2-HYDROXYACETYLINDOLES AND 2-INDOLYLETHYLENE GLYCOLS

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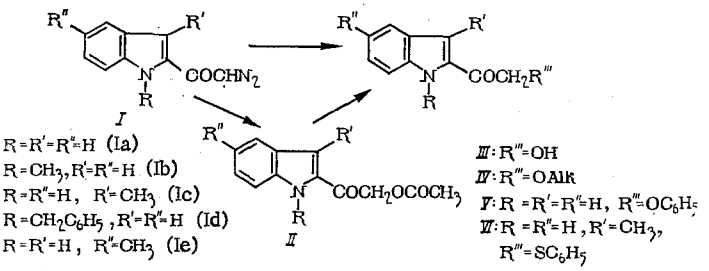
We synthesized a series of 2-hydroxy(alkoxy)acetylindoles, 2-indolylethylene glycols, and their ethers in connection with the biological activity of some 3-hydroxyacetyl indoles [1-3].

The 2-acetoxyacetyl indoles (II) are obtained by decomposing diazoketones (I) in acetic acid, and the acid hydrolysis of the former yields 2-hydroxyacetylindoles (III) (Table 1). We failed to isolate III during the alkaline hydrolysis of 2-haloacetylindoles or directly by the hydrolysis of I.



If the decomposition of I is carried out in alcohols at 30-60°C in the presence of boron trifluoride etherate, 2-alkoxyacetylindoles (IV) are obtained (see Table 1). The ethers IV are also formed during the thermal decomposition of I in alcohols in the presence of copper. If the pyrolysis of I is carried out in benzene with phenol or thiophenol, the reaction proceeds with considerable resinification. We succeeded in isolating the phenoxy- and phenthioxyketones (V and VI) by this route, but with a low yield.

2-Acylindoles in the presence of strong acids can be isomerized to 3-acylindoles [4,5]. We did not observe the formation of the isomeric 3-acylindoles during the synthesis of I, III, and IV.

The C=O (1685-1640 cm^{-1}) and N–H (3350-3250 cm^{-1}) absorption bands for the 2-acylindoles are shifted toward higher frequencies because of the lesser conjugation of the ring with the carbonyl group; this had been mentioned previously [6,7]. In addition, the overlap of the vibration bands of the C=O and C=C bonds is characteristic for the 3-acylindoles because of the anomalously low frequencies of the C=O group. A band in the 1620-1610 cm^{-1} region which can be attributed to the C=C vibrations of the ring appears in the spectra of the 2-acylindoles. There is practically no change in its position (1620 and 1618 cm^{-1}, respectively) in the transition from 2-acetyl to 2-thioacetylindole (VIII) which we obtained from 2-acetylindole (VII) and phosphorus pentasulfide.

The formation of tricyclic structures through intramolecular cyclization could be expected during the decomposition of I in allyl alcohol.

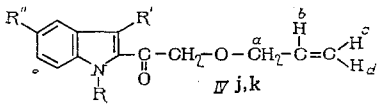


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TABLE 1. 2-Acetylindoles

Compound	R	R′	R″	R‴	Yield, %	mp, °C	Found, %			Empirical formula	Calc., %		
							C	H	N		C	H	N
IIa	H	H	H		82	143—144	66,76	5,03	6,51	$C_{12}H_{11}NO_3$	66,34	5,10	6,44
IIb	CH_3	H	H		85	74—75	67,41	5,66	5,99	$C_{13}H_{13}NO_3$	67,51	5,66	6,05
IIc	H	CH_3	H		85	146—147	67,31	5,57	5,97	$C_{13}H_{13}NO_3$	67,51	5,66	6,05
IId	$CH_2C_6H_5$	H	H		85	108—108,5	74,01	5,51	4,58	$C_{19}H_{17}NO_3$	74,24	5,57	4,55
IIIa	H	H	H	OH	69	137—137,5	68,50	5,25	7,87	$C_{10}H_9NO_2$	68,55	5,17	7,99
IIIb	CH_3	H	H	OH	80	87,5—88	69,85	5,73	7,38	$C_{11}H_{11}NO_2$	69,99	5,82	7,44
IIIc	H	CH_3	H	OH	78	151—151,5	69,80	5,64	7,31	$C_{11}H_{11}NO_2$	69,99	5,82	7,44
IIId	$CH_2C_6H_5$	H	H	OH	75,5	109—110	77,00	5,77	4,99	$C_{17}H_{15}NO_2$	76,96	5,69	5,27
IVa	H	H	H	OCH_3	81	91—92*	—	—	—	—	—	—	—
IVb	CH_3	H	H	OCH_3	80	41,5—42	70,75	6,25	7,02	$C_{12}H_{13}NO_2$	70,91	6,44	6,89
IVc	H	CH_3	H	OCH_3	61	113—114	70,96	6,50	6,89	$C_{12}H_{13}NO_2$	70,91	6,44	6,89
IVd	$CH_2C_6H_5$	H	H	OCH_3	70	55,5—56	77,32	6,17	4,75	$C_{18}H_{17}NO_2$	77,39	6,12	5,01
IVe	H	H	CH_3	$OCH_2C_6H_5$	24	123,5—124,5	77,38	6,28	4,94	$C_{18}H_{17}NO_2$	77,39	6,12	5,01
IVf	H	H	H	$OC(CH_3)_3$	57	84,5—85	71,39	7,25	5,89	$C_{14}H_{17}NO_2$	71,46	7,28	5,95
IVg	H	CH_3	H	$OC(CH_3)_3$	70	140—141	73,20	7,69	5,72	$C_{15}H_{19}NO_2$	73,43	7,69	5,70
IVh	H	H	H	$OCH_2C_6H_5$	75	145—145,5	76,81	5,53	5,16	$C_{17}H_{15}NO_2$	76,96	5,69	5,27
IVi	H	CH_3	H	OC_2H_5	59	94—95	71,67	6,89	6,38	$C_{13}H_{15}NO_2$	71,83	6,96	6,45
IVj	H	H	H	$OCH_2CH=CH_2$	27	56—57	72,32	5,94	6,37	$C_{13}H_{13}NO_2$	72,34	6,08	6,50
IVk	H	CH_3	H	$OCH_2CH=CH_2$	61	72,5—73	73,21	6,47	6,00	$C_{14}H_{15}NO_2$	73,33	6,59	6,10

* According to the literature [15], the mp is 92–93°C.

However, the IR and PMR spectra of the compounds obtained from Ia and Ic during their decomposition in allyl alcohol corresponded to structures IVj and IVk (see Table 1).

Bands for the stretching vibrations of NH (3225 cm^{-1}) and C=O (1670 and 1642 cm^{-1}, respectively) occurred in the IR spectra of compounds IVj and IVk. The PMR spectrum of IV* in trichloroacetonitrile also corresponded to the allyl oxyketone structure by the presence of signals from the olefinic protons of the allyl group (sixteen signals from protons bc δ 6.4 ppm, octets from protons c, d, a, with δ 5.45, 5.67, and 4.37 ppm, respectively; Jbd ≈ 16 Hz; Jbc ≈ 10 Hz; Jab ≈ 6 Hz; Jac ≈ Jad ≈ Jbc ≈ 1 Hz).

Ketones IV (R=H) are alkylated with dimethylsulfate or alkyl halides with respect to the ring nitrogen. But in contrast to the 3-acylindoles, the alkylation proceeds only under drastic conditions and with a low yield.

It is known that 3-(benzyloxyacetyl)indole is converted into 3-hydroxyacetylindole with the elimination of the benzyl group [8] by boiling it with Raney nickel. The analogously structured 2-isomer (IVh) is not debenzylated at room temperature by Raney nickel, but when heated in alcohol (45–55°C), the reduction of the keto group and the hydrogenolysis of the carbon–oxygen bond from the side adjacent to the keto group took place. At this time, the known 2-ethylindole (IX) [9] and 2-(2-hydroxyethyl)indole (X) were isolated.

Evidently, debenzylation of structures of the type IVh takes place but the hydroxyketone obtained IIIa (which was confirmed by a separate experiment) is reduced to IX and X under these conditions.

Compound IX was similarly obtained from ketone VII. When the benzyloxy group was substituted by a methoxy group, only the reduction of the oxo group to a methylene group with the formation of 2-(methoxyethyl)indole (XI) takes place.

There are data on the reduction of the 2-acyl group with lithium aluminum hydride for some indole

* The chemical shifts of the protons were determined within the first order of approximation.

TABLE 2. Products from the Reduction of 2-Acylindoles with Lithium Aluminum Hydride

Compound	R	R′	R‴	Yield, %	mp, °C	Found, %			Empirical formula	Calc., %		
						C	H	N		C	H	N
XII	H	H	H	78	Oil	74,32	6,59	8,71	$C_{10}H_{11}NO$	74,50	6,87	8,68
XIIIa	H	H	OH	85,5	130—130,5	67,92	6,27	7,66	$C_{10}H_{11}NO_2$	68,34	6,31	7,90
XIIIb	CH_3	H	OH	87	113—113,5	69,11	6,86	7,15	$C_{11}H_{13}NO_2$	69,10	6,85	7,33
XIVa	H	H	OCH_3	86	81,5—82	69,29	6,56	7,14	$C_{11}H_{13}NO_2$	69,10	6,85	7,33
XIVb	CH_3	H	OCH_3	90	61—61.5	69,98	7,20	6,76	$C_{12}H_{15}NO_2$	70,20	7,37	6,82
XIVc	H	CH_3	OCH_3	82	Oil	70,17	7,38	6,70	$C_{12}H_{15}NO_2$	70,20	7,37	6,82
XIVd	H	H	$OCH_2C_6H_5$	92	71—72	76,67	6,25	5,06	$C_{17}H_{17}NO_2$	76,38	6,41	5,24
XIVe	H	CH_3	OC_2H_5	92	87,5—88	70,85	7,48	6,40	$C_{13}H_{17}NO_2$	71,19	7,82	6,39

Note: For all the compounds, R″ = H.

alkaloids [10, 11]. Alcohols are usually formed here [12,13], but instances of reduction to the methylene group are known [14]. It was shown that prolonged boiling of ketone VII in ether or tetrahydrofuran with excess lithium aluminum hydride leads to methyl-(2-indolyl) carbinol (XII). The reduction of the carbonyl group for other 2-acylindoles which do not contain an alkyl group in position 3 proceeds analogously. Only carbinols are formed both in ether (Table 2) and in tetrahydrofuran. Thus, we obtained the corresponding glycols (XIIIa and XIIIb) from ketones IIa and IIb, IIIa and IIIb, and the monoethers of the glycols (XIV) from the alkoxy ketones IV. If position 3 is substituted by a methyl group, the completely reduced products are formed along with the alcohols in low yield during prolonged boiling in tetrahydrofuran. Thus, carbinol XIVc and XI are obtained from ketone IVc with a yield of 5%. Using thin-layer chromatography, we succeeded in showing that 3-methyl-2-ethoxyethylindole is also formed during the reduction of IVi.

The O,O-diacetates (XV and XVI) were obtained by acylating glycols XIIIa and XIIIc with acetic anhydride in pyridine. The vibration bands of the unassociated hydroxy groups in the IR spectra of X, XII, and XIII are located in the 3618-3625 cm^{-1} region. A second band (bonded OH) with ν = 3590-3593 cm^{-1} appears for glycols XIII because of the weak intramolecular hydrogen bonds between the hydroxyl groups. The hydroxyl band for glycol ethers XIV appears in the 3585-3592 cm^{-1} region, i.e., the protons of the hydroxyl groups are associated completely because of their interaction with the p-electrons of the oxygen in the alkoxy groups. The position of the NH vibration bands practically does not change (3468-3472 cm^{-1}) for all the indolyl-2-carbinols (X, XII-XIV), which confirms that there are no intramolecular interactions between the nitrogen proton and the hydroxyl groups.

The investigation of the pharmacological activity (on white mice) showed that within 1 h after their intraperitoneal injection in doses equal to $\frac{1}{5}$ of the LD_{50}, substances III and IV prove to have a depressing effect on the central nervous system of the mice, cause a considerable (up to 6°C) drop in the rectal temperature, disrupt the coordination of movements, and increase by $1\frac{1}{2}$ to $2\frac{1}{2}$ times the duration of chloral hydrate sleep. Substances III and IV have low toxicity: the intraperitoneal LD_{50} comes to 350-1000 mg/kg. The compounds which have a methyl group in position 3 of the ring possessed a more expressed activity. The susceptibility of mice toward the convulsive action of Corazol decreases against the background of IVc and IVg. Weakly expressed central antiseratonin properties are expressed by IIIc and IIId.

The antibacterial activity of the compounds obtained was evaluated in vitro in relation to the following species of microorganisms: staphylococcus, streptococcus, pneumococcus, intestinal salmonella, dysentery, diphtheria, Bacillus pyocyaneus, Proteus, anthracoid organisms; also strains of tuberculosis mycobacteria: $H_{37}Rv$ and Academia.

The minimum bacteriostatic concentration (MBC) versus pyogenic cocci and the intestinal typhoid-dysentery group of bacteria came to 200 μg/ml or more for all the compounds. The MBC in relation to certain species of Gram-positive and Gram-negative bacteria was 12-50 μg/ml only for compounds IIIc and IV. The majority of the compounds possess average antitubercular activity (MBC = 16-500 mg/ml) in relation to both strains of mycobacteria used, whereby their activity does not substantially depend on the presence of whey in the culture medium.

EXPERIMENTAL

The IR spectra of II-IV, VII, and VIII were run on a UR-10 instrument as mineral oil mulls, and of X-XIV in carbon tetrachloride (0.005 mole/liter).

The synthesis of diazoketones I was previously described [16-18].

2-Acetoxyacetylindoles (II). A mixture of 0.01 mole of I and 30 ml of glacial acetic acid was heated at 45-50°C until the evolution of nitrogen ceased. The mixture was cooled and diluted with water, and the precipitate was filtered off and recrystallized from water.

2-Hydroxyacetylindoles (III). A mixture of 0.005 mole of II, 50 ml of water, 50 ml of alcohol, and 1 ml of concentrated sulfuric acid was boiled 6-8 h. The solution was cooled and neutralized with sodium bicarbonate, and the precipitate III was filtered off and recrystallized from aqueous alcohol.

2-Alkoxyacetylindoles (IV). To a suspension of 0.02 mole of I in 50 ml of the appropriate absolute alcohol was added 0.1 g of boron trifluoride etherate. At the end of the reaction, the alcohol was evaporated in vacuo, and the residue was dissolved in a mixture of benzene and ether. The extract was washed with a sodium bicarbonate solution and water and dried over magnesium sulfate. The solvent was evaporated in vacuo, the residue was recrystallized from (a mixture of) benzene and hexane. The yields and constants obtained for II, III, and IV are given in Table 1.

2-Phenoxyacetylindole (V). A mixture of 0.9 g of Ia, 2.4 g of phenol, and 0.3 g of copper powder was boiled for 8 h in 40 ml of benzene, the copper powder was filtered off, and the filtrate was washed with 10% sodium hydroxide and water and dried with magnesium sulfate. The benzene was evaporated in vacuo. Compound V, 0.37 g (30%), was obtained, mp 99-100°C (from a mixture of benzene and hexane). Found %: C 76.28; H 5.04; N 5.52. $C_{16}H_{13}NO_2$. Calculated %: C 76.47; H 5.25; N 5.57.

3-Methyl-2-phenylthioacetylindole (VI). This compound was obtained similarly to V from 1 g of Ic and 3 g of thiophenol. The yield was 30%, mp 138-139°C (from a mixture of benzene and hexane). Found %: C 72.51; H 5.41; N 5.19. $C_{17}H_{15}NOS$. Calculated %: C 72.56; H 5.37; N 4.97.

Methylation of 2-Methoxyacetylindole (IVa). a. Into a boiling solution of 0.95 g of IVa in 30 ml of dioxane was poured a solution of 0.3 g of sodium hydroxide in 1.5 ml of water, and then 1.26 g of dimethylsulfate was added by drops. The mixture was boiled for 8 h, diluted with water, and the oily precipitate was extracted with ether. The solvent was evaporated off, and the residue was subjected to preparative chromatography on aluminum oxide in a 9:1 benzene–methanol system. Starting compounds IVa, 0.76 g (72%), and 0.2 g (20%) of 1-methyl-2-methoxyacetylindole were obtained; their constants corresponded to those of compound IVb (see Table 1) which was obtained by decomposing Ib in methanol.

b. A suspension of 0.48 g of IVa and 0.17 g of sodium ethylate in 20 ml of dioxane was evaporated to dryness, and to the residue was added 1.4 g of methyl iodide and 1 drop of dimethylformamide. The solution was boiled 8 h and evaporated, and the residue was subjected to preparative chromatography on aluminum oxide in a 9:1 benzene–methanol system. The starting compounds IVa, 0.44 g, and IVb, 0.03 g (6%), were obtained.

2-Thioacetylindole (VIII). A mixture of 0.3 g of VII and 0.65 g of phosphorus pentasulfide was boiled for 3 h in 40 ml of benzene. The hot solution was filtered, and the solvent evaporated. Compound VIII, 0.09 g (29.7%), was obtained, mp 111-112°C (from a mixture of benzene and hexane). IR spectrum, cm^{-1}: 1618 (C=C), 3390 (NH). Found %: C 68.15; H 5.30; S 18.63. $C_{10}H_9NS$. Calculated %: C 68.58; H 5.17; S 18.29.

Reduction of the 2-Acylindoles with Raney Nickel. A total of 0.01 mole of the 2-acylindole in 200 ml of absolute alcohol was heated with 5 g of Raney nickel to 45-50°C until the starting substance disappeared from the chromatogram (Silufol, benzene–methanol, 10:1). The catalyst was filtered off, the alcohol was evaporated, and the residue was recrystallized from a mixture of benzene and hexane. When IIIa, IVc, and

IVh were reduced, the residue was subjected to preparative chromatography on aluminum oxide in a 10:1 benzene–methanol system.

From 1 g of IVc was obtained 0.7 g (70%) of XI as an oil. IR spectrum, cm^{-1}: 3475 (N–H). Found %: C 75.95; H 8.06; N 7.18. $C_{12}H_{15}NO$. Calculated %: C 76.15; H 7.98; N 7.40. The substance was unstable and decomposed on standing.

From 2 g of IVh was obtained 0.7 g (64%) of IX, mp 35°C (from hexane); according to the literature, the mp is 35°C [9]; and 0.3 g (32.5%) of X, mp 75.5-76°C; IR spectrum of X, cm^{-1}: 3625 (OH), 3472 (NH). Found %: C 74.31; H 6.58; N 8.47. $C_{10}H_{11}NO$. Calculated %: C 74.50; H 6.87; N 8.69.

From 0.35 g of IIIa was obtained 0.19 g (65%) of IX and 0.1 g (31%) of X.

From 1 g of VII was obtained 0.86 g (95%) of IX.

Reduction of 2-Acylindoles II, III, IV, and VII with Lithium Aluminum Hydride. To 0.05 mole of lithium aluminum hydride in 30 ml of absolute ether at 25-28°C was added a suspension of 0.05 mole of the 2-acylindole in 75 ml of ether. The mixture was agitated for 1 h and treated in the usual way. After recrystallization from a mixture of benzene and hexane, the products, yields, and constants which are given in Table 2 were obtained.

Prolonged boiling (15-20 h) of the 2-acylindoles without a methyl group in position 3 of the ring with a large excess of lithium aluminum hydride in ether or tetrahydrofuran leads to those same products. An analogous carrying out of the reaction for IVc in tetrahydrofuran (boiling for 20 h) leads to a mixture of two substances which were preparatively separated on silica gel in a 4:1 hexane–ethylacetate system. From 1 g of IVc was isolated 0.8 g (80%) of XIVc and 0.047 g (5%) of XI (R_f 0.3 and 0.75, respectively). The constants for XI corresponded to the constants of the substance obtained during the reduction of IVc with Raney nickel. Chromatographic monitoring of the reduction of IVi under the same conditions also revealed the formation of two substances.

Acylation of Indolyl-2-ethylene Glycols (XIII). A mixture of 0.3 g of XIIIa, 13 ml of pyridine, and 1.5 ml of acetic anhydride was maintained for 12 h at room temperature, diluted with water, and the precipitate was filtered off. The diacetate (XV), 0.35 g (80%), was obtained, mp 60-60.5°C (from alcohol). IR spectrum, cm^{-1}: 1720 (C=O), 3330 (N–H). Found %: C 64.57; H 6.09; N 5.25. $C_{14}H_{15}NO_4$. Calculated %: C 64.34; H 5.78; N 5.36.

Similarly, from 0.3 g of XIIIb was obtained 0.4 g (95%) of diacetate (XVI), mp 57-57.5°C (from aqueous alcohol). IR spectrum, cm^{-1}: 1738 (C=O). Found %: C 65.66; H 6.17; N 5.04. $C_{15}H_{17}NO_4$. Calculated %: C 65.44; H 6.22; N 5.08.

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