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A NEW ROUTE FOR THE SYNTHESIS OF ISOMERIC BENZO[*b*]FUROINDOLES

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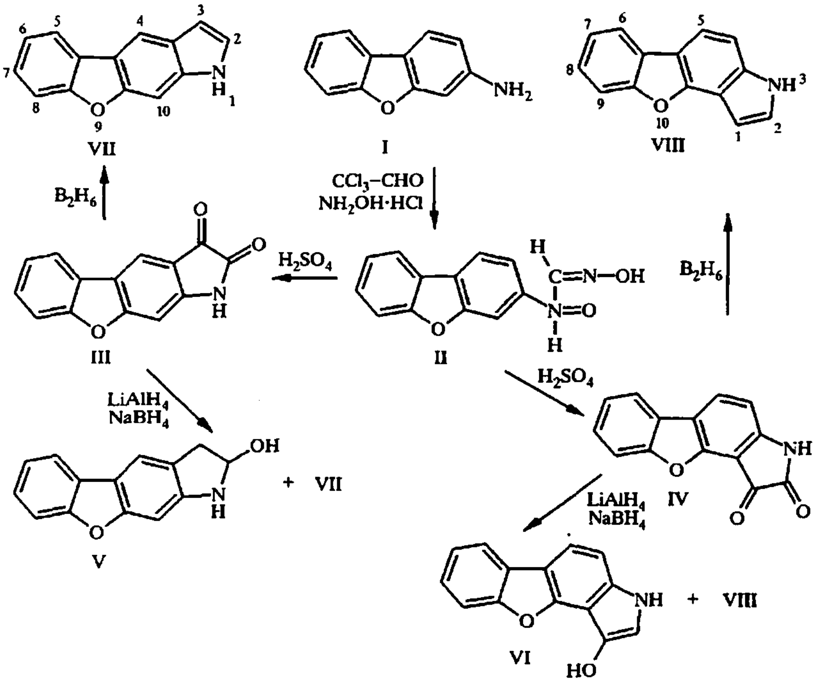
A new synthesis of 1H-benzo[b]furo[3,2-f]- and 1H-benzo[b]furo[2,3-e]indoles was described. The corresponding ring-fused isatins, synthesized by the Sandmeyer reaction, were utilized as initial compounds. The reduction of the last to the unsubstituted benzo[b]furoindoles depends both on the nature of the substituent, and on the reaction conditions.

With the purpose of seeking new routes for the synthesis of tetracyclic condensed systems – isomeric benzo[*b*]furoindoles, which we obtained by the classical reaction of E. Fischer [1], a preparative method for the synthesis of the indicated heterocyclic systems was developed according to the following scheme:



Cyclization of the isonitrosoacetamidodibenzofuran (II), synthesized by the reaction of 3-aminodibenzofuran (I) with chloral hydrate and hydroxylamine hydrochloride under conditions of the Sandmeyer reaction [2, 3], led to the mixture of the corresponding isomeric ring-fused isatins III and IV. Sulfuric acid was utilized as the cyclizing agent.

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TABLE 1. Chemical Shifts (δ, ppm) and SSCCs (*J*, Hz) in the PMR Spectra of Isomeric [3,2-*f*]- and [2,3-*e*]-Ring-Fused Benzo[*b*]furoindoles and their Derivatives

Compound	Solvent	δ, ppm										*J*, Hz
		NH	2-H	3-H/1-H	10-H	8-H/9-H	7-H/8-H	6-H/7-H	5-H/6-H	4-H/5-H	4-H	
III	DMSO-d$_6$	11.22	—	—	7.11	7.66	7.49	7.40	8.12	8.37	—	$J_{4,10} = 0.8$; $J_{6,7} = 7.7$; $J_{7,8} = 8.1$; $J_{5,6} = 7.3$
IV	DMSO-d$_6$	11.65	—	—	—	7.72	7.66	7.48	8.19	8.33	6.93	$J_{4,5} = 8.1$; $J_{7,8} = 7.3$; $J_{6,7} = 7.2$; $J_{8,9} = 8.3$
V	Acetone-d$_6$	10.21	~7.22	8.13*	7.76	7.64	7.34	7.22	8.17	8.36	—	$J_{4,10} = 0.9$; $J_{6,7} = 7.4$; $J_{5,6} \approx J_{7,8} = 7.5$
VI	Acetone-d$_6$	10.15	~7.15	8.19*	—	7.68	7.38	7.41	8.20	8.31	7.04	$J_{4,5} = 8.4$; $J_{6,7} = 7.5$; $J_{7,8} = 7.3$; $J_{8,9} = 8.0$
VII	Acetone-d$_6$	10.30	~7.36	6.59	7.64	7.50	7.34	7.40	8.09	8.24	—	$J_{1,2} = 2.2$; $J_{1,3} = 2.0$; $J_{2,3} = 3.1$
VIII	DMSO-d$_6$	11.40	~7.40	6.73	—	7.63	—	7.39	7.92	8.04	7.34	$J_{3,10} \approx J_{4,10} = 0.8$; $J_{1,3} \approx J_{2,3} = 2.2$; $J_{1,2} = 3.3$; $J_{1,4} = 0.4$; $J_{4,5} = 8.7$

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* The proton of the hydroxyl group.

The separation of the isomers was accomplished by the sequential treatment of the alkaline solution of the mixture of the compounds III and IV with acetic acid to the pH 3 and, after removal of the precipitated crystals, the treatment of the filtrate with conc. HCl to the pH 1. Compound III (25%) is precipitated in the first case, and compound IV (60%) is precipitated in the second case.

In the process of studying the properties of the heterocyclic systems indicated, it was established that the compounds III and IV can be converted to the corresponding benzo[*b*]furoindoles VII and VIII, whereby the yield of the last depends both on the nature of the reducing agent, and on the reaction conditions. Thus, the reduction of the isatins III and IV by lithium aluminum hydride in abs. pyridine or sodium borohydride in propan-2-ol results in the mixture consisting of the corresponding hydroxybenzo[*b*]furoindoles V and VI, an insignificant amount of the unsubstituted benzo[*b*]furoindoles VII and VIII, and the unreacted initial compounds III and IV. The utilization of diborane in tetrahydrofuran as the reducing agent leads to the isolation of the corresponding unsubstituted 1H-benzo[*b*]furo[3,2-*f*]- and 1H-benzo[*b*]furo[2,3-*e*]indoles, VII and VIII respectively, with acceptable yields.

The proposed method reduces, by far, the number of stages in the synthesis of the indicated heterocyclic systems VII and VIII by comparison with their preparation by the reaction of E. Fischer. Moreover, just as important is that the reduction process leads to the isolation and characterization of the corresponding 3- and 1-hydroxy derivatives V and VI, undescribed in the literature, which present significant interest from a pharmacological viewpoint [4].

The IR spectrum of compound II contains the absorption band of the carbonyl group at 1670 cm^{-1}. The absorption band at 3250 cm^{-1} indicates the presence of the NH group in the compound indicated. The absorption bands of the C=O group in the compounds III and IV (1700 cm^{-1} and 1720 cm^{-1} correspondingly) are close to the corresponding band in isatin. Regrettably, there was no success in taking the UV spectra of the compounds III and IV due to their poor solubility in ethanol.

The assignment of the PMR spectral signals (Table 1) of the compounds III and IV was made on the basis of differences in the multiplicity of signals for the indole part of the molecules – the two signals of the weakly interacting *p*-protons in the case of the linear molecule III, or the spectrum of the AB system with the spin–spin coupling constant characteristic of *o*-protons in the case of the angular ring connection in compound IV.

The mass spectra of the isomeric ring-fused isatins III and IV have the intense peak of the molecular ion $[M^+]$ with the *m/z* 237, and the character of the further fragmentation, confirmed by metastable transitions, does not contradict the proposed structures.

The IR spectra of the compounds V and VI reveal the absorption band at 3460-3500 cm^{-1} and 3490-3510 cm^{-1} correspondingly, characteristic of the hydroxyl group, and the UV spectrum recalls the spectrum of indole. The PMR spectrum of the compounds V and VI shows the narrow singlet of the the hydroxyl group proton at 8.1 ppm and 8.2 ppm correspondingly.

The IR spectra of the compounds VII and VIII have absorption bands of the NH group at 3410 cm^{-1} and 3380 cm^{-1} respectively. The UV spectra of the compounds VII and VIII are analogous to the spectra of the compounds which we synthesized previously by the reaction of E. Fischer.

The tests of mixed melting for the compounds VII and VIII with analogous compounds, synthesized [1] by the E. Fischer reaction, do not give a depression.

EXPERIMENTAL

The UV absorption spectra were measured in ethanol on the Specord UV-vis instrument; measurements were performed in cuvettes with a 1 cm thickness layer. The IR spectra were taken on the UR-20 spectrophotometer in mineral oil. The PMR spectra were recorded in deuterated solvents using the Varian CFT-20 spectrometer having the working frequency of 80 MHz; chemical shifts were measured in relation to tetramethylsilane as the internal standard, with the accuracy of 0.01 ppm. The SSCCs had the accuracy of 0.1 Hz. The mass spectrum was taken on the MX-1303 instrument with the direct input of the sample at the ion source; the emission current of the cathode was 1.5 μA, and the ionizing voltage was 50 eV.

3-Isonitrosoacetamidodibenzofuran (II). Crystalline sodium sulfate $Na_2SO_4 \cdot 10H_2O$ (260 g, 0.8 mol), 3-aminodibenzofuran (I) (18.3 g, 0.1 mol) dissolved in 3 liters of water with the addition of conc. HCl (20 ml) and hydroxylamine hydrochloride (22.3 g, 0.32 mol) dissolved in water (100 ml) were added sequentially to the solution of chloral hydrate (16.5 g, 0.1 mol) in water (240 ml). The mixture was heated rapidly to boiling, and boiled with constant stirring for 2 h, after which the reaction mass was cooled with water. The precipitated crystals of compound II were filtered, thoroughly washed with water, and dried. Yield 22.8 g (90%); mp 210-212°C. IR spectrum: 3250 (NH), 1670 cm^{-1} (C=O). UV spectrum, λ_{max} (log ε): 240 (4.45), 275 (4.15), 290 (4.25), 340 (4.00), 345 nm (3.90). Found, %: C 66.0; H 4.0; N 11.1. $C_{14}H_{10}N_2O_3$. Calculated, %: C 66.1; H 3.9; N 11.1.

2,3-Dioxo-2,3-dihydrobenzo[*b*]furo[3,2-*f*]indole (III) and 1,2-Dioxo-1,2-dihydrobenzo[*b*]furo[2,3-*e*]-indole (IV). Dry 3-isonitrosoacetamidodibenzofuran (II) (25.2 g, 0.1 mol) was added with constant stirring in small portions to 75% sulfuric acid (29.4 g, 0.3 mol) at 50°C (temperature not exceeding 80°C). The reaction mixture was heated for an additional 1 h at 80°C and then cooled slowly and poured onto the tenfold to twelvefold amount of ice. After 1 h, the residue was filtered off and washed with water. The crude product was suspended in the fivefold amount of hot water prior to the addition, with stirring, of the 40% solution of NaOH until complete solution is effected, and 12 % hydrochloric acid is added carefully until the onset of residue formation. The residue was filtered off and discarded. Acetic acid was added with care to the filtrate until the pH 3, and the mixture was left for 0.5 h. The precipitated residue was filtered off again, thoroughly washed with water, and dried. The compound III was obtained. Yield 5.9 g (25%); mp 290-291°C. IR spectrum: 3400 (NH), 3240 (NH···O=C), 1710 cm^{-1} (C=O). Found, %: C 71.0, H 2.8, N 6.1. $C_{14}H_7NO_3$. Calculated, %: C 70.8, H 2.8, N 5.9.

The filtrate remaining after the separation of the substance III was acidified with conc. HCl until the pH 1, and was left for 1 h. The precipitated crystals were filtered off, washed thoroughly with water until a neutral reaction, and dried. The substance IV was obtained. Yield 14.2 g (60%); mp 310-315°C. IR spectrum: 3410 (NH), 3260 (NH···O=C), 1720 cm^{-1} (C=O). Found, %: C 71.1; H 3.1; N 6.0. $C_{14}H_7NO_3$. Calculated, %: C 70.8; H 2.8; N 5.9.

3-Hydroxy-1H-benzo[*b*]furo[3,2-*f*]indole (V) and 1-Hydroxy-1H-benzo[*b*]furo[2,3-*e*]indole (VI). A. Lithium aluminum hydride (2.4 g, 0.09 mol) was mixed, with cooling, with 240 ml of abs. pyridine. The dried compound III (4.8 g, 0.02 mol) was added with stirring in portions so that the temperature of the reaction mixture do not exceed 25°C. After 8 h of stirring, 20 ml of water were added dropwise followed by 240 g of tartaric acid dissolved in 960 ml of water. The product was extracted with ether, washed with a diluted solution of tartaric acid and again with water, and dried over Na_2SO_4. The solvent was distilled off. The gradually crystallized substance V (2.9 g) was obtained. The product was purified on a silica gel column. Yield 35%; mp 210-211°C. IR spectrum: 3290 (NH), 3480-3500 cm^{-1} (OH). UV spectrum, λ_{max} (log ε): 240 (4.55), 270 (4.90), 290 (4.75), 300 nm (4.30). Found, %: C 75.4; H 4.2; N 6.2. $C_{14}H_9NO_2$. Calculated, %: C 75.3; H 4.0; N 6.3.

1-Hydroxy-1H-benzo[*b*]furo[2,3-*e*]indole (VI). This compound was obtained analogously from the ring-fused isatin IV. Yield 40%; mp 184-185°C. IR spectrum: 3300 (NH), 3490-3510 cm^{-1} (OH). UV spectrum, λ_{max} (log ε): 240 (4.50), 265 (4.95), 325 nm (4.10). Found, %: C 75.1; H 4.2; N 6.2. $C_{14}H_9NO_2$. Calculated, %: C 75.3; H 4.0; N 6.3.

B. The compound III (0.1 mol) was added with stirring to the solution of sodium borohydride (0.04 mol) in propan-2-ol (50 ml) at 20°C. The mixture was heated to 50°C for 3 h, and left overnight at 20°C. Then dilute hydrochloric acid was added carefully until the release of hydrogen ceases. The product was extracted from the resulting solution with small portions of ether. The extracts were washed thoroughly with water and dried over Na_2SO_4. The solvent was distilled off. The product V was purified on a silica gel column. The yield is 37%.

Compound VI was obtained analogously from the ring-fused isatin IV. The yield is 35%.

Mixed tests of the compounds V and VI, obtained by the methods A and B, do not give a depression of the melting temperature.

1H-Benzo[*b*]furo[3,2-*f*]indole (VII). A solution of diborane (1.7 g, 0.06 mol) (obtained *in situ* from sodium borohydride and boron trifluoride etherate) was added dropwise with stirring to a solution of the compound III (2.4 g, 0.06 mol) in abs. tetrahydrofuran (2.5 ml) at -78°, and the mixture was held for 30 h at 0°C. The reaction mixture was poured into 1.5 liters of water prior to weak acidification, and the reaction product was extracted with ether. The extract was washed with water and dried over Na_2SO_4. After the distillation of the solvent, the product was purified on a silica gel column. Compound VII was obtained. Yield 1.2 g (60%); mp 160-161°C. IR spectrum: 3410 cm^{-1} (NH). UV spectrum, λ_{max} (log ε): 208 (4.51), 245 (4.80), 252 (4.81), 270 (4.21), 295 (4.18), 312 (4.50), 310 nm (4.40). Found, %: C 81.4; H 4.5; N 7.2. $C_{14}H_9NO$. Calculated, %: C 81.1; H 4.3; N 6.8.

1H-Benzo[*b*]furo[2,3-*e*]indole (VIII). This compound was obtained by analogy with the preceding description for compound IV. Yield 70%; mp 144-145°C. IR spectrum: 3380 cm^{-1} (NH). UV spectrum, λ_{max} (log ε): 255 (5.13), 297 (4.45), 310 (4.45), 325 nm (4.25). Found, %: C 81.0; H 4.6; N 6.5. $C_{14}H_9NO$. Calculated, %: C 81.1; H 4.3; N 6.8.

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