INDOLE DERIVATIVES

LXXV.* MONO-β-HYDROXYETHYLATION OF TRYPTAMINES AND SYNTHESIS OF N,N'-BIS[β-(3-INDOLYL)ETHYL]ETHYLENEDIAMINES

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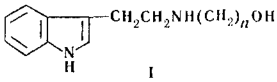
A method was developed for the mono-β-hydroxyethylation of tryptamines by the reaction of benzaltryptamine with ethylene iodohydrin in ethanol with subsequent hydrolysis of the intermediate quaternary ammonium salt to the corresponding dialkylamine. The alkylation of tryptamines with 1,2-dibromoethane gives N,N'-bis[2-(3-indolyl)ethyl]ethylenediamines.

Amino alcohols of the indole series – β-hydroxy derivatives of tryptamines – are of great interest in both chemical and pharmacological respects [2]. Another type of alcohols (I), which are also derivatives of indolylalkylamines, have received extremely little study.



I

The first representatives of this series of compounds (n = 2 or 3) were obtained [3] from 3-indolylglyoxylyl chlorides and the appropriate ω-aminoalkanols with subsequent reduction of the resulting keto amide by a large excess of lithium aluminum hydride. In this case, it is necessary to use excess amino alcohol in the step involving reaction of the amino alcohols with 3-indolylglyoxylyl chloride in order to avoid rearrangement to the isomeric esters.

It is well-known that the direct alkylation of primary amines by alkyl halides leads to a complex mixture of products, and special methods [4, 5] were therefore developed to obtain N-monomethylated tryptamines.

A known method for the monoalkylation of primary amines [6] consists in the reaction of Schiff bases with alkyl iodides (in the absence of solvent or in benzene) and subsequent hydrolysis of the intermediate quaternary ammonium salts to the corresponding dialkylamine and aldehyde. However, it has been shown that benzaltryptamine is cyclized to the corresponding 1,2,3,4-tetrahydro-β-carboline [7] during monoalkylation of tryptamine under the conditions in [6].

We obtained satisfactory results when we carried out the mono-β-hydroxyethylation of tryptamines via the method in [6] using absolute ethanol [8] as the solvent. In this case, the yields of secondary amines reached 44-53%.

The benzylidene derivatives (II-V, Table 1) of tryptamines were obtained by refluxing equimolar amounts of the tryptamines with benzaldehyde. Heating of the Schiff bases with ethylene iodohydrin in absolute ethanol and subsequent hydrolysis of the intermediate ammonium bases gave benzaldehyde and the hydriodides of the mono-β-hydroxyethyl derivatives of tryptamines, from which free bases VI-IX were isolated by the usual method.

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*See [1] for communication LXXIV.

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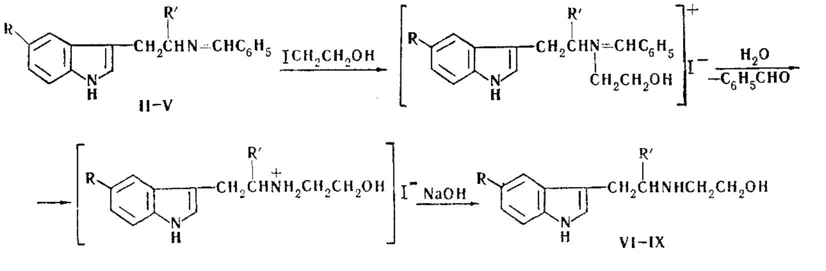
TABLE 1. Benzylidene Derivatives of Tryptamines (II-V)

Compound	R	R′	Mp, °C[a]	Empirical formula	Found, %			Calc., %			Yield, %
					C	H	N	C	H	N	
II	H	H	119—120[b]	$C_{17}H_{16}N_2$	85,2	6,4	11,1	82,2	6,5	11,3	72[c]
III	OCH_3	H	98,5—100	$C_{18}H_{18}N_2O$	77,7	6,3	10,0	77,8	6,5	10,0	68,2[d]
IV	$OCH_2C_6H_5$	H	78,5—80,5	$C_{24}H_{22}N_2O$	81,8	6,2	8,0	81,4	6,3	7,9	100
V	H	CH_3	99,5—101[e]	$C_{18}H_{18}N_2$	82,5	6,7	10,9	82,4	6,9	10,7	100

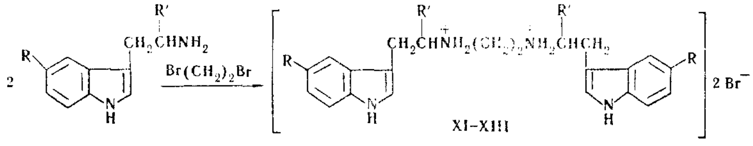
a) Compounds II and III were recrystallized from benzene, and IV and V were recrystallized from benzene–hexane (1 : 4 and 3 : 7, respectively). b) According to [3], mp 120.5-121.5°. c) About one-third of the initial volume of solvent was separated from the reaction mixture during the reaction by means of a Dean–Stark adaptor. The reaction mixture was allowed to stand at 20° for 18 h. d) Here and in the remaining cases, the solvent was completely removed at the end of the reaction. e) According to [11], V is a viscous oil.



II, VI R=R′=H; III, VII R=OCH$_3$, R′=H; IV, VIII R=OCH$_2$C$_6$H$_5$, R′=H; V, IX R=H, R′=CH$_3$

In an attempt to replace the hydroxyl group of VI by halogen by the action of thionyl chloride at room temperature [9], we isolated bis{2-[2-(3-indolyl)ethylamino]ethyl} sulfite (X) – one of the intermediates in the synthesis of alkyl halides from alcohols by the action of thionyl chloride [10].

In an effort to synthesize 2-[2-3(-indolyl)ethylamino]ethyl bromide, we performed a number of experiments on the alkylation of tryptamine by 1,2-dibromoethane. However, we obtained the corresponding N,N'-bis[2-(3-indolyl)ethyl]ethylenediamines (XI-XIII).



XI R=OCH$_3$, R′=H; XII R=R′=H; XIII R=H, R′=CH$_3$

The β-hydroxyethyl derivatives of tryptamines, as well as XI and XII, have weak physiological activity.

EXPERIMENTAL

The PMR spectra of CD_3COCD_3 (VI-IX) and CD_3OD (XI, XII) solutions were recorded with a JNM-4H-100 spectrometer with tetramethylsilane as the internal standard.

Benzylidene Derivatives of Tryptamines (II-V). These compounds were obtained by refluxing equimolar amounts of the appropriate 3-indolylalkylamines with benzaldehyde in benzene (~200 ml of benzene per 0.1 mole of tryptamine) for 1 h, after which the solvent was partially or completely removed (Table 1).

2-[2-(3-Indolyl)ethylamino]ethanol (VI). A mixture of 10.97 g (0.045 mole) of II, 5.4 ml (0.068 mole) of ethylene iodohydrin, and 110 ml of absolute ethanol was refluxed for 2.5 h in a stream of dry nitrogen; 110 ml of water was added, and the mixture was refluxed for another 30 min. The reaction mixture was then allowed to stand at 20° for 18 h, after which the alcohol was removed with a rotary evaporator. The slight amount of precipitate was removed by filtration, and the filtrate was washed with ether. The aqueous layer was made alkaline with sodium hydroxide solution, and the oil was extracted with chloroform. The extract was dried with sodium sulfate, and the solution was concentrated to 20 ml. The residue was allowed to stand at 0° for 12 h, and the resulting precipitate was removed by filtration and washed with ether to give 4.38 g (49%) of amino alcohol VI with mp 94-95.5° [from benzene (1:55)]. PMR spectrum*: δ 2.71 (t, α'-CH_2), 2.91 (s, α-CH_2, β-CH_2), 3.58 (t, β'-CH_2), 6.8-7.6 ppm (m, aromatic protons). Found: C 70.8; H 7.8; N 13.7%. $C_{12}H_{16}N_2O$. Calculated: C 70.6; H 7.9; N 13.7%. The hydrochloride was prepared as follows. A solution of 1.5 g of VI in 15 ml of absolute ethanol was cooled to 5°, and an alcohol solution of HCl was added until the pH of the mixture was 2. The mixture was allowed to stand in a refrigerator for 18 h, and the resulting precipitate was removed by filtration and washed with ether to give 1.18 g (67%) of the hydrochloride of VI with mp 147-148° (mp 148° [3]).

2-[2-(5-Methoxy-3-indolyl)ethylamino]ethanol (VII). This compound was similarly obtained from 0.02 mole of III and 0.03 mole of ethylene iodohydrin in 50 ml of absolute ethanol. The solvent was removed completely from chloroform extract, 30 ml of absolute ether was added to the resulting oil (3.91 g), and the mixture was cooled with ice water; the oil began to crystallize on trituration. The mixture was placed in a refrigerator for 8 h, and the resulting precipitate was removed by filtration to give 2.47 g (52%) of amino alcohol VII with mp 95-96.5° (from benzene). PMR spectrum: δ 2.70 (t, α'-CH_2), 2.88 (s, α-CH_2, β-CH_2), 3.87 (t, β'-CH_2), 3.77 (s, OCH_3), 6.72-7.23 ppm (m, aromatic protons). Found: C 66.7; H 7.7; N 12.1%. $C_{13}H_{18}N_2O_2$. Calculated: C 66.6; H 7.7; N 12.0%. The hydrochloride had mp 119-120.5°. Found: C 57.5; H 7.1; Cl 13.2; N 10.6%. $C_{13}H_{18}N_2O_2 \cdot HCl$. Calculated: C 57.7; H 7.1; Cl 13.1; N 10.3%.

2-[2-(5-Benzyloxy-3-indolyl)ethylamino]ethanol (VIII). This compound was similarly obtained from 0.04 mole of IV and 0.06 mole of ethylene iodohydrin in 100 ml of absolute ethanol. The reaction mixture was allowed to stand for 24 h after hydrolysis (100 ml of water). The solution was separated from the resinous residue by decantation, the alcohol was removed, and the residue was washed in ether. The aqueous layer was made alkaline with sodium hydroxide solution, and the resulting oil quickly began to crystallize. The precipitate was removed by filtration and washed with water to give 2.55 g of amino alcohol VIII. Repeated treatment of the resinous residue with 50% ethanol (200 ml) for 1 h, as in the previous case, yielded an additional 1.95 g of amino alcohol VIII. The overall yield of product with mp 121-121.5° (from benzene) was 44%. PMR spectrum: δ 2.73 (t, α'-CH_2), 2.90 (s, α-CH_2, β-CH_2), 3.61 (t, β'-CH_2), 5.12 (s, CH_2O), 6.70-7.70 ppm (m, aromatic protons). Found: C 73.8; H 7.0; N 8.8%. $C_{19}H_{22}N_2O_2$. Calculated: C 73.5; H 7.1; N 9.0%. The hydrochloride had mp 177-178.5°. Found: C 65.7; H 6.5; Cl 9.8%. $C_{19}H_{22}N_2O_2 \cdot HCl$. Calculated: C 65.8; H 6.7; Cl 10.2%.

2-{[1-(3-indolyl)-2-propyl]amino}ethanol (IX). A mixture of 7.85 g (0.03 mole) of V, 3.6 ml (0.046 mole) of ethylene iodohydrin, and 75 ml of absolute ethanol was refluxed for 2.5 h in a stream of dry nitrogen; 75 ml of water was added, and the mixture was refluxed for 5 min. The mixture was then stirred at room temperature for 2 h and allowed to stand for 48 h. The unchanged V was removed by filtration to give 3.2 g of a material with mp 99-100.5° (this material did not depress the melting point of an authentic sample of V), and the alcohol was removed from the filtrate with a rotary evaporator. The slight amount of precipitate was removed by filtration, and the filtrate was washed with ether. The mixture was made alkaline with sodium hydroxide solution, and the oil was extracted with chloroform. The extract was dried with sodium sulfate, and the solvent was removed with a rotary evaporator. The residue was treated with 25 ml of hexane with stirring, the solvent was decanted, and the oil was dissolved in absolute ether. The solvent was removed with a rotary evaporator, and the resulting viscous mass was dried in vacuo to give 20.6 g (53%, based on unchanged V) of IX as a viscous white mass. PMR spectrum: δ 1.07 (d, CH_3), 2.6-2.9 (m, α'-CH_2, β-CH_2), 3.00 (m, CH), 3.64 (t, β'-CH_2), 7.04-7.65 ppm (m, aromatic protons). Found: C 71.7; H 8.3%. $C_{13}H_{18}N_2O$. Calculated: C 71.5; H 8.3%. The hydrochloride was prepared as follows. Alcoholic HCl (pH 2) was added at 0° to a solution of 1.85 g of IX in 18 ml of absolute ethanol, and 80 ml of absolute ether was added to the mixture with stirring. After 30 min, the solvents were separated from the resulting oil by decantation. Absolute ether (25 ml) was added with stirring to the residue, after which the bulk of the ether was separated by decantation, and the remainder was removed with a rotary evaporator

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*The following designation of the protons of the CH_2 groups was adopted for amino alcohols VI-IX: $-\overset{\beta}{CH_2}\overset{\alpha}{CH_2}NH\overset{\alpha'}{CH_2}\overset{\beta'}{CH_2}OH$. The abbreviations used here and elsewhere are as follows: s is singlet, d is doublet, t is triplet, and m is multiplet.

to give 2.06 g (95%, vacuum dried) of the hydrochloride of IX with mp 41-44°. Found: C 61.2; H 7.6; Cl 13.8; N 10.8%. $C_{13}H_{18}N_2O \cdot HCl$. Calculated: C 61.3; H 7.5; Cl 13.9; N 11.0%.

Bis {2-[2-(3-indolyl)ethylamino]ethyl} Sulfite Dihydrochloride (X). A total of 0.37 ml (0.005 mole) of thionyl chloride was added dropwise in the course of 7-8 min under nitrogen at 9-11° to a mixture of 1.02 g (0.005 mole) of VI in 7 ml of benzene, and the reaction mixture was stirred at 20° for 10 h. The solvent was removed with a rotary evaporator, and the residue was crystallized from 35 ml of absolute ethanol to give 0.26 g (20%) of X with mp 168-169.5°. Found: C 54.8; H 6.5; Cl 13.3; N 10.5; S 6.0%. $C_{24}H_{30}N_4O_3S \cdot 2HCl$. Calculated: C 54.7; H 6.1; Cl 13.4; N 10.6; S 6.1%.

N,N'-Bis[2-(5-methoxy-3-indolyl)ethyl]ethylenediamine Dihydrobromide (XI). A mixture of 11.4 g (0.06 mole) of 5-methoxytryptamine, 15.6 ml (0.18 mole) of dibromoethane, and 20 ml of absolute ethanol was stirred at 95-100° (bath temperature) for 6.5 h. The mixture was allowed to stand at 20° for 18 h, and the resulting precipitate was removed by filtration, washed with 5 ml of ethanol, treated with 20 ml of water at 20°, and dried to give 3.21 g (19%) of dihydrobromide XI with mp 237-238.5° (from ethanol). Found: C 50.7; H 5.6; Br 27.8; N 10.1%. $C_{24}H_{30}N_4O_2 \cdot 2HBr$. Calculated: C 50.7; H 5.7; Br 28.1; N 9.9%. Base XIa was obtained as follows. A 1.12-g sample of dihydrobromide XI was dissolved in 110 ml of water by heating to 60°, 2.5 ml of 10 N NaOH was added, and the mixture was allowed to stand at 20° for 24 h. The crystalline precipitate was removed by filtration and washed with water to give 0.63 g (79%) of XIa with mp 147.5-148.5° (from benzene). PMR spectrum*: δ 2.65 (s, $2\alpha'$-CH_2), 2.83 (s, 2α-CH_2, 2β-CH_2), 3.79 (s, 2-OCH_3), 6.74-7.20 ppm (m, aromatic protons). Found: C 71.4; H 7.5; N 13.5%. $C_{24}H_{30}N_4O_2$. Calculated: C 70.9; H 7.4; N 13.8%. Dihydrochloride XIb was obtained as follows. A 0.4-g sample of base XIa was dissolved at 30° in 27 ml of absolute ethanol, and alcoholic HCl was added to pH 1. After 3 h, the precipitate was removed by filtration and washed with ethanol to give 0.42 g (89%) of dihydrochloride XIb with mp 245-246.5° (from ethanol). Found: Cl 14.9%. $C_{24}H_{30}N_4O_2 \cdot 2HCl$. Calculated: Cl 14.8%.

N,N'-Diacetyl Derivative (XIc). A total of 0.37 g (0.0036 mole) of acetic anhydride was added at 40° to a mixture of 0.74 g (0.0018 mole) of base XIa and 75 ml of benzene, and the mixture was refluxed for 1 h. It was then cooled and allowed to stand at 20° for 3 h. The resulting precipitate was removed by filtration and washed with benzene to give 0.81 g (91%) of N,N'-diacetyl-N,N'-bis[2-(5-methoxy-3-indolyl)-ethyl]ethylenediamine with mp 237-238.5° (from 80% ethanol). Found: C 67.9; H 6.8; N 11.2%. $C_{28}H_{34}N_4O_4$. Calculated: C 68.5; H 7.0; N 11.4%.

N,N'-Bis[2-(3-indolyl)ethyl]ethylenediamine Dihydrobromide (XII). A mixture of 9.6 g (0.06 mole) of tryptamine, 15.6 ml (0.18 mole) of dibromoethane, and 16 ml of absolute ethanol was stirred at a bath temperature of 95-100° for 4 h. The mixture was allowed to stand at room temperature for 18 h, and 10 ml of absolute ethanol was then added to it. The resulting precipitate was removed by filtration, washed with ethanol, dried, and treated with 125 ml of water at 20° to give 4.01 g (26%) of dihydrobromide XII with mp 275-278°. Found: C 52.1; H 5.6; Br 31.1; N 10.7%. $C_{22}H_{26}N_4 \cdot 2HBr$. Calculated: C 52.0; H 5.6; Br 31.4; N 11.0%. Base XIIa was prepared as follows. A 4-g sample of XII was dissolved in 1600 ml of water by heating to 50°, and the solution was filtered. The filtrate was made alkaline with sodium hydroxide solution and allowed to stand at 20° for 24 h to give 2.57 g (94%) of XIIa with mp 70-72° (from benzene). PMR spectrum: δ 2.64 (s, $2\alpha'$-CH_2), 2.85 (s, 2α-CH_2, 2β-CH_2), 7.00-7.60 ppm (m, aromatic protons). Found: C 81.4; H 7.4; N 11.2%. $C_{22}H_{26}N_4 \cdot 2C_6H_6$. Calculated: C 81.2; H 7.6; N 11.1%. Dihydrochloride XIIb had mp 275-277°. Found: C 62.9; H 6.5; Cl 16.7; N 13.0%. $C_{22}H_{26}N_4 \cdot 2HCl$. Calculated: C 63.0; H 6.7; Cl 16.9; N 13.4%.

N,N'-Bis[1-(3-indolyl)-2-propyl]ethylenediamine Dihydrobromide (XIII). A mixture of 6.96 g (0.04 mole) of α-methyltryptamine, 10.4 ml (0.12 mole) of dibromoethane, and 10.6 ml of absolute ethanol was stirred at a bath temperature of 95-100° for 10.5 h. Two layers formed when the mixture was cooled. The lower layer was separated from the upper viscous layer by decantation, and the residue in the flask was washed with benzene, after which 50 ml of benzene was added, and the mixture was stirred at room temperature for 16 h. The resulting precipitate was removed by filtration, washed with benzene, dried, and crystallized from 135 ml of benzene to give 1.56 g (15%) of dihydrobromide XIII with mp 249-250.5° (from benzene). Found: C 54.2; H 6.1; Br 30.1; N 10.3%. $C_{24}H_{30}N_4 \cdot 2HBr$. Calculated: C 53.8; H 6.0; Br 29.8; N 10.45%.

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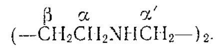
*The following designation of the protons of the CH_2 groups was adopted:  $(\text{—}\overset{\beta}{C}H_2\overset{\alpha}{C}H_2NH\overset{\alpha'}{C}H_2\text{—})_2$.

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