TRYPTAMINES, CARBOLINES, AND RELATED COMPOUNDS

PART V. 3-(α-ALKYL-β-AMINOETHYL)INDOLES[1,2]

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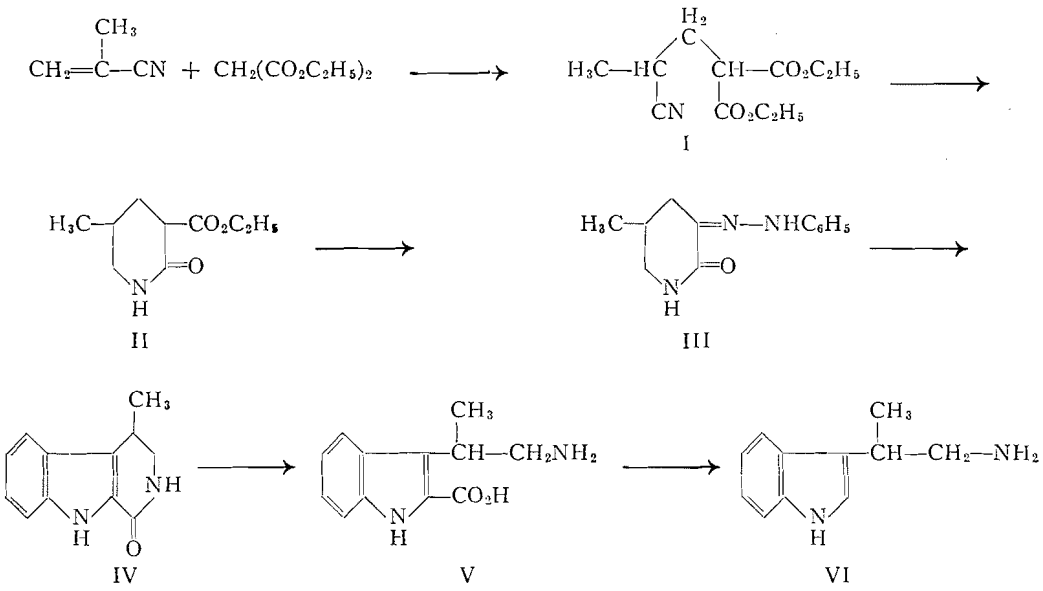
ABSTRACT

The scope of the tryptamine synthesis via 1-oxo-1,2,3,4-tetrahydro-β-carbolines has been extended to tryptamines bearing a side-chain α-alkyl group. The preparation of 3-(2-amino-1-methylethyl)indole by this procedure is described.

In a previous paper (1) an attempt was made to extend the method of synthesis of tryptamines via 1-oxo-1,2,3,4-tetrahydro-β-carbolines (2, 3) to the elaboration of the physostigmine ring system. The intermediate 4-methyl-2,3-dioxopiperidine 3-phenylhydrazone did not, however, undergo Fischer cyclization but instead rearranged to the geometrically isomeric phenylhydrazone. In order to examine the scope of this method of tryptamine synthesis the cyclization of 5-alkyl-substituted 2,3-dioxopiperidine 3-phenylhydrazones was examined, in particular that of 5-methyl-2,3-dioxopiperidine 3-phenylhydrazone (III). This reaction sequence should eventually lead to 3-(2-amino-1-methylethyl)indole (VI). This type of compound may be of physiological interest since Velluz (4) has shown that when a methyl substituent is introduced into the corresponding position in reserpine a more physiologically active compound is obtained.

The synthesis of the required indole was uneventful and followed the path described in the previous examples (2, 3):



Ethyl malonate was condensed with methacrylonitrile in the presence of sodium ethoxide giving diethyl 2-cyanopropylmalonate (I), which was hydrogenated to 3-ethoxycarbonyl-5-methyl-2-oxopiperidine (II). This underwent a Japp–Klingemann

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reaction with benzenediazonium chloride at pH 5 to give 5-methyl-2,3-dioxopiperidine 3-phenylhydrazone (III) which, unlike the corresponding 4-methyl-derivative, was cyclized quite smoothly to 4-methyl-1-oxo-1,2,3,4-tetrahydro-β-carboline (IV). Hydrolysis gave the amino acid (V). Decarboxylation of this acid takes place less readily than in the case of the unsubstituted tryptamine-2-carboxylic acid itself. Thus, whereas the latter yielded tryptamine in 75% yield after it was boiled for 1 hour with 10% hydrochloric acid, the methyl substituted acid only gave a 49% yield of 3-(2-amino-1-methylethyl)indole (VI) after it was boiled with 10% hydrochloric acid for 2 hours. In the latter case, an appreciable amount (44%) of unchanged acid is recovered. The methyltryptamine so obtained was identical with the product described by Noland and Lange (5) which these authors prepared from indole and 1-nitro-1-propene.

The method described above should be amenable to extension to the introduction of other alkyl groups, besides methyl, into the α-position of the tryptamine side chain, as well as to the preparation of such tryptamines bearing substituents in the benzene ring or on the nitrogen atoms (3).

EXPERIMENTAL

Melting points and boiling points are uncorrected. Infrared spectra were measured on a Perkin–Elmer Model 21 double-beam instrument using sodium chloride optics.

Diethyl 2-Cyanopropylmalonate (I)

To a cold solution of sodium (0.1 g) in absolute ethanol (10 ml) was added freshly distilled ethyl malonate (9.3 g). Methacrylonitrile (1.8 g) was added dropwise to the solution at such a rate that the temperature did not exceed 35°. The mixture was then stirred for 5 hours at room temperature, treated with acetic acid (0.3 g), diluted with water (15 ml), and extracted with ether (3×15 ml). The dried ($MgSO_4$) ether extract was evaporated and the residue distilled, ethyl malonate and any other low boiling products being collected below 130°. Vacuum distillation of the residual oil gave diethyl 2-cyanopropylmalonate (5.0 g, 84%) as a colorless liquid, b.p. 101–105°/0.23 mm. Calc. for $C_{10}H_{15}O_4N$: C, 58.16; H, 7.55. Found: C, 58.14; H, 7.79. Infrared spectrum (liquid film) (main bands only): 2240 (w), 1743 (s), 1728 cm^{-1} (s).

3-Ethoxycarbonyl-5-methyl-2-oxopiperidine (II)

Diethyl 2-cyanopropylmalonate (5.5 g) in absolute alcohol (100 ml) was hydrogenated over Raney nickel (0.2 g) at 80° and 1200 p.s.i. for 6 hours. The cooled solution was then filtered, evaporated on a steam bath, and the residue poured into 100 ml of light petroleum (b.p. 60–80°). The product crystallized immediately as a colorless solid (2.7 g, 60.2%). Recrystallization from light petroleum (b.p. 60–80°) containing a small amount of benzene gave colorless needles, m.p. 100–101°. Calc. for $C_9H_{15}O_3N$: C, 58.36; H, 8.16. Found: C, 58.47; H, 8.06. Infrared spectrum (Nujol mull) (main peaks only): 3196 (w), 1728 (s), 1674 (s), 1658 cm^{-1} (s).

5-Methyl-2,3-dioxopiperidine 3-Phenylhydrazone (III)

3-Ethoxycarbonyl-5-methyl-2-oxopiperidine (2.1 g) in water (25 ml) containing potassium hydroxide (0.7 g) was kept at room temperature overnight. The solution was cooled in an ice bath, stirred, and treated with a solution of benzenediazonium chloride (30 ml) (prepared from aniline (1.2 g), sodium nitrite (1.0 g), and concentrated hydrochloric acid (3 ml)). The mixture was immediately adjusted to pH 5 by the addition of cold 45% aqueous sodium acetate (25 ml). Stirring was continued at 0–10° for 4 hours, after which time the orange solid was filtered and dried, to give the phenylhydrazone

(2.0 g, 81.2%). Recrystallization from dilute alcohol gave light yellow needles, m.p. 238–239°. Calc. for $C_{12}H_{15}ON_3$: C, 66.34; H, 6.96. Found: C, 66.35; H, 7.05. Infrared spectrum (Nujol mull) (main peaks only): 3174 (m) (br), 1660 (s), 1603 (m), 1564 (s), 753 (m), 693 cm^{-1} (m).

4-Methyl-1-oxo-1,2,3,4-tetrahydro-β-carboline (IV)

The phenylhydrazone (2.2 g) was boiled under reflux with 90% formic acid (10 ml) for 1 hour, the hot solution diluted with water, and the brown oil which separated just brought into solution with hot absolute alcohol. The hot solution, on cooling, gave the oxocarboline (1.6 g, 80%) which, on recrystallization from absolute alcohol, gave white plates, m.p. 204–206°. Calc. for $C_{12}H_{12}ON_2$: C, 71.98; H, 6.04. Found: C, 71.58; H, 6.17. Infrared spectrum (Nujol mull)(main peaks only): 3195 (m) (br), 1649 (s), 1620 (m), 747 cm^{-1} (s). The picrate separated from alcohol as deep red rectangular rods, m.p. 185–187°.

3-(2-Amino-1-methylethyl)indole-2-carboxylic Acid (V)

4-Methyl-1-oxo-1,2,3,4-tetrahydro-β-carboline (0.45 g) in 50% aqueous ethanol (10 ml) containing potassium hydroxide (1.1 g) was boiled under reflux for 6 hours. The solvent was evaporated down to 5 ml, water (5 ml) was added, and the cooled solution filtered and acidified with acetic acid giving the amino acid (0.48 g, 96.8%). Recrystallization from dilute ethanol gave lustrous white plates, m.p. 242–243° (decomp.). Calc. for $C_{12}H_{14}O_2N_2$: C, 66.03; H, 6.47. Found: C, 65.65; H, 6.86. Infrared spectrum (Nujol mull) (main peaks only): 3420 (w), 2121 (w), 1642 (w) (br), 1624 (m), 1563 (m), 1544 (m) (br), 755 cm^{-1} (s).

3-(2-Amino-1-methylethyl)indole (VI)

3-(2-Amino-1-methylethyl)indole-2-carboxylic acid (0.30 g) was boiled under reflux with 10% hydrochloric acid (10 ml) for 2 hours. The cooled solution was made alkaline with dilute sodium hydroxide, extracted with ether, the ether layer dried ($MgSO_4$), and evaporated leaving the tryptamine (0.117 g, 48.8%) as a light brown oil. Neutralization of the aqueous layer with dilute hydrochloric acid resulted in the recovery of unreacted amino acid (0.133 g). The indole was converted to the picrate (from ether). Recrystallization from water gave the picrate as deep orange plates, m.p. 224–226° (decomp.). Noland and Lange (5) report m.p. 224–226° for this picrate. Calc. for $C_{11}H_{14}N_2$, $C_6H_3O_7N_3$: C, 50.62; H, 4.25. Found: C, 50.18; H, 3.90.

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