PHTHALAZINE AND RELATED HETEROCYCLES

X. DERIVATIVES OF 3-SUBSTITUTED PHTHALAZON-4-YL-1-ACETIC ACIDS

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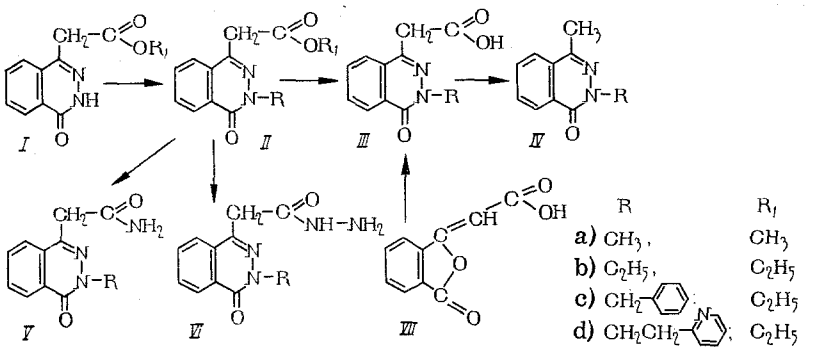
The effect of nicotinic acid on the coagulation system of blood has been described in some detail [1]. It is able to activate blood profibrinolysin and in this way increase the fibrinolytic activity. The fibrinolytic potential of blood can also be increased under the influence of other pyridine derivatives, among them 3-pyridylacetic acid [2]. The fibrinolytic activity increases sharply in the series of biarylcarboxylic acids if the carboxyl group is bonded with the aromatic ring through a carbon atom [3]. Therefore, continuing the search for new biologically active materials among phthalazon-4-yl-1-acetic acid derivatives [4], it was of interest to study the effect of 3-substituted phthalazon-4-yl-1-acetic acids on the coagulation system of blood.

A known synthesis of 3-phenylphthalazon-4-yl-1-acetic acid is by reaction of phenylhydrazine and o-carboxybenzoylacetic acid [5]. Direct alkylation of phthalazon-4-yl-1-acetic acid and its derivatives was not studied. It was found that alkylation of esters of phthalazon-4-yl-1-acetic acid (I) with methyl sulfate, diethylsulfate, and ethyl iodide in the presence of sodium alkoxide yields the corresponding esters of 3-alkylphthalazon-4-yl-1-acetic acids (IIa, IIb). Benzylation with benzyl chloride occurs analogously. Pyridylethylation was carried out by heating 2-vinylpyridine directly with ethyl phthalazon-4-yl-1-acetate (1b). The obtained esters (II) were easily saponified to the corresponding 3-substituted phthalazon-4-yl-1-acetic acids (III) (Table 1). 3-Methylphthalazon-4-yl-1-acetic acid (IIIa) was also obtained by reaction of methylhydrazine



sulfate and phthalidenacetic acid (VII) in basic medium. A new synthesis of 2-substituted 4-methylphthalazones-1 (IV) was accomplished by decarboxylation of acids (III) (Table 2), which simultaneously served as confirmation of the structure of the initial acids. The phthalazone structure of acids (III), in the synthesis of which formation of phthalazine or pyrazolone structures can also be considered probable, is also indicated by the UV spectra of acids (III): absorption maxima in them are found in bands characteristic for phthalazone derivatives [4]. Strong absorption bands of both the ester (1719 cm^{-1}) and ring (1657 cm^{-1}) carbonyl groups are clearly seen in the IR spectrum of (IIa). The reaction of ammonia or hydrazine and esters (II) yielded the corresponding amides (V) and hydrazides (IV) of acids (III) (Table 3).

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TABLE 1. 3-Substituted Phthalazon-4-yl-1-acetic Acids

Compound	Yield (%)	Decomposition temp., (°C)	Found N (%)	Empirical formula
IIIa	96,2	195(from water)	12,75, 12,89	$C_{11}H_{10}N_2O_3$
IIIb	99	178 (from a mixture of water–ethanol 9:1)	12,28, 12,11	$C_{12}H_{12}N_2O_3$
IIIc	99	147–8 (from a mixture of water–ethanol 2:1)	9,28, 9,41	$C_{17}H_{14}N_2O_3$
IIId	82,7	177–8 (from water)	13,67, 13,48	$C_{17}H_{15}N_3O_3$

(Continuation)

Compound	Calc. N (%)	R_f^1	UV spectra			
			λ_{max} (mμ)	lgε	λ_{max} (mμ)	lgε
IIIa	12,83	0,60	253–254	3,77	285,5	3,83
IIIb	12,06	0,66	254	3,76	285–287	3,84
IIIc	9,52	0,69	254–255	3,77	285	3,84
IIId	13,58	0,57	256–257	4,00		

*On aluminum oxide in a system of benzene–acetic acid (6:1).

TABLE 2. 2-Substituted 4-Methylphthalazones-1

Compound	Yield (%)	Mp (deg)	Found N (%)	Empirical formula	Calc. N (%)	R_f^1
IVa	80,4	112†	—	—	—	0,58
IVb	42,5	77–8‡ (from petroleum ether)	15,02, 15,11	$C_{11}H_{12}N_2O$	14,88	0,67
IVc	79,9	113,5–4,5 (from a mixture of ethanol–water 1:1)	10,93, 11,05	$C_{16}H_{14}N_2O$	11,19	0,78
IVd	92,4	140–1 (ditto)	15,78, 15,83	$C_{16}H_{15}N_3O$	15,84	0,37

*On aluminum oxide in a system of benzene–ethanol (49:1).
†Corresponds to literature data [7].
‡Literature data [8]: mp 75-76°.

TABLE 3. Hydrazides of 3-Substituted Phthalazon-4-yl-1-acetic Acids

Compound	Yield (%)	Mp (deg)	Found N (%)	Empirical formula	Calc. N (%)
VIa	90,4	233,5	24,11, 24,00	$C_{11}H_{12}N_4O_2$	24,12
VIb	83,3	200–1	22,53, 22,48	$C_{12}H_{14}N_4O_2$	22,75
VIc	90,8	213,5–214,5	18,17, 18,32	$C_{17}H_{16}N_4O_2$	18,17
VId	89,7	184–5	21,91, 21,94	$C_{17}H_{17}N_5O_2$	21,66

In the first stage of the study of the effect of acids (III) on the coagulation system of blood we investigated the effect of their potassium salts on the thromboplastin time of Kvik [6]. It was found that all of the indicated compounds in a 1% concentration (0.1 ml of a physiological solution in a control system was replaced by 0.1 ml of a solution of the investigated material) reliably lengthen ($P < 0.05$) the thromboplastin time. Solutions of 0.5% and of 0.2% concentration act differently. Thus, salts of acids (IIIa-IIIc) shorten and salts of acid (IIId) lengthen the thromboplastin time. In this way, potassium salts of acids (IIIa-IIIc) act oppositely depending on concentration, and the salt of acid (IIId) has an identical effect at all of the investigated concentrations, which is probably associated with the presence of a pyridine residue in its molecule.

EXPERIMENTAL

Homogeneity of the obtained compounds was confirmed by chromatography on a thin layer of aluminum oxide (Grade II activity) or silica gel G (gypsum fixation). Chromatograms were developed with iodine vapors. UV spectra were taken on an SF-4A instrument in water at a concentration of 10^{-4} mole/liter. IR spectra were taken on a UR-10 instrument as a KBr pellet.

Methyl 3-Methylphthalazon-4-yl-1-acetate (IIa). To a solution of 5.9 g of sodium methoxide in 200 ml of anhydrous methanol were added 21.8 g of (Ia) and 14 g of dimethyl sulfate and the mixture was boiled on a water bath for 30 min. Then an additional solution of 2.7 g of sodium methoxide in 50 ml of anhydrous methanol and 12.6 g of dimethyl sulfate were added and the mixture was boiled for 30 min and filtered. The filtrate was diluted with 800 ml of water. The precipitated colorless solid was separated, washed with water, and dried. Yield 18.7 g (80.5%), mp 109-110° (from methanol), R_f 0.37 (benzene–ethanol, 49:1 , aluminum oxide) and 0.54 (benzene–ethanol, 9:1, silica gel G). Found %: C 62.10; H 5.24; N 12.33. $C_{12}H_{12}N_2O_3$. Calculated, %: C 62.05; H 5.21; N 12.06.

Ethyl 3-Ethylphthalazon-4-yl-1-acetate (IIb). A. To a solution of 7.5 g of sodium ethoxide in 200 ml of anhydrous ethanol were added 23.2 g of (Ib) and 30.83 g of diethyl sulfate; the mixture was boiled on a water bath for 1 h and cooled. The precipitate of unreacted (Ib) was separated (1.4 g) and the filtrate was diluted with 600 ml of water. The product which crystallized out was filtered, washed with water, and dried. Yield 18.8 g (72.3%).

B. To a boiling mixture of 69.6 g of (Ib), 300 ml of anhydrous ethanol, and 117 g of ethyl iodide, was added over 0.5 h a solution of 13.8 g of sodium in 300 ml of anhydrous ethanol. The mixture was boiled an additional 40 min, then strongly cooled and diluted with 1800 ml of ice water. The precipitate was filtered, washed with water, and dried. Yield 49 g (62.7%), mp 71-72° (from a mixture of ethanol–water), R_f 0.46 (benzene–ethanol, 49:1, aluminum oxide) and 0.60 (benzene–ethanol, 9:1, silica gel G). Found, %: C 64.25; H 5.76; N 10.71. $C_{14}H_{16}N_2O_3$. Calculated, %: C 64.60; H 6.19; N 10.76.

Ethyl 3-Benzylphthalazon-4-yl-1-acetate (IIc). Analogously to the synthesis of (IIa), (IIc) was obtained from (Ib), benzyl chloride, and sodium ethoxide in alcohol solution and crystallized out from the hot filtrate of the reaction mixture upon cooling. Yield 45.3%, mp 126-127° (from ethanol), R_f 0.55 (benzene–ethanol, 49:1, aluminum oxide) and 0.68 (benzene–ethanol, 9:1, silica gel G). Found, %: C 70.94; H 5.81; N 8.74. $C_{19}H_{18}N_2O_3$. Calculated, %: C 70.79; H 5.63; N 8.69.

Ethyl 3-(2'-Pyridylethyl)phthalazon-4-yl-1-acetate (IId). A mixture of 23.2 g of (Ib) and 21 g of 2-vinylpyridine was heated for 6 h at 150°, cooled, and diluted with 200 ml of ether. The precipitate was filtered and recrystallized from 70 ml of isooctane. Yield 27.8 g (82.4%), mp 108-109° (from isooctane), R_f 0.16 (benzene–ethanol, 49:1, aluminum oxide). Found, %: N 12.58, 12.40. $C_{19}H_{19}N_3O_3$. Calculated, %: N 12.46.

3-Substituted Phthalazon-4-yl-1-acetic Acids (III). We dissolved 5.6 g of potassium hydroxide in 50 ml of water and added 0.05 mole of (II) [to improve solubility, particularly of (IIb-IIc), 25 ml of ethanol can be added], then heated the mixture at 100° for 30 min. The obtained solution was filtered and acidified with concentrated hydrochloric acid. The precipitated colorless solid was filtered and washed with water, alcohol, and ether. Yields and constants of the obtained materials are indicated in Table 1.

3-Methylphthalazon-4-yl-1-acetic Acid (IIIa). To a solution of 34.5 g of potassium carbonate in 100 ml of water was added 17.3 g of methylhydrazine sulfate and 19 g of (VII) and the mixture was heated for 2 h at 100°. The reaction mixture was filtered and the filtrate was acidified with concentrated hydrochloric acid. The formed precipitate was separated and washed with water, acetone, and ether. Yield was 17.6 g (80.7%); the material was identical with the material obtained by basic hydrolysis of (IIa) in mixed decomposition sample, UV spectra, and chromatography.

2-Substituted 4-Methylphthalazones-1 (IV). A mixture of 0.01 mole of (III) and 2 ml of nitrobenzene was heated at 200° for 10 min, cooled, and 2 ml of petroleum ether was added. The precipitated colorless crystals were filtered, washed with petroleum ether, and dried. Yields and constants of the obtained materials are indicated in Table 2.

3-Methylphthalazon-4-yl-1-acetamide (Va). In a closed flask at room temperature for 72 h were shaken 11.6 g of (IIa) and 150 ml of a 38% aqueous ammonia solution. The precipitate was separated, washed with water, and dried. Yield 9.75 g (89.7%), mp 248-249° (from a mixture of ethanol–water, 1:1), R_f 0.55

(chloroform–ethanol–benzene, 5:3:2, silica gel G). Found, %: C 61.08; H 5.22; N 18.98. $C_{11}H_{11}N_3O_2$. Calculated, %: C 60.81; H 5.10; N 19.34.

3-Ethylphthalazon-4-yl-1-acetamide (Vb). The compound was obtained analogously to (Va) from 13 g of (IIb) and 150 ml of a 38% aqueous ammonia solution after shaking for 120 h. Yield 10.25 g (97.7%); mp 251-252° (from ethanol), R_f 0.61 (chloroform–ethanol–benzene, 5:3:2, silica gel G). Found, %: C 62.16; H 5.84; N 18.14. $C_{12}H_{13}N_3O_2$. Calculated, %: C 62.33; H 5.76; N 18.17.

3-Benzylphthalazon-4-yl-1-acetamide (Vc). In a 1-liter autoclave were placed 12.9 g of (IIc) and 100 ml of ethanol; the autoclave was saturated with ammonia to a pressure of 5 atm and heated at 100° for 12 h. The precipitate was separated, washed with water, and dried. Yield 8.7 g (72.2%), mp 244.5-245.5° (from n-amyl alcohol), R_f 0.70 (chloroform–ethanol–benzene, 5:3:2, silica gel G). Found, %: C 69.90; H 5.29; N 14.64. $C_{17}H_{15}N_3O_2$. Calculated, %: C 69.60; H 5.15; N 14.34.

3-(2'-Pyridylethyl)phthalazon-4-yl-1-acetamide (Vd). In a closed flask at room temperature for three weeks were shaken 16.8 g of (IId) and 150 ml of a 25% aqueous ammonia solution. The precipitate was separated, washed with water, and dried. Yield 12.7 g (80.5%), mp 219° (from ethanol), R_f 0.47 (benzene–ethanol, 9:1, aluminum oxide). Found, %: N 18.02, 18.21. $C_{17}H_{16}N_4O_2$. Calculated, %: N 18.17.

Hydrazides of 3-Substituted Phthalazon-4-yl-1-acetic Acids (IV). A solution of 0.01 mole of (II) and 4 ml of hydrazine hydrate in 20 ml of ethanol was boiled on a water bath for 4 h. After cooling, the precipitate was separated. For purification it can be recrystallized from ethanol. Yields and constants of the obtained materials are presented in Table 3.

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