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INTERCONVERSIONS OF ISATIN-CONTAINING CONDENSED TETRACYCLIC SYSTEMS

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A new pathway has been proposed for the synthesis of dioxodihydro-1H-benzo[b]thiophenoindoles from the corresponding isomeric "amino acids" with amino groups at $C_{(2)}$ and $C_{(3)}$. This method yields these tetracyclic systems not only as a single isomer but also permits their interconversion. Linear isomers may be obtained from angular tetracyclic systems and, vice versa, the isomer with angular fusion of the pyrrole ring may be obtained from the linear isomer. The classical Sandmeyer reaction was used as a model for such conversions.

Keywords: isatin, indole, pyrrole.

Syntheses have been reported for benzo[*b*]thiopheno-1H-indoles, which are tetracyclic systems [1, 2]. In light of the strong antibacterial activity of methisazone (β-thiosemicarbazone of N-methylisatin, Marboran), which belongs to the 1-methylisatin system containing a thiosemicarbazide fragment [3-6], we developed methods for the synthesis of tetracyclic condensed systems, containing "amino acid" elements as well as benzothiophene structures with linear and angular fusion of the pyrrole and benzene rings. We found that it is relatively facile to convert the angular structures into linear structures and *vice versa*.

The starting "amino acids" **5-8** were obtained according to our previous procedure [1, 2].

The physicochemical and spectral characteristics of these compounds are given in Tables 1-3.

EXPERIMENTAL

The reaction course and purity of the products were monitored by thin-layer chromatography on Silufol UV-254 silica gel plates. The UV spectra of the samples in ethanol were taken on a Specord UV-vis spectrophotometer and the IR spectra of the samples in vaseline mull were taken on a UR-20 spectrometer using NaCl and LiF prisms. The ^{1}H NMR spectra were taken on a Bruker WP-200 SY spectrometer at 200 MHz with TMS as the internal standard.

2-Isonitrosoacetamidodibenzothiophene (3). $Na_2SO_4 \cdot 10H_2O$ (25.7 g, 0.8 mol), 2-aminodibenzothiophene **1** (19.9 g, 0.1 mol) dissolved in water (3 l) acidified with conc. HCl (20 ml), and hydroxylamine hydrochloride (22.0 g, 0.32 mol) dissolved in water (100 ml) was added consecutively to a solution of chloral hydrate (16.5 g, 0.1 mol) in water (150 ml). The mixture was heated at reflux for 2 h. The crystalline precipitate was filtered, thoroughly washed with water, dried, and recrystallized from ethyl acetate.

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TABLE 1. ^{1}H NMR Spectra of Compounds **3-20**

Compound	Chemical shifts, δ, ppm (SSCC, *J*, Hz)*													*J*, Hz
	1(H)	2(H)	3(H)	4(H)	5(H)	6(H)	7(H)	8(H)	9(H)	10H	11H	12H	13H	
3	8.69 d	—	7.78 dd	7.98 d	—	8.02 m	7.5-8.2 m		8.20 m	10.4 br. s	7.71 s	12.2 br. s	—	$J_{1,3} = 2$; $J_{3,4} = 9$
4	8.30 dd	7.73 dd	—	8.45 d	—	7.98 m	~7.5		8.27 m	10.4 br. s	7.7 s	12.2 br. s	—	$J_{1,2} = 8.8$; $J_{1,4} = 0.6$; $J_{2,4} = 2$
5	—	—	11.2 br. s	7.07 d	8.27 s	—	8.06 m	~7.5		9.41 m	—	—	—	$J_{4,5} = 8.3$
6	11.3 br. s		—	8.40 d	—	8.14 m	~7.5		8.42 m	7.71 d	—	—	—	$^5J_{4,10} = 0.8$
7	11.0 br. s	—	—	8.40 d	8.45 m	~7.5		7.85 m	—	8.40 m	—	—	—	$J_{4,10} = 0.8$
8	—	—	10.8 br. s	—	8.60 s	8.73 m	~7.5		8.23 m	—	11.5 br. s	—	—	$J_{6,9} = 0.6$
9	—	—	6.60 d	7.82 d	—	7.90 m	~7.5		8.15 m	8.2 br. s	9.0 br. s	—	—	$J_{3,4} = 8.7$
10	7.15 d	—	—	7.90 d	—	8.92 m	~7.5		8.20 m	8.0 br. s	8.2 br. s	—	—	$^5J_{1,4} = 0.5$
11	—	—	11.2 br. s	7.03 d	8.54 d	8.29 m	~7.5		8.04 m			—	—	$J_{4,5} = 8.3$
12	8.11 d	6.55 d	—	—	—	7.94 m	~7.5		8.25 m	7.2 br. s	7.1 br. s	—	—	$J_{1,2} = 8.6$
13	—	—	7.79 d	8.10 d	—	7.92 m	~7.5		8.96 m	10.4 br. s	8.5 br. s	8.0 s	10.55 br. s	$J_{3,4} = 8.8$; $J_{6,9} = 0.6$
14	8.10 d	—	—	7.20 d	—	8.09 m	~7.5		8.20 m	10.1 br. s	8.44 br. s	7.80 d	10.22 br. s	$J_{1,4} = 0.8$
15	8.40 d	—	—	7.60 d	—	8.10 m	~7.5		8.25 m	7.9 br. s	8.2 br. s	—	—	$J_{1,4} = 0.4$
16	7.90 d	7.75 d	—	—	—	7.90 m	~7.5		8.24 m	9.0 br. s	7.94 br. s	5.99 br. s	9.10 br. s	$J_{1,2} = 8.7$; $J_{6,9} = 0.6$
17	10.7 br. s	—	—	8.15 s	—	7.70 m	~7.5		8.10 m	—	10.6 br. s	—	—	$J_{6,9} = 0.7$
18	—	—	10.9 br. s	—	8.60 s	—	8.10 m	~7.5		8.77 m	11.1 br. s	—	—	$J_{7,10} = 0.7$
19	8.87 d	—	—	7.60	—	7.73 m	~7.5		8.23 m	12.5 br. s	12.6 br. s	8.95 s	13.5 br. s	$J_{1,4} = 0.7$
20	10.7 br. s	—	—	8.86 s	8.24 m	~7.5		7.79 m	—	—	$\Sigma H_2O \leftrightarrow OH$	—	—	$J_{5,8} = 0.7$

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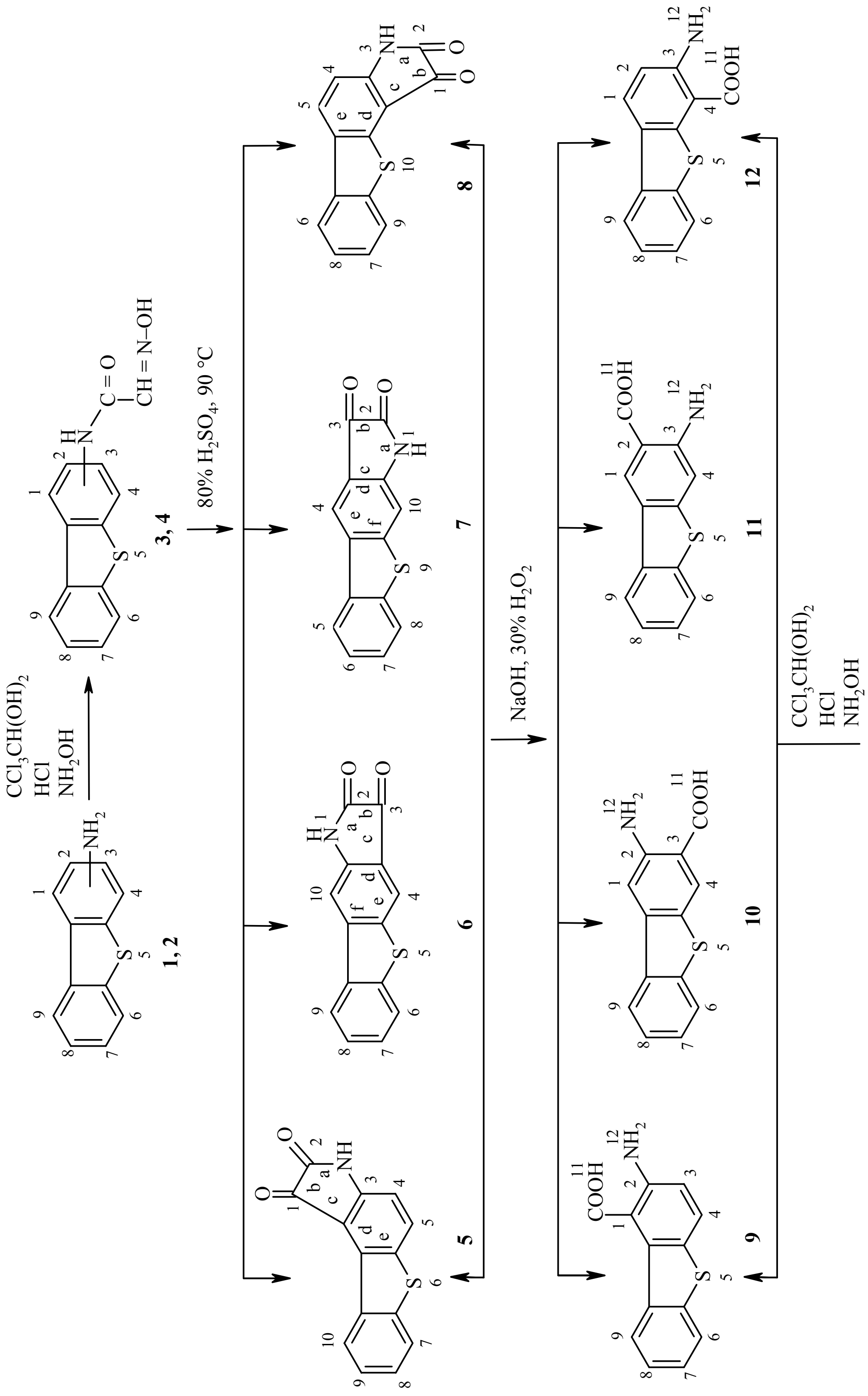
* ^{1}H NMR spectrum recorded in DMSO-d_6 (compounds **3-8, 10-20**) and acetone-d_6 (compound **9**).


1, 2
CCl3CH(OH)2
HCl
NH2OH
3, 4
80% H2SO4, 90 °C
5
6
7
8
NaOH, 30% H2O2
9
10
11
12
CCl3CH(OH)2
HCl
NH2OH
NH2
COOH
S

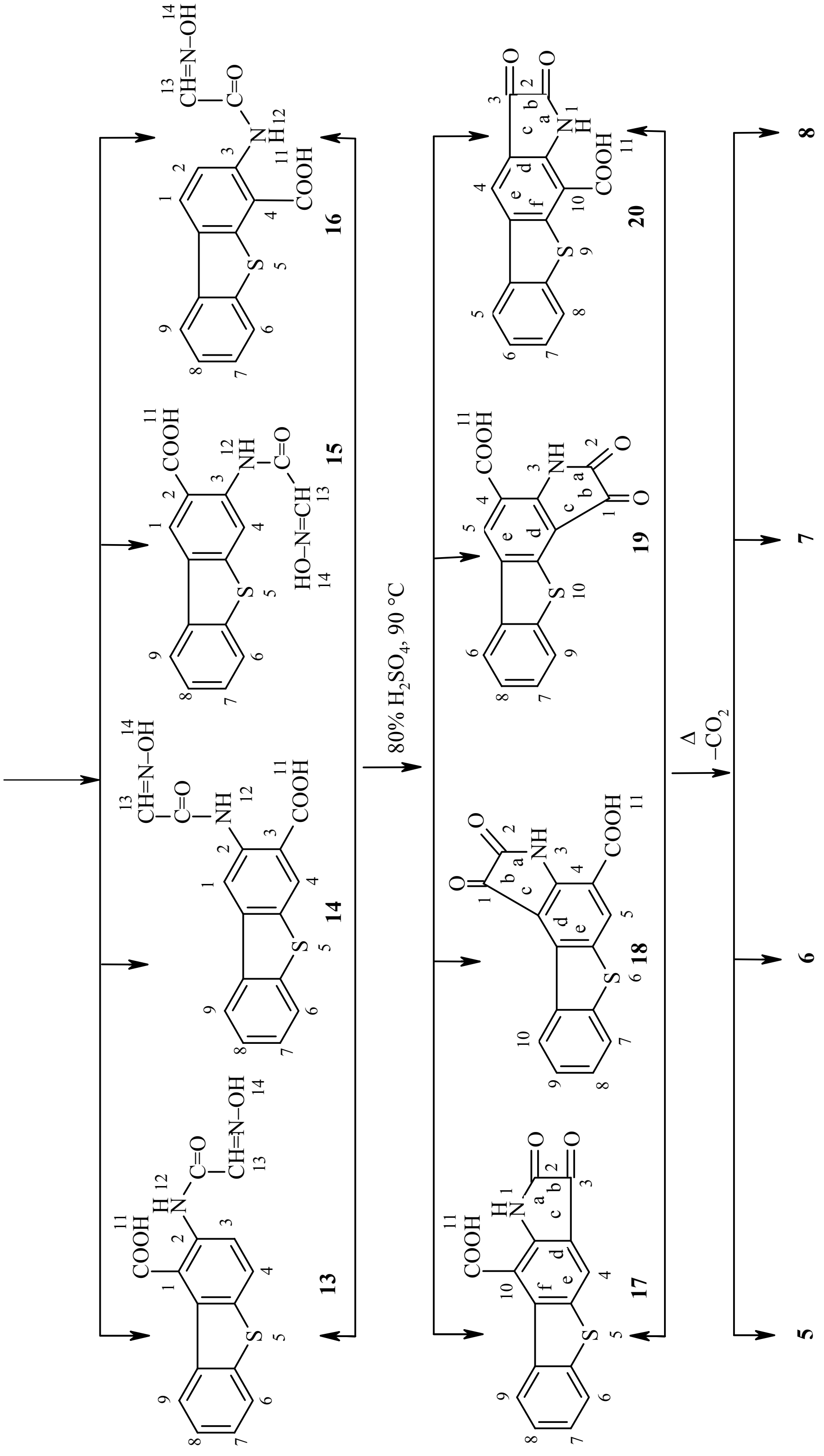

13
14
15
16
80% H_2SO_4, 90 °C
17
18
19
20
Δ
$-CO_2$
5
6
7
8

TABLE 2. Characteristics of Compounds **3-20**

Compound	Empirical formula	Found, % Calculated, %				mp, °C	Yield, %
		C	H	N	S		
3	$C_{14}H_{10}N_2O_2S$	62.5 62.22	3.5 3.70	10.6 10.37	12.1 11.85	213-215	75
4	$C_{14}H_{10}N_2O_2S$	62.3 62.22	3.6 3.70	10.5 10.37	11.9 11.85	235-236	85
5	$C_{14}H_7NO_2S$	66.1 66.40	2.8 2.76	5.8 5.53	12.9 12.64	275-277	60
6	$C_{14}H_7NO_2S$	66.7 66.40	2.8 2.76	5.7 5.53	12.8 12.64	262-264	20
7	$C_{14}H_7NO_2S$	66.6 66.40	2.9 2.76	5.8 5.53	12.9 12.64	210-213	15
8	$C_{14}H_7NO_2S$	66.1 66.40	2.8 2.76	5.8 5.53	12.8 12.64	230-231	70
9	$C_{13}H_9NO_2S$	64.3 64.19	3.6 3.70	5.7 5.76	13.3 13.16	196-198	80
10	$C_{13}H_9NO_2S$	64.4 64.19	3.8 3.70	5.5 5.76	13.0 13.16	165-167	80
11	$C_{13}H_9NO_2S$	64.4 64.19	3.8 3.70	5.4 5.76	13.5 13.16	157-159	69
12	$C_{13}H_9NO_2S$	64.2 64.19	4.0 3.70	5.4 5.76	13.4 13.16	180-183	73
13	$C_{15}H_{10}N_2O_4S$	57.4 57.32	3.0 3.18	8.8 8.91	10.5 10.19	213-215	69.6
14	$C_{15}H_{10}N_2O_4S$	57.2 57.32	4.0 3.18	8.7 8.91	10.4 10.19	220-221	70.7
15	$C_{15}H_{10}N_2O_4S$	57.5 57.32	3.5 3.18	8.7 8.91	10.5 10.19	199-200	90
16	$C_{15}H_{10}N_2O_4S$	57.7 57.32	2.5 3.18	9.0 8.91	10.5 10.19	178-180	80
17	$C_{15}H_7NO_4S$	60.4 60.60	2.4 2.35	4.9 4.71	10.9 10.77	305-306	85
18	$C_{15}H_7NO_4S$	60.3 60.60	2.7 2.35	4.8 4.71	10.7 10.77	325-327	75
19	$C_{15}H_7NO_4S$	60.7 60.60	2.7 2.35	5.0 4.71	11.1 10.77	317-320	90
20	$C_{15}H_7NO_4S$	60.9 60.60	2.7 2.35	4.9 4.71	10.5 10.77	350 (dec.)	88

3-Isonitrosoacetamidodibenzothiophene (4) was obtained from 3-aminodibenzothiophene **2** by analogy to the procedure for **3** and recrystallized from ethyl acetate.

1,2-Dioxo-1,2-dihydro-1H-benzo[*b*]thiopheno[3,2-*e*]indole and 2,3-Dioxo-2,3-dihydro-1H-benzo[*b*]thiopheno[2,3-*f*]indole (6). Dry compound **3** (13.5 g, 0.05 mol) was added with constant stirring to a solution of 80% sulfuric acid (14.7 g, 0.3 mol), maintaining the temperature below 50°C. The mixture was heated for an additional 2 h at 80°C, cooled, and poured into a 10-12-fold volumetric excess of ice. After 3 h, the precipitate was filtered off and washed with water. The crude product was suspended in a five-fold excess of hot water and 40% aq. NaOH was added with stirring until complete dissolution. Then, 12% hydrochloric acid was carefully added until the onset of precipitate formation. The precipitate was filtered off and discarded. The filtrate was acidified to pH 3 by adding acetic acid and left for 1.5 h. The precipitate of **5** was filtered off, washed with water, and dried. After removal of isomer **5**, the filtrate was brought to pH 1 by adding concentrated hydrochloric acid and left for 24 h. The crystalline precipitate was filtered off, washed with water until the wash water was neutral, and dried to give 2.5 g **6**.

TABLE 3. UV and IR Spectra of Compounds **3-20**

Compound	IR spectrum, cm^{-1}			UV spectrum, λ_{max}, nm (log ε)*
	CO	NH	NH···O=C	
3	1690	3385	—	235 (4.41), 265 (4.10), 285 (4.15), 333 (4.05), 350 (4.00)
4	1710	3400	—	245 (4.21), 255 (4.22), 276 (4.30), 310 (4.05), 330 (4.00)
5	1700	3390	3250	—
6	1710	3400	3260	—
7	1710	3410	3300	—
8	1690	3390	3335	—
9	1690	3385	—	240 (4.45), 275 (4.15), 290 (4.25), 340 (4.00), 345 (3.90)
10	1700	3410	—	241 (4.30), 257 (4.05), 266 (4.00), 288 (3.86), 315 (3.97)
11	1680	3390	—	238 (4.05), 260 (4.35), 277 (4.40), 297 (3.99), 315 (4.77)
12	1700	3400	—	230 (3.90), 255 (4.15), 276 (4.00), 295 (3.86), 315 (4.10)
13	1690	3400	—	242 (4.15), 270 (4.27), 289 (4.40), 299 (4.19), 333 (4.56)
14	1690	3420	—	234 (4.07), 233 (4.35), 278 (4.44), 300 (3.92), 325 (4.18)
15	1710	3400	—	244 (4.17), 265 (4.45), 280 (4.55), 300 (4.00), 315 (4.27)
16	1710	3400	—	225 (4.20), 237 (4.33), 265 (4.39), 287 (4.10), 315 (3.86)
17	1690	3395	3240	—
18	1695	3400	3330	—
19	1680	3390	3250	—
20	1700	3400	3345	—

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* UV spectra of compounds **5-8** and **17-20** could not be taken due to their poor solubility in ethanol.

2,3-Dioxo-2,3-dihydro-1H-benzo[*b*]thiopheno[3,2-*f*]indole (7) and 1,2-Dioxo-1,2-dihydro-1H-benzo[*b*]thiopheno[2,3-*e*]indole (8) were obtained from **4** analogously to the procedure for **5** and **6**.

2-Amino-1-carboxydibenzothiophene (9). A mixture of "amino acid" **5** (2.53 g, 0.01 mol), water (70 ml), and 30% aq. NaOH (20 ml) was heated at reflux for 3 h and cooled. Then, 30% aq. H_2O_2 (46 ml) was added [7]. The mixture was stirred at room temperature for an additional 14 h, let stand overnight, and brought to pH 5-6 by adding hydrochloric acid. The precipitate formed was filtered off, washed with water, and dried.

Aminodibenzothiophenes 10-12 were obtained analogously to the procedure for **9** described by Ponci et al. [7].

2-Amino-3-carboxydibenzothiophene (10) was obtained from **6**.

3-Amino-2-carboxydibenzothiophene (11) was obtained from **7**.

3-Amino-4-carboxydibenzothiophene (12) was obtained from **14**.

Isonitrosoacetamidodibenzothiophenes 13-16 were obtained from **3**.

1-Carboxy-2-isonitrosoacetamidodibenzothiophene (13) was obtained from **9**.

3-Carboxy-2-isonitrosoacetamidodibenzothiophene (14) was obtained from **10**.

2-Carboxy-3-isonitrosoacetamidodibenzothiophene (15) was obtained from **11**.

4-Carboxy-3-isonitrosoacetamidodibenzothiophene (16) was obtained from **12**.

10-Carboxy-2,3-dioxo-2,3-dihydro-1H-benzo[*b*]thiopheno[2,3-*f*]indole (17). Thoroughly dried **13** (15.7 g, 0.05 mol) was added with constant stirring in small portions to 80% H_2SO_4 (140 g) at 50°C. At the end of the addition, the temperature of the reaction mixture was raised to 80°C. The mixture was maintained at this temperature for 2 h and then cooled. The mixture was poured into a 10-12-fold excess of chopped ice and left overnight. The crystalline precipitate was filtered off, suspended in a five-fold volume of hot water and then, 40% aq. NaOH was added with constant stirring until the precipitate was completely dissolved. Then, 12% hydrochloric acid was added cautiously to the solution obtained until the appearance of turbidity. The precipitate was filtered off and discarded. The filtrate was brought to pH 1 by adding concentrated hydrochloric acid. The crystalline precipitate was filtered off, thoroughly washed with water, and dried in a vacuum desiccator to give 9.01 g of pure **17**.

Dihydrobenzothiophenoindoles 18-20, 6, and **7** were obtained analogously to **17**.

4-Carboxy-1,2-dioxo-1,2-dihydro-1H-benzo[*b*]thiopheno[3,2-*e*]indole (18) was obtained from **14**.

4-Carboxy-1,2-dioxo-1,2-dihydro-1H-benzo[*b*]thiopheno[2,3-*e*]indole (19) was obtained from **15**.

10-Carboxy-2,3-dioxo-2,3-dihydro-1H-benzo[*b*]thiopheno[3,2-*f*]indole (20) was obtained from **16**.

1,2-Dioxo-1,2-dihydro-3H-benzo[*b*]thiopheno[3,2-*e*]indole (5) was also obtained by decarboxylation upon heating **17** in the vicinity of its melting point (±10-15°C).

2,3-Dioxo-2,3-dihydro-1H-benzo[*b*]thiopheno[2,3-*f*]indole (6) was obtained by the decarboxylation of **18**.

2,3-Dioxo-2,3-dihydro-1H-benzo[*b*]thiopheno[3,2-*f*]indole (7) was obtained by the decarboxylation of **19**.

1,2-Dioxo-1,2-dihydro-3H-benzo[*b*]thiopheno[2,3-*e*]indole (8) was obtained by the decarboxylation of **20**.

Mixed probes of these products with independently synthesized authentic samples of **5-8** did not give a depressed melting point.

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