PHTHALAZINE AND HETEROCYCLES RELATED TO IT.

VI. DERIVATIVES OF 4-PHTHALAZONE-1-CARBOXYLIC ACIDS WITH AMINOALKYL CHAINS

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We have previously reported the synthesis of a number of 4-phthalazone-1-carboxylic acids and their derivatives. With simple model compounds it was shown that they exist in the lactam structure.

In a pharmacological study, they proved to have little activity. It is known that the introduction of a dialkylaminoalkyl chain into aromatic and heterocyclic compounds (including phthalazines [2,3]) leads to pharmacologically active substances. For this reason, we have also carried out the synthesis of a number of dialkylaminoalkyl esters and the analogous amides of 4-phthalazone-1-carboxylic acids. Direct esterification and aminolysis were unsuitable for these purposes. Consequently, the required substances were obtained via the acid chlorides, which were not isolated in the pure state but were subjected in the crude form to the action of amino alcohols or diethylaminoethylamine. The yields and constants of the substances obtained are given in Tables 1 and 2.

In experiments on the sciatic nerve of frogs (0.5% solution) by the Bülbring-Wajda method [4] and on guinea pigs (0.25% solution subcutaneously), some of them showed conduction and infiltration of local anaesthetic activity. Among the esters it was strongest in the case of the diethylaminoethyl esters of 3-aryl- and 3-aralkyl-4-phthalazone-1-carboxylic acids (compounds I, V, and VI) although weaker than that of novocaine and dicaine.

The toxicity of the compounds studied was low. Thus, LD_{50} for compounds I and III, with intraperitoneal administration to mice, was 94 and 141 mg/kg, respectively. In acute experiments on cats (both sexes) anaesthetized with urethane-chloralose, the intraperitoneal administration of 0.3 mg/kg produced no appreciable changes in the blood circulation and respiration. When compounds VII-IX were administered in a dose of 2-3 mg/kg, there was a fall in the blood pressure by 30-40 mm Hg, but after 10 min it had returned almost to the initial level. Moreover, under the influence of substances I-III, V, VI, and X, which had the most pronounced local anaesthetic properties, when administered in large doses (3-5 mg/kg) there was a retardation or even a temporary cessation of respiration. None of the substances modified the pressor effect of epinephrine or the depressor effects of acetylcholine and histamine.

Substances with a similar pharmacological activity to that of the esters, but stronger and more prolonged, were found among the amines. This can apparently be connected with their greater resistance to hydrolytic decomposition in the organism.

All the substances obtained had practically no effect (in dilutions of 1 mg/ml) on the growth of standard strains of staphylococci, streptococci, the bacilli of typhoid fever and paratyphoids A and B, and colibacillus or on dysentery and anthrax bacteria.

EXPERIMENTAL

The synthesis of the initial acids has been described previously [5]. The amino alcohols were vacuum-distilled before use. The aminoalkylamides were obtained by Nakajima's method [6]. The purity of the substances was checked by ascending chromatography on "Leningrad slow" paper in the butanol–acetic acid–water (4:1:5) system. The spots on the chromatograms were revealed under UV light and by means of Dragendorff's reagent as modified by Munier [7]. The R_f values are given in Tables 1 and 2.

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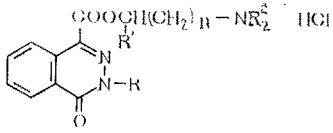
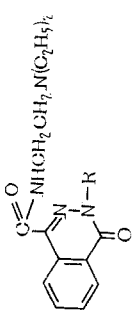
TABLE 1. Dialkylaminoalkyl Esters of 4-Phthalazone-1-carboxylic Acids



Compound	R	R′	n	$-NR_2^2$	Yield (in %)	Mp (in°)	Method of preparation	Solvent for crystallization	Found (in %) Cl	Empirical formula	Calculated (in %) Cl	R_f on paper
I	C_6H_5	H	1	$-N(C_2H_5)_2$	75	221—2	A	Abs. ethanol	8,77;8,53	$C_{21}H_{24}ClN_3O_3$	8,82	0,78
II	C_6H_5	CH_3	1	$-N(CH_3)_2$	66	184—5	B	Abs. ethanol-ether	8,93;8,75	$C_{20}H_{22}ClN_3O_3$	9,14	0,72
III	C_6H_5	H	2	$-N(CH_3)_2$	85	197—8	»	Abs. ethanol	8,59;8,67	$C_{20}H_{22}ClN_3O_3$	9,14	0,67
IV	C_6H_5	H	1	Piperidyl	61	240(decomp)	»	Propanol	8,44;8,66	$C_{20}H_{24}ClN_3O_3$	8,57	0,82
V	$M-CH_3-C_6H_4$	H	1	$-N(C_2H_5)_2$	64	200—1	»	Abs. ethanol	8,19;8,09	$C_{22}H_{26}ClN_3O_3$	8,52	0,87
VI	$C_6H_5CH_2$	H	1	$-N(C_2H_5)_2$	64	212—3	A	Propanol	8,27;7,72	$C_{22}H_{26}ClN_3O_3$	8,52	0,87
VII	$C_6H_5CH_2$	CH_3	1	$-N(CH_3)_2$	65	234(decomp)	»	Isobutanol	8,48;8,44	$C_{21}H_{24}ClN_3O_3$	8,82	0,86
VIII	$C_6H_5CH_2$	H	2	$-N(CH_3)_2$	85	149	»	»	8,67;7,90	$C_{21}H_{24}ClN_3O_3$	8,82	0,82
IX	$C_6H_5CH_2$	H	1	Piperidyl	47	200-1(decomp)	B	Propanol	8,00;8,01	$C_{23}H_{26}ClN_3O_3$	8,28	0,86
X	CH_3	H	1	$N(C_2H_5)_2$	76	220—1	A	Abs. ethanol	10,23;10,37	$C_{16}H_{22}ClN_3O_3$	10,43	0,70
XI	CH_3	CH_3	1	$N(CH_3)_2$	66	218—9	»	Propanol	11,05;11,60	$C_{15}H_{20}ClN_3O_3$	10,88	0,73
XII	CH_3	H	2	$N(CH_3)_2$	66	205—6	»	»	11,06;11,09	$C_{15}H_{20}ClN_3O_3$	10,88	0,67
XIII	CH_3	H	1	Piperidyl	71	219-20(decomp)	B	Butanol	10,50;10,46	$C_{17}H_{24}ClN_3O_3$	10,02	0,83

TABLE 2. Diethylaminoethylamides of 4-Phthalazone-1-carboxylic Acids



Compound	R	Yield (%)	Mp (in °C)	Solvent	Found (in %)		Empirical formula	Calculated (in %)		R_f on paper
					N	Cl		N	Cl	
XIV	H	74	208,5—209	Benzene	19,29	—	$C_{15}H_{20}N_4O_2$	19,43	—	0,65
	HCl salt		245-6(decomp)	Isobutanol	17,54	11,19	$C_{15}H_{21}ClN_4O_2$	17,25	10,91	0,59
XV	CH_3	52	57,5—58	Petroleum ether	18,42	—	$C_{16}H_{22}N_4O_2$	18,53	—	0,77
	HCl salt		225	Abs. ethanol	51,91	10,54	$C_{16}H_{23}ClN_4O_2$	16,54	10,47	0,71
XVI	$C_6H_5CH_2$	71	101	Petroleum ether	14,88	—	$C_{22}H_{26}N_4O_2$	14,80	—	0,78
	HCl salt		168	Isobutyl acetate–butanol	13,20	8,40	$C_{22}H_{27}ClN_4O_2$	13,51	8,54	0,85
XVII	C_6H_5	88	91,5		15,66	—	$C_{21}H_{24}N_4O_2$	15,37	—	0,84
	HCl salt		199—200	Abs. ethanol-ether	—	8,82	$C_{21}H_{25}ClN_4O_2$	—	8,84	0,83

Synthesis of Dialkylaminoalkyl Esters of 4-Phthalazone-1-carboxylic Acids. A mixture of 0.1 mole of the appropriate acid, 20 ml of thionyl chloride, and 200 ml of dry chloroform was heated with a reflux condenser fitted with a calcium chloride tube in the glycerol bath at 90°C until dissolution was complete, which took 1-2 h. The volatile substances were distilled off in vacuum, the residue was dissolved in 200 ml of dry benzene, and the solution was immediately poured into a mixture of 0.1 mole of tert-aminoalkanol and 60 ml of dry benzene. After stirring for 1 h with heating to 90°C under reflux, the precipitate formed was filtered off, washed with dry benzene, and dried.

A. The crude reaction product obtained was recrystallized from a suitable solvent.

B. The crude product obtained was dissolved in water and the solution was made alkaline with sodium carbonate and extracted with ether, the extract was dried with sodium sulfate, and the amine was precipitated with dry hydrogen chloride with subsequent crystallization. The elementary analyses, yields, and constants of the compounds obtained, are given in Table 1.

Diethylaminoethylamide of 4(3H)-Phthalazone-1-carboxylic Acid. A mixture of 5.7 g of 4(3H)-phthalazone-1-carboxylic acid, 4.2 ml of thionyl chloride, 0.5 ml of dimethylformamide, and 20 ml of dry chloroform was boiled under reflux for 1 h and was then cooled to room temperature and filtered, and the residue was washed with dry chloroform. The substance obtained was added to a mixture of 3.48 g of diethylaminoethylamine and 30 ml of dry benzene and the resulting mixture was boiled for ½ h under reflux. After this, 30 ml of absolute ethanol was added, the mixture was heated for a further 1 h, and the solvent was driven off in vacuum. The residue was dissolved in water, and the solution was acidified to Congo Red and treated with carbon. The reaction product was isolated by the careful addition of a 10% solution of caustic soda. This gave 6.3 g (74%) of the colorless diethylaminoethylamide of 4(3H)-phthalazone-1-carboxylic acid with mp 208.5-209°C (from benzene).

The other diethylaminoethylamides were obtained in a similar manner to the corresponding esters. The results of elementary analysis, yields, and constants are given in Table 2.

CONCLUSION

The synthesis of a number of dialkylaminoalkyl esters and the corresponding amides of 4-phthalazone-1-carboxylic acids has been described. Some of these compounds possess local anaesthetic and short-term hypotensive activity.

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