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The Synthesis of 3,5-Disubstituted Indoles by Cyclization under Mild Conditions

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3-Benzyloxy-6-formylaminotoluene (III) could not be converted by Madelung cyclization into the corresponding indole derivative.

It was found, that 4-aminobutanal diethyl acetal and *p*-benzyloxyphenylhydrazine hydrochloride cyclize into 5-benzyloxytryptamine hydrochloride (V) in 25% acetic acid at 80° in 68% yield. Under these mild conditions also other 3,5-substituted indoles were obtained: 3-methyl-5-benzyloxyindole (VI), 3-ethyl-5-benzyloxyindole (VII), 5-methoxytryptamine picrate (VIII) and *N'*-acetyl-5-methoxytryptamine (Melatonin, IX).

For our experiments on the metabolism of 5-hydroxytryptamine[1] (serotonin), a labelled 5-hydroxytryptamine with ^{14}C-atom in the pyrrole part of the indole ring was required. As a paper on a considerably improved Madelung cyclization of o-^{14}C-formylaminotoluene into indole-2-^{14}C has been published by Pichat and coworkers[2], our first intention was to prepare by this method 5-benzyloxyindole-2-^{14}C. From 4-acetylamino-*m*-cresol[3] we prepared therefore 3-benzyloxy-6-formylaminotoluene (III) *via* the compounds I and II.

However, the Madelung cyclization of III failed, and from the dark resinous products no 5-benzyloxytryptamine could be isolated. Apparently, the drastical conditions under which the end of Madelung cyclization is performed, could not be applied to a substance having a sensitive benzyloxy residue in the molecule. Is is interesting that Marion and Ashford[4] trying the same cyclization on 3-methoxy-6-formylaminotoluene obtained only small quantities of an indole derivative containing no methoxyl group.

Our attention was then directed to a synthesis published in 1911 by Ewins[5], where 4-aminobutanal diethyl acetal and phenylhydrazine were cyclized by the Fischer method at 180° with zinc chloride into tryptamine. In 1930 Späth and Lederer[6] fused *m*-methoxyphenylhydrazine, 4-aminobutanal diethyl acetal and zinc chloride to obtain an oil which they have not characterized, but presumed to be a mixture of 4- and 6-methoxytryptamine. Hoshino and coworkers[7] used the same method to obtain 5-ethoxytryptamine in a poor yield. In 1953 Bernini[8] modified the Ewins procedure for the synthesis of serotonin; from equimolar quantities of zinc chloride, 4-aminobutanal diethyl acetal and *p*-benzyloxyphenylhydrazine in hot xylene he obtained 45% of 5-benzyloxytryptamine hydrochloride. In our hands the yields of this preparation were always lower and the purity of the product was rather poor, although special care was taken for the purity of the unstable *p*-benzyloxyphenylhydrazine base.

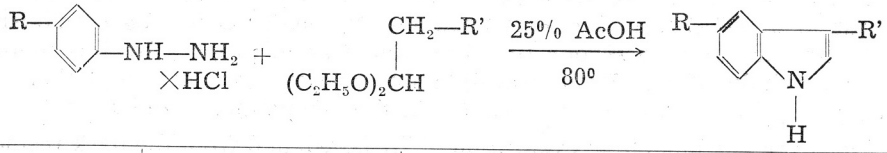
We started then to examine the conditions under which 4-aminobutanal hydrazones were formed from 4-aminobutanal diethyl acetal. As expected, it was found that hydrolysis of the acetal group proceeded very easily; in an ethanolic-dilute hydrochloric acid solution after 24 hours at room temperature an almost quantitative yield of 2,4-dinitrophenylhydrazone hydrochloride (IV) was obtained. When *p*-benzyloxyphenylhydrazine hydrochloride[10] was used under the same conditions, the corresponding hydrazone could not be isolated. However, on the chromatograms of the reaction mixture a spot of 5-benzyloxytryptamine appeared which could be identified as early as five hours after the beginning of the reaction.

Presuming that Ewins synthesis proceeds through the formation of a hydrazone, which is then cyclized by the Fischer reaction into indole, the latter experiment indicates clearly that the ring closure occurs extremely easily. When an ethanolic-dilute hydrochloric acid solution of the acetal and *p*-benzyloxyphenylhydrazine hydrochloride was gently refluxed for 4 hours, 68% of 5-benzyloxytryptamine hydrochloride was obtained. Even milder conditions — reaction in 25% acetic acid at 80° for 2 hours — resulted in the same yield but in a purer product.

Thus, neither high temperature and zinc chloride[11], nor the hydrazine in the form of the unstable base are required in this case. It was shown that also other 3,5-disubstituted indoles are formed under such mild conditions. Table I shows the substances prepared and the yields obtained.

TABLE I

Yields of 3,5-disubstituted indoles



Compound	R	R'	Yield %
V	C_6H_5—CH_2—O—	—CH_2—CH_2NH_2×HCl	68
VI	C_6H_5—CH_2—O—	—CH_3	54
VII	C_6H_5—CH_2—O—	—CH_2—CH_3	53
VIII	CH_3—O—	—CH_2—CH_2—NH_2×$C_6H_3N_3O_7$	35
IX	CH_3—O—	—CH_2—CH_2—NH—CO—CH_3	26

Except VI, the prepared indoles are already known biologically interesting compounds, which synthesis is often multistep and cumbersome. The one-step preparation of *N'*-acetyl-5-methoxytryptamine (melatonin, IX) is especially encouraging, because it indicates that biologically active compounds with similar structure could be also obtained in this way.

The condensation of acetals with *m*-substituted phenylhydrazine hydrochlorides, where 4- and 6-substituted indoles could be formed, was tried only

in one case. No indole derivative could be obtained from *m*-benzyloxyphenylhydrazine hydrochloride (XI) and 4-aminobutanal diethyl acetal under these conditions.

EXPERIMENTAL

All melting points are uncorrected.

Chromatography. Chromatograms were run on Whatman No. 1 paper in butanol: acetic acid: water (4:1:5) if not stated otherwise. For the detection of indole spots they were sprayed with Ehrlich reagent (2% *p*-dimethylaminobenzaldehyde in 5% hydrochloric acid).

3-Benzyloxy-6-acetylaminotoluene (I)

I was prepared from 9.1 g. (0.055 mole) of 4-acetylamino-*m*-cresol[13], 7.2 g. (0.057 mole) benżylchloride and 2.2 g. (0.055 mole) sodium hydroxide in water (15 ml.), following the procedure by Burton and Stoves[12]. Yield: 12.7 g. (90.5%), m. p. 130—131.5°. Recrystallization from benzene gave white needles, m. p. 134—135°.

Anal. $C_{16}H_{17}NO_2$ (255.304) calc'd.: C 75.27; H 6.71; N 5.48%
found: C 75.04; H 6.62; N 5.58%

3-Benzyloxy-6-aminotoluene (II)

Deacetylation of I (5.0 g., 19.6 mmoles) was performed with potassium hydroxide (5.5 g.) in 96% ethanol (36 ml.) at reflux temperature for 20 hours according to Boehme's[13] general procedure. 4.0 g. (95.5%) of a viscous oil was obtained, which was redistilled for analysis, b. p. 120—122°/0.01 mm.

Anal. $C_{14}H_{15}NO$ (213.268) calc'd.: C 78.84; H 7.09; N 6.57%
found: C 78.62; H 7.13; N 6.56%

3-Benzyloxy-6-formylaminotoluene (III)

The formylation of II was carried out following the directions for the synthesis of o-^{14}C-formylaminotoluene[2]. From 333.5 mg. (4.9 mmoles) sodium formate and II (1.781 g., 8.35 mmoles), 1.115 g. of III was obtained. Yield: 94.5% based on sodium formate. After two recrystallizations from benzene-petroleum ether, the substance was analytically pure, m. p. 108—109°, white needles.

Anal. $C_{15}H_{15}NO_2$ (241.278) calc'd.: C 74.66; H 6.27; N 5.81%
found: C 74.41; H 6.21; N 5.98%

p-*Benzyloxyphenylhydrazine hydrochloride* (XII)

XII was prepared after Mentzer and coworkers[10]. When the base was used, it was liberated from its salt immediately before the reaction, filtered off and sublimed at 120—125°/0.04 mm., m. p. 105.5—106.5°, reported: 100° [10] and 105—106° [8].

Anal. $C_{13}H_{14}N_2O$ (214.258) calc'd.: C 72.87; H 6.59%
found: C 72.65; H 6.81%

4-Aminobutanal 2',4'-dinitrophenylhydrazone hydrochloride (IV)

To 2,4-dinitrophenylhydrazine (250 mg., 1.26 mmole) dissolved in a mixture of ethanol (50 ml.) and 5% hydrochloric acid (15 ml.), 4-aminobutanal diethyl acetal[9] (203 mg., 1.26 mmole) in 2.5 ml. ethanol was added and the mixture left at room temperature 24 hours. Yellow plates separated, and a second crop was obtained on concentration of the mother liquor *in vacuo*. Yield: 347 mg. (91%), m. p. 197—198°. For analysis it was recrystallized from ethanol, m. p. 198—199° (decomp.)

Anal. $C_{10}H_{14}ClN_5O_4$ (303.709) calc'd.: C 39.54; H 4.65; N 23.06%
found: C 39.60; H 4.82; N 23.05%

When IV was refluxed for 6 hours in a mixture of ethanol and 5% hydrochloric acid, no traces of indole derivatives could be detected on the reaction mixture chromatograms.

Attempted synthesis of 4-aminobutanal p-benzyloxyphenylhydrazone hydrochloride

To XII (313 mg., 1.25 mmole) in 50 ml. ethanol and 14 ml. 5% hydrochloric acid, 4-aminobutanal diethyl acetal (201 mg., 1.25 mmole) in 2.5 ml. ethanol was added. A sample of the reaction mixture gave after 5 hours on the chromatogram a blue spot ($R_f = 0.78$), identified as 5-benzyloxytryptamine. After 24 hours the still clear solution was concentrated *in vacuo*, whereupon a precipitate was obtained (273 mg.), identified as a mixture of XII and 5-benzyloxytryptamine hydrochloride

Cyclization into indole derivatives. A) *In ethanol-hydrochloric acid:*

5-Benzyloxytryptamine hydrochloride. To XII (690 mg., 2.75 mmoles) in 30 ml. of 50% ethanol and 7 ml. 5% hydrochloric acid, a solution of 4-aminobutanal diethyl acetal (403 mg., 2.5 mmoles) in 5 ml. ethanol was gradually added at 90°. The mixture was stirred and refluxed gently for 4 hours, concentrated *in vacuo* to about 10 ml. and cooled in the ice-box. 5-Benzyloxytryptamine hydrochloride separated (515 mg., yield 68.0%, m. p. 232—234°). One recrystallization from ethanol with charcoal gave 372 mg. (49%) of a product m. p. 248—249°, showing no depression with a sample obtained by the gramine procedure.

B) *In 25% acetic acid:*

General procedure: To the corresponding phenylhydrazine hydrochloride, dissolved in 25% acetic acid, the aldehyde diethyl acetal was added under stirring at 80°. The stirring was continued at the same temperature for 2 hours, except for IX, the mixture cooled and worked up.

5-Benzyloxytryptamine hydrochloride (V)

From 345 mg. (1.37 mmole) XII and 201 mg. (1.25 mmole) 4-aminobutanal diethyl acetal in 15 ml. acid. The reaction mixture was evaporated to dryness *in vacuo*, traces of acetic acid removed by *re*-evaporation with abs. ethanol, and abs. ethanol (3 ml.) added on the residue. 258 mg. (68%) of V, m. p. 236.5—237.5° were obtained, which after one recrystallization from water gave the analytically pure substance (208 mg., 55%), m. p. 250—251°, reported:[14] 263—264° (corr.)

Anal. $C_{17}H_{19}ClN_2O$ (302.795) calc'd.: N 9.25%
found: N 9.48%

3-Methyl-5-benzyloxyindole (VI)

From 464 mg. (1.85 mmole) XII and 244 mg. (1.85 mmole) propanal diethyl acetal in 25 ml. acid. The reaction mixture was neutralized (sodium carbonate), extracted with petroleum ether, the extracts dried over Na_2SO_4 and the solvent concentrated to about 5 ml. 236 mg. (54%) of creamy coloured crystals separated after cooling, m. p. 107—109°. For analysis they were recrystallized from petroleum ether, m. p. 117—118°, white needles, $R_f = 0.93$; 0.95 (phenol-water).

Anal. $C_{16}H_{15}NO$ (237.288) calc'd.: C 80.98; H 6.37; N 5.90%
found: C 81.21; N 6.65; N 5.93%

3-Ethyl-5-benzyloxyindole (VII)

From 940 mg. (3.75 mmoles) XII and 549 mg. (3.75 mmoles) butanal diethyl acetal in 50 ml. acid. The mixture was neutralized as by VI, extracted with ether, ether extracts washed with water and dried over Na_2SO_4. After removing the solvent *in vacuo*, the red oil was distilled, b. p. 177—181°/0.03 mm., yielding 500 mg. (53%) of a viscous oil which solidified, m. p. 71—73°. It was recrystallized from petroleum ether, colourless needles, m. p. 78—79°, reported:[15] 78—79°. $R_f = 0.93$; 0.95 (phenol-water).

Anal. $C_{17}H_{17}NO$ (251.314) calc'd.: C 81.24; H 6.82; N 5.57%
found: C 81.25; H 7.03; N 5.73%

5-Methoxytryptamine picrate (VIII)

From 218 mg. (1.25 mmole) *p*-methoxyphenylhydrazine hydrochloride[16] and 201 mg. (1.25 mmole) 4-aminobutanal diethyl acetal in 10 ml. acid. In order to remove coloured by-products, the reaction mixture was extracted with ether, the acidic layer basified with sodium hydroxide and the base extracted with ether. After drying over K_2CO_3 and evaporation of the solvent, the remaining oil was dissolved in 2 ml. ethanol and 200 mg. picric acid in 4 ml. ethanol added. On cooling, 183 mg. (35%) of red crystals separated, m. p. 212°. They were recrystallized from ethanol, m. p. 219° (decomp.), reported:[17] 219° (decomp.)

Anal. $C_{11}H_{14}N_2O \times C_6H_3N_3O_7$ (419.346) calc'd.: C 48.69; H 4.09; N 16.70%
found: C 48.62; H 4.32; N 16.86%

N'-*Acetyl-5-methoxytryptamine* (IX)

From 437 mg. (2.5 mmole) *p*-methoxyphenylhydrazine hydrochloride and 508 mg. (2.5 mmole) 4-acetylaminobutanal diethyl acetal (X) in 15 ml. acid. The reaction mixture was stirred at 80° for only one hour, adjusted to *p*H 5 (sodium carbonate) and extracted with methylene chloride. After drying over Na_2SO_4 and evaporation of the solvent, the red viscous oil was extracted with hot toluene. On cooling overnight in the ice-box, 152 mg. (26%) of yellowish crystals separated, m. p. 108—112°. They were recrystallized from toluene, m. p. 115—116°, reported:[18] 116—118°.

Anal. $C_{13}H_{16}N_2O_2$ (232.276) calc'd.: C 67.22; H 6.94; N 12.06%
found: C 67.06; H 7.19; N 12.29%

4-Acetylaminobutanal diethyl acetal (X)

2.0 g. (12.4 mmoles) 4-aminobutanal diethyl acetal was acetylated in a 5% sodium carbonate solution (4 ml.) with 3 ml. acetic anhydride under cooling. The solution was neutralized with solid sodium carbonate, extracted with ether, dried over Na_2SO_4 and the solvent evaporated. The remaining oil was distilled, b. p. 112—118°/0.03 mm., yield: 1.55 g. (61.5%). For analysis it was redistilled, b. p. 115—118°/0.03 mm., colourless viscous oil. The compound did not decompose during distillation as indicated for 3-acetylaminopropanal diethylacetal[19].

Anal. $C_{10}H_{21}NO_3$ (203.276) calc'd.: C 59.08; H 10.41; N 6.89%
found: C 58.90; H 10.69; N 7.12%

m-*Benzyloxyphenylhydrazine hydrochloride* (XI)

20 g. (0.10 mole) *m*-benzyloxyaniline[20] dissolved in ethanol (70 ml.) was converted to the hydrochloride by introducing dry HCl into solution. Ether (20 ml.) was added and the crystals (22 g., 93%, m. p. 163—165°) filtered off. Portions of 6.5 g. (27.6 mmoles) were diazotized with conc. HCl (75 ml.) and sodium nitrite (1.9 g. in 10 ml. water) at 0°. Stannous chloride (16 g. in 25 ml. conc. HCl) was gradually added under stirring at —6° and the reaction mixture held at these conditions for an additional 1 hour. The precipitate was filtered off, washed with ether and dried. It was recrystallized from ethanol-water (2:1), yield: 3.5 g., 50.5%, m. p. 149—151°. For analysis it was recrystallized from ethanol; white plates, m. p. 152—153°.

Anal. $C_{13}H_{15}ClN_2O$ (250.723) calc'd.: C 62.27; H 6.03; N 11.18%
found: C 62.37; H 6.27; N 11.19%

When XI and 4-aminobutanal diethyl acetal were stirred in 25% acetic acid at 80° for 2 hours, an oil was obtained from which no indole compound could be isolated.

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IZVOD

Sinteza 3,5-disupstituiranih indola ciklizacijom pod blagim uvjetima

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3-Benziloksi-6-formilaminotoluen nije uspjelo prevesti Madelungovom ciklizacijom u 5-benziloksitriptamin.

Nađeno je, da 4-aminobutanal dietil acetal i *p*-benziloksifenilhidrazin hidroklorid reagiraju u 25% octenoj kiselini kod 80° i daju 5-benziloksitriptamin hidroklorid (V) u 68% iskorištenju. Pod tim blagim uvjetima i bez $ZnCl_2$ kao katalizatora pripravljeni su iz odgovarajućih fenilhidrazin hidroklorida i aldehid acetala još slijedeći 3,5-disupstituirani indoli: 3-metil-5-benziloksiindol (VI), 3-etil-5-benziloksiindol (VII), 5-metoksitriptamin pikrat (VIII) i *N'*-acetil-5-metoksitriptamin (melatonin, IX).

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