Chemistry of Heterocyclic Compounds, Vol. 43, No. 3, 2007

NEW METHOD FOR THE SYNTHESIS OF INDOLE- AND BENZOTHIOPHENE-CONTAINING CONDENSED SYSTEMS

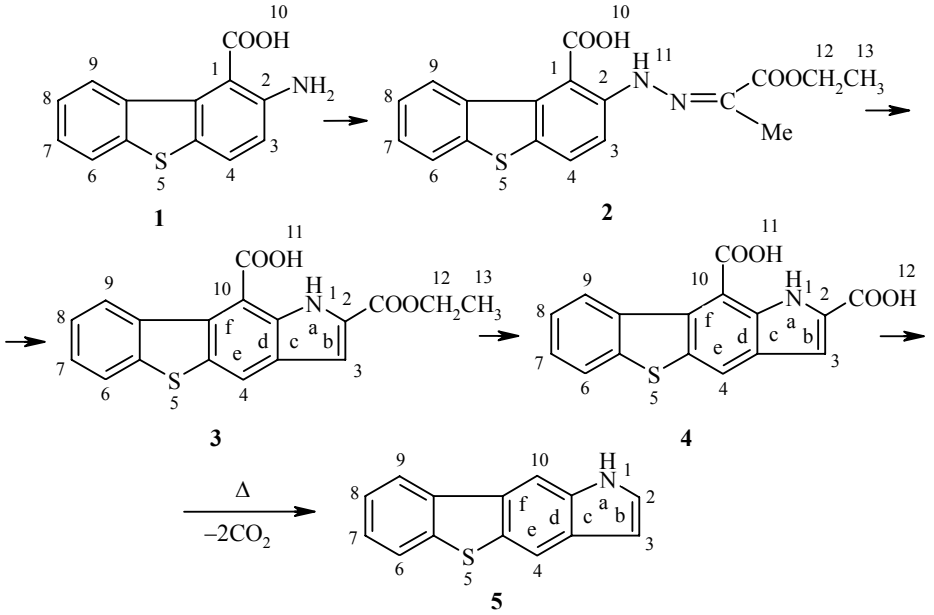
T. E. Khoshtariya, L. N. Kurkovskaya, K. T. Batsikadze, M. M. Matnadze, M. I. Sikharulidze, V. O. Ananiashvili, T. O. Dzhashi, I. G. Abesadze, and M. G. Alapishvili

A new method is described for the synthesis of the heterocyclic systems of benzo[b]thiophenoindoles from the respective isomeric amino acids with amino groups at positions 2 and 3. The method makes it possible to produce the tetracyclic systems with both angular and linear structure. The classical Fischer reaction served as model for such transformations.

Keywords: indole, pyrrole.

The high activity of the derivatives of indole and benzofuran [1-3] prompted us to start investigations into the synthesis of the isomeric tetracyclic systems of benzo[*b*]furoindoles. The complexity of the synthesis of such heterocycles [4] led us to the idea of using *ortho*-substituted amines of dibenzothiophene as starting compounds. If there is a substituent at the *ortho* position only one isomer is undeniably formed. The carboxyl group COOH proved to be the most suitable substituent.

Scheme 1



Georgian Technical University, Tbilisi 380075; e-mail: t_khoshtaria@yahoo.com. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 361-367, March, 2007. Original article submitted August 4, 2004.

The isomeric *ortho*-substituted aromatic amino acids can be obtained fairly easily from the corresponding isomeric dioxodihydrobenzo[*b*]thiophenoindoles [5, 6] by treating the latter with an aqueous solution of alkali followed by oxidation with a 30% solution of H_2O_2 [7].

By the proposed method it is possible to obtain tetracyclic systems with both linear and angular structure.

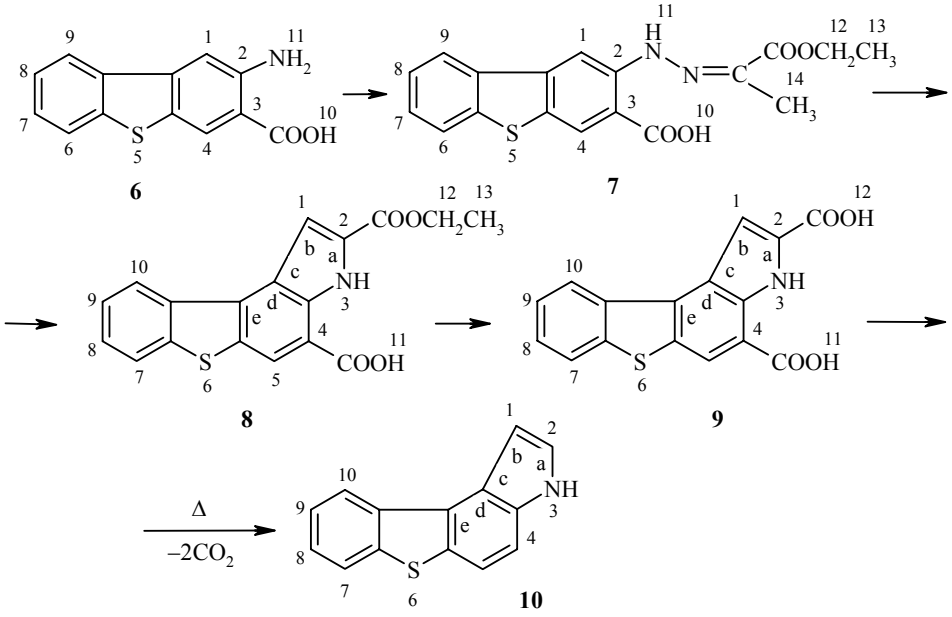
The initial amino acids **1**, **6**, **11**, and **16** were obtained by the method in [8].

Like the corresponding carboxylic acids **4**, **9**, **14**, and **19**, the half-esters **2**, **3**, **7**, **8**, **12**, **13**, **17**, and **18** are interesting both in their own right and as starting compounds for the production of a whole series of physiologically active substances.

Compounds **2-5**, **7-10**, **12-15**, and **17-20** were synthesized by the methods described in [4].

The yields and properties of the obtained compounds are presented in Tables 1-3.

Scheme 2



Scheme 3

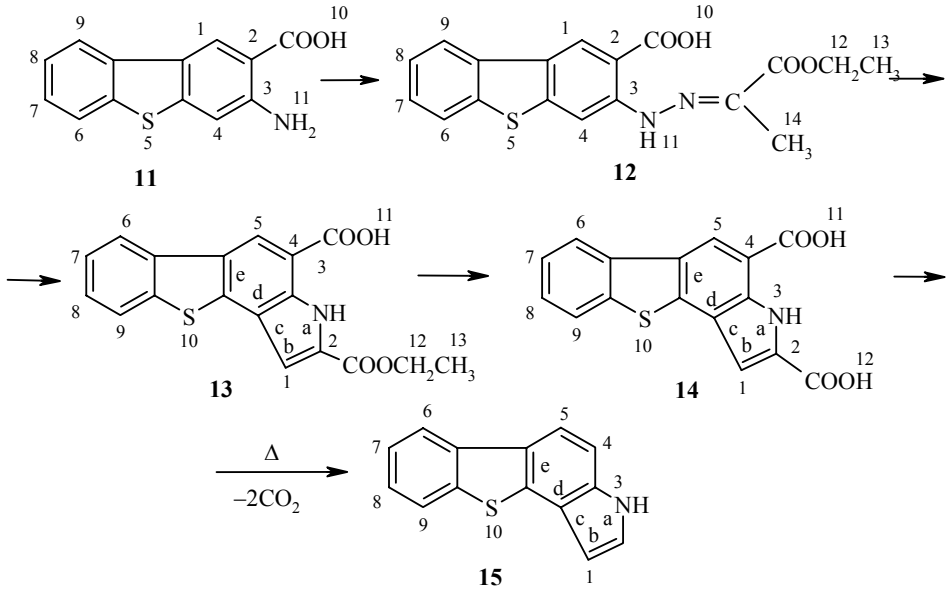


TABLE 1. The ^{1}H NMR Spectra of Compounds **2-5**, **7-10**, **12-15** and **17-20**

Com-pound	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)	10(H)	11(H)	12(H)	13(H)	14(H)	
2	—	—	7.10 d	7.90 d	—	7.95 m	~7.5	8.25 m	10.00 br. s	10.3 br. s	4.30 q	1.35 t	2.10 s	$J_{3,4}$ = 9; $J_{12,13}$ = 7.2
3	11.90 br. s	—	8.30 s	7.80 s	—	7.90 m	~7.5	8.30 m	—	11.8 br. s	4.40 q	1.37 t	—	$J_{12,13}$ = 7.0
4	10.7 br. s	—	7.77 s	8.41s	—	7.99 m	~7.5	8.35 m	—	10.5 br. s	10.3 br. s	—	—	
5	10.4 br. s	7.42 dd	6.53 dd	7.99 d		7.79 m	~7.5	8.17 m	8.27 d	—		—	—	$J_{1,2}$= 2.4; $J_{1,3}$ = 2.0; $J_{2,3}$ = 3.0; $J_{4,10}$ = 0.7
7	7.45 d	—	—	8.07 d	—	8.10 m	~7.5	8.50 m	9.80 br. s	10.06 br. s	4.30 q	1.37 t	2.06 s	$^5J_{1,4}$ = 0.5; $J_{12,13}$ = = 7.2
8	8.10 s	—	12.1 br. s	—	8.10 s	—	8.20 m	~7.5	8.70 m	4.40 q	1.40 t	12.0 br. s	—	$J_{12,13}$ = 7.0
9	8.15 s	—	10.2 br. s	—	8.55 s	—	8.10 m	~7.5	8.67 m	10.8 br. s	10.7 br. s	.	—	
10	7.22 dd	7.54 dd	10.6 br. s	7.62 d	7.62 d	—	7.94m	~7.5	8.52 m	—		—	—	$J_{1,2}$ = 3.0; $J_{1,3}$ = 2; $J_{2,3}$ = 2.2; $J_{1,4}$ = 0.5
12	8.50 d	—	—	8.00 d	—	8.12 m	~7.5	8.25 m	9.90 br. s	10.00 br. s	4.35 q	1.39 t	2.10 s	$^5J_{1,4}$ = 0.82; $J_{12,13}$ = 7.1
13	8.21 s	—	11.9 br. s	—	8.55 s	8.30 m	~7.5	8.35 m	—	12.0 br. s	4.40 q	1.43 t		$J_{12,13}$ = 7.1
14	8.39 s	—	10.3 br. s	—	8.73 s	8.25 m	~7.5	8.25 m	—	10.7 br. s	10.5 br. s	—	—	
15	6.65 dd	7.44 dd	10.6 br. s	7.54 dd	7.95 d	8.16 m	~7.5	7.90 m	—	—	—	—	—	$J_{1,2}$ = 3.0, $J_{1,3}$ = 2.1; $J_{2,3}$ = 2.4; $J_{1,4}$ = 0.8; $J_{4,5}$ = 8.7
17	8.25 d	7.34 d		—	—	7.95 m	~7.5	8.30 m	8.9 br. s	9.0 br. s	4.35 q	1.38 t	2.06 s	$J_{1,2}$ = 8.6; $J_{12,13}$ = 7.2
18	10.0 br. s	—	7.67 s	8.70 s	8.30 m	~7.5	8.00 m	—	—	9.5 br. s	4.30 q	1.40 t		$J_{12,13}$ = 7.1
19	10.2 br. s	—	7.93 s	8.71 s	8.32 m	~7.5	7.99 m	—	—	9.8 br. s	9.5 br. s	—	—	
20	10.3 br. s	7.41 dd	6.53 dd	8.27 d	8.17 m	~7.5	7.79 m	—	7.70 t	—	—	—	—	$J_{1,2}$ = 2.2; $J_{1,3}$ = 2.0; $J_{2,3}$ = 3.0; ≈ $J_{4,10}$ = 0.8

* The ^{1}H NMR spectra were recorded in DMSO-d_6 (compounds **2-4**, **7-9**, **12-14** and **17-19**) and acetone-d_6 (compounds **5**, **10**, **15**, **20**).

Scheme 4

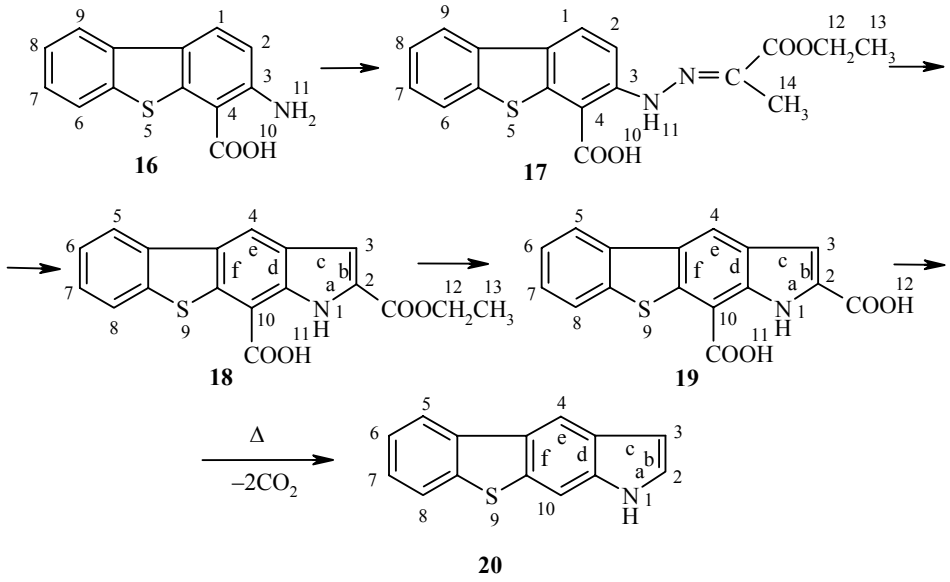


TABLE 2. The Characteristics of Compounds **2-5**, **7-10**, **12-15**, and **17-20**

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Yield, %
		C	H	N	S		
2	$C_{18}H_{16}N_2O_4S$	60.5 / 60.67	4.8 / 4.49	7.6 / 7.86	9.0 / 8.98	201-203	82
3	$C_{18}H_{13}NO_4S$	63.5 / 63.71	3.8 / 3.83	4.4 / 4.12	9.7 / 9.43	178-179	89
4	$C_{16}H_9NO_4S$	61.5 / 61.73	2.8 / 2.89	4.4 / 4.50	10.4 / 10.28	288-290	80
5	$C_{14}H_9NS$	75.2 / 75.33	4.1 / 4.03	6.2 / 6.27	14.3 / 14.34	190-192	78
7	$C_{18}H_{16}N_2O_4S$	60.5 / 60.67	4.7 / 4.49	7.5 / 7.86	8.7 / 8.98	177-179	80
8	$C_{18}H_{13}NO_4S$	63.7 / 63.71	3.5 / 3.83	4.3 / 4.12	9.7 / 9.43	194-195	72
9	$C_{16}H_9NO_4S$	61.7 / 61.73	3.0 / 2.89	4.2 / 4.50	10.3 / 10.28	300-301	90
10	$C_{14}H_9NS$	75.3 / 75.33	4.2 / 4.03	6.2 / 6.27	14.4 / 14.34	138-140	60
12	$C_{18}H_{16}N_2O_4S$	60.7 / 60.67	4.6 / 4.49	7.4 / 7.86	8.9 / 8.98	185-186	79
13	$C_{18}H_{13}NO_4S$	63.6 / 63.71	3.9 / 3.83	4.2 / 4.12	9.3 / 9.43	215-216	77
14	$C_{16}H_9NO_4S$	61.8 / 61.73	2.7 / 2.89	4.4 / 4.50	10.6 / 10.28	290-291	95
15	$C_{14}H_9NS$	75.5 / 75.33	4.1 / 4.03	6.3 / 6.27	14.0 / 14.34	132-135	61
17	$C_{18}H_{16}N_2O_4S$	60.7 / 60.67	4.8 / 4.49	7.4 / 7.86	9.0 / 8.98	195-197	55
18	$C_{18}H_{13}NO_4S$	64.0 / 63.71	4.0 / 3.83	4.2 / 4.12	9.2 / 9.43	245-247	85
19	$C_{16}H_9NO_4S$	61.6 / 61.73	2.7 / 2.89	4.6 / 4.50	10.0 / 10.28	305-307	95
20	$C_{14}H_9NS$	75.5 / 75.33	4.1 / 4.03	6.3 / 6.27	14.6 / 14.34	148-150	42

TABLE 3. The IR and UV Spectra of Compounds **2**-**5**, **7**-**10**, **12**-**15**, and **17**-**20**

Compound	IR spectrum, ν, cm^{-1}		UV spectrum, λ_{max}, nm (log ε)
	CO	NH	
2	1690	3380	245 (4.35), 275 (4.05), 280 (4.25), 298 (3.90), 338 (4.10)
3	1670	3365	233 (4.22), 250 (4.15), 278 (4.35), 290 (3.75), 335 (3.90)
4	1700 1680	3410	233 (4.00), 267 (4.35), 286 (4.45), 299 (4.55), 335 (4.80)
5	—	3415	224 (4.66), 236 (4.63), 266 (4.01), 311 (4.30)
7	1690	3400	237 (4.20), 245 (4.35), 269 (4.50), 295 (3.76), 325 (3.85)
8	1670	3390	270 (4.00), 280 (4.35), 290 (4.44), 345 (4.20)
9	1680, 1710	3390	247 (4.15), 275 (4.45), 288 (4.14), 297 (4.66), 300 (3.97)
10	—	3440	213 (4.23), 248 (4.66), 255 (4.63), 286 (4.14), 303 (4.23), 321 (3.75)
12	1700	3410	245 (4.32), 287 (4.35), 277 (4.00), 298 (3.77)
13	1700	3410	257 (4.05), 285 (4.44), 300 (4.65), 355 (4.77)
14	1720, 1690	3400	235 (4.15), 280 (4.45), 288 (3.95), 315 (4.05)
15	—	3350	217 (4.39), 252 (4.27), 285 (4.24), 303 (3.96)
17	1690	3395	268 (4.18), 277 (4.25), 269 (4.15), 335 (4.00)
18	1680	3395	236 (4.15), 275 (4.50), 296 (4.43), 310 (4.56), 315 (4.09)
19	1680, 1690	3390	241 (4.30), 257 (4.05), 266 (4.00), 288 (3.86), 315 (3.97)
20	—	3395	217 (4.42), 247 (4.59), 264 (4.60), 303 (3.58), 316 (3.91), 345 (3.28)

EXPERIMENTAL

The reactions and the purity of the synthesized compounds were monitored by TLC on Silufol UV-254 plates with a fixed layer of silica gel. The UV spectra were recorded in ethanol on a Specord UV-vis spectrophotometer. The IR spectra were obtained on a UR-2 instrument with sodium chloride and lithium fluoride prisms (in vaseline oil). The ^{1}H NMR spectra were measured on a Bruker VP-200 instrument at 200 MHz with TMS as internal standard.

Compounds 1-20 were obtained by the method described in [4].

Ethyl Pyruvate 1-Carboxydibenzothiophen-2-ylhydrazone (2) was obtained from 2-amino-1-carboxydibenzothiophene **1**.

Ethyl Pyruvate 3-Carboxydibenzothiophenyl-2-hydrazone (7) was obtained from 2-amino-3-carboxydibenzothiophene **6**.

Ethyl Pyruvate 2-Carboxydibenzothiophen-3-ylhydrazone (12) was obtained from 3-amino-2-carboxydibenzothiophene **11**.

Ethyl Pyruvate 4-Carboxy-3-dibenzothiophen-3-ylhydrazone (17) was obtained from 3-amino-4-carboxybenzothiophene **16**.

Ethyl 10-carboxy-1H-benzo[*b*]thiopheno[2,3-*f*]indole-2-carboxylate (3) was obtained from compound **2**.

Ethyl 4-carboxy-3H-benzo[b]thiopheno[3,2-*e*]indole-2-carboxylate (8) was obtained from compound **7**.

Ethyl 4-carboxy-3H-benzo[*b*]thiopheno[2,3-*e*]indole-2-carboxylate (13) was obtained from compound **12**.

Ethyl 10-carboxy-1H-benzo[*b*]thiopheno[3,2-*f*]indole-2-carboxylate (18) was obtained from compound **17**.

1H-Benzo[*b*]thiopheno[2,3-*f*]indole-2,10-dicarboxylic acid (4) was obtained from compound **3**.

1H-Benzo[*b*]thiopheno[2,3-*f*]indole (5) was obtained from compound **4**.

1H-Benzo[*b*]thiopheno[3,2-*e*]indole-2,4-dicarboxylic acid (9) was obtained from compound **8**.
1H-Benzo[*b*]thiopheno[2,3-*e*]indole-2,4-dicarboxylic acid (14) was obtained from compound **13**.
3H-Benzo[*b*]thiopheno[3,2-*e*]indole (10) was obtained from compound **9**.
3H-Benzo[*b*]thiopheno[2,3-*e*]indole (15) was obtained from compound **14**.
1H-Benzo[*b*]thiopheno[3,2-*f*]indole-2,10-dicarboxylic acid (19) was obtained from compound **18**.
1H-Benzo[*b*]thiopheno[3,2-*f*]indole (20) was obtained from compound **19**.

REFERENCES

1. M. D. Mashkovskii, *Drugs* [in Russian], Meditsina, Moscow (1984*)*, Vol. 2, p. 190.
2. E. V. Naumenko and N. K. Popova, *Melatonin and the Thyroid Gland*, in: *Serotonin and Melatonin in the Regulation of the Endocrine System* [in Russian], Nauka, Sib. Otd., Novosibirsk (1975*)*, p. 145.
3. M. D. Mashkovskii, *Drugs* [in Russian]*, Meditsina, Moscow* (1984), Vol. 1, p. 112.
4. T. E. Khoshtariya, M. L. Kakhabrishivili, L. N. Kurkovskaya, and N. N. Suvorov, *Khim. Geterotsikl. Soedin.*, 1366 (1984). [*Chem. Heterocycl. Comp*., **20**, 1123 (1984)].
5. T. E. Khoshtariya, T. O. Dzhashi, and L. N. Kurkovskaya, *Khim. Geterotsikl. Soedin.*, 627 (1999*)*. [*Chem. Heterocycl. Comp*., **35**, 557 (1999)].
6. T. O. Dzhashi, T. E. Koshtariya, L. N. Kurkovskaya, N. T. Mirziashvili, and M. I. Sikharulidze, *Khim. Geterotsikl. Soedin.*, 1419 (1999). [*Chem. Heterocycl. Comp*., **35**, 1237 (1999)].
7. R. Ponci, F. Amatori, and P. Lorenco, *Farmaco*, **22**, 999 (1967).
8. T. E. Koshtariya, L. N. Kurkovskaya, K. T. Batsikadze, M. M. Matnadze, M. I. Sikharulidze, T. O. Dzhashi, V. O. Ananiashvili, I. G. Abesadze, and M. G. Alapishvili, *Khim. Geterotsikl. Soedin.*, 780 (2006). [*Chem. Heterocycl. Comp*., **42**, 686 (2006)].