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SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF GUANIDINE AND 2-AMINO 2-IMIDAZOLINE DERIVATIVES

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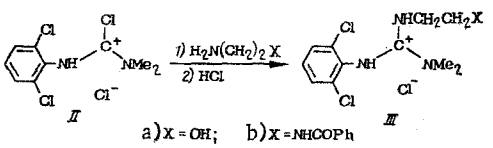
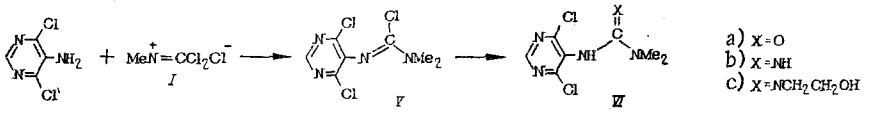
N,N-Dimethyl-N-dichloromethylene-immonium chloride (I) [1, 2] and N,N-dimethyl-N'-(2,6-dichlorophenyl)-C-chloroformamidine hydrochloride (II) [3], which we used in [3] to synthesize the medicinal preparation clofeline (hemiton, catapresan) are readily available starting compounds for the preparation of different derivatives of guanidine and 2-amino-2-imidazoline, which are interesting from the point of view of a search for new hypotensive agents.

In the present work, we synthesized and pharmacologically studied the previously unknown hydrochlorides of N-substituted N'-(2,6-dichlorophenyl)-N",N"-dimethylguanidines (III), obtained from (II) by treatment with 2-aminoethanol and N-benzoylethylenediamine in acetonitrile, according to a method developed by us in [4].



To obtain guanidine derivatives containing a pyrimidine ring as the substituent, N,N-dimethyl-N'-(4,6-dichloro-5-pyrimidyl)-C-chloroformamidine (V) was synthesized by the reaction of 4,6-dichloro-5-aminopyrimidine (IV) [5] with (I); reaction of (V) with dilute sodium hydroxide, aqueous ammonia and 2-aminoethanol gave N,N-dimethyl-N'-(4,6-dichloro-5-pyrimidyl)-urea (VIa) and substituted guanidines (VIb, c), respectively.



Besides the "open-ring" analogs of clofeline, it was interesting to obtain for biological studies derivatives of 2-aminoimidazoline containing 2,6-dichlorophenyl and 4,6-dichloropyrimidyl fragments attached to the nitrogen atom of the imidazoline ring. We therefore studied the reaction of substituted guanidines (IIIa) and (VIc) with thionyl chloride. We found that heating (IIIa) and (VIc) with thionyl chloride is accompanied by cyclization and formation of 1-(2,6-dichlorophenyl)- (VII) and 1-(4,6-dichloro-5-pyrimidyl)-2-dimethylaminoimidazolines (VIII). The action of methyl iodide, benzoyl and benzyl chlorides on (VII) yielded the corresponding quaternary salts (IXa-c). By alkaline hydrolysis of (IXa-c), the N-substituted N'-(2,6-dichlorophenyl)-ethylene-ureas (Xa,b) were synthesized. Transition from (Xa) to 1-(2,6-dichlorophenyl)-2-imino-3-methylimidazoline (XI) was carried out by heating (Xa) with phosphorus oxychloride, followed by treatment of the intermediate amidochloride with ammonia.

The structure of compounds obtained was confirmed by the data of IR and UV spectrometry (Table 1).

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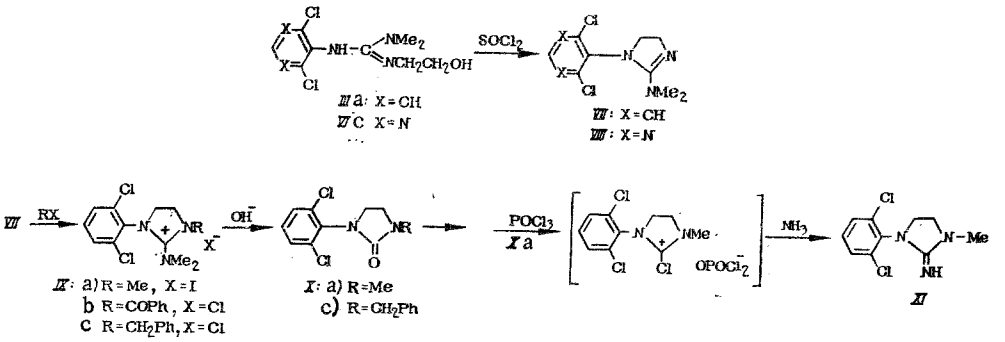
TABLE 1. Yields and Properties of Guanidine and 2-Aminoimidazoline Derivatives (III, V-XI)

Compound	Mp, °C (solvent)	Yield, %	Found, %				Empirical formula	Calculated, %				UV spectrum		IR spectrum, ν, cm^{-1}	
			C	H	Cl	N		C	H	Cl	N	λ_{max}, nm (log ε)		C=N	C=O
IIIa	162—4	80,6	41,85	4,69	33,87	13,36	$C_{11}H_{16}C_3N_3O$	42,24	5,12	34,08	13,44	265	(4,02)	1650	—
IIIb	228—30 (methanol—ethyl acetate)	63,7	51,93	5,15	25,61	13,33	$C_{18}H_{21}C_3N_4O$	51,99	5,05	25,63	13,48	220	(4,08)	1630,1650	—
V	81—3 (abs. alcohol	67,6	33,07	2,75	42,14	22,03	$C_7H_7C_3N_4$	33,14	2,77	42,01	22,09	244	(4,05)	1650	—
VIa	154—6 (abs. alcohol)	83	35,55	3,38	29,82	24,02	$C_7H_8C_2N_4O$	35,74	3,40	30,21	23,83	258	(3,64)	—	1625
VIb	264—6 (ethanol)	74,3	31,00	3,75	39,13	26,00	$C_7H_{10}C_3N_5$	31,05	3,70	39,37	25,87	284	(3,73)	1620,1650	—
VIc	141—3 (acetone)	37,6	38,82	4,72	25,44	25,47	$C_9H_{13}C_2N_5O$	38,75	4,68	25,54	25,18	237	(3,97)	1640	—
VII	293—5 (dec.) (isopropanol)	87	44,58	4,82	36,26	14,20	$C_{11}H_{14}C_3N_3$	44,82	4,75	36,16	14,26	274	(2,71)	1663	—
VIII	198—201 (ethanol)	46	36,04	4,16	36,01	23,63	$C_9H_{12}C_3N_5$	36,42	4,05	35,92	23,61	258	(3,56)	1665	
IXa	180—2 (acetonitrile—ethyl acetate)	82,2	35,95	3,57	—	10,31	$C_{12}H_{16}C_2N_3$	36,00	4,00	—	10,50	295	(4,59)	1640	
IXb	200—2 (dec.) (acetonitrile—ethyl acetate)	60	54,31	4,67	26,31	10,12	$C_{18}H_{18}C_3N_3O$	54,20	4,52	26,73	10,54	252	(4,30)	1635	1708
IXc	207—8 (acetonitrile—ethyl acetate)	51	55,67	5,17	27,64	10,85	$C_{18}H_{20}C_3N_3$	56,18	5,20	27,69	10,92	219	(3,74)	1640	—
Xa	136—8 (50% aqueous alcohol)	89	48,89	4,10	29,01	11,21	$C_{10}H_{10}C_2N_2O$	48,98	4,08	28,98	11,43	246	(3,38)	—	1700
Xb	105—8 (50% aqueous alcohol)	91	59,72	4,44	22,21	8,87	$C_{16}H_{14}C_2N_2O$	59,81	4,36	22,12	8,72	247	(3,43)	—	1692
XI	298—300 (dec.) (isopropanol—ethyl acetate)	86	42,62	4,33	38,08	14,94	$C_{10}H_{12}C_3N_3$	42,78	4,28	37,97	14,97	273 281	(2,77) (2,73)	1655	—



EXPERIMENTAL (PHARMACOLOGICAL)

Compounds (IIIa, b), (VIb, c), (VII), (VIII), (IXa, b, c), and (XI) have elements of slight structural similarity with the hypotensive preparations clofeline, octadine (guanethidine), and esbatal (bethanidine): In their molecule there is a guanidine grouping substituted or included in the ring. The purpose of the pharmacological study was to search for properties characteristic of these preparations: α-adrenomimetic and central hypotensive activity, sympatholytic and ganglio-blocking properties.

We used methods already described in [4]. In the experiments on animals, the compounds were administered intravenously.

In narcotized cats, compound (VIb) in a dose of 5 mg/kg induces a short-term hypertension, which is not changed by the ganglio-blocking agent hexonium (0.5 mg/kg), but is inhibited by the α-adrenolytic preparation phentolamine (1 mg/kg). Hence, (VIb) exhibits an α-adrenomimetic action. Compound (VIb) has no ganglio-blocking properties. In experiments on atropinized vagotomized rats, (VIb) does not lower the systolic frequency, i.e., it does not have a specific central action, characteristic of clofeline.

Compounds (IXa, b, c) in a dose of 2 mg/kg, and (IIIa), (VII), (XI) in a dose of 5 mg/kg cause a decrease in arterial pressure in narcotized cats, due to ganglio-blocking properties, because during hypotension, the nicotine-like preparation cytisine (20 μg/kg) does not increase arterial pressure and does not stimulate respiration. Compounds (IIIb), (VIb, c), and (VIII) do not have ganglio-blocking properties.

At concentrations of up to $1 \cdot 10^{-5}$ g/ml, all the compounds studied do not increase the amplitude of contractions of an isolated spermiduct of a rat, i.e., do not have sympatholytic action.

If we consider the problem of the relationship between the chemical structure of the compounds studied and their pharmacological properties, we note that the derivatives of guanidine and 2-amino-2-imidazoline studied have no action elements characteristic of clofeline, i.e., peripheral α-adrenomimetic properties and the ability, due to central action, to decrease the amount of palpitations in vagotomized rats. Compounds containing the 2,6-dichlorophenyl group, in particular, the quaternary salts (IXa, b, c) have a ganglio-blocking action, but in their activity they are much inferior to known ganglio-blocking agents. Derivatives containing the 4,6-dichloropyrimidine residue (IVb, c, VIII) have no ganglio-blocking properties, although their 2,6-dichloro-phenyl analogs (IIIa, VII) have such properties. The presence in the structure of a guanidine grouping, partially substituted or included in the imidazoline ring, does not impart sympatholytic properties to the compounds studied.

EXPERIMENTAL (CHEMICAL)

The UV spectra of the compounds were run in ethanol on an EPS-3 spectrophotometer, the IR spectra in a crystalline state, in the form of pastes with mineral oil, on Perkin-Elmer-457 (Sweden) and UR-10 (GDR) spectrometers with lithium chloride, sodium chloride, and potassium bromide prisms. The purity of the compounds was controlled chromatographically on Silufol UV-254 plates.

The yields and properties of the compounds studied are listed in Table 1.

Hydrochlorides of N-Substituted N'-(2,6-Dichlorophenyl)-N",N"- dimethylguanidines (IIIa, b). A 9.8-ml (63 mmoles) portion of ethanolamine in 10 ml of acetonitrile is gradually added at 10-15°C to a suspension of 15 g (52 mmoles) of II in 40 ml of acetonitrile. The mixture is left to stand for 16 h at 20°C. The precipitate is filtered, dried, and treated (20°C) with 35 ml of water. The insoluble precipitate is filtered and dried to yield 10.45 g of base (IIIa). An additional amount of (IIIa) is obtained by evaporation of the acetonitrile mother liquor, and treatment of the residue with water. The hydrochloride of (IIIa) is obtained by adding an alcoholic solution of hydrogen chloride to a hot solution of base (IIIa) in ethyl acetate. Compound (IIIb) is synthesized similarly.

N,N-Dimethyl-N'-(4,6-dichloro-5-pyrimidyl)-C-chloroformamidine (V). A solution of 4.45 g (27 mmoles) of (IV) in 70 ml of methylene chloride is added at the boiling point to a suspension of 4.43 g (27 mmoles) of (I) in 30 ml of dry methylene chloride, and the mixture is boiled for another hour. The reaction mixture is evaporated to dryness, and the residue crystallized from absolute alcohol to yield (V).

N,N-Dimethyl-N'-(4,6-dichloro-5-pyrimidyl)-urea (VIa). A 2.53-g (0.01 mole) portion of (V) in 10 ml of sodium hydrochloride is heated at 50°C for 1.5 h. The precipitate is filtered, washed with water and dried to yield (VIa).

Hydrochlorides of N-Substituted N'-(4,6-dichloro-5-pyrimidyl)-N", N"- dimethylguanidines (VI, b, c). A 1.27-g (5 mmoles) portion of (V) in 10 ml of 25% aqueous ammonia is heated at 50°C for 1.5 h. When cool, the precipitate is filtered, washed with water, and dried to yield base (VIb). The hydrochloride of (VIb) is obtained in the same way as (III). Compound (VIc) is synthesized similarly.

Hydrochlorides of 1-Substituted 2-dimethylamino-2-imidazolines (VII, VIII). A 3.25-g (0.01 mole) portion of (IIIa) is boiled for 1 h with 25 ml of thionyl chloride. The reaction mixture is evaporated to dryness, and the residue of thionyl chloride removed by distillation with chloroform. The reaction mixture is treated at 10-15°C with 15 ml of water, made alkaline with 40% sodium hydroxide solution to pH 10.0, and extracted with ethyl acetate. The extract is clarified with activated charcoal, and evaporated to 15-20 ml, and the hydrochloride of (VII) is isolated by adding an alcoholic solution of hydrogen chloride. Compound (VIII) is synthesized similarly.

Quaternary Salts of 1-(2,6-Dichlorophenyl)-2-dimethylamino-2-imidazoline (IXa-c). A mixture of 12.9 g (0.05 mole) of (VII) and 3.1 ml (0.05 mole) of methyl iodide in 50 ml of acetonitrile is heated at 40-50°C for 1.5 h. The mixture is cooled to 20°C, and the reaction mixture is treated with 100 ml of ethyl acetate. The precipitate is filtered to yield (IXa). Compounds (IXb, c) were synthesized similarly.

N-Substituted N'-(2,6-Dichlorophenyl)-ethylene-ureas (Xa, b). A 11.45-g (29 mmoles) portion of (IXa) in 57 ml (57 mmoles) of 1 N sodium hydroxide is boiled for 2 h. The precipitate is filtered, washed with water, and dried to yield (Xa). Compound (Xb) is similarly obtained from (IXc).

Hydrochloride of 1-(2,6-Dichlorophenyl)-2-amino-3-methylimidazoline (XI). A 5.1-g (0.02 mole) portion of (Xa) is boiled for 4.5 h with 20 ml of phosphorus oxychloride. The reaction mixture is evaporated *in vacuo* and the residue treated with 15 ml of toluene. The precipitate is filtered and washed with toluene and dry ether. The precipitate is added in portions at 0-5°C to 40 ml of acetonitrile saturated with ammonia, and the reaction mixture is held for 2 h at 20°C. The precipitate is filtered, washed with acetonitrile, dried, treated with 20 ml of water, made alkaline to pH 10, and extracted with chloroform. After removal of solvent, the residue is dissolved in 30 ml of ethyl acetate, and hydrochloride of (XI) is isolated by adding an alcoholic solution of hydrogen chloride.

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