α-Nitrophenylhydrazone of Benzoylformanilide (IVe). A salt with perchloric acid was prepared from 0.0025 mole of II ($R' = 4{=}NO_2$) by the method of [3], and then, with shaking, 0.0025 mole of I (R = H) in aqueous alcohol was added and the reaction mixture was heated for 3 h, until a precipitate formed. The precipitate was crystallized from toluene. Compound IVf was prepared similarly.

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ANTHELMINTIC ACTIVITY OF CERTAIN HYDRAZONES, PHTHALAZONES, AND PHTHALAZINYLHYDRAZONES DURING NIPPOSTRONGYLESIS OF MICE

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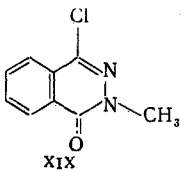
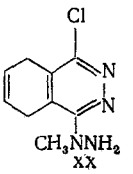
We have already reported [1] the discovery of the anthelmintic activity of acylhydrazones of aromatic aldehydes. In continuation of this research, we studied the anthelmintic properties of a series of N-unsubstituted hydrazones (I-III), aryl- (IV-VIII) and arylidenehydrazones of phthalazones (IX-XII), N-methyl-N-(4-chloro-1-phthalazinyl)- (XIII-XV) and N-methyl-N-(4-oxo-1-phthalazinyl)hydrazones of aromatic aldehydes (XVI-XVIII), as well as 2-methyl-4-chlorophthalazone (XIX) and N-methyl-N-(4-chloro-1-phthalazinyl)hydrazine (XX).



XIX



XX

The results of our research are given in Tables 1 and 2, and show that the groups of hydrazones studied are promising in the search for anthelmintic drugs. Moreover, the data obtained can lead to certain conclusions on the relationship between the structure and the anthelmintic activity of the phthalazone hydrazones and phthalazinylhydrazones.

4-Chlorophthalazone hydrazone (I) is fairly toxic compound, and in a dose of 400 mg/kg induced clinical symptoms of intoxication in animals, while in a dose of 100 mg/kg, its anthelmintic activity is not high (see Table 1). Increase in its solubility in water by conversion into a hydrochloride salt (compound II) leads, contrary to expectations, to a decrease in its effectiveness.

The introduction of a methyl group onto the nitrogen atom in the 2-position of the phthalazone ring leads to a decrease in activity, without any decrease in toxicity. 2-Methyl-4-chlorophthalazone hydrazone (III), in the same way as ketone XIX, does not show anthelmintic properties.

In contrast to this, substitution of the hydrogen atom at the amine nitrogen atom of the hydrazone fragment of compound I by aryl (transition to compounds IV-VIII) or arylidene groups (transition to compounds IX-XII) leads to a lower toxicity of the drugs, while their anthelmintic properties are determined by the nature of the substituent introduced. Thus, 4-chlorophthalazone 4-nitrophenylhydrazone (IV) is less active than its isomer (V) containing the nitro group in the ortho position of the phenyl substituent. Further increase in the electron-accepting properties of the group introduced (transition to 2,4-dinitrophenylhydrazone of the same

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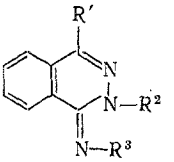
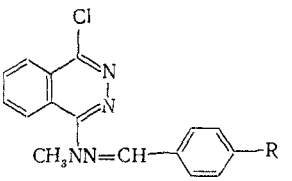
TABLE 1. Anthelmintic Activity of Hydrazones (I-III), Arylhydrazones (IV-VIII), and Arylidenehydrazones (IX-XII)



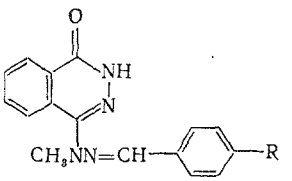
Compound	R^1	R^2	R^3	Melting point, °C	Dose, mg/kg	Effectiveness, %	LD_{50} for white mice, mg/kg
I	Cl	H	NH_2	200	100	36	—†
II	Cl	H	$NH_2 \cdot HCl$	200*	100	6	—†
III	Cl	CH_3	NH_2	106—8*	200	0	—†
IV	Cl	H	$NHC_6H_4NO_2$-4	232—3*	400	0	—†
V	Cl	H	$NHC_6H_4NO_2$-2	215—7*	400	28	2700
VI	Cl	H	$NHC_6H_3(NO_2)_2$-2,4	237—9*	400	23	—‡
VII	Cl	H	$N(CH_3)C_6H_5$	193—5	400	46	—‡
VIII	Cl	H	$N(C_6H_5)_2$	196—7*	400	84	3000
IX	Cl	H	$N\text{-}CHC_6H_5$	175—7	200	15	
					400	5	—‡
X	H	CH_3	$N\text{-}CHC_6H_4NO_2$-4	164—5	400	67	2000
XI	Cl	CH_3	$N\text{-}CHC_6H_4NO_2$-4	208—10	400	35	2000
XII	Cl	CH_3	$N\text{-}CHC_6H_4NO_2$-2	177—8	400	82	—‡

*With decomposition.
†In a dose of 400 mg kg induces clinical symptoms of intoxication.
‡Not determined.

TABLE 2. Anthelmintic Activity of N-Methyl-N-(4-chloro-1-phthalazinyl)-hydrazones (XIII-XV) and N-Methyl-N-(4-oxo-1-phthalzinyl)-hydrazones (XVI-XVIII) of Aromatic Aldehydes



XIII—XV



XVI—XVIII

Compound	R	Melting point, °C	Dose, mg/kg	Effectiveness, %		LD_{50} for white mice, mg/kg
				at nippostrongylesis	at hymenolepidosis	
XIII	H	174—5	200	48	—*	4000
			400	59	—*	
XIV	NO_2	304—5	200	61	—*	
			400	75	47	5000
XV	OH	201—2	400	65	40	—*
XVI	H	225—6,5	400	41	—*	5000
XVII	NO_2	298—300	200	43	—*	
			400	82	100	5000
XVIII	OH	165—7	400	74	40	5000

*Not determined.

ketone, compound VI) does not lead to any change in activity. However, monosubstituted arylhydrazones IV-VI are less effective than unsubstituted hydrazone I.

Substitution of two protons at the amine nitrogen atom leads to an increase in activity, and 4-chlorophthalazone diphenylhydrazone (VIII) is almost twice as active as 4-chlorophthalazone N-methyl-N-phenylhydrazone (VII).

Transition from arylhydrazones IV-VIII to arylidenehydrazones of phthalazones IX-VII (mixed azines of phthalazones and aromatic aldehydes), accompanied by the conversion of the amine nitrogen atom into an imine

nitrogen atom, does not lead to any appreciable change in the effectiveness. 4-Chlorophthalazone benzylidenehydrazone (IX) is a slightly active compound, but the introduction of the nitro groups increases the activity (compound X), especially in the ortho position of the aldehyde ring (compound XII). The fact that the effectiveness decreased in the presence of a chlorine atom in the 4 position of the phthalazone ring, while the arylidene residue was the same (compounds X and XI) was unexpected.

If the activity of 4-nitrobenzaldehyde azine (45%) [1] is compared with that of 2-methylphthalazone 4-nitrobenzylidenehydrazone (X) and 2-methyl-4-chlorophthalazone 4-nitrobenzylidenehydrazone (XI), it is seen that substitution of one 4-nitrobenzylidene fragment by the 2-methylphthalazone fragment leads to an increase and by 2-methyl-4-chlorophthalazone residue, to a decrease in the effectiveness in the azine series.

To clarify the influence of the nature of the substituents at the amine nitrogen atom in hydrazones on their anthelmintic properties, in the present work we studied N-methyl-N-(4-chloro-1-phthalazinyl)-hydrazones of aromatic aldehydes (XIII-XV) and N-methyl-N-(4-oxo-1-phthalazinyl)-hydrazones of the same aldehydes, (XVI-XVIII) the products of their hydrolytic transformation in an acid medium (possible metabolites).

The starting N-methyl-N-(4-chloro-1-phthalazinyl)hydrazine (XX) induces clinical symptoms of intoxication in animals. The transition of hydrazine XX to its hydrazones XIII-XV leads to an appreciable decrease in toxicity and increase in the effectiveness during both nippostrongylesis and hymenolepidosis of animals (see Table 2). These facts show that the hydrazone group plays an important role in the manifestation of the anthelmintic properties, although their effectiveness is determined by the nature of the carbonyl component. A similar conclusion was drawn in the study of the anthelmintic properties of benzoylhydrazones and azines of aromatic aldehydes [1].

When the anthelmintic properties of hydrazones XIII-XV are compared with those of hydrazones XVI-XVIII, it is seen that substitution of the chloroimine group in the phthalazone ring by an amide group affects the activity slightly. With compound XIX as an example, it can be seen that these groups do not impart anthelmintic properties to the phthalazine ring. Hence, in compounds XIII-XVIII, these properties are mainly determined by the presence of the hydrazone group.

It should be stressed that the effectiveness of the hydrazones XIII-XV and XVI and XVIII is higher than that of benzoylhydrazones and azines with the corresponding aldehyde residue (compare [1]), which shows the role of the substituent at the amine nitrogen atom in hydrazones of different groups. It is also interesting to note that 4-chlorophthalazone N-methyl-N-phenylhydrazone (VII), benzaldehyde N-methyl-(4-chloro-1-phthalazinyl)-hydrazone (XIII) and benzaldehyde N-methyl-N-(4-oxo-1-phthalazinyl)-hydrazone (XVI), which are the same type of hydrazones, and analogous in the nature of the substituents at the hydrazone fragment, manifest approximately equal activity, while the isomeric 4-nitrobenzaldehyde N-methyl-N-(4-chloro-1-phthalazinyl)hydrazone (XIV) and 2-methyl-4-chlorophthalazone 4-nitrobenzylidenehydrazone (XI) which differ in the position of the methyl group in the molecule (so that compound XIV is a disubstituted hydrazone, while compound XI is an asymmetric azine) differ appreciably in their activity (see Tables 1 and 2).

It follows that the anthelmintic properties of the phthalazone hydrazones and phthalazinylhydrazones, as in the case of other groups of hydrazones [1], are determined by a combination of different factors: the presence of the hydrazone group in the compound, the nature and number of substituents at the amine nitrogen atom of the hydrazone fragment, and the nature of the substituents in the phthalazone ring. For a more detailed knowledge of the dependence of the anthelmintic properties on the structure a further study in this series of hydrazones is necessary.

EXPERIMENTAL

4-Chlorophthalazone was prepared by the reaction of hydrazine hydrate and 1,4-dichlorophthalazine, according to [2]. The hydrazone structure of this compound has already been established [3]. The arylhydrazones IV-VIII were prepared by the action of 1,4-dichlorophthalazine on the corresponding arylhydrazines. Condensation of the corresponding aromatic aldehydes with the phthalazone hydrazones gave the arylidene hydrazones IX-XII, and with N-methyl-N-(4-chloro-1-phthalazinyl)hydrazine [3], the N-methyl-N-(4-chloro-1-phthalazinylhydrazones XIII-XV, which when heated in acetic acid, transform into N-methyl-N-(4-oxo-1-phthalazinyl)hydrazones XVI-XVIII.

The anthelmintic activity of the compounds was studied on 340 mongrel white mice weighing 15-17 g, experimentally inoculated with nematodes Nippostrongylus braziliensis and cestodes Hymenolepis nana, accord-

ing to known methods [4]. The mean number of nematodes in the control animals was 102 ± 19, and of cestodes 10 ± 1.8. The effectiveness of the compounds was estimated by the indirect activity [5].

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PREPARATION OF N-ALKYL-β-ALANINES AND THEIR SALTS AT THE AMINO GROUP

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It is known from the literature that higher N-alkylamino acids of structure I are highly effective bactericides [1-4] and fungicides [5], and have antituberculosis activity [6-9]. This is $RNH(CH_2CH_2NH)_n(CH_2)_m COOH \cdot HX$ (I), where $R = C_{12}H_{25}$; or $C_{10}H_{21}-C_{14}H_{29}$; $n = 0-2$; $m = 1-11$; and $X = Cl$.

Advantages of the preparations of this group over other classes of disinfectants are the broad spectrum of antimicrobial action, the absence of odor, and mild action on the human skin [10-12]. Metallic surfaces do not corrode in solutions of these preparations [13].

We have previously synthesized a series of such compounds with one nitrogen atom in the molecule by the reaction of higher aliphatic amines with ω-chlorocarboxylic acids [14]. However, in this case the reaction does not take place in an unequivocal manner. Along with the object compound, salts of the amines are also formed, as is shown below in the case of monochloroacetic acid.

$$RNH_2 + CH_2ClCOOH \begin{cases} \rightarrow RNHCH_2COOH \\ \rightarrow RNH_2 \cdot HX \end{cases}$$

where X = Cl or CH_2ClCOO.

To selectively prepare ampholytes of the higher N-alkylamino acids we settled on the reaction of higher aliphatic amines with esters of acrylic or methacrylic acid, with subsequent hydrolysis.

Compounds of type I were prepared from the N-monoalkyl-β-alanines so obtained by reaction with inorganic acids.

$$RNH_2 + CH_2{=}CR'COOCH_3 \longrightarrow RNHCH_2CHR'COOCH_3 \xrightarrow{\text{hydrolysis}}$$
$$\longrightarrow \underset{\text{(III)}}{RNHCH_2CHR'COOH} \xrightarrow{HX} \underset{\text{(I)}}{RNHCH_2CHR'COOH \cdot HX}$$

Throughout I—III: a) $R = C_{12}H_{25}$, $R' = H$;
b) $R = (C_{11}H_{23}-C_{13}H_{27})$, $R' = H$;
c) R = naphthenyl $R' = H$;
d) $R = C_{12}H_{25}$, $R' = CH_3$;
e) $R = C_{11}H_{23}-C_{13}H_{27}$, $R' = CH_3$;
X = Cl.

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