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RESEARCHES ON IMIDAZOLES

XXV. Some S-Substituted 1-Alkyl- and 1,2-Dialkyl-4-Nitro-5-mercaptoimidazoles*

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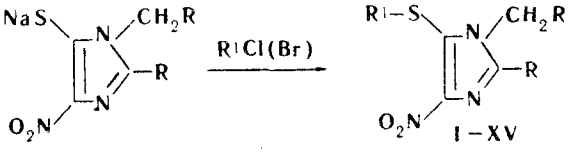
A study is made of the reaction of the sodium and ammonium salts of 1-alkyl- and 1,2-dialkyl-4-nitro-5 mercaptoimidazoles with α-halogenoketones, α-halogenoalcohols, and α- and β-halogeno acids, to give a number of 1-alkyl- and 1,2-dialkyl-4-nitro-5-[β-ketoalkyl (aralkyl)-, α-hydroxyethyl-, and α- and β-carboxyalkyl] mercaptoimidazoles.

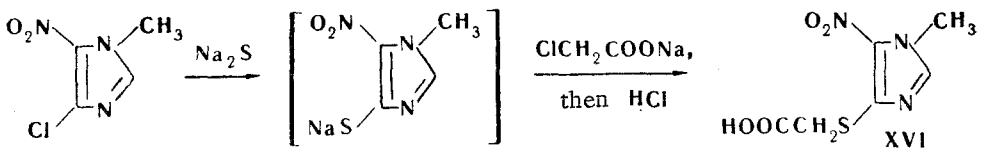
Previously a study was made of the reaction between 2-mercaptoimidazoles and α-halogenocarbonyl and α-halogenocarboxyl compounds [1, 2]. The action of α-halogenoketones, β-halogenoalcohols, and α- and β-halogeno acids on 4(5)-nitro-5(4)-mercaptoimidazoles has never been investigated. The preparation of some (3 in all) 4(5)-nitro-5(4)-carboxymethylmercaptoimidazoles by treatment of 4(5)-nitro-5(4)-chloro (bromo) imidazoles with thioglycolic acid has been described [3].

We have now synthesized a number of 1-alkyl- and 1,2-dialkyl-4-nitro-5-[β-ketoalkyl (aralkyl)-, β-hydroxyethyl- and α- and β-carboxyalkyl mercaptoimidazoles (I-XV, table), as well as of 1-methyl-5-nitro-4-carboxymethylmercaptoimidazoles (XVI), which was prepared by a method other than that described in the literature [3]. These compounds were of interest from the point of view of biological testing, and as starting materials for synthesizing some bicyclic derivatives of imidazole.

Heating the sodium salts of 1-alkyl- and 1,2-dialkyl-4-nitro-5-mercaptoimidazoles [4-6] with α-halogenoketones of the aliphatic, alicyclic, and aliphatic-aromatic series, in aqueous ethanolic solution gives good yields of the corresponding 4-mitro-5-β-ketoalkyl (aralkyl)-mercaptoimidazoles (I-IX). Reaction of the sodium salt of 1-methyl-4-nitro-5-mercaptoimidazole [4-6], and of the ammonium salts of 1-ethyl-2-methyl-4-nitro-5-mercapto- and 1-propyl-2-ethyl-4-nitro-5-mercaptoimidazole [5] with ethylene bromohydrin in water, gives 4-nitro-5-(β-hydroxyethyl) mercaptoimidazoles (X-XII).



1-Alkyl- and 1,2-dialkyl-4-nitro-5-carboxyalkylmercaptoimidazoles (XIII-XV) were synthesized by heating the sodium salts of 1-alkyl- and 1,2-dialkyl-4-nitro-5-mercaptoimidazoles with the sodium salts of bromoacetic, α-bromoisovaleric, and β-bromopropionic acids in aqueous solution, followed by acidification with hydrochloric acid. 1-Methyl-5-nitro-4-carboxymethylmercaptoimidazole (XVI) was prepared similarly, with this difference, that the synthesis was effected starting from 1-methyl-4-chloro-5-nitroimidazole [7], without isolating 1-methyl-5-nitro-4-mercaptoimidazole or its sodium salt.



The biological testing of the compounds for antibacterial action (spectrum for 16 kinds of microbes) was done in the chemotherapy division of VNIKhFI (All-Union Scientific Research Chemical and Pharmaceutical Institute) by S. N. Milovanova and A. L. Mikerina, under the guidance of G. N. Pershin, and showed that they were chemotherapeutically

*For Part XXIV see [6].

1-RCH_2-2-R-5-R'S-4-nitroimidazoles

Compound number	R	R′	Mp, °C	Formula	Found, %				Calculated, %				Yield, %
					C	H	N	S	C	H	N	S	
I	H	CH_3COCH_2*	143.5—144	$C_7H_9N_3O_3S$	39.04	3.93	20.13	14.84	39.06	4.21	19.52	14.89	95.5
II	H	$CH_3COCH(CH_3)$	104—105	$C_8H_{11}N_3O_3S$	41.82	4.72	18.46	14.24	41.92	4.83	18.33	13.99	82.8
III	H	C_6H_9O**	182—183	$C_{10}H_{13}N_3O_3S$	47.28	5.20	16.66	12.70	47.05	5.13	16.49	12.52	78.4
IV	H	$C_6H_5COCH_2$	140—141	$C_{12}H_{11}N_3O_3S$	51.76	3.92	15.16	11.76	51.97	4.00	15.15	11.56	99
V	H	m-$O_2NC_6H_4COCH_2$	146—148	$C_{12}H_{10}N_4O_5S$	44.55	3.03	17.59	10.11	44.72	3.13	17.38	9.95	96.2
VI	H	p-$O_2NC_6H_4COCH_2$	183—184	$C_{12}H_{10}N_4O_5S$	45.00	3.45	17.22	9.72	44.72	3.13	17.38	9.95	95
VII	CH_3	$CH_3COCH(CH_3)$	77—79	$C_{10}H_{15}N_3O_3S$	46.96	5.77	16.23	12.13	46.68	5.87	16.33	12.46	67.3
VIII	n-C_3H_7	CH_3COCH_2	72—73	$C_{13}H_{21}N_3O_3S$	51.93	7.06	13.75	10.62	52.15	7.07	14.03	10.71	99
IX	n-C_3H_7	p-$BrC_6H_4COCH_2$	98—99	$C_{18}H_{22}BrN_3O_3S$***	49.02	5.16	9.45	6.97	49.09	5.04	9.54	7.28	82
X	H	$HOCH_2CH_2$	110—111	$C_6H_9N_3O_3S$	35.61	4.60	20.65	15.74	35.46	4.46	20.68	15.78	86.7
XI	CH_3	$HOCH_2CH_2$	92—93	$C_8H_{13}N_3O_3S$	41.43	5.50	18.46	14.06	41.54	5.67	18.17	13.86	62.2
XII	C_2H_5	$HOCH_2CH_2$	87—88	$C_{10}H_{17}N_3O_3S$	46.11	6.44	16.55	11.91	46.31	6.61	16.21	12.36	68.4
XIII	H	$HOOCCH_2$	208—209****	$C_6H_7N_3O_4S$									80.7
XIV	CH_3	$(CH_3)_2CHCH(COOH)$	172.5—173	$C_{11}H_{17}N_3O_4S$	45.75	6.13	14.70	11.58	45.98	5.96	14.62	11.16	84.3
XV	C_2H_5	$HOOCCH_2CH_2$	148—148.5	$C_{11}H_{17}N_3O_4S$	45.60	6.13	14.69	11.14	45.98	5.96	14.62	11.16	88.9

* For analysis the compounds were purified by recrystallization: I, III, IV, ex EtOH; II, VII, VIII, XIV, XV ex aqueous EtOH; V ex dioxane; VI ex glacial AcOH; IX ex isoPrOH; X, XI, XIII ex H_2O; XII ex EtOAc.

** 2-Oxocyclohexyl.

*** Found: Br 17.76%. Calculated Br 18.15%.

**** The literature [3] gives mp 209°-210°.

inactive.

Experimental

Synthesis of the sodium and ammonium salts of 1-alkyl- and 1,2-dialkyl-4-nitro-5-mercaptoimidazoles was previously described [4–6].

1-Alkyl- and 1,2-dialkyl-4-nitro-5-β-ketoalkyl (aralkyl) mercaptoimidazoles (I–IX, Table). 0.33 mole of the halogenoketone (chloroacetone, α-chloroethylmethylketone, 2-chlorocyclohexanone) was added to a solution of 0.03 mole Na salt of 1-alkyl- or 1,2-dialkyl-4-nitro-5-mercaptoimidazole in 15–20 ml water, and the mixture heated for 1–2 hr at 60°–90° C, when the bright orange color of the solution changed to pale-yellow, and a precipitate rapidly formed. The products were then cooled, the precipitate filtered off, washed with water, and I—III, VII, VIII thus obtained. Compounds IV–VI, IX, were synthesized similarly, but with the difference that theoretical quantities of the halogenoketones (phenacylbromide or its nitro (bromo) derivatives) were used, and the reaction was run in 70% EtOH (20 ml per 1 g phenacylbromide). I–IX formed yellow or pale-yellow crystals, readily soluble in most organic solvents, slightly soluble in water, ether, CCl_4, and petrol ether, V and VI were slightly soluble in organic solvents, insoluble in water.

1-Alkyl- and 1,2-dialkyl-4-nitro-5-(β-hydroxyethyl) mercaptoimidazoles (X–XII). 0.0044 mole ethylene bromohydrin was added to a solution of 0.004 mole ammonium salt of 1,2-dialkyl-4-nitro-5-mercaptoimidazole in 3–4 ml water, the mixture heated at 95°–98° for 1–2 hr, and after cooling the oil which separated crystallized. The solid was filtered off and washed with water. This procedure was used to synthesize XI and XII. The sulfide X was prepared similarly, the difference being that the sodium salt of 1-methyl-4-nitro-5-mercaptoimidazole was used. Pale-yellow crystals, soluble in most organic solvents, and in hot water.

1-Alkyl- and 1 2-dialkyl-4 nitro-5-carboxyalkylmercaptoimidazoles (XIII–XV). A solution of Na salt of the halogeno acid (bromoacetic, α-bromoisovaleric, β-bromopropionic), prepared from 0.011 mole halogeno acid, 0.011 mole NaOH, and 10 ml water, was added to a solution of 0.01 mole Na salt of 1-alkyl- or 1,2-dialkyl-4-nitro-5-mercaptoimidazole in 10 ml water, the mixture refluxed for 4–8 hr, the solution cooled, acidified to pH 2–3 with concentrated HCl, the precipitate filtered off, and washed with water. Pale-yellow crystals, soluble in most organic solvents, slightly soluble in hot water.

1-Methyl-5-nitro-4-carboxymethylmercaptoimidazole (XVI) and its ammonium (XVII) and sodium (XVIII) salts. a) The acid XVI and its salt XVII were prepared as described in [3], with the difference that the reaction mixture of 1-methyl-4-chloro-5-nitroimidazole [7], thioglycolic acid, and NH_4OH were kept at 0°–3° for 48 hr, the precipitate of salt XVII filtered off, washed with a small amount of EtOH and then with acetone, yield 88.5%, mp 187.5°–188° (decomp, ex H_2O). The literature gives [3] mp 185°. Decomposition of salt XVII with HCl gave the acid XVI, mp 163°–164° (ex EtOH). The literature gives [3] mp 163°–164°.

b) 0.01 mole 1-methyl-4-chloro-5-nitroimidazole was added to a solution of 0.01 mole $Na_2S \cdot 9H_2O$ in 15 ml EtOH, and this was followed by 0.011 Na chloroacetate in 5 ml water, the mixture was then left overnight. The yellow precipitate of the Na salt XVIII was filtered off, and washed with acetone. Yield 61.2%, mp 257°–260° (decomp, ex 50% aqueous EtOH). The salt was readily soluble in water, slightly soluble in EtOH, insoluble in acetone. Found: N 17.50; S 13.63%. Calculated for $C_6H_6N_3O_4SNa$: N 17.64; S 13.46%.

Acidification of an aqueous solution of salt XVIII with HCl led to isolation of the acid XVI, mp 163°–165°, identical with that obtained by procedure a) above.

REFERENCES

1. P. M. Kochergin and M. N. Shchukina, ZhOKh, **26**, 458, 2905, 1956.
2. P. M. Kochergin, ZhOKh, **31**, 184, 3257, 1961.
3. M. H. Fisher, W. H. Hicholson, and R. S. Stuart, Can. J. Chem., **39**, 785, 1961.
4. P. M. Kochergin, Author's Certificate, no. 158280.
5. P. M. Kochergin, KhGS [Chemistry of Heterocyclic Compounds], 749, 1966.
6. P. M. Kochergin and E. A Bashkir, KhGS [Chemistry of Heterocyclic Compounds], 754, 1966.
7. P M Kochergin, KhGS [Chemistry of Heterocyclic Compounds], 761, 1965.

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