SYNTHESIS AND PHARMACOLOGICAL STUDY OF SOME BENZIMIDAZOLE DERIVATIVES.

VIII. BENZIMIDAZOLE DERIVATIVES OF UREA

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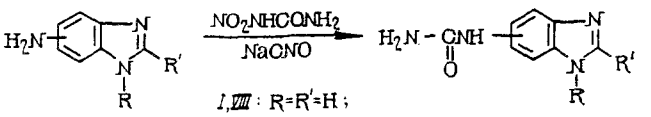
The synthesis and pharmacological properties of some 1-(2-ureidoethyl)benzimidazoles were described earlier [1]. Several of these compounds showed diuretic activity. We now present a study of the effect of the introduction of the ureido group into the benzene ring of benzimidazoles on diuresis in experimental animals. Reaction of nitrourea or sodium cyanate with the corresponding aminobenzimidazole (I-VII) resulted in the synthesis of 5(6)-ureidobenzimidazole VIII, its 2-alkylsubstituted derivatives (IX, X), 1-methyl-, 1-benzyl-, and 1-(2-hydroxyethyl)-5-ureidobenzimidazoles (XI-XIII), and 1-(2-ureidoethyl)-6-ureido benzimidazole (XIV) (cf. Table 1).

5(6)-Aminobenzimidazole I and its 2-methyl- and 2-ethyl-substituted derivatives (II, III) were treated with nitrourea without isolation in the free state from the reaction mixture after reduction of the corresponding nitro-substituted benzimidazole [2, 3] with iron filings in acetic acid. 1-Methyl-, 1-benzyl-, and 1-(2-hydroxyethyl)-5-aminobenzimidazoles (IV-VI) were allowed to react with nitrourea as a suspension of the free base in water or in alcohol. For reaction with sodium cyanate, the free base was first converted to the hydrochloride. The starting aminobenzimidazoles IV and V were synthesized by known methods [4, 5]. Compounds VI and 1-(2-ureidoethyl)-6-aminobenzimidazoles (VII) were obtained by reduction of the corresponding 1-(2-hydroxyethyl)-5-nitrobenzimidazole [6] and 1-(2-ureidoethyl)-6-nitrobenzimidazole [1] with hydrazine hydrate in the presence of Rainey nickel.



I-VII

I, VIII: R=R'=H;
II, IX: R=H, R'=CH3;
III, X: R=H, R'=C2H5;
IV, XI: R=CH3, R'=H;
V, XII: R=CH2C6H5, R'=H;
VI, XIII: R=CH2CH2OH, R'=H;
VII, XIV: R=CH2CH2NHCONH2, R'=H.

VIII-XIV

The interaction of 5(6)-aminobenzimidazoles (I-III) unsubstituted in position 1 with nitrourea takes place on the amino group. This was confirmed by the identity of the fingerprint region of their IR spectra with samples of VIII prepared by interaction of nitrourea with I, and by debenzylation of XII with sodium in liquid ammonia, and also by the absence of melting point depression for mixtures of the samples.

Methylation of VIII with dimethyl sulfate gave a substance identified by IR and UV spectra, melting point, and microanalytical data as compound XI, i.e., methylation takes place on position 1 of the benzimidazole nucleus and does not affect the ureido group.

Compounds VII, XIII, and XIV were acylated with the acid chlorides of anisic, propionic, and phenoxyacetic acids to give the corresponding diacylated compounds (XV-XXII) (see Tables 2 and 3). An excess of the corresponding acid chloride was used as solvent in the reactions.

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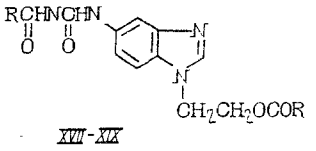
TABLE 1. 5-,6-, and 5(6)-Ureidobenzimidazoles (VIII-XIV)

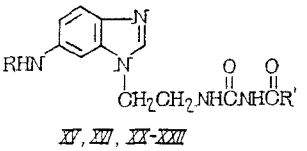
Compound	R	R_1	Position of ureido group	Melting point, °C*	Yield, %†	Found, %			Empirical formula	Calculated, %		
						C	H	N		C	H	N
VIII (hydrate)	H	H	5 (6)	291	57,11	49,21	5,11	28,60	$C_8H_8N_4O \cdot H_2O$	49,51	5,19	28,27
IX (hydrate)	H	CH_3	5 (6)	312—4	82	51,50	4,78	25,90	$C_9H_{10}N_4O \cdot H_2O$	51,92	4,80	26,29
X (dihydrate)	H	C_2H_5	5 (6)	277	42	50,20	6,34	23,50	$C_{10}H_{12}N_4O \cdot 2H_2O$	49,98	6,71	23,32
XI	CH_3	H	5	320	91,25	56,82	5,37	29,06	$C_9H_{10}N_4O$	56,83	6,29	29,45
XII (hydrate)	$CH_2C_6H_5$	H	5	186	75	63,30	5,70	19,67	$C_{15}H_{14}N_4O \cdot H_2O$	63,34	5,67	19,71
XIII	CH_2CH_2OH	H	5	205	95	54,74	5,56	25,61	$C_{10}H_{12}N_4O_2$	54,63	5,47	25,51
XIV	$CH_2CH_2NHCONH_2$	H	6	209	89	49,98	5,51	31,85	$C_{11}H_{14}N_6O_2$	50,35	5,38	32,05

*All compounds melted with decomposition. Compounds VIII and IX crystallized from a mixture of dimethylformamide (DMF) and water; X, XI, XIV from water; XII from aqueous ethanol; XIII from aqueous dioxane.

†Yield of VIII by reaction of nitrourea with I, 57%; by debenzylation of XII, 11%. Yield of XI by reaction of sodium cyanate with IV, hydrochloride, 91%; by alkylation with dimethyl sulfate, 25%. Compound XII was prepared in ethanol, XIII and XIV in water.



XVII-XIX



XV, XVI, XX-XXII

XV: R = C_2H_5CO, R′ = C_2H_5; XVI: R = $C_6H_5OCH_2CO$, R = $C_2H_5OCH_2$;
XVII: R = C_2H_5; XVIII: R = $C_6H_5OCH_2$; XIX: R = 4-$CH_3OC_6H_4$;
XX: R = $C_2H_5CONHCO$, R′ = C_2H_5; XXI: R = $C_6H_5OCH_2CONHCO$, R′ = $C_6H_5OCH_2$;
XXII: R = 4-$CH_3OC_6H_4CONHCO$, R′ = 4-$CH_3OC_6H_4$.

Earlier we compared the properties of samples of 1-(2-benzoylureidoethyl)benzimidazole, prepared by interaction of 1-(2-ureidoethyl)benzimidazole with benzoyl chloride and from the corresponding benzoylisocyanate, and showed that acylation with acid chlorides takes place on the terminal nitrogen of the ureido group [1].

Randomly-bred white rats of both sexes were used for a study of the diuretic action of the synthesized compounds. The samples were introduced intraperitoneally or orally in the form of a starch suspension at a dosage of 1/200 to 1/10 LD_{50}. Spontaneous diuresis was recorded after 1, 2, 4, and 6 h, and, in separate experiments, after 24 h. Flame photometry was used to determine the excretion of sodium and potassium ions in the urine. Compounds VIII, XII, XV, XIX, and XXI showed definite diuretic action and a two-to-fourfold increase of diuresis in comparison with the standard. Prolonged diuretic action continued for 6 h, and thus significantly exceeded saluresis, The electrolyte excretion of the experimental animals was unchanged compared to that of the control group. Compounds IX, XI, XVI, and XXII did not show diuretic activity, and compounds XVII and XVIII showed an antidiuretic effect.

EXPERIMENTAL METHOD

All of the compounds prepared were white substances, soluble with difficulty in water, alcohol, and other organic solvents.

The progress of reactions and the homogeneity of the compounds was monitored by chromatography on Silufol plates in chloroform—methanol—ammonia (7:3:0.1).

1-(2-hydroxyethyl)-5-aminobenzimidazole (VI). A solution of 10 g (0.0483 mole) of 1-(2-hydroxyethyl)-5-aminobenzimidazole in 500 ml of methanol was heated to boiling, approximately 0.1 g of Raney nickel was added, followed by the slow dropwise addition of 50 ml of hydrazine hydrate to the stirred mixture, and boiling was continued for an additional 30 min. The precipitate was filtered off and the solvent was removed under vacuum to give a residue which solidified, 6.3 g (74%), which was purified by crystallization from ethanol. The resulting white crystalline solid had mp 179-183°C. Found, %: C 60.63; H 6.36; N 24.0. $C_9H_{11}N_3O$. Calculated, %: C 61.0; H 6.26; N 23.7.

1-(2-Ureidoethyl)-6-aminobenzimidazole (VII). To a solution of 15 g of hydrazine hydrate in 400 ml of alcohol was added with stirring 24.9 g (0.1 mole) of 1-ureidoethyl-6-nitrobenzimidazole and approximately 0.3 g of Raney nickel, and the mixture was heated to 50-60°C. This temperature was maintained for 2-3 h until thin-layer chromatography indicated the disappearance of the starting material spot. The mixture was then heated to boiling, the catalyst was removed by filtration, and the filtrate was cooled. The resulting precipitate was filtered off, washed with alcohol, and purified by crystallization from alcohol to give 7.47 g (34%) of cream-colored powder, mp 193°C (with decomposition). Found, %: C 55.15; H 6.04; N 32.17. $C_{10}H_{13}N_5O$. Calculated, %: C 54.79; H 5.98; N 31.96.

5(6)-Ureidobenzimidazoles (VIII-X). To a boiling solution of 10 ml of acetic acid in 150 ml of water was added portionwise with stirring a mixture of 0.1 mole of 5(6)-nitrobenzimidazole, 2-methyl- or 2-ethyl-5(6)-nitrobenzimidazole and 12.5 g of iron filings. The reaction mixture was boiled for 1 h, treated with activated charcoal, and the charcoal and iron filings were filtered off. To the filtrate, containing I, II, or III, was added 11.6 g (0.11 mole) of nitrourea and the mixture was stirred at 60-70°C and maintained at this temperature until cessation of gas evolution. The reaction mixture was neutralized with an aqueous solution of sodium bicarbonate, the resulting precipitate was filtered off, washed with water, and purified by crystallization from an appropriate solvent.

TABLE 2. 6-Acylamido- (XV, XVI) and 6-Acylureido-(XX-XIII) 1-(2-acylureidoethyl)benzimidazoles

Compound	R	R′	Melting point °C*	Yield, %	Found, %			Empirical formula	Calculated, %		
					C	H	N		C	H	N
XV	C_2H_5CO	C_2H_5	220—2	89	57,58	6,30	20,94	$C_{16}H_{21}N_5O_3$	57,95	6,39	21,13
XVI	$C_6H_5OOH_2CO$	$C_6H_5OCH_2$	191—9	84	63,90	5,14	14,50	$C_{28}H_{25}N_5O_5$	64,07	5,17	14,36
XX	$C_2H_5CONHCO$	C_2H_5	229	89	54,74	5,96	22,79	$C_{17}H_{22}N_6O_4$	54,53	5,92	22,44
XXI	$C_6H_5OCH_2CONHCO$	$C_6H_5OCH_2$	210	85	61,20	5,12	16,20	$C_{27}H_{26}N_6O_6$	61,12	4,94	15,84
XXII	$4\text{-}CH_3OC_6H_4CONHCO$	$4\text{-}CH_3OC_6H_4$	250	67	60,86	5,19	16,16	$C_{27}H_{26}N_6O_6$	61,12	4,94	15,84

*All compounds melted with decomposition. Crystallization solvents: XV, aqueous alcohol; XVI, alcohol-DMF; XX and XXI, aqueous DMF; XXII, dilute acetic acid.

TABLE 3. 1-(2-acyloxyethyl)-5-acylureidobenzimidazoles (XVII-XIX)

Compound	R	Melting point, °C *	Yield, %	Found, %			Empirical formula	Calculated, %		
				C	H	N		C	H	N
XVII	C_2H_5	171—2	87	58,19	6,14	17,28	$C_{16}H_{20}N_4O_4$	57,79	6,06	16,86
XVIII	$C_6H_5OCH_2$	194—5	97	63,60	4,63	11,82	$C_{26}H_{24}N_4O_6$	63,95	4,95	11,48
XIX	$4\text{-}CH_3OC_6H_4$	228—9	93	64,24	5,18	11,78	$C_{26}H_{24}N_4O_6$	63,95	4,95	11,48

*All compounds melted with decomposition. Crystallization solvents: XVII, alcohol; XVIII, DMF-alcohol; XIX, DMF.

5(6)-Ureidobenzimidazole (VIII) was also prepared by debenzylation of 1-benzyl-5-ureidobenzimidazole (XII). To a suspension of 5.7 g (0.02 mole) of XII in 250 ml of liquid ammonia was added 0.1 g of metallic sodium in small portions. The ammonia was allowed to evaporate and the residue was stirred with 45 ml of 10% aqueous sodium hydroxide. The insoluble residue was filtered off, and the filtrate was neutralized with concentrated hydrochloric acid to pH 8.0, and the resulting precipitate was filtered off and purified by recrystallization.

1-Methyl-5-ureidobenzimidazole (XI). A. A solution of 21 g (0.1 mole) of the dihydrochloride of IV and 20 g (0.25 mole) of sodium cyanate in 500 ml of water was concentrated to a volume of 200 ml, the resulting precipitate was filtered off and purified by crystallization.

B. To a suspension of 17.6 g (0.1 mole) of VIII in a mixture of 175 ml of water and 45 ml of 5 N aqueous sodium hydroxide was added 16.5 ml (0.17 mole) of dimethyl sulfate and the reaction mixture was heated to 80°C and maintained at this temperature for 2 h. The reaction mixture was then cooled and the resulting precipitate was filtered off, washed with water, and purified by crystallization.

1-Benzyl-,1-(2-hydroxyethyl)-5-ureidobenzimidazole (XII and XIII) and 1-(2-Ureidoethyl)-6-ureidobenzimidazole (XIV). To a suspension of 0.1 mole of V in 300 ml of ethanol (VI or VII in 150 ml of water) was added 0.11 mole of nitrourea, and the mixture was heated in a water bath at 60-70°C until the cessation of gas evolution. Compound XII was separated from the aqueous alcohol by the addition of 500 ml of water, XIII and XIV precipitated from the reaction mixture spontaneously. The resulting residue was filtered off, washed with water, and purified by crystallization from an appropriate solvent.

Yields, crystallization solvents, melting points, and analytical data for compounds VIII-XIV are given in Table 1.

Acyl Derivatives of 1-(2-Ureidoethyl)-6-aminobenzimidazoles (XV and XVI), 1-(2-Hydroxyethyl)-5-ureidobenzimidazoles (XVII-XIX), and 1-(2-Ureidoethyl)-6-ureidobenzimidazoles (XX-XXII). To 0.1 mole of VII, XIII, or XIV was added 0.36 mole of the corresponding acid chloride and the reaction mixture was heated in a boiling water bath until the disappearance of the starting material spot on a thin-layer chromatogram (2-3 h). The resulting residue was filtered off, washed with benzene, and then with a hot saturated solution of sodium bicarbonate. The resulting product was crystallized from an appropriate solvent.

Yields, melting points, crystallization solvents, and analytical data are given in Tables 2 and 3.

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