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# INDOLE DERIVATIVES. XXIII.* 3-INDOLYLETHYLENE GLYCOL

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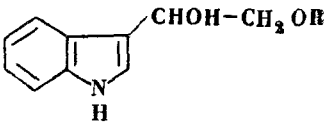
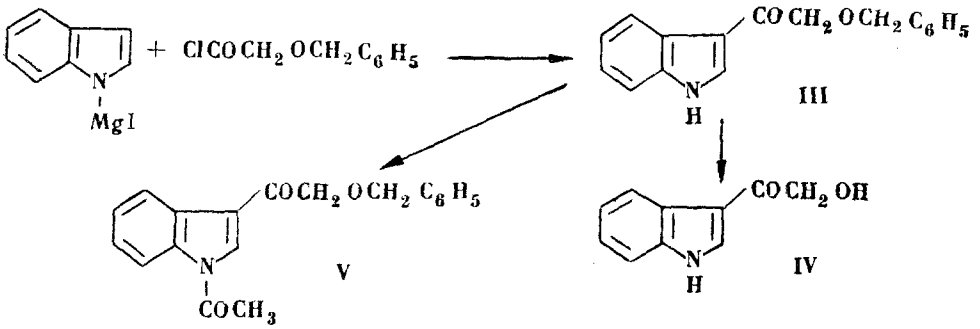
Lithium aluminum hydride reduction at room temperature of 3-hydroxyacetylindole and 3-benzyloxyacetylindole in tetrahydrofuran gives, respectively, 3-indolyethyleneglycol and 3-indolylethylene glycol monobenzylate. Sodium borohydride reduction of 3-hydroxyacetylindole gives tryptophol, and the reduction of 3-benzyloxyacetylindole gives tryptophol benzylate. Aluminum amalgam converts 3-hydroxyacetylindole and 3-benzyloxyacetylindole to 3-acetylindole.

The role of 3-indolylglycerol as an intermediate in the biosynthesis of tryptophan has recently been elucidated [2-5], at least in certain microorganisms. In this connection, considerable interest attaches to an investigation of monohydric alcohols of the indole series. Further, this class of compounds, and many other hydroxylic indole derivatives have so far remained practically uninvestigated. Only β-3-indolylethanol (tryptophol) is accessible. Its isomer, 3-indolylmethylcarbinol, has not actually been isolated [6]. The synthesis of optically inactive 3-indolylglycerol [7, 8] has been described. It was prepared [9] by acetylating 3-indolylanhydrosorbite from acetobromoglucose and indolylmagnesium iodide, but the product was not deacetylated, and its homogeneity was not shown by chromatography.

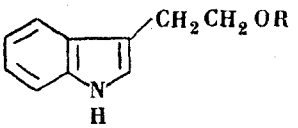
The simplest of the dihydric alcohols of the indole series, 3-indolylethylene glycol (I), and its monobenzylate (II) have been synthesized.



Indolylmagnesium iodide and benzyloxyacetyl chloride gave 3-benzyloxyacetylindole (III), which when refluxed with Raney nickel in absolute alcohol gave hydroxyacetylindole (IV). There are indications that the latter can be obtained by treating 3-chloroacetylindole with alkali [10]. The benzyloxyketone III was characterized by its oxime and N-acetyl derivative V. The reduction of the benzyloxyketone III, hydroxyketone IV, and N-acetylbenzyloxyketone V by various reducing agents was also studied.



The action of $NaBH_4$ on benzyloxyketone III in moist pyridine at room temperature gave tryptophol benzylate VI. Dealkylation of tryptophol benzoate with sodium in liquid ammonia gave tryptophol VII, as proved by paper chromatography.

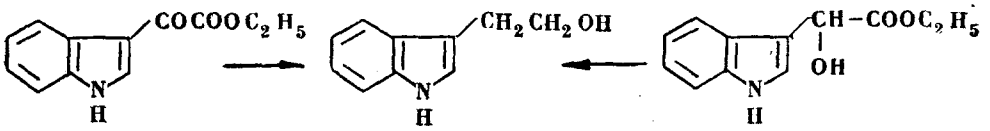


R=$CH_2C_6H_5$ (VI); R=H (VII)

The 3-hydroxyacetylindole IV undergoes practically no reaction with $NaBH_4$ in anhydrous ethanol at room temperature, and it was only by paper chromatography that it was possible to demonstrate the formation of tryptophol VII. $NaBH_4$

*For part XXII see [1].

reduction of 1-acetyl-3-benzyloxyacetylindole (V) in moist pyridine gave the benzyloxyketone III, and at the same time the formation of traces of benzyltryptophol VI was demonstrated chromatographically. The readiness with which the carbonyl group of 3-acylindoles reduces to a methylene group has repeatedly been observed by other workers. Thus it is known [11, 16] that $LiAlH_4$ reduction of 3-indolylglyoxalic and 3-indolylglycolic esters in tetrahydrofuran gives tryptophol.




The reduction of 3-acetylindole by alkali metal borohydrides, where the main product is 3-ethylindole, has also been reported [13]. At the same time there are indications that treatment of a 3-indolylglyoxalic ester with sodium amalgam in moist ether [12] gives an ester of 3-indolylglycolic acid. Good results were obtained [14] by reducing N-acetyl derivatives of an ester of 3-indolylglyoxalic acid with aluminum amalgam. In the present work 3-acetylindole VIII is obtained by reducing hydroxyketone IV with aluminum amalgam in moist ether, or compound III in moist dioxane.


Paper chromatography demonstrated the presence of 3-indolylethylene glycol, though it could not be isolated. In an analogous reduction of 1-acetyl-3-benzyloxyacetylindole (V) the reaction product also could not be isolated in crystalline form. Saponification gave 3-acetylindole (VIII) in 30% yield. Paper chromatography demonstrated the formation of the glycol monobenzylate (II). The formation of 3-acetylindole was surprising, though the literature states that reduction of 2-acetoxyacetylbenzofuran with sodium amalgam gives 2-acetylbenzofuran [15].

Hydroxyketone IV is not hydrogenated with Raney nickel and hydrogen at room temperature and pressure, but a quantitative yield of tryptophol is obtained at 55°.

Reduction of hydroxyketones with lithium aluminum hydride in tetrahydrofuran at room temperature was also investigated. Under these conditions the hydroxyacetylindole IV gave 3-indolylethylene glycol in practically quantitative yield. The benzyloxyketone III gave the monobenzylic ester of 3-indolylethylene glycol, viz., benzylhydroxymethyl-3-indolylcarbinol (II), yield 79.5%. Debenzylation of this monobenzylic ester to 3-indolylethylene glycol has not so far been effected; refluxing it with Raney nickel and absolute alcohol gives tryptophol. The structure of the 3-indolylethylene glycol was proved by oxidizing it with sodium periodate to 3-indole aldehyde (yield 61.2%). 3-Indolyl glycol is a crystalline substance readily soluble in water.

Obviously formation of 3-acetylindole on reducing the hydroxyketone IV or the benzyloxyketone III with aluminum amalgam is not due to any rearrangement of the initially formed 3-indolylethylene glycol, as the latter is unchanged when treated with aluminum amalgam in moist ether. Table 1 gives all the experimental results.

TABLE 1

Experimental results

| Starting compound | Reducing agent | Reduction conditions | Reaction product: yield, % |
|---|---|---|---|
| IV | $LiAlH_4$ | Tetrahydrofuran; 20° | I; 98.9 |
| | $NaBH_4$ | Dry ethanol; 20° | IV; traces of VII |
| | Aluminum amalgam | Moist ether; 20° | VIII, 43; traces I |
| | $H_2$ (Raney nickel) | Alcohol, pressure; 20° | Does not react |
| | $H_2$ (Raney nickel) | Alcohol, pressure; 55° | VII; 100 |
| III | $LiAlH_4$ | Tetrahydrofuran; 20° | II; 79.5 |
| | $NaBH_4$ | Moist pyridine; 20° | VI; 52.6 |
| | The same | Moist pyridine; 50° | VI; 84.5 |
| | $H_2$ (palladium black | Alcohol solution, pressure; 20° | Does not react |
| | Raney nickel | Boiling alcohol | IV; 68 |
| | Aluminum amalgam | Moist dioxane; 20° | VIII; 100 |

Table 2 gives $R_f$ values of substances obtained by paper chromatography using isopropanol-ammonia-water (10:1:1). In the system $CCl_4$-acetic acid (100:2) tryptophol has $R_f$ 0.2. In the system n-butanol-pyridine-water

TABLE 2

$R_f$ values of the substances isolated by paper chromatography

| Substance | $R_f$ | Color when visualized with Ehrlich's reagent |
|---|---|---|
| VII | 0.96 | Violet |
| VI | 0.91 | Violet |
| II | 0.97 | Rose |
| I | 0.79 | Yellowish-rose |

(3:1:1.5) 3-indolylethylene glycol monobenzylate II has $R_f$ 0.97. When chromatographed on paper impregnated with formamide-acetone, and with isooctane as the mobile phase, tryptophol benzylate VI has $R_f$ 0.56.

## EXPERIMENTAL

3-Benzyloxyacetylindole (III). 1.7 g magnesium in 50 ml ether are stirred, and 4.5 ml methyl iodide in 50 ml ether added dropwise. The mixture is refluxed 30 min on a water bath, a solution of 8.3 g indole in 200 ml ether added dropwise with cooling and vigorous stirring, and the whole refluxed for 1 hr 30 min-2 hr until methane evolution has ceased. 13 g benzylglycolic chloroanhydride in 50 ml ether are slowly added dropwise to the reaction mixture blanketed with a current of nitrogen and well cooled, and when addition is complete the whole is refluxed for 1 hr 30 min. The products are treated with a saturated solution of ammonium chloride, using ice cooling, then stirred 15 min, and the precipitate of 3-benzyloxyacetylindole filtered off, washed with ether, and dried. Yield 9.3 g (49.6%), mp 212° (from ethanol). Found: C 77.03; H 5.81; N 5.09%. Calculated for $C_{17}H_{15}NO_2$: C 76.95; H 5.70; N 5.28%. Ir spectrum 3238 $cm^{-1}$ (N–H), 1660 $cm^{-1}$ (C=O).

3-Benzyloxyacetylindole oxime. 0.69 g hydroxylamine hydrochloride and 0.82 g sodium acetate are dissolved in water, 0.5 g 3-benzyloxyacetylindole dissolved in hot alcohol, and the former solution added to the latter. The mixture is heated for 1 hr on a steam bath, part of the alcohol taken off under vacuum, and the crystals which separate are filtered off. Yield 0.5 g (94.4%), mp 133° (from water, then aqueous alcohol). Found: C 72.92; H 5.76; N 10.22%. Calculated for $C_{17}H_{16}N_2O_2$: C 72.85; H 5.75; N 9.96%.

N-Acetyl-3-(benzyloxyacetyl)indole (V). A mixture of 3 g benzyloxyacetylindole, 5 g acetic anhydride, and 1.8 g anhydrous sodium acetate are heated for 3 hr on a steam bath, and then poured onto ice. The precipitated crystals are filtered off, and crystallized from alcohol. Yield 2.5 g (74%), mp 140°. Found: C 74.01; H 5.78; N 4.41. Calculated for $C_{19}H_{17}NO_3$: C 74.24; H 5.57; N 4.55%. Ir spectrum 1670 and 1715 $cm^{-1}$ (C=O).

3-Hydroxyacetylindole IV. A mixture of 2 g 3-benzyloxyacetylindole and 15 g Raney nickel in 200 ml absolute alcohol are stirred and refluxed on a water bath for three hours, after which the catalyst is filtered off, and the filtrate evaporated in a vacuum. The crystalline precipitate is triturated with ether and filtered. Yield 0.9 g (68%), mp 160° (from water or benzene). The literature [10] gives mp 160°. Found: C 68.62; H 5.29; N 7.87%. Calculated for $C_{10}H_9NO_2$: C 68.55; H 5.18; N 7.99%. Ir spectrum 3238 $cm^{-1}$(N—H); 3480 $cm^{-1}$(O—H); 1620 $cm^{-1}$(C=O).

3-Benzoyloxyacetylindole. 2 g benzoyl chloride are added dropwise with stirring and cooling to a solution of 0.5 g 3-hydroxyacetylindole in 35 ml pyridine, and the whole left overnight, then poured onto ice. The crystals precipitated are filtered off and recrystallized from methanol. Yield 0.64 g (quantitative), mp 187-189°. Found: C 72.82; H 4.62; N 4.90%. Calculated for $C_{17}H_{13}NO_3$: C 73.11; H 4.69; N 5.01%.

3-Indolylethylene glycol (I). A solution of 0.5 g 3-hydroxyacetylindole in 15 ml dry tetrahydrofuran is added dropwise, in a nitrogen atmosphere, to a suspension of 0.25 g lithium aluminum hydride in 15 ml of the same solvent, and the whole stirred for three hours at room temperature, then cooled in ice, and the hydride decomposed by adding, in succession, 0.25 ml water, 0.25 ml 15% NaOH, and 0.75 ml water. The whole is stirred 15 min, then filtered, and the filtrate evaporated in a vacuum. On standing the residue of oil crystallizes. Yield 0.5 g (98.9%), mp 87° (from benzene). Ir spectrum 3330 $cm^{-1}$(N—H); 3420 $cm^{-1}$(O—H). Found: C 67.66; H 6.28; N 7.90%. Calculated for $C_{10}H_{11}NO_2$: C 67.78; H 6.26; N 7.91%.

Sodium metaperiodate oxidation of 3-indolylethylene glycol. A cooled solution of 0.2 g 3-indolylethylene glycol in 10 ml water is added to 10 ml of a cold 0.1 N solution of $NaIO_4$, and the precipitate that separates is filtered off after 5 min. Yield 0.1 g (61.2%), mp 190° (from water). The literature [17] gives mp 193-195°. Mixed mp undepressed with authentic 3-indole aldehyde, and ir spectra identical.

3-Indolylethylene glycol monobenzylate (II). A solution of 1 g 3-benzyloxyacetylindole (III) in 75 ml tetrahydrofuran is added dropwise to a suspension of 0.5 g lithium aluminum hydride in 25 ml of the same solvent, and the mixture stirred for three hours under nitrogen. Next, it is cooled in ice, and the $LiAlH_4$ successively decomposed by 1 ml water, 1 ml 15% NaOH, and 3 ml water. After stirring for 15 min, the mixture is filtered, the filtrate evaporated in a vacuum, and the oil left triturated with a mixture of benzene and petroleum ether, after which the crystals which formed are filtered off. Yield 0.8 g (79.5%), mp 66-67° (from toluene). Ir spectrum 3280 $cm^{-1}$(N—H); 3460 $cm^{-1}$(O—H). Found: C 76.29; H 6.30; N 5.27%. Calculated for $C_{17}H_{17}NO_2$: C 76.35; H 6.41; N 5.24%.

Tryptophol benzylate (VI). A solution of 0.4 g sodium borohydride in 10 ml water and 10 ml pyridine is added slowly dropwise to a solution of 1 g 3-benzyloxyacetylindole (III) in 35 ml pyridine. The mixture is stirred for four hours

at room temperature, the whole acidified to pH 1 with 2N hydrochloric acid, the precipitate of starting material (0.4 g) filtered off, and the dissolved material extracted from the filtrate with ethyl acetate (3-4 times). The extract is washed with saturated $NaHCO_3$ solution, and dried over anhydrous $Na_2SO_4$. The ethyl acetate is evaporated under a vacuum, the oily residue crystallizing on standing. Yield 0.3 g (31.6% on the ketone taken, or 52.6% on the ketone used). If the reaction is at 50°/2 hr, no starting material can be isolated; working up in the way described gives 0.8 g (84.5%) tryptophol benzylate, mp 60-61° (from 50% methanol). Found: C 81.19; H 6.76; N 5.63%. Calculated for $C_{17}H_{17}NO$: C 81.26; H 6.82; N 5.57%. Ir spectrum: 3310 $cm^{-1}$ (N—H).

3-Acetylindole (VIII).

a) 1 g aluminum shavings are treated with 10% NaOH till hydrogen is vigorously evolved, after which they are washed with water and shaken with a 1% mercuric chloride solution. The resultant slime is washed with plenty of water, ethanol, and finally ethanol, and finally ether, and then introduced into a solution of 0.5 g benzyloxyacetylindole in 100 ml dry dioxane, 1 ml water, and 1 ml methanol. The mixture is vigorously stirred for 3 hr, filtered, and the filtrate evaporated in a vacuum; the crystalline precipitate, 0.3 g (quantitative yield) is 3-acetylindole, mp 186° (from methanol). The literature [18] gives mp 190-191°.

b) A solution of 0.5 g 3-hydroxyacetylindole in a mixture of 100 ml dry ether, 1 ml water, and 1 ml methanol is vigorously stirred with the same aluminum amalgam as above for three hours at room temperature, after which it is worked up in the way previously described to give 0.2 g (43%) 3-acetylindole, mp 186° (from methanol). Mixed mp with authentic 3-acetylindole undepressed; the ir spectra were identical.

Trytophol (VII). 1 g Raney nickel in 10 ml ethanol is saturated with hydrogen at 55° (approx. 10 ml $H_2$), then 0.2 g 3-hydroxyacetylindole dissolved in 10 ml methanol added, and hydrogenated till hydrogen ceases to be taken up (approx. 30 ml). The reaction products are filtered, and the filtrate evaporated. The residual oil crystallizes on standing; yield 0.1 g (62.1%), mp 59° (from benzene-petroleum ether). For comparison authentic tryptophol is prepared by lithium aluminum hydride reduction of indolylacetic acid, mixed mp showed no depression.

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