CARBANILIDES WITH AMIDE AND IMIDAZOLINE GROUPINGS

V. B. Piskov, V. P. Kasperovich, E. I. Tsvetkov, A. V. Khval'kovskaya, I. A. Koblova, and V. Sh. Poluéktov

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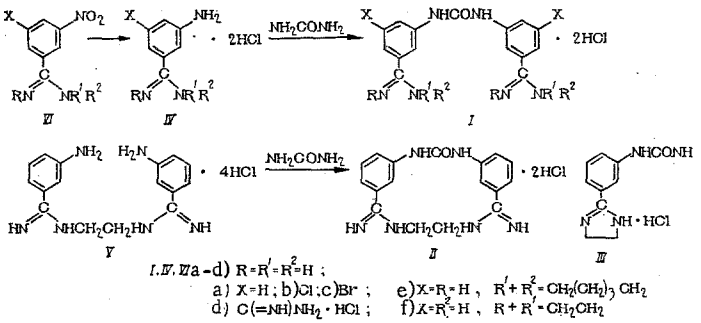
Carbanilides and structurally similar compounds that contain amide and imidazoline groupings display antitubercular, antitumorigenic, antiprotazoic, and antihelminthic action [1-3]

In the present paper we describe the preparation of carbanilides (I, II) and an N-phenylurea (III) that contain the above-mentioned groupings and present the results of biological tests run on them.



I, IV, Va-d) R=R'=R²=H;
a) X=H; b) Cl; c) Br; e) X=R=H, R'+R²=CH₂(CH₂)₃CH₂; d) C(=NH)NH₂·HCl; f) X=R²=H, R+R'=CH₂CH₂

Compound Ia was previously synthesized by the Pinner method from 3,3'-dicyanocarbanilide [2], while If was synthesized by treatment of amine IVf with phosgene [1]. We developed a new method for the preparation of I, which is based on heating the hydrochlorides of aminobenzamidines (IVa-e) or aminophenylimidazoline (IVf) with urea in the presence of a small amount of water. It should be noted that a prior attempt to carry out the reaction of urea with m-aminobenzamidine hydrochloride (IVa) was unsuccessful [2]. The conversion of IV to I does not occur or proceeds in low yield in the presence of excess water or in the presence of hydrochloric and acetic acids. Our method is simple and suitable for the preparation of various carbanilides, including cyclic carbanilide II.

Compound III was synthesized by treatment of IVf with potassium cyanate at pH 4.0-5.0.

Anilines IV and V were obtained by reduction of the corresponding nitrobenzenes with stannous chloride or iron in the presence of catalytic amounts of hydrochloric acid. The latter method was applied for the first time for the reduction of nitrobenzamidines and nitrophenylimidazolines (see [4-6]).

The properties of the synthesized compounds are present in Tables 1 and 2. Anilines IV and V give a positive reaction with furfural [7], while I, II, and III gave a negative result.

The IR spectra of I and II contain strong absorption bands at 1690-1710* (ν C=O), 1560-1570 (δ NH),* 1440-1460, 1285-1310, and 1210-1225 (ν C-N) cm^{-1}, which are peculiar to compounds of the ArNHCONHA type [8, 9]. Similar frequencies are also found in the spectrum of III: 1680 (s), 1560 (s),* 1430 (m) 1350 (s), and 1260 (s) cm^{-1}.

*In a number of cases, the absorption band appears as a shoulder on the adjacent more intense band or coincides with another band; this is accompanied by an increase in its width and intensity.

Scientific-Control Institute of Veterinary Preparations, Ministry of Agriculture of the USSR, Moscow.
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TABLE 1. N-Aryl- and N,N'-Diaryl Derivatives of Urea

Compound	Yield, %	mp, °C[1]	Found, %					Empirical formula	Calc., %					Tolerable dose, mg/kg[4]
			C	H	Cl[3]	N	H_2O		C	H	Cl[3]	N	H_2O	
Ia (2)	79	282—3	46,49	5,04	—	21,74	—	$C_{15}H_{16}N_6O \cdot 2HCl \cdot H_2O$	46,52	5,21	—	21,70	—	50
Ib	51	299—30	37,91	4,47	14,85	17,81	7,79	$C_{15}H_{14}Cl_2N_6O \cdot 2HCl \cdot 2H_2O$	37,99	4,25	14,95	17,72	7,58	150
Ic	43	300—1	32,03	3,96	12,41	15,13	5,95	$C_{15}H_{14}Br_2N_6O \cdot 2HCl \cdot 2H_2O$	31,99	3,58	12,54	14,93	6,40	200
Id	36	267—8	34,23	5,50	23,60	22,60	—	$C_{17}H_{20}N_{10}O \cdot 4HCl \cdot 4H_2O$	34,12	5,39	23,70	23,41	—	5
Ie	49	281—2	57,54	7,08	14,00	15,83	3,74	$C_{25}H_{32}N_6O \cdot 2HCl \cdot H_2O$	57,36	6,93	13,55	16,05	3,44	5
If [1]	77	310—11[2]	—	—	15,60	—	6,35	$C_{19}H_{20}N_6O \cdot 2HCl \cdot 1,5H_2O$	—	—	15,85	—	6,03	60
II	61	283—4	49,23	5,40	17,10	20,51	4,48	$C_{17}H_{18}N_6O \cdot 2HCl \cdot H_2O$	49,40	5,36	17,16	20,34	4,36	20
III	72	212—3	46,50	5,84	14,10	22,10	6,73	$C_{10}H_{12}N_4O \cdot HCl \cdot H_2O$	46,42	5,86	13,71	21,66	6,97	200

[1]Compounds Ia-f and II were crystallized from 2 N hydrochloric acid, while III was crystallized from methanol.
[2]This is the melting point of the hydrate in an evacuated capillary [12]; the melting point of anhydrous If is 359-360°.
[3]Ionic chlorine.
[4]A single dose for mice (subcutaneous injection).

TABLE 2. m-Amidino- and m-Imidazolinylanilines

Compound	Yield, %	mp, °C[1]	Found, %				Empirical formula	Calc., %			
			C	H	Cl[2]	N		C	H	Cl[2]	N
IVa (4)	81	83—4	—	—	17,10	—	$C_7H_9N_3HCl \cdot 2H_2O$	—	—	17,08	—
IVb	59	207—15	32,45	4,52	27,60	16,45	$C_7H_8ClN_3 \cdot 2HCl \cdot H_2O$[3]	32,26	4,64	27,30	16,13
IVc	72	231—2	29,83	3,88	23,80	14,72	$C_7H_8BrN_3 \cdot 2HCl$	29,29	3,51	24,71	14,64
IVd	79	284—5	31,61	5,52	34,90	22,74	$C_8H_{11}N_5 \cdot 3HCl \cdot H_2O$	31,54	5,29	34,92	22,99
IVe	58	275—6	60,14	8,10	14,75	17,63	$C_{12}H_{17}N_3 \cdot HCl$	60,11	7,57	14,79	17,52
IVf	82	215—6	54,70	5,85	17,60	21,42	$C_9H_{11}N_3 \cdot HCl$	54,68	6,12	17,94	21,26
V	68	250—2	42,05	5,84	30,79	18,12	$C_{16}H_{20}N_6 \cdot 4HCl \cdot H_2O$[4]	41,75	5,69	30,79	18,26

[1]Compounds IVa, d-f were crystallized from water, while IVc, IVb, and V were crystallized from 2 N, 4 N, and 6 N hydrochloric acid, respectively.
[2]Ionic chlorine.
[3]Found, %: H_2O 6.62. Calculated, %: H_2O 6.92.
[4]Found, %: H_2O 3.96. Calculated, %: H_2O 3.92.

TABLE 3. Antibacterial Activity of Carbanilides in vitro (in μg/ml)

Compound	Staph. aureus 625	E. coli 853
Ib	50	200
Ic	25	25
If	50	50
II	12,5	12,5

The presence of an unsubstituted amidine group in Ia-d is confirmed by the presence of absorption bands at 1680-1690 (s)* (ν_{asym} N⋯C⋯N·), 1640-1670 (m),* 1520 (s), 1090-1125 (m), and 710-720 (s) cm^{-1}. With the following exception, the characteristic frequencies of the N-alkyl-substituted amidine grouping in Ie and II are similar: the intensity of the secondary amidine band at 1630-1640 cm^{-1} increases considerably, but the maximum at 1520 cm^{-1} vanishes. The bands at 1600-1610 (s), 1560-1575 (s),* 1370 (s), 1280-1295 (s), 1040 (m), and 700-720 (s) cm^{-1} in the spectra of If and III attest to the presence of an imidazoline ring. The bands characteristic for the indicated groupings were previously isolated and assigned in [10, 11].

The antibacterial activity with respect to Staphylococcus aureus and Escherichia coli, which are resistant to penicillin and streptomycin, was determined by the method of successive double culture in a liquid culture medium (Hottinger broth). The results were tallied after 24 h. The carbanilides that displayed pronounced antibacterial action are presented in Table 3. The most active carbanilide proved to be cyclic analog II, which to an equal degree suppressed the growth of both forms of microorganisms.

The in vivo antiprotazoic action was studied with white mice infected with Babesia rodhaini and chicks infected with Eimeria tenella. Only Ia and If, injected subcutaneously on the day of infection in doses of 25 and 4 mg/kg, respectively, completely protected the mice from destruction. In control groups, all of the animals died on the fifth to seventh day. When I, II, and III were fed to chicks in doses of 200-400 mg per kilogram of feed in the course of 10 days, they did not increase the survival rate of the test poultry as compared with a control group.

None of the preparations applied per os once in doses of 0.3 g/kg displayed anthelmintic activity in white mice artificially infested with Hymenolepis nana and Ganguleterakis spumosa.

EXPERIMENTAL

The IR spectra of potassium bromide pellets were recorded with a UR-10 spectrophotometer.

Carbanilides (I, II). A mixture of 0.04 mole of IV or V, 0.02 mole of urea, and 4 ml of water was heated at 105-110° under a reflux condenser for 16 h, after which the condenser was removed and heating was continued at 110-120° for 8-10 h. The mixture was then cooled, triturated with a three- to fivefold (by weight) amount of water, and acidified to pH 3.0 with hydrochloric acid. The precipitate was separated, washed twice with an equal volume of acetone, and dried in a vacuum desiccator initially over sodium hydroxide and then over phosphorus pentoxide. To purify the carbanilides, they were dissolved in water at 60-70°, and the solution was clarified with charcoal and filtered. The filtrate was cooled to 20° and acidified with concentrated hydrochloric acid up to a 2 N concentration of the latter. The resulting precipitate was treated as in the isolation of the carbanilides from the reaction mixture.

The carbanilides (see Table 1) lost their water of crystallization on vacuum drying with phosphorus pentoxide at 100° in the course of a few hours.

Aminobenzamidine Hydrochlorides (IVa-e, V) and Aminophenylimidazoline Hydrochloride (IVf). A. Concentrated hydrochloric acid (1 ml) was added to a suspension of 37 g of powdered iron in 200 ml of water heated to 80°, and the mixture was refluxed for 10 min. A solution of 0.3 g of copper sulfate and 0.8 g of ferrous sulfate in 10 ml of water was then added, and the mixture was stirred for 10 min. The nitro compound (0.1 mole) was then added in portions in the course of 1-2 h with vigorous stirring. After this, the mixture was stirred at 90-100° for 6-8 h, cooled to 70-80°, made alkaline to pH 8.5 with concentrated ammonium hydroxide, clarified with charcoal, and filtered. The clarification with charcoal was then repeated, and the solution was vacuum evaporated (bath temperature 100°). The residue was crystallized from a two- to fourfold (by weight) amount of water, washed twice with equal volumes of acetone, and dried in a vacuum desiccator over phosphorus pentoxide. This method was used to obtain hydrochlorides IVa, f, e (see Table 2).

B. Nitroamidine hydrochloride (0.1 mole) was added in portions in the course of 1 h to a solution of 0.45 mole of stannous chloride dihydrate in 250 ml of concentrated hydrochloric acid heated to 90°, after which the mixture was stirred at 95-100° for 4 h and cooled to 0°. The precipitated complex with tin was removed by filtration and dissolved in a 20 fold (by weight) amount of water. The solution was freed of tin

*See page 343 for footnote.

by bubbling in hydrogen sulfide and vacuum evaporated at 100°, and the residue was crystallized to give hydrochlorides IVb, c, d and V (see Table 2).

2-(m-Ureidophenyl)-Δ^2-imidazoline Hydrochloride (III). A solution of 0.011 mole of potassium cyanate in 4 ml of water was added to a solution of 0.01 mole of IVf in 8 ml of water, and the mixture was stirred at 20° for 3 h while maintaining the pH at 4.0-5.0 by means of hydrochloric acid (1 : 1). The precipitate was separated, washed with an equal volume of water and acetone, and dried in a vacuum desiccator over phosphorus pentoxide.

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