Synthesis of 3-Amino-1,2,3,4-tetrahydro-6-hydroxycarbazole, an Analogue of 5-Hydroxytryptamine

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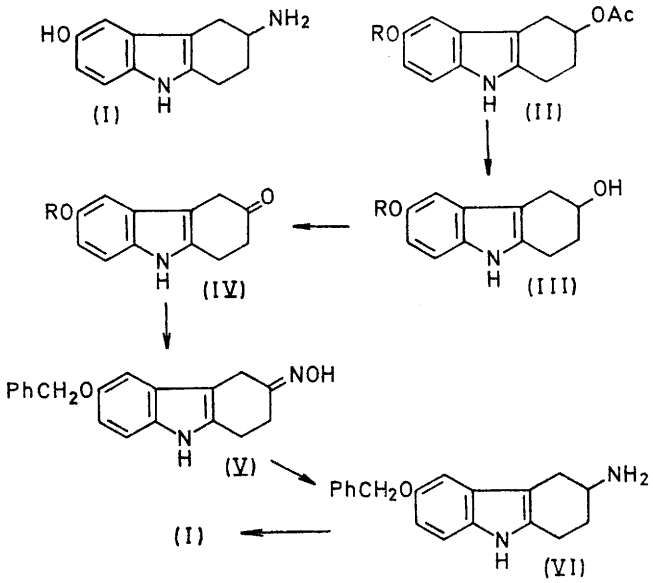
The synthesis of 3-amino-1,2,3,4-tetrahydro-6-hydroxycarbazole is reported. 1,2-Dihydrocarbazol-3(4*H*)-one was successfully obtained by oxidation of 1,2,3,4-tetrahydro-3-hydroxycarbazole.

CONTINUING interest [1] in the significance of 5-hydroxytryptamine (serotonin) in the central nervous system prompted us to undertake the synthesis of 5-hydroxytryptamine analogues in which the position of the primary amino-group relative to the planar 5-hydroxyindole nucleus is fixed within small limits. We here record the synthesis of 3-amino-1,2,3,4-tetrahydro-6-hydroxycarbazole (I). 3-Amino-1,2,3,4-tetrahydrocarbazole has been synthesised from 3-aminocarbazole,[2] and 1,2,3,4-tetrahydro-6-hydroxycarbazole has been prepared by several methods,[3,4] the most successful being by hydrogenolysis of 6-benzyloxy-1,2,3,4-tetrahydrocarbazole.[3]



a; R = $PhCH_2$
b; R = Me

In our synthesis, the tetrahydrocarbazole system was constructed by a Fischer indole cyclisation employing 4-acetoxycyclohexanone [5] and a *p*-substituted phenylhydrazine; 4-acetoxycyclohexanone, when treated with *p*-benzyloxyphenylhydrazine or *p*-methoxyphenylhydrazine in refluxing acetic acid gave, without isolation of the intermediate hydrazone, the 3,6-disubstituted 1,2,3,4-tetrahydrocarbazole (IIa or b) in good yield. The corresponding 1,2,3,4-tetrahydro-3-hydroxycarbazoles (IIIa and b) were obtained from the 3-acetoxy-derivatives by hydrolysis with sodium hydroxide in aqueous ethanol.

The preferred approach to the introduction of a 3-amino-group involved oxidation of the fused cyclohexanol (III) to the corresponding ketone (IV), followed by reduction of its oxime (V). Despite two reported failures [6,7] to oxidise 1,2,3,4-tetrahydro-3-hydroxycarbazole to the 3-ketone, we achieved this conversion both in the 6-substituted series (IIIa and b) and in 1,2,3,4-tetrahydro-3-hydroxycarbazole itself and its *N*-methyl derivative, by means of an Oppenauer oxidation with aluminium isopropoxide and cyclohexanone in refluxing toluene.

No attempt was made to prepare the ketone (IV) by direct cyclisation of the appropriate monophenylhydrazone of cyclohexane-1,4-dione; other workers obtained only the diphenylhydrazone [6,8] of this diketone although monophenylhydrazones of cyclohexane-1,2-dione [9] and cyclohexane-1,3-dione [10] have been obtained and converted into 3,4-dihydrocarbazol-1(2*H*)-one and 1,2-dihydrocarbazol-4(3*H*)-one respectively.

The synthesis of (I) was completed by conversion of 6-benzyloxy-1,2-dihydrocarbazol-3(4*H*)-one (IVa) into the oxime (V) by treatment with hydroxylamine hydrochloride and sodium acetate in aqueous ethanol. The amine (VI) was obtained by reduction with lithium aluminium hydride.

The benzyloxy-group was removed by catalytic hydrogenation over 10% palladium–carbon. 3-Amino-1,2,3,4-tetrahydro-6-hydroxycarbazole (I) underwent ready oxidation in solution, and was therefore purified by vacuum sublimation. No attempt was made at resolution. The compound was inactive in tests for 5-hydroxytryptamine mimetic and antagonistic activity in the anaesthetised guinea pig at doses ten times greater than that for which 5-hydroxytryptamine gave a positive response.

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EXPERIMENTAL

3-Acetoxy-6-benzyloxy-1,2,3,4-tetrahydrocarbazole (IIa).—*p*-Benzyloxyphenylhydrazine hydrochloride [11] (3·3 g.) and anhydrous sodium acetate (1·1 g.) were added to a solution of 4-acetoxycyclohexanone [5] (2·0 g.) in glacial acetic acid (40 ml.), and the mixture was heated under reflux for 1 hr., cooled, poured into water, and extracted with ether. The extract was washed with aqueous sodium hydrogen carbonate solution and water, dried (Na_2SO_4), and evaporated to leave the *carbazole* (3·5 g., 84%), m.p. 148—151° (from aqueous ethanol) (Found: C, 74·9; H, 6·3; N, 4·05. $C_{21}H_{21}NO_3$ requires C, 75·2; H, 6·3; N, 4·2%), $\nu_{max.}$ ($CHCl_3$) 3475, 1725, 1595, and 1250 cm.$^{-1}$.

The following compounds were similarly prepared: *3-acetoxy-1,2,3,4-tetrahydrocarbazole*, m.p. 101—103° (from aqueous ethanol) (Found: C, 73·0; H, 6·5; N, 6·2. $C_{14}H_{15}NO_2$ requires C, 73·3; H, 6·6; N, 6·1%); *3-acetoxy-1,2,3,4-tetrahydro-N-methylcarbazole*, m.p. 95—97° (from ethanol) (Found: C, 73·9; H, 6·8. $C_{15}H_{17}NO_2$ requires C, 74·0; H, 7·0%); *3-acetoxy-1,2,3,4-tetrahydro-6-methoxycarbazole*, m.p. 107—111° (from aqueous ethanol) (Found: C, 69·7; H, 6·8; N, 5·4. $C_{15}H_{17}NO_3$ requires C, 69·5; H, 6·6; N, 5·4%).

6-Benzyloxy-1,2,3,4-tetrahydro-3-hydroxycarbazole (IIIa).—A solution of 3-acetoxy-6-benzyloxy-1,2,3,4-tetrahydrocarbazole (15·0 g.) in ethanol (300 ml.) was heated under reflux with sodium hydroxide (3·75 g.) in water (75 ml.) for 30 min. The ethanol was distilled off under reduced pressure; the solid precipitated on dilution with water gave the *3-hydroxy-derivative* (12·5 g., 95%), m.p. 144—147° (from aqueous ethanol) (Found: C, 78·1; H, 6·4. $C_{19}H_{19}NO_2$ requires C, 77·8; H, 6·5%), $\nu_{max.}$ ($CHCl_3$) 3600, 3475, 1625, and 1595 cm.$^{-1}$.

The following compounds were prepared from the corresponding 3-acetoxy-derivatives: *1,2,3,4-tetrahydro-3-hydroxycarbazole*, m.p. 149—150° (from water) (lit.,[6] 152—154°); *1,2,3,4-tetrahydro-3-hydroxy-N-methylcarbazole*, m.p. 99—103° (from aqueous ethanol) (Found: C, 77·7; H, 7·4. $C_{13}H_{15}NO$ requires C, 77·6; H, 7·5%) *1,2,3,4-tetrahydro-3-hydroxy-6-methoxycarbazole*, m.p. 103—106° (from aqueous ethanol) (Found: C, 72·1; H, 7·3; N, 6·4. $C_{13}H_{15}NO_2$ requires C, 71·8; H, 7·0; N, 6·4%).

6-Benzyloxy-1,2-dihydrocarbazol-3(4H)-one (IVa).—Aluminium isopropoxide (4·0 g.) in toluene (60 ml.) was added to a boiling solution of 6-benzyloxy-1,2,3,4-tetrahydro-3-hydroxycarbazole (13·5 g.) and cyclohexanone (70 ml.) in toluene (300 ml.) at a rate equal to that at which toluene was distilled off. Distillation was continued until the volume of the solution was reduced to 100 ml. Saturated aqueous sodium potassium tartrate (60 ml.) was added, and the mixture was steam distilled to give *ca.* 60 ml. of distillate. The residue was extracted with chloroform, and the chloroform solution was washed with water, dried (Na_2SO_4), and evaporated to give the *3-ketone* (8·4 g., 63%), m.p. 161—175° (from ethanol) (Found: C, 78·1; H, 6·0. $C_{19}H_{17}NO_2$ requires C, 78·3; H, 5·9%), $\nu_{max.}$ ($CHCl_3$) 3475, 1710, and 1595 cm.$^{-1}$.

The following ketones were also prepared by Oppenauer oxidation of the appropriate 1,2,3,4-tetrahydro-3-hydroxycarbazole: 1,2-dihydrocarbazol-3(4*H*)-one, m.p. 146—150° (lit.,[6] 148—152°); *1,2-dihydro-N-methylcarbazol-3(4H)-one*, m.p. 88—89° (from methanol) (Found: C, 78·25; H, 6·6; N, 6·9. $C_{13}H_{13}NO$ requires C, 78·4; H, 6·6; N, 7·0%); *1,2-dihydro-6-methoxycarbazole-3(4H)-one*, m.p. 142—152° (from aqueous ethanol) (Found: C, 73·1; H, 6·0. $C_{13}H_{13}NO_2$ requires C, 72·6; H, 6·1%).

6-Benzyloxy-1,2,3,4-tetrahydro-3-hydroxyiminocarbazole (V).—6-Benzyloxy-1,2-dihydrocarbazol-3(4*H*)-one (1·9 g.) in ethanol (160 ml.) was heated under reflux with a solution of hydroxylamine hydrochloride (1·3 g.) and anhydrous sodium acetate (2·6 g.) in water (15 ml.) for 1 hr. The solution was concentrated under reduced pressure, and poured on ice. The solid thus precipitated was filtered off, washed with water, and crystallised from benzene to give the *oxime* (1·5 g., 75%), m.p. 160° (Found: C, 74·8; H, 5·6. $C_{19}H_{18}N_2O$ requires C, 74·5; H, 5·9%), $\nu_{max.}$ ($CHCl_3$) 3580, 3475, 3300, and 1595 cm.$^{-1}$.

3-Amino-6-benzyloxy-1,2,3,4-tetrahydrocarbazole (VI).—6-Benzyloxy-1,2,3,4-tetrahydro-3-hydroxyiminocarbazole (2·25 g.) in dry ether (250 ml.) was heated under reflux with lithium aluminium hydride (2·0 g.) for 24 hr. Water was added carefully to decompose the excess of lithium aluminium hydride, and the ether layer was separated. The aqueous layer was again extracted with ether, and the combined ethereal solutions were washed with water and extracted with 2N-hydrochloric acid. The acid solution was made basic with aqueous ammonia, and extracted with ether. The resulting ethereal solution was washed with water, dried (Na_2SO_4), and evaporated to give the *amine* (1·5 g., 71%), m.p. 131—135° (from benzene) (Found: C, 77·9; H, 6·5. $C_{19}H_{20}N_2O$ requires C, 78·0; H, 6·9%), $\nu_{max.}$ 3475, 1625, and 1595 cm.$^{-1}$.

The *hydrochloride*, prepared by passing dry hydrogen chloride through an ethereal solution of the amine, had m.p. 238—240° (from methanol).

3-Amino-1,2,3,4-tetrahydro-6-hydroxycarbazole (I).—To a solution of 3-amino-6-benzyloxy-1,2,3,4-tetrahydrocarbazole (0·65 g.) in methanol (35 ml.) was added 10% palladium–carbon (0·3 g.); the mixture was shaken in hydrogen at room temperature and atmospheric pressure until uptake ceased. It was then filtered and the methanol was distilled off to give the *hydroxyamine*. This was purified by sublimation at 200°/1 mm. and had m.p. 250° (0·43 g., 97%) (Found: C, 71·6; H, 6·7. $C_{12}H_{14}NO_2$ requires C, 71·25; H, 7·0%), $\nu_{max.}$ (Nujol) 3370, 3280, 1620, and 1595 cm.$^{-1}$.

The *diacetate*, prepared in dry pyridine by use of acetic anhydride, had m.p. 117—121° (from benzene), $\nu_{max.}$ ($CHCl_3$) 3475, 3440, 1750, 1655, and 1590 cm.$^{-1}$.

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