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RESEARCHES ON IMIDAZOLES

XXIII. 4(5)-Nitro-5(4)-Mercaptoimidazoles*

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A study is made of the actions of thiourea and ammonia and alkali metal sulfides and hydrosulfides on 4(5)-nitro-5(4)-chloro (bromo) imidazoles. It is shown that, depending on the structure of the nitrohalogenoimidazoles, the nature of the sulfur compound, and the reaction conditions, the products are 4(5)-nitro-5(4)-mercaptoimidazoles, or their sulfides or disulfides. A convenient method of preparing nitromercaptoimidazoles, by reacting 4(5)-nitro-5(4)-chloroimidazoles with sodium sufide is offered.

4(5)-Nitro-5(4)-mercaptoimidazoles have been inadequately studied [1-3]. Among other things, these compounds can be used to synthesize S-substituted nitro (amino) mercaptoimidazoles and some bicyclic imidazole derivatives of interest for biological testing.

The aim of the present work was developing methods of preparing 4(5)-nitro-5(4)-mercaptoimidazoles, and investigation of some of their physicochemical properties. The starting materials were 4(5)-nitro-5(4)-chloro (bromo) imidazoles [1, 4, 5], with a halogen atom which was rather mobile, due to the presence of a nitro group. This halogen atom was readily replaced by a mercapto group by reacting the compounds with thiourea, and ammonium and alkali metal sulfides and hydrosulfides.

It was shown that, depending on the structure of the nitrochloro(bromo) imidazoles, the nature of the sulfur compound, and the reaction conditions, nitromercaptoimidazoles and the corresponding sulfides and disulfides are formed.

Passing hydrogen sulfide into a suspension of nitrohalogenoimidazoles in aqueous ammonia [1] gives a number of known and new ammonium salts of nitromercaptoimidazoles (II, IV, VIII-X, XIII, XV, Table). In one case attempts to carry out this reaction in ethanol solution resulted in formation of the corresponding diimidazolylsulfide XVII, whose formation is due to the high rate of the side reaction, reaction of the ammonium salt X formed with the starting 1-ethyl-2-methyl-4-nitro-5-chloroimidazole.

The inconvenience of working with hydrogen sulfide, particularly the difficulty of measuring it out with large amounts of nitrohalogenoimidazoles, stimulated a search for other methods of preparing nitromercaptoimidazoles. Good results (90-95% yields of ammonium salts of nitromercaptoimidazoles) were obtained by using ammonium hydrosulfide, and running the reaction in aqueous ammonia.

Boiling 1-methyl-4-nitro-5-chloroimidazole with potassium hydrosulfide in ethanol, or with thiourea in the same solvent, gives the sulfide XVIII. Only by decomposing with alkali the intermediate thiournium compound at the instant of its formation was it possible to isolate the mercaptan III, and then in low yield (15%).

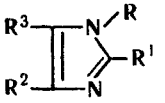
It was more convenient to prepare nitromercaptoimidazoles and their sodium salts [6] by the action of sodium sulfide on nitrochloroimidazoles. Depending on the solubility of the starting halogenonitroimidazole, the reaction was run in water, water-ethanol or ethanol solution. Reaction was fast (5-20 min), and as a rule the yield of mercaptan or its sodium salt (III, VIII, XI, XII, XIV, XVI) was high (77-93%). Deviation of the run conditions from optimal lead to formation of side products, sulfides and disulfides.

Thus, when 1-methyl-4-chloro-5-nitroimidazole and sodium sulfide are reacted together in water in the hot, the disulfide XIX is formed. 1-Ethyl-2-methyl-4-chloro-5-nitroimidazole and sodium sulfide in methanol at 50° C gives a mixture of sulfide XX and disulfide XXI. The formation of disulfides indicates the ease of oxidation of 4-mercapto-5-nitroimidazoles in alkaline medium by oxygen of the air. Even in the cold the sole product of reaction of sodium sulfide with 2-methyl 4(5)-nitro-5(4) bromoimidazole in water is the sulfide XXII, and this is probably due to the high mobility of the bromine as compared with chlorine. The sulfide XXII gives the stable mono and disodium salts XXIII and XXIV, whose formation involves the imino group.

The following equations show the products of reaction of nitrohalogenoimidazoles with one of the sulfur reagents:

* For Part XXII see [8].

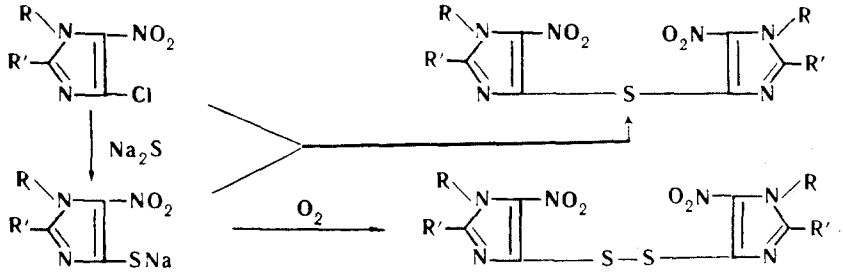
Nitromercaptoimidazoles and Their Salts



Compound number	R	R¹	R²	R³	Reagent	Mp, °C (decomp)	Formula	Found, % C	Found, % H	Found, % N	Found, % S	Calculated, % C	Calculated, % H	Calculated, % N	Calculated, % S	Yield, %
I	H	CH_3	NO_2	SH	H_2S	250 —257 a	$C_4H_5N_3O_2S$	—	—	—	—	—	—	—	—	90
II	H	CH_3	NO_2	SNH_4	H_2S	190 —210 b	$C_4H_8N_4O_2S$	—	—	—	—	—	—	—	—	90 —92
III	CH_3	H	NO_2	SH	H_2S, NH_4HS Na_2S	135 —142	$C_4H_5N_3O_2S \cdot H_2O$ c	26.94	3.85	23.41	18.33	27.10	3.98	23.72	18.10	90 —92 92.3
IV	CH_3	H	NO_2	SNH_4	H_2S NH_4HS	194 —197 d	$C_4H_8N_4O_2S$	—	—	—	—	—	—	—	—	91.7 98.5
V	CH_3	H	NO_2	SNa	—	251 —252 e	$C_4H_4N_3O_2SNa$	—	—	23.27	—	—	—	23.20	—	—
VI	CH_3	H	NO_2	SNa	Na_2S	271 —272	$C_4H_4N_3O_2SNa \cdot H_2O$ f	—	—	—	15.84	—	—	—	16.10	92 —97
VII	CH_3	H	NO_2	SK	—	276 —278	$C_4H_4N_3O_2SK$	24.87	1.97	21.10	15.88	24.35	2.04	21.30	16.25	—
VIII	CH_3	H	SH	NO_2	Na_2S	139 —141	$C_4H_5N_3O_2S$ g	30.45	3.21	26.22	20.06	30.19	3.16	26.40	20.15	83 —93.7
IX	CH_3	H	SNH_4	NO_2	H_2S NH_4HS	140 —143 h	$C_4H_8N_4O_2S$	—	—	31.79	—	—	—	31.80	—	62.5—74.5 76 —78
X	C_2H_5	CH_3	NO_2	SNH_4	H_2S NH_4HS	167 —168	$C_6H_{12}N_4O_2S$	35.61	5.67	28.07	15.42	35.28	5.92	27.43	15.70	88.7 90
XI	C_2H_5	CH_3	NO_2	SNa	Na_2S	156 —157	$C_6H_8N_3O_2SNa \cdot H_2O$ i	31.84	4.46	18.49	13.98	31.69	4.44	18.49	14.11	83
XII	C_2H_5	CH_3	SH	NO_2	Na_2S	154 —154.5	$C_6H_9N_3O_2S$ j	38.30	4.93	22.29	16.80	38.49	4.84	22.44	17.13	50
XIII	n-C_3H_7	C_2H_5	NO_2	SNH_4	H_2S	156 —158	$C_8H_{16}N_4O_2S$	41.41	7.12	24.44	13.93	41.36	6.94	24.12	13.80	95.7
XIV	n-C_3H_7	C_2H_5	NO_2	SNa	Na_2S	233.5—234	$C_8H_{12}N_3O_2SNa \cdot H_2O$ k	38.11	5.55	16.56	12.17	37.64	5.53	16.46	12.56	77.5
XV	n-C_4H_9	n-C_3H_7	NO_2	SNH_4	H_2S NH_4HS	155 —156	$C_{10}H_{20}N_4O_2S$	45.97	7.77	21.17	12.45	46.13	7.75	21.52	12.34	54.5 90
XVI	n-C_4H_9	n-C_3H_7	NO_2	SNa	Na_2S	157.5—158	$C_{10}H_{16}N_3O_2SNa \cdot H_2O$ l	42.66	6.55	14.56	11.50	42.39	6.40	14.83	11.32	91.5

a) IR spectrum, cm^{-1} ; 2470, 2590. Literature [1] mp 260° C (decomp). b) Literature [1] mp 190°–210° (decomp). c) Found: H_2O 9.80% (Karl Fischer). Calculated: H_2O 10.17%. IR spectrum, cm^{-1} 2500, 2700. d) Literature [2] mp 197°–198° (decomp). e) Recrystallized from dry PrOH. f) Found: H_2O 8.95%. Calculated: H_2O 9.00%. g) IR spectrum, cm^{-1} 2610, 2700. h) Literature [3] mp 140°–141° (decomp) i) Found: H_2O 9.44%. Calculated: H_2O 9.73%. j) IR spectrum, cm^{-1} 2540, 2710. k) Found: H_2O 9.30%. Calculated: H_2O 7.06%. l) Found: H_2O 6.50%. Calculated: H_2O 6.36%.

Note: For analysis all the salts except V, were purified by recrystallizing from water; I and III were precipitated by HCl from NaOH solution, VIII and XII were precipitated from NH_4OH with AcOH. The IR spectra were determined by E. M. Pereseleni and Yu. I. Pomerantsev, using solid (paste with vaseline) and a UR-10 instrument.



The action of acids (hydrochloric, acetic) on ammonium or sodium salts led to the isolation of free nitromercaptoimidazoles (I, III, VII, and XII), which are stronger acids than carbonic acid.

Study of the IR absorption spectra of 4(5)-nitro-5(4) mercaptoimidazoles also showed that these compounds behave as typical thiols, (absorption band in the range 2470–2720 cm^{-1}, characteristic of the SH group). In that way they differ from 2-mercaptoimidazoles, which in the solid state behave as thiones [7].

Experimental*

The starting 2-methyl-4-(5)-nitro-5(4)-bromo-, 1-alkyl(1,2-dialkyl)-4-nitro-5-chloro- and 1-alkyl(1,2-dialkyl)-4-chloro-5-nitroimidazoles have previously been prepared [1, 4, 5].

Nitromercaptoimidazoles (I, III, IX) and ammonium salts of nitromercaptoimidazoles (II, IV, IX, X, XIII, XV, Table). a) H_2S was passed for 15–20 min into a suspension of 0.01 mole nitrochloro(bromo) imidazole in 15 ml 8.5% NH_3 in H_2O, when the temperature rose to 40°–60° C, the starting material dissolved, and a solid quickly separated, after cooling this was filtered off, washed with EtOH and Et_2O. Orange crystals, readily soluble in water, slightly soluble in EtOH, insoluble in acetone. Acidification of aqueous solutions of salts II, IV, and IX with HCl or AcOH resulted in the mercaptans I, III, and VIII separating out. They formed orange crystals, insoluble in water, and most organic solvents, readily soluble in aqueous ammonia, and in aqueous solutions of alkalies, and carbonates and bicarbonates of alkali metals. They decomposed on prolonged storage.

b) A mixture of 0.02 mole nitrochloroimidazole, 0.022 mole NH_4SH and 10–12 ml 8.5% NH_3 in H_2O was stirred, and left overnight, the precipitate filtered off, and washed with EtOH.

Di(1-ethyl-2-methyl-4-nitroimidazol-5-yl) sulfide (XVII). H_2S was passed for 15 min into a warm (40°–50°) solution of 1.9 g 1-ethyl-2-methyl-4-nitro-5-chloroimidazole in 15 ml 7.5% ethanolic NH_3. The reaction products were allowed to stand for 40 hr, the pale-yellow precipitate filtered off, washed with water, then with EtOH. Yield 1.56 g (82.1%), mp 225°–227° C (decomp, ex AcOH). Found: C 42.40; H 4.61; N 24.44; S 9.23%. Calculated for $C_{12}H_{16}N_6O_4S$: C 42.34; H 4.74; N 24.69; S 9.42%.

Di(1-methyl-4-nitroimidazol-5-yl) sulfide (XVIII). a) A mixture of 8.1 g 1-methyl-4-nitro-5-chloroimidazole and 5.4 g KSH in 100 ml EtOH was refluxed for 5 hr, cooled, the precipitate filtered off, washed with water, EtOH, and acetone, yield 4.5 g (63%), mp 264° (decomp, ex AcOH). Found: C 33.71; H 2.98; N 29.15; S 11.22%. Calculated for $C_8H_8N_6O_4S$: C 33.78; H 2.83; N 29.58; S 11.28%.

b) A solution of 4 g 1-methyl-4-nitro-5-chloroimidazole, 2 g thiourea, and 20 ml EtOH was refluxed for 40 min, 7 ml 10% aqueous NaOH added, the whole refluxed for 30 min, cooled, neutralized with HCl and made acid, the precipitate filtered off, washed with water, then with acetone, yield 2.4–2.7 g (69.8–77%), mp 264°–274° C (decomp). Undepressed mixed mp with the compound prepared by method a).

1-Methyl-4-nitro-5 mercaptoimidazole (III). a) 57 g 1-methyl-4-nitro-5-chloroimidazole was added in 5–7 min to a stirred solution of 97 g $Na_2S \cdot 9H_2O$** in 350 ml water which had been heated to 40° C, when the temperature of the mixture rose to 66°–68°. The solution was held at 90° for 10–15 min (in the presence of decolorizing charcoal), filtered, cooled, and acidified with 40 ml concentrated HCl, and the orange precipitate filtered off and washed with water. Yield 58.1 g. The Na salt VI was readily isolated by evaporating the reaction products (without acidifying with HCl) to small volume, or by dissolving III in aqueous NaOH and precipitating with EtOH. The K salt VII was prepared by

* Compounds X, XIII, XV, and XVII were prepared with the assistance of a student, E. A. Bashkir.

** In all the other runs the nonahydrate was used too.

dissolving III in aqueous KOH and precipitating with EtOH.

b) A mixture of 2.4 g 1-methyl-4-nitro-5-chloroimidazole, 1.2 g thiourea, and 8 ml water was rapidly brought to the boil (in 1–2 min), cooled to 80°–85° C, 4 ml 36% aqueous NaOH added, the solution boiled for 6–7 min, filtered, cooled, and acidified with 6 ml concentrated HCl. The precipitate was filtered off washed with water, then with acetone. Yield of III 0.4 g (15%).

1-Methyl-4-mercapto-5-nitroimidazole (VIII). 4.8 g 1-methyl-4-chloro-5-nitroimidazole was added, with cooling, to a solution of 7.8 g sodium sulfide in 45 ml MeOH. The solvent was vacuum-distilled off, 10 ml water added to the residue, the solution heated, filtered, and acidified with AcOH, the precipitate filtered off, and washed with water, yield 4-4.5 g.

Di (1-methyl-5-nitroimidazol-4-yl) disulfide (XIX). 4.8 g 1-methyl-4-chloro-5-nitroimidazole was added to a stirred and cooled solution of 7.8 g sodium sulfide in 10 ml water, over a period of 15 min. The whole was left for 1 hr 30 min, filtered, acidified with AcOH, the yellow precipitate filtered off, and washed with water, yield 2.4 g (50.6%), mp 234°–234.5° C (ex 80% AcOH). Found: C 30.48; H 2.61; N 26.62; S 20.54%. Calculated for $C_8H_8N_6O_4S_2$: C 30.38; H 2.55; N 26.57; S 20.21%.

Sodium salt of 1-ethyl-2-methyl-4-nitro-5-mercaptoimidazole (XI). 3.8 g 1-ethyl-2-methyl-4-nitro-5-chloroimidazole was gradually added to a hot (70°) solution of 5.1 g sodium sulfide in 15 ml water, the mixture heated to 80°–85° C (with decolorizing charcoal), filtered, cooled to 0°, the precipitate filtered off, and washed with acetone. Yield 3.8 g, XIV and XVI were prepared similarly. In the preparation of XVI, the solvent was 50% aqueous EtOH.

1-Ethyl-2-methyl-4-mercapto-5-nitroimidazole (XII) and di (1-ethyl-2-methyl-5-nitroimidazol-4-yl) disulfide (XX). A solution of 1.5 sodium sulfide in 30 ml 50% aqueous MeOH was heated to 30°, and 1.1 g 1-ethyl-2-methyl-4-chloro-5-nitroimidazole added, the mixture filtered, vacuum-evaporated to 10 ml, 3 ml AcOH added and the mixture cooled to 0°. The orange precipitate was filtered off, and washed with water, yield 0.15 g (14%) disulfide XX, mp 218.5° C (ex 90% AcOH). Yellow crystals, readily soluble in acetone. Found: C 38.68; H 4.39; N 22.56; S 17.05%. Calculated for $C_{12}H_{16}N_6O_4S_2$: C 38.70; H 4.33; N 22.57; S 17.22%.

Di (1-ethyl-2-methyl-5-nitroimidazol-4-yl) sulfide (XXI) and di (1-dethyl-2-methyl-5-nitroimidazol-4-yl) disulfide (XX). A hot solution of 1.2 g sodium sulfide in 12 ml MeOH and 1 ml water was cooled to 18°–20°, 0.95 g 1-ethyl-2-methyl-4-chloro-5-nitroimidazole added, the mixture brought to the boil, filtered, and solvent vacuum-distilled off, then 10 ml hot water was added to the residue, and the insoluble yellow precipitate filtered off and washed with water. Yield 0.37 g (43.5%) sulfide XXI, mp 169.5°–170° C (ex 50% EtOH). Found: C 42.52; H 4.81; N 24.77; S 9.38%. Calculated for $C_{12}H_{16}N_6O_4S$: C 42.35; H 4.74; N 24.69; S 9.42%.

After removing XXI, the mother liquor was acidified with 2 ml concentrated HCl, the precipitate filtered off, and washed with water. Yield 0.32 g (34.4%) disulfide XX, mp 217°–218° C (ex AcOH). Undepressed mixed mp with XX prepared as described in the preceding experiment.

Di [2-methyl-4(5)-nitroimidazol-5(4)-yl] sulfide (XXII) and its sodium salts (XXIII and XXIV). a) 1.55 g 2-methyl-4(5)-nitro-5(4)bromoimidazole was added to a warm (25°–40°) solution of 1.9 g sodium sulfide in 5 ml water, the solution heating to boiling (with decolorizing charcoal, filtered, and made acid with 3 ml 36% HCl. The yellow precipitate was filtered off, and washed with water. Yield of sulfide XXII 0.93 g (85%), decomposes at 250°–280° C (ex EtOH), soluble in aqueous alkalies and solutions of alkali metal carbonates. Found: C33.61; H 3.56; N 29.20; S 11.17%. Calculated for $C_8H_8N_6O_4S$: C 33.80; H 2.84; N 29.57; S 11.28%.

b) 3.1 g 2-methyl-4(5)-nitro-5(4) bromoimidazole was added to a hot (60°–70°) solution of 3.8 g sodium sulfide in 20 ml aqueous EtOH (1:1), the solution heated with decolorizing charcoal, filtered, the solvent vacuum-distilled off, the residue washed with a small amount of MeOH, then with acetone. Yield 1.93 g (84.6%) of monosodium salt XXIII, forming bright-orange needles mp > 360° C (ex 80% EtOH), readily soluble in water and MeOH. Found: C 31.60, H 2.91; N 27.62; S 9.99%. Calculated for $C_8H_7N_6O_4SNa$: C 31.38; H 2.30; N 27.44; S 10.47%.

c) 0.5 g XXIII was dissolved in 10 ml water, 2 ml 10% NaOH added, the solution filtered, 80 ml EtOH added, the precipitate of disodium salt XXIV filtered off, and washed with plenty of EtOH. Bright-brown crystals mp 290°–295° C (decomp), readily soluble in water. Found: C 27.13; H 2.29; N 23.80; S 8.75%. Calculated for $C_8H_6N_6O_4SNa_2 \cdot H_2O$: C 27.75; H 2.33; N 24.28; S 9.26%.

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