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Indole Compounds. III.* The Direct Indolization to 5-Methoxy- and 5-Benzyloxy-*N,N*-Disubstituted Tryptamines

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The one-step indolization of 5-methoxy- and 5-benzyloxy--phenylhydrazine hydrochloride with a number of *N,N*-disubstituted 4-aminobutanal acetals is described. The reaction (equimolar amounts, 80°, 25% acetic acid as the catalyst) showed to be generally applicable to this class of compounds. The resulting 5-methoxy- (II—VIII) and 5-benzyloxy-*N,N*-disubstituted tryptamines (IX—XV) were obtained in good yields and isolated as picrates, hydrochlorides and oxalates respectively. Hydrogenolysis of 5-benzyloxytryptamines led to the corresponding 5-hydroxy--derivatives (XVI—XVII).

In a previous communication[1] we reported that *p*-benzyloxy- or *p*-methoxy-phenylhydrazine hydrochloride in 25% acetic acid with 4-aminobutanal diethyl acetal cyclized directly into the corresponding tryptamines. The fact that this reaction, which is in fact the Fischer indole synthesis, proceeds smoothly under very mild conditions prompted us to investigate it as a direct route to 5-hydroxy- and 5-methoxy-*N,N*-disubstituted tryptamines. These substances, structurally related to serotonin and melatonin, were desired in our studies on serotonin metabolism.

5-Hydroxy- and 5-methoxy-*N,N*-disubstituted tryptamines described so far in the literature were all prepared by a sequence of reactions where the indolization step took place at an early stage of the synthesis. The one-step indolization of *N,N*-disubstituted 4-aminobutanal acetals with *p*-methoxy- or *p*-benzyloxy-phenylhydrazine hydrochloride would offer an attractive route to this class of compounds.

The ease of the Fischer indole synthesis compares directly with the enolizability of the aldehyde, as well as with the nucleophilic character of the substituent on the aromatic ring of phenylhydrazine[3]. According to the accepted mechanism[4–6] of this reaction, the formation of the new C-C bond depends on the polarization of the enhydrazine intermediate. Thus, in our case the acetal molecule, the nucleophilic methoxy- or benzyloxy- substituent and the catalyst acetic acid would all contribute to the polarization of the

* Papers cited in ref. 1. and 2. should be considered as Part I and II of this series.

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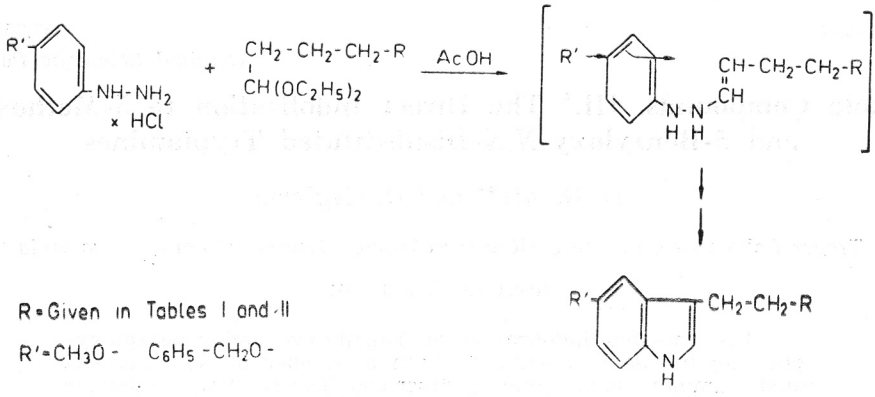
enhydrazine intermediate. Consequently, a smooth indolization under mild conditions could be expected:



A general procedure for the preparation of the *N,N*-disubstituted 4-aminobutanal diethyl acetals has been already worked out in this laboratory[7]. All but one of the aminoacetals used in the present work were prepared[7] by this procedure. 4-Dimethylaminobutanal diethyl acetal[8] (I) was prepared from 4-aminobutanal diethyl acetal[9] by exhaustive methylation[10] and subsequent demethylation[11] of the quaternary salt with ethanolamine.

The indolization of *p*-methoxyphenylhydrazine hydrochloride with typical representatives of *N,N*-disubstituted 4-aminobutanal acetals was performed on the 2.5—5 mmole scale in 25% acetic acid at 80° (procedure *A*). From the reaction mixture the corresponding tryptamines were isolated as free bases and converted to the stable monopicrates in high yields. Several attempts to obtain crystalline hydrochlorides failed. In Table I the yields and physical data of 5-methoxy-*N,N*-disubstituted tryptamine picrates are presented.

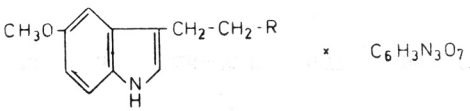
When *p*-benzyloxyphenylhydrazine hydrochloride and 4-dimethylaminobutanal diethyl acetal were condensed by procedure *A*, the corresponding tryptamine hydrochloride IX crystallized immediately after the evaporation of the reaction mixture. However, other 5-benzyloxytryptamines could not be obtained as crystalline products, at this stage. By studying the procedure *A* in more details it was established that ammonia evolved during the indolization formed either ammonium chloride or acetate — the kind of the salt depending on the relative basicity of ammonia toward the particular tryptamine. The addition of an excess of hydrochloric acid (2 mole per 1 mole of hydrazine) at the beginning of the reaction (procedure *B*) resulted in the exclusive formation of the corresponding tryptamine hydrochlorides.

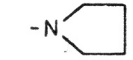
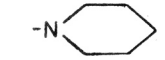
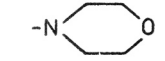
In Table II are given the procedures of preparation, yields and physical data of 5-benzyloxy-*N,N*-disubstituted tryptamines. Procedure *B* proved to be advantageous for the synthesis of tryptamines which formed easily crystallisable hydrochlorides (IX, XIII, XIV and XV). However, by the same procedure X, XI and XII could not be isolated as crystalline hydrochlorides; they were converted *via* the free base to the crystalline well-defined oxalates.

In order to find out whether the addition of hydrochloric acid improves

TABLE I

5-Methoxy-N,N-disubstituted tryptamine picrates

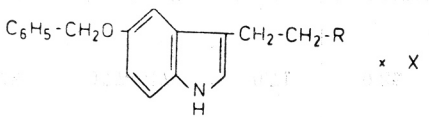


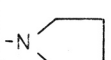
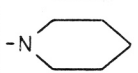
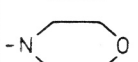
Comp. No.	R	Procedure	Yield %	M. p. °C[1]	R_f-values in[2] A	R_f-values in[2] B	Formula	Analyses Calc'd / Found % C	% H	% N
II	$-N(CH_3)_2$[3]	A B	74 76	169—170	0.67	0.84	$C_{19}H_{21}N_5O_8$	51.00 51.23	4.73 4.98	15.65 15.56
III	$-N(C_2H_5)_2$	A	61	134—136	0.79	0.86	$C_{21}H_{25}N_5O_8$	53.05 52.85	5.30 5.17	14.73 14.68
IV	$-N(CH(CH_3)_2)_2$	A	57	179—180	0.82	0.88	$C_{23}H_{29}N_5O_8$	54.86 54.54	5.81 5.76	13.91 13.88
V	$-N(CH_3)(CH_2-C_6H_5)$	A* B*	52 21	153—154	0.86	0.88	$C_{25}H_{25}N_5O_8$	57.36 57.04	4.81 4.65	13.38 13.41
VI		A	76	182—184	0.79	0.87	$C_{21}H_{23}N_5O_8$	53.27 53.01	4.90 4.60	14.79 14.83
VII		A	79	148—150	0.82	0.88	$C_{22}H_{25}N_5O_8$	54.20 54.47	5.17 4.92	14.37 14.23
VIII		A	45	177—179	0.71	0.85	$C_{21}H_{23}N_5O_9$	51.53 51.30	4.74 4.42	14.31 14.58

[1] Recrystallized from ethanol. [2] A = *n*-butanol-acetic acid-water (4 : 1 : 5); B = *iso*propanol-ammonia-water (10 : 1 : 1); blue spots with Ehrlich reagent. [3] Hydrochloride reported (ref. 12) m.p. 145—146°. * The crude base was purified on Al_2O_3

TABLE II

5-Benzyloxy-N,N-disubstituted tryptamine salts



Comp. No.	R	Procedure	X	Yield %	Recryst. from[1]:	M. p. °C	R_f-values in[2] A	R_f-values in[2] B	Formula	Analyses Calc'd % C	Analyses Calc'd % H	Analyses Calc'd % N
										Found % C	Found % H	Found % N
IX	$-N(CH_3)_2$	A B	HCl	42 52	a	157—158[3]	0.73	0.89	$C_{19}H_{23}ClN_2O$	68.97 69.20	7.01 7.24	8.47 8.36
X	$-N(C_2H_5)_2$	A* B*	$C_2H_2O_4$	49 51	a	158—159[4]	0.82	0.89	$C_{23}H_{28}N_2O_5$	66.97 67.22	6.84 7.18	6.79 6.76
XI	$-N(CH(CH_3)_2)_2$ [5]	A* B*	$C_2H_2O_4$	35 36	b	103—106	0.84	0.92	$C_{25}H_{32}N_2O_5$	68.16 68.13	7.32 7.28	6.36 6.60
XII	$-N(CH_3)(CH_2-C_6H_5)$ [6]	A* B*	$C_2H_2O_4$	58 40	a	155—158	0.85	0.92	$C_{27}H_{28}N_2O_5$	70.42 70.15	6.13 6.38	6.08 6.15
XIII		B	HCl	65	a	188—189	0.79	0.93	$C_{21}H_{25}ClN_2O$	70.67 70.93	7.06 7.09	7.85 7.78
XIV	 [7]	B	HCl	83	a	206—207	0.85	0.94	$C_{22}H_{27}ClN_2O$	71.24 71.51	7.34 7.23	7.55 7.45
XV		B	HCl	73	a	226—228[8]	0.77	0.90	$C_{21}H_{25}ClN_2O_2$	67.64 67.82	6.76 6.50	7.51 7.47

[1] a = ethanol; b = *iso*propanol. [2] A = *n*-butanol-acetic acid-water (4 : 1 : 5); B = *iso*propanol - amonia - water (10 : 1 : 1); blue spots with Ehrlich reagent. [3] Reported 154—155° (ref. 13). [4] Reported 162° (ref. 14). [5] Hydrochloride reported (ref. 15) m.p. 215—218° (dec.). [6] Hydrochloride reported (ref. 16) m.p. 110—112°. [7] Free base reported (ref. 14) m.p. 133—138°. [8] Reported 227—229° (dec.) (ref. 15). * The crude base was purified on Al_2O_3.

the indolization, the synthesis of several tryptamines was performed by both procedures. In the cases where a crystalline hydrochloride could not be isolated (II, X and XI) the procedures *A* and *B* proved to be of an equal validity. However, procedure *B* showed to be inferior in the synthesis of acid-sensitive *N*-methyl, *N*-benzyl-derivatives V and XII.

Thus, the described indolization provides a direct route to 5-methoxy- and 5-benzyloxy-*N,N*-disubstituted tryptamines. Because of the simple isolation procedure, this route seemed to be particularly suitable in the preparation of easily crystallisable tryptamine hydrochlorides.

The hydrogenolysis of 5-benzyloxy-*N,N*-disubstituted tryptamines led to the corresponding 5-hydroxy derivatives. Except the pyrrolidino derivative XVII, other 5-hydroxy-tryptamines were already described in the literature.

EXPERIMENTAL

All melting points are uncorrected.

4-Dimethylaminobutanal diethyl acetal (I)

To a stirred mixture of 4-aminobutanal diethyl acetal[9] (4.19 g., 0.026 mole), sodium bicarbonate (5.60 g., 0.066 mole) and 26 ml. of absolute methanol, methyl iodide (14.50 g., 0.104 mole) was added at room temperature. The mixture was refluxed for 9 hours, and then a second portion of methyl iodide (7.25 g., 0.052 mole) was dropped in. The stirring and refluxing was continued for further 12 hours. After cooling the mixture was filtered, the filtrate evaporated *in vacuo* and the residue extracted with chloroform. The combined extracts were evaporated to dryness leaving an oil which crystallized on drying over sulphuric acid in a vacuum desiccator; 8.2 g., 95% of the methiodide of I, m.p. 64—66° was obtained. (reported[8]: m.p. 40—50°)

Anal. $C_{11}H_{26}JNO_3$ (331.25) calc'd.: C 39.88; H 7.91; N 4.23%
found: C 39.77; H 7.69; N 4.45%

The above quaternary methiodide (8.2 g., 0.025 mole) was refluxed with ethanolamine (7.6 g., 0.125 mole) for half an hour. After cooling, water (20 ml.) was added, the solution extracted with chloroform, the extracts dried over anhydrous potassium carbonate and the solvent evaporated *in vacuo* at 30°. From the liquid residue which separated in two layers the upper one was distilled at 20 mm; 2.23 g. of I, b.p. 80—90° (45% calc'd. on 4-aminobutanal diethyl acetal) was obtained. An analytical sample was redistilled: b.p. 92—93°/18 mm. (reported[8]: 94—95°/11 mm.)

Anal. $C_{10}H_{23}NO_2$ (189.29) calc'd.: N 7.40%
found: N 7.28%

*Preparation of 5-methoxy- and 5-benzyloxy-*N,N*-disubstituted tryptamines*

The reaction was carried out on a 2.5—5 mmole scale with equimolar amounts of the reactants. The condensation was performed in a three-necked flask fitted with a mechanical stirrer, a condenser and a dropping funnel.

Procedure A. 5-Methoxy- or 5-benzyloxy- phenylhydrazine hydrochloride was dissolved in 25% acetic acid (15—25 ml.) at 80° and under stirring the corresponding *N,N*-disubstituted 4-aminobutanal diethyl acetal was dropped in during 5 minutes. The stirring and heating was continued for 2.5 hours. If the reaction mixture was very dark, charcoal (0.10—0.15 g.) was added to the warm solution. After filtration the filtrate was evaporated *in vacuo* to dryness.

Procedure B. was identical with *A.* except that after the addition of acetal, concentrated hydrochloric acid (2 moles per 1 mole of hydrazine) was added to the reaction mixture.

Isolation of tryptamines. a) Picrates and oxalates. To the oily residue left after evaporation of the reaction mixture, saturated potassium carbonate solution (10—20 ml.) was added, and the tryptamine base was extracted with ether. The combined extracts were washed with saturated sodium chloride solution, dried over anhydrous potassium carbonate and the solvent was removed *in vacuo*. In the preparations of V, X, XI and XII the crude bases were previously purified on alumina columns.

Picrates were obtained by mixing equimolar hot ethanolic solutions of the base and picric acid. For analysis they were recrystallised from ethanol. Oxalates were prepared from equimolar hot acetone solutions of the base and oxalic acid dihydrate. The solvents for recrystallization are given in Table II.

b) Hydrochlorides. On the evaporation of the reaction mixture to dryness the easily crystallizable tryptamine hydrochlorides solidified immediately. The isolation of XIII, XIV and XV was performed as follows: the solid residue was digested with cold absolute ethanol (2—3 ml.) and the coloured solution filtered off. The precipitate consisting of the corresponding tryptamine hydrochloride and ammonium chloride was dissolved in the minimum amount of hot water to which few drops of concentrated hydrochloric acid were added. By cooling very pure products separated. For the isolation of IX the solid residue was extracted several times with hot absolute acetone, and the combined extracts concentrated to about 10 ml. After standing at 0° pure IX crystallized.

In Tables I and II the methods of preparation and characterization data of the obtained tryptamine derivatives are given.

Chromatography of crude tryptamine bases. Alumina (Lachema, after Brockmann) column (25×1 cm. for a preparation on 2.5 mmole scale) was prepared with petroleum ether — benzene (1:1). The crude base was dissolved in the same solvent (5 ml.) and chromatographed by elution with a) petroleum ether — benzene (1:1) and b) benzene. The first solvent (100—150 ml.) eluted coloured non-indolic compounds, and benzene (150—200 ml) eluted the tryptamine base. The bases were obtained as oily products.

Debenzylation of 5-benzyloxy-N,N-disubstituted tryptamines

To the corresponding tryptamine salt (1 mmole) ammonium hydroxide was added and the free base was extracted several times with ether. The combined extracts were washed with saturated sodium chloride solution, dried over anhydrous potassium carbonate and the solvent was removed *in vacuo*. The remaining oily base was dissolved in methanol (25 ml.) and hydrogenated at atmospheric pressure over 5% $Pd/BaSO_4$ (0.075 g.). The catalyst was removed by centrifugation, the solvent evaporated *in vacuo* and the remaining base was crystallized from the suitable solvent or converted to the oxalate.

5-Hydroxy-3-(2-methylaminoethyl)-indole hydrogenoxalate (XVI) was obtained from XII after consumption of two mmoles of hydrogen; yield 50%; m.p. 154—156° (methanol); R_f-values: solvent A. 0.55, solvent B. 0.69. Stoll *et al.*[14] gave for the same oxalate (obtained by debenzylation of 5-benzyloxy-3-(2-methylaminoethyl)--indole hydrogenoxalate), m.p. 153—156°.

Anal. $C_{13}H_{16}N_2O_5$ (280.27) calc'd.: N 10.01%
found: N 9.82%

5-Hydroxy-3-(2-pyrrolidinoethyl)-indole (XVII) was obtained from XIII. The free base was recrystallized from acetone: yield 64%; m.p. 196—200°; R_f-values: solvent A. 0.66, solvent B. 0.84.

Anal. $C_{14}H_{18}N_2O$ (230.30) calc'd.: C 73.01; H 7.88; N 12.16%
found: C 72.91; H 8.06; N 12.00%

Paper chromatography

Descending one-dimensional chromatography was performed on Whatman No. 1 paper in A. *n*-butanol — acetic acid — water (4:1:5) and B. *iso*propanol — ammonia — water (10:1:1). By spraying with Ehrlich reagent (2% *p*-dimethylaminobenzaldehyde in 5% hydrochloric acid) all tryptamine derivatives gave blue spots. R_f-values are tabulated in Tables I and II.

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IZVOD

Indolski spojevi. III. Izravna indolizacija u 5-metoksi- i 5-benziloksi-*N,N*-disupstituirane triptamine

D. Desaty i D. Keglević

Opisana je jednostepena indolizacija 5-metoksi- i 5-benziloksi-fenilhidrazin hidroklorida s nizom *N,N*-disupstituiranih 4-aminobutanal acetala. Reakcija (ekvimolarne količine, 80°, 25%-tna octena kiselina kao katalizator) se pokazala kao općenita za tu vrstu spojeva. 5-Metoksi- (II—VIII) i 5-benziloksi-*N,N*-disupstituirani triptamini (IX—XV) dobiveni su u dobrim iskorištenjima, a izolirani su kao pikrati, hidrokloridi, odnosno oksalati. Hidrogenolizom 5-benziloksitriptamina dobiveni su odgovarajući 5-hidroksi-derivati (XVI—XVII).

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