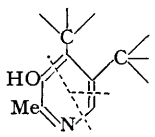
838. *Synthetical Experiments in the B Group of Vitamins. Part IV.* A Synthesis of Pyridoxine.*

By A. COHEN, J. W. HAWORTH, and E. G. HUGHES.

Condensation of *N*-alkyl- or *N*-arylalkyl-alanine esters with α-formylsuccinic esters yields *N*-alkyl- or *N*-arylalkyl-*N*-1-carbalkoxyethylaminomethylenesuccinic esters (I). These are cyclised (Dieckmann) to basic keto-esters (II), the hydrochlorides of which yield pyridinium salts (IV) by dehydrogenation. The 1-benzylpyridinium salt (IV) gives, on hydrogenolysis, dialkyl 3-hydroxy-2-methylpyridine-4 : 5-dicarboxylates which are convertible into pyridoxine by standard reactions (VI ⟶ X). Suitable quaternary ammonium bases convert 3-hydroxypyridines into their 3-ethers, *e.g.*, diethyl 3-benzyloxy-2-methylpyridine-4 : 5-dicarboxylate (VI; R = Et, R′ = CH_2Ph) which during the reactions (VI ⟶ X) gives the 3-hydroxy-diamine (IX; R = H) by simultaneous hydrogenolysis and reduction of the nitrile groups in (VIII). By a shorter route, the 3-benzyloxy-diester is directly reduced by lithium aluminium hydride to pyridoxine benzyl ether which is hydrogenolysed to pyridoxine.

THIS communication presents details of a synthesis of pyridoxine which has been outlined elsewhere (cf. Festschrift E. C. Barrell, Basle, 1946, p. 71; XIth Internat. Congr. Pure and Appl. Chem., 1947, Abs. 247/3) and disclosed in patents (B.P. 551,216, 556,044, 591,170, 603,811, 625,997, 629,423, 629,450). Unlike syntheses based on an initial pyridone condensation (Harris, Folkers, and their co-workers, *J. Amer. Chem. Soc.*, 1939, **61**, 1245, 3307; Morii and Makino, *Enzymologia*, 1939, **7**, 385; Mowat, Pilgrim, and Carlson, *J. Amer. Chem. Soc.*, 1943, **65**, 954) or on oxidative degradation of an *iso*quinoline derivative (Kuhn, Westphal, Wendt, and Westphal, *Naturwiss.*, 1939, **27**, 469), the present synthesis was based on a hypothetical derivation of the B_6 group of vitamins from units of alanine, formaldehyde, and a four-carbon compound, as shown in the formula inset. This conception was independent of Snell and Guirard's evidence (*Proc. Nat. Acad. Sci.*, 1943, **29**, 66) that alanine was a microbiological precursor of vitamin B_6. Subsequent work has shown that, although D-alanine, a common cell-constituent for many micro-organisms, can replace vitamin B_6 in culture media, it does not produce additional vitamin.

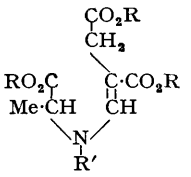


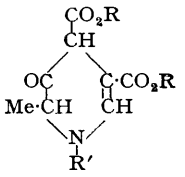
The reaction between DL-alanine ester and ethyl α-formylsuccinate was first studied as one of a number of analogous condensations (*J.*, 1950, 3005). The resulting *N*-substituted aminomethylenesuccinic ester (I; R = Et, R′ = H), like analogous compounds of this series, was found (*loc. cit.*) to yield, on cyclisation, not the desired cyclic keto-ester (cf. II) which was to be dehydrogenated to a 3-hydroxypyridine derivative, but a derivative of Δ^4-pyrrolin-2-one. It was realised that cyclisation to compounds of type (II) required an aminomethylenesuccinic ester completely substituted at the nitrogen atom, and therefore derived from a secondary α-amino-ester.

Accordingly, in a model synthesis, ethyl DL-α-methylaminopropionate was condensed with ethyl α-formylsuccinate, yielding ethyl *N*-1-carbethoxyethyl-*N*-methylaminomethylenesuccinate (I; R = Et, R′ = Me). This was cyclised by sodium, sodium ethoxide, or sodamide under the conditions of a Dieckmann reaction to the cyclic keto-ester (II; R = Et, R′ = Me). Although cyclisations to piperidones are well known and have often been reported since the initial conversion of bis-2-carbethoxyethylmethylamine into ethyl 3-keto-1-methylpiperidine-4-carboxylate by Prill and McElvain (*J. Amer. Chem. Soc.*, 1933, **55**, 1233), it is believed that this is the first instance of a Dieckmann cyclisation of aminomethylene compounds of type (I) to a dihydropyridone (cf. II). That such was the nature of the product was observable in the β-keto-ester character (ferric chloride reaction) and the formation, under anhydrous conditions, of a hydrochloride of a weak base, readily hydrolysed in water. Moreover, although simple

* Part III, Bergel, Hindley, Morrison, and Moss, *Chem. Ber.*, 1952, **85**, 711. Part II, *J.*, 1950, 3005.

dehydrogenation of the free base (II; R′ = Me) was not feasible, its hydrochloride was dehydrogenated when exposed to dry air or repeatedly recrystallised from alcohol–ether, yielding the pyridinium salt (IV). Dehydrogenation was more controllable when the keto-ester was treated with sulphuryl chloride: the primary oily product was readily converted when warmed under reduced pressure into crystalline 4 : 5-dicarbethoxy-3-hydroxy-1 : 2-dimethylpyridinium chloride (IV; R = Et, R′ = Me, X = Cl). It is presumed that, initially, chlorination occurs at the reactive 4-position, the liberated hydrogen chloride forming a salt with the base. The resulting postulated intermediate (III; R = Et, R′ = Me) could lose hydrogen chloride to give the quaternary salt. The latter is a stable water-soluble salt which is converted into the phenol-betaine (V; R = Et, R′ = Me) when treated with sodium hydrogen carbonate or one mol. of sodium hydroxide. This compound, related to the phenol-betaine derived from pyridoxine methiodide (Harris, Webb, and Folkers, *J. Amer. Chem. Soc.*, 1940, **62**, 3198), exists as a colourless hydrate which is converted into a yellow anhydrous form when dried in a vacuum or heated. Alkaline hydrolysis of the ester groups of (IV), followed by neutralisation, leads to an acid-betaine. This is not formulated since either the 4- or the 5-carboxyl group may be involved in the betaine group.


(I)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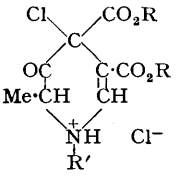
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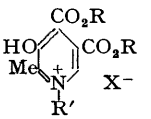
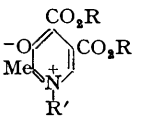

(IV)


(V)

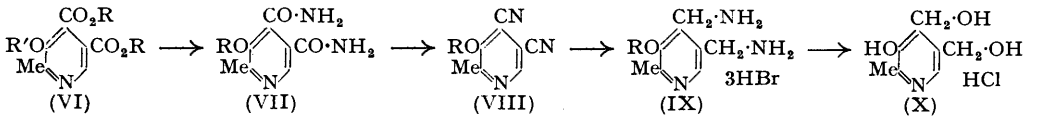
These results were applied to the synthesis of a pyridinium salt capable of conversion into a pyridine derivative, by using the *N*-benzyl compounds. Methyl α-formylsuccinate and methyl DL-α-benzylaminopropionate (cf. Bischoff, *Ber.*, 1897, **30**, 3169) gave an excellent yield of methyl *N*-benzyl-*N*-1-carbomethoxyethylaminomethylenesuccinate (I; R = Me, R′ = CH_2Ph), a high-boiling oil of remarkable thermal stability (the corresponding triethyl ester was equally stable). Dieckmann cyclisation afforded a crude cyclic keto-ester (II; R = Me, R′ = CH_2Ph), converted by the methods already mentioned, and also by direct chlorination, into 1-benzyl-4 : 5-dicarbomethoxy-3-hydroxy-2-methylpyridinium chloride (IV; R = Me, R′ = CH_2Ph, X = Cl). Bromination of the cyclic keto-ester yielded the corresponding bromide (IV; R = Me, R′ = CH_2Ph, X = Br) and these quaternary salts were also converted into the phenol-betaine (V; R = Me, R′ = CH_2Ph) by sodium hydrogen carbonate or by one equivalent of sodium hydroxide. Like the 1-methyl-betaine already mentioned, this 1-benzyl-betaine is a colourless hydrate convertible into a yellow anhydrous form. The quaternary chloride in the ethyl ester series was similarly synthesised from (I; R = Et, R′ = CH_2Ph).

Hydrogenolysis of the 1-benzylpyridinium chlorides yielded methyl and ethyl 3-hydroxy-2-methylpyridine-4 : 5-dicarboxylate (VI; R = Me or Et, R′ = H) in the form of hydrochlorides from which the free basic esters were obtained by mild alkaline treatment. The esters were readily hydrolysed by alkali to 3-hydroxy-2-methylpyridine-4 : 5-dicarboxylic acid (VI; R = R′ = H) (Itiba and Emoto, *Sci. Papers. Inst. Phys. Chem. Res., Tokyo*, 1941, **38**, 347). Methylation of the hydroxy-esters with diazomethane followed by hydrolysis yielded the known 3-methoxy-2-methylpyridine-4 : 5-dicarboxylic acid (Itiba and Miti, *ibid.*, 1939, **36**, 173; Kuhn *et al.*, *loc. cit.*; Harris, Stiller, and Folkers, *J. Amer. Chem. Soc.*, 1939, **61**, 1242).

Since the conversion of the tetrahydroketopyridine (II; R′ = CH_2Ph) into the 3-hydroxypyridine derivative (VI; R′ = H) involved consecutive dehydrogenation and hydrogenation, the possibility of direct conversion by a single-stage elimination of the elements of toluene was attempted by heating (II; R = Me, R′ = CH_2Ph) at low pressure. There was considerable decomposition and only a small amount of, probably, a 3-hydroxypyridine was found in the distillate (Gibbs's test).

The further conversion of the 3-hydroxypyridine diester (VI; R = Me, R′ = H) into

pyridoxine hydrochloride (cf. VI ⟶ X) was accomplished by routine procedures previously outlined by Kuhn *et al.* (*loc. cit.*). Although references to these intermediates have been made in patents (cf. U.S.P. 2,359,260, 2,371,694, 2,410,531; G.P. 701,955, 702,829) their characterisation has in some cases been meagre, and the compounds are described in the Experimental section.

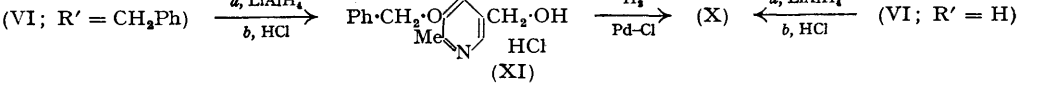


The methylation of the 3-hydroxyl group with diazomethane (VI; R′ = H ⟶ Me) and the necessary subsequent demethylation have been eliminated in an improved modification employing the principle of alkylation of phenols by a quaternary base. It was first found in model experiments that the 3-hydroxypyridine derivative (VI; R′ = H) was *O*-methylated by trimethylphenylammonium hydroxide, and that 3-hydroxypyridine yielded 3-benzyloxypyridine when heated with benzyldimethylphenylammonium hydroxide ("leucotrope"), a reaction analogous to the benzylation of phenols described by Baw (*J. Indian Chem. Soc.*, 1926, **3**, 101). By a similar procedure (VI; R = Me or Et, R′ = H) were benzylated to the 3-benzyloxypyridine diesters (VI; R = Me or Et respectively, R′ = CH_2Ph).

Attempts to achieve intramolecular *O*-benzylation of (VI; R′ = H) by thermal rearrangement of the *N*-benzyl-phenol-betaine (V; R′ = CH_2Ph) failed.

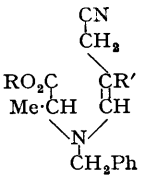
The 3-benzyloxy-esters yielded the same diamide (VII; R = CH_2Ph) which was dehydrated to the 3-benzyloxy-dinitrile (VIII; R = CH_2Ph). When this was hydrogenated to the diamine in acidic methanol, simultaneous hydrogenolysis of the benzyl group furnished directly 4 : 5-bisaminomethyl-3-hydroxy-2-methylpyridine trihydrochloride (cf. IX; R = H) which yielded pyridoxine hydrochloride (X) on treatment with nitrous acid.

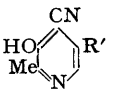
Finally, a further considerable improvement of the synthesis was effected, which eliminated the stages of the amide, nitrile, and aminomethyl derivatives, by reducing the 4 : 5-dicarboxylate groups with lithium aluminium hydride (cf. Nystrom and Brown, *J. Amer. Chem. Soc.*, 1947, **69**, 1197). It was first found that the method could be applied to the pyridine series by reducing ethyl nicotinate to 3-hydroxymethylpyridine (B.P. 631,078). Methyl and ethyl 3-benzyloxy-2-methylpyridine-4 : 5-dicarboxylate (VI; R′ = CH_2Ph, R = Me and Et, respectively) were then reduced to pyridoxine benzyl ether which was readily isolated as a hydrochloride (XI) and smoothly hydrogenolysed to pyridoxine hydrochloride. Further the free 3-hydroxypyridine diester (VI; R′ = H) was similarly reduced to pyridoxine but the separtion of this amphoteric substance was inconvenient. Lithium aluminium hydride reduction of pyridinecarboxylic esters was applied to the synthesis of pyridoxine in 1947 (B.P. 629,450); similar results have since been described by Jones and Kornfeld (*J. Amer. Chem. Soc.*, 1951, **73**, 107).



Attempts at a modified synthesis were made by using substituted aminomethylenesuccinic acid derivatives obtained from *N*-benzyl-DL-alanine ester and (*a*) hydroxymethylenesuccinodinitrile (Part II, *loc. cit.*) or (*b*) ethyl β-cyano-α-formylpropionate. It was hoped that cyclisation of such compounds (XII; R′ = CN or CO_2Et) would yield, after dehydrogenation and debenzylation, the 3-hydroxypyridine derivative (XIII; R′ = CN or CO_2Et). However, treatment of (XII; R = CN) with sodium or sodium alkoxides in benzene caused only isomerisation; the elements of methanol were not eliminated (the possibility of methanol of crystallisation was excluded by suitable experiments); the product may be a dimeride of imino-nitrile character. A similarly abnormal cyclisation product of bis-2-cyanoethylmethylamine has been recorded by Cook and Reed (*J.*, 1945,

399). Treatment of (XII; R′ = CO_2Et) with sodium gave a low yield of a base, which could not be converted into a suitable 3-hydroxypyridine derivative. This approach was abandoned.

(XII) 

 (XIII)

In the course of abortive attempts to reduce the pyridine diesters with other reagents, ethyl 3-benzyloxy-2-methylpyridine-4 : 5-dicarboxylate (VI; R = Et, R′ = CH_2Ph) was reduced by aluminium amalgam in aqueous alcohol to a dihydro-ester, a result agreeing with the similar reduction of ethyl 2 : 6-dimethylcinchomeronate to its dihydro-derivative (Mumm and Beth, *Ber.*, 1921, **54**, 1591).

Experimental

Ethyl N-1-*Carbethoxyethyl*-N-*methylaminomethylenesuccinate* (I; R = Et, R′ = Me).—A mixture of ethyl α-methylaminopropionate (30 g.) and ethyl α-formylsuccinate (46 g.) was heated at 90° for 1 hour, cooled, dissolved in ether, filtered, and freed from solvent, and the residue was distilled at low pressure. After small forerunnings of unchanged materials, the *triester* was obtained as a yellow oil, b. p. 165—170°/0·25 mm. (64·2 g., 89·5%) (Found : C, 57·1; H, 8·0; N, 4·8. $C_{15}H_{25}O_6N$ requires C, 57·2; H, 7·9; N, 4·5%).

4 : 5-*Dicarbethoxy*-3-*hydroxy*-1 : 2-*dimethylpyridinium Chloride* (IV; R = Et, R′ = Me, X = Cl).—(*a*) A solution of the foregoing compound (30 g.) in dry " AnalaR " benzene (150 ml.) was refluxed with powdered sodium (2·1 g.) under dry nitrogen. After the vigorous reaction had subsided and all sodium had dissolved, heating was continued for 1 hour. The dark solution was cooled to 0° and made just acid to litmus with aqueous acetic acid containing a little sulphuric acid. The benzene extract was separated and combined with a further ethereal extract; the combined extracts were washed with sodium hydrogen carbonate solution and water and dried (Na_2SO_4). The solvents were removed and the residual dark oil was dissolved in a slight excess of saturated anhydrous alcoholic hydrogen chloride with ice-cooling. Addition of anhydrous ether precipitated a gummy hydrochloride which was repeatedly ground with fresh dry ether till solid. Repeated recrystallisation from alcohol–ether gave the desired *pyridinium* salt (13 g.), m. p. 160—162° (decomp.), identical with that obtained as described in (*b*) (Found : Cl, 11·9. $C_{13}H_{18}O_5NCl$ requires Cl, 11·7%).

(*b*) A 20% benzene solution of ethyl *N*-1-carbethoxyethyl-*N*-methylaminomethylene-succinate (16 g.) was refluxed with alcohol-free sodium ethoxide (from 1·7 g. of sodium). The oily product obtained from the benzene extract as described in (*a*) was dissolved in dry benzene (100 ml.) and treated dropwise with sulphuryl chloride (6 g.) at 45°. The dark oil which was precipitated was separated from the supernatant liquid and warmed at 45° at water-pump vacuum until it had completely solidified. This was triturated with dry acetone, filtered, and dried (9·8 g., 63%); recrystallised from alcohol–ether, it had m. p. 161—162° (decomp.) (Found : C, 51·4; H, 5·77; N, 4·45; Cl, 11·7. $C_{13}H_{18}O_5NCl$ requires C, 51·4; H, 5·9; N, 4·6; Cl, 11·7%).

(*c*) Cyclisation of the same starting material (16 g.) was effected with sodamide (3 g.), conditions being otherwise as in (*b*). The yield was 8·5 g.

This pyridinium salt gives a red colour with ferric chloride. When its concentrated aqueous solution was treated with sodium hydrogen carbonate or one equivalent of sodium hydroxide the corresponding *phenol-betaine* (V; R = Et, R′ = Me) separated in fine needles as a hydrated form, m. p. *ca.* 90° (Found : loss *in vacuo* over phosphoric anhydride at 56°, 9·9. $C_{13}H_{17}O_5N,1·5H_2O$ requires loss, 9·1%). The vacuum-dried yellow anhydrous *form*, crystallised from ethyl acetate, had m. p. 160° (Found : C, 59·1; H, 6·6; N, 5·3. $C_{13}H_{17}O_5N$ requires C, 58·4; H, 6·4; N, 5·2%).

Anhydro-4 : 5-*dicarboxy*-3-*hydroxy*-1 : 2-*dimethylpyridinium Hydroxide*.—A solution of the above pyridinium salt (6·1 g.) in water (20 ml.) was treated with a concentrated aqueous solution of sodium hydroxide (2·4 g.) at room temperature. After 0·5 hour the solution was acidified to litmus with acetic acid and cooled. The product was collected and recrystallised

from water, yielding the *betaine* (2·0 g.) in colourless leaflets, decomp. 230° (Found: C, 51·5; H, 4·0; N, 6·7. $C_9H_9O_5N$ requires C, 51·2; H, 4·3; N, 6·7%).

Methyl α-Benzylaminopropionate.—This *ester* was prepared by reductive condensation of alanine methyl ester with benzaldehyde, or from methyl α-bromopropionate and benzylamine as described by Bishoff (*Ber.*, 1897, **30**, 3171) for the ethyl ester; the product had b. p. 132—133°/11 mm. (Found: C, 68·8; H, 7·9; N, 7·1. $C_{11}H_{15}O_2N$ requires C, 68·4; H, 7·8; N, 7·25%). The *hydrochloride*, prepared in the usual way, crystallised from methanol–ether in needles, m. p. 177° (decomp.) (Found: Cl, 15·4. $C_{11}H_{16}O_2NCl$ requires Cl, 15·5%).

Methyl N-*Benzyl*-N-1-*carbomethoxyethylaminomethylenesuccinate* (I; R = Me, R′ = CH_2Ph). —A mixture of methyl α-formylsuccinate (17·4 g.) and methyl α-benzylaminopropionate (19·5 g.) was heated at 100° for 1·5 hours and left to cool overnight. An ether solution of the viscous product was washed with sodium hydrogen carbonate and water, dried, and evaporated, and the residue distilled. The *product*, a deep yellow viscous oil (27·4 g.), had b. p. 195—198°/0·35 mm. (Found: C, 62·6; H, 6·8; N, 4·2. $C_{18}H_{23}O_6N$ requires C, 62·0; H, 6·6; N, 4·0%).

Ethyl N-*Benzyl*-N-1-*carbethoxyethylaminomethylenesuccinate* (I; R = Et, R′ = CH_2Ph) was similarly prepared from ethyl α-formylsuccinate in 90% yield, forming a similar viscous oil, b. p. *ca.* 210°/0·3 mm. (Found: N, 3·6. $C_{21}H_{29}O_6N$ requires N, 3·58%).

1-*Benzyl*-4 : 5-*dicarbomethoxy*-3-*hydroxy*-2-*methylpyridinium Chloride* (IV; R = Me, R′ = CH_2Ph).—(*a*) A solution of the above trimethyl ester (36 g.) in dry " AnalaR " benzene (150 ml.) was refluxed with sodium powder (2·4 g.) in an atmosphere of nitrogen. The sodium gradually dissolved with formation of a dark reddish solution, initial reaction being hastened by addition of a trace of sodium ethoxide. Heating was continued for 1 hour after dissolution of the sodium. The mixture was cooled to 0° and acidified to litmus with acetic acid and ice. Combined benzene extracts of the product were washed with sodium hydrogen carbonate, and water, and dried (Na_2SO_4). After removal of benzene under reduced pressure, the residual oil (*ca.* 33 g.) was treated with an equivalent quantity of saturated absolute alcoholic hydrogen chloride, and the hydrochloride precipitated with anhydrous ether as a gum. This was separated by decantation and redissolved in methanol. Anhydrous ether was added till the solution was just turbid and the mixture was kept at room temperature for some days, with gradual addition of further amounts of dry ether as the crystalline quaternary chloride separated. A preferable procedure is to digest the primary ether-precipitated hydrochloride with dry ether, decant the liquid, and expose the residue to dry air for a few days. On addition of dry acetone the pigmented material was dissolved, leaving the quaternary *chloride* as a crystalline product. It crystallised from methanol–ether in colourless prisms, m. p. 148—150° (decomp.) (Found: C, 58·3; H, 5·3; Cl, 10·0; N, 4·0. $C_{17}H_{18}O_5NCl$ requires C, 58·0; H, 5·1; Cl, 10·1; N, 4·0%).

(*b*) The above cyclisation was carried out on the same scale with the equivalent amount of alcohol-free sodium methoxide (5·55 g.). The benzene extract of the free cyclic keto-ester was dried, filtered, and partly evaporated to remove traces of water. This solution was stirred and treated dropwise with sulphuryl chloride (12 g.) at 40°. A dark oil separated and, after it had settled, the benzene was decanted and the oil washed with a little more benzene. The oil was warmed at 40° at the water-pump for 2 hours. The resulting frothy mass was digested with warm dry acetone (50 ml.), leaving the pyridinium chloride as a slightly pink crystalline solid, identical with that obtained as described in (*a*) (yield, 22·5 g., 62%).

(*c*) Similar results were obtained by cyclisation with an equivalent amount of sodamide.

Dehydrogenations with Halogens.—(a) *Chlorine.* After cyclisation with sodium methoxide as described above [(*b*)], the crude, dried cyclic keto-ester was treated in benzene solution with a N-solution of chlorine in carbon tetrachloride (100 ml.) with stirring at room temperature. After settling, the oil which had precipitated gradually was separated by decantation and gently warmed *in vacuo*. The residue was digested with warm acetone (20 ml.), leaving 1-benzyl-4 : 5-dicarbomethoxy-3-hydroxy-2-methylpyridinium chloride, m. p. and mixed m. p. 149° (decomp.) (4·0 g.).

(b) *Bromine.* A solution of the crude cyclic keto-ester obtained with sodium methoxide from (I; R = Me, R′ = CH_2Ph) (35 g.) in dry benzene (200 ml.) was stirred at 0° and a solution of bromine (16 g.) in carbon tetrachloride (100 ml.) was added gradually. A light brown viscous gum was precipitated and this process appeared to be complete when about 60 ml. of bromine solution had been added. Bromine addition was stopped, any excess of bromine was removed in a stream of dry nitrogen, and the benzene decanted. The residue became more mobile, and deep red, as hydrogen bromide was evolved freely. It was kept at water-pump vacuum for

some hours and treated with warm acetone (25 ml.). When solid began to separate, dry ether (50 ml.) was added gradually with shaking. After 4 hours the precipitated solid was filtered off, washed with acetone–ether, and dried *in vacuo* (yield, 18·2 g., 52%). Recrystallisation from methanol–ether gave 1-*benzyl*-4 : 5-*dicarbomethoxy*-3-*hydroxy*-2-*methylpyridinium bromide*, colourless prisms, m. p. 134—135° (decomp.) (Found : C, 52·1; H, 4·9; N, 3·4; Br, 20·0. $C_{17}H_{18}O_5NBr$ requires C, 51·5; H, 4·5; N, 3·5; Br, 20·2%).

This bromide is readily converted into the corresponding chloride, identical with that described above, by shaking it in methanol solution with excess of freshly prepared silver chloride.

When a solution of the quaternary chloride (7·03 g.) in water (15 ml.) was treated with 2N-sodium hydroxide (10 ml.) at 0°, the *phenol-betaine* (V; R = Me, R′ = CH_2Ph) crystallised (6·15 g.). It recrystallised from water in colourless flat needles or prisms which are hydrated, losing *ca.* 3·3% by weight on vacuum-drying over phosphoric anhydride at 66°, then becoming yellow and having m. p. 138—140° (purple-red liquid) (Found : N, 4·3. $C_{17}H_{17}O_5N$ requires N, 4·4%).

1-*Benzyl*-4 : 5-*dicarbethoxy*-3-*hydroxy*-2-*methylpyridinium Chloride* (IV; R = Et, R′ = CH_2Ph).—Cyclisation of (I; R = Et, R′ = CH_2Ph) was carried out with sodium ethoxide as described for the methyl ester, and sulphuryl chloride was used for dehydrogenative chlorination. The product was somewhat soluble in warm acetone but could be purified by digestion with ethyl acetate. Recrystallisation from acetone–ether gave the *pyridinium* salt as colourless needles, m. p. 135—136° (decomp.) (Found : C, 60·0; H, 5·9; N, 4·25; Cl, 9·4. $C_{19}H_{22}O_5NCl$ requires C, 60·1; H, 5·80; N, 3·7; Cl, 9·3%).

Dimethyl 3-*Hydroxy*-2-*methylpyridine*-4 : 5-*dicarboxylate Hydrochloride*.—A solution of 1-benzyl-4 : 5-dicarbomethoxy-3-hydroxy-2-methylpyridinium chloride (35·15 g.) in methanol (120 ml.) was shaken with palladium–charcoal (4 g.; 1 : 10) in hydrogen at room temperature and slightly >1 atm. After 2·5 l. of hydrogen had been absorbed in 1 hour, hydrogenation ceased. The catalyst was filtered off and the solution evaporated to small volume under reduced pressure. The crystalline salt was collected, washed with dry ether, and dried (23·4 g.; m. p. *ca.* 153°). From methanol–ether, it separated in colourless needles, m. p. 165—168° (decomp.) (Found : C, 46·6; H, 4·7; N, 5·25; Cl, 13·4. $C_{10}H_{12}O_5NCl$ requires C, 45·9; H, 4·6; N, 5·35; Cl, 13·6%). Another form of the hydrochloride, with m. p. 223° (decomp.), showed the same composition and yielded the identical free base.

The hydrochloride (either form) (28·8 g.) was treated in a minimal amount of water at 0° with powdered sodium hydrogen carbonate till the solution was slightly alkaline. The precipitated *base* was filtered off, washed with ice water, and dried. A further crop was obtained by salting out of the filtrate and extraction with ether. The total yield was 16·5 g. Recrystallisation from light petroleum (b. p. 60—80°) or methanol gave colourless felted needles, m. p. 138—140° (Found : C, 53·3; H, 4·9; N, 6·3. $C_{10}H_{11}O_5N$ requires C, 53·4; H, 4·9; N, 6·2%).

When the hydrochloride (5 g.) in dry pyridine (50 ml.) was treated with toluene-*p*-sulphonyl chloride (3·8 g.) at room temperature for 24 hours, *methyl* 2-*methyl*-3-*toluene*-p-*sulphonyloxypyridine*-4 : 5-*dicarboxylate* was obtained. It was precipitated by water from the reaction mixture, dried (6 g.), and recrystallised from methanol in colourless rectangular prisms, m. p. 99—100° (Found : C, 53·55; H, 4·6; N, 3·7. $C_{17}H_{17}O_7NS$ requires C, 53·8; H, 4·5; N, 3·7%). By the action of concentrated aqueous ammonia, this compound undergoes slow reaction at all three ester groups with formation of 3-*hydroxy*-2-*methylpyridine*-4 : 5-*dicarboxyamide* in low yield. Unchanged ester was filtered off from the ammonia solution, and the solution evaporated to dryness. Recrystallisation from methanol gave pale yellow prisms, slowly decomposing above 250° (Found : N, 22·0. $C_8H_9O_3N_3$ requires N, 21·6%). Direct treatment of methyl 3-hydroxy-2-methylpyridine-4 : 5-dicarboxylate with ammonia (*d* 0·88) resulted in hydrolysis of at least one ester group, as well as amidation, and only mixed products containing ammonium salts of half-amides were obtained. The hydroxy-diamide was also formed by the following indirect but more reliable route. The betaine (V; R′ = CH_2Ph, R = Me) (3·15 g.) was finely powdered and added to ice-cold ammonia (*d* 0·88; 15 ml.). After being kept overnight, the brownish suspension of solid was filtered off and the product washed with cold water and dried (2·1 g.). Purification was effected by dissolution in dilute hydrochloric acid, filtration (charcoal), and reprecipitation with sodium hydrogen carbonate, yielding buff crystals, m. p. 255—257° (decomp.), of *anhydro*-1-*benzyl*-4 : 5-*dicarbamyl*-3-*hydroxy*-2-*methylpyridinium hydroxide* (Found : Total N, 13·9; amide-N, 9·8. $C_{15}H_{15}O_3N_3$ requires 14·7 and 9·8%, respectively). When this was hydrogenolysed in methanol containing hydrochloric acid, with palladised charcoal as catalyst, 3-*hydroxy*-2-*methylpyridine*-4 : 5-*dicarboxyamide hydrochloride*

was obtained, decomp. >200° (Found: Cl′, 14·9. $C_8H_{10}O_3N_3Cl$ requires Cl′, 15·3%). When treated with dilute sodium hydrogen carbonate solution the free hydroxy-diamide crystallised in pale yellow prisms, identical with that described above.

Diethyl 3-Hydroxy-2-methylpyridine-4 : 5-dicarboxylate Hydrochloride.—A solution of 1-benzyl-4 : 5-dicarbethoxy-3-hydroxy-2-methylpyridinium chloride (20 g.) in ethanol (80 ml.) was hydrogenated as described for the corresponding methyl ester. Evaporation of the filtered solution under reduced pressure to low volume yielded the product (11·1 g.) which crystallised from alcohol–ether in colourless needles, m. p. 144—145° (Found: C, 49·9; H, 5·55; N, 5·1. $C_{12}H_{16}O_5NCl$ requires C, 49·7; H, 5·5; N, 4·8%). The corresponding base was obtained as a low-melting solid which was not further purified but could be satisfactorily used in further operations. This ester as well as the dimethyl ester was readily hydrolysed by brief heating in dilute sodium hydroxide solution on the water-bath. The solution, just acidified to Congo-red, deposited 3-hydroxy-2-methylpyridine-4 : 5-dicarboxylic acid, m. p. 259° (decomp.) after recrystallisation from water (Found: C, 48·9; H, 3·7. Calc. for $C_8H_7O_5N$: C, 48·7; H, 3·6%).

Dimethyl 3-Methoxy-2-methylpyridine-4 : 5-dicarboxylate (VI; R = R′ = Me).—(*a*) The 3-hydroxypyridine derivative (11·25 g.) was added at 0° to ethereal diazomethane [from nitroso-methylurethane (15 ml.)], and kept at 3—5° for 3 days while most of the solid dissolved with evolution of nitrogen. The filtered solution was freed from excess of diazomethane and ether, and the residual oil distilled at 114—116°/0·5 mm. (8 g.) (Found: C, 55·55; H, 5·5; N, 5·6. Calc. for $C_{11}H_{13}O_5N$: C, 55·3; H, 5·4; N, 5·8%). Ichiba, Michi, and Emoto (*Sci. Papers Inst. Phys. Chem. Res. Tokyo*, 1941, **39**, 126) record m. p. 40—41°. The present material was satisfactorily amidated as shown below.

(*b*) Methyl 3-hydroxy-2-methylpyridine-4 : 5-dicarboxylate was treated in methanol with one equivalent of sodium methoxide. Addition of excess of dry ether precipitated the sodium salt which was filtered off and dried *in vacuo*. A solution of this salt (10·5 g.) in methanol (25 ml.) was mixed with one of trimethylphenylammonium chloride (8 g.) in methanol (15 ml.), and the mixture added, during 10 minutes, to boiling xylene (100 ml.) which was stirred in an atmosphere of nitrogen in an apparatus arranged to distil off the methanol and a little xylene. After 1 hour's heating the xylene solution was filtered from sodium chloride, washed with sodium hydrogen carbonate, and dried. After removal of xylene and dimethylaniline under reduced pressure, the residual oil was distilled yielding the product (5·9 g., 71%), b. p. 109—112°/0·2 mm. (Found: C, 55·1; H, 5·7; N, 6·0. Calc. for $C_{11}H_{13}O_5N$: C, 55·3; H, 5·4; N, 5·8%).

3-Methoxy-2-methylpyridine-4 : 5-dicarboxyamide (VII; R = Me).—This was obtained from the crude methoxy-diester by keeping its solution in liquid ammonia for 2 days. After evaporation, the residue was recrystallised from methanol, yielding small colourless leaflets (>90% yield) (Found: total N, 20·15; amide-N, 13·0. Calc. for $C_9H_{11}O_3N_3$: total N, 20·1; amide-N, 13·4%) which decompose at 210°, with liberation of ammonia and formation of the imide which melts about 250° (cf. Ichiba *et al.*, *loc. cit.*). The latter is reconverted into the diamide by concentrated ammonia.

4 : 5-Dicyano-3-methoxy-2-methylpyridine (VIII; R = Me).—The methoxy-diamide (10 g.) was added gradually to a stirred mixture of dry benzene (31 ml.), dry pyridine (31 ml.), and phosphorus oxychloride (7·9 g.) at 0—5°. The bath was gradually heated and finally kept at 60—70° for 1 hour. The dark mixture was mixed with ice and excess of sodium acetate, and benzene and pyridine were removed under reduced pressure. The aqueous residue was cooled and the solid filtered off and dried (5·1 g.). This was purified by vacuum-sublimation and recrystallised from aqueous methanol from which it separated in flat needles, m. p. 78° (Found: C, 62·3; H, 3·85; N, 24·4. Calc. for $C_9H_7ON_3$: C, 62·4; H, 4·05; N, 24·2%). Kuhn *et al.* (*loc. cit.*) gave m. p. 70°.

4 : 5-Bisaminomethyl-3-methoxy-2-methylpyridine Trihydrochloride (cf. IX; R = Me).—A solution of 4 : 5-dicyano-3-methoxy-2-methylpyridine (2·5 g.) in methanol (180 ml.) was dripped into a suspension of palladium chloride (1·5 g.) in methanol (50 ml.) acidified with dilute hydrochloric acid, with shaking in a hydrogen atmosphere. Hydrogen was absorbed fairly readily with formation of a pale yellow solution with intense blue fluorescence. The solution was filtered until clear, partly concentrated, and treated with anhydrous ether which precipitated the product as a *trihydrochloride hemihydrate*; this crystallised from methanol–ether in colourless leaflets, decomp. 200°, readily soluble in water (slightly acid to Congo-red) and sparingly soluble in alcohol (Found: C, 35·8; H, 6·8; N, 13·9; Cl, 35·1. $C_9H_{18}ON_3Cl_3,0{\cdot}5H_2O$ requires C, 36·05; H, 6·4; N, 14·0; Cl, 35·6%).

4 : 5-Bisaminomethyl-3-hydroxy-2-methylpyridine Trihydrobromide (IX; R = H).—A solution of the above methoxy-compound (5·8 g.) in concentrated hydrobromic acid (*d* 1·5; 145 ml.) was

refluxed for 30 minutes, cooled, mixed with alcohol (200 ml.), and treated with ether (250 ml.). The *trihydrobromide* which crystallised on chilling was collected and washed with alcohol–ether (yield, 7·5 g.). It is sparingly soluble in alcohol and can be recrystallised from aqueous alcohol by addition of ether; it decomposes at about 280° (Found : Br′, 58·7. $C_8H_{16}ON_3Br_3$ requires Br′, 58·5%).

Demethylation with concentrated hydrochloric acid at 130° for 4 hours yielded a product containing about 12% of residual methoxy-compound.

3-*Benzyloxypyridine*.—A solution of 3-hydroxypyridine (0·95 g.) in methanol (5 ml.) was mixed with a solution of sodium (0·23 g.) in methanol (5 ml.), and to this was added a solution of benzyldimethylphenylammonium chloride (2·5 g.) in methanol (5 ml.). The whole was added gradually to boiling xylene in a bath at 150—160°, as described for the similar methylation of the 3-hydroxypyridine diester above. Similar working up yielded the product as an oil, b. p. 114°/0·6 mm. (0·7 g.). This gave 3-*benzyloxypyridinium picrate*, yellow needles (from ethanol), m. p. 118—120° (Found : C, 52·5; H, 3·4; N, 13·8. $C_{18}H_{14}O_8N_4$ requires C, 52·2; H, 3·4; N, 13·5%).

Methyl 3-*Benzyloxy*-2-*methylpyridine*-4 : 5-*dicarboxylate* (VI; R = Me, R′ = CH_2Ph).—A solution of methyl 3-hydroxy-2-methylpyridine-4 : 5-dicarboxylate hydrochloride (13 g.) in methanol (30 ml.) was treated with a solution of sodium (2·3 g., 2 equivs.) in methanol (25 ml.) and then mixed with a solution of benzyldimethylphenylammonium chloride (12·1 g.) in methanol (15 ml.). The whole was added to boiling xylene (100 ml.) as described above and heating continued for 1 hour. The *product* was obtained by vacuum-distillation, having b. p. 173—176°/0·3 mm. (12·4 g., 80%), and crystallised from light petroleum (b. p. 60—80°) in colourless needles, m. p. 68° (Found : C, 64·9; H, 5·5; N, 4·6. $C_{17}H_{17}O_5N$ requires C, 64·7; H, 5·4; N, 4·4%).

Ethyl 3-*Benzyloxy*-2-*methylpyridine*-4 : 5-*dicarboxylate* (VI; R = Et, R′ = CH_2Ph).—This *ester* was prepared in 80% yield as described for the dimethyl ester. It had b. p. 187—189°/0·3 mm., and crystallised from light petroleum (b. p. 40—60°) in colourless prisms, m. p. 48—49° (Found : C, 65·8; H, 6·1; N, 4·1. $C_{19}H_{21}O_5N$ requires C, 66·4; H, 6·1; N, 4·1%).

3-*Benzyloxy*-2-*methylpyridine*-4 : 5-*dicarboxyamide* (VII; R = CH_2Ph).—Methyl 3-benzyloxy-2-methylpyridine-4 : 5-dicarboxylate (11·2 g.) was gradually added to liquid ammonia (30 ml.), and the mixture kept sealed at room temperature for 3 days. After evaporation of the ammonia, the product was digested with ether, filtered, and recrystallised from methanol in pale cream-coloured leaflets which decomposed at 194° with evolution of ammonia (Found : N, 15·2. $C_{15}H_{15}O_3N_3$ requires N, 14·7%). This *amide* was identical with the product obtained by treatment of methyl 3-hydroxy-2-methylpyridine-4 : 5-dicarboxylate with diazotoluene, followed by amidation with liquid ammonia.

3-*Benzyloxy*-4 : 5-*dicyano*-2-*methylpyridine* (VIII; R = CH_2Ph).—The above diamide, finely powdered (9·4 g.), was gradually added to a stirred mixture of dry pyridine (27 ml.), dry benzene (13·6 ml.), and phosphoryl chloride (8·5 g.), cooled in ice-water. The temperature was slowly raised to 30°, whereupon the mixture became dark purple. This was then vigorously stirred at 65—70° for 1 hour, cooled to 0°, and mixed with crushed ice (40 g.). Benzene and pyridine were removed under reduced pressure and the solid which had separated was filtered off, washed with water, and dried *in vacuo* (5·1 g.). Vacuum-sublimation (90—95°/10^{-5} mm.) yielded the pale yellow crystalline *dinitrile*, m. p. 96° (Found : N, 16·6. $C_{15}H_{11}ON_3$ requires N, 16·9%).

4 : 5-*Bisaminomethyl*-3-*hydroxy*-2-*methylpyridine Trihydrochloride* (cf. IX; R = H).—A solution of the foregoing benzyloxy-dinitrile (3·95 g.) in methanol (115 ml.) containing concentrated hydrochloric acid (5·5 ml.) was added in 6 portions to a suspension of active palladium–charcoal (1 : 10; 1 g.) in methanol (20 ml.) and shaken in hydrogen. The initial hydrogen consumption corresponding to debenzylation was rapid but slowed down until, after 20—25 minutes, 5 mols. of hydrogen had been absorbed. Finally a total uptake of about 2 l. of hydrogen was recorded. The solution, filtered from catalyst, yielded the trihydrochloride (1·85 g.) when chilled and a further crop of 2·05 g. was obtained by evaporating the solution to dryness and triturating the residue with absolute alcohol. The product crystallised as a *trihydrate* (from aqueous alcohol) in flat needles, decomposing above 280° with partial sublimation (Found : loss at 100°, 10·7. $C_8H_{16}ON_3Cl_3,3H_2O$ requires loss, 11·5%. Found, in anhydrous material : N, 15·5; Cl, 37·9. $C_8H_{16}ON_3Cl_3$ requires N, 15·2; Cl, 38·5%).

Reductions with Lithium Aluminium Hydride.—3-*Hydroxymethylpyridine*. A solution of ethyl nicotinate (15·1 g.) in dry ether (30 ml.) was added slowly to a vigorously stirred suspension of lithium aluminium hydride (2·4 g.) in dry ether (100 ml.) at 0—5°. The gummy yellow

precipitate was stirred for a further hour at 0°, decomposed with ice-water (50 ml.), and treated with excess of sodium hydroxide. The mixture was continuously extracted with ether from which was obtained some unchanged ethyl nicotinate (0·8 g.) and 3-hydroxymethylpyridine (2·35 g.), b. p. 141—146°/15 mm. Redistillation gave material of b. p. 142—143°/15 mm., $n_D^{18\cdot5}$ 1·5451, in agreement with known constants, and the picrate had m. p. 158—160° not depressed on admixture with authentic material.

3-Benzyloxy-4 : 5-bishydroxymethyl-2-methylpyridine (cf. XI).—A solution of ethyl 3-benzyloxy-2-methylpyridine-4 : 5-dicarboxylate (17·15 g.) in dry ether (50 ml.) was added slowly to lithium aluminium hydride (4 g.) in dry ether (250 ml.) as described above. After 1¾ hours, the mixture was decomposed with ice-water (300 ml.), and 50% aqueous sodium hydroxide (75 ml.) was added. Continuous ether-extraction (16 hours) yielded 2·8 g. of product but the alumina retained a considerable proportion which was only removed by filtering it off, drying it, and extracting it with boiling ethyl acetate and chloroform. In this way further crops of product were isolated. The total yield was 6·75 g. (52%). Recrystallisation from benzene or ethyl acetate gave colourless prisms, m. p. 118—120° (Found: C, 69·3; H, 6·65; N, 5·5. $C_{15}H_{17}O_3N$ requires C, 69·5; H, 6·5; N, 5·4%).

When the reduction mixture (same scale as above) was worked up by the addition of ice-cold 5N-hydrochloric acid (60 ml.), inorganic material was dissolved and the product separated in the form of *3-benzyloxy-4 : 5-bishydroxymethyl-2-methylpyridine hydrochloride* (12·7 g., 85%) which, crystallised from alcohol–ether, had m. p. 178° (Found: N, 4·6; Cl, 12·3. $C_{15}H_{18}O_3NCl$ requires N, 4·7; Cl, 12·0%).

4 : 5-Bishydroxymethyl-3-methoxy-2-methylpyridine (*Pyridoxine Methyl Ether*).—A solution of ethyl 3-methoxy-2-methylpyridine-4 : 5-dicarboxylate (5·7 g.) in dry ether (25 ml.) was similarly reduced with lithium aluminium hydride (1·3 g.). Ethereal extracts of the alkaline decomposition mixture yielded an oil which, crystallised from ethyl acetate, had m. p. 102—104° (Stiller *et al.*, *J. Amer. Chem. Soc.*, 1939, **61**, 1240, give m. p. 101—102°) (Found: N, 7·3. Calc. for $C_9H_{13}O_3N$: N, 7·65%).

3-Hydroxy-4 : 5-bishydroxymethyl-2-methylpyridine Hydrochloride (*Pyridoxine Hydrochloride*) (X).—(*a*) A solution of ethyl 3-hydroxy-2-methylpyridine-4 : 5-dicarboxylate (12 g.) in dry ether (50 ml.) was dropped into lithium aluminium hydride (5 g.) in dry ether (300 ml.), vigorously stirred at 0° in nitrogen. The pale yellow precipitate was stirred for 1½ hours and left overnight at room temperature. To the mixture were added ice-water (100 ml.) and an aqueous solution (50 ml.) of sodium hydroxide (21 g.). The alkaline mixture was saturated with carbon dioxide and continuously extracted with ether (2 days). The residue after removal of ether from the extract was dissolved in a small volume of absolute alcohol and treated with ethereal hydrogen chloride, yielding pyridoxine hydrochloride (2·3 g.) as a light brown crystalline powder, m. p. 202° (decomp.). It was identified as such by direct comparison with authentic material.

The ethereal reaction mixture obtained as just described was gently refluxed with acetic anhydride (30 ml.) for 2 hours. The ether was evaporated and acetic anhydride (30 ml.) again added. The mixture was heated on the water-bath for some hours, then filtered hot, and excess of acetic anhydride and more volatile material were removed under reduced pressure. The residue was fractionated, yielding pyridoxine triacetate (6·0 g.), b. p. 145—150°/0·5 mm. (Found, on material redistilled at 148°/0·5 mm.: C, 56·96; H, 5·7; N, 4·9. Calc. for $C_{14}H_{17}O_6N$: C, 56·95; H, 5·8; N, 4·75%).

(*b*) A solution of 3-benzyloxy-4 : 5-bishydroxymethyl-2-methylpyridine hydrochloride (43·5 g.) in warm water (500 ml.) was hydrogenated by shaking it with 10% palladised charcoal (6·0 g.; prepared by reduction of palladium chloride–charcoal suspension in sodium acetate solution, filtered off, and washed with water) in hydrogen, of which 3060 ml. were absorbed. After filtration from the catalyst the solution was evaporated under reduced pressure to dryness and the residue (28·2 g.) recrystallised from concentrated aqueous solution; it had m. p. 208—210° (decomp.) and was identical with authentic pyridoxine hydrochloride (Found: C, 47·1; H, 6·05; N, 6·7; Cl, 17·7, 17·4. Calc. for $C_8H_{12}O_3NCl$: C, 46·7; H, 5·8; N, 6·8; Cl, 17·3%).

(*c*) A solution of 4 : 5-bisaminomethyl-3-hydroxy-2-methylpyridine trihydrobromide (4·1 g.) in water (40 ml.) was stirred at 100° for 1 hour with an excess of freshly prepared, washed silver chloride, and filtered clear from silver bromide and residual chloride. The filtrate was stirred with 2N-hydrochloric acid (80 ml.) at 30° while a solution of sodium nitrite (1·7 g.) in water (17 ml.) was run in. The mixture was then heated at 90° for 20 minutes. It was evaporated to dryness under reduced pressure and the dry residue extracted several times with boiling absolute alcohol. The extract, filtered from sodium chloride, was chilled overnight and the pyridoxine

hydrochloride which crystallised was filtered off, washed with acetone, and vacuum-dried (yield, 1·2 g., 58%; m. p. 204—208°). Recrystallisation as above provided pure pyridoxine hydrochloride. Small crops of less pure product separated from the alcoholic mother-liquor when concentrated, the final mother-liquor being set aside for isolation of a by-product (see succeeding paper).

Ethyl 3-Benzyloxy-2-methyldihydropyridine-4 : 5-dicarboxylate.—Aluminium amalgam, freshly prepared from cut metal foil (5 g.), was added to ethyl 3-benzyloxy-2-methylpyridine-4 : 5-dicarboxylate (VI; R = Et, R′ = CH_2Ph) (17·15 g.) in alcohol (100 ml.). Water (10 ml.) was added and the mixture refluxed for 45 minutes. Alcohol (50 ml.) and water (5 ml.) were again added and refluxing was continued for an hour. The filtered solution was mixed with a boiling alcoholic extract of the alumina residue, and the combined solutions were evaporated to dryness under reduced pressure. The residual solid (16·1 g.) recrystallised from ethyl acetate–light petroleum (b. p. 60—80°) as fine colourless needles, m. p. 102—104°, with an intense blue fluorescence in ultra-violet light (Found: C, 66·1; H, 6·95. $C_{19}H_{23}O_5N$ requires C, 66·1; H, 6·7%).

Methyl α-(N-Benzyl-N-1-carbomethoxyethylaminomethylene)-β-cyanopropionate (XII; R = Me, R′ = CO_2Me).—Methyl β-cyano-α-formylpropionate (9·5 g.) and methyl α-benzylaminopropionate (13 g.) were heated on a steam-bath for 1 hour, cooled, and digested with ether. Insoluble material, probably the diketopiperazine from the amino-ester, was filtered off, and, after removal of the ether, the residual oil was distilled, yielding, after a lower-boiling fraction of mixed unchanged materials (5 g.), the ester (12·5 g.) as a viscous yellow oil, b. p. 203—205°/0·1 mm. (Found: C, 64·5; H, 6·4; N, 8·8. $C_{17}H_{20}O_4N_2$ requires C, 64·5; H, 6·3; N, 8·9%).

N-Benzyl-N-1-carbomethoxyethylaminomethylenesuccinonitrile (XII; R = Me, R′ = CN).—An intimate mixture of methyl α-benzylaminopropionate hydrochloride (45·9 g.) and potassium α-hydroxymethylenesuccinonitrile (29·5 g.; see Part II, *loc. cit.*) was heated at 105—115° for 3 hours under nitrogen. The dark melt was extracted with boiling benzene and filtered, and the extract washed with water, sodium hydrogen carbonate solution, water again, and dried (Na_2SO_4). After removal of the solvent and material volatile at up to 150°/0·1 mm., the residue was degassed at low pressure and submitted to short-path distillation, yielding a viscous oily *nitrile* (23·1 g.) at 140—150°/5 × 10^{-4} mm. (Found: N, 15·0. $C_{16}H_{17}O_2N_3$ requires N, 14·8%).

Cyclisation Attempts.—A solution of the last-mentioned nitrile (10 g.) in dry "AnalaR" benzene (100 ml.) was refluxed with sodium powder (0·9 g.) under nitrogen for 1·5 hours. The resulting dark solution was cooled and shaken at 0° under nitrogen with sufficient ice-cold dilute acetic acid containing a little dilute sulphuric acid to render the mixture just acid to litmus. The benzene extract was washed free of acid and dried ($MgSO_4$). Addition of anhydrous methanolic hydrogen chloride (*ca.* 1 equiv.) precipitated first an oil, from which the solution was decanted, and then a crystalline hydrochloride which was collected, washed with acetone, and dried (2·2 g.). Recrystallisation from alcohol–ethyl acetate yielded colourless fibrous needles, m. p. 197° (decomp.) (Found: C, 60·1; H, 5·4; N, 13·0; Cl, 11·2. $C_{16}H_{17}O_2N_3$,HCl requires C, 60·2; H, 5·6; N, 13·1; Cl, 11·1%). A pure specimen of this *salt*, heated for some hours at 140° *in vacuo*, showed no loss of methanol and gave the same analytical figures. That the substance was not the hydrochloride (m. p. 117·5°) of the starting material was shown by a considerable m. p. depression.

The same product was obtained in similar experiments with sodium methoxide, potassium ethoxide, and sodium *iso*amyloxide, and when the use of methanol in working up was avoided.

In one experiment with sodium, the first, oily fraction of hydrochloride (cf. above) eventually crystallised from methanol–ether, and had m. p. 190—192°, depressed to 170° by the product already described. The *substance* was oxygen-free and analysis also indicated elimination of a carbomethoxy-group (Found: C, 64·7; H, 6·7; N, 15·3; Cl, 13·5. $C_{14}H_{15}N_3$,HCl requires C, 64·2; H, 6·1; N, 16·1; Cl, 13·6%).

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