INDOLE DERIVATIVES

LXXXI.* SIMPLIFIED METHOD FOR MONO-β-HYDROXYETHYLATION OF TRYPTAMINES

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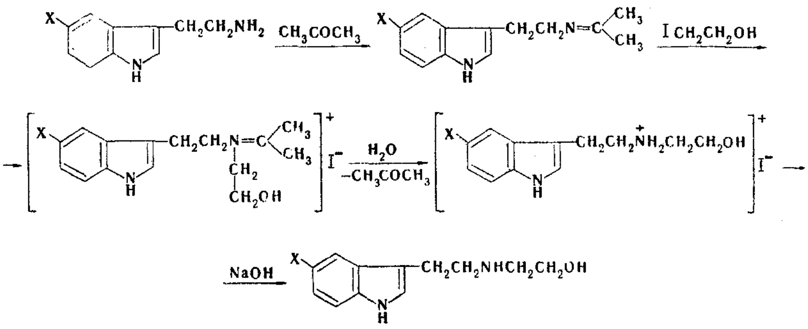
The action of ethylene iodohydrin on tryptamines in acetone, which proceeds through the intermediate formation of N-isopropylidene derivatives, is a convenient method for the N-mono-β-hydroxyethylation of tryptamines.

It is known that the alkylation of primary amines with alkyl halides leads to a complex mixture of products with different degrees of alkylation. Special one-step methods [2,3] have therefore been developed to obtain N-monoalkyltryptamines. The reaction of 3-indolylglyoxylyl chlorides with amino alcohols and subsequent reduction of the corresponding keto amides with a large excess of lithium aluminum hydride [4] has been used for the synthesis of N-(β-hydroxyalkyl)tryptamines.

For the synthesis of 2-[2-(3-indolyl)ethylamino]ethanols, we have previously [5] used monoalkylation of primary amines [6]; this method consists in the reaction of Schiff bases with ethylene iodohydrin and subsequent hydrolysis of the resulting quaternary ammonium salts to the corresponding dialkylamines and aldehydes. The starting Schiff bases – benzylidene derivatives of tryptamines – should be specially prepared for these syntheses.

It is known that the formation of isopropylidene derivatives is observed when tryptamines are heated in acetone [7]. We therefore attempted to use them in the reaction with ethylene iodohydrin for the synthesis of 2-[2-(3-indolyl)ethylamino]ethanols. The experiments demonstrated that the reaction of tryptamine and 5-methoxy- or 5-benzyloxytryptamines with ethylene iodohydrin in acetone gives the corresponding dialkylamines (I-III), which are identical to the corresponding derivatives that we previously obtained [5].



I–III

I $X = OCH_3$; II $X = H$; III $X = OCH_2C_6H_5$

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*See [1] for communication LXXX.

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This selectivity of the monoalkylation of tryptamines makes it possible to assume that their alkylation in this case proceeds in the same way as the alkylation in [6], i.e., through a step involving the formation of isopropylidene derivatives and the corresponding quaternary ammonium salts.

Thus our method for the mono-β-hydroxyethylation of tryptamines is simple to accomplish and may serve as a convenient method for the synthesis of β-hydroxyethyl derivatives.

EXPERIMENTAL

2-[2-(5-Methoxy-3-indolyl)ethylamino]ethanol (I). A mixture of 3.97 g (0.021 mole) of 5-methoxytryptamine, 5 ml of ethylene iodohydrin, and 50 ml of acetone (chemically pure) was refluxed for 1.5 h in a flask equipped with a condenser with a calcium chloride tube. The solvent was removed with a rotary evaporator, 100 ml of water was added to the residue, and the mixture was heated to 50°. The solution was separated from the small amount of resinous precipitate by decantation, and the impurities were extracted with ether. The aqueous layer was made alkaline with sodium hydroxide solution, and the oil was extracted with chloroform. The extract was dried with Na_2SO_4, and the solvent was removed with a rotary evaporator to give 4.4 g (90%) of I with mp 95-96° (from benzene, with activated charcoal). Found,%: C 67.1; H 7.6; N 11.9. $C_{13}H_{18}N_2O_2$. Calculated,%: C 66.6; H 7.7; N 12.0.

2-[2-(3-Indolyl)ethylamino]ethanol (II). This compound was similarly obtained in 89% yield from 4.8 g (0.03 mole) of tryptamine, 4.7 ml of ethylene iodohydrin, and 75 ml of acetone. The product had mp 94-95° (from benzene). Found,%: C 70.8; H 7.7; N 13.7. $C_{12}H_{16}N_2O$. Calculated,%: C 70.6; H 7.9; N 13.7.

2-[2-(5-Benzyloxy-3-indolyl)ethylamino]ethanol (III). A mixture of 7.98 g (0.03 mole) of 5-benzyloxytryptamine, 4.7 ml of ethylene iodohydrin, and 75 ml of acetone was refluxed for 1.5 h, after which the solvent was evaporated at above 40°, and the residue was dissolved in 150 ml of water at 50°. The solution was cooled, and the impurities were extracted with three 75-ml portions of ether. The aqueous layer was made alkaline with 5 ml of 10 N NaOH (pH 10), and another 2 ml of sodium hydroxide solution was added. The resulting oil crystallized after the mixture had been shaken for 10-15 min. The precipitate was removed by filtration after 1 h, washed with 40 ml of water, and vacuum dried to give 8.39 g (85%) of III with mp 121.5-122.5° (from benzene). Found,%: C 73.7; H 7.1; N 8.7. $C_{19}H_{22}N_2O_2$. Calculated,%: C 73.5; H 7.1; N 9.0.

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