INDOLOBENZOFURANS. 1. SYNTHESIS OF ISOMERIC INDOLOBENZO[b]FURANS

T. E. Khoshtariya, M. L. Kakhabrishvili,
L. N. Kurkovskaya, and N. N. Suvorov

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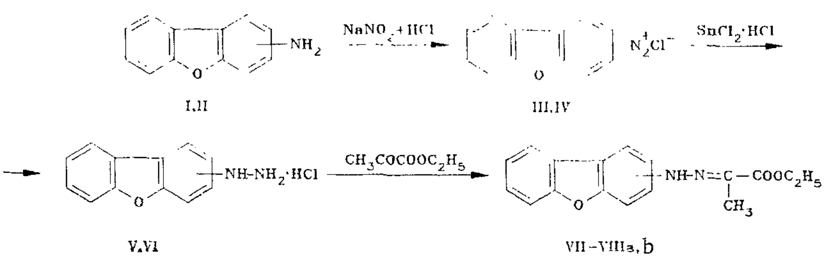
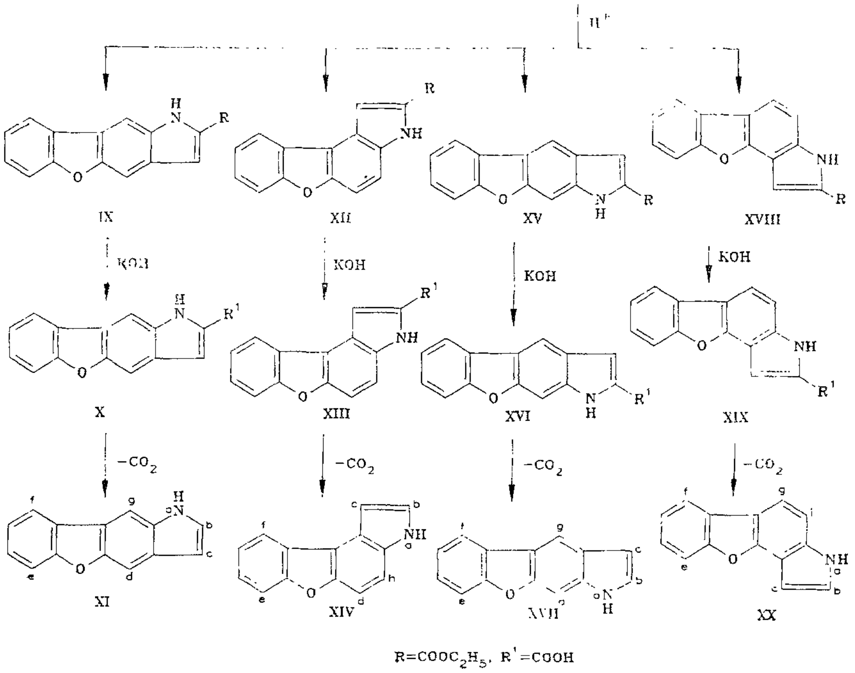
The synthesis of four progenitors of a new tetracyclic condensed system of indolobenzo[b]furans on the basis of the Fischer reaction has been described. It has been shown that the cyclization of 2-dibenzofuranyl- and 3-dibenzofuranylhydrazones of ethyl pyruvate in ethyl polyphosphate results in the simultaneous formation of the corresponding cyclic ethers with both angular and linear structures.

Continuing the investigations in the field of tetracyclic pyrrole-containing condensed systems, we developed a preparative method for the synthesis of indolobenzo[b]furans not described in the literature with the use of the Fischer reaction.



The starting compounds selected were 2- and 3-aminodibenzofuran. 2-Aminodibenzofuran (1) was obtained from 3-aminodibenzofuran according to the method in [1]. 3-Aminodibenzofuran (II) was synthesized by reduction 3-nitrobenzofuran, which was obtained by the direct nitration of dibenzofuran [2]. 2-Amino- and 3-aminodibenzofuran were converted into



$R=COOC_2H_5$, $R'=COOH$

I. G. Kutateladze Institute of Pharmaceutical Chemistry, Academy of Sciences of the Georgian SSR, Tbilisi 380059. D. I. Mendeleev Moscow Chemical-Engineering Institute, Moscow 125047. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1366-1370, October, 1984. Original article submitted December 1, 1983.

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TABLE 1.

Compound	Solvent	Chemical shifts, δ, ppm				
		CH_3	CH_2CH_3	CH_3CH_2	NH	$J_{CH_2 \cdot CH_3}$, Hz
VIIa	$CDCl_3$	2,16	4,25	1,34	12,2	7,2
	Acetone-d_6	2,15	4,27	1,34	12,2	7,2
VIIb	$CDCl_3$	2,12	4,31	1,40	7,8	7,1
VIIIa	Acetone-d_6	2,14	4,27	1,34	12,1	7,2
VIIIb	DMSO	2,11	4,23	1,31	9,7	7,1

TABLE 2. Parameters of the PMR spectra of the Compounds Obtained (in DMSO-d_6)

Compound	Chemical shifts, δ, ppm									J, Hz
	a-H	b-H	c-H	d-H	e-H	f-H	g-H	h-H	i-H	
IX	11,7	4,37; 1,37 (Et)	7,21	7,75	7,50	8,05	8,03	—	—	$J_{CH_2, CH_3}=7{,}0$; $J_{ac}=2{,}0$
XI	11,0	7,40	6,52	7,66	7,5	8,05	7,99	—	—	$J_{ab}=2{,}7$; $J_{ac}=2{,}0$; $J_{bc}=3{,}1$; $J_{cg}=J_{dg}=0{,}8$
XII	12,0	4,38; 1,39 (Et)	7,69	7,59	7,65	8,30	—	7,59	—	$J_{CH_2, CH_3}=7{,}0$; $J_{ac}=1{,}5$
XIV	11,3	~7,5	6,99	7,54	~7,6	8,18	—	7,37	—	$J_{ac}=1{,}6$; $J_{bc}=3{,}1$; $J_{ch}=0{,}9$; $J_{dh}=8{,}1$
XV	11,6	4,35; 1,36 (Et)	7,27	7,54	~7,6	8,03	8,27	—	—	$J_{CH_2, CH_3}=7{,}1$; $J_{ac}=1{,}9$; $J_{ag}=J_{cd}=J_{dg}=0{,}9$
XVII*	10,3	7,36	6,58	7,55	~7,5	8,00	8,15	—	—	$J_{ac}=2{,}0$; $J_{ab}=2{,}2$; $J_{ag}\approx J_{cd}\approx J_{cg}=0{,}8$; $J_{bc}=3{,}1$
XVIII	12,2	4,37; 1,37 (Et)	7,36	—	7,68	8,01	7,90	—	7,34	$J_{CH_2, CH_3}=7{,}1$; $J_{ac}=2{,}0$; $J_{ci}=0{,}9$; $J_{gi}=8{,}9$
XX	11,4	7,37	6,73	—	~7,6	7,98	7,72	—	7,31	$J_{ab}=2{,}2$; $J_{ac}=2{,}0$; $J_{bc}=3{,}0$; $J_{ci}=0{,}8$; $J_{gi}=8{,}7$

*In acetone-d_6.

diazonium salts III and IV and then into the corresponding hydrazine hydrochlorides V and VI, which react with ethyl pyruvate to form hydrazones VII and VIII in the form of mixtures of two geometric isomers.

The latter could be separated with the aid of preparative column chromatography into syn (VIIa and VIIIa) and anti (VIIb and VIIIb) forms, whose structure were proved by investigating their PMR, IR, and UV spectra. The PMR spectra of syn isomers VIIa and VIIIa show downfield signals of the protons of the NH groups at 12.1 and 12.2 ppm, respectively, which point out the presence of a fairly strong intramolecular hydrogen bond between the NH proton and the carbonyl group. The signals of the protons of the NH groups for the anti form are more upfield and depend on the solvent (Table 1).

The corresponding changes caused by the formation of the intramolecular hydrogen bond are observed in the IR and UV spectra of the compounds indicated.

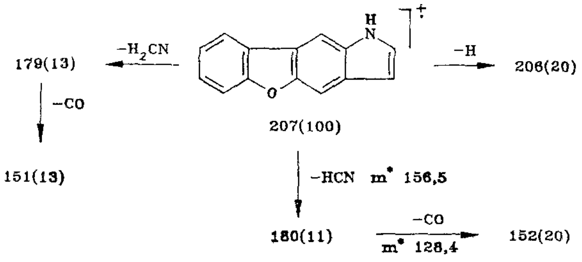
By means of the cyclization of hydrazone VII under the action of ethyl polyphosphate [3] under the conditions of the Fischer indole synthesis we were able to obtain a mixture of the ethyl esters of indolo[6,5-d]- (IX) and indolo[4,5-d]benzo[b]furan-2-carboxylic acid (XII). With the aid of column chromatography we were able to isolate compound IX with a 15% yield and compound XII with a 45% yield. The saponification of IX and XII gives the corresponding carboxylic acids X and XIII, whose decarboxylation provides unsubstituted indolo[6,5-d]- (XI) and indolo[4,5-d]benzo[b]furan (XIV).

Ethyl indolo[5,6-d]benzo[b]furan-2-carboxylate (XV) was obtained in a mixture with ethyl indolo[5,4-d]benzo[b]furan-2-carboxylate (XVIII) by cyclizing hydrazone VIII under the conditions described above. The mixture of compounds was separated with the aid of column chromatography. The yields of compounds XV and XVIII were 10 and 40%, respectively. Saponification of esters XV and XVIII resulted in the synthesis of XVI and XIX, whose thermal decarboxylation gave unsubstituted indolo[5,6-d] (XVII) and indolo[5,4-d]benzo[b]furan (XX).

The assignment of the PMR signals (Table 2) of compounds IX-XX was determined on the basis of the changes in the multiplicity of the signals of the indole part of the molecule: the presence of the spectrum of an AB system with a spin—spin coupling constant characteristic of ortho protons in the case of the angular attachment of the ring ($J_o \sim 8$ Hz) or two signals of weakly interacting para protons in the case of a linear molecule ($J_p \simeq 1$ Hz). The possibility of observing spin—spin coupling constant of the transoid type through five bonds (^5J) in the PMR spectrum also aided the unequivocal assignment of the lines.

According to the downfield shifts of the signals of the c-H and f-H protons, the angular ring in XIV and its derivatives experience the greatest steric hindrances.

The mass spectra of the isomeric indolobenzo[b]furans show an intense peak molecular ion (M^+) with m/z 207, and the nature of the further fragmentation does not contradict the proposed structures. As a consequence of the similarity of the fragmentation scheme for the mass spectra of the isomeric heterocycles, we present the fragmentation scheme for indolo[6,5-d]benzo[b]furan (XI) alone:*



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*Metastable transitions.

EXPERIMENTAL

The course of the reaction and the purity of the compounds were monitored on Silufol UV-254 plates. The UV spectra were recorded on a Specord spectrophotometer in ethanol, and the IR spectra were recorded on a UR-20 instrument with NaCl and LiF prisms (in liquid petrolatum). The scanning rate was 160 with a spectral slit width of 4 cm^{-1}. The mass spectrometer recorded on an MKh-1303 spectrometer with direct admission of the sample into the ion source, an emission current of the cathode equal to 1.5 μA, and an ionizing voltage equal to 50 V. The PMR spectra were recorded on a Variant CFT-20 spectrometer (80 MHz) with TMS as an internal reference, δ being measured with an accuracy of 0.01 ppm and the spin—spin coupling constants being measured to within 0.1 Hz.

Ethyl Pyruvate 2-Dibenzofuranylhydrazone (VII). A mixture of 3.7 g (20 mmole) of 2-aminodibenzofuran (I) in 100 ml of water and 20 ml of conc. HCl is given a dropwise addition of a solution of 1.6 g (23 mmole) of $NaNO_2$ in 7 ml of water over the course of 20 min at —5°C, and the stirring is continued for 1 h at —5°C. The solution of the diazonium salt obtained is slowly given an addition at —5°C of a solution of 9.02 g (40 mmole) of $SnCl_2 \cdot 2H_2O$ in 30 ml of conc. HCl, and the stirring is continued for an additional 2 h. The precipitate of hydrazine hydrachloride V formed is filtered out, dissolved in hot water, and quickly filtered The pH of the filtrate is adjusted to 3 by a saturated solution of sodium acetate, and 2.5 ml (20 mmole) of ethyl pyruvate in 4 ml of ethanol are gradually added to it with stirring. The yellow precipitate of hydrazone VII is filtered out, washed with water, and dried. The yield is 3.2 g (58%). In order to separate the stereoisomers of hydrazone VII, the product is passed through a column with silica gel with elution by a 1:4 ether—hexane mixture. The first fraction consists of the syn isomer VIIa. The yield is 0.37 g (10%), and the mp 93-95°C. IR spectrum: 3220 (NH), 1690 cm^{-1} (C═O). UV spectrum, λ_{max} (log ε): 206 (4.59), 217-225 (4.51), 240 (4.46), 250 (4.43), 256 (4.35), 291 (4.23), 330 nm (4.35). Found: C, 68.5; H, 5.6; N. 8.9%. Calculated for $C_{17}H_{16}N_2O_3$: C, 58.9; H, 5.4; N, 9.4%. The second fraction consists of the anti isomer VIIb. The yield is 1.55 g (42%), and the mp 151-157°C. IR spectrum: 3310 (NH), 1730 cm^{-1} (C═O). UV spectrum, λ_{max} (log ε): 208 (4.55), 224 (4.47),

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*The values of m/z are given, and the relative intensities of the peaks as percentages of the maximum intensity are indicated in parentheses.

235 (4.48), 250 (4.42), 258 (4.35), 282 (4.48), 322 nm (4.51). Found: C, 68.4; H, 5.8; N, 9.3%. Calculated for $C_{17}H_{16}N_2O_3$: C, 68.9; H, 5.4; N, 9.4%.

Ethyl Pyruvate 3-Dibenzofuranylhydrazone (VIII) is obtained in analogy to compound VII from 3-aminodibenzofuran (II). The yield is 1.7 g (62.2%). The separation of stereoisomers VIIIa and VIIIb is carried out similarly to the separation of the isomers of VII. The yield of the syn isomer VIIIa is 0.15 g (9%), and the mp 105-106°C. IR spectrum: 3220, 3240 (NH), 1680 cm^{-1} (C=O). UV spectrum, λ_{max} (log ε): 202 (4.28), 217 (4.60), 251 (4.10), 260 (4.10), 299 nm (3.92). Found: C, 68.7; H, 5.6; N, 9.5%. Calculated for $C_{17}H_{16}N_2O_3$: C, 68.9; H, 5.4; N, 9.4%. The yield of the anti isomer VIIIb is 0.85 g (50%), and the mp 153-155°C. IR spectrum: 3320 (NH), 1695 cm^{-1} (C=O). UV spectrum, λ_{max} (log ε): 217 (4.84), 250 (4.27), 266 (4.03), 300 (3.88), 257 nm (4.44). Found: C, 69.2; H, 5.7; N, 9.3%. Calculated for $C_{17}H_{16}N_2O_3$: C, 68.9; H, 5.4; N, 9.4%.

Ethyl Indolo[6,5-d]benzo[b]furan-2-carboxylate and Ethyl Indolo[4,5-d]benzo[b]furan-2-carboxylate (IX and XII). A 5.7-g portion (49 mmole) of hydrazone VII is added to 60 g of ethyl polyphosphate preliminarily heated to 50°C. After the addition of the entire portion of the hydrazone, the temperature of the reaction mixture is raised to 90°C, and the mixture is stirred at that temperature for 1 h. The mixture is cooled and poured into water. The precipitate formed is filtered out, washed with water, and dried. The yield of the mixture of esters IX and XII is 4.6 g (86%). Compounds IX and XII are separated in a column with silica gel in benzene. The yield of ester IX is 0.69 g (15%), and the mp is 196-197°C. IR spectrum: 3300 (NH), 1700 cm^{-1} (C=O). UV spectrum, λ_{max} (log ε): 219 (4.65), 242 (4.59), 252 (4.65), 335 (4.83), 352 nm (4.57). Found: C, 73.41 H, 4.6; N, 5.0%. Calculated for $C_{17}H_{13}NO_3$: C, 73.1; H, 4.6; N, 5.3%. The yield of ester XII is 2.07 g (45%), and the mp is 190-191°C. IR spectrum: 3320 (NH), 1680 cm^{-1} (C=O). UV spectrum, λ_{max} (log ε): 211 (4.67), 219 (4.66), 240 (4.46), 253 (4.23), 273 (4.28), 281 (4.46), 331 (4.60), 323 (4.77), 346 nm (4.40). Found: C, 73.8; H, 5.0; N, 5.8%. Calculated for $C_{17}H_{13}NO_3$: C, 73.1; H, 4.6; N, 5.3%.

Ethyl Indolo[5,6-d]benzo[b]furan-2-carboxylate and Ethyl Indolo-[5,4-d]benzo[b]furan-2-carboxylate (XV and XVIII) are obtained similarly to compounds IX and XII from hydrazone VIII. The yield of the mixture of esters XV and XVIII is 1.27 g (81%). After the separation of the mixture, the yield of isomer XV is 0,25 g (11%), and the mp is 235-236°C. IR spectrum: 3320 (NH), 1685 cm^{-1} (C=O). UV spectrum, λ_{max} (log ε): 205 (4.65), 233-237 (4.42), 241 (4.47), 256 (4.51), 274 (4.72), 290 (4.78), 330 (4.47), 345 nm (4.54). Found: C, 72.6; H, 5.2; N, 5.2%. Calculated for $C_{17}H_{13}NO_3$: C, 73.1; H, 4.6; N, 5.3%. The yield of ester XVIII is 0.9 g (40%), and the mp 215-216°C. IR spectrum: 3300 (NH), 1700 cm^{-1} (C=O). UV spectrum, λ_{max} (log ε): 250-255 (4.50), 273 (4.91), 286 (4.66), 295 nm (4.65). Found: C, 73.6; H, 4.9; N, 5.4%. Calculated for $C_{17}H_{13}NO_3$: C, 73.1; H, 4.6; N, 5.3%.

Indolo[6,5-d]benzo[b]furan-2-carboxylic Acid (X). A suspension of 0.36 g (1.4 mmole) of ester IX, 20 ml of ethanol, 25 ml of water, and 0.12 g (3 mmole) of NaOH is boiled with stirring for 1 h. The solution is cooled and filtered, the pH of the filtrate is adjusted to 7-8 with a dilute HCl solution, the precipitate formed is filtered out, and the filtrate is acidified to pH 1. The precipitate of X obtained is filtered out, washed with water, and dried. The yield is 0.25 g (78%), and the mp 280-281°C. IR spectrum: 3400 (NH), 1680 cm^{-1} (C=O). UV spectrum, λ_{max} (log ε): 204 (4.49), 216 (4.56), 242 (4.54), 250 (4.59), 327 nm (4.71). Found: C, 71.2; H, 3.8; N, 5.4%. Calculated for $C_{15}H_9NO_3$: C, 71.7; H, 3.6; N, 5.5%.

Indolo[4,5-d]benzo[b]furan-carboxylic Acid (XIII) is obtained similarly to compound X. The yield is 0.18 g (78%), and the mp 255-257°C. IR spectrum: 3360 (NH), 1720 cm^{-1} (C=O). UV spectrum, λ_{max} (log ε): 208 (4.55), 220 (4.54), 273 (4.10), 281 (4.28), 324 nm (4.59). Found: C, 72.1; H, 4.0; N, 5.5%. Calculated for $C_{15}H_9NO_3$: C, 71.7; H, 3.6; N, 5.5%.

Indolo[4,5-d]benzo[b]furan-2-carboxylic Acid (XVI) is obtained similarly to compound X. The yield is 2.6 g (74%), and the mp 275-276°C (with decomposition). IR spectrum: 3370 (NH), 1720 cm^{-1} (C=O). UV spectrum, λ_{max} (log ε): 206 (4.59), 241 (4.42), 253 (4.53), 263 (4.67), 280 (4.44), 290 (4.62), 328 (4.38), 342 nm (4.38). Found: C, 71.4; H, 3.81; N, 5.6%. Calculated for $C_{15}H_9NO_3$: C, 71.7; H, 3.6; N, 5.5%.

Indolo[5,4-d]benzo[b]furan-2-carboxylic Acid (XIX) is obtained similarly to compound X. The yield is 1.6 g (80%), and the mp 254-255°C. IR spectrum: 3330 (NH), 1730 cm^{-1} (C=O). UV spectrum, λ_{max} (log ε): 205 (4.57), 269 (4.85), 288 nm (4.61). Found: C, 72.0; H, 4.0; N, 5.4%. Calculated for $C_{15}H_9NO_3$: C, 71.7; H, 3;6; N, 5.5%.

Indolo[6,5-d]benzo[b]furan (XI). A 1-g portion (3.9 mmole) of acid X is held at 280-300°C in a stream of argon. Compound XI is purified in a colum filled with silica gel, the eluent being a 1:3 ether—hexane mixture. The yield is 0.57 g (69%), and the mp 197-198°C. IR spectrum: 3320 cm^{-1} (NH). UV spectrum, λ_{max} (log ε): 233 (4.57), 247 (4.57), 315 (4.56), 334 nm (4.38). Found: C, 81.3; H, 4.61; N, 6.8%. Calculated for $C_{14}H_9NO$: C, 81.3; H, 4.6; N, 6.8%. Calculated for $C_{14}H_9NO$: C, 81.2; H, 4.4; N, 6.8%.

Indolo[4,5-d]benzo[b]furan (XIV) is obtained similarly to compound XI. The yield is 0.62 g (75%), and the mp 127-128°C. IR spectrum: 3385 cm^{-1} (NH). UV spectrum, λ_{max} (log ε): 208 (5.36), 218 (5.44), 241 (5.14), 267 (4.52), 276 (4.68), 299 (5.04), 310 (5.22), 325 nm (5.24). Found: C, 80.8; H, 4.7; N, 6.9%. Calculated for $C_{14}H_9NO$: C, 81.15; H, 4.39; N, 6.76%.

Indolo[5,6-d]benzo[b]furan (XVII) is obtained similarly to compound XI. The yield is 0.6 g (73%), and the mp 160-161°C. IR spectrum: 3410 cm^{-1} (NH). UV spectrum, λ_{max} (log ε): 208 (4.50), 243 (4.70), 252 (4.80), 268 (4.15), 282 (4.08), 308 (4.41), 320 nm (4.43). Found: C, 81.7; H, 4.5; N, 7.3%. Calculated for $C_{14}H_9NO$: C, 81.2; H, 4.4; N, 6.8%.

Indolo[5,4-d]benzo[b]furan (XX) is obtained similar to compound XI. The yield is 0.56 g (68%), and the mp 144-145°C. IR spectrum: 3380 cm^{-1} (NH). UV spectrum, λ_{max} (log ε): 250 (5.03), 297 (4.43), 301 (4.36), 315 nm (4.19). Found: C, 80.9; H, 4.9; N, 6.6%. Calculated for $C_{14}H_9NO$: C, 81.2; H, 4.4; N, 6.8%.

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