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Facile synthesis of 2,3-phthaloylpyrocoline-1-carboxylic acid and its new derivatives

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Summary. New amide and ester derivatives of 2,3-phthaloylpyrocoline-1-carboxylic acid were synthesized. The preparation of 2,3-phthaloylpyrocoline-1-carboxylic acid was improved. Obtained heterocycles are very important in organic synthesis for the search of new biologically active compounds with a wide spectrum of activity. Biological activity prediction using computer program *PASS C&T* was performed to indicate that newly synthesized compounds require further evaluation.

Keywords: 2,3-phthaloylpyrocoline-1-carboxylic acid.

Introduction. Most of early work on the reactivity of halogen atoms of 2,3-dihalo-1,4-naphthoquinone deals with the formation of mono- and disubstituted compounds by replacement of one or both of the halogen atoms. Cyclization with the formation of a heterocyclic ring involving both halogens was reported first in 1899 by Liebermann [1] who prepared 3-hydroxybenzo[b]naphtho[2,3-*d*]furan-6,11-dione.

However, from 1899 to about 1940 very little interest had been shown in the cyclization reactions of 2,3-dichloro-1,4-naphthquinone. The discovery that some heterocyclic quinones possess attractive properties as dyes [2-4], catalysts [5, 6] and drugs [7-9] attracted attention to their synthesis from 2,3-dihalo-1,4-naphthquinone.

Cyclization involving the halogens of 2,3-dihalo-1,4-naphthquinone can yield 5- and 6-membered heterocyclic rings [10]. The review [11] is concerned with chemistry of polynuclear quinones containing a 5- and 8-membered heterocyclic ring fused with naphthoquinonyl residue.

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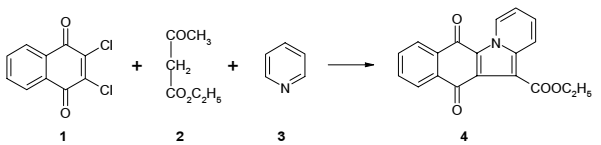
Our work is devoted to the synthesis of new amide and ester derivatives of 2,3-phthaloylpyrocoline-1-carboxylic acid.

Results and discussion. ***Synthesis of 2,3-phthaloylpyrocoline-1-carboxylic acid and 2,3-phthaloylpyrrocoline-1-carbonyl chloride.*** Technical 2,3-dichloronaphthoquinone-1,4 was used as starting compound. Synthesis of 1-carbetox-2,3-phthaloylpyrrocoline **4** was performed by the interaction of 2,3-dichloronaphthoquinine-1,4 **1** with ethyl ether of acetoacetic acid **2** and pyridine **3** at room temperature (Scheme 1), C_2H_5OH was used as a solvent [12]. The preparation of **4** from **1** was modified and the yields and purity of products improved.

Upon the hydrolysis of 1-carbetox-2,3-phthaloylpyrrocoline **4** with the solution of sodium ethylate in ethanol we have obtained sodium salt of phthaloylpyrrocoline-1-carboxylic acid **5**, which by acidification with the excess of hyd-

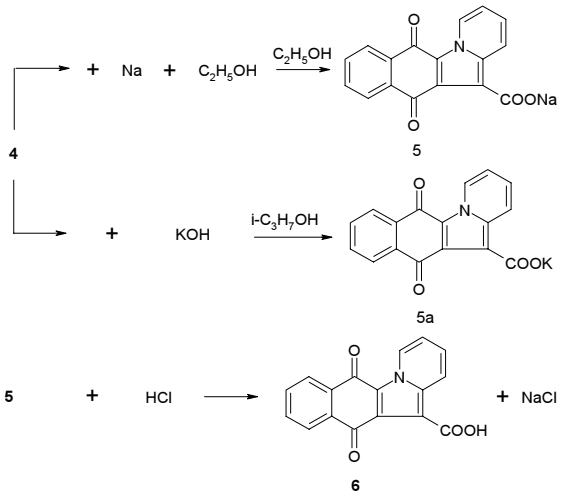
Scheme 1
Synthesis of the 1-carbetox-2,3-phthaloylpyrrocoline



1 2 3 4

Scheme 2

Synthesis of 2,3-phthaloylpyrrocoline-1-carbonic acid



rochloric acid produced phthaloylpyrrocoline-1-carboxylic acid **6**. We have optimized the reaction conditions of the hydrolysis of compound **4**, in order to increase an economic efficiency. In our case we were using KOH solution in aqueous *i*-propanol; in this way we have reduced the cost of final products and increased the safety of synthesis (Scheme 2).

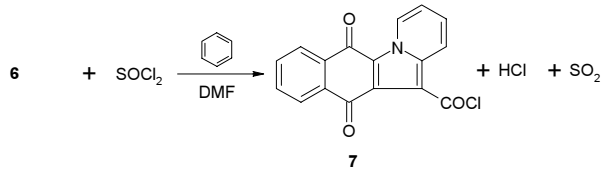
Synthesis of 2,3-phthaloylpyrrocoline-1-carbonyl chloride **7** was carried out by the interaction of phthaloylpyrrocoline-1-carboxylic acid **6** with a small excess of thionyl chloride, with dry benzene as a solvent. Reaction mixture was kept at the temperature below 60 ˚C until the evolution of gases was over. We have used DMF as a catalyst (Scheme 3). The reaction yield was up to 99 % of crude product. Compound **7** was recrystallized from chlorobenzene.

Synthesis of amide derivatives of 2,3-phthaloylpyrrocoline-1-carboxylic acid. From 2,3-phthaloylpyrrocoline-1-carbonyl chloride **7** we have obtained a series of amide derivatives of 2,3-phthaloylpyrrocoline-1-carboxylic acid **6**.

Reaction of 2,3-phthaloylpyrrocoline-1-carbonyl chloride **7** with amines and amino acids was performed in chlorobenzene at the temperature that did not exceed 100 ˚C. Triethylamine was used as an acceptor of hydrogen chloride. We have obtained the following amides **8a-h** (Scheme 4).

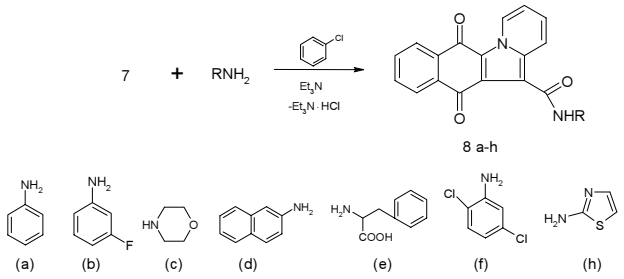
Scheme 3

Synthesis of 2,3-phthaloylpyrrocoline-1-carbonyl chloride



Scheme 4

Synthesis of the amide derivatives of the 2,3-phthaloylpyrrocoline-1-carbonic acid



Synthesis of the esters of 2,3-phthaloylpyrrocoline-1-carboxylic acid. Reaction of 2,3-phthaloylpyrrocoline-1-carbonyl chloride **7** with alcohols was carried out at room temperature in chlorobenzene. As with amines, we have used triethylamine as a base. The esters **9a,b** have been obtained (Scheme 5).

Prediction of the potential biological activity spectrum for amides **8a-h** was made on the basis of their structure using computer program *PASS C&T* [17, 18] with appropriate Pa>0.5 (Table 1).

Conclusions. Therefore, we have accomplished an optimization of the reaction of 1-carbetoxy-2,3-phthaloylpyrrocoline **4** hydrolysis to increase its economic efficiency. In our case we have used a solution of KOH in aqueous *i*-propanol, and in this way we have reduced the cost of final products and increased the safety of

Scheme 5

Synthesis of the 2,3-phthaloylpyrrocoline-1-carbonic acid's esters

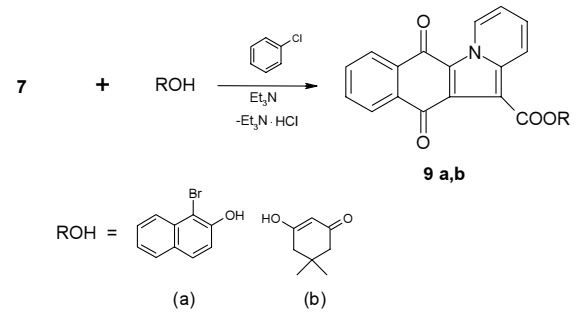


Table 1

The results of prediction with appropriate Pa>0.5 for amides ***8a-h***

Compound	Pa	Effects
8a	0.606	Antineoplastic
	0.519	Mediator release inhibitor
	0.516	HDL-cholesterol increasing
8b	0.680	Antineoplastic (colorectal cancer)
	0.539	HDL-cholesterol increasing
	0.518	Mediator release inhibitor
8c	0.576	Cardiovascular analeptic
	0.572	Antineoplastic (colorectal cancer)
	0.508	Arrhythmogenic
8d	0.604	Antineoplastic
	0.601	Kinase inhibitor
	0.505	HDL-cholesterol increasing
8e	0.652	Antiseborrheic
	0.615	Sickle-cell anemia treatment
	0.565	Antihypoxic
8f	0.543	HDL-cholesterol increasing
	0.511	Acetylcholine release stimulant
	0.511	Mediator release inhibitor
8h	0.550	Mediator release inhibitor
	0.500	Antithrombocytopenic

Table 2

Amides ***8a-h*** *prepared from 2,3-phthaloylpyrrocoline-1-carbonyl chloride*

	Yield, %	Calculated, Found, %					
		C	H	N	Cl	F	S
8a	73	75.40 75.29	3.85 3.93	7.65 7.81			
8b	73	71.87 71.60	3.41 4.80	7.29 7.55		4.94 3.57	
8c	70	69.99 69.75	4.48 4.41	7.77 7.95			
8d	75	69.57 69.75	3.29 4.41	8.14 7.95			
8e	73	71.06 69.80	4.36 4.17	6.37 6.55			
8f	72	63.47 63.32	2.78 2.39	6.44 6.61	16.29 16.13		
8h	73	64.34 64.12	2.97 2.63	6.37 6.57			8.59 8.76

synthesis. Newly obtained amide and ester derivatives of 2,3-phthaloylpyrocoline-1-carboxylic acid are stable crystalline substances. NMR, IR (Table 4) and elemental analysis confirmed the structures of these compounds. Preliminary computer screening of amides indicated the need of further evaluation of compounds of this class.

Experimental. Melting points were measured on Nagema melting-point apparatus and were uncorrected. ^{1}H NMR spectra were recorded on Varian VXR (300 MHz) spectrometer in DMSO-d_6 with TMS as an internal standard. IR spectra were obtained on Specord M80 instrument in KBr pellets.

Synthesis of l-carbetoxy-2,3-phthaloylpyrrocoline 4. To the suspension of 0.022 mol of 2,3-dichcloronathoquinone-l,4 in 70 ml of ethanol, 0.022 mol of ethyl acetoacetate and 0.022 mol of pyridine were added at room temperature with stirring. The mixture was refluxed for 4 h. Reaction mass was cooled to 25 ˚C and then kept in refrigerator for 12 h. Precipitate was filtered, washed with water and dried at room temperature. Yield of the product was 4.26 g (63 %), M.p.=157-158 ˚C (what corresponds to literature data [12]) Found, %: C 71.40; H 4.15; N 4.56. Calculated for $C_{19}Hi_3NO_4$, %: C 71.47; H 4.10; N 4.39.

Synthesis of 2,3-phthaloilpirokoline 2,3-1-carboxylic acid 6. *Method A*. To 13.71 g (0.043 mol) of l-carbethoxy-2,3-phthaloylpyrrocoline suspended in 50 ml of ethyl alcohol was added dropwise at room temperature with stirring sodium ethylate solution in dry ethanol (prepared by dissolving 3 g of sodium (0.13 mol) in 50 ml of ethanol). Reaction mass was refluxed for 0.5 h, cooled to 20 ˚C and filtered. The filtrate was acidified with excess of hydrochloric acid, precipitate was filtered, washed with water and dried at room temperature. Yield of the product was 11.13 g (89 %). Found, %: C 70.03; H 3.18; N 4.90. Calculated for $C_{17}H_9NO_4$, % : C 70.10; H 3.12; N 4.81.

Method B. To the suspension of 13.71 g (0.043 mol) of 1-carbethoxy-2,3-phthaloylpyrrocoline in 60 ml of isopropyl alcohol, at room temperature and with stirring, was added the solution of 9.89 g (0.215 mol) of KOH in 40 ml of *i*-propanol. Reaction mixture refluxed for 1 hour. It was cooled to 20 ˚C and filtered. Filtrate was acidified with excess of hydrochloric acid, precipitate was filtrated, washed with water and dried at room temperature. Yield of the product was 11.24 g (90 %).

Synthesis of 2,3-phthaloylpyrrocoline -1-carbonyl chloride 7. 1.043 ml (0.0143 mol) of thionyl chloride and 0.005 ml DMF were added at room temperature with stirring to the suspension of 3.20 g (0.011 mol) of 2,3-phthaloylpyrrocoline-1-carboxylic acid in 80 ml of dry benzene. The mixture was heated at 60 ˚C for 3 h. It was cooled to room temperature and evaporated in vacuum. The residue was recrystallized from chlorobenzene and dried in vacuum. Yield of the product

Table 3

*Esthers **9a,b** prepared from 2,3-phthaloylpyrrocoline-1-carbonyl chloride*

	Yield, %	Calculated, Found, %			
		C	H	N	Br
9a	70	65.34 65.26	2.84 2.90	2.82 2.98	16.10 16.26
9b	71	72.63 72.35	4.63 4.30	3.39 3.70	

was 3.37 g (99 %). Found, %: N 4.78; Cl 11.61. Calculated for $C_{17}H_8ClNO_3$, % : C 65.93; H 2.60; N 4.52; Cl 11.45.

General procedure of the synthesis of amide derivatives of 2,3-phthaloilpirokoline-1-carboxylic acid 8a-h. To the suspension of 5.57 g (0.018 mol) of 2,3-phthaloylpyrrocoline-1-carbonyl chloride in 100 ml of chlorobenzene was added, at room temperature and with constant stirring, the solution of 1.65 ml (0.018 mol) of aniline and 2.76 ml (0.018 mol) of triethylamine in 20 ml of chlorobenzene. The reaction mixture was kept at 80 ˚C for 2 h, cooled to room temperature and evaporated in vacuum. The residue was washed with water, filtered, dried at room temperature and recrystallized from DMF or chlorobenzene (Table 2).

General procedure of the synthesis of 2,3-phthaloylpyrrocoline-1-carboxylic acid esthers 9a,b. To the solution of 5.57 g (0.018 mol) of 2,3-phthaloylpyrrocoline-1-carbonyl chloride in 100 ml of chlorobenzene was added with stirring at room temperature the solution of 4.04 ml (0.018 mol) of alcohol and 2.76 ml (0.018 mol) of triethylamine in 20 ml of chlorobenzene. The reaction mixture was kept at 60 ˚C for 2 h, cooled to the room temperature and evaporated in vacuum. The residue was washed with water, filtered, dried and then recrystallized from chlorobenzene (Table 3).

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Table 4

Experimental data for the synthesized compounds

	Formula, m.p., ˚C	^{1}H NMR (δ, ppm)	IR, cm^{-1}
4	$C_{19}H_{13}NO_4$ 157-158	10.16 (1H, m, CH); 7.89-8.10 (2H, m, CH_{Ar}); 7.58-7.8 (2H, m, CH_{Ar}); 7.46 (1H, m, CH); 7.23 (1H, m, CH); 6.54 (1H, m, CH); 4.35 (2H, m, CH_2); 1.37 (3H, s, CH_3)	1650 (C=O)
6	$C_{17}H_9NO_4$ 313-314	10.14 (1H, m, CH); 7.87-8.06 (2H, m, CH_{Ar}); 7.58-7.75 (2H, m, CH_{Ar}); 7.56 (1H, m, CH); 7.24 (1H, m, CH); 6.69 (1H, m, CH)	3500 (OH); 1670 (C=O)
7	$C_{17}H_8ClNO_3$ 130-131	12.64 (1H, s, OH); 10.23 (1H, m, CH); 8.04-8.88 (2H, m, CH_{Ar}); 7.57-8.14 (2H, m, CH_{Ar}); 7.69 (1H, m, CH); 7.23 (1H, m, CH); 6.67 (1H, m, CH)	1680 (C=O)
8a	$C_{23}H_{14}N_2O_3$ >300	10.01 (1H, m, CH); 9.44 (1H, s, NH); 7.89-7.98 (2H, m, CH_{Ar}); 7.58-7.67 (2H, m, CH_{Ar}); 7.45 (1H,m, CH); 7.36-7.29 (5H, m, Ar); 7.23-7.24 (1H, m, CH); 6.65-6.67 (1H, m, CH)	1655 (C=O); 3300 (NH_2)
8b	$C_{23}H_{13}FN_2O_3$ >300	10.00 (1H, m, CH); 9.76 (1H, s, NH); 7.89-7.98 (2H, m,CH_{Ar}); 7.57-7.67 (2H, m, CH_{Ar}); 7.15-7.21 (3H, m, CH); 6.56-6.65 (2H, m, CH)	3400 (NH_2); 1650 (C=O)
8c	$C_{21}H_{16}N_2O_4$ >300	10.01 (1H, m, CH); 7.65-7.89 (2H, m,CH_{Ar}); 7.58-7.68 (2H, m, CH_{Ar}); 7.42-7.45 (1H, m, CH); 7.23-7.25 (1H, m, CH); 6.65-6.67 (1H, m, CH); 3.96-4.04 (4H, m, $2CH_2$); 3.86-3.95 (4H, m, $2CH_2$)	1670 (C=O)
8d	$C_{27}H_{16}N_2O_3$ >300	10.01 (1H, m, CH); 9.83 (1H, s, NH); 8.3-8.32 (1H, m, CH); 7.16-7.97 (10H, mm, CH); 6.89-6.91 (1H, m, CH); 6.63-6.67 (1H, m, CH)	3300 (NH_2); 1680 (C=O)
8e	$C_{26}H_{19}N_2O_5$ >300	10.01-10.04 (2H, m, OH+CH); 7.9-7.98 (2H, m, CH); 7.58-7.68 (2H, m, CH_{Ar}); 7.45-7.47 (1H, m, CH); 6.66-7.42 (7H, m, CH); 6.63-6.67(1H, m, CH); 5.8 (1H, d, NH); 4.97-5.01 (1H, m, CH); 3.35-3.38 (2H, m, CH_2)	3400 (NH_2); 1650 (C=O)
8f	$C_{23}H_{12}Cl_2N_2O_3$ >300	10.00-10.02 (1H, m, CH); 8.63 (1H, s, NH); 8.12-8.14 (1H, m, CH); 7.89-7.97 (2H, dd, CH_{Ar}); 7.58-7.69 (2H, m, CH_{Ar}); 7.45-7.47 (1H, m,CH); 7.22-7.24 (1H, m, CH); 6.93-6.95 (1H, m, CH); 6.64-6.67 (2H, m, CH_2)	3300 (NH_2); 1655 (C=O)
8h	$C_{20}H_{11}N_3O_3S$ >300	10.01-10.04 (1H, m, CH); 8.54 (1H, s, NH); 7.89-7.98 (2H, m, CH); 7.58-7.68 (3H, m, CH); 7.45-7.47 (1H, m, CH); 7.34-7.36 (1H, m, CH); 7.22-7.24 (1H, m, CH); 6.63-6.67 (1H, m, CH)	3400 (NH_2); 1680 (C=O); 1608 (thiazol)
9a	$C_{27}H_{14}BrNO_4$ >270	10.17 (1H, m, CH); 8.35-8.37 (1H, m, CH); 8.13-8.15 (1H, m,CH); 7.88-8.12 (2H, dd, CH_{Ar});7.56-7.8 (3H, m, CH); 7.45-7.47 (1H, m, CH); 7.35-7.37 (1H, m, CH); 7.22-7.25 (1H, m, CH); 6.53-6.56 (1H, m, CH)	3400 (OH); 1670 (C=O)
9b	$C_{25}H_{19}NO_5$ >270	10.16 (1H, m, CH); 7.89-8.10 (2H, dd, CH_{Ar}); 7.58-7.81 (2H, m, CH_{Ar}); 7.22-7.25 (1H, m, CH); 6.53-6.56 (1H, m, CH); 6.15-6.17 (1H, m, CH); 2.11-2.43 (4H, m, $2CH_2$); 1.07 (6H, d, $2CH_3$)	3300 (OH); 1650 (C=O)

Легкий синтез 2,3-фталоїлпіроколін-1-карбонової кислоти та її нові похідні

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Резюме. Синтезовано нові амідні й ефірні похідні 2,3-фталоїлпіраколін-1-карбонової кислоти. Модернізовано одержання 2,3-фталоїлпіраколін-1-карбонової кислоти. Синтезовані гетероцикли дуже важливі в органічному синтезі для пошуку нових біологічно активних сумішей із широким спектром дії. Проведений прогноз біологічної активності з використанням комп'ютерної програми *PASS C&T* показав доцільність подальших досліджень нових синтезованих сполук.

Ключові слова: 2,3-фталоїлпіраколін-1-карбонова кислота.

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