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Abstract

Full Text

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SYNTHESIS OF 1-BENZYL-2-METHYL-5-METHOXYTRYPTAMINE

In 1955, Shaw ([1]), from the substituted phenylhydrazone of the methyl ester of levulinic acid, synthesized 1-benzyl-2-methyl-5-methoxyindolyl-3-acetic acid by the Fischer reaction. Reduction of the amide of this acid with lithium aluminum hydride gave 1-benzyl-2-methyl-5-methoxytryptamine. As clinical trials showed, the latter, being a benzyl analogue of serotonin (BAS), possesses high physiological activity as an antimetabolite of serotonin ([2–5]).

In the present work a new synthesis of 1-benzyl-2-methyl-5-methoxytryptamine (VII) has been carried out according to the following scheme:

$$\text{p-benzoquinone} + \text{ethyl } N\text{-benzyl-}\beta\text{-aminocrotonate} \longrightarrow \text{[intermediate]} \longrightarrow \text{ethyl 1-benzyl-2-methyl-5-}$$

$$\longrightarrow \text{ethyl 1-benzyl-2-methyl-5-methoxyindole-3-carboxylate } (II) \longrightarrow \text{1-benzyl-2-methyl-5-}$$

$$\longrightarrow \text{1-benzyl-2-methyl-3-dimethylaminomethyl-5-methoxyindole } (IV) \longrightarrow \text{1-benzyl-2-methyl-5-methoxyindol-3}$$

$$\longrightarrow \text{1-benzyl-2-methyl-5-methoxyindol-3-ylacetonitrile } (VI) \longrightarrow \text{1-benzyl-2-methyl-5-methoxytryp}$$

The condensation of p-benzoquinone with the ethyl ester of N-benzyl-β-aminocrotonic acid to give 1-benzyl-2-methyl-3-carbethoxy-5-hydroxyindole (I) could be carried out only under conditions differing from those used for obtaining other nitrogen-substituted 5-hydroxyindoles ([6–9]). Methylation of the hydroxy group of indole (I) proceeds smoothly under the action of dimethyl sulfate in alkaline medium. The elimination of the carbethoxy group from 1-benzyl-2-methyl-3-carbethoxy-5-methoxyindole (II) under the action of sulfuric acid in acetic acid solution most probably proceeds through the stage of formation of the indolenine form:

$$\text{(II)} \longrightarrow \left[\begin{array}{c} \text{indolenine intermediate with COOH, } CH_3, \ CH_3O, \\ N^+ - CH_2C_6H_5, \ HSO_4^- \end{array} \right] + CH_3COOC_2H_5 \longrightarrow \text{(III)} + CO_2 + H_2SO_4.$$

The other stages of the process were carried out by methods analogous to those described in the literature ([10,11]).

Experimental

1-Benzyl-2-methyl-3-carbethoxy-5-oxyindole (I).
Thirty-four grams of *p*-benzoxyquinone are dissolved in 300 ml of dichloroethane. To the resulting solution are added 102 g of the ethyl ester of N-benzyl-β-aminocrotonic acid (^{12}). The reaction mixture is boiled in a distillation flask on a water bath for one and a half hours, distilling off 220 ml of solvent. At the beginning of the reaction the dichloroethane distilled off together with water. The reaction mixture is cooled, and the crystals of (I) are filtered off and washed with ether.

Yield 43 g (44%), m.p. 195° (from alcohol).

$C_{19}H_{19}O_3N$. Found %: C 73.58; 73.66; H 6.28; 6.31
Calculated %: C 73.76; H 6.19

1-Benzyl-2-methyl-3-carbethoxy-5-methoxyindole (II).
To a suspension of 70 g of oxyindole (I) in 150 ml of dioxane are added 380 ml of 2 N sodium hydroxide, and then 75 ml of dimethyl sulfate. The reaction mixture is shaken for 40 min at room temperature, diluted with three volumes of water, and cooled. The separated crystals of (II) are filtered off.

Yield 63 g (86%), m.p. 102° (from methanol).

$C_{20}H_{21}O_3N$. Found %: C 74.25; 74.12; H 6.61; 6.58
Calculated %: C 74.28; H 6.55

1-Benzyl-2-methyl-5-methoxyindole (III).
To a solution of 30 g of (II) in 100 ml of acetic acid, heated in a flask with a reflux condenser to boiling, are added 30 ml of concentrated sulfuric acid in 50 ml of acetic acid. The reaction solution is heated for 15 min at boiling. The reaction mixture is cooled and neutralized with cooling with 2 N sodium hydroxide. The crystals of (III) are filtered off, washed with water, boiled in dioxane solution with charcoal, and recrystallized from aqueous dioxane.

Yield 16 g (70%), m.p. 115.5–116°.

$C_{17}H_{17}ON$. Found %: N 5.54; 5.52
Calculated %: N 5.57

1-Benzyl-2-methyl-3-dimethylaminomethyl-5-methoxyindole (IV).
With cooling, 19.4 g of dimethylamine hydrochloride in the form of a 25% solution, 17 ml of formalin, and 30 g of (III) in 100 ml of dioxane are mixed. The resulting suspension is shaken for 4 hours at room temperature and left overnight. Isolation of the Mannich base (IV) is carried out in the usual manner.

Yield 30 g (80%), m.p. 83–84° (from aqueous dioxane).

$C_{20}H_{24}ON_2$. Found %: N 8.89; 8.74
Calculated %: N 9.08

Methyl iodide of 1-benzyl-2-methyl-3-dimethylaminomethyl-5-methoxyindole (V).
Thirty grams of (IV) are dissolved in 200 ml of absolute alcohol. To the resulting solution, with cooling, are added 6.7 g of methyl iodide. The reaction mixture is left for 1 hour at room temperature. The separated crystals are filtered off and washed with absolute alcohol and ether.

Yield 40 g (93%), m.p. above 170° (with decomposition).

$C_{21}H_{27}ON_2I$. Found %: C 55.89; 56.06; H 6.14; 6.08
Calculated %: C 56.00; H 6.00

Nitrile of 1-benzyl-2-methyl-5-methoxyindole-3-acetic acid (VI). To a solution of 7.2 g of sodium cyanide in 100 ml of water are added 27 g of (V) and 5 ml of dioxane. The resulting solution is boiled for 2 hours, then cooled, and the precipitated crystals of (VI) are filtered off.

Yield 23.2 g (90%), m.p. 128–9° (from toluene).

Found, %: C 78.89; 78.83; H 6.40; 6.34
$C_{19}H_{18}ON_2$. Calculated, %: C 78.59; H 6.25

1-Benzyl-2-methyl-5-methoxytryptamine (VII). To a boiling-hot solution of 3 g of (VI) in 70 ml of absolute alcohol is added, over 5 min, 1 g of finely cut sodium. The reaction solution is heated at reflux until the sodium has dissolved, diluted with a volume of water, and the alcohol is distilled off. The aqueous solution is extracted with a mixture of ether and benzene (50 ml of ether and 30 ml of benzene). From the ether–benzene layer, tryptamine (VII) is extracted with 1*N* hydrochloric acid. The aqueous layer is concentrated until crystals begin to separate, cooled, and the crystals are filtered off.

Yield of tryptamine hydrochloride (VII) 0.6 g (15%), m.p. 228–230° (from water). According to the literature, m.p. 230–231° (1).

Found, %: C 68.67; 68.67; H 7.19; 7.00; N 8.56; 8.35
$C_{19}H_{23}ON_2Cl$. Calculated, %: C 68.97; H 7.00; N 8.48

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Note: Figure translations are in progress. See original paper for figures.

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