.211° (decomp.).

Found: C,22.0; H,5.4; N,12.5%

$C_4H_{12}O_8N_2$ requires: C,22.2; H,5.6; N,13.0%

Reaction of Methyl 6-chloro-5-nitronicotinate with Cuprous Cyanide.— (a) An intimate mixture of methyl 6-chloro-5-nitronicotinate (0.45 g.) and cuprous cyanide (0.40 g.) was heated on a metal-bath in a flask fitted with an air-cooled reflux condenser plugged at the top with cotton-wool. Reaction took place at 240°, a vacuum was applied and the heat source removed after 15 seconds. On cooling, the vacuum was released and the cotton-wool, apparatus and residue washed thoroughly with acetone. The residue obtained on evaporation of the washings was crystallised from light petroleum (60-80°) to give pale yellow leaflets (0.35 g.), m.p.75°, alone or mixed with authentic methyl 6-chloro-5-nitronicotinate. No crystalline material was obtained from the mother liquors.

(b) Methyl 6-chloro-5-nitronicotinate (0.45 g.), cuprous cyanide (0.40 g.) and quinoline (5 c.c.) were refluxed for 1 hour, cooled, filtered and the residue extracted with ether (2 x 10 c.c.). The combined filtrate and extracts were shaken with water (15 c.c.) containing just enough hydrochloric acid to extract the quinoline from the ether layer. Evaporation of the ether layer gave a residue (0.06 g.) from which no crystalline material was obtained.

Reaction of Ethyl 6-chloro-5-nitronicotinate with Cuprous Cyanide.— (a) An intimate mixture of ethyl 6-chloro-5-nitronicotinate (0.50 g.) and cuprous cyanide (0.40 g.) was heated on a metal-bath in a flask fitted with an air-cooled reflux condenser plugged at the top with cotton-wool. The temperature was maintained at 250° for 5 minutes and on cooling, the residue was thoroughly extracted with acetone and the extract evaporated. The residue so obtained was crystallised from aqueous ethanol to give prisms (0.20 g.), m.p.60°, alone or mixed with authentic ethyl 6-chloro-5-nitronicotinate. No crystalline material was obtained from the mother liquors.

(b) Ethyl 6-chloro-5-nitronicotinate (0.50 g.), cuprous cyanide (0.40 g.) and quinoline (5 c.c.) were refluxed for 1 hour, cooled, filtered and the residue extracted with ether (2 x 10 c.c.). The combined filtrate and extracts were shaken with water (15 c.c.) containing just enough hydrochloric acid to extract the quinoline from the ether layer. Evaporation of the ether layer gave a residue (0.1 g.) from which no crystalline material was obtained.

Methyl 6-*cyano*-5-*nitronicotinate* (CXXXI).— An intimate mixture of methyl 6-bromo-5-nitronicotinate (0.5 g.) and cuprous cyanide (0.4 g.) was heated on a metal-bath in a flask fitted with an air-cooled reflux condenser plugged at the top with cotton-wool. Reaction took place at 240°, a vacuum was applied and the heat source removed after 15 seconds. On cooling, the vacuum was released and the cotton-wool, apparatus and residue washed thoroughly with acetone. The residue obtained on evaporation of the washings was crystallised from benzene-light petroleum (60-80°) to give *methyl* 6-*cyano*-5-*nitronicotinate* (0.13 g.) as needles, m.p. 80°.

Found: N,20.0%

$C_8H_5O_4N_3$ requires: N,20.3%

BIBLIOGRAPHY.

(1) Barger, *Ergot and Ergotism*, Gurney and Jackson: London and Edinburgh, 1931.

(2) Tanret, *Compt.rend.*,1875,*81*,896.

(3) Smith and Timmis, *J.*,1932,1543.

(4) Smith and Timmis, *J.*,1934,674.

(5) Smith and Timmis, *J.*,1936,1440.

(6) Jacobs and Craig, *J.Biol.Chem.*,1934,*104*,547.

(7) Jacobs and Craig, *Science*,1935,*82*,16.

(8) Stoll and Hofmann, *Z.physiol.Chem.*,1938,*251*,155.

(9) Jacobs, *J.Biol.Chem.*,1932,*97*,739.

(10) Jacobs, *Science*,1936,*83*,38.

(11) Jacobs, *J.Biol.Chem.*,1935,*111*,455.

(12) Jacobs, *J.Biol.Chem.*,1939,*128*,715.

(13) Jacobs, Craig and Rothen, *Science*,1936,*83*,166.

(14) Uhle and Jacobs, *J.Org.Chem.*,1945,*10*,76.

(15) Stoll, Hofmann and Troxler, *Helv.Chim.Acta*,1949,*32*,506.

(16) Graf, *J.prakt.Chem.*,1932,*133*,19.

(17) *U.S.P.*, 1,880,645.

(18) *D.R.P.*, 326,446.

(19) Caldwell, Tyson and Lauer, *J.A.C.S.*,1944,*66*,1479.

(20) Pechmann, *Ber.*,1884,*17*,936.

(21) Pechmann and Welsh, *Ber.*,1884,*17*,2384.

(22) Tschitschibabin and Tjashelowa, *J.Russ.Phys.Chem.Soc.*, 1920,*50*,483.

(23) Petrow and Saper, J.,1948,1389.

(24) Tschitschibabin and Jegorow, J.Russ.Phys.Chem.Soc., 1928,60,683.

(25) Tschitschibabin and Kirssanow, Ber.,1927,60,766.

(26) Tschitschibabin, J.Russ.Phys.Chem.Soc.,1914,46,1236.

(27) Tschitschibabin and Bylinkin, J.Russ.Phys.Chem.Soc., 1920,50,471.

(28) Mills and Widdows, J.,1908,1372.

(29) Forrest and Walker, J.,1948,1939.

(30) Phillips, J.,1941,9.

(31) Schickh, Binz and Schulz, Ber.,1936,69,2593.

(32) Tschitschibabin and Kirssanow, Ber.,1924,57,1161.

(33) Tschitschibabin and Schapiro, J.Russ.Phys.Chem.Soc., 1921,53,233.

(34) Tschitschibabin and Rjasanzew, J.Russ.Phys.Chem.Soc., 1915,47,1571.

(35) Reissert, Ber.,1895,28,119.

(36) Marckwald, Ber.,1894,27,1317.

(37) Räth and Prange, Annalen,1929,467,1.

(38) Tschitschibabin and Rasorenow, J.Russ.Phys.Chem.Soc., 1915,47,1286.

(39) Tschitschibabin and Kirssanow, Ber.,1928,61,1223.

(40) Räth and Prange, Ber.,1925,58,1208.

(41) Meyer, Monatsh.,1905,26,1311.

(42) D.R.P., 522,060.

(43) Tschitschibabin and Konowalowa, Ber.,1925,58,1712.

(44) Räth, Annalen,1930,484,52.

(45) Fischer and Chur, J.prakt.Chem.,1916,93,363.

(46) Bystritskaya and Kirssanow, J.Gen.Chem.,U.S.S.R., 1940,10,1827.

(47) U.S.P., 1,778,784.

(48) D.R.P., 597,974.

(49) Clemo and Koenig, J.,1949,S231.

(50) Binz and Maier-Bode, Angew.Chem.,1936,49,486.
