234. *Synthesis in the Octahydropyrrocoline Series.*

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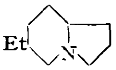
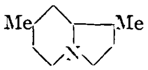
6-Ethyl- and 1 : 7-*dimethyl-octahydropyrrocolines* have been prepared, but differ from the octahydro-derivative of the bicyclic base obtained by the alkaline degradation of strychnine (*J.*, 1936, 1695).

One of us (G. R. C.) obtained, by the alkaline degradation of strychnine, a bicyclic base ($C_{10}H_{11}N$), whose octahydro-derivative has the composition of an ethyl- or dimethyl-octahydropyrrocoline. Clemo and Metcalfe (*J.*, 1937, 1518) prepared 1- and 2-ethyloctahydropyrrocolines and 2-methyloctahydropyridocoline but no correspondence was found with the reduced strychnine derivative. We have now prepared 6-ethyl- and 1 : 7-dimethyl-octahydropyrrocolines (I and II), but again neither of these was identical with the reduced base obtained from the alkaloid.


(I.)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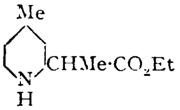
(III.)

Attempts to prepare (I) by condensation of pyrrole-2-aldehyde with diethyl malonate, catalytic reduction of the resulting *ethyl 2-pyrrylmethylenemalonate*, and subsequent decarboxylation, condensation with ethyl bromoacetate, cyclisation, and treatment with ethylmagnesium bromide were unsuccessful owing to difficulties at the reduction and decarboxylation stages. The base was obtained from *ethyl 5-ethyl-2-piperidylacetate* by condensation with ethyl bromoacetate, cyclisation, and reduction of the resulting ketone. While this work was in progress, Prelog and Metzler (*Helv. Chim. Acta*, 1946, **29**, 1163) recorded its preparation by another method, and in the main the properties of our base and its derivatives agree with those of their product. The base (I), however, has two centres of asymmetry and should therefore exist in two externally compensated forms. Our base gave two picrates, one identical with that of Prelog and Metzler, and the other presumably that of its stereoisomer.

The dimethyl base (II) was obtained from the potassium derivative of *ethyl 4-methyl-2-piperidylacetate*. This by methylation gave (III), which, by successive condensation with ethyl bromoacetate, cyclisation, and reduction, yielded (II). No evidence of inhomogeneity was found in this case.

EXPERIMENTAL.

(All m. p.s are uncorrected.)

Ethyl 2-Pyrrylmethylenemalonate.—Pyrrole-2-aldehyde (Fischer and Orth, " Die Chemie des Pyrrols," Vol. I, p. 152) (3·5 g.), ethyl malonate (7 ml.), piperidine (0·5 ml.), and ethanol (35 ml.) were refluxed for 6 hours and fractionated, yielding a golden-yellow oily *ester* which became red at higher temperatures (5·0 g.; b. p. 145—150°/1 mm.) (Found : C, 60·4; H, 6·5. $C_{12}H_{15}O_4N$ requires C, 60·7; H, 6·4%).

Ethyl 2-Pyrrolidylmethylmalonate.—The above ester (2·0 g.), platinum oxide (0·1 g.), and glacial acetic acid (10 ml.) were shaken in hydrogen at 120 lb./sq. in. for 18 hours, the platinum was filtered off, the solvent was removed, and the product was basified (potassium carbonate), extracted with ether, dried, and distilled, giving an oily *ester* (1·6 g.), b. p. 140—143°/1 mm. The product from two such experiments was shaken with platinum oxide (0·1 g.) and glacial acetic acid, as before, for 18 hours and worked up giving a colourless oil (1·9 g.; b. p. 140—142°/1 mm.) (Found : C, 59·0; H, 9·0. $C_{12}H_{21}O_4N$ requires C, 59·2; H, 8·7%). Frequently, however, the reduction was unsuccessful or gave a product which was contaminated with unreduced ester and became tarry at subsequent stages.

Ethyl β-2-Pyrrolidylpropionate.—The preceding methylmalonate (0·5 g.) and concentrated hydrochloric acid (10 ml.) were refluxed 20 hours and taken to dryness. Ethanol, saturated with hydrogen chloride (10 ml.), was added, the whole refluxed for 5 hours, evaporated to dryness and then basified (potassium carbonate), and the *ester* extracted with ether, dried, and distilled as a colourless oil (0·15 g.; b. p. 80—90°/1 mm.) (Found : C, 63·5; H, 10·25. $C_9H_{17}O_2N$ requires C, 63·2; H, 10·0%). Its *picrolonate* has m. p. 138° (Found : C, 52·7; H, 5·8. $C_9H_{17}O_2N,C_{10}H_8O_5N_4$ requires C, 52·4; H, 5·8%).

Ethyl 1-Carbethoxymethyl-2-pyrrolidylmethylmalonate.—Ethyl 2-pyrrolidylmethylmalonate (1·35 g.), ethyl bromoacetate (0·7 ml.), anhydrous potassium carbonate (0·45 g.), and ethanol (6 ml.) were heated for 17 hours. The ethanol was removed, water added, and the *ester* extracted, dried and fractionated (0·45 g.; b. p. 135—140°/1 mm.) (Found : C, 58·3; H, 7·8. $C_{16}H_{27}O_6N$ requires C, 58·3; H, 8·3%).

Ethyl 5-Ethyl-2-pyridylacetate.—This was prepared from 2-methyl-5-ethylpyridine (Frank, Blegen, Dearborn, Myers, and Woodward, *J. Amer. Chem. Soc.*, 1946, **68**, 1368; picrate m. p. 164°) by the method of Oparina (*Chem. Zentr.*, 1935, I, 2536). The following intermediates were characterised. *5-Ethyl-2-stilbazole* (*2-styryl-5-ethylpyridine*), b. p. 205—208°/12 mm., m. p. 61°, after crystallisation from light petroleum (b. p. 80—100°) (Found : C, 85·9; H, 7·2. $C_{15}H_{15}N$ requires C, 86·1; H, 7·2%); *5-ethyl-2-(1 : 2-dibromo-2-phenylethyl)pyridine*, colourless prisms, m. p. 133°, after recrystallisation from light petroleum (b. p. 80—100°) (Found : C, 48·7; H, 4·5. $C_{15}H_{15}NBr_2$ requires C, 48·8; H, 4·1%); *5-ethyl-2-(2-phenylacetylenyl)pyridine*, a colourless oil, b. p. 178—180°/1 mm. (Found : C, 86·7; H, 6·1. $C_{15}H_{13}N$ requires C, 86·9; H, 6·3%), and its *picrate*, m. p. 160° (from ethanol) (Found : C, 57·8; H, 3·7. $C_{15}H_{13}N,C_6H_3O_7N_3$ requires C, 57·8; H, 3·7%); *5-ethyl-2-phenacylpyridine*, unstable yellow prisms [from light petroleum (b. p. 60—80°)], m. p. 72° (Found : C, 79·95; H, 6·7. $C_{15}H_{15}ON$ requires C, 80·0; H, 6·7%), and its *oxime*, colourless prisms, m. p. 101° from dilute ethanol (Found : C, 75·1; H, 6·7. $C_{15}H_{16}O_2N$ requires C, 75·0; H, 6·7%).

Ethyl 5-ethyl-2-pyridylacetate is a pale yellow oil, b. p. 97—98°/1 mm. (Found : C, 68·15; H, 7·9. $C_{11}H_{15}O_2N$ requires C, 68·4; H, 7·8%), and forms a *picrate*, lemon-yellow plates or needles (from ethanol), m. p. 143—144° (Found : C, 48·4; H, 4·5. $C_{11}H_{15}O_2N,C_6H_3O_7N_3$ requires C, 48·4; H, 4·3%).

and a *picrolonate*, yellow prisms (from ethanol), m. p. 142° (Found: C, 55·1; H, 5·3. $C_{11}H_{15}O_2N,C_{10}H_8O_5N_4$ requires C, 55·1; H, 5·1%).

Ethyl 5-Ethyl-2-piperidylacetate.—The pyridyl ester (10·0 g.) in glacial acetic acid (30 ml.) was shaken with platinum oxide (0·1 g.) in hydrogen at 100 lbs./sq. in. for 24 hours, platinum oxide (0·05 g.) was added, and the shaking continued for a further 12 hours. After filtration, the acetic acid was removed under reduced pressure, the residue cooled, basified (potassium hydroxide, 50%), extracted with ether, and dried, and the *ester* distilled as a colourless oil (9·7 g.; b. p. 77—78°/1 mm.) (Found: C, 66·0; H, 10·2. $C_{11}H_{21}O_2N$ requires C, 66·3; H, 10·6%). Its *picrate*, golden yellow prisms, very soluble in ethanol, has m. p. 137°, depressed to 118° by admixture with the picrate of the unreduced ester (Found: C, 47·7; H, 6·0. $C_{11}H_{21}O_2N,C_6H_3O_7N_3$ requires C, 47·7; H, 5·6%).

*Diethyl 5-Ethylpiperidine-*1 : 2-*diacetate.*—The above piperidyl ester (8 g.), ethyl bromoacetate (7 ml.), and anhydrous potassium carbonate (9·0 g.) were heated in a water-bath for 10 hours with frequent shaking. Water was added and the *diester* extracted with ether, dried, and distilled as a colourless oil (8·8 g.), b. p. 125—128°/1 mm. (Found: C, 63·1; H, 9·0. $C_{15}H_{27}O_4N$ requires C, 63·1; H, 9·5%); *picrate*, yellow prisms (from ether), m. p. 84—85° (Found: C, 48·9; H, 5·65. $C_{15}H_{27}O_4N,C_6H_3O_7N_3$ requires C, 49·0; H, 5·9%).

2-*Keto*-6-*ethyloctahydropyrrocoline.*—The diester (7·5 g.) in dry toluene (7 ml.) was added to powdered potassium (2·5 g.) in dry toluene (7 ml.), cooled in ice. After heating for 4 hours on a water-bath, ethanol was added to remove unused potassium, followed by water (30 ml.) and hydrochloric acid (20 ml.). The solution was heated on a water-bath for 20 hours and taken to dryness under reduced pressure. The residue was basified (potassium hydroxide, 50%), extracted with ether, dried, and distilled, giving the *ketone* as a colourless oil (2·5 g.), b. p. 53—55°/1 mm., 120—125°/15 mm., which became brown if kept some days (Found: C, 72·1; H, 10·1. $C_{10}H_{17}ON$ requires C, 71·8; H, 10·2%). This gives a *picrate*, yellow prisms (from ethanol), m. p. 143° (Found: C, 48·9; H, 5·2. $C_{10}H_{17}ON,C_6H_3O_7N_3$ requires C, 48·5; H, 5·1%), and a *picrolonate*, yellow crystals (from methanol), m. p. 150—151° (Found: C, 56·2; H, 5·95. $C_{10}H_{17}ON,C_{10}H_8O_5N_4$ requires C, 55·7; H, 5·8%).

6-*Ethyloctahydropyrrocoline* (I).—The above ketone (2·0 g.) and hydrazine hydrate (7·5 ml., 95%) were refluxed for 18 hours, the hydrazone was extracted with ether, and dried (K_2CO_3), and the ether removed. The resulting yellow oil was heated with sodium ethoxide [from sodium (1·5 g.) and ethanol (12 ml.)] in a sealed tube for 20 hours at 165—170°. After addition of water, acidification (hydrochloric acid), evaporation to dryness under reduced pressure, and basification (potassium hydroxide, 50%), the *base* was extracted with ether, dried, and distilled as a colourless oil (1·1 g.), b. p. 77—78°/15 mm. (Found: C, 78·6; H, 12·5. $C_{10}H_{19}N$ requires C, 78·4; H, 12·5%). Two picrates were obtained on addition of alcoholic picric acid: (*a*) yellow needles, m. p. 177° (Prelog and Metzler give 178°) from methanol (Found: C, 50·6; H, 5·9. Calc. for $C_{10}H_{19}N,C_6H_3O_7N_3$: C, 50·3; H, 5·8%); (*b*) yellow hexagonal prisms, more soluble in ethanol than the needles and having m. p. 118—119° (from ether) (Found: C, 50·35; H, 5·8%). The picrolonate formed yellow decahedral prisms, m. p. 185° (Prelog and Metzler give 182—183°), from methanol (Found: C, 57·2; H, 6·4. Calc. for $C_{10}H_{19}N,C_{10}H_8O_5N_4$: C, 57·5; H, 6·5%). The methiodide crystallised in colourless crystals, m. p. 222° (Prelog and Metzler give 222—223°), from acetone–ether (Found: C, 45·1; H, 7·55. Calc. for $C_{10}H_{19}N,CH_3I$: C, 44·8; H, 7·5%).

Ethyl 4-Methyl-2-pyridylacetate.—This was prepared from 2 : 4-dimethylpyridine by the same method as the 5-ethyl-2-pyridylacetate, the following being characterised. 4-Methyl-2-stilbazole (4-methyl-2-styrylpyridine), b. p. 160°/1 mm., m. p. 69°, after crystallisation from light petroleum (b. p. 40—60°) (Found: C, 85·8; H, 6·7. Calc. for $C_{14}H_{13}N$: C, 86·1; H, 6·7%), and its picrate, m. p. 258° (from ethanol) (Found: C, 56·6; H, 4·0. Calc. for $C_{14}H_{13}N,C_6H_3O_7N_3$: C, 56·6; H, 3·8%); 4-*methyl*-2-(1 : 2-*dibromo*-2-*phenylethyl*)*pyridine*, colourless needles, m. p. 149° (Found: C, 47·7; H, 4·0. $C_{14}H_{13}NBr_2$ requires C, 47·4; H, 3·7%), and its *picrate*, yellow prisms (from ethanol), m. p. 172° (Found: C, 41·5; H, 2·8. $C_{14}H_{13}NBr_2,C_6H_3O_7N_3$ requires C, 41·1; H, 2·8%); 4-*methyl*-2-(2-*phenylacetylenyl*)-*pyridine*, a pale yellow oil, b. p. 130°/1 mm., 166—168°/3 mm., 186—190°/20 mm. (Found: C, 86·7; H, 5·9; $C_{14}H_{11}N$ requires C, 87·0; H, 5·7%), and its *picrate*, yellow crystals (from ethanol), m. p. 215° (Found: C, 56·8; H, 3·9. $C_{14}H_{11}N,C_6H_3O_7N_3$ requires C, 56·9; H, 3·3%); 4-*methyl*-2-*phenacylpyridine*, a yellow oil, b. p. 150°/1 mm., 176°/3 mm., 189—192°/20 mm. (Found: C, 79·6; H, 6·4. $C_{14}H_{13}ON$ requires C, 79·6; H, 6·2%), and its *picrate*, fine yellow needles, m. p. 155° (from water) (Found: C, 54·9; H, 3·8. $C_{14}H_{13}ON,C_6H_3O_7N_3$ requires C, 54·5; H, 3·7%); *oxime*, colourless prisms (from ethanol), m. p. 153° (Found: C, 74·4; H, 6·35. $C_{14}H_{14}ON_2$ requires C, 74·3; H, 6·3%), and *oxime picrate*, yellow prisms (from ethanol), m. p. 152° (Found: C, 52·7; H, 4·1. $C_{14}H_{14}ON_2,C_6H_3O_7N_3$ requires C, 52·7; H, 3·8%).

Ethyl 4-methyl-2-pyridylacetate is a pale yellow oil, b. p. 96—99°/1 mm. (Found: C, 66·8; H 7·2. $C_{10}H_{13}O_2N$ requires C, 67·0; H, 7·3%), and gives a *picrate*, yellow plates (from ethanol), m. p. 116° (Found: C, 47·3; H, 4·3. $C_{10}H_{13}O_2N,C_6H_3O_7N_3$ requires C, 47·1; H, 3·95%), and *picrolonate*, yellow prisms (from ethanol), m. p. 166° (Found: C, 54·5; H, 4·7. $C_{10}H_{13}O_2N,C_{10}H_8O_5N_4$ requires C, 54·2; H, 4·8%).

Ethyl α-(4-*Methyl*-2-*pyridyl*)*propionate* (III).—Ethyl 4-methyl-2-pyridylacetate (9·0 g.) was added to powdered potassium (2·0 g.) under ether (100 ml.) and left overnight. Methyl iodide (7·4 g.) was carefully added, the mixture refluxed for 10 hours, water added, and the *ester* extracted with ether, dried, and distilled as a pale yellow oil (7·1 g.), b. p. 75—78°/1 mm., 94—97°/3 mm. (Found: C, 68·7; H, 7·9. $C_{11}H_{15}O_2N$ requires C, 68·4; H, 7·8%). This gives a *picrate*, yellow prisms (from ethanol), m. p. 103° (Found: C, 48·35; H, 4·15. $C_{11}H_{15}O_2N,C_6H_3O_7N_3$ requires C, 48·4; H, 4·3%), and *picrolonate*, yellow prisms (from ethanol), m. p. 138° (Found: C, 55·25; H, 5·1. $C_{11}H_{15}O_2N,C_{10}H_8O_5N_4$ requires C, 55·1; H, 5·1%).

Ethyl α-(4-*Methyl*-2-*piperidyl*)*propionate.*—Prepared from the above pyridyl ester (5·0 g.) in the same way as ethyl 5-ethyl-2-piperidylacetate, this *ester* was obtained as a colourless oil (4·5 g.), b. p. 90—93°/3 mm. (Found: C, 66·8; H, 9·8. $C_{11}H_{21}O_2N$ requires C, 66·3; H, 10·6%), and gives a *picrate*, yellow prisms (from ether), m. p. 141° (Found: C, 47·7; H, 5·5. $C_{11}H_{21}O_2N,C_6H_3O_7N_3$ requires C, 47·7; H, 5·6%), and *picrolonate*, yellow prisms (from ethanol), m. p. 190° (Found : C, 54·7; H, 6·5. $C_{11}H_{21}O_2N,C_{10}H_8O_5N_4$ requires C, 54·4; H, 6·3%).

Diethyl 4-*Methylpiperidine*-1-*acetate*-2-α-*propionate*.—(*a*) The above reduced ester (2·0 g.), ethyl bromoacetate (2·0 g.), and silver oxide (1·4 g.) in ethanol (10 ml.; 97%) were warmed to 50° and shaken overnight. The silver bromide was coagulated and removed by filtration, the solution fractionated after removal of the alcohol, and the *diester* obtained as a colourless oil (1·7 g.), b. p. 110—115°/1 mm.

(*b*) The diester was also obtained in the usual manner from the piperidyl ester (2·0 g.), ethyl bromoacetate, and anhydrous potassium carbonate as a colourless oil (1·5 g.), b. p. 110°/1 mm., 130°/3 mm. (Found : C, 63·3; H, 9·5. $C_{15}H_{27}O_4N$ requires C, 63·1; H, 9·5%).

2-*Keto*-1 : 7-*dimethyloctahydropyrrocoline*.—This *ketone* was obtained by Dieckmann cyclisation of the above diester (1·4 g.) in the usual manner as a colourless oil (0·3 g.), b. p. 80°/3 mm. (Found : C, 71·2; H, 10·3. $C_{10}H_{17}ON$ requires C, 71·8; H, 10·2%), and gave a *picrate*, yellow prisms (from ethanol), m. p. 175°, decomp. 181° (Found : C, 48·5; H, 5·1. $C_{10}H_{17}ON,C_6H_3O_7N_3$ requires C, 48·5; H, 5·1%).

1 : 7-*Dimethyloctahydropyrrocoline* (II).—The *base* was prepared as above by the Wolff–Kishner reduction of the ketone (0·23 g.) as a colourless oil (0·08 g.), b. p. (bath-temperature) 150°/15 mm. (Found : C, 78·5; H, 12·1. $C_{10}H_{19}N$ requires C, 78·4; H, 12·5%). The picrate crystallised from ethanol in yellow prisms, m. p. 116°.

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