REDOX REACTIONS IN A NUMBER OF PYRROLE-RING-SUBSTITUTED 5-HYDROXYINDOLES

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Some 3-substituted 5-hydroxyindoles are smoothly hydrogenated in acid media in the presence of a palladium catalyst to the corresponding indolines, which in turn are readily oxidized by air oxygen in aqueous solutions at pH 10 to the corresponding 5-hydroxyindoles.

The catalytic hydrogenation of indoles that have substituents in the pyrrole ring usually leads to the reduction of the aromatic ring [1,2]. Although there are papers in which the authors assert the formation of indolines during the hydrogenation of 3-substituted indoles [3,4], this more frequently occurs under severe conditions at high pressure. In this paper it is demonstrated that 3-substituted 5-hydroxyindoles [5-hydroxytryptamine (I), 5-hydroxy-N,N-dimethyltryptamine methiodide (II), and 5-hydroxytryptophan (III)] are smoothly hydrogenated in acid media in the presence of a palladium catalyst at room temperature and are converted to the corresponding indolines (IV-VI).

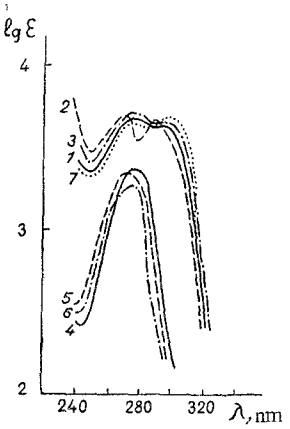
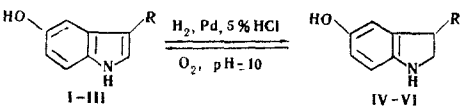


Fig. 1. UV spectra: 1) 5-hydroxytryptamine hydrochloride; 2) 5-hydroxy-N,N-dimethyltryptamine methiodide; 3) 5-hydroxytryptamine; 4) 2,3-dihydro-5-hydroxytryptamine dihydrochloride; 5) 2,3-dihydro-5-hydroxy-N,N-dimethyltryptamine methylchloride hydrochloride; 6) 2,3-dihydro-5-hydroxytryptamine; 7) reaction mixture obtained after bubbling oxygen into a solution of 2,3-dihydroserotonin.

The hydrogenation of I yielded 2,3-dihydro-5-hydroxytryptamine (IV), the structure of which was confirmed by the PMR spectrum, which showed the presence of three protons in the aromatic ring. The formation of indolines IV-VI was confirmed by the UV spectra (Fig. 1) in which the long-wave maximum at 285-295 nm characteristic for the starting indole vanishes.



I, IV R = $CH_2CH_2NH_2$; III, VI R = $CH_2\underset{\underset{COOH}{|}}{C}HNH_2$;

II, V R = $CH_2CH_2\overset{+}{N}(CH_3)_3X^-$ (II X=I; V X=Cl)

Dihydrotryptophan VI was not isolated from the solution, but paper chromatography demonstrated that it is the only reaction product.

The rate of hydrogenation of 3-substituted 5-hydroxyindoles increases with the acid concentration in the reaction medium: the initial reaction rate in 5% hydrochloric acid is higher by a factor of two to three than in 1% hydrochloric acid.

This makes it possible to suppose that the protonated form of indole enters into the reaction. The protonation of indole disrupts the aromatic system of the pyrrole ring. This results in the formation of a structure that is analogous in properties to un-

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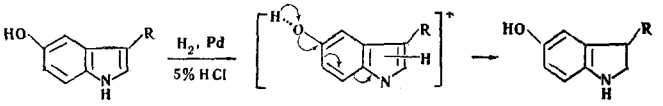
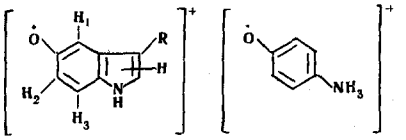
TABLE 1. R_f Values of the Investigated Compounds

Compound	Solvent system			Color on development with the Erlich reagent
	butanol–acetic acid–water (4:1:5)	2 N hydrochloric acid	butanol–25% methylamine (8:3)	
I	0,40	0,45	0,55	Blue-violet
II	0,44	0,60		Blue-violet
III	0,23	0,42	0,1	Blue-green
IV	0,20	0,85		Bright yellow
V	0,17	0,94		Bright yellow
VI	0,14	0,81		Bright yellow

saturated nonaromatic compounds, which are known to be hydrogenated under relatively mile conditions.



A more complete picture of the reduction was obtained by a comparison of the reduction of 5-hydroxyindoles with a free and with a methylated hydroxy group. It turned out that 5-methoxytryptamine is not reduced to the corresponding indoline under the standard reaction conditions. The role of a free OH group in the reduction of the hydroxyindole becomes clear if one compares the structure of the semiquinoneimine free radical (VIII):



VII VIII

The close structural similarity of the radicals indicates the possibility of the occurrence of redox reactions of the same type in a number of 5-hydroxyindoles and p-aminophenols. An examination of the reduction of 5-hydroxyindoles from this point of view makes it possible to assume that the presence of a free OH group in the structure of these compounds and protonation of the indole ring jointly ensure the relatively high stability of the intermediate product of the reduction of indole–radical VII; as a result of this, rapid reduction via a one-electron mechanism becomes possible. At the same time, as indicated above, protonation should lead to dearomatization of the pyrrole system, which in turn may facilitate the hydrogenation.

We observed that the ease of hydrogenation of 3-substituted 5-hydroxyindoles correlates with the unusual ease of the reverse oxidation of 5-hydroxyindolines to the corresponding indoles. In aqueous solutions (pH 10), 5-hydroxyindolines IV-VI are rapidly oxidized by air oxygen and are readily converted to the starting 5-hydroxyindoles (I-III), as confirmed by the UV spectra (Fig. 1) and by paper chromatography of the reaction mixture. The oxidation of 2,3-dihydro-5-hydroxytryptamine gave a good yield of 5-hydroxytryptamine as the picrate.

The observed ease of oxidation by air oxygen of 5-hydroxyindolines serves as an additional confirmation of the similarity in the reactivities of 5-hydroxyindoles and p-aminophenols.

EXPERIMENTAL

The UV spectra of 5% hydrochloric acid solutions were obtained with an SF-4A spectrometer. The pH of the solutions was measured with an LPU-01 pH meter. The chromatographic behavior of the compounds on paper (Table 1) was studied on Leningrad "B" chromatographic paper by the descending method.

2,3-Dihydro-5-hydroxytryptamine (IV). Dihydrochloride. A total of 10 g of 5% palladium on carbon was added to a solution of 5 g (23.5 mmole) of I in 200 ml of 5% hydrochloric acid, the air was thoroughly removed, and the compound was hydrogenated at atomospheric pressure and room temperature until hydrogen absorption had ceased. The hydrogenation time was 5 h, and 530 ml (23.6 mmole) of hydrogen was

absorbed. The catalyst was removed by filtration, and the aqueous solution was concentrated in vacuo to a small volume. Cooling of the solution precipitated 5.31 g (95%) of crystals of the dihydrochloride with mp 262-263 deg (from 10% hydrochloric acid). UV spectrum: λ_{max} 275 nm (log ε 3.69). The dihydrochloride was soluble in water, slightly soluble in alcohol, and insoluble in benzene and chloroform. Found: C 47.8; H 6.4; N 11.0; Cl 28.0%. $C_{10}H_{14}N_2O \cdot 2HCl$. Calculated: C 47.8; H 6.4; N 11.1; Cl 28.2%. In the region of the absorption of aromatic protons, the PMR spectrum of IV contains a broad singlet at 6.93 ppm, which can be ascribed to the H_1 proton, which has a weak spin-spin interaction with the H_2 and H_3 protons; a group of signals that form an AB system (J 9 Hz) and is related to the H_2 protons ($\delta \sim 6.8$ ppm) is partially overlapped by the signals of the H_1 and H_3 protons (~7.3 ppm); the fine structure is caused by the interaction of each of these protons with the H_1 proton. The dipicrate was obtained as follows. An aqueous solution of picric acid was added dropwise to a solution of 500 mg (1.98 mmole) of the dihydrochloride of IV in 25 ml of water. (The latter solution had been passed through a 10 by 60 mm column filled with the OH^- form of AB-17 anion-exchange resin.) Large, needle-shaped, light-yellow crystals of the dipicrate with mp 196 deg (from water) precipitated. Found: C 41.1; H 3.2; N 17.5%. $C_{10}H_{14}N_2O \cdot 2C_6H_3N_3O_7$. Calculated: C 41.5; H 3.2; N 17.6%.

5-Hydroxy-N,N-dimethyltryptamine Methiodide (Bufotenidine) (II). A solution of 1 g of sodium hydroxide in 20 ml of anhydrous methanol was added to a solution of 4 g (18.8 mmole) of the hydrochloride of I in 50 ml of anhydrous methanol. The solution was filtered, 20 g of methyliodine was added to the filtrate, and the mixture was allowed to stand at room temperature in the dark. After 48 h, the solution was concentrated in vacuo to 10 ml and cooled to 5 deg. to give 2 g (24%) of crystals with mp 217 deg (from anhydrous alcohol). The picrate had mp 197-198 deg. The analytical data and physicochemical properties of the product indicated that it was identical to 5-hydroxy-N,N-dimethyltryptamine methiodide [5].

2,3-Dihydro-5-hydroxy-N,N-dimethyltryptamine Methylchloride (V). A solution of 1 g (2.8 mmole) of the methiodide of II in 50 ml of water was passed through a 10 by 150 mm column filled with the OH^- form of AB-17 anion-exchange resin, collected in a flask containing 50 ml of 10% hydrochloric acid, and hydrogenated on a palladium catalyst by the method described above. The catalyst was removed by filtration, and the reaction solution was passed through a layer of aluminum oxide (the layer height was ~2 cm). The aluminum oxide was washed three to four times with 50 ml of 5% hydrochloric acid, the washings were concentrated in vacuo, and anhydrous alcohol and several drops of solution of HCl in anhydrous alcohol were added. The mixture was evaporated to dryness in vacuo to give 0.80 g (96%) of an amorphous, hygroscopic substance. Found: C 50.0; H 7.8; N 8.5; Cl 22.8%. $C_{13}H_{21}ClN_2O \cdot HCl \cdot H_2O$. Calculated: C 50.2; H 7.8; N 9.0; Cl 22.8%. UV spectrum: λ_{max} 270 nm (log ε 3.31).

Oxidation of 2,3-Dihydro-5-hydroxytryptamine (IV) to 5-Hydroxytryptamine (I). A solution of 1 g (4.0 mmole) of the dihydrochloride of IV in 30 ml of water was passed through a 10 by 150 ml column filled with the OH^- form of AB-17 anion-exchange resin and allowed to stand in an open flask at 5 deg (the pH of the solution was 10.0). The solution darkened after 24 h, and a small amount of precipitate formed and was separated by filtration. Only one spot with R_f 0.4 was detected by chromatography of the reaction solution on paper. Serotonin with R_f 0.4 was used as the reference spot. An alcohol solution of picric acid was added to the filtrate to give 1.5 g of a crystalline precipitate with mp 209-210 deg (dec., from water). This picrate did not depress the melting point of the picrate of 5-hydroxytryptamine.

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