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INTERACTION OF SPIRO-HETEROCYCLIC OXINDOLE SYSTEM WITH SODIUM DIFORMYLIMIDE

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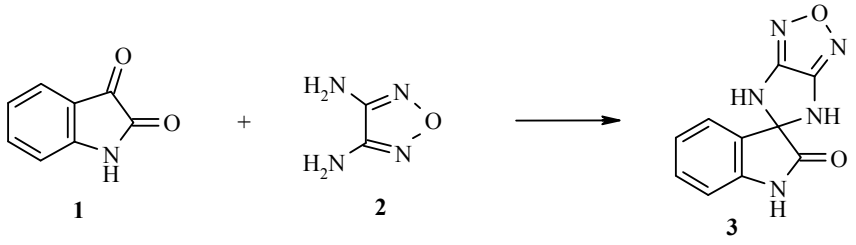
New functionalized condensed benzazoles have been synthesized based on isatin, 3,4-diaminofurazane, and sodium diformylimide.

Keywords: diaminofurazane, isatin, sodium diformylimide.

Many dyes, plant growth stimulators, analytical reagents, and medical preparations have been obtained based on isatin [1-3]. The furazane ring is found in energy-rich materials, intermediates in organic synthesis, and biologically active compounds [4, 5].

With the objective of finding new biologically active compounds based on isatin **1** and 3,4-diaminofurazane **2** as nucleophilic reagent we have synthesized heterocycles containing indole and furazane rings at the same time. The interaction of compounds **1** and **2** was carried out by boiling in acetonitrile. The reaction did not occur at room temperature which is probably connected with the low nucleophilicity of the amino groups in 3,4-diaminofurazane.



1 **2** **3**

The course of the reaction was monitored by the disappearance in the IR spectrum of the C=O vibration in position 3 of isatin and by TLC. The reaction mixture became darker during the course of the reaction. Analytically pure compound **3** was obtained by column chromatography with subsequent recrystallization from absolute ethanol. The spiro compound **3** was isolated in 77% yield.

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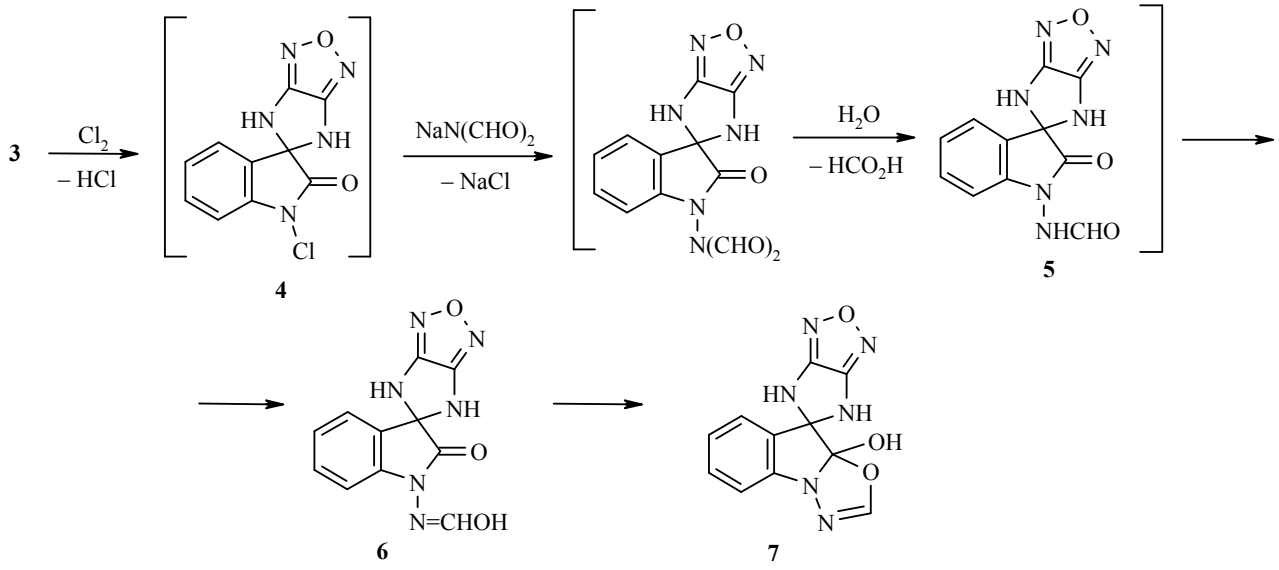
The IR spectrum of compound **3** contains absorption bands in the region of 3100 (the NH group of furazane), 3260 (the NH amide group), and 1630 cm^{-1} (2-C=O). The ^1H NMR spectrum, apart from the signals of the aromatic protons, is characterized by broad singlets at 9.00 and 10.50 ppm, with a 2:1 ratio of integrated intensities, corresponding to the protons of the furazane and indole NH groups.

Analysis of the literature data [6-8] showed that reactions of carbonyl derivatives having a mobile hydrogen or halogen atom in the α-position relative to a carbonyl group, may with a nucleophilic anion, lead to compounds initially formed by substitution of the hydrogen or halogen atom. Moreover, it is possible to form substances formed from adducts from the first addition of anion of the nucleophile to the carbonyl group of the initial substrate.

We chose sodium diformylimide, $NaN(CHO)_2$, the anion of which exists in several resonance forms, as the anionic nucleophile.

The intermediate compound **4**, obtained by chlorination of the spiro heterocycle **3**, reacts with $NaN(CHO)_2$ in dioxane. The interaction is accompanied by darkening of the reaction mixture. After evaporating the dioxane, the residue was treated with water, extracted with chloroform and separated compound **6** in the form of the oil, formed in all probability from the intermediate **5**.

Bands in the region 3210-3260 cm^{-1}, characteristic of the NH unit of the indole ring, are absent from the IR spectrum of compound **6**. Absorptions of the C=N and OH groups appear in the range 1650 and 3330, and for 2-C=O at 1620 cm^{-1}. In the ^1H NMR spectrum the singlet signal of the azomethine proton appears at 8.00 and the proton of the OH group as broad singlet at 9.20 ppm.



There are two reactive centers in compound **6**: nucleophilic – the hydroxyl groups bonded to the methine carbon, and electrophilic – the C=O carbonyl group in position 2 of the isatin unit. The relative position of these two groups permits their cyclization *via* an intramolecular nucleophilic interaction.

Cyclization of compound **6** into the heterocycle **7** was carried out in boiling toluene with the addition of a catalytic amount of triethylamine. The structure of compound **7** was established by matrix-activated laser desorption/ionization (MALDI). A maximal peak at *m/z* 273, corresponding to the ion $[M+H]^+$ was observed in the MALDI mass spectrum. The following facts confirm the formation of the heterocycle **7**: The disappearance in the IR spectrum of the absorption bands for the carbonyl group at 1620 and the hydroxyl group at 3330 cm^{-1}; The appearance of new absorption bands at 1150 (CH-O) and 3420 cm^{-1} (OH group, formed as a result of the nucleophilic attack of the oxygen atom at the electrophilic carbon of the keto group). It should be noted that the

appearance of the hydroxyl group at 3420 cm^{-1} is associated with the formation of an intramolecular hydrogen bond in the molecule of compound **7** between the hydrogen atom of the NH group and an unshared pair of electrons of the oxygen atom of the hydroxyl group. As a result of the formation of the hydrogen bond, one of the NH groups of the furazane unit appears at 3150 and the other at 3100 cm^{-1}. The heterocyclization is confirmed by the data of the ^1H NMR spectrum. The hydroxyl group is recorded as a normal singlet at 5.20 in contrast to the broad singlet (9.20 ppm) for compound **6**. The signal of the azomethine proton is shifted to weak field and appears at 8.25 ppm. While in compound **6** the protons of the NH group appear as a broad singlet at 9.70 ppm, in the heterocycle **7** two signals of these groups are observed: in the region of 9.80 ppm (the free NH group) and at 10.5 ppm (the NH group forming the intramolecular hydrogen bond). The latter signal is the broader.

EXPERIMENTAL

IR spectra of KBr disks or nujol mulls were recorded with a UR-20 spectrometer. TLC (Silufol plates, solvent 1:3 benzene–ethanol, developer: a mixture of 2 g $KMnO_4$ + 3 ml H_2SO_4 + 97 ml H_2O). ^1H NMR spectra of acetone-d_6 solutions with HMDS (δ 0.05 ppm) as internal standard were recorded with a Tesla BW-567 (200 MHz) instrument MALDI mass spectra were recorded on a time-of-flight Bruker (Germany) ULTRAFLEX mass-spectrometer. A UV laser with a wavelength of 337 nm was used for laser desorption. Dihydroxybenzoic acid served as the matrix. Samples were treated by the "dried drop" method: a mixture of a solution of the matrix in acetone (1% by mass) and a solution of the analyzed substance in acetone (0.1% by mass) were placed on the carrier and dried at 30°C.

4,6-Dihydrospiro(imidazo[4,5-*c*][1,2,5]oxadiazol-5,3'-indol)-2'(1'H)-one (3). A mixture of isatin (2.94 g, 0.02 mol) and 3,4-diaminofurazane (2 g, 0.02 mol) in acetonitrile (40 mol) was boiled for 3 h. The reaction mixture became dark. The solvent was evaporated in vacuum. $CHCl_3$ (60 ml) was added to the residue and the solution was passed through an Al_2O_3 column, the solvent was evaporated, and the finely dispersed residue was recrystallized from ethanol. Yield 3.93 g (77%); mp 233-235°C. IR spectrum, ν, cm^{-1}: 1630 (C=O), 3100 (NH), 3260 (NH amide). ^1H NMR spectrum, δ, ppm: 6.80 (2H, m, C_6H_4); 7.28 (2H, m, C_6H_4); 9.00 (2H, br. s, NH furazane); 10.50 (1H, br. s, indole). Found, %: N 30.89. $C_{10}H_7N_5O_2$. Calculated, %: N 30.57.

(2'-Oxo-4,6-dihydrospiro(imidazo[4,5-*c*][1,2,5]oxadiazol-5,3'-indol)-1'(2'H)-yl)imidoformic Acid (6). Dry chlorine was passed through a suspension of compound **3** (4.58 g, 0.02 mol) in CCl_4 (50 ml) for 20 min and the mixture was stirred for 2 h at room temperature. The solvent was removed in vacuum and a suspension of $NaN(CHO)_2$ (1.90 g, 0.02 mol) in dioxane (60 ml) was added to the residue and the mixture was boiled for 6 h. The solvent was removed in vacuum, the residue was dissolved in $CHCl_3$ (30 ml), water (5-7 ml) was added dropwise, the mixture was extracted three times with $CHCl_3$, the solution was dried over $MgSO_4$, and the solvent was evaporated. Compound **6** was obtained as a brown oil. Yield 3.70 g (68%). IR spectrum, ν, cm^{-1}: 1620 (C=O), 1650 (C=N), 3100 (NH), 3330 (OH). ^1H NMR spectrum, δ, ppm (*J*, Hz): 6.87 (2H, m, C_6H_4); 7.45 (2H, m, C_6H_4); 8.00 (1H, s, CH=N); 9.20 (1H, br. s, OH); 9.70 (2H, br. s, NH). Found, %: N 30.5. $C_{11}H_8N_6O_3$. Calculated, %: N 30.88.

4,6-Dihydrospiro(imidazo[4,5-*c*][1.2.5]oxadiazol-5,9'-[1,3,4]oxadiazolo[3,2-*a*]indol)-9a'-ol (7). Toluene (20 ml) and triethylamine (0.5 ml) were added to compound **6** (2.72 g, 0.01 mol) and the mixture was boiled for 3 h. The solvent was evaporated in vacuum. A mixture of 1:2:1 hexane–ether–ethanol (30 ml) was added to the residue and the mixture was kept in a refrigerator for 1 day. The orange crystals were filtered off, washed with ether, and dried. Yield of compound **7** 1.93 g (71%); mp 247-249°C. IR spectrum, ν, cm^{-1}: 1150 (C–OH), 1670 (C=N), 3100 (NH), 3150 (NH), 3420 (OH). ^1H NMR spectrum, δ, ppm: 5.20 (1H, s, OH); 6.90 (2H, m, C_6H_4); 7.20 (2H, m, C_6H_4); 8.20 (1H, s, CH=N); 9.80 (1H, br. s, NH); 10.50 (1H, br. s, NH). Mass spectrum, *m/z* (I_{rel}, %): 273 $[M+H]^+$ (100). Found, %: N 31.14. $C_{11}H_8N_6O_3$. Calculated, %: N 30.88.

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