

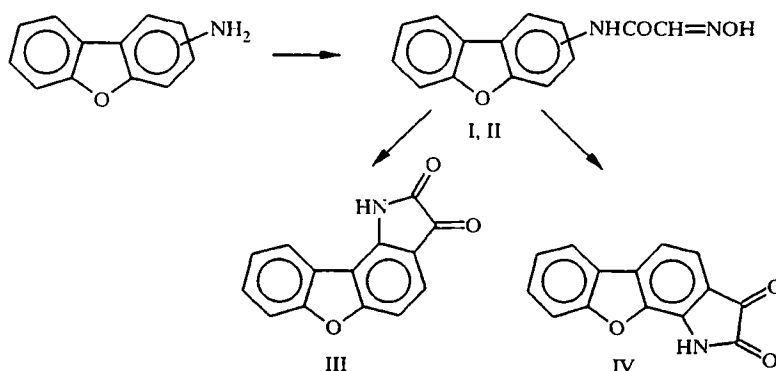
DIOXODIHYDROBENZO[b]FUROINDOLES

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The synthesis and some properties of the isomeric 2,3-dioxo-2,3-dihydro-1H-benzo[b]furo[2,3-g]- and 2,3-dioxo-2,3-dihydro-1H-benzo[b]furo[3,2-g]indoles are described.

For many years isatin has been the most studied derivative of indole. A multitude of dyes, pesticides, plant growth stimulators, analytical reagents, etc., have been made based on this compound. Isatin may be successfully used as the starting material for the synthesis of drugs with a wide range of physiological effects [1, 4].

In a continuation of studies of the synthesis of tetracyclic condensed systems including a pyrrole ring we have developed a preparative method for the production of the isomeric 2,3-dioxo-2,3-dihydro-1H-benzo[b]furo[2,3-g]- (III) and 2,3-dioxo-2,3-dihydro-1H-benzo[b]furo[3,2-g]indoles (IV) from benzofuran derivatives I and II.



1- and 4-aminodibenzofurans [5, 6] were used as starting materials. Reaction of the amines with chloral hydrate and hydroxylamine hydrochloride in acid medium gave the corresponding isonitrosoacetamidodibenzofurans I and II, cyclization of which in sulfuric acid gave the desired systems III and IV.

During a study of these heterocycles it was established that compounds III and IV can be successfully converted by reduction into the corresponding benzo[b]furoindoles V and VI, the yield depending on the choice of reducing agent. For example with lithium tetrahydroaluminate in anhydrous pyridine mixtures are formed which consist of the corresponding 3-hydroxybenzo[b]furoindoles VII and VIII (40 and 45 %), small amounts of the unsubstituted compounds V and VI (5 and 10%), and the unreacted starting materials III and IV. Use of diborane in tetrahydrofuran at -78°C gave the corresponding benzo[b]furoindoles V and VI in quantitative yields.

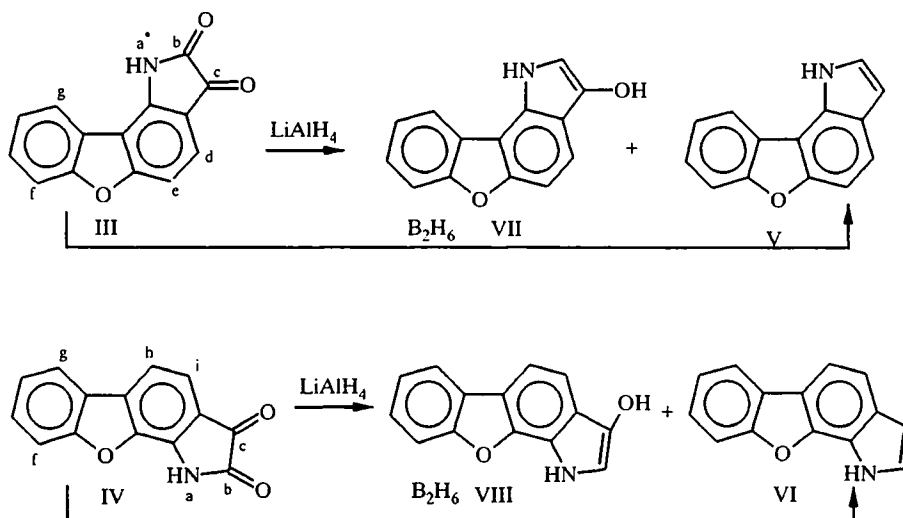
The method we have developed permits to reduce the number of steps in the synthesis of heterocycles V and VI in comparison with the Fischer method [7], and, no less important, it permits the isolation and characterization during the reduction process of the corresponding hydroxy derivatives VII and VIII, which have not been reported previously, and which are of considerable interest from the pharmacological point of view [8].

TABLE 1. Chemical Shifts (δ , ppm) and Coupling Constants for Compounds III-VIII

| Compound | Solvent | δ , ppm | | | | |
|----------|----------------|----------------|----------|----------|----------|----------|
| | | <i>a</i> | <i>b</i> | <i>c</i> | <i>d</i> | <i>e</i> |
| III | Acetone- d_6 | 9,9 | — | — | 8,0 | 8,2 |
| IV | Acetone- d_6 | 10,1 | — | — | — | — |
| V | Acetone- d_6 | 10,2 | ~7,2 | 8,3* | 7,5 | 8,3 |
| VI | Acetone- d_6 | 10,0 | 7,1 | 8,2* | — | — |
| VII | DMSO- d_6 | 11,5 | ~7,4 | ~7,0 | 7,5 | 7,7 |
| VIII | DMSO- d_6 | 11,7 | ~7,4 | 6,6 | — | — |

| Compound | Solvent | δ , ppm | | | | <i>J</i> , Hz |
|----------|----------------|----------------|----------|----------|----------|---------------------------------|
| | | <i>f</i> | <i>g</i> | <i>h</i> | <i>i</i> | |
| III | Acetone- d_6 | 7,9 | 8,3 | — | — | $J_{de} = 8,8$ |
| IV | Acetone- d_6 | 8,0 | 8,4 | 8,4 | 8,1 | $J_{hi} = 8,9$ |
| V | Acetone- d_6 | 8,0 | 8,2 | — | — | $J_{de} = 8,6$ |
| VI | Acetone- d_6 | 7,9 | 8,1 | 8,4 | 7,1 | $J_{hi} = 8,6$ |
| VII | DMSO- d_6 | 8,0 | 8,8 | — | — | $J_{ab} = 2,0$; $J_{ac} = 1,7$ |
| VIII | DMSO- d_6 | ~7,7 | 8,0 | 7,6 | 7,5 | $J_{bc} = 2,9$; $J_{de} = 8,1$ |
| | | | | | | $J_{ac} = 1,5$; $J_{bc} = 2,3$ |
| | | | | | | $J_{hi} = 8,8$ |

* Proton of the hydroxyl group.



Letters used for proton positions to permit comparison of the chemical shifts in the ^1H NMR spectra of these compounds.

Carbonyl absorption bands are observed in the IR spectra of compounds I and II at 1680 and 1670 cm^{-1} respectively. The presence of the NH group in these compounds is indicated by absorptions at 3240 and 3265 cm^{-1} respectively. The C=O absorption bands in compounds III and IV (1720 and 1730 cm^{-1}) are close to the corresponding band in isatin.

The UV spectra of compounds III and IV are similar to that of isatin: only small bathochromic shifts of the long wavelength maxima were observed.

The ^1H NMR spectra of compounds III and IV indicate the angular structure. In each case an AB system is present with spin-spin coupling constants characteristic of the *ortho* position ($J = 8.8$ and 8.9 Hz respectively).

Intense molecular ion peaks, $[M^+]$ 237, appear in the mass spectra of compounds III and IV, and the characteristics of further fragmentations, confirmed by metastable transitions, do not disagree with the suggested structures.

Absorption bands characteristic of the hydroxyl group were observed at 3470-3510 and 3490-3520 cm^{-1} in the IR spectra of compounds VII and VIII while their UV spectra resembled that of indole. Sharp singlets for the hydroxyl proton at 8.3 and 8.2 ppm were observed in the ^1H NMR spectra of these compounds.

EXPERIMENTAL

The course of reactions and the purity of products were monitored by TLC on Silufol UV-253, UV spectra of ethanol solutions were recorded with a Specord spectrophotometer, IR spectra in Nujol mulls on a UR-20 with NaCl and LiF prisms with a scanning rate of 160 and a spectral width of 4 cm^{-1} . Mass spectra were recorded with an MX-1303 instrument with direct insertion of the sample into the ionization chamber, a cathode emission current of 1.5 μA , and an ionizing voltage of 50 eV. ^1H NMR spectra were recorded with a Bruker WP-200-SY (200 MHz) spectrometer. Chemical shifts were measured on the δ scale relative to tetramethylsilane as internal standard with a precision of 0.05 ppm and coupling constants with a precision of 0.1 Hz.

1-Isonitrosoacetamidodibenzofuran (I). Crystalline sodium sulfate, $\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O}$ (260 g, 0.8 mol), 1-aminodibenzofuran (18.3 g, 0.1 mol) and 20 ml of conc. hydrochloric acid in 3 l water, and solution of hydroxylamine hydrochloride (22.3 g, 0.32 mol) in 100 ml water were added in turn to a solution of chloral hydrate (16.5 g, 0.1 mol) in 240 ml water in a five liter flask. The mixture was heated to boiling and kept at that temperature for 0.5 h with constant stirring. The mixture was then cooled with a stream of water. The precipitated crystals of isonitrosoacetamidodibenzofuran were filtered off, carefully washed with water and dried in vacuum. The product was purified on a silica gel column to give compound I, yield 85%; mp 176-177°C. IR Spectrum: 3240 (NH), 1680 cm^{-1} (C=O). UV Spectrum: λ_{max} (log ϵ): 245 (4.50), 295 (4.12), 336 (4.29), 342 nm (4.00). Found, %: C 66.0; H 4.0; N 11.1. $\text{C}_{14}\text{H}_{10}\text{N}_2\text{O}_3$. Calculated, %: C 66.1; H 3.9; N 11.0.

4-Isonitrosoacetamidodibenzofuran (II) was prepared analogously to compound I from 4-amino-dibenzofuran. Yield 90%; mp 182-183°C. IR Spectrum: 3265 (NH), 1670 cm^{-1} (C=O). UV Spectrum: λ_{max} (log ϵ): 210 (3.74), 235 (3.99), 265 (4.00), 320 nm (3.81). Found, %: C 65.9; H 4.1; N 11.0. $\text{C}_{14}\text{H}_{10}\text{N}_2\text{O}_3$. Calculated, %: C 66.1; H 3.9; N 11.0.

2,3-Dioxo-2,3-dihydro-1H-benzo[b]furo[2,3-g]indole (III). Dry 1-isonitrosoacetamidodibenzofuran I (25.2 g, 0.1 mol) was added in small portions with constant stirring to 75% sulfuric acid (29.4 g, 0.3 mol) in a 100 ml beaker at 50°C. The temperature should not exceed 80°C. When the addition was complete the mixture was heated for a further 1 h at 80°C, then cooled slowly and poured onto a 10-12 fold excess of ice. After 1 h the precipitate was filtered off and washed with water. The crude product was suspended in 5-fold amount of boiling water and 40% NaOH solution was added with stirring until the product had dissolved completely. Then 12% hydrochloric acid was added carefully until precipitation began. The precipitate was filtered off and discarded. The filtrate was acidified to pH 3-4 with conc. hydrochloric acid and kept for 1 h. The precipitate of compound III was filtered off, carefully washed with water, dried, and recrystallized from glacial acetic acid to give compound III, yield 80%, mp 285-286°C. IR Spectrum: 3410 (NH), 3250 (NH \cdots O=C), 1720 cm^{-1} (C=O). UV Spectrum: λ_{max} (log ϵ): 270 (4.38), 295 (3.39), 300 (3.50), 410 nm (2.70). Found, %: C 70.7; H, 2.8; N 5.8. $\text{C}_{14}\text{H}_7\text{NO}_3$. Calculated, %: C 70.8; H 2.9; N 5.9.

2,3-Dioxo-2,3-dihydro-1H-benzo[b]furo[3,2-g]indole (IV) was obtained analogously to compound III from 4-isonitrosoacetamidodibenzofuran II. Yield 80%; mp 197-198°C. IR Spectrum: 3400 (NH), 3230 (NH \cdots O=C), 1730 cm^{-1} (C=O). UV Spectrum: λ_{max} (log ϵ): 258 (4.30), 330 (3.50), 420 nm (2.90). Found, %: C 70.6; H 2.9; N 6.0. $\text{C}_{14}\text{H}_7\text{NO}_3$. Calculated %: C 70.8; H 2.9; N 5.9.

3-Hydroxybenzo[b]furo[2,3-g]indole (VII). Lithium tetrahydroaluminate (1.7 g, 0.045 mol) was mixed with anhydrous pyridine (120 ml) with cooling. Carefully dried compound III (2.4 g, 0.01 mol) was added portionwise with stirring so that the temperature of the reaction mixture did not exceed 25°C. After stirring for 8 h at room temperature water (8 ml) was added dropwise. Then a solution of tartaric acid (120 g) in water (480 ml)

was added, the product extracted with ether, the extract washed with dilute tartaric acid solution and then with water. The extract was dried over Na_2SO_4 and the solvent was evaporated to give 0.9 g of compound VII which gradually crystallized and was purified on a silica gel column. Yield 40%; mp 200-201°C. IR Spectrum: 3300 (NH), 3470-3510 cm^{-1} (OH). UV Spectrum, λ_{max} , (log ϵ): 230 (4.50), 265 (4.80), 290 (4.65), 310 nm (4.20). Found, %: C 75.2; H 4.0; N 6.2. $\text{C}_{14}\text{H}_9\text{NO}_2$. Calculated, %: C 75.3; H 4.0; N 6.3.

3-Hydroxybenzo[*b*]furo[3,2-*g*]indole (VIII) was prepared analogously to compound VII from compound IV. Yield 45%; mp 179-180°C. IR Spectrum: 3290 (NH), 3480-2520 cm^{-1} (OH). UV Spectrum, λ_{max} (log ϵ): 225 (4.44), 255 (4.60), 270 (4.55), 318 nm (4.14). Found, %: C 75.3; H 3.9; N 6.1. $\text{C}_{14}\text{H}_9\text{NO}_2$. Calculated, %: C 75.3; H 4.0; N 6.3.

Benzo[*b*]furo[2,3-*g*]indole (V). To a solution of compound III (2.4 g, 0.01 mol) in abs. tetrahydrofuran (2.5 ml) cooled to -78°C, a solution of diborane (1.7 g, 0.06 mol, prepared from sodium tetrahydroborate and boron trifluoride etherate) in tetrahydrofuran (20 ml) was added dropwise with stirring. The solution was kept at 0°C for 30 h, then poured into water (1.5 l), slightly acidified, and the product was extracted with ether. The extract was washed with water and dried over Na_2SO_4 . After evaporation of the solvent the reaction product was purified on a column of silica gel to give compound V, yield 1.82 g (90%); mp 146-147°C. IR Spectrum: 3410 cm^{-1} (NH). UV Spectrum, λ_{max} (log ϵ): 219 (4.44), 251 (4.88), 289 (4.35), 312 (4.62), 320 nm (4.30). Found, %: C 81.1; H 4.3; N 6.8. $\text{C}_{14}\text{H}_9\text{NO}$. Calculated, %: C 81.2; H 4.3; N 6.8.

Benzo[*b*]furo[3,2-*g*]indole (VI) was obtained analogously to compound V from compound IV. Yield 90%; mp 162-163°C. IR Spectrum: 3380 cm^{-1} . UV Spectrum, λ_{max} (log ϵ): 242 (4.70), 248 (4.87), 263 (4.28), 318 nm (4.37). Found, %: C 81.1; H 4.2; N 6.7. $\text{C}_{14}\text{H}_9\text{NO}$. Calculated, %: C 81.2; H 4.3; N 6.8.

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