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ISOMERIC DIOXODIHYDRO-1H-BENZO[*b*]THIOPHENOINDOLE SYNTHESIS AND PROPERTIES

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The synthesis and properties of new heterocyclic systems are described: isomeric 2,3-dioxo-2,3-dihydro-1H-benzo[b]thiopheno[2,3-g]-, 1,2-dioxo-1,2-dihydro-1H-benzo[b]thiopheno[3,2-e]-, and 2,3-dioxo-2,3-dihydro-1H-benzo[b]thiopheno[2,3-f]indoles. The reduction of the latter to the corresponding unsubstituted benzo[b]thiophenoindoles depends on both the nature of the reducing agent and the reaction conditions.

Keywords: benzothiophenoindole, dibenzothiophene, isatin, indole.

In a continuation of studies of the synthesis of tetracyclic condensed systems containing indole, we have developed a preparative method for the synthesis of isomeric dioxodihydro-1H-benzo[*b*]thiophenoindoles based on the amino derivatives **1** and **2** of dibenzothiophene by the scheme cited.

By cyclization of the (isonitrosoacetamido)dibenzothiophenes **3** and **4**, prepared by the reaction of 1-amino derivatives (**1**) and 2-amino derivatives (**2**) of dibenzothiophene with chloral hydrate and hydroxylamine hydrochloride in conditions of the Sandmeyer reaction [1, 2], the corresponding isomeric isatins **5-7** were synthesized. Sulfuric acid was used as the cyclizing agent.

As expected, the single isomer **5** with an angular structure was formed on cyclization of 1-isonitrosoacetamidodibenzothiophene. The isomers with an angular (**6**) and linear (**7**) structure obtained by cyclization of 2-isonitrosoacetamidodibenzothiophene (**4**) were separated by successive acidification of the alkaline solution of the isomer mixture initially with acetic acid to pH 3, and, after removal of the crystals which formed, concentrated hydrochloric acid to pH 1.

Compound **6** (70%) precipitated first and compound **7** (20%) second. Compounds **5-7** can be converted into the corresponding benzo[*b*]thiophenoindoles **8-10**, the yields of which depend on the nature of the reducing agent and the reaction conditions. For example, reduction of isatins **5-7** with diborane in THF gave the corresponding unsubstituted benzo[*b*]thiophenoindoles in satisfactory yield. Using lithium aluminum hydride in absolute pyridine or sodium borohydride in 2-propanol as reducing agents gave mixtures of products consisting of the corresponding hydroxybenzo[*b*]thiophenoindoles **11-13**, a small quantity of the unsubstituted benzo[*b*]thiophenoindoles **8-10**, and unreacted isatin starting materials **5-7**.

The structures of the synthesized compounds were established by spectroscopic methods.

The IR spectra of compounds **3** and **4** contain C=O absorption bands at 1680 and 1700 cm^{-1} respectively. Absorption bands at 3300 and 3350 cm^{-1} indicated the presence of NH groups in them.

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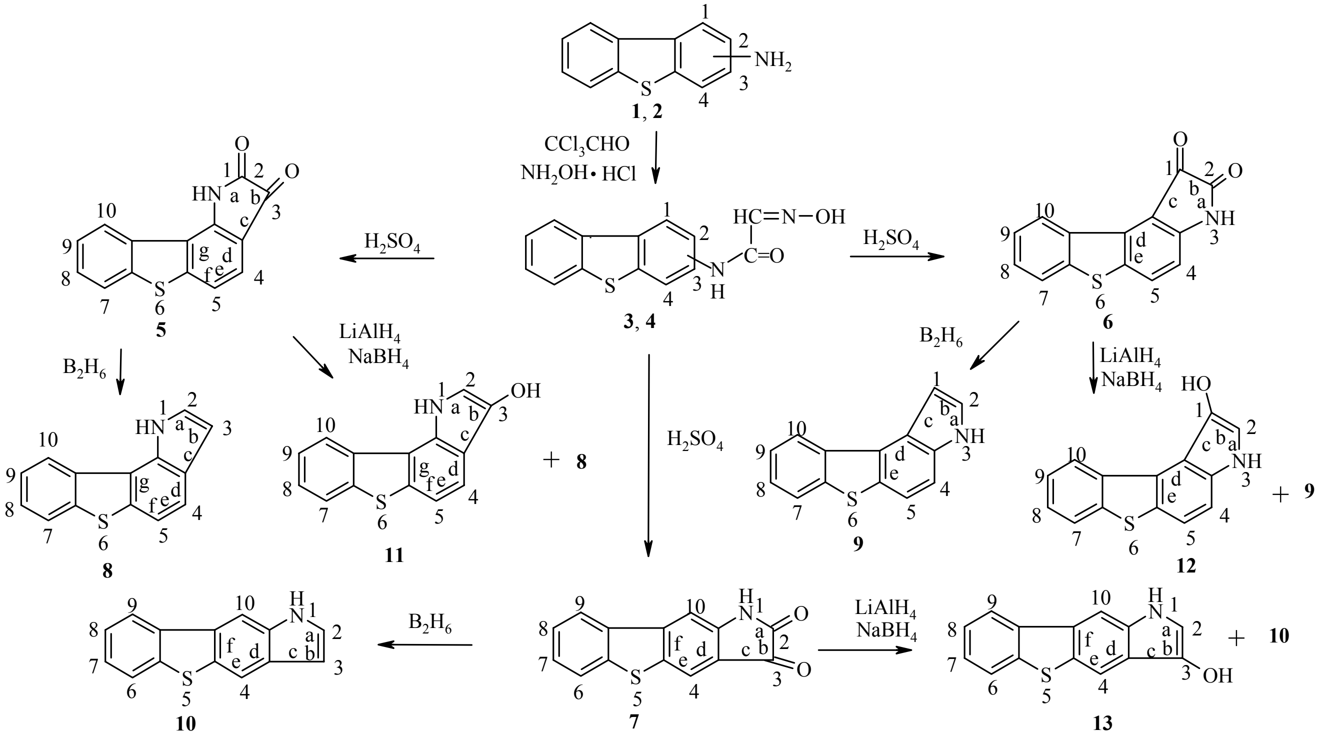
1, 2
CCl_3CHO
$NH_2OH \cdot HCl$
3, 4
H_2SO_4
5
H_2SO_4
6
B_2H_6
$LiAlH_4$
$NaBH_4$
8
11
+ 8
H_2SO_4
B_2H_6
$LiAlH_4$
$NaBH_4$
9
12
+ 9
10
B_2H_6
7
$LiAlH_4$
$NaBH_4$
13
+ 10

TABLE. ^{1}H NMR Spectra of the Compounds **5-13**

Compound	Solvent	δ, ppm										*J*, Hz
		NH	2-H	3-H/1-H	4-H	4-H/5-H	5-H/6-H	6-H/7-H	7-H/8-H	8-H/9-H	10-H	
5	DMSO-d_6	11.13	—	—	8.26	7.06	—	8.02	7.60	7.54	9.39	$J_{45} = 8.5$
6	DMSO-d_6	11.20	—	—	7.20	7.90	—	8.00	7.54	7.50	9.50	$J_{45} = 8.2$
7	DMSO-d_6	11.30	—	—	7.78	—	8.00	7.50	7.54	9.40	7.80	$J_{410} = 0.9$
8	DMSO-d_6	11.50	7.44	7.39	7.65	7.80	—	8.00	7.39	7.45	9.05	$J_{12} = 1.8$; $J_{13} = 1.5$; $J_{23} = 2.7$; $J_{45} = 8.2$
9	Acetone-d_6	10.60	7.54	7.22	7.62	7.62	—	7.94	7.45	7.50	8.52	$J_{12} = 3.0$; $J_{13} = 1.9$; $J_{14} = 0.5$; $J_{23} = 2.2$; $J_{45} = 8.4$
10	Acetone-d_6	10.40	~7.40	6.53	7.99	—	7.79	7.40	7.54	8.17	8.27	$J_{12} = 2.4$; $J_{13} = 2.0$; $J_{23} = 3.0$; $J_{410} = 0.7$
11	Acetone-d_6	10.65	7.45	8.20*	7.60	8.10	—	8.02	7.61	7.53	8.50	$J_{45} = 8.2$
12	Acetone-d_6	10.40	7.50	8.15*	7.40	7.85	—	8.00	7.50	7.54	8.70	$J_{45} = 8.8$
13	Acetone-d_6	10.50	7.50	8.13*	7.74	—	7.80	7.40	7.50	8.00	8.20	$J_{410} = 0.9$

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* Proton of the hydroxy group.

In the IR spectra of compounds **5-7** the C=O absorption bands (1710, 1720, and 1700 cm^{-1} respectively) are close to the corresponding band in isatin. Unfortunately because of the poor solubility of these compounds in ethanol we were unsuccessful in recording their UV spectra.

Assignment of the signals in the ^{1}H NMR spectra of compounds **5-7** was based on the differences in the multiplicity of the signals of the indole part of the molecule: the presence of an AB system with coupling constants characteristic for *o*-protons in the case of angular fused rings (compounds **5** and **6**) or the presence of two signals from the weakly interacting *p*-protons in the case of linear molecules (compound **7**).

In the mass spectra of the isomeric annelated isatins **5-7** intense molecular ion peaks [M$^+$] were observed with *m/z* 253, and the character of further fragmentation, confirmed by metastable transitions, did not contradict the proposed structure.

Absorption bands for the NH groups were observed at 3490, 3440, and 3415 cm^{-1} respectively in the IR spectra of compounds **8-10**. The UV spectra of compounds **8-10** were analogous to compounds we had prepared previously by the Fischer reaction [3]. Mixed melting points of compounds **8-10** with authentic compounds made by the Fischer reaction gave no depressions of the melting points.

Absorption bands characteristic for the OH group are present in the IR spectra of compounds **11-13** in the regions 3480-3500, 3470-3490, and 3500-3510 cm^{-1} respectively. Their UV spectra are reminiscent of that of indole. The ^{1}H NMR spectra of compounds **11-13** have sharp singlets of the OH proton at 8.20, 8.15, and 8.13 ppm respectively.

Thus our proposed method of the synthesis of heterocyclic systems **8-10** is much shorter than that *via* the Fischer reaction [3]. As a result of the choice of reduction conditions the 1- and 3-hydroxy derivatives **10-12**, which have not been described previously, were obtained. These compounds are of interest from the pharmacological point of view [4].

EXPERIMENTAL

UV spectra of ethanol solutions were measured in 1 cm cuvettes with a Specord UV-vis instrument. IR spectra of nujol mulls were recorded with UR-20 spectrophotometer. ^{1}H NMR spectra of solutions in deuterated solvents with TMS as internal standard were recorded with a Varian CFT-20 instrument (working frequency 80 MHz).

Mass spectra were recorded by direct introduction into the ion source (emission current of the cathode 1.5 μA, ionization voltage 50 eV) of an MX 1303 machine.

1-(Isonitrosoacetamido)dibenzothiophene (3). The following were added consecutively to a solution of chloral hydrate (16.5 g, 0.1 mol) in water (240 ml): crystalline $Na_2SO_4\cdot10H_2O$ (260 g, 0.8 mol), 1-aminodibenzothiophene (**1**) (19.9 g, 0.1 mol), dissolved in hot water (3 l) plus conc. HCl (20 ml), and a solution of $NH_2OH\cdot HCl$ (22.3 g, 0.32 mol) in water (100 ml).

The mixture was rapidly heated to boiling and was boiled with constant stirring for 2 h, after which the reaction mixture was cooled in water. The crystals of compound **3** were filtered off, carefully washed with water and dried. Yield 24.3 g (90%); mp 213-215°C. IR spectrum, ν, cm^{-1}: 1680 (C=O), 3300 (NH). UV spectrum, λ_{max}, nm (log ε): 235 (4.41), 265 (4.10), 285 (4.15), 333 (4.05), 350 (4.00). Found, %: C 62.0; H 4.0; N 10.4; S 11.6. $C_{14}H_{10}N_2O_2S$. Calculated, %: C 62.2; H 3.7; N 10.13; S 11.9.

2-(Isonitrosoacetamido)dibenzothiophene (4) was obtained from 2-aminodibenzothiophene (**2**) analogously to compound **3**. Yield 80%; mp 190-192°C. IR spectrum, ν, cm^{-1}: 1700 (C=O), 3350 (NH). UV spectrum, λ_{max}, nm (log ε): 208 (4.51), 245 (4.80), 252 (4.81), 270 (4.21), 295 (4.18), 312 (4.50), 310 (4.40). Found, %: C 62.0; H 4.0; N 10.4; S 11.6. $C_{14}H_{10}N_2O_2S$. Calculated, %: C 62.2; H 3.7; N 10.3; S 11.9.

2,3-Dioxo-2,3-dihydro-1H-benzo[*b*]thiopheno[2,3-*g*]indole (5). Dried compound **3** (13.5 g, 0.05 mol) was added in small portions with constant stirring at 50°C to 85% H_2SO_4 (14.7 g, 0.3 mol). At the completion of the addition the reaction mixture was heated at 80°C for 1 h, then slowly cooled and poured into 10-12 times the amount of crushed ice. After 1 h the precipitate was filtered off and washed with water. The crude product was suspended in 5 times as much hot water and 40% NaOH solution was added with stirring until solution was complete. 12% HCl solution was added cautiously until formation of a precipitate began. The filtrate was filtered off and discarded. Conc. HCl was added to the filtrate to pH 1 and the mixture was left for 2.5 h. The precipitate was filtered off, thoroughly washed with water, and dried to give compound **5** (7.59 g, 60%); mp 312-314°C. IR spectrum, ν, cm^{-1}: 1710 (C=O), 3390 (NH), 3270 (NH···O=C). Found, %: C 66.2; H 3.0; N 5.2; S 12.9. $C_{14}H_7NO_2S$. Calculated, %: C 66.4; H 2.7; N 5.5; S 12.6.

1,2-Dioxo-1,2-dihydro-1H-benzo[*b*]thiopheno[3,2-*e*]indole (6) and 2,3-Dioxo-2,3-dihydro-1H-benzo[*b*]thiopheno[2,3-*f*]indole (7) were obtained from the 2-isonitroso derivative (**4**) analogously to compound **5**. The mixture of isomers **6** and **7** was separated as follows. The crude product was suspended in a five-fold excess of hot water and 40% aqueous NaOH was added with stirring until the product dissolved completely. Acetic acid was then added carefully to pH 3 and the mixture left for 3 h. The precipitate was filtered off, carefully washed with water and dried to give isomer **6** (7.59 g, 60%); mp 312-314°C. IR spectrum, ν, cm^{-1}: 1720 (C=O), 3400 (NH), 3260 (NH···O=C). Found, %: C 66.2; H 3.0; N 5.2; S 12.8. $C_{14}H_7NO_2S$. Calculated, %: C 66.4; H 2.7; N 5.5; S 12.6. After separation of isomer **6**, the filtrate was acidified to pH 1 with conc. HCl and the mixture was kept overnight. The precipitated crystals, thoroughly washed with water until free from acid and dried to give isomer **7** (2.5 g, 25%); mp 294-296°C. IR spectrum, ν, cm^{-1}: 1700 (C=O), 3385 (NH), 3260 (NH···O=C). Found, %: C 66.1; H 2.8; N 5.8; S 12.3. $C_{14}H_7NO_2S$. Calculated, %: C 66.4; H 2.7; N 5.5; S 12.6.

Benzo[*b*]thiopheno[2,3-*g*]indole (8). A solution of diborane (1.7 g, 0.06 mol) (prepared *in situ* from sodium borohydride and boron trifluoride etherate) was added dropwise to a solution of compound **5** (2.53 g, 0.01 mol) in abs. THF (2.5 ml) at -78°C. The reaction mixture was kept for 30 h at 0°C and then poured into water (1.5 l), slightly acidified with HCl, and the reaction product was extracted with ether. The ether extract was washed with water and dried over Na_2SO_4. After removal of the solvent, the product was purified on a column of silica gel (eluent 1:5 diethyl ether–petroleum ether) to give compound **8** (1.34 g, 70%); mp 150-151°C. IR spectrum, ν, cm^{-1}: 3490 (NH). UV spectrum, λ_{max}, nm (log ε): 206 (4.29), 215 (4.29), 236 (4.40), 246 (4.50), 264 (4.00), 305 (4.10), 330 (3.90), 340 (3.80). Found, %: C 75.1; H 3.8; N 6.1; S 14.0. $C_{14}H_9NS$. Calculated, %: C 75.3; H 4.0; N 6.3; S 14.3.

Benzo[*b*]thiopheno[3,2-*e*]indole (9) was obtained from isatin **6** analogously to compound **8**. Yield 50%; mp 138-140°C. IR spectrum, ν, cm^{-1}: 3440 (NH). UV spectrum, λ_{max}, nm (log ε): 213 (4.30), 250 (4.70), 260 (4.63), 290 (4.21), 300 (4.25), 320 (3.80). Found, %: C 75.2; H 4.2; N 6.4; S 14.5. $C_{14}H_9NS$. Calculated, %: C 75.3; H 4.0; N 6.3; S 14.3.

Benzo[*b*]thiopheno[2,3-*f*]indole (10) was obtained from isatin **7** analogously to compound **8**. Yield 50%; mp 190-192°C. IR spectrum, ν, cm^{-1}: 3415 (NH). UV spectrum, λ_{max}, nm (log ε): 230 (4.70), 240 (4.80), 280 (4.10), 310 (4.30). Found, %: C 75.3; H 3.9; N 6.5; S 14.6. $C_{14}H_9NS$. Calculated, %: C 75.3; H 4.0; N 6.3; S 14.3.

3-Hydroxybenzo[*b*]thiopheno[2,3-*g*]indole (11). A. Lithium aluminum hydride (2.4 g, 0.09 mol) was mixed with cooling with absolute pyridine (240 ml) and dried compound **5** (5.1 g, 0.02 mol) was added in portions with stirring so that the temperature of the reaction medium did not exceed 25°C. Water (20 ml) was added by drops with stirring over an 8 h period, followed by tartaric acid (240 g) in water (960 ml). The product was extracted with ether. The extract was washed with dilute tartaric acid and water, dried over Na_2SO_4, and the solvent evaporated. The product was purified on a silica gel column (eluent 1:3 diethyl ether–hexane) to give **11** which crystallized slowly (1.9 g, 40%); mp 215-216°C. IR spectrum, ν, cm^{-1}: 3300 (NH), 3480-3500 (OH). UV spectrum, λ_{max}, nm (log ε): 235 (4.45), 260 (4.70), 275 (4.65), 310 (4.40). Found, %: C 70.4; H 4.0; N 6.0; S 13.6. $C_{14}H_9NOS$. Calculated, %: C 70.2; H 3.7; N 5.8; S 13.4.

B. Compound **5** (2.5 g, 0.01 mol) was added with stirring at ~20°C to a solution of sodium borohydride (1.1 g, 0.03 mol) in 2-propanol (50 ml). The mixture was heated to 50°C, kept at that temperature for 3 h, and left overnight at ~20°C. Dilute HCl was then added carefully until evolution of hydrogen ceased. The product was extracted from this solution with small portions of ether. The ether extract was carefully washed with water and dried over Na_2SO_4, and the solvent was evaporated. Compound **11** was purified on a silica gel column (eluent 1:3 diethyl ether–hexane). Yield 35%.

1-Hydroxybenzo[*b*]thiopheno[3,2-*e*]indole (12) was obtained analogously to compound **11** by method A from isatin **6**. Yield 30%; mp 180-194°C. IR spectrum, ν, cm^{-1}: 3320 (NH), 3470-3490 (OH). UV spectrum, λ_{max}, nm (log ε): 230 (4.40), 260 (4.90), 335 (4.15). Found, %: C 70.2; H 3.8; N 6.1; S 13.2. $C_{14}H_9NOS$. Calculated, %: 70.2; H 3.7; N 5.8; S 13.4. Yield by method B, 30%.

1-Hydroxybenzo[*b*]thiopheno[2,3-*f*]indole (13) was obtained analogously to compound **11** by method **A** from isatin **7**. Yield 30%; mp 180-194°C. IR spectrum, ν, cm^{-1}: 3310 (NH), 3500-3510 (OH). UV spectrum, λ_{max}, nm (log ε): 230 (4.40), 260 (4.90), 335 (4.15). Found, %: C 70.2; H 3.8; N 6.1; S 13.2. $C_{14}H_9NOS$. Calculated, %: 70.2; H 3.7; N 5.8; S 13.4. Yield by method **B**, 35%.

Mixed samples of compounds **11-13** prepared by methods **A** and **B** gave no depression of the melting points.

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