INDOLOBENZO[b]FURANS.
3.* SYNTHESIS OF UNSUBSTITUTED INDOLO[7',6':2,3]- AND INDOLO[6',7':2,3]BENZO[b]PYRANS

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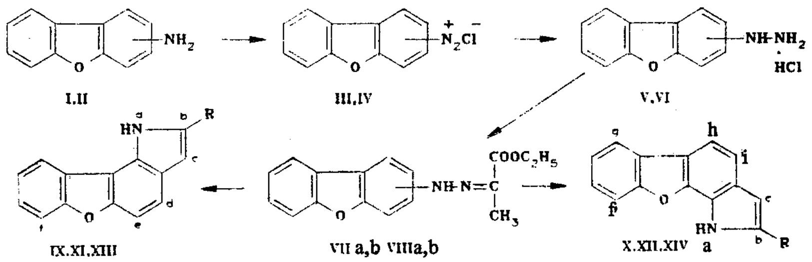
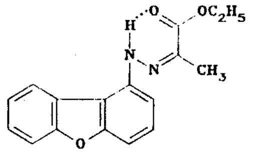
Indolo[7',6':2,3]- and indolo[6',7':2,3]benzo[b]furans have been synthesized with the aid of the Fischer reaction. The physicochemical characteristics of the compounds synthesized are considered.

In connection with the study of properties in a series of isomeric indolobenzo[b]furans, with the evaluation of the nature of the annelation of the pyrrole ring relative to the central heterocycle on the reactivity of the molecule as a whole, and the elucidation of the interrelation of biological activity and structure of compounds, we have synthesized unsubstituted indolo[7',6':2,3]- and indolo[6',7':2,3]benzo[b]furans, which have not been described in the literature previously, using the Fischer reaction, by the following scheme:

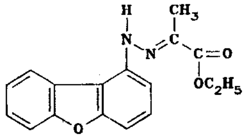


IX, X R=COOC$_2$H$_5$; XI, XII R=COOH; XIII, XIV R=H

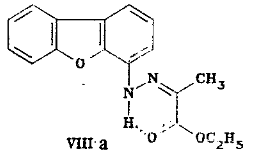
As the starting compounds we selected 1- and 4-aminodibenzofurans (I) and (II) [2, 3]. These amines were converted via their diazonium salts into the corresponding hydrazine hydrochlorides (V) and (VI), which, with ethyl pyruvate, gave the hydrazines (VII) and (VIII), each in the form of mixtures of two geometric isomers. It was possible to separate the latter with the aid of preparative column chromatography into the syn (VIIa) and (VIIIa) and anti (VIIb) and (VIIIb) forms:



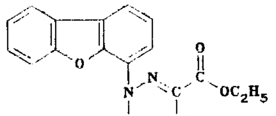
VIIa



VII b



VIII a



VIII b

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*For communication 2, see [1].

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TABLE 1. PMR Spectra of the Compounds Synthesized (in DMSO-d_6)

Compound	δ, ppm										J, Hz				
	a	b	c	d	e	f	g	h	i	CH_2CH_3	ab	ac	bc	ed	hi
IX	11,7, s	—	7,37, d	7,63, d	7,74, d	7,79, d.d	8,90, d.d	—	—	4,35, q, 1,38, t		2,1		8,7	
X	11,5, s	—	7,45, d	—	—	7,6, d.d	8,05, d.d	7,58, d	7,64, d	4,38, q; 1,40 t		2,1			8,5
XI	11,6, s	—†	7,30, s	7,65, d	7,75 d	7,80, d.d	8,7, d.d	—	—	—				8,6	
XII	12,3, s	—†	7,20, s	—	—	7,6, d.d	8,03, d.d	7,71, d	7,55, d	—					8,4
XIII	11,5, s	7,4, m	7,0, d.d	7,51, d	7,71, d	7,98, d.d	8,79, d.d	—	—	—	2,0	1,7	2,9	8,1	
XIV	11,7, s	7,4, m	6,61, d.d	—	—	7,7, d.d	8,00, d.d	7,64, d	7,49, d			1,5	2,3		8,8

*The PMR spectrum of compound (X) was taken in acetone-d_6 and those of compounds (XI-XIV) at a temperature of 80°C.

†The COOH signal was not observed (broadened as the result of intermolecular exchange).

In the PMR spectra of both isomers the signals of the protons of the NH groups in the syn forms of the hydrazones (VIIa) and (VIIIa) were observed in a weaker field (12.2 ppm) than the corresponding signals of the anti isomers (VIIb) and (VIIIb) (~9.5 ppm). This shift can be explained by the participation of the NH proton in a strong intramolecular hydrogen bond in the case of the syn configuration. In the IR spectra of the isomeric hydrazones, the characteristic frequencies of the absorption of the CO and NH groups in the syn isomers were shifted in the low-frequency direction as compared with the corresponding frequencies for the anti isomers. In the UV spectra, the presence of a hydrogen bond caused a bathochromic shift of the maxima and a marked rise in the intensity of absorption.

The intramolecular condensation of the hydrazones (VIIa, b) and (VIIIa, b) in polyphosphate ester under the conditions of the Fischer reaction [4] gave ethyl indolo[7',6':2,3]- and indolo[6',7':2,3]benzo[b]furan-2-carboxylates (IX and X), respectively, the saponification of which, in an aqueous ethanolic solution of KOH gave the corresponding acids (IX) and (XII). The thermal decarboxylation of the latter in an inert gas medium led to indolo[7',6':2,3]- and indolo[6',7':2,3]benzo[b]furans ((XIII) and (XIV), respectively).

The results of elementary analysis of PMR, UV, and IR spectroscopy, and of mass spectrometry confirmed the structures of all the compounds synthesized.

The assignment of the signals in the PMR spectra of compounds (IX-XIV) (Table 1) was made on the basis of the change in the multiplicity of the signals in the indole moiety of the molecule.

The mass spectra of the unsubstituted indolobenzo[b]furans (XIII) and (XIV) had a strong M^+ peak (207)* and the nature of the subsequent fragmentation was, using compound (XIV) as an example, as follows:

$$M^+ \xrightarrow{-H} (M-H)^+(206);$$

$$M^+ \xrightarrow{-H_2CN} (M-H_2CN)^+(179) \xrightarrow{-CO} [(M-H_2CN)-CO]^+(151);$$

$$M^+ \xrightarrow{-HCN} (M-HCN)^+(180) \xrightarrow{-CO} [(M-HCN)-CO]^+(152).$$

EXPERIMENTAL

The course of the reactions and the purity of the compounds were checked on Silufol UV-254 plates with a fixed layer of silica gel. UV spectra were taken on a Specord spectrophotometer (in ethanol) and IR spectra on a UR-20 instrument with NaCl and LiF prisms (in

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*Here and below the values of m/z are given for the peaks of ions with intensities >5%.

paraffin oil). Mass spectra were taken on the MK-1303 instrument with direct introduction of the sample into the ion source at a cathode emission current of 1.5 μA and an ionizing energy of 50 eV. PMR spectra were recorded on a Varian CFT-20 spectrometer (80 MHz) with tetramethylsilane as internal standard.

Dibenzofuran-1-ylhydrazone of Ethyl Pyruvate (VII). A solution of 1.6 g (23 mmole) of $NaNO_2$ in 7 ml of water was added dropwise over 20 min at -5°C to a mixture of 3.7 g (20 mmole) of 1-aminobenzofuran (I) in 100 ml of water and 20 ml of concentrated HCl, and the mixture was stirred at -5°C for 1 h. To the resulting diazonium salt solution at -5°C was slowly added a solution of 9.0 g (40 mmole) of $SnCl_2 \cdot 2H_2O$ in 30 ml of concentrated HCl and stirring was continued for another 2 h. The resulting precipitate of the hydrazine hydrochloride (V) was filtered off and dissolved in hot water, the solution was rapidly filtered, the pH of the filtrate was brought to 3 with a saturated solution of sodium acetate, and, with stirring, 2.5 ml (20 mmole) of ethyl pyruvate in 4 ml of ethanol was gradually added to it. The resulting yellow precipitate of the hydrazone (VII) was filtered off, washed with water, and dried. Yield 3.5 g (64%).

The stereoisomers were separated by passing the hydrazone (VII) through a column filled with silica gel, with elution by ether—hexane (1:4).

The first fraction contained the syn isomer (VIIa). Yield 0.42 g (11%), mp 114-115°C, R_f 0.61 [(Silufol; ether—hexane (1:1)]. PMR spectrum ($CDCl_3$), ppm: 1.34 (3 H, t, J = 7.2 Hz, $CH_2{-}\underline{CH_3}$); 4.31 (2 H, q, J = 7.2 Hz, $\underline{CH_2}CH_3$); 2.16 (3 H, s, CH_3); 12.2 (1 H, s, NH). IR spectrum, cm^{-1}: 3300 (NH); 1680 ($C{=}O$). UV spectrum, λ_{max}, nm (log ε): 218 (5.50), 237 (4.30), 265 (4.07), 296 (3.99), 306 (4.11), 346 (4.69). Found: C 68.8; H 5.4; N 9.4%. $C_{17}H_{16}N_2O_3$. Calculated: C 68.9; H 5.4; N 9.4%.

The second fraction contained the anti isomer (VIIb). Yield 1.98 g (54%), mp 176-177°C, R_f 0.33 [(Silufol; ether—hexane (1:1)]. PMR spectrum ($CDCl_3$), ppm: 1.27 (3 H, t, J = 7.0 Hz, $CH_2\underline{CH_3}$); 4.22 (2 H, q, J = 7.0 Hz, $\underline{CH_2}CH_3$); 2.21 (3 H, s, CH_3); 9.4 (1 H, s, NH). IR spectrum, cm^{-1}: 3300 (NH); 1700 ($C{=}O$). UV spectrum, λ_{max}, nm (log ε): 216 (4.67), 246 (4.30), 265 (4.07), 296 (3.99), 306 (4.11), 346 (4.69). Found: C 68.8; H 5.4; N 9.4%. $C_{17}H_{16}N_2O_3$. Calculated: C 68.9; H 5.4; N 9.5%.

The dibenzofuran-4-ylhydrazone of ethyl pyruvate (VIII) was obtained in a similar manner to (VII) from 4-aminodibenzofuran (II), the yield of unpurified product being 67%. The stereoisomers (VIIIa) and (VIIIb) were separated in the same way as compounds (VIIa) and (VIIb). The yield of the syn isomer (VIIIa) was 10% (mp 146-147°C, R_f 0.63 (Silufol; ether—hexane (1:1). PMR spectrum (DMSO-d_6), ppm: 1.34 (3 H, t, J = 7.2 Hz, $CH_2\underline{CH_3}$), 4.31 (2 H, q, J = 7.2 Hz, $\underline{CH_2}CH_3$); 2.16 (3 H, s, CH_3); 12.2 (1 H, s, NH). IR spectrum, cm^{-1}: 3310 (NH); 1680 ($C{=}O$). UV spectrum, λ_{max}, nm (log ε): 212 (4.45), 247 (4.35), 291 (4.12), 358 (4.17). Found: C 68.5; H 5.5; N 9.4%. $C_{17}H_{16}N_2O_3$. Calculated: C 68.9; H 5.4; N 9.5%.

The yield of the anti isomer (VIIIb) was 64%, mp 178-179°C, R_f 0.31 (Silufol; ether—hexane (1:1)). PMR spectrum (DMSO-d_6), ppm: 1.3 (3 H, t, J = 7.0 Hz, $CH_2\underline{CH_3}$; 4.25 (2 H, q, J = 7.0 Hz, $\underline{CH_2}CH_3$); 2.21 (3 H, s, CH_3); 9.5 (1 H, s, NH). IR spectrum, cm^{-1}: 3325 (NH); 1710 ($C{-}O$). UV spectrum, λ_{max}, nm (log ε): 215 (4.51), 238 (4.45), 248 (4.35), 278 (4.71), 285 (4.44), 299 (4.25), 355 (4.16), 358 (4.16). Found: C 68.7; H 5.5; N 9.6%. $C_{17}H_{16}N_2O_3$. Calculated: C 68.9; H 5.4; N 9.5%.

Ethyl indolo[7',6':2,3]benzo[b]furan-2-carboxylate (IX). With stirring, 5.7 g (49 mmole) of the hydrazone (VII) was added to 60 g of polyphosphate ester heated to 50°C. After the addition of the whole of the hydrazone, the temperature of the reaction mixture was raised to 90°C and the mixture was stirred at this temperature for 1 h and was then cooled and poured into water. The precipitate that deposited was filtered off, washed with water, and dried. The compound (IX) was purified on a column of silica gel (eluent: ether—hexane (1:3)); yield 4.4 g (82%); mp 118-121°C. IR spectrum, cm^{-1}: 3460 (NH); 1675 ($C{=}O$). UV spectrum, λ_{max}, nm (log ε): 210 (5.15), 225 (5.27), 249 (5.10), 270 (5.21), 295 (4.99), 333 (5.05), 343 (5.18). Found: C 73.0; H 4.4; N 5.0%. $C_{17}H_{13}NO_3$. Calculated: C 73.1; H 4.7; N 5.0%.

Ethyl indolo[6',7':2,3]benzo[b]furan-2-carboxylate (X) was obtained in a similar manner to compound (IX) from the hydrazone (VIII) with a yield of 74%; mp 199-200°C. IR spectrum, cm^{-1}: 3300 (NH); 1720 ($C{=}O$). UV spectrum, λ_{max}, nm (log ε): 218 (4.50), 237 (4.46), 277 (4.76), 278 (4.30), 3.17 (4.56). Found: C 73.0; H 4.8; N 5.1%. $C_{17}H_{14}NO_3$. Calculated: C 73.1; H 4.7; N 5.0%.

Indolo[7',6':2,3]benzo[b]furan-2-carboxylic acid (XI). A mixture of 2.79 g (10 mmole) of the ester (IX), 150 ml of water, 60 ml of ethanol, and 1.6 g (30 mmole) of KOH was boiled with stirring for 1 h. The solution was cooled and filtered, the pH of the filtrate was brought to 7-8 with dilute HCl solution, the resulting precipitate was filtered off, and the filtrate was brought to pH 1. The product that then precipitated was filtered off, washed with water, and dried. The yield of the acid (XI) was 2.03 g (81%), mp 297°C (decomp.). IR spectrum, cm^{-1}: 3430 (NH); 1675 (C=O). UV spectrum, λ_{max}, nm (log ε): 210 (4.99), 221 (5.01), 233 (5.03), 247 (5.09), 259 (4.87), 284 (4.75), 310 (5.16), 330 (5.00). Found: C 71.6; H 4.0; N 5.3%. $C_{15}H_9NO_3$. Calculated: C 71.7; H 3.6; N 5.6%.

Indolo [6',7':2,3]benzo[b]furan-2-carboxylic acid (XII) was obtained in a similar manner to compound (X) with a yield of 94%, mp 265-267°C. IR spectrum, cm^{-1}: 3410 (NH); 1680 (C=O). UV spectrum, λ_{max}, nm (log ε): 216 (4.99), 219 (4.99), 233 (4.09), 243 (5.00), 261 (4.34), 286 (4.78), 313 (5.17), 325 (4.99). Found: C 71.7; H 4.0; N 5.7%. $C_{15}H_9NO_3$. Calculated: C 71.7; H 3.6; N 5.6%.

Indolo[7',6':2,3]benzo[b]furan (XIII). The acid (XI) (1 g; 4 mmole) was heated at 310-330°C in a current of inert gas. The resulting compound (XIII) was purified on a column filled with silica gel (eluent: ether—hexane (1:3)). Yield 0.3 g (42%); mp 146-147°C. IR spectrum, cm^{-1}: 3410 (NH). UV spectrum, λ_{max}, nm (log ε): 219 (4.44), 239 (4.67), 251 (4.88), 273 (4.31), 289 (4.35) 312 (4.62), 320 (4.30). Found: C 81.0; H 4.1; N 6.4%. $C_{14}H_9NO$. Calculated: C 81.1; H 4.3; N 6.7%.

Indolo[6',7':2,3]benzo[b]furan (XIV) was obtained in a similar manner to compound (XIII) with a yield of 62%; mp 162-163°C. IR spectrum, cm^{-1}: 3380 (NH). UV spectrum, λ_{max}, nm (log ε): 230 (4.67), 242 (4.79), 248 (4.87), 263 (4.28), 277 (4.28), 305 (4.56), 318 (4.37). Calculated: C 81.0; H 4.1; N 6.5%. $C_{14}H_9NO$. Calculated: C 81.1; H 4.3; N 6.7%.

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