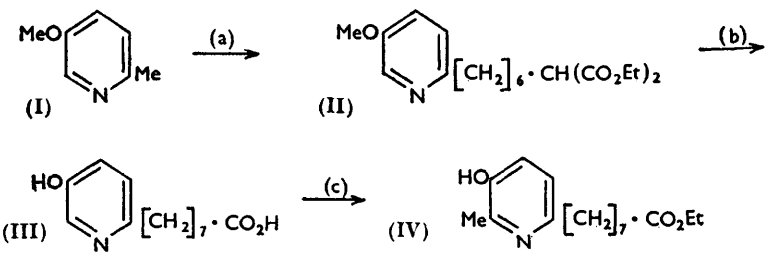
113. *Synthesis of Ethyl Carpyrinate.**

By T. R. GOVINDACHARI, N. S. NARASIMHAN, and S. RAJADURAI.

Ethyl carpyrinate, a degradation product from carpaine, has been synthesised.

ETHYL CARPYRINATE, a degradation product [1] from carpaine, was assigned structure (IV) on the basis of selective oxidation studies [2] and the structure already assigned [3] to carpaine. We now report a synthesis of ethyl carpyrinate from 5-methoxy-2-picoline according to the following scheme :



(*a*) 1, KNH_2–Cl·$[CH_2]_5$·OAc. 2, $LiAlH_4$. 3, $SOCl_2$. 4, $Na^+[CH(CO_2Et)_2]^-$.
(*b*) HBr.
(*c*) 1, H·CHO–NaOH. 2, EtOH–HCl. 3, $SOCl_2$. 4, Pt–H_2. 5, Pd–C.

* This work was briefly described in *Chem. and Ind.*, 1956, 53. Two other syntheses by different methods, one of ethyl carpyrinate (W. Gruber, *Chem. Ber.*, 1955, **88**, 178) and another of carpyrinic acid (H. Rapoport and E. J. Volcheck, *J. Amer. Chem. Soc.*, 1956, **78**, 2451), have also been reported.

[1] Govindachari and Narasimhan, *J.*, 1953, 2635.
[2] Govindachari, Narasimhan, and Rajadurai, preceding paper.
[3] Rapoport, Baldridge, and Volcheck, *J. Amer. Chem. Soc.*, 1953, **75**, 5290.

Preliminary experiments with 2-picoline and 5-hydroxy-2-picoline demonstrated the feasibility of the scheme and also established that hydroxymethylation proceeded in the α-position relative to the β-hydroxy-group.

Condensation of 5-methoxy-2-picoline (I) with 5-chloropentyl acetate in the presence of potassium amide in liquid ammonia yielded 2-6′-acetoxyhexyl-5-methoxypyridine. Hydrolysis and treatment with thionyl chloride gave 2-6′-chlorohexyl-5-methoxypyridine, which with sodiomalonic ester yielded 2-(7 : 7-diethoxycarbonylheptyl)-5-methoxypyridine (II). The last compound was hydrolysed by boiling hydrobromic acid, demethylated, and decarboxylated yielding 2-7′-carboxyheptyl-5-hydroxypyridine (III). Treatment of this with formaldehyde in alkaline solution yielded 2-7′-carboxyheptyl-5-hydroxy-6-hydroxymethylpyridine, whose ethyl ester on treatment with thionyl chloride followed by reduction in alcoholic solution afforded a mixture of stereoisomers, dehydrogenated in *p*-cymene solution with palladised charcoal catalyst to ethyl carpyrinate (IV), identical with a sample obtained by dehydrogenation of ethyl carpamate.

Experimental

2-6′-Acetoxyhexylpyridine.—2-Picoline (4·7 g.) was added to a vigorously stirred solution of sodium amide in liquid ammonia (from 1·8 g. of sodium, 200 mg. of ferric chloride, and 100 ml. of liquid ammonia). The mixture was stirred for 5 min. and then 5-chloropentyl acetate (8·2 g.) was added as rapidly as possible with continued stirring. Next morning the mixture was decomposed with water and extracted with ether. The ether extract was shaken with N-hydrochloric acid, and the acid extract cooled and made alkaline with sodium carbonate, and the mixture repeatedly extracted with ether. The combined ether extracts were dried (Na_2SO_4) and solvent was removed; distillation gave 2-picoline (2 g.) and then *2-6′-acetoxyhexylpyridine* (3·3 g.), b. p. 138°/1 mm. (Found : C, 70·5; H, 8·4. $C_{13}H_{19}O_2N$ requires C, 70·6; H, 8·6%).

2-6′-Bromohexylpyridine.—A mixture of the acetate (3 g.), hydrobromic acid (60%, 25 ml.), and glacial acetic acid (80 ml.) was heated on a water-bath for 6 hr. It was then evaporated to dryness *in vacuo*; the crude hydrobromide would not crystallise. However, it readily gave a *picrate*, m. p. 155—159° (from alcohol) (Found : C, 43·0; H, 4·2. $C_{11}H_{16}NBr,C_6H_3O_7N_3$ requires C, 43·3; H, 4·0%).

A solution of hydrobromide in water (10 ml.) was covered with ether (150 ml.), and concentrated potassium hydroxide solution added with shaking. The ether layer was then dried (Na_2SO_4), and the solvent removed *in vacuo*. The residual free base was dried thoroughly over sulphuric acid *in vacuo*.

2-(7 : 7-Diethoxycarbonylheptyl)pyridine.—To a solution of sodium ethoxide in ethyl alcohol (from 110 mg. of sodium and 20 ml. of alcohol) was added diethylmalonate (750 mg.) with stirring. After ½ hr. a solution of the bromohexylpyridine (1·5 g.) in alcohol (10 ml.) was added followed by powdered potassium iodide (500 mg.). The stirred mixture was heated on a water-bath for 6 hr., the alcohol was then removed, and water added. The mixture was repeatedly extracted with ether. The combined ether extracts were shaken with N-hydrochloric acid, the acid extracts made alkaline with sodium carbonate, and the base taken up in ether. Removal of solvent from the dried (Na_2SO_4) extract and distillation furnished *2-(7 : 7-diethoxycarbonylheptyl)-pyridine* (1·5 g.), b. p. 158—160°/0·5 mm. (Found : C, 67·0; H, 8·0. $C_{18}H_{27}O_4N$ requires C, 67·3; H, 8·4%).

5-Hydroxy-6-hydroxymethyl-2-picoline.—A solution of 5-hydroxy-2-picoline (1·09 g.) in aqueous sodium hydroxide (10%; 4·7 ml.) was treated with formalin (36%; 2·1 ml.). The mixture was heated on a water-bath for 2 hr. and was then cooled, acidified with 4N-acetic acid, and evaporated to dryness *in vacuo*. The residue was treated with sodium hydrogen carbonate solution and extracted with ether containing a little alcohol. Removal of ether from the dried (Na_2SO_4) extract furnished *5-hydroxy-6-hydroxymethyl-2-picoline* (750 mg.), m. p. 153° (from acetone) (Found : C, 60·1; H, 7·0. $C_7H_9O_2N$ requires C, 60·4; H, 7·1%).

6-Chloromethyl-5-hydroxy-2-picoline.—A cold solution of the hydroxymethyl compound (500 mg.) in chloroform (10 ml.) was treated with thionyl chloride (0·33 ml.). Next day it was evaporated to dryness *in vacuo* and the residue washed well with ether. On crystallisation

from alcohol–ether *6-chloromethyl-5-hydroxy-2-picoline hydrochloride*, darkening at 205°, was obtained (Found: C, 53·0; H, 5·2. $C_7H_9ONCl_2$ requires C, 53·3; H, 5·1%).

3-Hydroxy-2 : 6-lutidine.—A solution of the hydrochloride (500 mg.) in alcohol (20 ml.) was shaken with Adams's catalyst (200 mg.) in a hydrogen atmosphere at 60 lb./sq. in. pressure for 6 hr. The solution was filtered and the filtrate on evaporation gave a white hydrochloride from which, however, no sharp-melting material could be isolated.

The hydrochloride was treated with sodium hydrogen carbonate solution and extracted with ether containing alcohol. The dried ether extract on removal of solvent gave an oil (500 mg.) which, on dehydrogenation by Govindachari and Narasimhan's method,[1] yielded a solid (300 mg.), m. p. 209° [from light petroleum (b. p. 40—60°)]. It did not depress the m. p. of an authentic sample of 3-hydroxy-2 : 6-lutidine.

2-6′-Acetoxyhexyl-5-methoxypyridine.—This was prepared as described above for 2-6′-acetoxyhexylpyridine, except that potassium amide was used instead of sodium amide. From 9·5 g. of 5-methoxy-2-picoline and 12·8 g. of 5-chloropentyl acetate 4 g. of *2-6′-acetoxyhexyl-5-methoxypyridine*, b. p. 162°/1 mm. (Found: C, 67·1; H, 8·8. $C_{14}H_{21}O_3N$ requires C, 66·9; H, 8·4%), were obtained.

2-6′-Hydroxyhexyl-5-methoxypyridine.—The acetate was not hydrolysed by alcoholic potassium hydroxide. However, the removal of the acetyl group was effected by lithium aluminium hydride. The acetate (4 g.) in ether (20 ml.) was added gradually to a stirred suspension of lithium aluminium hydride (2 g.) in ether (50 ml.). After 12 hr. water was added and the mixture extracted with ether. Removal of solvent from the dried (Na_2SO_4) extract and distillation gave *2-6′-hydroxyhexyl-5-methoxypyridine* (3·5 g.), b. p. 152°/0·5 mm. (Found: C, 68·4; H, 9·1. $C_{12}H_{19}O_2N$ requires C, 68·9; H, 9·1%).

2-6′-Chlorohexyl-5-methoxypyridine.—A cold solution of the hydroxyhexylpyridine (1 g.) in chloroform (10 ml.) was treated with thionyl chloride (0·4 ml.). Working up of the reaction mixture as for chlorocarpamol,[2] gave *2-6′-chlorohexyl-5-methoxypyridine* (940 mg.), b. p. 124°/0·5 mm. (Found: C, 63·2; H, 8·3. $C_{12}H_{18}ONCl$ requires C, 63·3; H, 7·9%).

2-(7 : 7-Diethoxycarbonylheptyl)-5-methoxypyridine.—This was prepared as described for 2-(7 : 7-dicarbethoxyheptyl)pyridine. From 5·2 g. of the chloro-compound 5 g. of *2-(7 : 7-diethoxycarbonylheptyl)-5-methoxypyridine*, b. p. 204°/1·5 mm. (Found: C, 64·6; H, 8·2. $C_{19}H_{29}O_5N$ requires C, 64·9; H, 8·3%), were obtained.

2-7′-Carboxyheptyl-5-hydroxypyridine.—The diester (1·8 g.) was refluxed with hydrobromic acid (60%; 30 ml.) for 45 hr. The mixture was then evaporated to dryness. The crude 2-7′-carboxyheptyl-5-hydroxypyridine hydrobromide could not be crystallised nor would it give any crystalline derivative.

2-7′-Ethoxycarbonylheptyl-5-hydroxy-6-hydroxymethylpyridine.—The crude hydrobromide was dissolved in water (4 ml.) containing sodium hydroxide (620 mg.). Formalin (35%; 1 ml.) was added and the mixture heated on a water-bath for 2—3 hr. The mixture was then evaporated to dryness *in vacuo*, and the residue acidified with N-hydrochloric acid (to Congo-red) and again evaporated to dryness *in vacuo*. The residue was extracted with alcohol, and the alcoholic extract esterified by Fischer's method. After removal of alcohol, the residue was dissolved in water (10 ml.), and extracted with ether. It was then basified with solid sodium carbonate and extracted thoroughly with ether containing a little alcohol. The dried (Na_2SO_4) ether extract, after removal of solvent, gave the crude 2-7′-ethoxycarbonylheptyl-5-hydroxy-6-hydroxymethylpyridine. The *picrate* had m. p. 115° (from alcohol) (Found: C, 50·7; H, 5·2. $C_{22}H_{28}O_{11}N_4$ requires C, 50·4; H, 5·3%).

2-7′-Ethoxycarbonylheptyl-6-chloromethyl-5-hydroxypyridine.—A cooled solution of the crude hydroxymethyl-compound (500 mg.) in chloroform (10 ml.) was treated with thionyl chloride (1 ml.) and set aside overnight. The chloroform was then removed *in vacuo*, more chloroform was added, and the mixture again evaporated to dryness *in vacuo*. The residual crude 2-7′-ethoxycarbonylheptyl-6-chloromethyl-5-hydroxypyridine hydrochloride (500 mg.) was hygroscopic and did not yield any crystalline derivative.

Ethyl Carpyrinate.—A solution of the chloromethyl hydrochloride (500 mg.) in alcohol (20 ml.) was shaken with Adams's catalyst (200 mg.) in an atmosphere of hydrogen at 60 lb./sq. in. pressure for 6 hr. The alcohol was then removed and the residue basified with saturated sodium hydrogen carbonate solution. It was then repeatedly extracted with benzene. The benzene extract was dried (Na_2SO_4); removal of solvent gave an oil (250 mg.). This on dehydrogenation by Govindachari and Narasimhan's method [1] and crystallisation from ether gave

material, m. p. 78—80°, which did not depress the m. p. of an authentic sample of ethyl carpyrinate (Found: C, 68·7; H, 8·8; N, 4·7. Calc. for $C_{16}H_{23}O_3N$: C, 68·8; H, 9·0; N, 5·0%).

We thank Mr. Selvavinayagam for the microanalyses, and the Government of India for a National Research Post-doctoral Fellowship (to N. S. N.) and a Research Scholarship (to S. R.).

PRESIDENCY COLLEGE, MADRAS-5, INDIA. [*Received, September 24th*, 1956.]