CARBOLINES

V.* SYNTHESIS OF 1-METHYL-4-(ω-DIMETHYLAMINOPROPYL)-β-CARBOLINE

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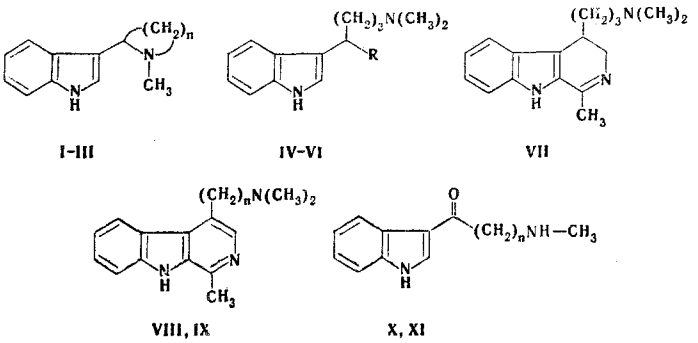
The synthesis of 1-methyl-4-(ω-dimethylaminopropyl)-β-carboline from 3-(1-methyl-2-pyrrolidyl)indole is described.

1-Methyl-4-(ω-dimethylaminopropyl)-β-carboline, which is the lower homolog of the alkaloid brevicarine and is of interest from a pharmacological point of view, was previously [2] obtained in low yield. In order to increase the accessibility of this substance, we investigated another synthetic route, at the basis of which was the same idea of construction of an aminoalkyl side chain by closing of cyclic gramine I [2].

The quaternization of 3-(1-methyl-2-pyrrolidyl)indole (I) with methyl iodide and subsequent treatment with alkali cyanide gave aminonitrile IV. Heating of the latter with Raney nickel and hydrazine hydrate in isopropyl alcohol via the method in [3] gave tryptamine V, which was characterized as the dipicrate. Lithium aluminum hydride and catalytic hydrogenation did not reduce IV. Amorphous N-acetyl derivative VI, which was obtained by treatment of the amine with acetic anhydride in pyridine, was subjected, without purification, to the action of phosphorus pentachloride in warm nitrobenzene, during which it underwent cyclization to give 3,4-dihydro-β-carboline VII. Dehydrogenation of the latter via a previously described method [4] gave completely aromatic β-carboline VIII.

An attempt was made to use a similar method for the synthesis of IX – the higher homolog of the alkaloid brevicarine – from III. It is known from the literature that cyclic lactams readily undergo the Vilsmeier–Haack reaction with indole. In this case, 1-methyl-2-pyrrolidone forms 2-pyrrolidylidene-3-indolenine, which can be readily reduced to I [5].



I, VIII n=3; II, IX, X n=4; III, XI n=5; IV R=CN; V R=CH_2NH_2; VI R=$CH_2NHCOCH_3$

Aminoketone X, which is in equilibrium with the cyclic hydroxyamine form and is readily reduced to II [6], was obtained from 1-methyl-2-piperidone. In order to obtain azepinylindole III, we investigated the

* See [1] for communication IV.

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reaction of indole with N-methylcaprolactam. The use of the usual method with phosphorus oxychloride in excess amide with subsequent hydrolysis gave amino ketone XI, which was not cyclized to III when different reducing agents were used. The use of workup methods that hinder hydrolysis of the intermediate Vilsmeier complex [7, 8] also gave only ketone XI but in lower yields. The steric strain arising in the seven-membered ring probably facilitates cleavage of the enamine structure of the complex.

EXPERIMENTAL

The melting points (none of which were corrected) were measured with a Kofler apparatus. The UV spectra of ethanol solutions were recorded with a Specord spectrometer. The IR spectra of mineral oil suspensions were recorded with a UR-10 spectrometer.

5-Dimethylamino-2-(3-indolyl)pentanenitrile (IV). A 9.5-g (67 mmole) sample of methyl iodide was added to 12.4 g (62 mmole) of pyrrolidylindole I [5] in 120 ml of ethanol, and the solution was held at room temperature for 2 h, after which 7.6 g (157 mmole) of sodium cyanide in a small amount of water was added, and the mixture was refluxed for 1 h. The cooled reaction mixture was poured into water, and the aqueous mixture was extracted with ether. The extract was dried and the solvent was removed. The residue was worked up to give a solid, which was crystallized from trichloroethylene to give 12.6 g (85.7%) of a product with mp 126-127°. Found: C 74.7; H 8.1; N 17.4%. $C_{15}H_{19}N_3$. Calculated: C 74.7; H 7.9; N 17.4%. IR spectrum, cm^{-1}: 3330 (NH), 2260 (C≡N).

5-Dimethylamino-2-(3-indolyl)pentylamine (V). A mixture of 3 g (12.5 mmole) of IV, 2.2 g of Raney nickel, and 40 ml of isopropyl alcohol was refluxed and stirred for 2 h while 40 ml of hydrazine hydrate was added gradually. The mixture was then heated for another 15 min and cooled. The catalyst was removed by filtration, and the solution was vacuum-evaporated to dryness at no higher than 65° to give 3.2 g of a very viscous liquid. The dipicrate had mp 162-164° (from alcohol). Found: C 46.3; H 4.1; N 18.0%. $C_{15}H_{23}N_3 \cdot 2C_6H_3N_3O_7$. Calculated: C 46.1; H 4.2; N 17.9%. IR spectrum, cm^{-1}: 3390 (indole NH), 2740 ($-NH_3^+$).

1-Methyl-4-(3-dimethylaminopropyl)-3,4-dihydro-β-carboline (VII). An 8.5-g (83 mmole) sample of acetic anhydride was added to 9.1 g (37.2 mmole) of V in 93 ml of cooled pyridine, and the mixture was allowed to stand at room temperature for 16 h. It was then poured into water, and the aqueous mixture was made alkaline with sodium hydroxide and extracted with ether. The ether and pyridine were removed from the dried extract by vacuum distillation below 75° to give 8.6 g of acetyl derivative VI.

A solution of 3.1 g (10.8 mmole) of crude VI in 31 ml of nitrobenzene was added with stirring to 6.9 g (32.4 mmole) of PCl_5 in 31 ml of nitrobenzene heated to 65°. The addition took 30 sec, during which the temperature rose to 70°. After another minute, the mixture was cooled with ice water, the excess PCl_5 was decomposed with chunks of ice, and the solution was diluted with ether. The aqueous layer was separated, and the organic phase was washed with dilute hydrochloric acid. Alkalization of the combined aqueous extracts with sodium hydroxide gave a precipitate, which was dried and crystallized from aqueous isopropyl alcohol to give 1 g (34.5%) of VIII with mp 56-58°. UV spectrum, λ_{max}, nm (ε) in neutral solution: 235 (14,400), 317 (13,200); in 0.01 N HCl: 246 (9900), 354 (19,200). IR spectrum, cm^{-1}: 3450 (NH), 1620 (C≡N). The dipicrate had mp 209° (alcohol–dimethylformamide). Found: C 48.0; H 4.3; N 17.6%. $C_{17}H_{23}N_3 \cdot 2C_6H_3N_3O_7$. Calculated: C 47.9; H 4.0; N 17.1%. The dibenzoate had mp 150-152° (isopropyl alcohol).

1-Methyl-4-(3-dimethylaminopropyl)-β-carboline (VIII). A solution of 0.59 g of sodium borohydride in 33 ml of water was added under nitrogen in the course of 1-2 min at 25° to a stirred solution of 1.1 g of $PdCl_2 \cdot 2H_2O$ in 100 ml of water. The mixture was then acidified with HCl, and, after the layers had separated, a large portion of the water was decanted while preventing contact of the catalyst with air. A 14.5-ml sample of ethylene glycol and a solution of 1.37 g of the dihydrochloride of VII in the minimum amount of water were added to the resulting catalyzate. The apparatus was connected to a condenser set for distillation and placed on an oil bath heated to 150°. The mixture was heated and stirred under carbon dioxide for 1.5 h, during which a large portion of the water was removed by distillation. The mixture was then cooled and diluted with water, and the catalyst was removed by filtration. The filtrate was made alkaline with sodium hydroxide, and the precipitated crystals were removed by filtration to give 1.1 g of VIII (81%). Stirring a suspension of base VIII with an ether solution of HCl gave the dihydrochloride (mp 270-271°), which was identical to a genuine sample [2].

6-Methylamino-1-(3-indolyl)hexanone (XI). A 7.85-g (0.051 mole) sample of freshly distilled phosphorus oxychloride was added in the course of 10 min to 10 ml of stirred ice-cooled N-methylcaprolactam. After 15 min, 5.85 g (0.05 mole) of indole in 10 ml of N-methylcaprolactam was added in the course of 1 h to the resulting solution. The resulting thick paste was stirred at room temperature for 30 min and at 50° for 2.5 h, after which it was diluted with water and made alkaline with sodium hydroxide. The precipitate was separated and crystallized from isopropyl alcohol to give 7.9 g (65%) of colorless crystals with mp 137-138° (ethanol). Found: C 73.6; H 8.3; N 11.2%. $C_{15}H_{20}N_2O$. Calculated: C 73.7; H 8.3; N 11.5%. IR spectrum, cm^{-1}: 3300 (NH), 1630 (CO), 775 (benzene ring). UV spectrum λ_{max}, nm (ε), in neutral solution: 209 (33,600), 242 (14,400), 256 (9900), 297 (13,500); in 0.01 N KOH: 217 (28,000), 242 (12,600), 263 (11,800), 274 (10,400), 297 (12,600), 3300 (6000). These values practically coincide with the spectra of X presented in [6]. The formate of XI had mp 114-115° (isopropyl alcohol).

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