α-(3-INDOLYL)-β-HYDROXYETHYLAMINE AND ITS DERIVATIVES

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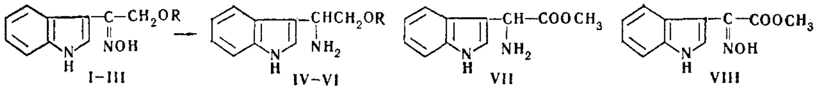
The reduction of oximes of 3-hydroxyacetylindole, 3-benzyloxyacetylindole, and 3-ethoxyacetylindole (mixtures of syn and anti isomers) gave α-(3-indolyl-β-hydroxyethylamine, α-(3-indolyl)-β-benzyloxyethylamine, and α-(3-indolyl)-β-ethoxyethylamine, the structures of which were confirmed by PMR and mass spectrometry.

α-(3-Indolyl-β-hydroxyethylamine and its derivatives can be considered to be gramine derivatives or compounds that are isomers of β-hydroxytryptamines, which have interesting biological properties [1, 2].

As key substances in the preparation of these compounds we used the oximes of 3-hydroxyacetylindole and its derivatives.



I, IV R = H; II, V R = $CH_2C_6H_5$; III, VI R = C_2H_5

3-Hydroxyacetylindole was synthesized by the method in [3]. 3-Benzyloxyacetylindole and 3-ethoxyacetylindole were obtained from indolylmagnesium iodide and the acid chlorides of the appropriate alkoxyacetic acids [4]. It was demonstrated by chromatographic methods and PMR spectroscopy that oximes I-III are formed as mixtures of syn and anti isomers (two spots during chromatography, and a double set of chemical shifts in the PMR spectra), which were not isolated in individual form. Reduction of the mixture of syn and anti oximes (I) with aluminum amalgam in tetrahydrofuran gave 13.6% of amino alcohol IV. Compound IV was also obtained by hydrogenation of I over Raney nickel in alcoholic ammonia (21.7% yield) and over Pd C in acid (26.0%). The other possible route to the preparation of IV consists in the reduction of the oxime of methyl (3-indolyl)aminoacetate (VII) with $LiAlH_4$. Ester VII was obtained by the reduction of the oxime of methyl (3-indolyl)glyoxylate (VIII) with aluminum amalgam [5].

The reduction of a mixture of geometrical isomers of 3-benzyloxyacetylindole oxime (II) or 3-ethoxyacetylindole oxime (III) leads to β-benzyloxy- or β-ethoxy-α-(3-indolyl)ethylamines (V or VI), respectively. Ethoxyamine VI decomposes with ammonia evolution on storage, while benzyloxyamine V is more stable. Acetylation of benzyloxyethylamine V with acetic anhydride in pyridine gave the N-acetyl derivative (IX).

The values of the vicinal spin–spin interaction constants $J_{\alpha\beta}$ and $J_{\alpha\beta'}$ (Table 1) are evidence that rotation about the $C_\alpha - C_\beta$ bond is not free for all three amines (IV-VI); the conformation in which the proton attached to C_α is in the trans position relative to one of the C_β –H protons ($J_{\alpha\beta}$ ~ 8 Hz) and in the gauche position relative to the other C_β –H proton ($J_{\alpha\beta}$ ~ 4 Hz) predominates. Thus, of all three possible conformations relative to the $C_\alpha - C_\beta$ bond (A, B, and C) the predominant one is conformation A with maximally remote bulky substitutents which is stabilized by the presence of an intramolecular hydrogen bond of the D or E type.

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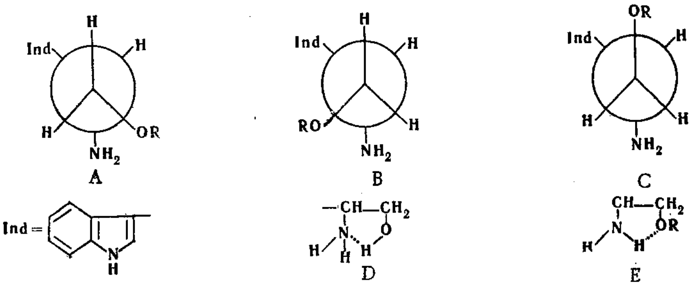
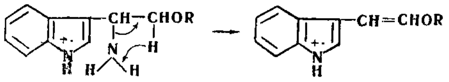
TABLE 1. PMR Spectra of Amines IV-VI

Compound	δ, ppm (in CD_3OD)				$J_{\alpha\beta'}$, Hz	$J_{\alpha\beta'}$, Hz	$J_{\beta\beta'}$, Hz
	$C_\alpha=H$	$C_\beta=H$	$CH_3=$	$=OCH_2=$			
IV	4,31	3,75	—	—	4,0	8,0	12,0
V	4,48	3,70	—	4,58	4,0	8,0	9,5
VI	4,44	3,62	1,21	3,53	3,3	8,5	9,5

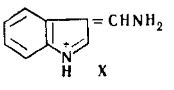
The contribution of sterically hindered conformation B is insignificant, while conformation C, by virtue of steric hindrance and the absence of an intramolecular hydrogen bond, appears unlikely. The change in the geminal spin–spin interaction constant ($J_{\beta\beta'}$) in V and VI as compared with amino alcohol IV, attests to a change in the conformation of the C–O–R bond on passing from the alkoxy compounds (R = C_2H_5, C_7H_7) to the amino alcohol (R = H) [6]. This is apparently associated with the existence of an intramolecular hydrogen bond of the E type for V and VI and of the D and E types for IV.



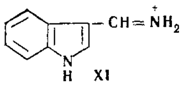
Low-intensity molecular peaks with mass numbers 204 (VI) and 266 (V) are observed in the mass spectra of V and VI. There is no molecular peak in the spectrum of amino alcohol IV, probably as a consequence of the ease of disintegration of the molecular ion. The first act of disintegration of IV-VI is cleavage of ammonia from the molecular ion. A study of the spectrum of deuterium-labeled benzyloxyamine V showed that ammonia is ejected in the following way:



The ion thus formed disintegrates with subsequent elimination of R, CO, and HC≡CH fragments of the side chain, which leads to the appearance in the spectra of IV-VI of peaks with mass numbers 158, 130, and 103. The disintegration is confirmed by the presence of metastable peaks. Another path for fragmentation is the cleavage of a CH_2OR group from the molecular ions, which leads to the appearance of a peak with m/e 145, corresponding to ion X or XI in the spectra.



X



XI

The disintegration of this fragment is responsible for peaks with m/e 118, 117, 91, and 90 in the spectra.

A molecular peak with m/e 308, a peak with m/e 187, which corresponds to cleavage of $CH_2OC_7H_7$ from the molecular ion, as well as peaks previously observed for IV-VI are observed in the mass spectrum of IX; this confirms the proposed structure.

EXPERIMENTAL

The PMR spectra were recorded with a JNM-4H-100 spectrometer with an operating frequency of 100 MHz. The IR spectra of mineral oil suspensions were obtained with a UR-10 spectrometer. The UV spectra of alcohol solutions were obtained with an EPS-3 recording spectrophotometer. The mass spectra were recorded with an MKh-1303 spectrometer at an ionizing voltage of 50 V.

3-Hydroxyacetylindole Oxime (I). A 0.7 g (0.0039 mole) sample of 3-hydroxyacetylindole was dissolved with heating in 20 ml of alcohol, an aqueous solution of 1.38 g (0.02 mole) of hydroxylamine hydrochloride, and 1.64 g (0.02 mole) of sodium acetate was added to it, and the mixture was refluxed for 1 h. It was then allowed to stand overnight at room temperature, and the alcohol was evaporated in vacuo. Cooling of the aqueous solution gave 0.33 g (43.5%) of oxime with mp 116-118° (from water). Found %: C63.0; H 5.1; N 14.2. $C_{10}H_{10}N_2O_2$. Calculated %: C 63.1; H 5.3; N 14.7. R_f 0.78 and 0.49 (on Silufol in ether), 0.17 and 0.10 [on Silufol in alcohol–benzene (1 : 9)]. PMR spectrum (in CDOD): δ_{CH_2} 4.64 and 4.74 ppm, δ_{C_2H} 8.23 and 7.62 ppm. The ratio of the two forms was 55 : 45.

3-Ethoxyacetylindole. An ether solution of 11.68 g (0.09 mole) of ethoxyacetyl chloride was added dropwise with cooling to an ether solution of indolylmagnesium iodide [prepared from 2.31 g (0.09 mole) of Mg, 5.62 ml (0.09 mole) of methyl iodide, and 11.13 g (0.09 mole) of indole], and the mixture was refluxed for 30 min and then stirred for 30 min at room temperature. The resulting precipitate was recrystallized from 50% alcohol to give 3.58 g (18.5%) of ketone with mp 157-158°. Found %: C 71.1; H 6.4; N 7.1. $C_{12}H_{13}NO_2$. Calculated %: C 70.9; H 6.4; N 6.9. IR spectrum: 3200 (broad, NH), 1645 (CO), 1620 cm^{-1} $[C_{(2)} = C_{(3)}]$. UV spectrum, λ_{max} (ε): 244 (11,500), 263 (8400), 302 nm (11,600).

3-Ethoxyacetylindole Oxime (III). An alcohol solution of 4.04 g (0.02 mole) of 3-ethoxyacetylindole and an aqueous solution of 7.02 g (0.1 mole) of hydroxylamine hydrochloride and 8.07 g (0.1 mole) of sodium acetate were mixed, and the mixture was heated for 4 h on a water bath and evaporated to dryness. The residue was recrystallized from benzene to give 2.34 g (53.9%) of III as a mixture of isomers. The melting point depended on the ratio of isomers in the mixture: mp 111-112° (R_f 0.59 on Silufol in ethyl acetate), mp 101-103° (mixture of isomers with R_f 0.70 and 0.59 in the same system). Compound III with mp 111-112°. Found %: C 66.1; H 6.4; N 12.6. $C_{12}H_{14}N_2O_2$. Calculated %: C 66.0; H 6.4; N 12.8. IR spectrum: 3300 (NH, OH), 1630, 1645 (C = N), 1615 cm^{-1} $[C_{(2)}-C_{(3)}]$. UV spectrum, λ_{max} (ε): 224 (19,200), 264 (10,200), 288 nm (19,600). UV spectrum for a mixture of isomers of III, λ_{max} (ε): 224 (26,250), 265 (9750), 282 (9250), 288 nm (9150). PMR spectrum (in CD_3OD) of III with mp 111-112°: δ_{COCH_2} 4.51 ppm, $\delta_{C_{(2)}H}$ 8.28 ppm; for the other isomer of III: δ_{COCH_2} 4.69 ppm, $\delta_{C_{(2)}H}$ 7.65 ppm. The positions of the signals of the protons of the CH_3 groups (δ 1.15 ppm) and $(CH_3)CH_2$ (δ 3.72 ppm) coincided for both isomers. The isomer ratio was 60 : 40 in the sample with mp 101-103°. (The isomer with mp 111-112° predominates.)

3-Benzyloxyacetylindole Oxime (II). This was obtained by the method in [4] and was a mixture of isomers with R_f 0.12 and 0.42 (on Silufol in ether).

α-(3-Indolyl)-β-hydroxyethylamine (IV). A. A solution of 0.65 g (0.003 mole) of methyl amino(3-indolyl)acetate (VII) in 70 ml of tetrahydrofuran was added to a suspension of 0.65 g (0.017 mole) of $LiAlH_4$ in 40 ml of tetrahydrofuran. The mixture was stirred for 3 h at room temperature, cooled, and 0.65 ml of water, 0.65 ml of 15% NaOH, and 2 ml of water were added successively. The precipitate was filtered and washed with tetrahydrofuran. The filtrate was evaporated in vacuo to give 0.24 g (42.9%) of IV with mp 128-129° (from ethyl acetate). Found %: C 68.4; H 6.7; N 15.8. $C_{10}H_{12}N_2O$. Calculated %: C 68.2; H 6.9; N 15.9. UV spectrum, λ_{max} (ε): 282 (5700), 289 nm (4700), R_f 0.42 [on Silufol in butanol–acetic acid–water (4 : 1 : 1)]; 0.64 [on paper in butanol–ethyl acetate–acetic acid–water (15 : 1 : 4 : 4)]. Leningrad paper (slow) was used for the chromatography.

B. A 0.5 g (0.003 mole) sample of I was dissolved in a mixture of 50 ml of alcohol and 20 ml of ammonium hydroxide and hydrogenated over Raney nickel under standard conditions until hydrogen evolution had ceased. The mixture was then filtered, and the filtrate was evaporated in vacuo. The residue was dissolved in ethyl acetate, filtered, and evaporated. Benzene (3 ml) was added to the residue to give 0.1 g (21.7%) of IV with mp 124-125° (from benzene). The compound was identical to the sample obtained by method A.

C. A total of 0.2 ml of hydrochloric acid (sp. gr. 1.19) was added to a solution of 0.5 g (0.003 mole) of oxime I in 50 ml of alcohol, and the mixture was hydrogenated over Pd/C under standard conditions until hydrogen evolution had ceased. The mixture was then filtered, and the mother liquor was evaporated. The resulting precipitate was dissolved in absolute acetone and precipitated with absolute ether. The precipitate was then dissolved in a small amount of water, the solution was cooled, and alkali was added. Product IV was extracted with ethyl acetate, and the solution was evaporated to give 0.12 g (26.0%) of IV.

Picrate of α-(3-Indolyl)-β-hydroxyethylamine. This was obtained as yellow crystals with mp 163° (decomp.) in alcohol. Found %: C 47.1; H 3.9; N 17.1. $C_{10}H_{12}N_2O \cdot C_6H_3N_3O_7$. Calculated %: C 47.4; H 3.7; N 17.3.

α-(3-Indolyl)-β-benzyloxyethylamine (V). Aluminum amalgam (from 0.9 g of aluminum foil) was added to a solution of 0.50 g (0.0017 mole) of II in moist ether. The reaction mixture was stirred for 24 h at room temperature and filtered. The filtrate was evaporated, and the residue began to crystallize on standing to give 0.14 g (29.7%) of V with mp 99-101° (from ether) and R_f 0.80 [on Silufol in butanol–acetic acid–water (4:1:1)]. Found %: C 76.5; H 6.8; N 10.4. $C_{17}H_{18}N_2O$. Calculated %: C 76.7; H 6.8; N 10.5.

N-Acetyl-α-(3-indolyl)-β-benzyloxyethylamine (IX). A 0.2 g (0.001 mole) sample of V was dissolved in 5 ml of pyridine, and 1.5 ml of acetic anhydride was added to it. The reaction mass was allowed to stand overnight in a refrigerator and poured over ice. An oily substance was isolated and slowly crystallized to give 0.16 g (66.6%) of IX with mp 114.5-115.5° (from benzene). Found %: C 74.6; H 6.5; N 9.0. $C_{19}H_{20}N_2O_2$. Calculated %: C 74.0; H 6.5; N 9.1. IR spectrum: 3330, 3240 (NH), 1668 cm^{-1} (NHCO).

α-(3-Indolyl)-β-ethoxyethylamine (VI). This was obtained like V by the reduction of III with aluminum amalgam in moist ether. After 2 days, the reaction mixture was filtered and evaporated, the residue was dissolved in ether, and an equimolar amount of adipic acid in dry acetone was added. The resulting precipitate was filtered and dissolved in a small amount of water. The solution was cooled and made alkaline with KOH solution. Amine VI was extracted with ether, and the ether extract was dried with potassium carbonate and evaporated in vacuo. Amine VI crystallized in the refrigerator in the course of several days to give 12.5% of a product with mp 79-81° (from ether) and R_f 0.38 [on Silufol in butanol–acetic acid–water (4:1:1)]. Found %: C 71.0; H 7.6; N 13.6. $C_{12}H_{16}N_2O$. Calculated %: C 70.6; H 7.9; N 13.7. The picrate of VI was obtained in absolute ether and had mp 150° (decomp.). Found %: C 49.5; H 4.2; N 15.9. $C_{12}H_{16}N_2O \cdot C_6H_3N_3O_7$. Calculated %: C 48.9; H 4.4; N 16.2.

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