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A NEW APPROACH TO THE SYNTHESIS OF INDOLE- AND BENZOFURAN-CONTAINING TETRACYCLIC CONDENSED SYSTEMS

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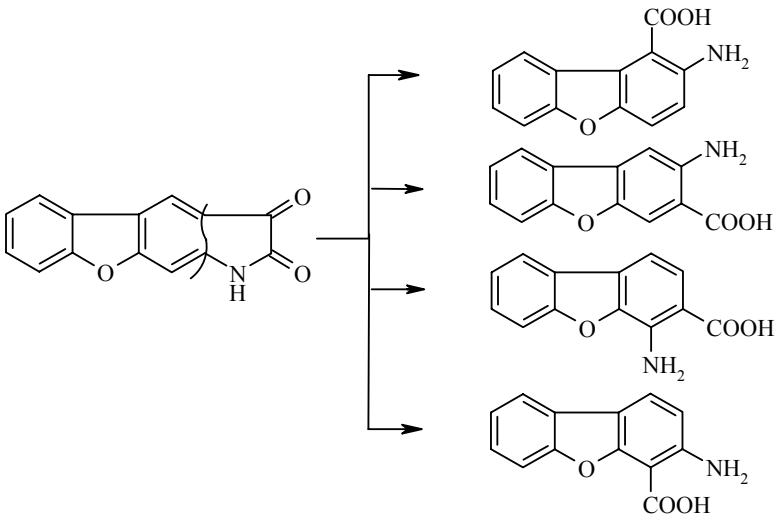
A new method is described for the synthesis of the 1H-benzo[b]furoindole heterocyclic systems from the corresponding isomeric amino acids with amino groups at positions 2 and 3. By this method it is possible to obtain these tetracyclic systems not only in the form of one isomer but also to convert them from one to the other. From the tetracyclic systems with angular structure it is possible to obtain the corresponding linear isomers. On the other hand, from the isomer with the linear structure it is possible to change to the isomer with angular fusion of the pyrrole ring. The classical Fischer reaction served as model for such transformations.

Keywords: indole, pyrrole.

The high reactivity of indole and benzofuran derivatives prompted us to start investigations into the synthesis of the isomeric tetracyclic systems of 1H-benzo[*b*]furoindoles [1,2]. The complexity in the synthesis of such heterocycles [3] led us to the idea of using *ortho*-substituted amines of dibenzofuran as starting compounds. If there are substituents at the *ortho* position only one isomer is formed.



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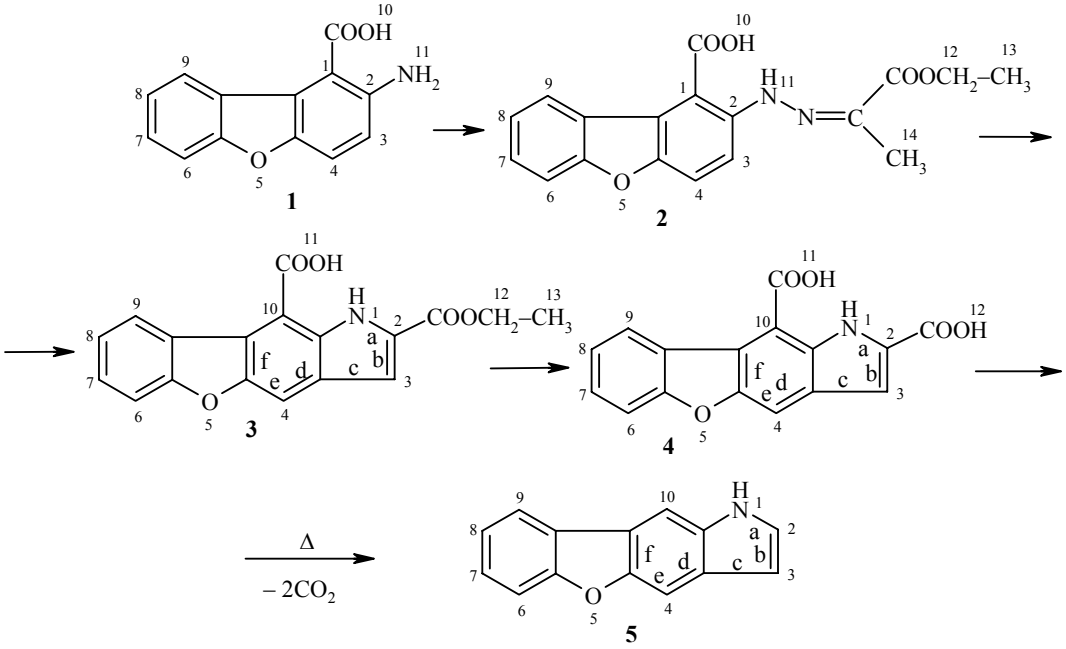
The carboxyl group proved the most suitable substituent for modification [4].

The isomeric *ortho*-substituted aromatic amino acids can be obtained fairly easily from the corresponding dioxodihydro-1H-benzo[*b*]furoindoles by treatment of the latter with an aqueous solution of alkali followed by oxidation with a 30% solution of hydrogen peroxide [5].

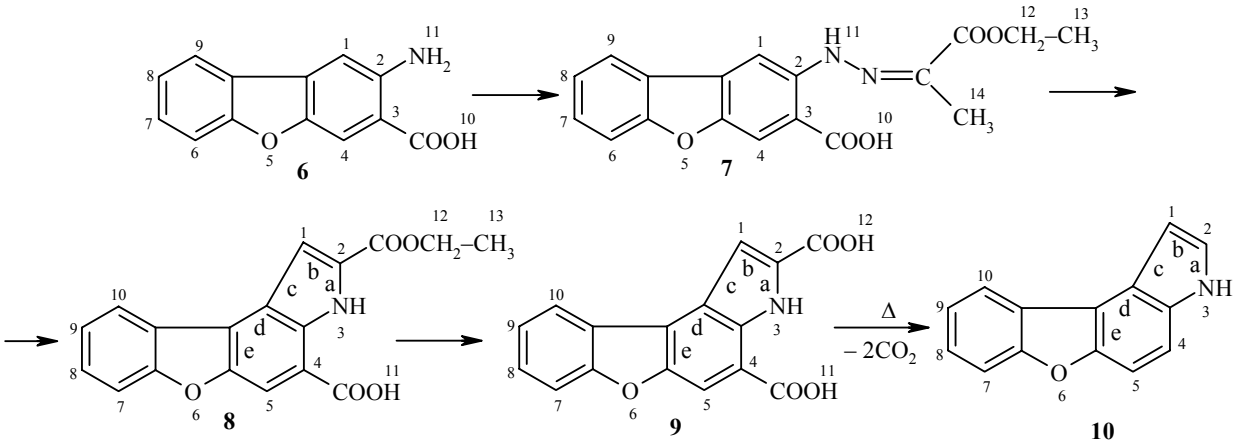
The proposed method makes it possible to obtain the tetracyclic systems not only in the form of one isomer but also to interconvert them from tetracyclic systems with angular structure to the corresponding isomers with linear structure and *vice versa*.

The synthesis was realized according to schemes 1-4 presented below.

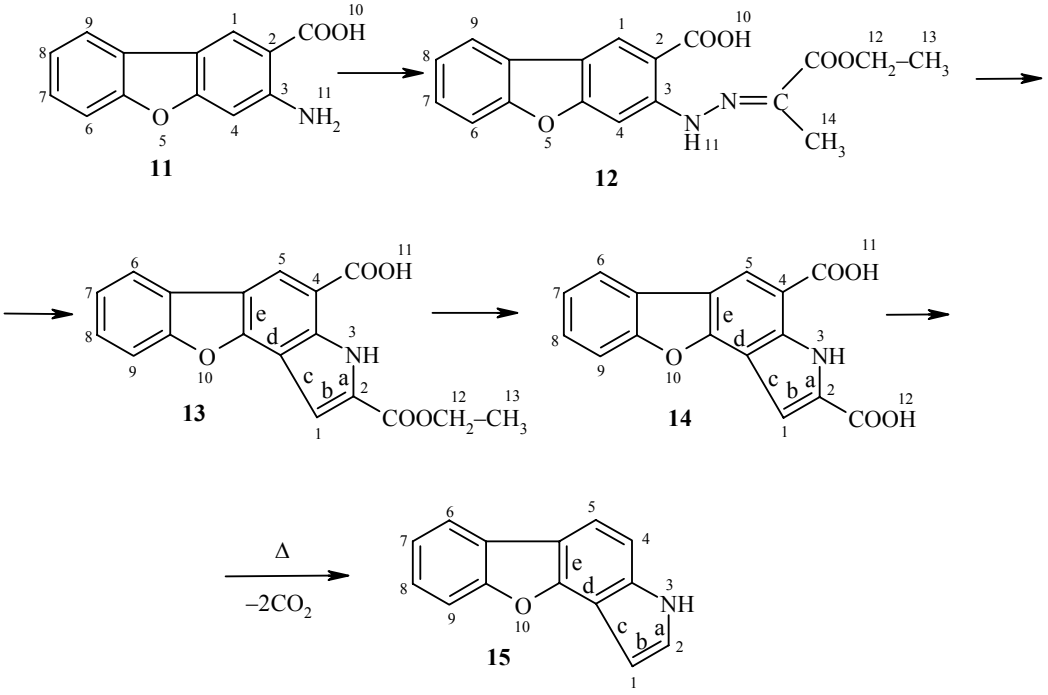
Scheme 1



Scheme 2



Scheme 3



Scheme 4

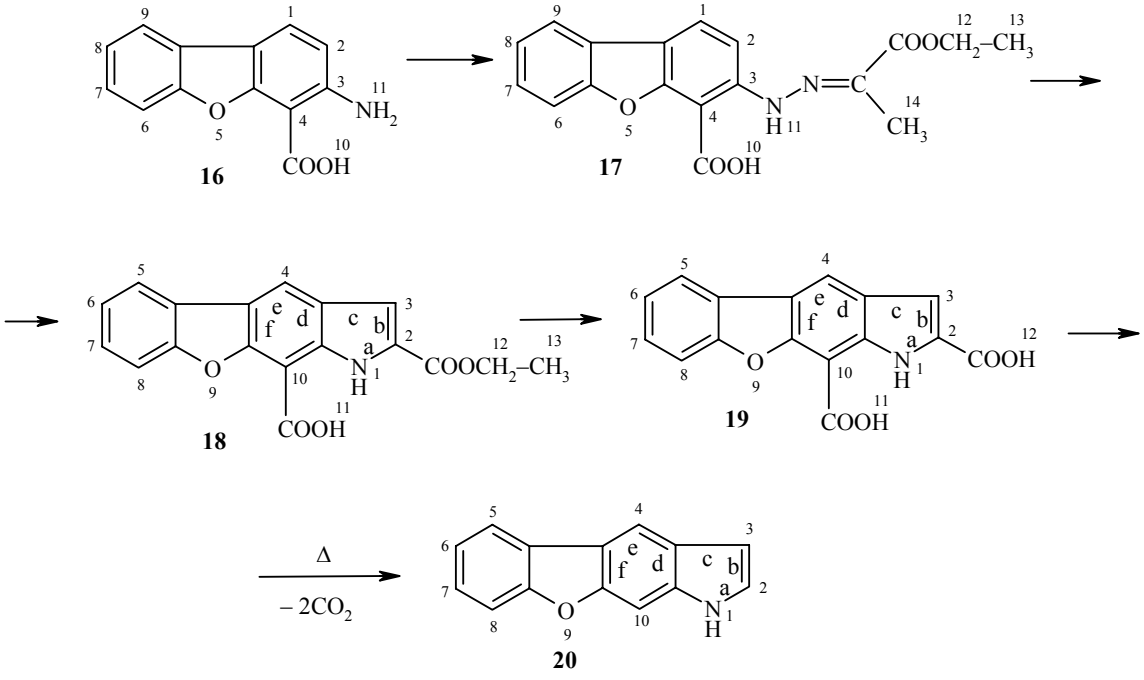


TABLE 1. ^{1}H NMR Spectra of Compounds **2-5, 7-10, 12-15,** and **17-20**

Com-pound	Chemical shifts, d, ppm. (DMSO-d_6)* and SSCC (J, Hz)														J, Hz
	H-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	
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
2	—	—	7.10, d	7.90, d	—	7.95, m	~ 7.50		8.25, m	10.00, br. s	10.30, br. s	4.30, q	1.35, t	2.10, s	$J_{3,4}$ = 9.0; $J_{12,13}$ = 7.2
3	11.90, br. s	—	7.80, s	8.30, s	—	7.90, m	~ 7.50		8.30, m	—	11.80, br. s	4.40, q	1.37, t	—	$J_{12,13}$ = 7.0
4	10.70, br. s	—	7.77, s	8.40, s	—	7.99, m	~ 7.50		8.35, m	—	10.50, br. s	10.30, br. s	—	—	
5	11.00, br. s	7.40, dd	6.52, dd	7.99, d	—	7.66, m	~ 7.50		8.05, m	7.82, d	—	—	—	—	$J_{1,2}$ ≈ 2.0; $J_{2,3}$ = 3.1; $J_{1,3}$ = 2.0; $J_{4,10}$≈0.8
7	7.45, d	—	—	8.07, d	—	8.10, m	~ 7.50		8.50, m	9.80, br. s	10.10, br. s	4.30, q	1.37, t	2.06, s	$^{5}J_{1,4}$ ≈ 0.5; $J_{12,13}$ = 7.2
8	8.10, s	—	12.10, br. s	—	8.10, s	—	8.20, m	~ 7.50		8.70, m	12.00, br. s	4.40, q	1.40, t	—	$J_{12,13}$ = 7.0
9	8.20, s	—	10.20, br. s	—	8.60, s	—	8.10, m	~ 7.50		8.67, m	10.80, br. s	10.70, br. s	—	—	
10	7.50, m	6.90, dd	11.30, br. s	7.37, dd	7.54, d	—	7.60, m	~ 7.50		8.18, m	—	—	—	—	$J_{1,2}$ = 3.1; $J_{2,3}$ ≈ 2.0; $J_{1,3}$ = 1.8; $J_{1,4}$ = 0.9; $J_{5,4}$ = 8.1

TABLE 1. (continued)

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
12	8.50, d	—	—	8.00, d	—	8.12, m	~ 7.50		8.25, m	9.90, br. s	10.00, br. s	4.35, q	1.39, t	2.10, s	$^5J_{1,4} = 0.8$; $J_{12,13} = 7.1$
13	8.21, s	—	11.90, br. s	—	8.55, s	8.30, m	~ 7.50		8.35, m	—	12.00, br. s	4.40, q	1.43, t	—	$J_{12,13} = 7.1$
14	8.39, s	—	10.30, br. s	—	8.73, s	8.30, m	~ 7.50		8.25, m	—	10.70, br. s	10.50, br. s	—	—	
15	6.73, m	7.40, dd	11.40, br. s	7.64, dd	7.98, d	7.72, m	~ 7.50		7.31, m	—	—	—	—	—	$J_{1,2} = 3.3$; $J_{2,3} \approx 2.0$; $J_{1,3} = 2.2$; $J_{1,4} = 0.4$; $J_{4,5} = 8.7$
17	8.25, d	7.34, d	—	—	—	7.95, m	~ 7.50		8.30, m	8.90, br. s	9.00, br. s	4.35, q	1.38, t	2.06, s	$J_{1,2} = 8.6$, $J_{12,13} = 7.2$
18	10.00, br. s	—	7.67, s	8.70, s	8.30, m	~ 7.50		8.00, m	—	—	9.50, br. s	4.30, q	1.40, t	—	$J_{12,13} = 7.1$
19	10.20, br. s	—	7.93, s	8.70, s	8.32, m	~ 7.50		7.99, m	—	—	9.80, br. s	9.50, br. s	—	—	
20	10.30, br. s	7.36, dd	6.59, m	8.13, d	8.17, m	~ 7.50		7.79, m	—	7.70, t	—	—	—	—	$J_{1,2} = 2.2$; $J_{2,3} = 3.1$; $J_{1,3} = 2.0$; $J_{3,10} \approx J_{4,10} = 0.8$

* The spectrum of compound **9** was recorded in acetone-d_6.

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

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
2	$C_{18}H_{16}N_2O_5$	63.5 / 63.52	4.8 / 4.70	8.4 / 8.23	188-189	80
3	$C_{18}H_{13}NO_5$	66.6 / 66.87	3.8 / 4.02	4.4 / 4.33	199-200	90
4	$C_{16}H_9NO_5$	65.0 / 65.08	3.3 / 3.05	4.5 / 4.75	277-279	78
5	$C_{14}H_9NO$	81.2 / 81.15	4.2 / 4.34	6.6 / 6.76	197-198	80
7	$C_{18}H_{16}N_2O_5$	63.4 / 63.52	4.7 / 4.70	8.3 / 8.23	177-178	92
8	$C_{18}H_{13}NO_5$	66.7 / 66.87	3.9 / 4.02	4.3 / 4.33	203-205	70
9	$C_{16}H_9NO_5$	65.2 / 65.08	3.0 / 3.05	4.4 / 4.75	280-281	93
10	$C_{14}H_9NO$	81.3 / 81.15	4.2 / 4.34	6.4 / 6.76	127-128	65
12	$C_{18}H_{16}N_2O_5$	63.5 / 63.52	4.6 / 4.70	8.0 / 8.23	165-166	88
13	$C_{18}H_{13}NO_5$	66.6 / 66.87	4.1 / 4.02	4.2 / 4.33	211-212	80
14	$C_{16}H_9NO_5$	65.4 / 65.08	3.4 / 3.05	4.5 / 4.75	290-291	94
15	$C_{14}H_9NO$	81.3 / 81.15	4.2 / 4.34	6.5 / 6.76	144-145	60
17	$C_{18}H_{16}N_2O_5$	63.7 / 63.52	4.8 / 4.70	8.4 / 8.23	169-201	65
18	$C_{18}H_{13}NO_5$	66.7 / 66.87	4.0 / 4.02	4.2 / 4.33	233-234	82
19	$C_{16}H_9NO_5$	65.0 / 65.08	2.9 / 3.05	4.6 / 4.75	312-313	90
20	$C_{14}H_9NO$	81.4 / 81.15	4.2 / 4.34	6.6 / 6.76	160-161	47

Like the corresponding dicarboxylic acids, the carboxylic acids with ester groups formed in the synthesis are interesting both in their own right and as starting materials for the production of a whole series of physiologically active substances.

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

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 spectrometer. The IR spectra were obtained on a UR-20 instrument with NaCl and LiF prisms (in vaseline oil). The ^{1}H NMR spectra were measured on a Bruker WM-250 instrument (250 MHz) with TMS as internal standard.

Compounds **2-5**, **7-10**, **12-15**, and **17-20** were obtained according to the procedure in [3].

Ethyl Pyruvate 1-Carboxydibenzofuran-2-ylhydrazone (2). This compound was obtained from 2-amino-1-carboxydibenzofuran.

Ethyl Pyruvate 3-Carboxydibenzofuran-2-ylhydrazone (7). This compound was obtained from 2-amino-3-carboxydibenzofuran.

TABLE 3. The Spectral Characteristics of Compounds **2**-**5**, **7**-**10**, **12**-**15**, and **17**-**20**

Compound	IR spectrum, δ, cm^{-1}		UV spewctrum, 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	3410	233 (4.00), 267 (4.35), 286 (4.45), 299 (4.55), 335 (4.80)
5	—	3385	233 (4.57), 247 (4.57), 315 (4.56), 334 (4.38)
7	1690	3415	237 (4.20), 245 (4.35), 269 (4.50), 295 (3.76), 325 (3.85)
8	1670	3400	270 (4.00), 280 (4.35), 290 (4.44), 345 (4.20)
9	1680	3390	247 (4.15), 275 (4.45), 288 (4.14), 297 (4.66), 300 (3.97)
10	—	3320	208 (5.36), 218 (5.44), 241 (5.14), 267 (4.52), 299 (5.04), 310 (5.22), 325 (5.24)
12	1700		245 (4.32), 287 (4.35), 277 (4.00), 298 (3.77)
13	1700	3440	257 (4.05), 285 (4.44), 300 (4.65), 355 (4.77)
14	1720	3410	235 (4.15), 280 (4.45), 288 (3.95), 315 (4.05)
15	—	3400	208 (4.50), 243 (4.70), 252 (4.80), 268 (4.15), 282 (4.08), 308 (4.41), 320 (4.43)
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			241 (4.30), 257 (4.05), 266 (4.00), 288 (3.86), 315 (3.97)
20	—	3380	250 (5.03), 297 (4.43), 301 (4.36), 315 (4.19)

Ethyl Pyruvate 2-Carboxydibenzofuran-3-ylhydrazone (12). This compound was obtained from 3-aminod-2-carboxy-ibenzofuran.

Ethyl Pyruvate 4-Carboxydibenzofuran-3-ylhydrazone (17). This compound was obtained from 4-carboxy-3-aminodibenzofuran.

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

Ethyl 4-Carboxy-1H-benzo[*b*]furo[3,2-*e*]indole-2-carboxylate (8). This compound was obtained from compound **7**.

Ethyl 4-Carboxy-1H-benzo[*b*]furo[2,3-*e*]indole-2-carboxylate (13). This compound was obtained from compound **12**.

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

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

1H-Benzo[*b*]furo[3,2-*e*]indole-2,4-dicarboxylic Acid (9). This compound was obtained from compound **8**.

1H-Benzo[*b*]furo[2,3-*e*]indole-2,4-dicarboxylic Acid (14). This compound was obtained from compound **13**.

1H-Benzo[*b*]furo[3,2-*f*]indole-2,10-dicarboxylic Acid (19). This compound was obtained from compound **18**.

1H-Benzo[*b*]furo[2,3-*f*]indole (5). This compound was obtained from compound **4** by the method in [4].

1H-Benzo[*b*]furo[3,2-*e*]indole (10). This compound was obtained from compound **9**.

1H-Benzo[*b*]furo[2,3-*e*]indole (15). This compound was obtained from compound **14**.

1H-Benzo[*b*]furo[3,2-*f*]indole (20). This compound was obtained from compound **19**.

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