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Alkaloids of *Daphnandra* Species. Part IX.[1] Synthesis of (±)-Hemirepanduline, the Racemate of a Degradation Product of Repanduline

By **K. Aoki** and **John Harley-Mason**, University Chemical Laboratory, Cambridge

(±)-7-Hydroxy-6-methoxy-1-(4-methoxybenzyl)-2,8-dimethyl-1,2,3,4-tetrahydroisoquinoline has been synthesised by a conventional route. The i.r., n.m.r., and mass spectra of this material are superposable on those of (−)-hemirepanduline, thus proving the structure of the latter.

(−)-HEMIREPANDULINE [1] is one of the potassium–liquid ammonia cleavage products of the bisbenzylisoquinoline alkaloid repanduline and its structure was thought to be 7-hydroxy-6-methoxy-1-(4-methoxybenzyl)-2,8-dimethyl-1,2,3,4-tetrahydroisoquinoline (I) on the basis of chemical and n.m.r. studies. We report here the synthesis of (±)-hemirepanduline by standard methods, confirming the above structure.

4-Hydroxy-3-methoxy-5-methylbenzaldehyde [2] (II) was benzylated and the resulting 4-benzyloxy-3-methoxy-5-methylbenzaldehyde (III) was condensed with nitromethane to yield 4-benzyloxy-3-methoxy-5-methyl-β-nitrostyrene (IV). The nitrostyrene (IV) was reduced with lithium aluminium hydride to yield 4-benzyloxy-3-methoxy-5-methylphenethylamine (V), which was then

[1] Part VIII, I. R. C. Bick, J. H. Bowie, J. Harley-Mason, and D. H. Williams, preceding Paper.

[2] (*a*) R. I. T. Cromartie and J. Harley-Mason, *J. Chem. Soc.* 1952, 1052; (*b*) J. & P. Koetschet, *Helv. Chim. Acta*, 1930, **13**, 476.

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condensed without purification with 4-methoxyphenylacetyl chloride to give *N*-(4-benzyloxy-3-methoxy-5-methylphenethyl)-4-methoxyphenylacetamide (VI). Bischer–Napieralski cyclisation of the amide (VI) with phosphoryl chloride gave 7-benzyloxy-6-methoxy-1-(4-methoxybenzyl)-8-methyl-3,4-dihydroisoquinolinium chloride (VII), which was converted into the methiodide (VIII).

Reduction and debenzylation[3] of the amorphous methiodide (VIII) with zinc powder and hydrochloric acid gave crystalline 7-hydroxy-6-methoxy-1-(4-methoxybenzyl)-2,8-dimethyl-1,2,3,4-tetrahydroisoquinoline (I). The i.r., n.m.r., and mass spectra of the synthetic tetrahydroisoquinoline (I) and of (−)-hemirepanduline were superposable.

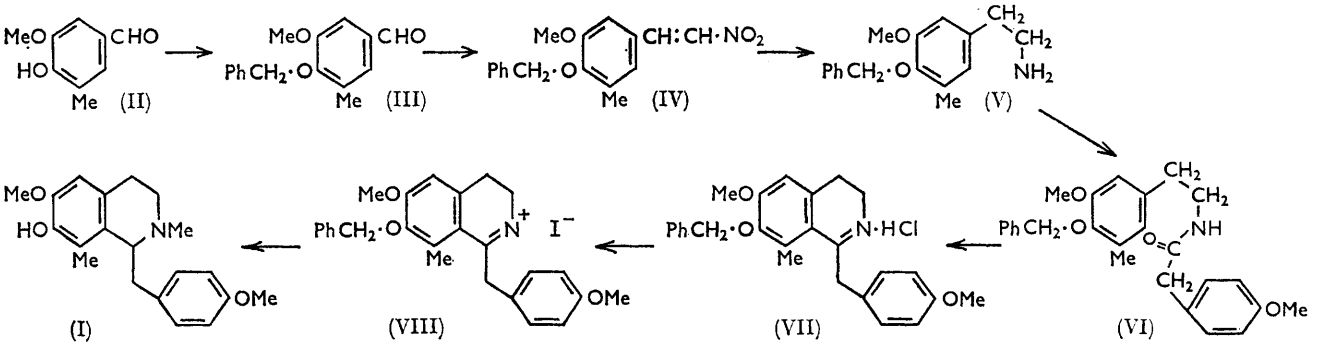
EXPERIMENTAL

4-Benzyloxy-3-methoxy-5-methylbenzaldehyde.— To 4-hydroxy-3-methoxy-5-methylbenzaldehyde, m. p. 98—99° (lit.,[2b] 99°) (5·2 g.), in dry methanol (50 ml.) containing anhydrous potassium carbonate (9·6 g.), was added benzyl chloride (8·8 g.). The mixture was heated under reflux for 10 hr. The solid was filtered off and to the filtrate was added water (30 ml.). Methanol was removed under vacuum and the solution was made alkaline with N-sodium hydroxide. The product (5·3 g.), extracted with ether, was a viscous oil; *2,4-dinitrophenylhydrazone*, red plates, m. p. 216—217° (from benzene) (Found: C, 60·6; H, 4·7; N, 12·7. $C_{22}H_{20}N_2O_6$ requires C, 60·6; H, 4·6; N, 12·85%).

4-Benzyloxy-3-methoxy-5-methyl-β-nitrostyrene.— The above 4-benzyloxy-3-methoxy-5-methylbenzaldehyde (10·9 g. crude material), nitromethane (5·5 g.), and ammonium acetate (1·7 g.) in acetic acid (50 ml.) were heated under reflux for 5 hr. Part of the acetic acid was removed under vacuum and addition of water precipitated the product (8·8 g.) as a yellow solid. Two recrystallisations from dilute acetic acid yielded *4-benzyloxy-3-methoxy-5-methyl-β-nitrostyrene*, yellow needles, m. p. 114·5—115·5° (Found: C, 68·2; H, 5·7; N, 4·6. $C_{17}H_{17}NO_4$ requires C, 68·3; H, 5·7; N, 4·7%).

N-(4-Benzyloxy-3-methoxy-5-methylphenethyl)-4-methoxyphenylacetamide (VI).—The above nitrostyrene (3·4 g.) was extracted overnight (Soxhlet) into stirred refluxing dry ether (300 ml.) containing lithium aluminium hydride (2·2 g.). The mixture was cooled in ice–water and stirred vigorously during the successive addition of water (40 ml.), 20% sodium hydroxide solution (50 ml.), and more water (50 ml.). After addition the mixture was stirred for 1 hr., the ether layer was decanted, and the residue was washed three times with ether. The extract was washed with water, dried (K_2CO_3), and the ether removed leaving the phenethylamine (V) (2·5 g.) as a thick oil.

4-Methoxyphenylacetyl chloride (from 1·8 g. of 4-methoxyphenylacetic acid) in dry benzene (10 ml.) was added dropwise to a stirred solution of 4-benzyloxy-3-methoxy-5-methylphenethylamine (3·4 g.) and triethylamine (5 ml.) in dry benzene (50 ml.) with ice cooling. After keeping overnight the precipitated triethylammonium chloride was filtered off and washed twice with dry benzene. The benzene solution was washed with 10% sodium hydroxide solution, then with 10% hydrochloric acid, and finally with water. After drying, the solvent was removed and the gummy residue was extracted with successive portions of boiling ethyl acetate. On concentration to small bulk, the ethyl acetate extracts gave a cream coloured solid. Recrystallisation from ethyl acetate gave the *amide* as needles (3·5 g.), m. p. 107·5—109° (Found: C, 74·6; H, 7·1; N, 3·2. $C_{26}H_{29}NO_4$ requires C, 74·5; H, 7·0; N, 3·3%), $\nu_{max.}$ (KBr disc.) 1644 (C=O) and 3280 (NH) cm.$^{-1}$.



(±)-*7-Hydroxy-6-methoxy-1-(4-methoxybenzyl-2,8-dimethyl-1,2,3,4-tetrahydroisoquinoline* (I).—A mixture of the above amide (1·1 g.) and phosphoryl chloride (0·45 g.) in dry toluene (40 ml.) was heated under reflux for 3 hr. and concentrated to dryness under vacuum. The remaining reddish solid was treated with boiling ethyl acetate. On cooling, the product was obtained as a crystalline solid, m. p. 105—107°. Recrystallisation from ethyl acetate gave needles, m. p. 113—115·5°, of the dihydroisoquinolinium chloride (VII), $\nu_{max.}$ (KBr disc.) 1630 (N=C) and 2650 cm.$^{-1}$ (broad: $C=\overset{+}{N}-H$), $\lambda_{max.}$ (EtOH) 320, 250, and 230 mμ.

The above dihydroisoquinolinium chloride (1·1 g.) in boiling ethanol (10 ml.) was treated under nitrogen with a solution of sodium ethoxide (from 0·5 g. of sodium) in ethanol (5 ml.), followed by methyl iodide (3 ml.). The mixture was boiled under nitrogen for 7 hr. Inorganic solid was filtered off and the solvent was removed yielding a dark red gum. On keeping, this solidified to an amorphous yellow solid which could not be recrystallised.

The amorphous methiodide (0·84 g.) in ethanol (130 ml.) containing zinc powder (4·8 g.) and concentrated hydrochloric acid (32 ml.) was heated under reflux for 2 hr., when more zinc powder (1·0 g.) was added. After a further 1 hr. the mixture was cooled and filtered. The ethanol

[3] Cf. T. Kametani, K. Wakisaka, and K. Fukumoto, *J. Pharm. Soc. Japan*, 1966, **86**, 422.

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was removed under vacuum. The residue was diluted with water (150 ml.) and washed with ether, this extract being discarded. Then the aqueous solution was made alkaline with 40% sodium hydroxide solution under ice cooling. The alkaline solution washed again with ether, adjusted to pH 10·6—10·8 by the addition of ammonium chloride, and extracted with ether. The ethereal extract was washed with saturated sodium chloride solution, dried ($MgSO_4$), and the ether removed leaving a brown gum. This was taken up in boiling light petroleum (b. p. 60—80°) containing a small amount of ether. Removal of the solvent left a yellowish gummy solid which on three recrystallisations from methanol gave the *tetrahydroisoquinoline* as needles, m. p. 125·5—127° (Found: C, 73·5; H, 7·8; N, 4·1. $C_{20}H_{25}NO_3$ requires C, 73·5; H, 7·7; N, 4·3%).

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