SYNTHESIS AND INVESTIGATION OF SOME IMIDAZOLE DERIVATIVES.

VII. ESTERS AND AMIDES OF NITROIMIDAZOLECARBOXYLIC ACIDS

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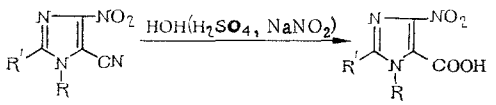
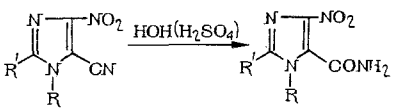
As a continuation of our research in the imidazole-derivative field, we have prepared a series of previously undescribed esters and amides of nitroimidazolecarboxylic acids which may present interest as potential biologically active substances or intermediates for their synthesis.

For the most part, unsubstituted amides of 1-alkyl- and 1,2-dialkyl-4-nitroimidazole-5-carboxylic acids have been described in the literature [1-6]; substituted amides of these acids are represented by a very small number of compounds [7, 8]. Esters of these acids have been studied to a still smaller degree [7].

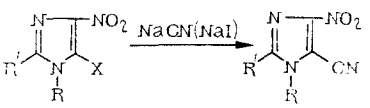
The nitroimidazolecarboxylic acids needed for the synthesis of the amides and esters were prepared by acid hydrolysis of nitrocyanoimidazoles in the presence of sodium nitrite, according to the procedure of [7].



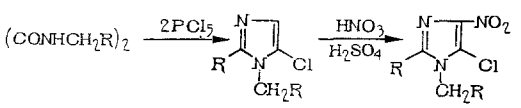
Unsubstituted amides were obtained upon incomplete hydrolysis of the nitriles in the absence of nitrite [1, 3, 5].



Synthesis of the starting nitrocyanoimidazoles was effected by cyanation [1] of nitrochloro (or bromo) imidazoles [9], whose halogen atom is easily replaced by a CN group upon heating with alkali metal cyanides in the presence of iodides of the same metals.



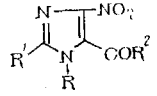
The nitrochloroimidazoles were prepared by the Wallach reaction [10] from dialkyloxamides, and with subsequent nitration of the alkyl (or dialkyl) chloroimidazoles formed [9].



1,2-Dimethyl-4-nitro-5-bromoimidazoles were synthesized by alkylation of 2-methyl-4(5)-nitroimi-

Novokuznets Scientific-Research Institute of Pharmaceutical Chemistry. S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal, No. 10, pp. 24-29, October, 1974. Original article submitted March 29, 1973.

TABLE 1. 4-Nitroimidazole-5-carboxylic Acids, their Amides, and Esters



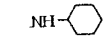
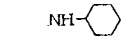
Compound	R	R^1	R^2	Yield (in %)	Mp (in deg)[1]	Found (in %)			Empirical formula	Calculated (in %)		
						C	H	N		C	H	N
II	CH_3	CH_3	NH_2	53,0	239—249	39,04	4,07	30,29	$C_6H_8N_4O_3$	39,13	4,30	30,43
III	C_5H_{11}-iso	C_4H_9-iso	NH_2	78,0	141—2	55,24	7,87	20,31	$C_{13}H_{22}N_4O_3$	55,31	7,80	19,85
IV	C_6H_{13}-n	C_5H_{11}-n	NH_2	93,9	129—130	58,0	8,14	18,03	$C_{15}H_{26}N_4O_3$	58,06	8,38	18,06
V	CH_3	CH_3	OH	70,0	144—5	38,23	4,08	22,71	$C_6H_7N_3O_4$	38,91	3,78	22,7
VI	C_4H_9-n	C_3H_7-n	OH	61,4	113—5	51,65	6,71	16,56	$C_{11}H_{17}N_3O_4$	51,76	6,66	16,47
VII	C_4H_9-iso	C_3H_7-iso	OH	60,7	138—9	51,64	6,46	16,12	$C_{11}H_{17}N_3O_4$	51,76	6,66	16,47
VIII	C_5H_{11} n	C_4H_9-n	OH	52,0	112—3	54,39	7,28	14,71	$C_{13}H_{21}N_3O_4$	55,12	7,42	14,84
IX	H	H	NHC_3H_7 iso	80,8	223,5—4	42,33	4,9	27,76	$C_7H_{10}N_4O_3$	42,42	5,05	28,28
X	H	H		87,9	244—6	50,53	5,80	23,06	$C_{10}H_{14}N_4O_3$	50,43	5,91	23,52
XI	CH_3	H	NHC_3H_7-iso	80,2	178—9	45,17	5,73	26,57	$C_8H_{12}N_4O_3$	45,28	5,66	26,41
XII	CH_3	H	NHC_4H_9-n	76,5	94—5	47,42	6,28	24,84	$C_9H_{14}N_4O_3$	47,78	6,19	24,77
XIII	CH_3	H	NHC_5H_{11}-n	71,8	92—92,5	49,95	6,66	22,85	$C_{10}H_{16}N_4O_3$	50,0	6,66	23,33
XIV	CH_3	H	NHC_5H_{11}-iso	62,0	89—90	49,94	6,82	23,44	$C_{10}H_{16}N_4O_3$	50,0	6,66	23,33
XV	CH_3	H	$NH(CH_2)_2N(C_2H_5)_2$	52,4	198—9	43,50	6,69	22,88	$C_{11}H_{19}N_5O_3 \cdot HCl$[2]	43,27	6,54	22,91
XVI	CH_3	H		60,9	125,5—6,5	50,35	5,97	23,17	$C_{10}H_{14}N_4O_3$	50,42	5,88	23,53
XVII	CH_3	H		97,3	303—5	38,98	5,25	25,25	$C_9H_{13}N_5O_3 \cdot HCl$[3]	39,2	5,08	25,41
XVIII	CH_3	H		54,8	162—3	45,04	5,03	23,32	$C_9H_{12}N_4O_4$	45,0	5,0	23,33
XIX	CH_3	H		58,1	182,5—3,5	52,25	6,31	22,17	$C_{11}H_{16}N_4O_3$	52,38	6,35	22,22

TABLE 1. (continued)

Compound	R	R^1	R^2	Yield (in %)	Mp(in deg)[2]	Found(in %)			Empirical formula			
						C	H	N		C	H	
XX	CH_3	H	$NHCH_2C_6H_5$	80,8	139—140	55,35	4,68	21,49	$C_{12}H_{12}N_4O_3$	55,38	4,61	21,55
XXI	CH_3	H	$NHC_6H_4NO_2$-n	67,5	293—4	45,04	3,24	23,83	$C_{11}H_9N_5O_5$	45,39	3,09	24,05
XXII	CH_3	CH_3	NHC_3H_7-iso	79,5	180	47,97	6,21	24,76	$C_9H_{14}N_4O_3$	47,78	6,19	24,78
XXIII	CH_3	CH_3	NHC_4H_9-n	76,5	142	49,7	6,7	23,67	$C_{10}H_{16}N_4O_3$	50,0	6,66	23,33
XXIV	CH_3	CH_3	$NH(CH_2)_2N(C_2H_5)_2$	75,7	189—190	45,37	6,98	21,74	$C_{12}H_{21}N_5O_3 \cdot HCl$[4]	45,07	6,88	21,9
XXV	CH_3	CH_3		63,0	162—3	47,11	5,57	22,39	$C_{10}H_{14}N_4O_4$	47,24	5,51	22,47
XXVI	C_3H_7	C_2H_5	NHC_4H_9-n	76,4	96—7	55,14	7,50	19,76	$C_{13}H_{22}N_4O_3$	55,32	7,80	19,86
XXVII	C_4H_9-n	C_3H_7-n	NHC_3H_7-iso	84,0	112	56,57	8,12	18,89	$C_{14}H_{24}N_4O_3$	56,75	8,18	18,92
XXVIII	C_4H_9-n	C_3H_7-n	NHC_4H_9-n	90,2	73—4	57,94	8,50	18,32	$C_{17}H_{36}N_4O_3$	58,06	8,39	18,01
XXIX	C_4H_9-n	C_3H_7-n	$NH(CH_2)_2N(C_2H_5)_2$	66,7	143—4	52,34	8,48	18,01	$C_{17}H_{31}N_5O_3 \cdot HCl$[5]	52,37	8,21	17,97
XXX	C_4H_9-n	C_3H_7-n		69,4	77,5—8,5	55,31	7,35	17,24	$C_{15}H_{24}N_4O_4$	55,55	7,40	17,28
XXXI	C_4H_9-n	C_3H_7-n		73,7	260—1	49,85	7,27	19,46	$C_{15}H_{25}N_5O_3 \cdot HCl$[6]	50,07	7,28	19,47
XXXII	C_4H_9-n	C_3H_7-n		79,4	120—1	60,75	8,24	16,57	$C_{17}H_{29}N_4O_3$	60,71	8,33	16,66
XXXIII	C_4H_9-n	C_3H_7-n	NHC_6H_5	68,8	142—3	61,10	6,67	17,05	$C_{17}H_{22}N_4O_3$	61,08	6,66	16,97
XXXIV	C_4H_9-n	C_3H_7-n	$NHC_6H_4NO_2$-n	69,3	217—8	54,29	5,62	18,47	$C_{17}H_{21}N_5O_5$	54,4	5,6	18,66
XXXV	C_4H_9-n	C_3H_7-n	$NHC_6H_4NHCOCH_3$-n	64,6	197—8	59,0	6,41	18,41	$C_{18}H_{25}N_5O_4$	58,91	6,41	18,09
XXXVI	CH_3	CH_3	OCH_3	70,3	66—8	42,79	4,81	—	$C_7H_9N_3O_4$	42,21	4,52	—
XXXVII	CH_3	CH_3	OC_2H_5	82,2	64—5	45,04	5,11	19,6	$C_8H_{11}N_3O_4$	45,07	5,16	19,71
XXXVIII	C_2H_5	CH_3	OCH_3	40,4	48—50	45,10	5,33	18,98	$C_8H_{11}N_3O_4$	45,07	5,16	19,71
XXXIX	C_2H_5	CH_3	OC_2H_5	—	Oil[7]	—	—	—	—	—	—	—
XL	C_3H_7	C_2H_5	OCH_3	78,4	41—2	50,23	6,40	17,4	$C_{10}H_{15}N_3O_4$	49,8	6,23	17,42
XLI	C_3H_7	C_2H_5	OC_2H_5	—	Oil[7]	—	—	—	—	—	—	—
XLII	C_4H_9-n	C_3H_7-n	OCH_3	95,4	Oil[7]	—	—	—	—	—	—	—
XLIII	C_4H_9-n	C_3H_7-n	OC_2H_5	97,5	Oil[7]	—	—	—	—	—	—	—

TABLE 1. (continued)

Compound	R	R'	R''	Yield (in %)	Mp (in deg)[2]	Found (in %)			Empirical formula	Calculated (in %)		
						C	H	N		C	H	N
XLIV	C_4H_9-iso	C_3H_7-iso	OCH_3	83,4	68—70	53,44	7,27	15,66	$C_{10}H_{19}N_3O_4$	53,53	7,02	15,61
XLV	C_4H_9-iso	C_3H_7-iso	OC_2H_5	44,0	38—9	55,03	7,52	14,3	$C_{13}H_{21}N_3O_4$	55,12	7,42	14,82
XLVI	C_5H_{11}-n	C_4H_9-n	OCH_3	84,7	Oil[7]		—	—	—	—	—	—
XLVII	C_5H_{11}-n	C_4H_9-n	OC_2H_5	93,5	Oil[7]		—	—	—	—	—	—

These substances melt with decomposition. For analysis the compounds were purified by crystallization: II-V, XXIV, XXV, XXX, XXXIII, and XXXIV, from alcohol; VI, XIX, XXVI, XXVII, XXXII, XXXV-XXXVIII, XL, XLIV, and XLV, from aqueous alcohol (1:1); VII, from benzene; VIII, from a mixture of benzene and petroleum ether (1:1); IX, XI, XII, XIV, XVI, XX, XXII, and XXIII, from water; XIII and XXVIII, from aqueous acetone (1:1); XV and XVIII, from absolute alcohol; XXI, from a mixture of dimethylformamide and water (1:1); XXIX, from a mixture of alcohol and ether (1:1). Compound X was isolated with dilute hydrochloric acid from a dilute sodium carbonate solution; XVII and XXXI were isolated from the reaction mixture in the form of hydrochlorides and were washed with alcohol.

[2]Found, %: Cl, 11.69. Calculated, % Cl, 11.62.

[3]Found, %: Cl, 12.78. Calculated, %: Cl, 12.88.

[4]Found, %: Cl, 11.48. Calculated, %: Cl, 11.11.

[5]Found, %: Cl, 9.19. Calculated, %: Cl, 9.11.

[6]Found, %: Cl, 9.62. Calculated: Cl, 9.87

[7]Does not distill at 250° (3 mm).

dazole [11] with dimethyl sulfate [12] and subsequent bromination in position 5 of the imidazole ring [11].

Unsubstituted 4(5)-nitroimidazole-5(4)-carboxlic acid was synthesized by nitration and oxidation of 4(5)-hydroxymethylimidazole [13].

The nitrocyanoimidazoles, nitroimidazolecarboxamides, and nitroimidazolecarboxylic acids not described in the literature were characterized by their melting points and elemental analyses (see Table 1).

The nitroimidazolecarboxylic acids were converted to the corresponding acid chlorides by the action of thionyl chloride. Substituted amides of the nitroimidazolecarboxylic acids were obtained by heating the acid chlorides with amines in benzene in the presence of triethylamine or an excess of the amine being acylated. The piperazides and diethylaminoethylamides were obtained in the form of hydrochloride and appropriate amine.

Esters of the nitroimidazolecarboxylic acids were prepared by the reaction of the acid chlorides with alcohols. Some nitroesters (XXXIX, XLI-XLIII, XLVII), which were undistillable oils (see Table 1), were later converted into aminoesters without purification.

In the IR spectra of the nitro derivatives, taken in vaseline oil on a UR-10 spectrometer, absorption bands were detected in the 1300-1350 cm^{-1} region, which corresponds to the symmetrical stretching vibration of the NO_2 group. There were also characteristic absorption bands at 2240 cm^{-1} for nitriles, 1710-1720 cm^{-1} for acids, 1725 cm^{-1} for esters, 1675-1685 cm^{-1} for primary amides, and 1645-1678 cm^{-1} for secondary amides.

Biological tests of the preparations (IX, XI, XIII-XXVII, XXIX-XXXI, and XXXIII-XXXV) for antitumor action, performed in the cancer chemotherapy laboratory of the Novokuznets Scientific-Research Pharmaceutical Chemistry Institute under the direction of L. F. Mal'tseva, showed that individual representatives (XVIII, XXV-XXVII, and XXX) display weak activity (a 32-60% retardation); the remaining substances, however, do not affect the growth of experimental tumors.

Pharmacological study of the compounds synthesized (IX, XI, XIII-XIX, XXV-XXVII, and XXIX-XXXI) was performed under the direction of V. M. Kurilenko in the laboratory of pharmacology and showed that these preparations exert some depressive action on the central nervous system, expressed in a reduction in body temperature, breakdown in motor coordination, and an increase in drug-induced sleep.

EXPERIMENTAL

The starting materials were prepared by the following literature procedures: 1,2-dimethyl-4-nitro-5-cyanoimidazole (I), [1]; 1,2-dialkyl-4-nitroimidazole-5-carboxamides (II-IV), [5]; and 1,2-dialkyl-4-nitroimidazole-5-carboxylic acids (V-VIII), [7].

Acid Chlorides of Nitroimidazolecarboxylic Acids. The nitroimidazolecarboxylic acid was boiled with a 9-11-fold excess of thionyl chloride until a homogeneous solution was formed (from 1 to 5 h). The excess thionyl chloride was distilled off under vacuum; dry benzene was added to the residue in an amount equal in volume to the thionyl chloride distilled off, and the benzene was distilled off. This operation was repeated two or three times. The acid chlorides obtained were used for synthesis of amides and esters without further purification.

In the preparation of 4(5)-nitroimidazole-5(4)-carbonyl chloride a solution in the thionyl chloride was not formed; therefore heating was carried out, with stirring, for 7 to 8 h. The acid chloride was filtered off and washed with benzene and petroleum ether.

Substituted Amides of Nitroimidazolecarboxylic Acids (IX – XXXV). A. To a solution of the nitro acid chloride in dry benzene (in an amount of 50 ml per 0.01 mole of starting acid) was added, with stirring and cooling in an ice bath, a two to three-fold amount of the amine to be acylated. The reaction mixture was stirred for 1 or 2 h without heating, and was allowed to stand overnight. The benzene was evaporated, and the crystalline residue was washed with cold dilute hydrochloric acid solution, water sodium carbonate solution, and water. It was dried and recrystallized from an appropriate solvent (see Tabel 1). Compounds XI-XIV, XVI, XIX, XX, XXII, XXIII, XXVI-XXVIII, XXXII, and XXXIII were prepared by this method. B. To a solution or suspension (for 4(5)-nitroimidazole-5(4)-carboxylic acid) of equimolar amounts of the nitro acid chloride and the amine in dry benzene (50 ml of benzene 0.01 mole of acid), with cooling and stirring, triethylamine was slowly added in an amount of 1.2-1.3 moles per mole of acid. Further operations were as in method A. Compounds IX, X, XVIII, XXII, XXV, XXX, XXXIV, and XXXV were prepared by this method.

Nitroimidazolecarboxylic Acid Piperazide Hydrochlorides (XVII, XXXI). Piperazine (1.78 g) containing 4% water (1.72 g, 0.02 mole calculated as 100% piperazine) was boiled with 50 ml of toluene which had been dried over metallic sodium, using a Dean and Stark water separator, until 0.07 ml of water had distilled. To the solution, with cooling and stirring, was added, dropwise, a solution of the nitro acid chloride, prepared from 0.02 mole of acid, in 40 ml of toluene. The reaction mixture was stirred 2 or 3 h longer and was allowed to stand overnight. The precipitate was filtered off, washed with hot water and with hot alcohol, and was dried in air. The piperazide hydrochlorides do not dissolve in water or ordinary organic solvents, and are soluble in dimethylformamide.

Nitroimidazolecarboxylic Acid Diethylaminoethylamide Hydrochlorides (XV, XXIV, and XXIX). To a solution of the acid chloride in dry benzene, with cooling and stirring, was added an equimolecular amount of diethylaminoethylamine in benzene (3.6 ml of benzene/0.01 mole of amine). The suspension formed was stirred without heating for 1 or 2 h and allowed to stand overnight. The precipitate was filtered off and crystallized from absolute alcohol with charcoal.

Esters of nitroimidazolecarboxylic acids (XXXVI-XLVII). A mixture of the acid chloride prepared from 0.02 mole of the corresponding nitroimidazolecarboxylic acid with 6 ml (0.1 mole) of absolute ethanol or 4 ml (0.1 mole) of methanol was boiled for 10 to 15 min, and the mixture was poured into cold water. The nitroesters separated in the form of a precipitate or oil. The precipitate was filtered off, dried, and crystallized from aqueous alcohol (1:1). The oil esters were extracted several times with benzene or ether. The extract was washed with a sodium carbonate solution and water, and it was dried with anhydrous magnesium or sodium sulfate. The dried solution was filtered, and the solvent was distilled off from the filtrate. The undistillable oil remaining was used for hydrogenation.

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