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Dedicated to Full Member of the Russian Academy of Sciences O.N. Chupakhin on his 80th anniversary

Modification of the Anticestodal Drug 5-Chloro-*N*-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide with a View to Improve Its Biological Effect

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Abstract—Reactions of 5-chloro-*N*-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide, the active substance of the drug Niclosamide (Phenasal), with higher amines (dodecan-1-amine, hexadecan-1-amine) and 1-(2-aminoethyl)-piperazine lead to the formation of the corresponding water-soluble ammonium salts with retention of pharmacophoric groups responsible for the antihelminthic effect, whereas no nucleophilic aromatic substitution of chlorine is observed. The product structure was determined by X-ray analysis.

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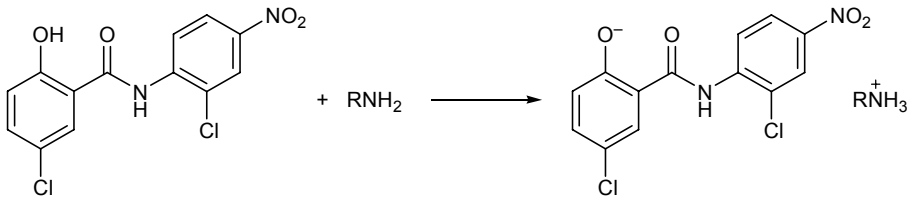
Phenasal [**I**, Niclosamide, 5-chloro-*N*-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide] is the only fairly accessible home-made drug active against cestodes (tape warms inducing helminthoses in animals and humans) [1]. Unfortunately, compound **I** is insoluble in water, and its efficiency does not exceed 70–80%.

Among other goals, the present study was aimed at synthesizing new bioavailable and water-soluble modifications of Phenasal possessing a lipophilic anchoring group to fix them on biomembranes of parasites and their larvae, which should lead to biomembrane degradation, penetration of host digestive juice into parasites, and hence death of the latter. A potential drug can be fixed in the parasite body with the aid of a lipid membrane anchor, such as higher aliphatic amines with an alkyl chain length of C_{12} and C_{16}. We believed that such modification of Phenasal should endow it with improved solubility and enhanced ability to be embedded into parasite cell membrane and destroy it, thus favoring both death of helminths and considerable deterioration of their life cycle from mature egg to invasive plerocercoids which are capable of developing both through intermediate hosts and in the lungs of the main host.

Compound **I** was treated with 2 equiv of dodecan-1-amine (**II**) and hexadecan-1-amine (**III**) in anhydrous ethanol at room temperature. However, the reaction gave not the expected chlorine substitution prod-

Scheme 1.



I **II**, **III** **IV**, **V**

II, **IV**, R = $C_{12}H_{25}$; **III**, **V**, R = $C_{16}H_{33}$.

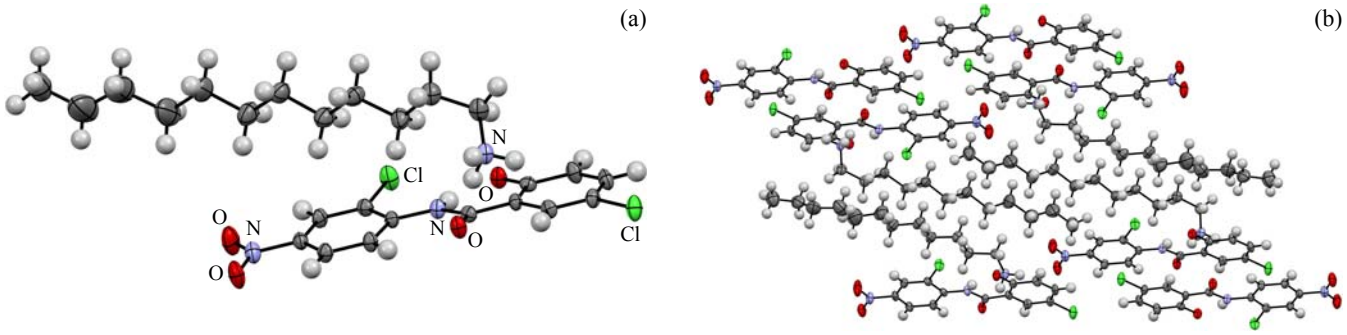


Fig. 1. (a) Structure of the molecule of dodecan-1-aminium 4-chloro-2-[(2-chloro-4-nitrophenyl)carbamoyl]phenoxide (**IV**) and (b) a fragment of its crystal packing according to the X-ray diffraction data.

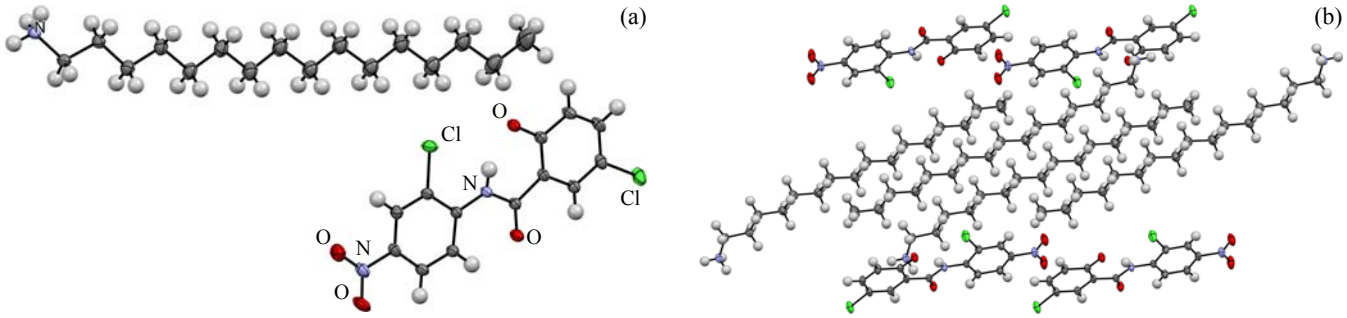


Fig. 2. (a) Structure of the molecule of hexadecan-1-aminium 4-chloro-2-[(2-chloro-4-nitrophenyl)carbamoyl]phenoxide (**V**) and (b) a fragment of its crystal packing according to the X-ray diffraction data.

ucts but water-soluble ammonium salts **IV** and **V** with retention of pharmacophoric groups responsible for the antihelminthic effect. The yield of **IV** and **V** was about ~80% (Scheme 1). The structure, purity, and stability of compounds **IV** and **V** were examined by physical, physicochemical, and chemical methods, IR spectroscopy, thermogravimetry in combination with differential scanning calorimetry (TG-DSC), and elemental and X-ray analyses.

The IR spectra of salts **IV** and **V** contained characteristic absorption bands in the regions 3366–2800 (NH), 1650 (C=O), 1510, 1250 (NO_2), and 740 cm^{-1} (C–Cl). The purity and thermal stability of **IV** and **V** (up to 148.2 and 167.7°C, respectively) were proved by the TG–DSC method.

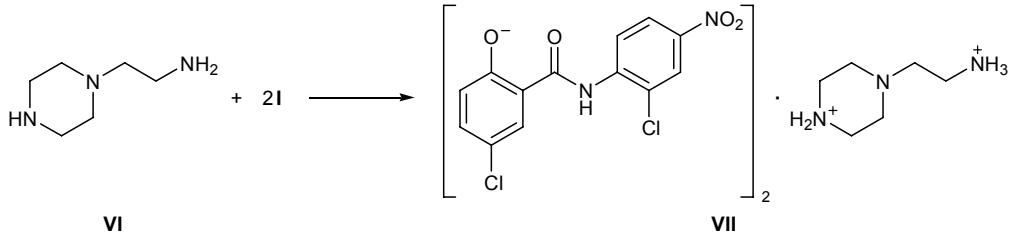
The X-ray diffraction data for Phenasal were reported in [2]; however, there are no X-ray diffraction data for its water-soluble form [3] which is necessary for devastation of helminth larvae (coracidia, procercoids, and plerocercoids) inhabiting out of intestine, in biological fluids of animals and humans.

The X-ray analysis data for compounds **IV** and **V** confirmed the formation of water-soluble ammonium salts with retention of pharmacophoric groups inherent to Phenasal (Figs. 1, 2).

One more modification of Phenasal was accomplished using 1-(2-aminoethyl)piperazine (**VI**) which is a substituted analog of piperazine and piperazine adipate that are well known antinematodal agents [4]. Such modification extends the spectrum of antiparasitic activity and gives rise to a new agent active against cestodes and nematodes simultaneously.

By reaction of Phenasal (**I**) with 1-(2-aminoethyl)-piperazine (**VI**) in anhydrous ethanol at room tempera-

Scheme 2.



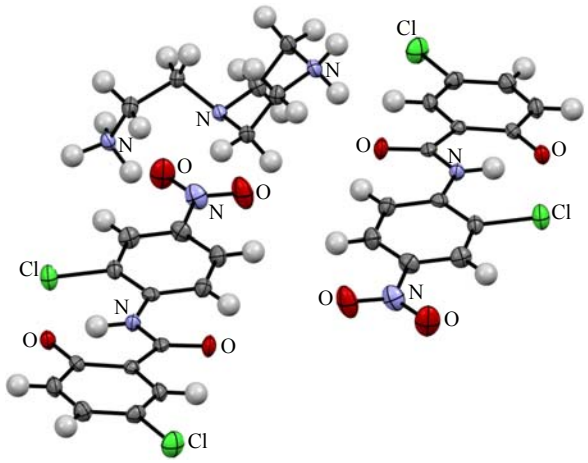


Fig. 3. Structure of the molecule of 4-(2-ammonioethyl)-piperazin-1-ium bis{4-chloro-2-[(2-chloro-4-nitrophenyl)-carbamoyl]phenoxide} (**VII**) according to the X-ray diffraction data.

ture we obtained 74% of bisammonium salt **VII** consisting of one molecule of **VI** (dication) and two molecules of **I** (anion; Scheme 2). The IR spectrum of **VII** contained absorption bands typical of functional groups present therein. The purity and thermal stability of **VII** (up to 228°C) were determined by simultaneous TG–DSC analysis.

The formation of water-soluble bis-ammonium salt **VII** with retention of pharmacophoric groups was confirmed by X-ray analysis (Fig. 3).

The Phenasal anions in the crystal structures of **IV**, **V**, and **VII** are almost planar, as in parent molecule **I** [2]. Deprotonation of the phenolic hydroxy group leads to shortening of the C–O bond to 1.306–1.318(3) Å against 1.354(3) Å in the neutral molecule. The ammonium groups in all crystalline salts **IV**, **V**, and **VII** are involved in numerous hydrogen bonds with oxygen atoms, the strongest bonds being those formed with the anionic oxygen atom; the $N\cdots O^-$ distance ranges from 2.58 to 2.71 Å, and the distance between the ammonium nitrogen atoms and oxygen atoms in the carbonyl and nitro groups varies within 2.96–3.01 Å.

The crystal packing of ammonium salts **IV** and **V** with higher alkyl substituents on the nitrogen is characterized by alternation of hydrophilic and hydrophobic layers. In the crystal structure of salt **IV** with dodecyl substituent transoid conformation in the middle of the hydrocarbon chain is distorted, and the ammonium group is oriented *gauche*, which favors intermolecular hydrogen bonding. The long-chain alkyl substituent in **V** in crystal has an ideal transoid conformation.

EXPERIMENTAL

The IR spectra were recorded on Specord M-80 and Thermo Avatar 360 FT-IR spectrometers from samples dispersed in mineral oil. The purity and thermal stability of the products were studied by simultaneous TG–DSC using a NETZSCH STA 449C TGA/S6TA85/E instrument (temperature range 20–400°C, heating rate 10 deg/min, argon atmosphere). The solvents used were purified according to standard procedures [5]. All initial reactants were distilled and purified just before use; their purity was checked by comparing their physical constants with published data.

Dodecan-1-aminium 4-chloro-2-[(2-chloro-4-nitrophenyl)carbamoyl]phenoxide (IV). A solution of 0.370 g (2 mmol) of amine **II** in 30 mL of anhydrous ethanol was added at 20°C to a solution of 0.327 g (1 mmol) of amide **I** in 30 mL of the same solvent, and the resulting red mixture was left to stand for 14 days to complete the reaction. The red crystals were filtered off and repeatedly washed with anhydrous ethanol and diethyl ether. Yield 0.43 g (84%), mp 148°C. IR spectrum, ν, cm^{-1}: 3366–2800 (NH); 1650 (C=O); 1510, 1250 (NO_2); 740 (C–Cl). Found, %: C 58.37; H 7.12; N 8.27. $C_{25}H_{35}Cl_2N_3O_4$. Calculated, %: C 58.59; H 6.84; N 8.20.

Hexadecan-1-aminium 4-chloro-2-[(2-chloro-4-nitrophenyl)carbamoyl]phenoxide (V). A solution of 0.482 g (2 mmol) of amine **III** in 30 mL of anhydrous ethanol was added at 20°C to a solution of 0.327 g (1 mmol) of amide **I** in 40 mL of the same solvent. After 14 days, the product was isolated as described above for salt **IV**. Yield 0.46 g (81%), mp 167.7°C. IR spectrum, ν, cm^{-1}: 3366–2800 (NH); 1650 (C=O); 1510, 1250 (NO_2); 740 (C–Cl). Found, %: C 61.30; H 7.62; N 7.38. $C_{29}H_{43}Cl_2N_3O_4$. Calculated, %: C 61.27; H 7.54; N 7.39.

4-(2-Ammonioethyl)piperazin-1-ium bis{4-chloro-2-[(2-chloro-4-nitrophenyl)carbamoyl]-phenoxide} (VII). A solution of 0.129 g (1 mmol) of diamine **VI** in 10 mL of anhydrous ethanol was added dropwise under stirring at 20°C to a solution of 0.654 g (2 mmol) of amide **I** in 20 mL of the same solvent. The red mixture was stirred for 2 h and was left to stand for 14 days to complete the reaction. The orange crystals were filtered off and washed with ethanol and diethyl ether. Recrystallization from chloroform–hexane gave an oily material which was kept for 2 months in a crystallizer; orange crystal druses were formed. Yield 0.577 g (74%), mp 228°C. IR spectrum, ν, cm^{-1}: 3370–

Crystallographic and refinement parameters for structures **IV**, **V**, and **VII**

Parameter	**IV**	**V**	**VII**
Formula	$C_{13}H_7Cl_2N_2O_4 \cdot C_{12}H_{28}N$	$C_{13}H_7Cl_2N_2O_4 \cdot C_{16}H_{36}N$	$2(C_{13}H_7Cl_2N_2O_4) \cdot C_6H_{17}N_3$
Molecular weight	512.46	568.56	783.44
Crystal system	Triclinic	Triclinic	Triclinic
Space group	$P\bar{1}$	$P\bar{1}$	$P\bar{1}$
Unit cell parameters:			
a, Å	8.2292(2)	8.0449(8)	9.0428(9)
b, Å	15.1823(4)	11.4595(7)	10.934(1)
c, Å	22.1426(7)	16.707(1)	17.647(4)
α, deg	104.662(2)	93.372(2)	75.886(5)
β, deg	92.365(2)	91.942(2)	78.646(4)
γ, deg	103.9930(10)	98.790(4)	84.125(3)
V, Å^3	2581.43(12)	1518.1(2)	1656.3(4)
Z	4	2	2
Temperature, K	198(2)	198(2)	150(2)
Absorption coefficient, μMo, mm^{-1}	0.287	0.251	0.422
Total number of reflections	64046	47456	21045
Number of independent reflections	10097	7915	6319
Number of variables	639	360	488
R_{int}	0.0637	0.0331	0.0648
R_1 [$I > 2\sigma(I)$]	0.0495	0.0336	0.0389
$wR(F^2)$ [$I > 2\sigma(I)$]	0.1239	0.0846	0.0659
R_1 (all reflections)	0.1188	0.0427	0.0773
$wR(F^2)$ (all reflections)	0.1486	0.0915	0.0735
Goodness of fit	0.978	0.918	0.856

2600 br (NH); 1650 (C=O); 1510, 1250 (NO_2); 740 (C–Cl). Found, %: C 49.17; H 4.07; N 12.38. $C_{32}H_{31}Cl_4N_7O_8$. Calculated, %: C 49.04; H 3.96; N 12.52.

The X-ray diffraction data for compounds **IV**, **V**, and **VII** were acquired on a Bruker AXS Kappa Apex II CCD diffractometer [λ(MoK_α) = 0.71073 Å, graphite monochromator]. A correction for absorption was applied semiempirically using SADABS [6]. The structures were solved by the direct method using SHELXS97 [7]. The positions and temperature factors of non-hydrogen atoms were refined in anisotropic approximation using SHELX-97 [7]. Hydrogen atoms attached to carbons were placed into geometrically calculated positions which were refined according to the riding model. Hydrogen atoms involved in hydrogen bonds were localized from the difference electron density maps. All calculations were performed using WinGX [8] and APEX2 [9]. The molecular and crystal structures were plotted using Mercury 3.1 [10]. The crystallographic parameters of compounds **IV**, **V**, and **VII** and parameters of X-ray diffraction experiments are collected in table. The CIF files containing complete information on the examined structures were deposited to the Cambridge Crystallographic Data Centre (entry nos. CCDC 995031–995033) and are available at *www.ccdc.cam.ac.uk/data_request/cif*.

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