285. *Synthesis of Analogues of Pyridoxine.*

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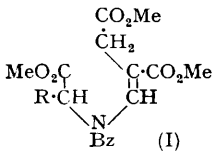
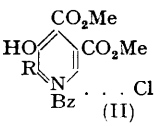
Three analogues of pyridoxine, the 2-*iso*propyl, 2-*iso*butyl, and 2-phenyl derivatives of 3-hydroxy-4 : 5-bishydroxymethylpyridine, have been synthesised. They have little or no pyridoxine-like activity.

Cohen, Haworth, and Hughes (*J.*, 1952, 4374) have described a synthesis of pyridoxine, and Cohen and Silk (*ibid.*, p. 4386) have applied this to an analogue of pyridoxine with a benzyl instead of the methyl group in the 2-position. Syntheses by the same methods of three more analogues of pyridoxine with respectively an *iso*propyl, an *iso*butyl, and a phenyl group in this position are now described : the work was indeed suggested to us by Professor F. Bergel in order to study the pyridoxine activity of such compounds. The results of the biological tests carried out by Roche Products Ltd. showed no pyridoxine activity, except for the *iso*propyl analogue, when tested in the presence of pyridoxine : in this case a pyridoxine activity 400 times less than that of pyridoxine was found. These results are similar to those of Cohen and Silk (*loc. cit.*) for the benzyl analogue.



(I)



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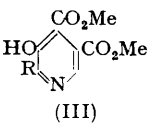

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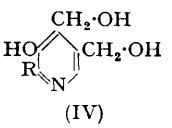

(IV)

(*a*) R = Me_2CH; (*b*) R = $Me_2CH{\cdot}CH_2$; (*c*) R = Ph.

The methyl ester of an α-benzylamino-acid was condensed with methyl α-formylsuccinate to give a compound of type (I) which was cyclised with sodium or sodium ethoxide and treated with sulphuryl chloride; the resulting pyridinium salt (II) was then debenzylated by reduction to (III). In the case of the phenyl analogue, (III*c*) was converted into (IV*c*) both by the method of Cohen, Haworth, and Hughes (*loc. cit.*) and by the subsequently discovered reduction with lithium aluminium hydride (cf. also Jones and Kornfeld, *J. Amer. Chem. Soc.*, 1951, **73**, 107) : with (III*a*) and (III*b*) only the latter method was used.

Experimental

*Methyl α-Benzylamino*isovalerate.—(*a*) Valine methyl ester [3·57 g.; b. p. 58—58·5°/12 mm.; prepared from the acid (*Org. Synth.*, **20**, 106) by the Fischer–Speier method] and benzaldehyde (3·16 g.) were stirred in methanol (25 ml.) with a little charcoal during 2 hr. The solution was filtered and hydrogenated at atmospheric pressure (10% palladised charcoal; 30 mg.); after filtration and removal of the solvent at 40°, distillation gave *methyl α-benzylamino*isovalerate (5·15 g., 86%; b. p. 84·5°/0·3 mm.) as a colourless oil (Found: C, 70·6; H, 9·2; N, 6·7. $C_{13}H_{19}O_2N$ requires C, 70·6; H, 8·6; N, 6·3%). In ether this gave the *hydrochloride* which crystallised from ethanol–ether in needles, m. p. 181° (Found: C, 60·8; H, 7·5; N, 6·0. $C_{13}H_{20}O_2NCl$ requires C, 60·6; H, 7·8; N, 5·4%).

(*b*) α-Bromo*iso*valeric acid (18·1 g.) was methylated with diazomethane in ether to give methyl α-bromo*iso*valerate, b. p. 170—175° (15·5 g., 80%). This ester (15·5 g.) was heated with benzylamine (17 g.) at 120° during 4 hr., water added to the cooled mixture, and the product extracted with ether, dried (Na_2SO_4), and distilled (6·9 g., 39% : b. p. 100°/0·5 mm.).

Dimethyl N-*Benzyl*-N-(1-*carbomethoxy*iso*butyl*)*aminomethylenesuccinate* (I*a*).—Methyl α-benzylamino*iso*valerate (6·9 g.) and dimethyl formylsuccinate (6 g.) were heated together during 1 hr. at 100°, and then under about 15 mm. during ½ hr. Distillation of the residue gave the *ester* (I*a*) (9·8 g., 83%; b. p. 175°/5 × 10^{-4} mm.) as a viscous yellow oil (Found: C, 64·0; H, 7·4; N, 3·8. $C_{20}H_{27}O_6N$ requires C, 63·6; H, 7·2; N, 3·7%).

1-*Benzyl*-4 : 5-*dicarbomethoxy*-3-*hydroxy*-2-iso*propylpyridinium Chloride* (II*a*).—The above ester (7·9 g.) in pure dry benzene (100 ml.) was added to powdered sodium (0·49 g.), and the mixture refluxed in nitrogen during 6 hr. A mixture of water (6·7 ml.), ice (3 g.), acetic acid (1·21 ml.), and 2N-sulphuric acid (0·35 ml.) was added to the cooled product, and the benzene layer washed successively with water and aqueous sodium hydrogen carbonate and dried (Na_2SO_4). Drying was completed by evaporation of some of the benzene, sulphuryl chloride (1·44 ml.) added dropwise at 40°, and the mixture kept at room temperature during 2 hr. The benzene was decanted from the oil which had separated and the latter warmed at 40° under reduced pressure (water-pump) during 2 hr. The resulting frothy product crystallised when warmed with acetone (5 ml.), and was washed with the same solvent till colourless [m. p. 143° (decomp.); 4·93 g., 62%]. Crystallisation from ethanol–ether gave prisms of the *pyridinium chloride*, m. p. 146° (decomp.) (3·77 g.) (Found: C, 58·5; H, 6·1; N, 3·6. $C_{19}H_{22}O_5NCl,\frac{1}{2}H_2O$ requires C, 58·7; H, 5·9; N, 3·6%).

Dimethyl 3-*Hydroxy*-2-iso*propylpyridine*-4 : 5-*dicarboxylate* (III*a*).—The above pyridinium chloride (1·75 g.) in methanol was reduced with hydrogen (0·1 g. of 10% palladised charcoal); the absorption was quantitative. The product was filtered, methanol and toluene were removed under reduced pressure, and the crystalline residue was dissolved in water (5 ml.) and methanol (2 ml.). Addition of sodium acetate trihydrate (1·24 g.) in water (3 ml.) to the ice-cold solution gave an oil which crystallised (1·04 g., 90%). Crystallisation from aqueous ethanol gave the *ester*, prisms, m. p. 68° (0·67 g.) (Found: C, 57·2; H, 6·1; N, 5·5. $C_{12}H_{15}O_5N$ requires C, 56·9; H, 5·9; N, 5·5%).

3-*Hydroxy*-4 : 5-*bishydroxymethyl*-2-iso*propylpyridine* (IV*a*).—The ester (III*a*) (0·835 g.) was placed in a Soxhlet thimble over lithium aluminium hydride (0·3 g.) in ether (50 ml.), and the solution heated with stirring until all the ester had been dissolved and then during a further 20 min. Water and hydrochloric acid (10%; 10 ml.) were added and the mixture was shaken (10 min.). The solution, after its pH had been brought to 7 with sodium hydroxide, was continuously extracted with ether (100 ml.) during 28 hr., the ether evaporated, and the dried residue dissolved in alcohol (10 ml.); passage of hydrogen chloride followed by addition of ether precipitated the *hydrochloride* as prisms (0·41 g., 58%) which, crystallised from acetone, had m. p. 192° (decomp.) (0·37 g.) (Found: C, 51·4; H, 6·6; N, 6·45. $C_{10}H_{16}O_3NCl$ requires C, 51·4; H, 6·9; N, 6·0%). In a second experiment the *base* (IV*a*) was obtained by subliming the residue from the evaporation of the ether at 160°/10^{-4} mm.; it gave prisms, m. p. 139°, when rubbed with acetone (Found: C, 60·8; H, 7·7; N, 7·1. $C_{10}H_{15}O_3N$ requires C, 60·9; H, 7·6; N, 7·1%).

Similar methods were used for preparation of the following, only method (*a*) (above) being used for the original esters:

Methyl α-benzylamino-γ-methylvalerate, b. p. 81—82°/10^{-4} mm. (Found: C, 71·7; H, 8·3; N, 6·4. $C_{14}H_{21}O_2N$ requires C, 71·5; H, 9·0; N, 6·0%); *hydrochloride*, needles (from ethanol–ether), m. p. 136° (Found: C, 62·4; H, 7·9; N, 5·4. $C_{14}H_{22}O_2NCl$ requires C, 61·9; H, 8·1; N, 5·2%).

Dimethyl N-*benzyl*-N-(1-*carbomethoxy*iso*amyl*)*aminomethylenesuccinate* (I*b*) (yield, 72%), b. p. 150°/3 × 10^{-3} mm. (Found : C, 63·8; H, 7·0; N, 4·2. $C_{21}H_{29}O_6N$ requires C, 64·4; H, 7·4; N, 3·6%).

1-*Benzyl*-2-iso*butyl*-4 : 5-*dicarbomethoxy*-3-*hydroxypyridinium chloride* (II*b*) (yield, 34%), prisms, m. p. 130° (decomp.), from ethanol–ether (Found : C, 60·4; H, 6·3; N, 3·8. $C_{20}H_{24}O_5NCl$ requires C, 61·0; H, 6·1; N, 3·6%).

Dimethyl 2-iso*butyl*-3-*hydroxypyridine*-4 : 5-*dicarboxylate* (III*b*) (yield, 82%), prisms from aqueous–ethanol (Found : C, 58·4; H, 6·4; N, 5·7. $C_{13}H_{17}O_5N$ requires C, 58·4; H, 6·4; N, 5·2%).

2-iso*Butyl*-3-*hydroxy*-4 : 5-*bishydroxymethylpyridine* (IV*b*).—This pyridoxine *analogue* had m.p. 134° (Found : C, 62·5; H, 7·8; N, 7·1. $C_{11}H_{17}O_3N$ requires C, 62·5; H, 8·1; N, 6·6%); *hydrochloride*, needles (from ethanol), m. p. 210° (decomp.) (Found : C, 53·1; H, 6·9; N, 5·6. $C_{11}H_{18}O_3NCl$ requires C, 53·3; H, 7·3; N, 5·7%).

Methyl α-*benzylaminophenylacetate*, b. p. 135—140°/10^{-4} mm. (Found : C, 75·6; H, 6·8; N, 5·3. $C_{16}H_{17}O_2N$ requires C, 75·3; H, 6·7; N, 5·5%).

Dimethyl N-*benzyl*-N-(α-*carbomethoxybenzyl*)*aminomethylenesuccinate* (I*c*), b. p. 125°/2 × 10^{-3} mm. (yield, 73%), needles (from ethanol), m. p. 83° (Found : C, 67·5; H, 6·1; N, 3·6. $C_{23}H_{25}O_6N$ requires C, 67·1; H, 6·1; N, 3·4%).

1-*Benzyl*-4 : 5-*dicarbomethoxy*-3-*hydroxy*-2-*phenylpyridinium Chloride* (II*c*).—The cyclisation of (I*c*) was carried out in benzene with sodium ethoxide instead of with sodium, but otherwise the preparation was the same as that of (II*a*) (yield of crude chloride, 64%). The *picrate* corresponding with (II*c*) gave yellow needles, m. p. 165°, from ethanol (Found : C, 55·9; H, 3·8; N, 9·8. $C_{28}H_{22}O_{12}N_4$ requires C, 55·5; H, 3·6; N, 9·2%).

Dimethyl 3-*Hydroxy*-2-*phenylpyridine*-4 : 5-*dicarboxylate* (III*c*).—Hydrogenation of (II*c*) gave pale yellow leaflets, m. p. 89° (from light petroleum containing a trace of ethanol) (yield, 74%). The *picrate* of (III*c*) gave yellow leaflets (from ethanol), m. p. 202° (Found : C, 48·6; H, 3·1; N, 11·1. $C_{21}H_{16}O_{12}N_4$ requires C, 48·9; H, 3·1; N, 10·9%). The *acid* was prepared by hydrolysing (III*c*) with baryta; it gave leaflets, m. p. 244°, from water (Found : C, 60·4; H, 3·7; N, 5·5. $C_{13}H_{19}O_5N$ requires C, 60·2; H, 3·5; N, 5·4%).

Dimethyl 3-*Methoxy*-2-*phenylpyridine*-4 : 5-*dicarboxylate*.—The ester (III*c*) (18 g.) in ether (100 c.c.) was treated with diazomethane in ether, prepared from nitrosomethylurea (20·6 g.); after 2 days, large, pale yellow prisms had separated. After evaporation, the residue crystallised from aqueous acetic acid as prisms (16·5 g., 84%), m. p. 109°, of the *methoxy*-ester (Found : C, 63·8; H, 5·0; N, 5·1. $C_{16}H_{15}O_5N$ requires C, 63·8; H, 5·0; N, 4·7%).

3-*Methoxy*-2-*phenylpyridine*-4 : 5-*dicarboxyamide*.—The above methylated product (16·5 g.) was heated with methanolic ammonia (250 ml., saturated at 0°) at 60° during 24 hr. in an autoclave. The white crystalline *diamide* (11·5 g., 77%) crystallised from methanol containing a few drops of light petroleum (b. p. 60—80°); it had m. p. 224° (decomp.) (Found : C, 61·4; H, 4·9; N, 15·6. $C_{14}H_{13}O_3N_3$ requires C, 62·0; H, 4·8; N, 15·5%).

4 : 5-*Dicyano*-3-*methoxy*-2-*phenylpyridine*.—The above diamide (11·5 g.) was added in portions, with stirring, to a mixture of pyridine (42 c.c.), benzene (21 c.c.), and phosphoryl chloride (12·9 g.) at 40°. The temperature was then raised to 65—70°, and the mixture stirred during 1 hr., cooled, and decomposed with ice (50 g.). After evaporation under reduced pressure from a bath at 40° to about 50 ml. (when frothing became troublesome) and cooling, the solid product was collected and dried : sublimation from a bath at 100° at 5 × 10^{-3} mm. gave colourless prisms, m. p. 128°, of the *dicyano*-compound (6·0 g., 60%) (Found : C, 71·5; H, 3·8; N, 17·6. $C_{14}H_9ON_3$ requires C, 71·4; H, 3·9; N, 17·9%).

4 : 5-*Bisaminomethyl*-3-*methoxy*-2-*phenylpyridine Trihydrochloride*.—The above dinitrile (0·25 g.) was dissolved in a mixture of methanol (40 ml.) and water (2 ml.), and concentrated hydrochloric acid (0·5 ml.) was added with cooling. This solution was added to reduced Adams' palladium oxide (0·05 g.) in methanol (8 ml.) and water (2 ml.). After hydrogenation at atmospheric pressure, the catalyst was removed and the filtrate evaporated to about 3 ml. under reduced pressure at 50—60° in an atmosphere of nitrogen. Addition of absolute ethanol (10 ml.) and a little ether gave a crystalline product which was washed with dry ethanol (2 ml.). Crystallisation from aqueous ethanol–ether gave the *trihydrochloride* in plates (0·11 g., 30%), m. p. 198° (decomp.) (Found : C, 45·4; H, 6·3; N, 11·5. $C_{14}H_{20}ON_3Cl_3,H_2O$ requires C, 45·4; H, 6·0; N, 11·3%).

4 : 5-*Bisaminomethyl*-3-*hydroxy*-2-*phenylpyridine Trihydrobromide*.—A mixture of the above trihydrochloride (1 g.) with aqueous hydrobromic acid (*d* 1·5; 8 ml.) was boiled gently under reflux during 2 hr. The solution was evaporated to dryness under reduced pressure at 85°, and

the residue cooled, triturated with dry acetone (10 ml.), and filtered. The washings were evaporated to about 2 ml. and cooled to obtain a further quantity of the trihydrobromide. The material thus obtained (1·06 g., 79%) was used directly for the next stage without further purification.

3-*Hydroxy*-4 : 5-*bishydroxymethyl*-2-*phenylpyridine Hydrochloride*.—(*a*) The above product (1·06 g.) in water (12 ml.) was stirred with an excess of moist silver chloride (freshly precipitated from 1·3 g. of silver nitrate) during 1 hr. at 90—100°. The solution was filtered hot and the residue washed with 0·1N-hydrochloric acid (1·5 ml.); the combined filtrates were then treated with 2N-hydrochloric acid (18 ml.). This solution was stirred at 30° and treated with a solution of sodium nitrite (0·37 g.) in water (5 ml.), then heated rapidly to 90—100° and kept at that temperature for 20 min. The solution was evaporated under reduced pressure from a bath at 50°, and the residue dried by distillation with benzene, extracted with boiling ethanol (3 × 10 ml.), and filtered hot from sodium chloride. The first extract on cooling deposited prisms (0·14 g.) of m. p. 185°. The filtrate from this was combined with the other two extracts, evaporated under reduced pressure to about 10 ml., and filtered hot. On cooling a further quantity (0·09 g.) of the same material was deposited (yield, 0·23 g., 38%). This material was recrystallised from alcohol without change of m. p., and proved to be identical (by mixed m. p.) with the product obtained by lithium aluminium hydride reduction (see below).

(*b*) Dimethyl 3-hydroxy-2-phenylpyridine-4 : 5-dicarboxylate (2 g.) in ether (60 ml.) was added dropwise with stirring to a solution of lithium aluminium hydride (0·44 g.) in ether (10 ml.). The mixture was stirred for 10 min. after the addition was complete, excess of the reagent was destroyed by the addition of water, and the mixture was then shaken for 5 min. with sulphuric acid (10%; 15 ml.). Sodium hydroxide solution (10%) was then added to bring the solution to pH 7, and the aqueous layer was continuously extracted with ether (100 ml.) during 14 hr. Oil which separated from the ethereal extract was dried in a desiccator, then dissolved in a little dry alcohol and treated with gaseous hydrogen chloride to give a crystalline precipitate. The ethereal extract was dried (Na_2SO_4), filtered, and treated with gaseous hydrogen chloride to give an oil which crystallised when scratched. The crystals were collected and recrystallised from alcohol, to give prisms (1 g., 54%), m. p. 185°, of the *hydrochloride* of (IV*c*) (Found : C, 58·2; H, 5·2; N, 5·0. $C_{13}H_{14}O_3NCl$ requires C, 58·3; H, 5·3; N, 5·2%).

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