PHTHALAZINE AND RELATED HETEROCYCLES

IX. DERIVATIVES OF PHTHALAZON-4-YL-1-ACETIC ACID

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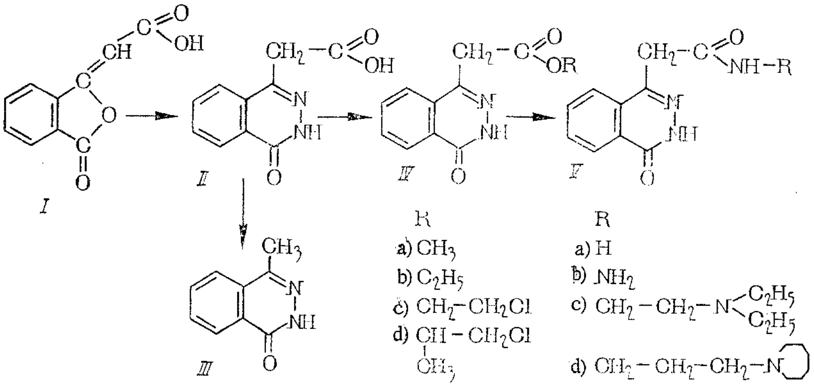
UDC 615.4:547

The synthesis of a series of derivatives of phthalazon-4-yl-1-carboxylic acid, which possess certain pharmacological activity, was described earlier [1-3].

In this connection, we undertook the synthesis of phthalazon-4-yl-1-acetic acid (II) and its derivatives.

The condensation of phthalidenacetic acid (I) or its nitrile with corresponding hydrazine [4, 5] has been described for synthesis of derivatives of (II). Under our conditions, acid (I) reacted with hydrazine without complication with formation of acid (II), which decarboxylated quite easily to 4-methyl-1-phthalazone (III).



In this way, a new synthesis of 4-methyl-1-phthalazone was accomplished, which simultaneously serves as a confirmation of the structure of compound (II) (the latter could have had the pyrazolone, and not the phthalazone, structure). The phthalazone structure of the hetero ring of (II) was also confirmed by the UV spectrum (see Table 1). Acid (II) has several absorption maxima in bands characteristic for phthalazone derivatives [3], while, for example, 3-phenyl-1-benzyl-5-pyrazolone has only one maximum at 252 mμ [6]. The disappearance of the absorption maximum at 246 mμ upon going from alcohol to aqueous solution is evidently due to solvation of the acid in one solution. In the IR spectrum of (IVb), the ethyl ester of (II), absorption bands are prominent at 3418, 3038, 1733, 1670 cm^{-1}, which can be assigned to stretching vibrations of N–H, C–H, ester, and ring carbonyls, respectively.

We did not find the reaction of acid (II) with phosphorus pentachloride or thionyl chloride a preparatively convenient method of obtaining the corresponding amides. We attempted to obtain these derivatives from the mixed anhydride of acid (II) and ethylcarbonic acid, but this anhydride spontaneously loses CO_2 with formation of ester (IVb). An attempt to use the analogous reaction to prepare amides by reaction of dimethylcarbamyl chloride instead of chlorocarbonic ester did not lead to the expected results. Decarboxy-

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lation of acid (II) occurred with formation of (III). In this connection, we obtained ester (IV) by normal esterification in the presence of sulfuric acid. Transesterification was found to be inconvenient for synthesis of aminoalkyl esters due to the poor solubility of both the methyl (IVa) and the ethyl (IVb) esters of (II). Therefore, we initially carried out the esterfication of the corresponding chlorohydrin. Attempts to exchange the halogen in the β-chloroethyl (IVc) and β-chloroisopropyl (IVd) esters by the diethylamino group gave difficult-to-isolate materials. Aminolysis of (IVb) yielded amides and reaction with hydrazine yielded (Vb), the hydrazide of (II). The very similar UV spectra of acid (II) and its transformation products indicate that in the course of these reactions (esterification, ammonolysis, aminolysis, hydrazinolysis) recyclization to the pyrazolone structure does not occur. A pharmacological examination of the hydrochlorides of β-diethylaminoethyl amide of (II) (Vc · HCl) and γ-hexamethyleniminopropyl amide of (II) (Vd · HCl) showed that the toxicity of these compounds is not high. Thus, LD_{50} upon intraperitoneal introduction into white mice was found to be equal to 291 and 74.5 mg/kg for compounds (Vc · HCl) and Vd · HCl), respectively. In fine experiments on cats narcotized with chloralose, upon intravenous introduction in a dose of 5-10% LD_{50} a brief (5-10 min) decrease of blood pressure by 30-80 mm of Hg was observed. Compound (Vd · HCl) causes a weak antiarrhythmic effect, preventing loss of white rats narcotized with Nembutal after intravenous introduction of a solution of calcium chloride.

TABLE 1. UV Spectra of Phthalazon-4-yl-1-acetic Acid and Its Derivatives

Compound	Solvent	λ_{max} (mμ)	lg ε	λ_{max} (mμ)	lg ε	λ_{max} (mμ)	lg ε	λ_{max} (mμ)	lg ε	λ_{max} (mμ)	lg ε
III	Ethanol	245	3,84	254	3,87	283,5	3,81				
II	Water			252	3,78	277,5—279,5	3,72	298	3,55	310	3,38
II	0,01 N solution KOH			252	3,77	279,5—281	3,72	298—299	3,63	309—310	3,51
II	0,01 " " H_2SO_4			251,5	3,85	278	3,77	298	3,58	310	3,43
II	Ethanol	246	3,82	255	3,82	284—285	3,78				
IVb	»	245	3,81	253,5	3,86	284	3,78				
Va	»	245	3,82	254	3,85	282—286	3,78				
Vb	»	245—246	3,92	253—254	3,92	284—285	3,83				
Vd	»	245	3,83	254	3,85	285	3,77				
Vd.HCl	»	245	3,81	254	3,85	285	3,78				

EXPERIMENTAL

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

Phthalazon-4-yl-1-acetic Acid (II). In a 3-liter flask were added 1250 ml of water, 345.5 g (2.5 moles) of potassium carbonate, and 156.2 (1.2 moles) of hydrazine sulfate, and 190.2 g (1 mole) of phthalidenacetic acid [7] in portions with stirring. The reaction mixture was heated in a boiling water bath for 2 h, cooled, filtered, and acidified with concentrated hydrochloric acid. The formed precipitate was separated and crystallized from 3 liters of water, adding about 30 g of activated carbon. Yield 153 g (75%), dec. t. 165°C (from water), R_f 0.37 (benzene-acetic acid, 3:1, aluminum oxide) and 0.31 (benzene-acetic acid, 3:1, silica gel G). Found, %: C 58.34, 58.46; H 3.83, 3.87; N 13.84, 13.76. $C_{10}H_8N_2O_3$. Calculated, %: C 58.83; H 3.95; N 13.73.

4-Methy-1-phthalazone (III). A mixture of 102.1 g (0.5 mole) of (II) and 200 ml of nitrobenzene was heated at 170° until evolution of carbon dioxide ceased (about 20 min). The solution was cooled and the precipitate was separated and washed with ether. Yield 78.3 g (98%), mp 221-222° (literature data [8]: mp 222°), R_f 0.56 (benzene-ethanol, 9:1, aluminum oxide).

Ethyl Ester of Phthalazon-4-yl-1-acetic Acid (IVb). A solution of 40.8 g (0.2 mole) of (II) in 1 liter of ethanol and 50 ml of concentrated sulfuric acid was boiled on a water bath for 30 min and the hot solution was filtered and cooled. The precipitate which crystallized out was separated, washed with a solution of sodium carbonate and water, and dried. Yield 43 g (92.5%), mp 177.5-178.5° (from ethanol), R_f 0.55 (benzene-ethanol, 9:1, aluminum oxide) and 0.45 (benzene-ethanol, 9:1, silica gel G). Found,%: C 61.80; H 5.21; N 12.18. $C_{12}H_{12}N_2O_3$. Calculated, %: C 62.05; H 5.21; N 12.06.

Methyl Ester of Phthalazon-4-yl-acetic Acid (IVa). The compound was prepared analogously to the preceding from 40.8 g (0.2 mole) of (II), 800 ml of methanol, and 50 ml of concentrated sulfuric acid. Yield 39.5 g (90.5%), mp 187-191° (from methanol), R_f 0.41 (benzene-ethanol, 9:1, silica gel G). Found,%: C 60.06, 59.93; H 4.46, 4.50; N 12.54, 12.68. $C_{11}H_{10}N_2O_3$. Calculated, %: C 60.53: H 4.62; N 12.83.

β-Chloroethyl Ester of Phthalazon-4-yl-1-acetic Acid (IVc). In a flask fitted via a Dean-Stark clarifier with a reflux condenser and calcium chloride tube were heated on a boiling water bath 20.4 g (0.1 mole) of (II), 16.1 g (0.2 mole) of ethylene chlorohydrin, 160 ml of benzene, and 2 ml of concentrated sulfuric acid until separation of water ceased (5 h). Upon cooling, the precipitate was separated, washed with a solution of sodium carbonate and water, and dried. We obtained 22.1 g of (IVc). By concentrating the benzene solution, the yield can be increased to 25 g (93.5%), mp 183.5-184.5° (from ethanol), R_f 0.55 (benzene-ethanol, 2:1, aluminum oxide). Found, %: Cl 13.21, 12.98; N 10.59, 10.52. $C_{12}H_{11}ClN_2O_3$. Calculated, %: Cl 13.29; N 10.51.

β-Chloroisopropyl Ester of Phthalazon-4-yl-1-acetic Acid (VId). The compound was obtained analogously to the preceding from 20.4 g (0.1 mole) of (II), 18.9 g (0.2 mole) of propylene chlorohydrin, 160 ml of benzene, and 2 ml of concentrated sulfuric acid after boiling for 30 h and concentration of the reaction solution. Yield 23.4 g (83.5%), mp 122.5-124° (from methylcyclohexane), R_f 0.56 (benzene-ethanol, 9:1, aluminum oxide). Found, %: Cl 12.48, 12.64: N 10.15, 10.12. $C_{13}H_{13}ClN_2O_3$. Calculated, %: Cl 12.63; N 9.98.

Amide of Phthalazon-4-yl-1-acetic Acid (Va). In a well-stoppered flask for 10 days were agitated 23.2 g (0.1 mole) of (IVb) and 200 ml of 35% aqueous solution of ammonia. The precipitate was separated, washed with water, and dried. Yield 20.2 g (99.5%), mp 262-264° (dec., from n-propanol), R_f 0.40 (chloroform-ethanol benzene, 5:3:2, silica gel G). Found, %: C 59.49; H 4.35; N 20.51, 20.70. $C_{10}H_9N_3O_2$. Calculated, %: C 59.11; H 4.46; N 20.67.

Hyrazide of Phthalazon-4-yl-1-acetic Acid (Vb). A mixture of 2.32 g (0.01 mole) of (IVb), 4 ml of hydrazine hydrate, and 40 ml of ethanol was heated on a boiling water bath for 4 h. After cooling, the precipitate was separated, washed with alcohol, and dried. Yield 2.1 g (96%), dec. t. 250-252° (from ethanol). Found, %: N 25.77, 25.83. $C_{10}H_{10}N_4O_2$. Calculated, %: N 25.67.

β-Diethylaminoethylamide of Phthalazon-4-yl-1-acetic Acid (IVc). A mixture of 14 g (0.06 mole) of (IVb) and 30 ml of β-diethylaminoethylamine was heated for 4 h at 140°. The precipitate which crystallized upon cooling was filtered and washed with ether. Yield 15.8 g (87.1%), mp 186° (from butanol), R_f 0.22 (benzene-ethanol, 9:1, aluminum oxide). Found, %: N 18.77, 18.72. $C_{16}H_{22}N_4O_2$. Calculated, %: N 18.52. Hydrochloride of (IVc), mp 191-192° (from n-propanol), R_f 0.66 (n-butanol-acetic acid-water, 4:1:1, paper). Found, %: Cl 10.68, 10.65; N 16.32, 16.30. $C_{16}H_{22}N_4O_2 \cdot HCl$. Calculated, %: Cl 10.47; N 16.54.

γ-Hexamethyleniminopropylamidephthalazon-4-yl-1-acetic Acid (Vd). A mixture of 5.8 g (0.025 ml) of (IVb) and 12.5 ml of γ-hexamethyleniminopropylamine was heated for 4 h at 170°. The solid which crystallized out upon cooling was filtered and washed with ether. Yield 8.3 g (73.6%), mp 202-203° (from ethanol), R_f 0.18 (benzene-ethanol, 9:1, aluminum oxide). Found, %: N 16.21, 16.28. $C_{19}H_{26}N_4O_2$. Calculated, %: N 16.36.

Hydrochloride of (Vd), mp 201-202° (from n-propanol), R_f 0.73 (n-butanol-acetic acid-water, 4:1:1, paper). Found, %: Cl 9.60, 9.56; N 15.00, 15.02. $C_{16}H_{26}N_4O_2 \cdot HCl$. Calculated, %: Cl 9.36; N 14.79.

LITERATURE CITED

1. V. B. Brasyunas and K. V. Krablyauskas, Transations of the Kaunassk Medicinal Institute [in Russian], 6, 277 (1958).
2. A. N. Kost, Sh. Fel'deak, and K. V. Grablyauskas, Khim.-Farmats. Zh., No. 3, 43 (1967).
3. K. V. Grablyauskas, V. Yu. Rekhlevichus, M. I. Grablyauskene, et al., ibid., No. 9, 35 (1968).
4. W. Roser, Ber. Dtsch. Chem. Ges., 18, 802 (1885).
5. I. Zugravescu, M. Petrovanu, and E. Rucinschi, An. Stiint. Univ. Iasi, Sect. I, 7, No. 1, 169 (1961); Ref. Zh. Khimiya, No. 5Zh297 (1962).
6. A. N. Kost and R. S. Sagitullin, Vestn. Moskovsk. In-ta., Seriya Khimiya, No. 1, 225 (1959).

7. S. Gabriel and A. Neumann, Ber. Dtsch. Chem. Ges., 26, 951 (1893).
8. S. Gabriel and A. Neumann, ibid., 26, 705 (1893).