INDOLE DERIVATIVES.

128.* SYNTHESIS AND PROPERTIES OF 5,6- AND 4,5-ETHYLENEDIOXYINDOLES

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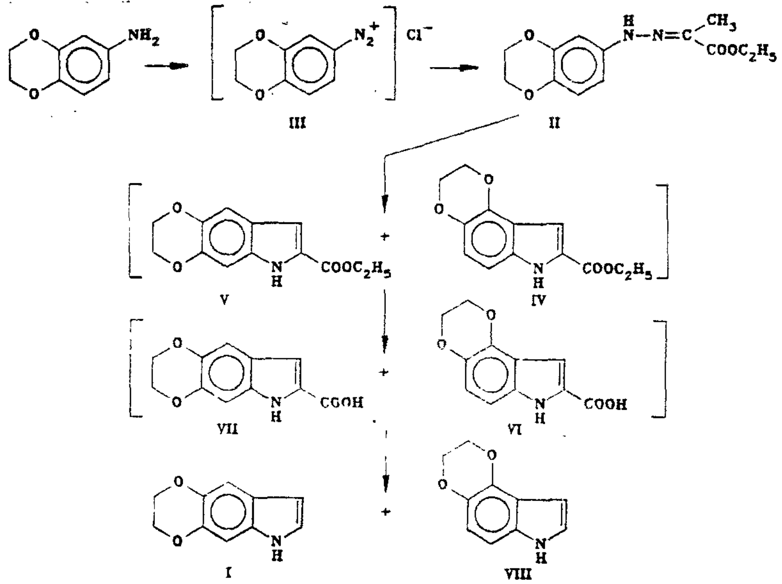
Reaction of 3,4-ethylenedioxyphenyldiazonium chloride with ethyl 2-methylacetoacetate and subsequent cyclization of the 3,4-ethylenedioxyphenylhydrazone of ethyl pyruvate gives a 1:4 mixture of 4,5- and 5,6-ethylenedioxy-2-ethoxycarbonylindoles, respectively, from which 4,5- and 5,6-ethylenedioxyindoles are formed by subsequent hydrolysis and decarboxylation. Mannich and Vilsmeyer reactions as well as acetylation and azo coupling have been studied for 5,6-ethylenedioxyindole.

Information about the synthesis and reactivity of 5,6-ethylenedioxyindole (I) and its derivatives is extremely scanty. At the same time, among derivatives of ethylenedioxyindole there are compounds which possess high antiinflammatory activity and low toxicity [2, 3].

In an effort to search for biologically active compounds based on 5,6-ethylenedioxyindole (I), we have carried out the synthesis of indole (I) according to the method in [4] and have studied its reactivity.



In contrast to the reported method [4] we achieved the synthesis of the 3,4-ethylenedioxyphenylhydrazone of ethyl pyruvate (II) by combining 3,4-ethylenedioxyphenyldiazonium chloride (III) with ethyl 2-methylacetoacetate by means of the Japp–Klingemann reaction [5]. The product of the indole-forming reaction of hydrazone II with an alcoholic solution of hydrogen chloride was a 1:4 mixture of 4,5- and 5,6-ethylenedioxy-2-ethoxycarbonylindoles (IV and V, respectively), which we succeeded in separating and identifying by means of PMR and IR spectra. It should be noted that in the PMR spectrum of indole IV, protons 6H and

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[*] For Communication 127, see [1].

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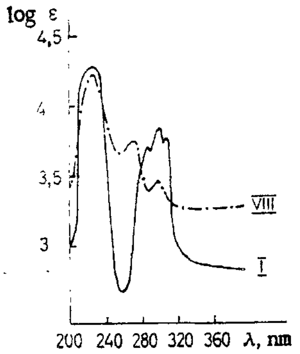
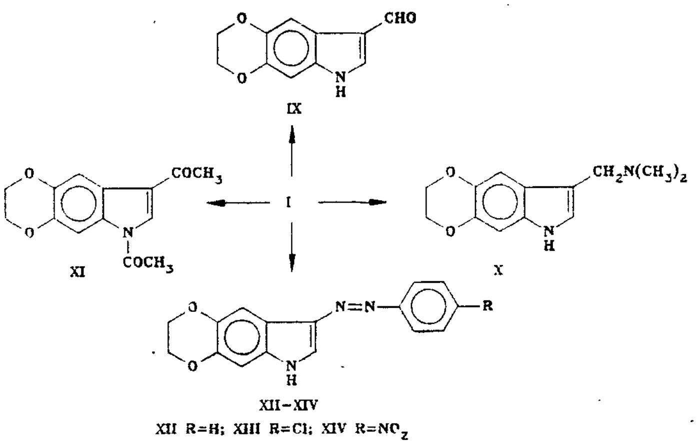


Fig. 1. UV spectra of compounds I and VIII (in ethanol).

7H form an AB system with constant J = 7.77 Hz, while protons 4H (7.00 ppm) and 7H (6.85 ppm) of indole V do not interact. Separation of the isomers proved to be extremely difficult and so for the subsequent stages – hydrolysis of esters and decarboxylation – we used a mixture of isomers IV and V. According to the data of the PMR spectrum, there is a 1:4 mixture of 4,5- and 5,6-ethylenedioxy-2-carboxyindoles (VI and VII, respectively) in the hydrolysis products. By maintaining the mixture of acids VI and VII at 275-285°C in a stream of argon, a mixture of 4,5- and 5,6-ethylenedioxyindoles (VIII and I, respectively) is obtained. We succeeded in separating indoles I and VIII by means of column chromatography with subsequent fractional crystallization. In the PMR spectrum of indole VIII protons 6H (6.88 ppm) and 7H (6.64 ppm) form an AB system with constant J = 8.77 Hz, while for indole I protons 4H (6.9 ppm) and 7H (6.8 ppm) are in the form of a singlet.

In the UV spectrum of the linear isomer I the absorption band in the region 270-330 nm has the form of an oscillation, while the angular isomer VIII has absorption maxima at 220, 280, and 308 nm (see Fig. 1).

We have studied the reactivity of indole I in Vilsmeier and Mannich reactions as well as in acetylation and azo coupling.



Reaction of indole I with a crystalline Mannich reagent [6] gives 3-N,N-dimethylaminomethyl-5,6-ethylenedioxyindole (X). The data of the PMR spectrum are given in Table 1.

As a result of the reaction of indole I with a complex ($POCl_3$ + DMF), 3-formyl-5,6-ethylenedioxyindole (IX) is formed. In the IR spectrum of 3-formylindole IX there is an absorption band at 1640 cm^{-1} from the carbonyl group.

Acetylation with acetic anhydride in acetic acid leads to the formation of a multicomponent mixture, from which we succeeded in isolating 1,3-diacetyl-5,6-ethylenedioxyindole (XI).

We have also investigated the azo coupling reaction of indole I with phenyl-, p-chlorophenyl-, and p-nitrophenyldiazonium chlorides. As a result of the reaction, 3-phenylazo-5,6-ethylenedioxyindole (XII), 3-(p-chlorophenylazo)-5,6-ethylenedioxyindole (XIII), and 3-(p-nitrophenylazo)-5,6-ethylenedioxyindole (XIV) are obtained.

TABLE 1. Values of Chemical Shifts (δ, ppm) and Spin-Spin Coupling Constants (J, Hz) in PMR Spectra of Compounds I, IV, VIII-XIV in Acetone-d_6

Compound	1-H	2-H	3-R	4-H	6-H	7-H	OCH_2CH_2O	$COOC_2H_5$	J, Hz
I	9,80 broad s	7,09 d.d	R=H, 6,22 m	6,90 s	—	6,80 s	4,18 s	—	$J_{1,2}=2,7$; $J_{2,3}=3,0$; $J_{1,3}=2,1$; $J_{3,4}=0,8$
IV	10,80 broad s	—	R=H, 7,09 s	—	7,00 d	6,85 d	4,28—4,38 m	4,35 (CH_2) d; 1,36 (CH_3) t	$J_{NHCH}=1,0$; $J_{6,7}=7,8$; $J_{CH_2CH_3}=7,2$
VIII	10,08 broad s	7,19 d.d	R=H, 6,39 d.d	—	6,88 d	6,64 d	4,26—4,31 m	—	$J_{1,2}=2,8$; $J_{1,3}=2,2$; $J_{2,3}=2,9$; $J_{6,7}=8,8$
IX	10,8 broad s	7,96 d	R=—CHO, 9,86 s	7,60 s	—	6,92 s	4,23 s	—	$J_{1,2}=2,8$
X	9,60 broad s	7,03 d	R=$CH_2N(CH_3)_2$, 3,46 (CH_2), 2,17 $(CH_3)_2$	7,05 s	—	6,76 s	4,19 s	—	$J_{1,2}=2,7$
XI	N—$COCH_3$, 2,75 s	8,51 s	R=—$COCH_3$, 2,51 s	7,82 s	—	7,72 s	4,30 s	—	—
XII	9,60 broad s	7,36 d	R=—N=N—Ph, 7—7,38	7,06 s	—	6,47 s	4,28 s	—	$J_{1,2}=2,7$
XIII	11,00 broad s	8,11 d	R=—N=N—C_6H_4Cl-p, 7,85 d; 7,52 d	7,95 s	—	6,96 s	4,28 s	—	$J_{NHCH}=3,2$; $J_0=8,8$
XIV	10,70 broad s	7,37 d	R=—N=N—$C_6H_4NO_2$-p, 8,02 d; 8,40 d	7,18 s	—	6,96 s	4,29—4,37 m	—	$J_{1,2}=1,7$; $J_0=7,4$

EXPERIMENTAL

Monitoring the course of reaction and the purity of compounds was carried out by means of TLC on Silufol UV-254 plates in a benzene—acetone, 5:2 system. The spots were developed with Ehrlich's reagent. Silica gel 100/250 was used for preparative chromatography of the compounds. IR spectra were recorded in petrolatum oil on a UR-20 instrument; UV spectra were recorded in ethanol (10^{-4} M) on a Specord UV-Vis spectrophotometer. PMR spectra were recorded on a Bruker WP-200SV instrument, with acetone-d_6 as solvent and TMS as internal standard. Mass spectra were obtained on a Varian MAT-311A instrument.

4,5- and 5,6-Ethylenedioxy-2-ethoxycarbonylindoles (IV, V). To a solution of 10.6 g (70 mmole) of 6-amino-1,4-benzodioxane in 80 ml of 18% HCl at 0°C was added a solution of 5 g (70 mmole) of sodium nitrite in 30 ml of water in such a manner that the temperature did not rise above 3°C. The reaction mass was agitated at 0°C for 30 min and then very rapidly added to a solution (cooled to −10°C) of 10.5 g (70 mmole) of ethyl 2-methylacetoacetate in 80 ml of isopropanol; then a solution of 30 g of potassium acetate in 30 ml of water was added and a 10% solution of NaOH was added dropwise until pH 6 was reached. The reaction mass was agitated for 3 h at 0°C and left to warm up to 20°C. The precipitated oil was separated off and the products of the mother liquor were extracted (3 × 100 ml) with chloroform. The oily layer and the chloroform extracts were combined and dried over sodium sulfate and the chloroform was distilled off under vacuum. The 3,4-ethylenedioxyphenylhydrazone of ethyl pyruvate (II) formed was dissolved in 10 ml of absolute alcohol, heated to boiling, and added to 50 ml of an alcoholic solution (~10-15%) of hydrogen chloride which had been heated to boiling. The reaction mass was boiled for 1 h with agitation, cooled to 20°C, concentrated under vacuum to 20 ml, and 50 ml of water was added. The cyclization product was extracted with ether (10 × 100 ml), the ether solution was dried over sodium sulfate, the ether was evaporated under vacuum, and from the residue by means of column chromatography (silica gel, petroleum ether—benzene, 1:3) was separated 6.9 g (40%) of a mixture of IV and V. Indole V was obtained by recrystallization from benzene, yield 5.2 g (30%), mp 135-136°C; according to the data of [4], mp 135-135.5°C. The mother liquor was evaporated and by means of fractional crystallization (benzene—isooctane, 10:1) 0.52 g (3%) of compound IV was separated, mp 139-140°C. IR spectrum: 3390 (NH), 1600 cm^{-1} (CO). Found, %: C 63.0, H 5.1, N 5.8. $C_{13}H_{13}NO_4$. Calculated, %: C 63.15, H 5.3, N 5.6.

4,5- and 5,6-Ethylenedioxyindoles (I, VIII). A mixture of 2.47 g (10.0 mmole) of esters IV and V was added to a solution of 1.12 g (20 mmole) of potassium hydroxide in 20 ml of water and 4 ml of ethanol; and the mixture was boiled for 4 h and cooled to 20°C, 200 ml of water was poured in, and a 4 N solution of hydrochloric acid was added until an acid reaction was given by Congo red indicator. The precipitate formed was filtered off, washed with water, and dried. 2 g (91%) of a mixture of acids VI and VII was obtained, and it was then used for decarboxylation without further purification and separation. 2 g of a mixture of acids VI and VII was maintained at 285°C for 30 min in an atmosphere of argon. After cooling, the reaction mass was extracted with acetone (5 × 50 ml), filtered, the aceton was evaporated under vacuum, and from the residue by means of column chromatography (silica gel, petroleum ether—benzene, varying the ratio from 1:0 to 1:3) was separated 1.2 g (75%) of a mixture of indoles VIII and I (1:4). After repeated recrystallization from benzene 0.8 g (50%) of compound I was obtained, mp 148-149°C; according to the data of [4], mp 148-149°C. UV spectrum, λ_{max} (log ε): 222 (4.39), 280 (3.65), 294 (3.87), 305 nm (3.76). IR spectrum: 3400 cm^{-1} (NH). Mass spectrum, m/z*: 175 (100), 148 (56), 147 (27), 119 (70), 91 (20). Found, %: C 68.2, H 4.7, N 7.7. $C_{10}H_9NO_2$. Calculated, %: C 68.5, H 5.1, N 8.0. Rf 0.4 (benzene—acetone, 5:2). A green color was given with Ehrlich's reagent.

From the mother liquor after distillation of benzene and subsequent recrystallization from benzene was obtained 0.13 g (8%) of indole VIII, mp 145-146°C. Found, %: C 68.2, H 5.1, N 7.8. $C_{10}H_9NO_2$. Calculated, %: C 68.5, H 5.1, N 8.0. UV spectrum, λ_{max} (log ε): 220 (4.25), 280 (3.74), 308 nm (3.12). Mass spectrum, m/z*: 175 (91), 148 (12), 147 (6.8), 119 (100), 91 (20). IR spectrum: 3400 cm^{-1} (NH). Rf 0.4 (benzene—acetone, 5:2). A blue color was given with Ehrlich's reagent.

3-Formyl-5,6-ethylenedioxyindole (IX). To 2.5 ml (24 mmole) of freshly distilled DMF cooled to −5°C was added 0.72 ml of $POCl_3$ in such a manner that the temperature did not rise above 0°C, and the mixture was agitated for 1 h 30 min at 20°C. Then a solution of

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*Relative intensities as a percentage of the maximum peak.

1.05 g (6.0 mmole) of product I in 2.5 ml DMF was added to the reaction mixture, which was then heated to 50-60°C and agitated at this temperature for 3 h. After cooling, the reaction mass was poured onto 30 g of ice and the pH of the medium was adjusted to 10 with a 20% solution of NaOH. The oil which had separated was extracted with ethyl acetate (3 × 50 ml), washed with water until neutral reaction, dried with sodium sulfate, and the ethyl acetate was concentrated to 5-10 ml under vacuum. The precipitate formed in the process was filtered off, washed with 5 ml of ethyl acetate, and dried. Yield 0.75 g (62%), mp 200-201°C (ethyl acetate). IR spectrum: 3120-3200 (NH), 1640 cm^{-1} (CO). UV spectrum, λ_{max} (log ε): 208 (4.30), 260 (4.06), 291 nm (4.14). Found, %: C 64.7, H 4.4, N 6.7. $C_{11}H_9NO_3$. Calculated, %: C 65.0, H 4.4, N 6.8.

3-N,N-Dimethylaminomethyl-5,6-ethylenedioxyindole (X). 0.2 g (1.14 mmole) of compound I was dissolved in 3 ml of absolute alcohol, 0.88 g (3 mmole) of crystalline Mannich reagent was added, and the mixture was agitated for 2 h at 70-75°C. The precipitate formed was filtered off, dissolved in 50 ml of water, and the pH was adjusted to 10 with a 20% solution of NaOH. The oil which had separated was extracted with ether (3 × 100 ml) and the ether was evaporated under vacuum. Yield 0.11 g (44%), mp 156-158°C (from benzene). IR spectrum: 3080-3120 cm^{-1} (NH). Found, %: C 67.2, H 6.9, N 12.4. $C_{13}H_{16}N_2O_2$. Calculated, %: C 67.2, H 6.9, N 12.1.

1,3-Diacetyl-5,6-ethylenedioxyindole (XI). To 1.05 g (6 mmole) of compound I was added 9 ml of freshly distilled acetic anhydride and 3.5 ml of acetic acid; the mixture was boiled with agitation for 22 h. After cooling, the reaction mixture was added to 50 ml of water, extracted with ethyl acetate (3 × 50 ml), washed with water, the ethyl acetate was evaporated under vacuum, and from the residue by means of column chromatography (silica gel, petroleum ether—benzene, 1:2) was separated 0.15 g (10%) of diacetylindole XI, mp 232-233°C (from ethyl acetate). IR spectrum: 1650 (CO), 1720 cm^{-1} (CO). UV spectrum, λ_{max} (log ε): 222 (4.45), 285 (3.90), 312 nm (3.56). Found, %: C 64.4, H 5.4, N 6.0. $C_{14}H_{13}NO_4$. Calculated, %: C 64.9, H 5.0, N 5.4.

3-Phenylazo-5,6-ethylenedioxyindole (XII). To a solution of 0.35 g (2 mmole) of compoun I in 15 ml of dioxane and 10 ml of water was added at 0°C a solution of phenyldiazonium chloride obtained from 0.22 g (2.4 mmole) of aniline; pH 6-7 was maintained by the addition of sodium acetate. The reaction mixture was agitated for 3 h at 0°C, extracted with ether (5 × 50 ml), the ether was evaporated, and from the residue by means of column chromatography (silica gel, chloroform) was separated 0.1 g (20%) of azoindole XII, mp 185-187°C (with decomp.). IR spectrum: 3100-3180 (NH), 1420 cm^{-1} (N═N). Found, %: C 68.3, H 4.8, N 14.7. $C_{16}H_{13}N_3O_2$. Calculated, %: C 68.8, H 4.6, N 15.0.

3-(p-Chlorphenylazo)-5,6-ethylenedioxyindole (XIII). This was obtained in a similar manner to XII. Yield 45%, mp 195-200°C (with decomp.). UV spectrum, λ_{max} (log ε): 218 (4.25), 298 nm (4.08). IR spectrum: 3330 (NH), 1415 cm^{-1} (N═N). Found, %: C 61.6, H 4.0, Cl 11.4, N 13.5. $C_{16}H_{12}ClN_3O_2$. Calculated, %: C 61.2, H 3.8, Cl 11.3, N 13.4.

3-(p-Nitrophenylazo)-5,6-ethylenedioxyindole (XIV). Yield 40%, mp 238-240°C (with decomp.). UV spectrum, λ_{max} (log ε): 211 (4.23), 310 nm (3.61). IR spectrum: 3460 (NH), 1530 (NO_2), 1410 (N N), 1330 cm^{-1} (NO_2). Found, %: C 59.0, H 4.0, N 16.9. $C_{16}H_{12}N_4O_4$. Calculated, %: C 59.2, H 3.7, N 17.3.

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