Meso-ionic Compounds derived from Pyridino(1′ : 2′-1 : 2)glyoxaline.

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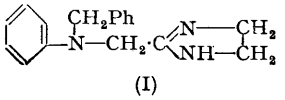
[Reprint Order No. 4748.]

The reactions of 2-pyridylaminoacetonitrile (II; R = H) show that it can also react as 5-aminopyridino(1′ : 2′-1 : 2)glyoxaline (III; R = R′ = R″ = H). *N*-Alkyl- or *N*-aryl-*N*-2-pyridylaminoacetonitriles (II) afford acyl derivatives for which a meso-ionic structure (cf. VIII; R = Ac, Bz, or Ph·SO_2) is suggested.

This investigation originated in a desire to prepare analogues of the antihistamine antazoline (I) in which the *N*-phenyl substituent is replaced by a 2-pyridyl group and the dihydroglyoxaline nucleus either remains or is replaced by an amidino-group. The starting point was 2-pyridylaminoacetonitrile (II; R = H), obtained from formaldehyde, sodium hydrogen sulphite, 2-aminopyridine, and sodium cyanide. On benzylation in chloroform solution this base afforded two monobenzyl derivatives, m. p. 83—84° and 100° respectively, and a dibenzyl derivative (picrate, m. p. 144°). The monobenzyl compound of lower m. p., obtained in 45% yield, afforded 2-benzylaminopyridine on oxidation with potassium permanganate and this indication that it is *N*-benzyl-*N*-2-pyridylaminoacetonitrile (II; R = Ph·CH_2) was confirmed by an independent synthesis (below). The other monobenzyl derivative and the dibenzyl compound arise from the capacity of 2-pyridylaminoacetonitrile to react in the tautomeric form (III; R = R′ = R″ = H). The structure of the monobenzyl compound, m. p. 100°, as (III; R = R″ = H, R′ = Ph·CH_2) follows from its hydrolysis to benzylamine and from its production by the catalytic reduction of 5-benzylideneaminopyridino(1′ : 2′-1 : 2)glyoxaline (III; R″ = H, RR′ = Ph·CH:) ob-



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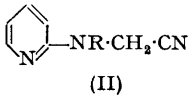

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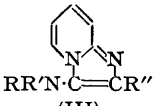
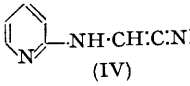


(III)

tained by the condensation of 2-pyridylaminoacetonitrile with benzaldehyde. Alternative formulæ for the benzylidene compound are excluded by the observation that it remains unchanged when heated with acetic anhydride. Reduction of the benzylidene derivative to the benzyl compound, m. p. 100°, shows that the latter cannot have the alternative structure (IV; R = Ph·CH_2). The dibenzyl compound obtained from 2-pyridylaminoacetonitrile is therefore regarded as 5-dibenzylaminopyridino(1′ : 2′-1 : 2)glyoxaline (III; R″ = H, R = R′ = Ph·CH_2). A monobenzoyl derivative obtained from 2-pyridylaminoacetonitrile is also assigned a cyclic structure (III; R = R″ = H, R′ = Bz), since it is converted by reduction with lithium aluminium hydride into the benzyl compound, m. p. 100°.

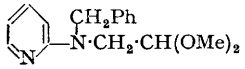


(IV)

Acetylation of 2-pyridylaminoacetonitrile affords an acetyl derivative, m. p. 199°, also obtained by pyrolysis of 5-acetamido-3-benzylpyridino(1′ : 2′-1 : 2)glyoxalinium chloride (below), and therefore regarded as 5-acetamidopyridino(1′ : 2′-1 : 2)glyoxaline (III; R = R″ = H, R′ = Ac). 2-Pyridylaminoacetonitrile and benzenesulphonyl chloride afford mono- and di-benzenesulphonyl derivatives, and since the first of these is soluble in aqueous sodium hydroxide it cannot have either of the structures (II; or IV; R = Ph·SO_2) but must have formula (III; R = R″ = H, R′ = Ph·SO_2) containing the ·SO_2·NH· group. The dibenzenesulphonyl derivative is consequently regarded as (III; R″ = H, R = R′ = Ph·SO_2). In accordance with these conclusions, the infra-red spectrum of the benzyl compound, m. p. 83—84°, showed an absorption band at 2250 $cm.^{-1}$ (in chloroform solution) due to the –CN group, whereas this band was absent from the spectrum of the benzyl compound, m. p. 100°. Absence of the –CN group was likewise indicated for the acetyl derivative of 2-pyridylaminoacetonitrile and of 2-pyridylaminoacetonitrile itself, showing

in the latter case that the cyclic tautomer (**III**; R = R′ = R″ = H) is the predominant form.

In an alternative synthesis of *N*-benzyl-*N*-2-pyridylaminoacetonitrile (**II**; R = $Ph{\cdot}CH_2$), 2-benzylamino-1 : 1-dimethoxyethane, prepared by a modification of the method of Rügheimer and Schön (*Ber.*, 1908, **41**, 17; cf. Jones, Kornfeld, McLaughlin, and Anderson, *J. Amer. Chem. Soc.*, 1949, **71**, 4001), was first condensed with 2-bromopyridine to give 2-(*N*-benzyl-*N*-2-pyridylamino)-1 : 1-dimethoxyethane (V), a compound subsequently prepared by Kaye (*J. Amer. Chem. Soc.*, 1951, **73**, 5467) by condensing 2-lithioaminopyridine with 2-chloro-1 : 1-dimethoxyethane and treating the resulting secondary amine with benzyl chloride and lithamide. 2-(*N*-Benzyl-*N*-2-pyridylamino)-1 : 1-dimethoxyethane was hydrolysed with 2N-hydrochloric acid, and the resultant aqueous solution of aldehyde was oximated to give *N*-benzyl-*N*-2-pyridylaminoacetaldoxime which was readily dehydrated by thionyl chloride to the nitrile (**II**; R = $Ph{\cdot}CH_2$). This compound exhibited the properties of a normal nitrile in most of its reactions. For example, it was hydrolysed to the corresponding amide and acid, and afforded a dihydroglyoxaline on being heated with 2-aminoethylammonium toluene-*p*-sulphonate (Oxley and Short, *J.*, 1947, 497). Difficulties were encountered in attempting to convert the nitrile into the corresponding amidine, which could not be obtained by the Pinner method or by the action of sodamide. The nitrile was readily converted into the corresponding thioamide by the action of hydrogen sulphide in pyridine–triethylamine (Fairfull, Lowe, and Peak, *J.*, 1952, 742) but aminating-desulphurisation with mercuriammonium chloride and alcoholic ammonia (cf. Bernthsen, *Ber.*, 1876, **9**, 429) gave very small and variable yields of amidine. The amidoxime, readily obtained from the nitrile and alcoholic hydroxylamine, gave a good yield of the amidinium chloride when reduced catalytically in alcoholic solution in presence of Raney nickel and ammonium chloride (cf. May and Baker, Ltd., Barber, and Self, B.P. 551,445). The same procedure also afforded α-(*N*-*p*-chlorobenzyl-*N*-2-pyridylamino)-acetamidine from *N*-*p*-chlorobenzyl-*N*-2-pyridylaminoacetonitrile. α-(*N*-Benzyl-*N*-2-pyridylamino)-*NN*′-diphenylacetamidine, prepared from 2-benzylaminopyridine and α-chloro-*NN*′-diphenylacetamidine, was recovered unchanged when heated with ammonium benzenesulphonate, ammonia, and aniline under conditions which usually result in the ammonolysis of *N*-phenylamidines (Oxley and Short, *J.*, 1949, 449).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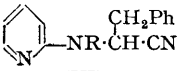
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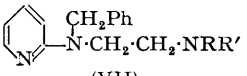
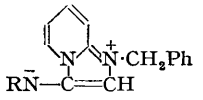
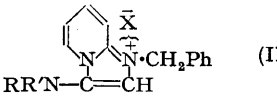

(VII)

N-Benzyl-*N*-2-pyridylaminoacetaldoxime and *N*-benzyl-*N*-2-pyridylaminoacetonitrile were both converted by acetic anhydride into an acetyl derivative of the nitrile, which from its infra-red spectrum no longer contained a –CN group. Since mild hydrolysis regenerated the nitrile, whereas energetic hydrolysis gave the corresponding acid, the possibility that this acetylation involves migration of the benzyl group from nitrogen to carbon giving the acetyl derivative (**VI**; R = Ac) or its cyclic tautomeride (**III**; R = Ac, R′ = H, R″ = $Ph{\cdot}CH_2$) appeared unlikely, and it was eliminated by the synthesis of α-benzyl-α-2-pyridylaminoacetonitrile (**VI**; R = H) which afforded an entirely distinct acetyl derivative.

Mignonac and Hoffmann (*Compt. rend.*, 1930, **191**, 718) obtained a compound from sodiobenzyl cyanide and benzoyl chloride to which they assigned the structure Bz·CPh:C:NBz although their evidence does not appear to exclude the alternative structure BzO·CPh:CPh·CN. The analogous formula, $C_5H_4N{\cdot}N(CH_2Ph){\cdot}CH{:}C{:}NAc$, for our acetyl derivative must be rejected since the tetrahydro-derivative obtained by catalytic reduction is not *N*′-acetyl-*N*-benzyl-*N*-2-pyridylethylenediamine (**VII**; R = H, R′ = Ac). The latter compound was obtained by reduction of *N*-benzyl-*N*-2-pyridylaminoacetonitrile with lithium aluminium hydride to the amine (**VII**; R = R′ = H), acetylation of which gave a mixture of the mono- and the di-acetyl (**VII**; R = R′ = Ac) derivatives. Phthaloylation of the amine gave [**VII**; RR′ = $(CO)_2C_6H_4$], also obtained from *N*-2-bromoethylphthalimide and 2-benzylaminopyridine. Reduction of the diacetyl derivative (**VII**;

R = R′ = Ac) with lithium aluminium hydride gave *N*-benzyl-*NN*′-diethyl-*N*-2-pyridylethylenediamine (VII; R = R′ = Et), also obtained from 2-benzylaminopyridine and 2-diethylaminoethyl chloride.

The production of the acetyl derivative cannot involve migration of the hydrogen atom at position 3 of the pyridine nucleus, because a similar acetyl derivative was prepared containing a methyl group in this position. Likewise the *ortho*-positions in the benzyl nucleus are not involved since an acetyl derivative was also obtained from a nitrile containing a mesitylmethyl group in the place of the benzyl group. We therefore propose a meso-ionic structure for the acetyl derivative, one of the contributing ionic forms, which may be called anhydro-5-acetamido-3-benzylpyridino(1′ : 2′-1 : 2)glyoxalinium hydroxide, being represented by formula (VIII; R = Ac). A similar meso-ionic ring structure, containing two nitrogen, two carbon, and one oxygen atom, was first proposed for the sydnones (Baker, Ollis, and Poole, *J.*, 1949, 307; 1950, 1542; Hill and Sutton, *J.*, 1949, 746). We cannot offer a formal proof of structure (VIII), which, however, rests on the

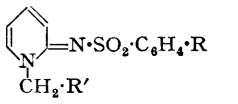
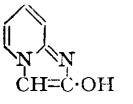
(VIII)   (IX)

exclusion of simpler alternatives and accounts satisfactorily for the formation and reactions of the compound. Thus, the acetyl derivative yields a hydrochloride, which would be a quaternary ammonium salt (IX; R = Ac, R′ = H, X = Cl), and, in agreement with this formula, decomposes on being heated, benzyl chloride and 5-acetamidopyridino(1′ : 2′-1 : 2)-glyoxaline (III; R = R″ = H, R′ = Ac) being formed. Methyl iodide in boiling acetone converts the acetyl derivative into a quaternary salt which is formulated as (IX; R = Me, R′ = Ac, X = I) since hydrolysis with boiling dilute sulphuric acid gives a 93% yield of methylamine. This suggests either that the structure (VIII; R = Ac) makes the largest contribution to the meso-ionic system or that, if the structure containing the group $^{-}$O·CMe:N· is predominant, the *O*-methyl derivative MeO·CMe:N· must immediately and completely isomerise to the *N*-methyl derivative. Hydrolysis of the quaternary salt with cold alcoholic hydrochloric acid removes the acetyl group and gives 3-benzyl-5-methylaminopyridino(1′ : 2′-1 : 2)glyoxalinium iodide (IX; R = Me, R′ = H, X = I), which is also formed directly at room temperature from the acetyl derivative (VIII; R = Ac) and methyl iodide in methanol, the acetyl group being eliminated. The presence of a benzyl group is not essential for the production of compounds of type (VIII), a number of analogues in which the benzyl group is replaced by phenyl, ethyl, 2-pyridyl, or 2-thienylmethyl radicals being readily prepared, usually by the route proceeding *via* the acetal and acetaldoxime (above). Meso-ionic compounds containing other acyl groups in place of the acetyl group were also prepared. For example, a benzoyl derivative (VIII; R = Bz) was obtained by the action of benzoyl chloride and pyridine either on *N*-benzyl-*N*-2-pyridylaminoacetaldoxime or on *N*-benzyl-*N*-2-pyridylaminoacetonitrile. A benzenesulphonyl derivative (VIII; R = Ph·SO_2), obtained from the nitrile and benzenesulphonyl chloride in pyridine was insoluble in alkali, showing that the ·NH·SO_2· group is absent. The benzenesulphonyl derivative gave a sulphonmethylamido-compound (IX; R = Ph·SO_2, R′ = Me, X = I) with methyl iodide in boiling alcoholic solution.

All these meso-ionic compounds exhibited a strong green fluorescence in ultra-violet light in chloroform solution but not in dilute hydrochloric acid solution. This was in marked contrast to the non-meso-ionic intermediates, most of which exhibited blue fluorescence in dilute hydrochloric acid solution but none in chloroform solution.

In connection with the elucidation of the structure of the arenesulphonyl derivatives we made some interesting observations on the reaction of 2-arenesulphonamidopyridines with chloroacetamide and chloroacetonitrile. Phillips (*Nature*, 1941, **148**, 409, 466) states that sulphapyridine, chloroacetamide, and alkali yield *N*-2-pyridyl-*N*-sulphanilylglycineamide which is hydrolysed by alkali to *N*-2-pyridyl-*N*-sulphanilylglycine, which affords 2-pyridylglycine with hot mineral acid. The introduction of the acetamide and acetonitrile residues into the ·SO_2NH· group seemed surprising in view of Kelly and Short's finding (*J.*, 1945,

242) that sulphapyridine is alkylated at the pyridine-nitrogen atom, giving 1-alkyl-1 : 2-dihydro-2-iminopyridines. Repetition of the condensation of sulphapyridine and chloroacetamide gave, as the only isolated products of the reaction, 15% of recovered sulphapyridine and a 62% yield of 1-carbamoylmethyl-1 : 2-dihydro-2-sulphanilimidopyridine (X; R = NH_2, R′ = $CO{\cdot}NH_2$), the structure of which was demonstrated by hydrolysis to 4-hydroxypyridino(1′ : 2′-1 : 2)glyoxaline (XI). The latter compound was first prepared by Reindel (*Ber.*, 1924, **57**, 1381) by cyclisation of the condensation product of 2-amino-

(X)  (XI) 

pyridine and chloroacetic acid, the structure of which was shown by Tschitschibabin (*ibid.*, pp. 1168, 2092) to be 1-carboxymethyl-1 : 2-dihydro-2-iminopyridine. Condensation has therefore occurred mainly on the pyridine nitrogen atom as expected. In boiling acetic anhydride, (X; R = NH_2, R′ = $CO{\cdot}NH_2$) cyclised with elimination of the sulphanilyl group to a compound formulated as 4-acetamidopyridino(1′ : 2′-1 : 2)glyoxaline. The same compound was obtained from the condensation product of 2-toluene-*p*-sulphonamidopyridine and chloroacetamide which must therefore have the structure (X; R = Me, R′ = $CO{\cdot}NH_2$). Condensation of 2-toluene-*p*-sulphonamidopyridine with chloroacetonitrile gave a compound presumably of the analogous structure (X; R = Me, R′ = CN).

Experimental

2-Pyridylaminoacetonitrile.—The conditions of reaction for this preparation have been studied in some detail, and the best yield was obtained under the following conditions.

A mixture of formalin (120 c.c., 1·5 mols.), sodium hydrogen sulphite (156 g., 1·5 mols.), and water (300 c.c.) was stirred for 0·5 hr., then heated to 95°, and 2-aminopyridine (141 g., 1·5 mols.) was added and stirring was continued for an hour. Sodium cyanide (150 g., 3 mols.) in water (300 c.c.) was run in, and heating and stirring were continued for 4 hr. The dark solution was cooled, then filtered from crystals of sodium sulphite, and the filtrate thoroughly extracted with chloroform (6 × 500 c.c.). The combined chloroform extracts were dried ($CaCl_2$) and evaporated, finally under reduced pressure. The brown solid residue was crystallised from ethyl acetate (600 c.c.), giving 90 g. (45%) of brown prisms, m. p. 123—124°.

The use of an equimolecular amount of sodium cyanide gave a lower yield, and an increase in the time of heating after the addition of the cyanide did not increase the yield. Material of this quality was suitable for most preparative purposes. If a purer material was required the following procedure was used.

The crude nitrile was distilled and the fraction of b. p. 155—160°/1·1 mm. (83·5%) was collected as a yellow-green mixture of crystals and oil. Trituration with a little benzene afforded the pure *nitrile* as pale yellow prisms (60%), m. p. 126° unchanged by recrystallisation from acetone–benzene (Found: N, 31·4. $C_7H_7N_3$ requires N, 31·6%). The *picrate* separated from 50% methanol in yellow rods, m. p. 209° (Found: N, 23·5. $C_{13}H_{10}O_7N_6$ requires N, 23·2%). The *hydrochloride* crystallised from *iso*propanol in yellow needles, m. p. 152—153° (Found: N, 24·5. $C_7H_8N_3Cl$ requires N, 24·8%). The *tartrate* separated from aqueous acetone in colourless hydrated needles, m. p. 125—126°, which, after drying, melted at 151° (Found, on dried material: C, 46·4; H, 4·8; N, 15·0. $C_{11}H_{13}O_6N_3$ requires C, 46·6; H, 4·6; N, 14·8%).

The nitrile deteriorated on storage and became black and tarry after a few months even when kept in tightly stoppered bottles.

5-Acetamidopyridino(1′ : 2′-1 : 2)*glyoxaline* (III; R = H, R′ = Ac).—2-Pyridylaminoacetonitrile (4·7 g.) was heated under reflux with acetic anhydride (25 c.c.) for 50 min. The cooled solution was poured on ice and basified, the *acetyl* derivative separating in long needles. Recrystallisation from *iso*propanol gave 3·9 g. (63%), m. p. 196—199°, raised to m. p. 199° by recrystallisation from water (Found: C, 62·1; H, 5·1; N, 23·6. $C_9H_9ON_3$ requires C, 61·7; H, 5·2; N, 24·0%). A further 0·9 g. (13%), m. p. 197—199°, was obtained by chloroform extraction of the combined mother-liquors.

5-Benzamidopyridino(1′ : 2′-1 : 2)*glyoxaline.*—A mixture of 2-pyridylaminoacetonitrile (6·65 g.), benzoyl chloride (6·9 g.), and pyridine (50 c.c.) was heated for a short time on the steam-bath,

cooled, and filtered. The resultant hydrochloride was washed with pyridine and acetone, and the free base precipitated from dilute aqueous alkaline solution by carbon dioxide. Crystallisation from ethanol gave the *base* as thin solvated prisms which, after drying *in vacuo* at 78° (Found: loss in weight, 16·0. $C_{14}H_{11}ON_3,C_2H_5{\cdot}OH$ requires loss in weight, 16·3%), had m. p. 170° (8·1 g., 68%) (Found: C, 71·3; H, 4·6; N, 17·7. $C_{14}H_{11}ON_3$ requires C, 70·9; H, 4·7; N, 17·7%). Some early preparations of this compound originally had m. p. 157° but this changed gradually to 170°. The *hydrochloride* separated from water as needles, m. p. 295—296° (decomp.) (Found: C, 61·5; H, 4·5; N, 15·5. $C_{14}H_{12}ON_3Cl$ requires C, 61·4; H, 4·4; N, 15·4%). The *picrate* separated from nitrobenzene in needles, m. p. 264° (decomp.) (dependent upon the rate of heating) (Found: N, 18·3. $C_{20}H_{14}O_8N_6$ requires N, 18·0%).

When the acylation was carried out with benzoic anhydride instead of benzoyl chloride the yield was less than 2%.

5-Benzenesulphonamido- and 5-Dibenzenesulphonamido-pyridino(1′ : 2′-1 : 2)*glyoxaline*.—Benzenesulphonyl chloride (9·5 g.) was added in portions to 2-pyridylaminoacetonitrile (7·15 g.) in anhydrous pyridine (25 c.c.), so that the temperature did not exceed 50°. The solid which separated overnight was filtered off and washed with a little methanol, giving the *dibenzenesulphonyl* derivative as large pale-yellow prisms (3·4 g.), m. p. 165° (decomp.). Crystallisation from acetone–ether gave large colourless prisms of unchanged m. p. (Found: C, 55·4; H, 3·6; N, 9·5. $C_{19}H_{15}O_4N_3S_2$ requires C, 55·2; H, 3·6; N, 10·15%). It was insoluble in water and in dilute sodium hydroxide.

The pyridine filtrate was poured into water (4 vols.) and stirred until the precipitate solidified. The dried solid was extracted with boiling acetone (2 × 30 c.c.), and the combined extracts were concentrated to half volume and diluted with ether (30 c.c.), another 1·2 g. of the dibenzenesulphonyl derivative, m. p. 165°, being slowly precipitated.

The brown powder insoluble in acetone was shaken with water (50 c.c.) and N-sodium hydroxide (20 c.c.), filtered from a little insoluble solid, and neutralised with N-hydrochloric acid (20 c.c.). Crystallisation of the buff solid (4·1 g.) from *n*-butanol afforded the *monobenzenesulphonyl* derivative as pale-green rods, m. p. 212° (decomp.) (Found: N, 15·8. $C_{13}H_{11}O_2N_3S$ requires N, 15·4%). The compound was insoluble in water but was soluble in both dilute hydrochloric acid and dilute sodium hydroxide.

5-Benzylideneaminopyridino(1′ : 2′-1 : 2)*glyoxaline*.—A mixture of 2-pyridylaminoacetonitrile (5·32 g.) and benzaldehyde (4·25 g.) was heated at 100° for 1 hr., cooled, ground with ether, and filtered, giving 4·95 g. of a brown solid, m. p. 102°. Two recrystallisations from light petroleum (b. p. 80—100°) gave *5-benzylideneaminopyridino*(1′ : 2′-1 : 2)*glyoxaline* as sheaves of yellow-brown needles (4·53 g., 51%), m. p. 114° (Found: C, 76·0; H, 5·0; N, 18·8. $C_{14}H_{11}N_3$ requires C, 76·0; H, 5·0; N, 19·0%). The compound (96%) was recovered after 2 hours' heating with acetic anhydride at 100°.

5-Benzylaminopyridino(1′ : 2′-1 : 2)*glyoxaline*.—(*a*) 5-Benzamidopyridino(1′ : 2′-1 : 2)glyoxaline (1·0 g.) in dry tetrahydrofuran (15 c.c.) was added to a solution of lithium aluminium hydride (0·24 g.) in ether (15 c.c.), and the mixture was refluxed for 0·5 hr. The excess of hydride was decomposed with ethyl acetate and a few drops of aqueous sodium hydroxide, and the resulting suspension was dried ($MgSO_4$), filtered, and evaporated to dryness. The residue was crystallised from acetone giving, after some concentration, starting material (0·70 g.), m. p. 169·5°. Addition of picric acid to the filtrate gave a crude picrate (0·30 g.), a hot alcoholic extract of which, on cooling, deposited *5-benzylaminopyridino*(1′ : 2′-1 : 2)*glyoxalinium picrate* (70 mg.), m. p. 180—181°, undepressed on admixture with the picrate prepared as in (*b*) below (Found: C, 53·8; H, 3·8; N, 18·7. $C_{20}H_{16}O_7N_6$ requires C, 53·1; H, 3·6; N, 18·6%).

(*b*) 5-Benzylideneaminopyridino(1′ : 2′-1 : 2)glyoxaline (5·9 g.) in methanol (50 c.c.) was hydrogenated at room temperature and pressure with palladium–charcoal (0·3 g. of 10%) as catalyst; approx. 1 mol. of hydrogen was absorbed and the final solution was almost colourless. The filtered solution was evaporated to a brown syrup which gradually crystallised. The solid separated from acetone as yellow-brown plates (2·8 g., 47%), m. p. 100°, and a further recrystallisation (charcoal) afforded *5-benzylaminopyridino*(1′ : 2′-1 : 2)*glyoxaline* as large yellow plates, m. p. 100° (Found: C, 75·2; H, 6·0; N, 18·7. $C_{14}H_{13}N_3$ requires C, 75·3; H, 6·0; N, 18·8%). The picrate separated from ethanol in needles, m. p. 182·5°.

Hydrolysis was effected by 5N-sulphuric acid for 1·5 hr. on the steam-bath. The cooled solution was basified and the resultant benzylamine isolated with ether and characterised as the picrate, m. p. and mixed m. p. 197°.

Benzylation of 2-Pyridylaminoacetonitrile.—(a) *N-Benzyl-N-2-pyridylaminoacetonitrile*. 2-Pyridylaminoacetonitrile (12·3 g.) and benzyl chloride (11·7 g.) were refluxed together in dry

chloroform (60 c.c.). A heavy oil separated after 15 min. but this largely redissolved after 24 hours' heating. The mixture was cooled and poured into ether (300 c.c.), the ether decanted from the gummy precipitate, and the product washed with ether by stirring and decantation. The dark gum was dissolved in warm *iso*propanol (50 c.c.), and the solution was kept at 0° for a day. The solid which separated was filtered off and washed with *iso*propanol until colourless, giving 8·55 g. (36%), m. p. 209°. Recrystallisation from *iso*propanol gave colourless needles of the *hydrochloride*, m. p. 214° (Found : N, 16·2. $C_{14}H_{14}N_3Cl$ requires N, 16·2%).

During the course of several preparations it was found that if seeds were added the crystalline hydrochloride separated directly from the reaction mixture in chloroform. After 6 hours' heating the mixture was cooled and the hydrochloride (28%) was collected. No more solid separated after heating of the filtrate under reflux for a further 16 hr. By addition of the cooled solution to excess of ether and crystallisation of the precipitated gum from ethanol–acetone a further crop of crystals was obtained, bringing the total yield of the salt to 45%.

The *picrate* crystallised from ethanol in plates, m. p. 149·5° (Found : C, 53·3; H, 3·55; N, 18·5; picric acid, 50·2. $C_{20}H_{16}O_7N_6$ requires C, 53·1; H, 3·6; N, 18·6; picric acid, 50·65%). The *toluene*-p-*sulphonate* separated from 80% ethanol as colourless prisms, m. p. 204° (Found : N, 10·7. $C_{21}H_{21}O_3N_3S$ requires N, 10·6%). The *base* separated slowly when an aqueous solution of the hydrochloride was made strongly alkaline with 5N-sodium hydroxide. Crystallisation from light petroleum (b. p. 60—80°) or ethanol afforded colourless needles, m. p. 83—84° (Found : C, 75·3; H, 5·8; N, 19·0. $C_{14}H_{13}N_3$ requires C, 75·3; H, 5·9; N, 18·85%).

(b) 5-*Benzylaminopyridino*(1′ : 2′-1 : 2)*glyoxaline*. The *iso*propanol mother-liquors from several benzylation reactions [see under (a)] were combined and poured into ether (5 vols.). The sticky brown precipitate was dissolved in water, and aqueous lithium picrate solution was added until precipitation was complete. The gummy precipitate, which hardened on stirring, was crystallised from 60% ethanol to give a yellow-brown mixture of picrates.

The mixture (69 g.) was extracted with hot chloroform (10 vols.), and the suspension cooled and filtered. The insoluble residue (42 g.) was refluxed with acetone (200 c.c.), cooled, and filtered. The filtrate was evaporated to dryness and the residual picrate recrystallised from 70% ethanol (300 c.c.) in yellow-brown plates (9·75 g.), m. p. 182—183°, raised to 184° by a further crystallisation.

The picrate was shaken with aqueous lithium hydroxide and ether until dissolved, the ether evaporated, and the base recrystallised from light petroleum (b. p. 80—100°) to give yellow plates, m. p. 100°.

Both the base and the picrate were undepressed in m. p. on admixture with 5-benzylaminopyridino(1′ : 2′-1 : 2)glyoxaline and its picrate respectively, obtained by catalytic reduction of the benzylidene derivative of 2-pyridylaminoacetonitrile.

(c) 5-*Dibenzylaminopyridino*(1′ : 2′-1 : 2)*glyoxaline*. The chloroform solution above was concentrated to 200 c.c. and diluted with ether (400 c.c.). The dark oily precipitate solidified when boiled with ethanol (50 c.c.), and the suspension was filtered hot; a dark tar separated from the filtrate. The solid on the filter was washed with hot ethanol to remove tars and then crystallised from ethanol, giving yellow needles of the *picrate*, m. p. 154° (Found : C, 59·2; H, 4·1; N, 15·1; picric acid, 42·35. $C_{27}H_{22}O_7N_6$ requires C, 59·8; H, 4·1; N, 15·5; picric acid, 42·25%). Attempts to isolate the base from the picrate were unsuccessful.

Oxidation of N-*Benzyl*-N-2-*pyridylaminoacetonitrile*.—A saturated solution of potassium permanganate in 70% acetone was added to a solution of *N*-benzyl-*N*-2-pyridylaminoacetonitrile (1·0 g.) in acetone (7 c.c.) and 5N-sulphuric acid (3 c.c.) until the reaction became sluggish; about 10 c.c. were required. The filtered solution was diluted with water and basified, giving 2-benzylaminopyridine (0·41 g., 50%), m. p. 93—94°, undepressed on admixture with an authentic sample, m. p. 94°. A similar result was obtained by the oxidation of *N*-benzyl-*N*-2-pyridylaminoacetaldoxime.

Hydrolysis of N-*Benzyl*-N-2-*pyridylaminoacetonitrile*.—The nitrile hydrochloride (2·60 g.) was dissolved in 10% hydrogen peroxide (15 c.c.), and 5N-sodium hydroxide (4 c.c.) was added dropwise. The precipitated gum was crystallised from ethanol (2 c.c.), and the crystals, together with those which separated from the supernatant liquid during 3 days, were extracted with boiling light petroleum (b. p. 80—100°) (3 × 5 c.c.). The residue was recrystallised from ethanol, affording α-(N-*benzyl*-N-2-*pyridylamino*)*acetamide* (0·11 g., 5%) as prisms, m. p. 139·5° (Found : C, 69·45; H, 5·8; N, 17·2. $C_{14}H_{15}ON_3$ requires C, 69·7; H, 6·3; N, 17·4%). The *picrate* separated from ethanol in needles, m. p. 155° (decomp.) (Found : N, 17·5. $C_{20}H_{18}O_8N_6$ requires N, 17·9%).

Heating the nitrile with 5N-hydrochloric acid for 1·5 hr. at 95° afforded *N*-benzyl-*N*-2-

pyridylaminoacetic acid, isolated as the *sodium* salt (44%), needles [from ethanol–ether (3 : 1)], m. p. 300° (Found: N, 10·1; Na, 8·4. $C_{14}H_{13}O_2N_2Na$ requires N, 10·6; Na, 8·7%). The *benzylammonium* salt crystallised from water in prisms, m. p. 165° (Found: C, 71·5; H, 6·4; N, 12·0. $C_{21}H_{23}O_2N_3$ requires C, 72·2; H, 6·6; N, 12·0%).

Heating the nitrile (6·0 g.) with ethanol (12 c.c.) and sulphuric acid (1·8 c.c.) for 5 hr. under reflux afforded *ethyl* N-*benzyl*-N-2-*pyridylaminoacetate* (2·0 g., 28%), long needles [from light petroleum (b. p. 60—80°)], m. p. 72° (Found: C, 71·8; H, 6·5; N, 10·7. $C_{16}H_{18}O_2N_2$ requires C, 71·1; H, 6·7; N, 10·4%).

Alternative Synthesis of N-*Benzyl*-N-2-*pyridylaminoacetonitrile*.—2-Bromo-1 : 1-dimethoxyethane (391 g.) (Bedoukian, *J. Amer. Chem. Soc.*, 1944, **66**, 651) was added (2 hr.) with stirring to benzylamine (550 g.) kept at 120—130° by an oil-bath at 100—105°. The bath-temperature was maintained for a further 45 min. and then the reaction mixture was allowed to cool to 80° and poured into benzene (2 l.). Filtration removed benzylammonium bromide (427 g., 98%). The filtrate was distilled under reduced pressure to give benzene, benzylamine (55 g.), and 2-benzylamino-1 : 1-dimethoxyethane (344 g., 76%), b. p. 102°/1 mm.

A mixture of 2-benzylamino-1 : 1-dimethoxyethane (97·5 g.), 2-bromopyridine (79 g.), and anhydrous potassium carbonate (140 g.) was stirred and heated in an ethylene glycol vapour bath for 19 hr. The filtered mixture was distilled, giving 2-(*N*-benzyl-*N*-2-pyridylamino)-1 : 1-dimethoxyethane (V) (89 g., 65%), b. p. 155—160°/1 mm., m. p. 50° (Found: C, 70·3; H, 7·05; N, 10·1. Calc. for $C_{16}H_{20}O_2N_2$: C, 70·6; H, 7·4; N, 10·3%). The *picrate* separated from alcohol in plates, m. p. 119° (Found: N, 14·2. $C_{22}H_{23}O_9N_5$ requires N, 14·0%). 2-Benzylamino-1 : 1-dimethoxyethane (24 g., 25%) was recovered.

The acetal (V) (27 g.) was dissolved in 2·1N-hydrochloric acid (107 c.c.), and the solution was heated on the steam-bath for 1·5 hr. [The *aldehyde picrate* could be isolated from this solution by neutralisation with lithium hydroxide and addition of an equivalent of aqueous lithium picrate solution. It separated from ethanol in prisms, m. p. 144° (Found: C, 52·15; H, 4·0; N, 15·6. $C_{20}H_{17}O_8N_5$ requires C, 52·8; H, 3·8; N, 15·4%).] Anhydrous sodium acetate (37 g.) and hydroxylamine hydrochloride (28 g.) were dissolved in the hot solution, which was then stored at room temperature for 2 days and poured into excess of saturated aqueous sodium carbonate. The precipitated gum was washed by decantation and boiled with a little ethanol, whereupon N-*benzyl*-N-2-*pyridylaminoacetaldoxime* crystallised in rhombs (20 g., 85%), m. p. 114° (Found: C, 70·3; H, 6·3; N, 17·2. $C_{14}H_{15}ON_3$ requires C, 69·7; H, 6·3; N, 17·4%). The *hydrochloride* separated from alcohol–ether in aggregates of crystals, m. p. 142° (Found: N, 15·0. $C_{14}H_{16}ON_3Cl$ requires N, 15·1%). The *picrate* separated from ethanol in rhombs, m. p. 134° (Found: N, 17·8. $C_{20}H_{18}O_8N_6$ requires N, 17·9%).

A solution of thionyl chloride (3·57 g.) in dry chloroform (10 c.c.) was slowly added to a suspension of the aldoxime (7·23 g.) in dry chloroform (30 c.c.). After the exothermic reaction had subsided, the mixture was heated under reflux for 15 min. and cooled. Dilution with ether precipitated a thick dark oil which was washed with ether and dissolved in water, and the solution was extracted with chloroform, which removed most of the colour. A solution of sodium toluene-*p*-sulphonate (6 g.) in water (25 c.c.) was added to the aqueous layer and the resulting precipitate (8·25 g., 69%; m. p. 192—195°) was recrystallised from 80% ethanol, giving *N*-benzyl-*N*-2-pyridylaminoacetonitrile toluene-*p*-sulphonate as prisms, m. p. 204°.

The toluene-*p*-sulphonate (7·9 g.) was dissolved in hot 75% methanol (40 c.c.) and 5N-sodium hydroxide (24 c.c.), and diluted with cold water (150 c.c.) and ice (20 g.). After 1 hr. at 0° the precipitate was collected and extracted with hot light petroleum (b. p. 80—100°) which left a residue (1·3 g., 16%) of the starting material. The cooled petroleum solution deposited *N*-benzyl-*N*-2-pyridylaminoacetonitrile (1·95 g., 44%), m. p. 83·5°, undepressed by the product prepared by the benzylation of 2-pyridylaminoacetonitrile. A further 1·0 g. (22%) of the nitrile separated from the aqueous-methanolic filtrate after 24 hr. at 0°.

2-(N-*Benzyl*-N-2-*pyridylaminomethyl*)*dihydroglyoxaline*.—*N*-Benzyl-*N*-2-pyridylaminoacetonitrile (4·75 g.) was heated with 2-aminoethylammonium toluene-*p*-sulphonate (5·45 g.) at 145° for 3·5 hr. The hot mixture was diluted with ethanol (15 c.c.) and set aside at room temperature for 2 hr. Filtration yielded the nitrile toluene-*p*-sulphonate (2·40 g., 29%), m. p. and mixed m. p. 203·5°. The filtrate was diluted with water, basified, and extracted with benzene. The extract was washed with water, dried, and evaporated to give 2-(N-*benzyl*-N-2-*pyridylaminomethyl*)*dihydroglyoxaline* (2·80 g., 50%), m. p. 105°. Recrystallisation from light petroleum (b. p. 80—100°) gave prisms, m. p. 108° (Found: N, 20·6. $C_{16}H_{18}N_4$ requires N, 21·0%).

N-*Benzyl*-N-2-*pyridylamino*(*thioacetamide*).—Treating *N*-benzyl-*N*-2-pyridylaminoacetonitrile with hydrogen sulphide in triethylamine–pyridine solution (Fairfull *et al.*, *loc. cit.*) afforded

N-*benzyl*-N-2-*pyridylamino*(*thioacetamide*) (85%) as prisms (from ethanol), m. p. 157° (Found : C, 66·0; H, 5·7; N, 16·1. $C_{14}H_{15}N_3S$ requires C, 65·3; H, 5·9; N, 16·3%).

N-*Benzyl*-N-2-*pyridylaminoacetamidoxime*.—A mixture of *N*-benzyl-*N*-2-pyridylaminoacetonitrile (11·0 g.), hydroxylamine hydrochloride (3·5 g.), sodium hydroxide (2·0 g.), ethanol (75 c.c.), and water (3 c.c.) was heated at 100° for 4 hr. in a glass pressure-bottle. The amber solution, when filtered and chilled overnight, deposited a mass of crystals (8·5 g., 68%), m. p. 128°. Recrystallisation from ethanol gave the *amidoxime* as colourless rods, m. p. 129—131° (Found : C, 65·6; H, 6·2; N, 21·4. $C_{14}H_{16}ON_4$ requires C, 65·6; H, 6·25; N, 21·9%).

α-(N-*Benzyl*-N-2-*pyridylamino*)*acetamidine*.—(*a*) A mixture of *N*-benzyl-*N*-2-pyridylamino(thioacetamide) (1·0 g.), mercuriammonium chloride (3·0 g.), absolute ethanol (100 c.c.), and 5N-alcoholic ammonia (3 c.c.) was shaken at room temperature for 4 days. The filtered solution was evaporated to give a residue which was extracted with hot light petroleum (b. p. 80—100°). *N*-Benzyl-*N*-2-pyridylaminoacetonitrile (0·51 g.; m. p. 84°) was deposited on cooling. The residue from the extraction was dissolved in absolute ethanol, filtered from ammonium chloride, and diluted with dry ether to precipitate the nitrile hydrochloride (0·12 g.), m. p. 204°. The alcoholic mother-liquors were diluted with water and mixed with aqueous lithium picrate; the *amidine picrate* then separated in needles, which on recrystallisation from acetonitrile had m. p. 167° (Found : C, 51·35; H, 3·9; N, 21·3. $C_{20}H_{19}O_7N_7$ requires C, 51·2; H, 4·1; N, 20·9%). The best yield was 0·04 g. (2%).

(*b*) A mixture of *N*-benzyl-*N*-2-pyridylaminoacetamidoxime (5·0 g.), methanol (40 c.c.), water (10 c.c.), and ammonium chloride (1·05 g.) was hydrogenated (Raney nickel catalyst, 1·0 g.) at 60°/30 atm. for 4 hr. When cold, the resulting ammoniacal solution was filtered from catalyst and evaporated to dryness under reduced pressure, giving a yellow gum which was readily soluble in water. The picrate separated from ethanol in bunches of yellow needles, m. p. 168° (decomp.), and m. p. 167° on admixture with the picrate (m. p. 167°) obtained as above. The *toluene*-p-*sulphonate* crystallised from *iso*propanol in colourless needles, m. p. 166° (Found : C, 61·7; H, 5·7; N, 13·3. $C_{21}H_{24}O_3N_4S$ requires C, 61·15; H, 5·9; N, 13·6%). When a solution of the toluene-*p*-sulphonate in dilute hydrochloric acid was quickly made alkaline with sodium hydroxide solution a crystalline precipitate of the free *amidine* was obtained, having m. p. 124—125° (Found : N, 23·0. $C_{14}H_{16}N_4$ requires N, 23·3%). When a dilute solution of the toluene-*p*-sulphonate in water was made alkaline no immediate precipitation occurred, but after several hours colourless needles of *N*-benzyl-*N*-2-pyridylaminoacetamide separated, having m. p. 139° alone or mixed with the hydrolysis product of *N*-benzyl-*N*-2-pyridylaminoacetonitrile (Found : C, 69·6; H, 6·2; N, 17·5%).

N-p-*Chlorobenzyl*-N-2-*pyridylaminoacetonitrile*.—2-Pyridylaminoacetonitrile (30 g.) and *p*-chlorobenzyl chloride (36·4 g.) were heated under reflux in dry chloroform (180 c.c.). After about an hour a heavy oil separated and the mixture was then seeded and heating continued for 2·5 hr. The oil gradually crystallised and, next day, the solid was collected and washed with chloroform, giving 20·5 g. (31%) of yellow plates, m. p. 208—209°. Recrystallisation from a mixture of ethanol (35 c.c.) and ethyl acetate (60 c.c.) afforded colourless plates of the *hydrochloride* (16·5 g., 25%), m. p. 211—212° (Found : N, 14·6. $C_{14}H_{13}N_3Cl_2$ requires N, 14·3%). The free *base* separated slowly in cream needles when an equivalent of N-sodium hydroxide was added to an aqueous solution of the hydrochloride. Two recrystallisations from light petroleum (b. p. 60—80°) afforded colourless needles, m. p. 83—84° (Found : N, 16·4. $C_{14}H_{12}N_3Cl$ requires N, 16·3%).

2-(N-p-*Chlorobenzyl*-N-2-*pyridylaminomethyl*)*dihydroglyoxaline*.—*N*-*p*-Chlorobenzyl-*N*-2-pyridylaminoacetonitrile (5·15 g.) and 2-aminoethylammonium toluene-*p*-sulphonate (4·64 g.) were heated together at 145° for 45 min. and then at 150° for 15 min. Ammonia was evolved rapidly above 140°. The cooled product was dissolved in warm methanol (10 c.c.) and added to water (50 c.c.) and 5N-sodium hydroxide (10 c.c.). The dark oil which was precipitated solidified on stirring. The solid was collected and suspended in water, and dilute hydrochloric acid was added with stirring until the solution was permanently acid to Congo-red paper. The solution was filtered, decolorised with charcoal, and made alkaline; the precipitated oil soon solidified (4·1 g., 68%). The crude dihydroglyoxaline was reconverted into the *toluene*-p-*sulphonate* (57%) which, after two crystallisations from ethyl acetate containing a little ethanol, melted at 161—162° (Found : N, 11·6. $C_{23}H_{25}O_3N_4ClS$ requires N, 11·85%).

α-(N-p-*Chlorobenzyl*-N-2-*pyridylamino*)*acetamidine*.—Sodium hydroxide (2·06 g.) in water (5 c.c.) was added slowly, with cooling and stirring to a suspension of *N*-*p*-chlorobenzyl-*N*-2-pyridylaminoacetonitrile (13·3 g.) and hydroxylamine hydrochloride (3·62 g.) in ethanol (50 c.c.). The mixture was heated in a glass pressure-bottle at 100° for 4·5 hr. and filtered hot

from sodium chloride, and the filtrate was then chilled overnight. The amidoxime separated in colourless needles (8·5 g., 57%), m. p. 166° after two crystallisations from ethanol. The compound appeared to be solvated and analytical results were unsatisfactory.

A mixture of the amidoxime (8·1 g.) in methanol (60 c.c.) and of ammonium chloride (1·5 g.) in water (10 c.c.) was hydrogenated (Raney nickel catalyst, 1·0 g.) at 60—65°/30 atm. for 4 hr. After cooling, the ammoniacal solution was evaporated under reduced pressure. The residual greenish-yellow gum (8·7 g.), which partly solidified, was stirred with water (100 c.c.), and the insoluble residue of amidoxime (3·4 g., 42%) was filtered off from the solution of the amidine hydrochloride. The amidine was isolated as its *toluene*-p-*sulphonate* which separated from ethanol–*iso*propanol in colourless needles, m. p. 168° (Found: C, 56·95; H, 5·05; N, 12·7. $C_{21}H_{23}O_3N_4ClS$ requires C, 56·4; H, 5·15; N, 12·5%). The *picrate* crystallised from ethanol in needles, m. p. 188° (Found: N, 19·6. $C_{20}H_{18}O_7N_7Cl$ requires N, 19·5%).

α-(N-*Benzyl*-N-2-*pyridylamino*)-NN′-*diphenylacetamidine*.—A mixture of 2-benzylaminopyridine (15·3 g.) and sodamide (3·3 g.) in benzene (100 c.c.) was heated under reflux with stirring for 1·5 hr., cooled, and treated with a solution of α-chloro-*NN*′-diphenylacetamidine (20·4 g.) in benzene (50 c.c.). The mixture was then refluxed for 2 hr., cooled, washed with dilute sodium hydroxide, dried ($MgSO_4$), and evaporated. The residue was stirred for 24 hr. with a little ethanol and filtered, giving α-(N-*benzyl*-N-2-*pyridylamino*)-NN′-*diphenylacetamidine* (3·3 g., 10%), which crystallised from ethanol–acetone (4 : 1) in prisms, m. p. 118—119° (Found: C, 79·2; H, 6·1; N, 14·4. $C_{26}H_{24}N_4$ requires C, 79·6; H, 6·2; N, 14·3%). The *monopicrate* separated from ethoxyethanol in stout needles, m. p. 192—192·5° (Found: N, 16·3. $C_{32}H_{27}O_7N_7$ requires N, 15·8%). The *dipicrate* separated from acetone in prisms, m. p. 150° (Found: C, 53·0; H, 3·4; N, 16·35. $C_{38}H_{30}O_{14}N_{10}$ requires C, 53·6; H, 3·6; N, 16·5%). The *sesquihydrochloride* separated from ethanol–ether in prisms, m. p. 199° (Found: N, 12·0; Cl′, 12·1. $C_{26}H_{24}N_4$,1·5HCl requires N, 12·5; Cl′, 11·9%).

Considerable decomposition occurred when the base (3·92 g.) was heated with ammonium benzenesulphonate (1·75 g.) and aniline (15 g.) at 100° for 2·5 hr. in a current of ammonia. No product could be isolated, the base being partly recovered as the monopicrate (1·5 g.), m. p. and mixed m. p. 192°.

Anhydro-5-*acetamido*-3-*benzylpyridino*(1′ : 2′-1 : 2)*glyoxalinium Hydroxide* (VIII; R = Ac).—(a) *From* N-*benzyl*-N-2-*pyridylaminoacetaldoxime*. Acetic anhydride (200 c.c.) was added cautiously to the oxime (50 g.). When the initial reaction had subsided the solution was refluxed for 1·5 hr., cooled, poured on ice, and basified with an excess of 5N-sodium hydroxide with seeding. *Anhydro*-5-*acetamido*-3-*benzylpyridino*(1′ : 2′-1 : 2)*glyoxalinium hydroxide* (48 g., 77%) separated in pale brown rhombs as a *dihydrate* (Found: loss at 90°, 12·3. $C_{16}H_{15}ON_3,2H_2O$ requires H_2O, 12·0%). When dried to constant weight at 90°/5 mm., the rhombs changed to a yellow powder, m. p. 201° (decomp.) (Found: C, 72·9; H, 5·8; N, 15·7. $C_{16}H_{15}ON_3$ requires C, 72·4; H, 5·7; N, 15·8%). The *toluene*-p-*sulphonate* separated from ethanol–ether in rhombs, m. p. 186° (Found: N, 9·5. $C_{23}H_{23}O_4N_3S$ requires N, 9·6%). The *picrate* separated from ethanol in needles, m. p. 147° (Found: N, 17·3. $C_{22}H_{18}O_8N_6$ requires N, 17·0%).

The oxime hydrochloride and acetic anhydride similarly gave a 90% yield of the same compound, m. p. 200° (decomp.).

(b) *From* N-*benzyl*-N-2-*pyridylaminoacetonitrile*. *N*-Benzyl-*N*-2-pyridylaminoacetonitrile hydrochloride (5·84 g.) was acetylated by heating it on the steam-bath for 3 hours with acetic anhydride (21 c.c.). The anhydro-compound (5·66 g., 95%) was obtained as a yellow powder, m. p. 200° (decomp.).

When the nitrile itself was treated similarly, the anhydro-compound was obtained, after a tedious purification, in a yield of 58%, m. p. 193° (decomp.).

Pyrolysis of Anhydro-5-*acetamido*-3-*benzylpyridino*(1′ : 2′-1 : 2)*glyoxalinium Chloride*.—Anhydro-5-acetamido-3-benzylpyridino(1′ : 2′-1 : 2)glyoxalinium hydroxide was converted into its gummy hydrochloride with hydrogen chloride (1 mol.) in absolute ethanol. This gum was heated at 180°/0·03 mm. for 5·5 hr. There was a yellow distillate which partly crystallised when kept, and benzyl chloride, recognised by its characteristic odour, was collected in a trap at −78°. Treatment of the yellow distillate with cold benzene gave 5-acetamidopyridino(1′ : 2′-1 : 2)-glyoxaline (0·28 g., 16%) as colourless needles, m. p. 155—176°, raised by recrystallisation from water to 196—197°, undepressed on admixture with a specimen, m. p. 198°, prepared by acetylation of 2-pyridylaminoacetonitrile.

α-*Benzyl*-N-2-*pyridylaminoacetonitrile*.—Phenylacetaldehyde sodium hydrogen sulphite compound (47·5 g.) in water (70 c.c.) was heated with 2-aminopyridine (21 g.) at 95° for 4 hr. Sodium cyanide (42 g.) in water (150 c.c.) was added and the heating was continued for a further 1·5 hr.

The cooled solution was extracted with chloroform (3 × 200 c.c.), and the extract was dried ($MgSO_4$) and evaporated. The residue afforded *α-benzyl-*N*-2-pyridylaminoacetonitrile* (20 g., 38%) as buff needles (from ethyl acetate), m. p. 105·5° (Found: C, 75·3; H, 6·15; N, 18·8. $C_{14}H_{13}N_3$ requires C, 75·3; H, 5·9; N, 18·8%). The *picrate* separated in needles, m. p. 205°, from ethoxyethanol (Found: N, 18·3. $C_{20}H_{16}O_7N_6$ requires N, 18·6%). The base and cold acetic anhydride–pyridine afforded *5-acetamido-4-benzylpyridino*(1′ : 2′-1 : 2)*glyoxaline* (70%) as colourless hydrated needles from 25% ethanol; after drying to constant weight at 56° the m. p. was 73—88°; when further heated the material resolidified and finally melted at 164° without any further loss in weight (Found: C, 71·9; H, 5·7; N, 15·7; active H, 0·68. $C_{16}H_{15}ON_3$ requires C, 72·4; H, 5·7; N, 15·8%; active H, 1·00). Recrystallisation regenerated the lower-melting form.

*N-Benzyl-*N*-2-pyridylethylenediamine.*—*N*-Benzyl-*N*-2-pyridylaminoacetonitrile (4·46 g.) was reduced with lithium aluminium hydride (0·76 g.) by the method of Amundsen and Nelson (*J. Amer. Chem. Soc.*, 1951, **73**, 242). *N-Benzyl-*N*-2-pyridylethylenediamine* (3·17 g., 70%) was obtained as a water-white oil, b. p. 152—155°/0·9 mm., n_D^{18} 1·6123 (Found: C, 74·3; H, 8·2; N, 18·5. $C_{14}H_{17}N_3$ requires C, 74·0; H, 7·5; N, 18·5%). The *phthaloyl* derivative had m. p. 120°, undepressed on admixture with a specimen prepared from 2-benzylaminopyridine and 2-bromoethylphthalimide (Gardner and Stevens, *J. Amer. Chem. Soc.*, 1949, **71**, 1868, who record m. p. 121—122°) (Found: C, 73·55; H, 5·2; N, 11·9. Calc. for $C_{22}H_{19}O_2N_3$: C, 73·9; H, 5·35; N, 11·8%).

Acetylation of *N*-benzyl-*N*-2-pyridylethylenediamine (2·7 g.) with boiling acetic anhydride (10 c.c.) for 45 min. gave a mixture, separated by ethanol into the *diacetyl* derivative (1·9 g., 52%), prisms, m. p. 125° (Found: C, 69·8; H, 6·85; N, 13·8. $C_{18}H_{21}O_2N_3$ requires C, 69·4; H, 6·8; N, 13·5%), and the *monoacetyl* derivative (1·3 g., 40%), a yellow gum with green fluorescence, b. p. 220° (bath)/1·5 mm. (Found: C, 71·7; H, 7·1; N, 15·9. $C_{16}H_{19}ON_3$ requires C, 71·35; H, 7·1; N, 15·6%). Further acetylation of the monoacetate gave a mixture of mono- and di-acetates as before.

*N-Benzyl-*N′*N′-diethyl-*N*-2-pyridylethylenediamine.*—The reduction of *NN*-diacetyl-*N′*-benzyl-*N′*-2-pyridylethylenediamine (3·11 g.) with ethereal lithium aluminium hydride (0·76 g.) gave *N*-benzyl-*N′N′*-diethyl-*N*-2-pyridylethylenediamine (1·0 g., 35%) as an oil, b. p. 163°/1·2 mm., n_D^{21} 1·5715. The *oxalate* separated from ethanol in needles, m. p. 141° (Found: C, 64·3; H, 7·1; N, 11·2. $C_{20}H_{27}O_4N_3$ requires C, 64·3; H, 7·3; N, 11·3%), undepressed on admixture with the oxalate, m. p. 142°, prepared from the condensation product of 2-benzylaminopyridine and 2-diethylaminoethyl chloride (cf. Huttrer, Djerassi, Beears, Mayer, and Scholz, *ibid.*, 1946, **68**, 1999).

Hydrolysis of Anhydro-5-acetamido-3-benzylpyridino(1′ : 2′-1 : 2)*glyoxalinium Hydroxide.*—A solution of the anhydro-compound (2·0 g.) in 3N-hydrochloric acid (4·5 c.c.) was kept at room temperature for 4 days, then neutralised to pH 4·5 with 5N-sodium hydroxide with ice-cooling and treated with a warm concentrated solution of sodium toluene-*p*-sulphonate (2·0 g.). *N*-Benzyl-*N*-2-pyridylaminoacetonitrile toluene-*p*-sulphonate (1·46 g., 49%), m. p. 196—198°, was collected and recrystallised from 80% ethanol; it had m. p. and mixed m. p. 203—205°.

The anhydro-compound was not hydrolysed by (*a*) boiling ethanolic sodium ethoxide (81% recovery after 4 hr.), (*b*) boiling ethanol containing toluene-*p*-sulphonic acid (89% recovery after 1 hr.), or (*c*) aqueous-ethanolic sodium hydroxide (82% recovery after 13 days at room temperature).

When the anhydro-compound (5·0 g.) was hydrolysed with hot 6N-hydrochloric acid (10 c.c.) and then basified with 40% aqueous sodium hydroxide, sodium *N*-benzyl-*N*-2-pyridylaminoacetate (3·2 g., 73%) separated in needles, m. p. 294—297°, undepressed on admixture with the specimen prepared from *N*-benzyl-*N*-2-pyridylaminoacetonitrile (above). The benzylammonium salt separated from ethoxyethanol in prisms, m. p. 165° (medium rate of heating), undepressed on admixture with the specimen prepared from *N*-benzyl-*N*-2-pyridylaminoacetonitrile (Found: N, 11·7%).

Hydrogenation of Anhydro-5-acetamido-3-benzylpyridino(1′ : 2′-1 : 2)*glyoxalinium Hydroxide.*—The anhydro-compound (10·0 g.), dissolved in glacial acetic acid (100 c.c.), was hydrogenated with Adams platinum catalyst at 45—60° and atmospheric pressure. The hydrogen absorption was 97·5% of theory for 2 mols. The residue after filtration and evaporation below 30° was dissolved in 4N-sodium hydroxide (120 c.c.), and the solution was extracted with chloroform (3 × 130 c.c.). The dried ($MgSO_4$) extract was evaporated and the solid residue was crystallised by dissolving it in 80% acetone (23 c.c.) and adding acetone (42 c.c.). The *tetrahydro*-derivative (7·8 g., 68%) separated in rhombs as a dihydrate, m. p. 274—275° (Found: loss at 100°, 12·0.

$C_{16}H_{19}ON_3,2H_2O$ requires H_2O, 11·8%. Found, on material dried at 100°: C, 70·9; H, 7·1; N, 15·5. $C_{16}H_{19}ON_3$ requires C, 71·3; H, 7·1; N, 15·6%).

After hot acid hydrolysis a product was obtained as a *picrate* (91% yield), m. p. 152·5—153°. On recrystallisation from ethanol it separated in dendrites, m. p. 153·5° (Found: C, 52·45; H, 3·9; N, 15·4. $C_{20}H_{19}O_8N_5$ requires C, 52·5; H, 4·2; N, 15·3%). A quantitative experiment showed the liberation of acetic acid (1·00 mol.) and ammonia (1·01 mol.). The base could not be crystallised, and it did not react with hydroxylamine, semicarbazide, or 2 : 4-dinitrophenylhydrazine. It was soluble in water and gave a non-crystalline, water-insoluble benzoate.

Alkylation of Anhydro-5-acetamido-3-benzylpyridino(1′ : 2′-1 : 2)glyoxalinium Hydroxide.—The anhydro-compound (7·95 g.), suspended in acetone (50 c.c.), was heated under reflux for 50 min. with methyl iodide (3·6 c.c.). *5-Acetmethylamido-3-benzylpyridino(1′ : 2′-1 : 2)glyoxalinium iodide* (10·6 g., 86%), m. p. 193°, was collected and recrystallised from ethanol–ether, separating in colourless plates, m. p. 194° (Found: C, 50·3; H, 4·3; N, 10·5; I′, 31·4; OMe, 1·35. $C_{17}H_{18}ON_3I$ requires C, 50·1; H, 4·45; N, 10·3; I′, 31·2; OMe, 0 or 7·6%).

A hot acid hydrolysate was basified and distilled into 0·1N-hydrochloric acid. Evaporation gave a 94% yield of methylammonium chloride, m. p. 214—220° after crystallisation from *iso*propanol, undepressed on admixture with an authentic specimen (Found: Cl′, 52·2, 55·4. Calc. for CH_6NCl: Cl′, 52·7%). This was converted into methylammonium picrate, m. p. and mixed m. p. 206—207° (decomp.).

A solution of the iodide (1·02 g.) in a mixture of 0·5N-hydrochloric acid (5 c.c.) and ethanol (2·5 c.c.) deposited a mixture of yellow needles and purple prisms after 4 weeks at room temperature. The solid was collected and extracted with cold methanol (5 c.c.); on the addition of ether *3-benzyl-5-methylaminopyridino(1′ : 2′-1 : 2)glyoxalinium iodide* (0·28 g., 31%) separated in yellow needles, m. p. 156° (Found: C, 49·1; H, 4·4; N, 11·7; I′, 34·1. $C_{15}H_{16}N_3I$ requires C, 49·3; H, 4·4; N, 11·5; I′, 34·8%). The residual purple prisms, m. p. 119° (0·20 g.) after recrystallisation from methanol, were not investigated further. Methylamine, identified as its hydrochloride (35 mg.) and picrate, was isolated from the aqueous hydrolysate in a parallel experiment after only 2 days.

When the anhydro-compound (2·65 g.) was treated with methyl iodide (1·6 g.) in methanol (10 c.c.) at room temperature for 4 weeks, the methylamino-derivative (2·38 g., 65%) separated in salmon-pink needles, m. p. 143—145°. Crystallisation from methanol–ether with charcoal gave yellow needles, m. p. 156°, undepressed on admixture with the product obtained above.

A mixture of the anhydro-compound (3·96 g.), ethyl iodide (3·0 g.), and acetone (30 c.c.) was heated under reflux for 3 hr., cooled, and seeded. The crude *5-acetethylamido-3-benzylpyridino(1′ : 2′-1 : 2)glyoxalinium iodide* crystallised from ethanol–ether in rhombs, m. p. 185° (Found: N, 10·2. $C_{18}H_{20}ON_3I$ requires N, 10·0%).

The anhydro-compound reacted completely in about 5 min. with allyl iodide in acetone. *5-Acetallylamido-3-benzylpyridino(1′ : 2′-1 : 2)glyoxalinium reineckate* separated from acetone–ethanol as a microcrystalline powder, m. p. 158—160° (Found: C, 44·2; H, 4·5; N, 19·7. $C_{23}H_{26}ON_9S_4Cr$ requires C, 44·2; H, 4·2; N, 20·2%).

When the anhydro-compound was treated with *n*-propyl toluene-*p*-sulphonate in hot *iso*butyl methyl ketone for 15 min. *5-acetpropylamido-3-benzylpyridino(1′ : 2′-1 : 2)glyoxalinium toluene-p-sulphonate* (60%) was obtained, separating from ethanol–ether in needles, m. p. 147·5° (Found: C, 64·4; H, 6·1; N, 9·0. $C_{26}H_{29}O_4N_3S$ requires C, 65·1; H, 6·1; N, 8·8%).

Anhydro-5-acetamido-3-benzyl-3′-methylpyridino(1′ : 2′-1 : 2)glyoxalinium Hydroxide.—This compound was obtained by the acetal–oxime route used for the preparation of (VIII; R = Ac). Condensation of 2-benzylamino-1 : 1-dimethoxyethane and 2-bromo-3-methylpyridine (Case, *J. Amer. Chem. Soc.*, 1946, **68**, 2574) afforded *2-[N-benzyl-N-(3-methyl-2-pyridyl)amino]-1 : 1-dimethoxyethane* (56%), b. p. 140—144°/0·25 mm., n_D^{22} 1·5583 (Found: N, 9·7. $C_{17}H_{22}O_2N_2$ requires N, 9·7%). Hydrolysis and oximation afforded a non-crystalline oxime which with acetic anhydride gave *anhydro-5-acetamido-3-benzyl-3′-methylpyridino(1′ : 2′-1 : 2)glyoxalinium hydroxide* (15%) as a *monohydrate*, red-brown rhombs, m. p. 245—247° (decomp.) (from water) (Found: H_2O, 6·1. $C_{17}H_{17}ON_3,H_2O$ requires H_2O, 6·1%). On drying at 100° the colour changed to yellowish green and the m. p. rose to 249—250° (decomp.) (Found: C, 73·2; H, 6·0; N, 14·95. $C_{17}H_{17}ON_3$ requires C, 73·1; H, 6·1; N, 15·05%).

Anhydro-5-acetamido-3-(2 : 4 : 6-trimethylbenzyl)pyridino(1′ : 2′-1 : 2)glyoxalinium Hydroxide.—Similarly, 1 : 1-dimethoxy-2-(2 : 4 : 6-trimethylbenzylamino)ethane, b. p. 125—132°/0·9 mm. (35% yield from the condensation of 2 : 4 : 6-trimethylbenzylamine and 2-bromo-1 : 1-dimethoxyethane) afforded, successively, *2-[N-2-pyridyl-N-(2 : 4 : 6-trimethylbenzyl)amino]-*

1 : 1-dimethoxyethane (61%; b. p. 174—176°/0·8 mm.), N-2-*pyridyl*-N-(2 : 4 : 6-*trimethylbenzyl*)*aminoacetaldoxime* (41%), needles (from ethanol), m. p. 172° (Found: C, 72·3; H, 7·1; N, 14·45. $C_{17}H_{21}ON_3$ requires C, 72·1; H, 7·5; N, 14·8%) [*hydrochloride*, plates (from water), m. p. 222—223° (Found: Cl′, 10·9. $C_{17}H_{21}ON_3$,HCl requires Cl′, 11·1%)], and *anhydro*-5-*acetamido*-3-(2 : 4 : 6-*trimethylbenzyl*)*pyridino*(1′ : 2′-1 : 2)*glyoxalinium hydroxide* (30%), which crystallised from water as colourless, hydrated needles, m. p. 210° (decomp.), which became yellow when dried at 100° (Found: C, 73·7; H, 6·8; N, 14·0. $C_{19}H_{21}ON_3$ requires C, 74·2; H, 6·9; N, 13·7%).

Anhydro-5-*acetamido*-3-(2-*thienylmethyl*)*pyridino*(1′ : 2′-1 : 2)*glyoxalinium Hydroxide.*—1 : 1-Dimethoxy-2-(2-pyridylamino)ethane, sodamide, and 2-thienylmethyl chloride in toluene gave 1 : 1-*dimethoxy*-2-(N-2-*pyridyl*-N-2′-*thienylmethyl*)*ethane* (61%), b. p. 166—173°/1 mm. (Found: C, 59·9; H, 6·2; N, 10·0. $C_{14}H_{18}O_2N_2S$ requires C, 60·4; H, 6·5; N, 10·1%). Hydrolysis and oximation yielded N-2-*pyridyl*-N-(2-*thienylmethyl*)*aminoacetaldoxime* (62%), plates (from ethanol), m. p. 106° (Found: C, 58·2; H, 5·4; N, 16·4. $C_{12}H_{13}ON_3S$ requires C, 58·3; H, 5·3; N, 17·0%). Boiling acetic anhydride afforded *anhydro*-5-*acetamido*-3-(2-*thienylmethyl*)*pyridino*-(1′ : 2′-1 : 2)*glyoxalinium hydroxide* (74%) as colourless, hydrated plates (from water), m. p. 93° (Found: loss at 78°, 11·7. $C_{14}H_{13}ON_3S,2H_2O$ requires H_2O, 11·7%). The dried product was a yellow powder, m. p. 185—186° (decomp.) (Found: C, 61·5; H, 4·9; N, 15·5. $C_{14}H_{13}ON_3S$ requires C, 62·0; H, 4·8; N, 15·5%). The *picrate* separated from ethanol in stout needles, m. p. 149—150° (Found: C, 48·5; H, 3·4; N, 16·6. $C_{20}H_{16}O_8N_6S$ requires C, 48·0; H, 3·2; N, 16·8%).

Anhydro-5-*acetamido*-3-*ethylpyridino*(1′ : 2′-1 : 2)*glyoxalinium Hydroxide.*—A mixture of 2-pyridylaminoacetonitrile (10·0 g.), ethyl iodide (11·9 g.), and chloroform (40 c.c.) was heated under reflux for 24 hr. and poured into ether (200 c.c.). The resulting N-*ethyl*-N-2-*pyridylaminoacetonitrile hydriodide* (11·8 g., 54%) separated from ethanol in prisms, m. p. 182° (Found: C, 37·85; H, 4·15; N, 14·5; I′, 43·8. $C_9H_{12}N_3I$ requires C, 37·4; H, 4·2; N, 14·5; I′, 43·9%). Boiling the finely powdered material with acetic anhydride for 10 min. yielded *anhydro*-5-*acetamido*-3-*ethylpyridino*(1′ : 2′-1 : 2)*glyoxalinium hydroxide trihydrate* as colourless needles (from water), m. p. 92° (Found: loss at 65°, 21·2. $C_{11}H_{13}ON_3,3H_2O$ requires H_2O, 21·0%). The yellow anhydrous *base* had m. p. 163° (decomp.) (Found: N, 20·4. $C_{11}H_{13}ON_3$ requires N, 20·7%). The hydriodide separated from ethanol in rhombs, m. p. 248°.

Anhydro-5-*acetamido*-3-*phenylpyridino*(1′ : 2′-1 : 2)*glyoxalinium Hydroxide.*—2-Anilinopyridine, sodamide, and 2-bromo-1 : 1-dimethoxyethane in benzene gave 1 : 1-dimethoxy-2-(*N*-phenyl-*N*-2-pyridylamino)ethane (19%), b. p. 140—145°/1·2 mm.; 2-anilinopyridine (47%) was recovered. Hydrolysis and oximation gave N-*phenyl*-N-2-*pyridylaminoacetaldoxime* (45%), prisms (from ethanol), m. p. 93° (Found: C, 69·3; H, 5·95; N, 18·2. $C_{13}H_{13}ON_3$ requires C, 68·7; H, 5·8; N, 18·5%). Boiling acetic anhydride afforded *anhydro*-5-*acetamido*-3-*phenylpyridino*(1′ : 2′-1 : 2)*glyoxalinium hydroxide* (69%) as pale brown hydrated needles from water. The anhydrous form was obtained as a yellow powder, m. p. 193° (Found: C, 71·15; H, 5·3; N, 16·8. $C_{15}H_{13}ON_3$ requires C, 71·7; H, 5·2; N, 16·7%).

Anhydro-5-*acetamido*-3-(2-*pyridyl*)*pyridino*(1′ : 2′-1 : 2)*glyoxalinium Hydroxide.*—2-(*Di*-2-*pyridyl*)*amino*-1 : 1-*dimethoxyethane* (34%) was prepared from 1 : 1-dimethoxy-2-(2-pyridylamino)ethane (Kaye, *loc. cit.*), sodamide, and 2-bromopyridine and had b. p. 155—160°/1 mm. (Found: C, 65·3; H, 6·8; N, 16·3. $C_{14}H_{17}O_2N_3$ requires C, 64·8; H, 6·6; N, 16·2%). It was also prepared in 25% yield from 2 : 2′-dipyridylamine, sodamide, and 2-bromo-1 : 1-dimethoxyethane. Hydrolysis and oximation gave crude *NN*-di-2-pyridylaminoacetaldoxime (36%) as an oil. Boiling acetic anhydride converted this into a water-soluble product which could be extracted from alkaline solution with chloroform. Addition of light petroleum to the chloroform extract afforded *anhydro*-5-*acetamido*-3-(2-*pyridyl*)*pyridino*(1′ : 2′-1 : 2)*glyoxalinium hydroxide* (17%) as needles, m. p. 210—212° (decomp.) with rapid heating (Found, on material dried at 100°: C, 66·5; H, 5·0; N, 21·9. $C_{14}H_{12}ON_4$ requires C, 66·65; H, 4·8; N, 22·2%). The crystals were variably solvated, depending on the relative proportions of chloroform and light petroleum in the solvent.

Anhydro-3-*benzyl*-5-*propionamidopyridino*(1′ : 2′-1 : 2)*glyoxalinium Hydroxide.*—Heating *N*-benzyl-*N*-2-pyridylaminoacetonitrile hydrochloride (3 g.) under reflux with propionic anhydride (10 c.c.) for 45 min. gave *anhydro*-3-*benzyl*-5-*propionamidopyridino*(1′ : 2′-1 : 2)*glyoxalinium hydroxide monohydrate* (3·1 g., 90%) as needles (from water), m. p. 135—136° (Found, on material dried at 78°: C, 69·2; H, 6·4; N, 14·3; H_2O, 5·5. $C_{17}H_{17}ON_3,H_2O$ requires C, 68·7; H, 6·4; N, 14·1; H_2O, 6·05%). Heating an acetone solution of this hydrate with methyl iodide under reflux for 15 min. gave 3-*benzyl*-5-*propionmethylamidopyridino*(1′ : 2′-1 : 2)-

glyoxalinium iodide (65%) as prisms (from ethanol–ether), m. p. 135° (Found: N, 10·1. $C_{18}H_{20}ON_3I$ requires N, 10·0%).

Anhydro-5-benzamido-3-benzylpyridino(1′ : 2′-1 : 2)*glyoxalinium Hydroxide.*—Heating *N*-benzyl-*N*-2-pyridylaminoacetonitrile hydrochloride with benzoyl chloride in pyridine for 2 hr. at 95° afforded *anhydro-5-benzamido-3-benzylpyridino*(1′ : 2′-1 : 2)*glyoxalinium hydroxide* (1·7 g., 33%) as solvated yellow-brown prisms, m. p. 188°, from chloroform–light petroleum (b. p. 60—80°) (Found: loss at 100°, 26·6. $C_{21}H_{17}ON_3,CHCl_3$ requires $CHCl_3$, 26·7%. Found, on material dried at 100°: C, 77·0; H, 4·9; N, 13·1. $C_{21}H_{17}ON_3$ requires C, 77·0; H, 5·2; N, 12·8%). When the oxime was substituted for the nitrile hydrochloride the yield was only 14%.

Anhydro-5-benzenesulphonamido-3-benzylpyridino(1′ : 2′-1 : 2)*glyoxalinium Hydroxide.*—Heating *N*-benzyl-*N*-2-pyridylaminoacetonitrile hydrochloride with benzenesulphonyl chloride in pyridine for 2 hr. at 95° yielded *anhydro-5-benzenesulphonamido-3-benzylpyridino*(1′ : 2′-1 : 2)-*glyoxalinium hydroxide* (64%), green needles (from methanol), m. p. 208° (Found: N, 11·7. $C_{20}H_{17}O_2N_3S$ requires N, 11·6%). Heating under reflux with ethanolic methyl iodide for 10 hr. yielded *5-benzenesulphonmethylamido-3-benzylpyridino*(1′ : 2′-1 : 2)*glyoxalinium iodide* (79%), plates (from water), m. p. 201° (Found: C, 48·95; H, 4·0; N, 8·3. $C_{21}H_{20}O_2N_3IS$ requires C, 49·9; H, 4·0; N, 8·3%).

1-*Carbamoylmethyl*-1 : 2-*dihydro*-2-*sulphanilimidopyridine* (X; R = NH_2, R′ = $CO{\cdot}NH_2$).—Chloroacetamide (10·0 g.) was added to a filtered solution of sulphapyridine (24·9 g.) in N-sodium hydroxide (100 c.c.), and the mixture was heated for 2 hr. at 95°. After cooling, the product was collected and washed with 4% sodium hydroxide solution, giving 1-*carbamoylmethyl*-1 : 2-*dihydro*-2-*sulphanilimidopyridine* (19·0 g., 62%) as minute prisms, m. p. 208—210° (decomp.) (Found: N, 18·3. $C_{13}H_{14}O_3N_4S$ requires N, 18·3%). Sulphapyridine (3·8 g., 15%; m. p. 186—187°) was recovered.

4-*Hydroxypyridino*(1′ : 2′-1 : 2)*glyoxaline* (XI).—1-Carbamoylmethyl-1 : 2-dihydro-2-sulphanilimidopyridine (9·5 g.) was heated with N-sodium hydroxide (40 c.c.) for 2·5 hr. at 95°. The clear, cooled solution was neutralised with N-hydrochloric acid (40 c.c.). The precipitated 1-carboxymethyl-1 : 2-dihydro-2-sulphanilimidopyridine [8·0 g., 84%; m. p. 127—157° (decomp.)] solidified on being seeded. The *anilinium* salt separated from water in clusters of prisms, m. p. 115° (Found: N, 13·8. $C_{19}H_{20}O_4N_4S$ requires N, 14·0%). The acid was heated under reflux with 5N-hydrochloric acid (50 c.c.) for 18 hr., then cooled. Sulphanilic acid (2·7 g., 60%) separated and was characterised by conversion into 2 : 4 : 6-tribromoaniline, m. p. and mixed m. p. 120°. The filtered solution was evaporated to dryness *in vacuo* and the residue was dissolved in water. Excess of aqueous lithium picrate precipitated 4-hydroxypyridino(1′ : 2′-1 : 2)glyoxalinium picrate (8·1 g., 86%) as needles, m. p. 208° (decomp.), undepressed on admixture with a specimen prepared by Reindel's method (*loc. cit.*) (Found: C, 43·2; H, 2·5; N, 18·9. Calc. for $C_{13}H_9O_8N_5$: C, 43·0; H, 2·5; N, 19·3%).

1-*Cyanomethyl*-1 : 2-*dihydro*-2-*toluene*-p-*sulphonimidopyridine.*—Condensation of chloroacetonitrile and 2-toluene-*p*-sulphonamidopyridine similarly afforded 1-*cyanomethyl*-1 : 2-*dihydro*-2-*toluene*-p-*sulphonimidopyridine* (67%) which separated from ethanol in rhombs, m. p. 160—162° (Found: N, 14·5. $C_{14}H_{13}O_2N_3S$ requires N, 14·6%).

1-*Carbamoylmethyl*-1 : 2-*dihydro*-2-*toluene*-p-*sulphonimidopyridine.*—Prepared by the method used for the sulphanilyl analogue, this *amide* (70%) separated from 50% ethoxyethanol in plates, m. p. 166—173° (Found: N, 13·6. $C_{14}H_{15}O_3N_3S$ requires N, 13·8%); 2-toluene-*p*-sulphonamidopyridine (24%) was recovered, m. p. 213°. Hydrolysis in hot N-sodium hydroxide yielded 1-*carboxymethyl*-1 : 2-*dihydro*-2-*toluene*-p-*sulphonimidopyridine* (95%), thick plates, m. p. 190°, from ethanol–ether (Found: C, 55·1; H, 4·45; N, 9·1. $C_{14}H_{14}O_4N_2S$ requires C, 54·9; H, 4·6; N, 9·1%). The *benzylammonium* salt crystallised from ethanol in plates, m. p. 173° (Found: N, 10·1. $C_{21}H_{23}O_4N_3S$ requires N, 10·2%).

4-*Acetamidopyridino*(1′ : 2′-1 : 2)*glyoxaline.*—1-Carbamoylmethyl-1 : 2-dihydro-2-toluene-*p*-sulphonimidopyridine (5·0 g.) was heated under reflux with acetic anhydride (15 c.c.) for 50 min. After evaporation of the solution under reduced pressure, the residue was dissolved in a little ethanol and basified with ice-cooling. 4-*Acetamidopyridino*(1′ : 2′-1 : 2)*glyoxaline* (1·0 g., 35%) was collected and recrystallised from ethanol or ethoxyethanol, from which it separated in long needles, m. p. 229° (Found: C, 61·5; H, 5·1; N, 23·6. $C_9H_9ON_3$ requires C, 61·7; H, 5·2; N, 24·0%).

Similar acetylation of 1-carbamoylmethyl-1 : 2-dihydro-2-sulphanilimidopyridine gave the same compound (36%), m. p. 230°, undepressed by the specimen prepared above.

Hydrolysis with hot 30% sodium hydroxide solution afforded 4-aminopyridino(1′ : 2′-1 : 2)-glyoxaline (58%) as a crude solid, m. p. 73—83° after rapid distillation at 2 mm. (some decomp.),

unstable in air. The *picrate* separated from 50% ethanol in clusters of brown needles, m. p. 200° (decomp.) (Found : C, 43·2; H, 2·9; N, 23·6. $C_{13}H_{10}O_7N_6$ requires C, 43·1; H, 2·8; N, 23·2%)

The authors are indebted to Dr. J. D. S. Goulden and Mr. P. G. Marshall for the determination of infra-red spectra.

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[*Received, October 24th,* 1953.]