SYNTHESIS OF MERCAPTONITROIMIDAZOLES AND THEIR REACTION WITH 2,4,6-TRINITROCHLOROBENZENE

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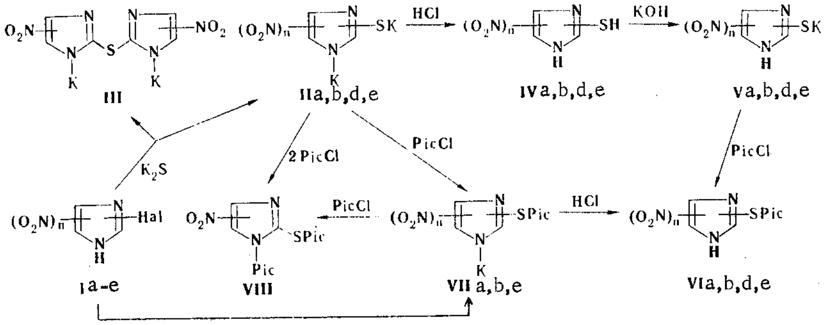
A number of derivatives of mercaptomono- and dinitroimidazoles were synthesized by the action of potassium sulfide on the corresponding halonitroimidazoles. Mono- and dipotassium salts of mercaptonitroimidazoles were obtained. It was established that the monopotassium salts of mercaptomono- and dinitroimidazoles react with 2,4,6-trinitrochlorobenzene to give picrylmercapto derivatives, dipotassium salts of mononitromercaptoimidazoles give, depending on the ratio of the components, picrylmercaptonitroimidazoles or S,N-dipicrylmercaptonitroimidazoles, and dipotassium salts of mercaptodinitroimidazole give only picrylmercaptonitroimidazoles.

Of the mercaptoimidazoles, the syntheses of derivatives with an alkyl substituent in the 1 position have been best described [1-4]. The aim of the present research was to develop methods for the preparation of "pyrrole" nitrogen-unsubstituted mercapto derivatives of mono- and dinitroimidazoles to estimate the nucleophilicities of their N and S reaction centers in substitution reactions. As a model, we investigated the reaction of the synthesized compounds with 2,4,6-trinitrochlorobenzene.

The reaction of 2-iodo-4(5)-nitro- and 4(5)-chloro-5(4)-nitroimidazoles (Ia, b) with potassium sulfide gives the dipotassium salts of the corresponding mercaptonitroimidazoles (IIa, b) in good yields. Regardless of the reagent ratio, the reaction of 2-chloro-4(5)-nitroimidazole (Ic) with potassium sulfide terminates with the formation of a single product, viz., 2,2'-bis[4(5),4'(5')-dinitroimidazolyl] disulfide dipotassium salt (III).



n=1,2; Pic–2,4,6-trinitrophenyl; I a 2-I-4(5)-NO_2, b 4(5)-Cl-5(4)-NO_2, c 2-Cl-4(5)-NO_2, d 2-Br-4,5-$(NO_2)_2$; e 4(5)-I-2.5(4)-$(NO_2)_2$; II, V a 2-SK-4(5)-NO_2, b 4(5)-SK-5(4)-NO_2, d 2-SK-4,5-$(NO_2)_2$, e 4(5)-SK-2.5(4)-$(NO_2)_2$; III 4(5),4'(5')-$(NO_2)_2$; IV a 2-SH-4(5)-NO_2, b 4(5)-SH-5(4)-NO_2, d 2-SH-4.5-$(NO_2)_2$, e 4(5)-SH-2,5(4)-$(NO_2)_2$; VIa, VIIa, VIII 2-SPic-4(5)-NO_2; VIb, VIIb 4(5)-SPic-5(4)-NO_2; VId 2-SPic-4.5$(NO_2)_2$; VIe; VIIe 4(5)-SPic-2.5(4)-$(NO_2)_2$

2-Bromo-4,5-dinitro- and 4(5)-iodo-2,5(4)-dinitroimidazoles (Id, e) react with K_2S so vigorously that spontaneous combustion of the reaction mixture occurs in some cases. The synthesis of the dipotassium salts of mercaptonitroimidazoles (IId, e) is therefore realized at low temperatures. Some characteristics of the dipotassium salts of nitro derivatives of mercaptoimidazoles (IIa, b, d, e) are presented in Table 1.

Treatment of aqueous solutions of the dipotassium salts with strong acids leads to the production of free mercaptonitroimidazoles IVa, b, d, e in satisfactory yields.

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TABLE 1. Characteristics of the Synthesized Compounds

Compound	Dec. temp., °C	Found, %			Empirical formula	Calculated, %			Yield, %
		C	N	S		C	N	S	
IIa	254—256	16,3	19,2	14,2	$C_3HK_2N_3O_2S$	16,3	19,0	14,5	88
IIb	260—261	16,4	18,7	14,4					84
IId	263—265	13,4	21,1	12,0	$C_3K_2N_4O_4S$	13,5	21,0	12,0	99
IIe	276—280	13,5	21,2	11,9					99
IVa	114—115	24,6	29,2	21,8	$C_3H_3N_3O_2S$	24,6	29,0	22,1	81
IVb	119—120	24,9	28,8	21,9					64
IVd	163—165	18,6	29,4	17,0	$C_3H_2N_4O_4S$	18,9	29,5	16,8	80
IVe	179—180	18,8	30,0	16,9					72
Va	195—197	19,4	23,1	17,4	$C_3H_2KN_3O_2S$	19,7	22,9	17,5	70
Vb	200—202	19,5	22,9						67
Vd	205—206	15,8	24,6	13,9	$C_3HKN_4O_4S$	15,8	24,6	14,0	89
Ve	218—221	15,8	24,9						94
VIa	214—215	30,6	23,3	8,9	$C_9H_4N_6O_8S$	30,3	23,6	9,0	98
VIb	210—211	30,8	23,6	8,9					96
VId	271—272	27,2	24,1	7,9	$C_9H_3N_7O_{10}S$	26,9	24,4	8,0	96
VIe	279—280	26,7	24,2	7,8					94

Monopotassium salts Va, b, d, e were obtained by the action of an equimolar amount of potassium hydroxide on mercaptonitroimidazoles IVa, b, d, e (Table 1). Monopotassium salts Va, b, d, e react with 2,4,6-trinitrochlorobenzene unambiguously, regardless of the ratio of the components: Only the corresponding picrylmercaptonitroimidazoles VIa, b, d, e were isolated in quantitative yields in this case.

The reaction of dipotassium salts IIa, b, e with 2,4,6-trinitrochlorobenzene in the case of an equimolar ratio of the components terminates with the formation of the potassium salts of the corresponding picrylmercaptonitroimidazoles VIIa, b, e, which, after treatment with mineral acids, undergo quantitative conversion to free picrylmercaptonitroimidazoles VIa, b, e, Dipotassium salt IIe reacts with 2,4,6-trinitrochlorobenzene to give only the potassium salt of picrylmercaptodinitroimidazole VIe, regardless of the ratio of the starting components. Under these conditions dipotassium salt IIa gives S, N-dipicrylmercaptonitroimidazole (VIII).

The structure of VIIa, e was confirmed by alternative synthesis from the potassium salt of 2,4,6-trinitrothiophenol and Ia, e, while VIII was synthesized by condensation of VIIa with 2,4,6-trinitrochlorobenzene.

The data obtained indicate that of the two nucleophilic centers (S and N) in the mercaptonitroimidazoles, the S center has greater reactivity. An increase in the number of nitro groups in the mercaptonitroimidazoles leads to loss of nucleophilic activity by the "pyrrole" nitrogen atom in the investigated model reaction; this is also observed in the case of dipotassium salt IIe.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-10 spectrometer. The starting halonitroimidazoles Ia-e were synthesized by the methods in [4-6]. The potassium salt of 2,4,6-trinitrothiophenol was obtained by the method in [7].

2-Mercapto-4(5)-nitroimidazole Dipotassium Salt (IIa). A 17.7-g (74 mmole) sample of Ia was added with vigorous stirring at room temperature to a solution of 4.2 g (74 mmole) of KOH in 50 ml of methanol. The mixture was stirred for 20 min, and a solution of 35 g (175 mmole) of methanol was added at 20°C to the resulting solution, and the mixture was stirred for 20 h. The resulting precipitate was removed by filtration, washed with methanol, and air dried to give 14.5 g (88%) of the dipotassium salt. Dipotassium salt IIb was similarly synthesized from Ib.

4(5)-Mercapto-2,5(4)-dinitroimidazole Dipotassium Salt (IIe). A 10-g (35 mmole) sample of Ie was added at 5°C to a methanol solution of 2 g (35 mmole) of KOH, and the mixture was stirred for 20 min. A solution of 7 g (35 mmole) of $K_2S \cdot 5H_2O$ in 40 ml of methanol was added at the same temperature in the course of 1 h, and the mixture was stirred for another hour. The precipitate was removed by filtration, washed with methanol, and dried to give 9.2 g (99%) of dipotassium salt IIe. Dipotassium salt IId was similarly obtained (Table 1).

2,2'-Bis[4(5),4'(5')-dinitroimidazolyl] Sulfide Dipotassium Salt (III). A 1.9-g (13 mmole) of Ic was added with vigorous stirring at room temperature to a solution of 0.7 g (13 mmole) of KOH in 15 ml of methanol. After 20 min, a solution of 2.6 g (13 mmole) of $K_2S \cdot 5H_2O$ in 10 ml of methanol was added dropwise to the resulting solution, and the mixture was maintained at 20°C for 20 h. The resulting precipitate was removed by filtration, washed with methanol, and dried to give 1.8 g (84%) of dipotassium salt III. IR spectrum: 1350, 1545 (NO_2); 720 cm^{-1} (S—C). Found: C 21.9; H 0.6; N 25.2; S 9.5%. $C_6H_2K_2N_6O_4S$. Calculated: C 21.7; H 0.6; N 25.3; S 9.6%.

2-Mercapto-4(5)-nitroimidazole (IVa). Hydrochloric acid (20%) was added with stirring at no higher than 20°C to a solution of 4.4 g (20 mmole) of dipotassium salt IIa in 20 ml of water until the mixture was slightly acidic. The yellow precipitate was removed by filtration, washed with water, and air dried. Recrystallization from ethyl acetate gave 2.3 g (81%) of free mercaptonitroimidazole IVa. Compounds IVb, d, e were synthesized by the method described above (Table 1).

2-Mercapto-4(5)-nitroimidazole Monopotassium Salt (Va). A solution of 1.1 g (20 mmole) of KOH in 10 ml of methanol was added slowly with vigorous stirring at 0°C to a solution of 2.9 g (20 mmole) of IVa in 30 ml of dimethylformamide (DMF), and the resulting light-red reaction mixture was stirred at the same temperature for 1 h. It was then diluted with 10 ml of ether, and the dark-red precipitate was removed by filtration, washed with ethyl acetate and ether, and dried. The product was purified by reprecipitation from DMF by the addition of ethyl acetate to give 2.6 g (70%) of product. Salts Vb, d, e were similarly synthesized (Table 1).

Reaction of Monopotassium Salts of Mercaptonitroimidazoles with 2,4,6-Trinitrochlorobenzene. A solution of 7 mmole of picryl chloride in 5 ml of DMF was added with stirring to a solution of 7 mmole of the monopotassium salt of the corresponding mercaptonitroimidazole (Va, b, d, e) in 25 ml of DMF, after which the mixture was stirred at 50°C for 3 h. The KCl was removed by filtration, the mother liquor was diluted with water, and the precipitate was removed by filtration, washed with a small amount of water, and air dried. All of the reaction products were purified by recrystallization from ethyl acetate. The experimental results are presented in Table 1 (VIa, b, d, e).

2-Picrylmercapto-4(5)-nitroimidazole (VIa). A) A solution of 1.7 g (7 mmole) of picryl chloride in 5 ml of DMF was added with stirring to a solution of 1.5 g (7 mmole) of salt IIa in 25 ml of DMF, during which KCl precipitated immediately. The mixture was stirred at 50°C for 3 h, and the precipitated KCl was removed by filtration. The mother liquor was diluted with water, and the yellow precipitate was removed by filtration, washed with a small amount of water, and air dried to give 1.95 g (72%) of product. Found: C 27.3; N 21.2; S 8.0%. $C_9H_3KN_6O_8S$. Calculated: C 27.4; N 21.3; S 8.1%.

This amount of the salt was dissolved in 50 ml of water at 50°C, and 50% H_2SO_4 was added until the mixture was slightly acidic. The precipitated substance was removed by filtration, washed with water, and dried. Recrystallization from ethyl acetate gave 1.6 g (90% with respect to the salt) of VIa with mp 214-215°C (dec.). IR spectrum: 1345, 1540 (NO_2); 790, 680 cm^{-1} (C–S–C). Found: C 30.3; N 23.5; S 8.9%. $C_9H_4N_6O_8S$. Calculated: C 30.3; N 23.6; S 9.0%.

No melting-point depression was observed for a mixture of this product with a sample obtained from monopotassium salt Va.

B) A 1-g (4 mmole) sample of Ia was added with vigorous stirring at room temperature to a solution of 0.24 g (4 mmole) of KOH in 15 ml of methanol. After the Ia had dissolved completely, a solution of 2 g (7 mmole) of potassium 2,4,6-trinitrophenoxide in 100 ml of methanol was added, and the mixture was stirred at room temperature for 10 h. The precipitate was removed by filtration, washed with methanol, and dried to give 1 g (58%) of salt VIIa with mp 257-258°C (dec.). Found: C 27.3; N 21.4; S 8.1%. $C_9H_3KN_6O_8S$. Calculated: C 27.4; N 21.3; S 8.1%.

4(5)-Picrylmercapto-5(4)-nitroimidazole (VIb). This compound was obtained in the same way as VIa by method A. The product had mp 210-211°C (dec., from ethyl acetate) and was obtained in 65% yield. IR spectrum: 1350, 1545 (NO_2); 785, 680 cm^{-1} (C–S–C). Found: C 30.8; N 23.6; S 9.0%. $C_9H_4N_6O_8S$. Calculated: C 30.3; N 23.6; S 9.0%. Potassium salt VIIb was obtained in 47% yield and had mp 266-267°C (dec.). Found: C 27.5; N 21.3; S 8.2%. $C_9H_3KN_6O_8S$. Calculated: C 27.4; N 21.3; S 8.1%.

4(5)-Picrylmercapto-2,5(4)-dinitroimidazole (VIe). A) A solution of 0.95 g (3.8 mmole) of picryl chloride in 5 ml of DMF was added to a solution of 1 g (3.8 mmole) of dipotassium salt IIe in 16 ml of DMF, and the mixture was stirred at room temperature for 24 h. The precipitated KCl was removed by filtration, the filtrate was diluted with water, and the precipitate was removed by filtration, washed with ice water, and air dried to give 0.65 g (40%) of potassium salt VIIe with mp 315°C (dec.). Found: C 24.5; N 22.0%. $C_9H_2KN_7O_{10}S$. Calculated: C 24.6; N 22.3%. The salt was decomposed by the method described above to give VIe with mp 279-280°C (dec., from ethyl acetate) in 94% yield. IR spectrum: 1350, 1535 (NO_2); 760, 680 cm^{-1} (C–S–C). Found: C 27.1; N 24.4; S 7.9%. $C_9H_3N_7O_{10}S$. Calculated: C 26.9; N 24.4; S 8.0%. No melting-point depression was observed for a mixture of this product with the substance obtained from monopotassium salt Ve.

B) a 1.4-g (5 mmole) sample of Ie was added with vigorous stirring at room temperature to a solution of 0.28 g (5 mmole) of KOH in 15 ml of methanol. After the Ie had dissolved completely, a solution of 2.8 g (10 mmole) of potassium 2,4,6-trinitrothiophenoxide in 120 ml of methanol was added, and the mixture was heated to 50°C and stirred at this temperature for 1 h. The precipitate was removed by filtration, washed with methanol, and dried to give 1.8 g (82%) of potassium salt VIIe with mp 314-315°C (dec.). Found: C 24.5; N 22.0%. $C_9H_2KN_7O_{10}S$. Calculated: C 24.6; N 22.3%. Decomposition of the indicated amount of the salt gave 1.5 g (92% with respect to the salt) of VIe with mp 279-280°C (dec., from ethyl acetate). IR spectrum: 1350, 1535 (NO_2); 760, 680 cm^{-1} (C–S–C). Found: C 27.1; N 24.6; S 8.1%. $C_9H_3N_7O_{10}S$. Calculated: C 26.9; N 24.4; S 8.0%. No melting-point depression was observed for a mixture of this product with the product obtained by method A.

1-Picryl-2-picrylmercapto-4(5)-nitroimidazole (VIII). A) A solution of 5.0 g (20 mmole) of picryl chloride in 30 ml of DMF was added to a solution of 2.2 g (10 mmole) of dipotassium salt IVa in 40 ml of DMF, and the mixture was stirred at room temperature for 24 h. The KCl was removed by filtration, the mother liquor was diluted with water, and the precipitate was removed by filtration, washed with hot water, and dried. It was then refluxed thoroughly and successively in chloroform and alcohol and dried again to give 2.4 g (42%) of a product with mp 317-318°C (dec.). IR spectrum: 1350, 1570 (NO_2); 800, 685 cm^{-1} (C–S–C). Found: C 32.0; N 22.4; S 5.6%. $C_{15}H_5N_9O_{14}S$. Calculated: C 31.7; N 22.2; S 5.6%.

B) A solution of 1.25 g (5 mmole) of picryl chloride in 10 ml of DMF was added at room temperature to a solution of 2.5 g of 2-picrylmercapto-4(5)-nitroimidazole potassium salt (VIIa) in 30 ml of DMF, and the mixture was maintained at the same temperature for 24 h. All of the subsequent operations for the isolation of the reaction product were similar to those in method A. The yield of product with mp 317-318°C (dec.) was 2 g (70%). IR spectrum: 1350, 1570 (NO_2); 800, 685 cm^{-1} (C–S–C). Found: C 31.7; N 22.2; S 5.5%. $C_{15}H_5N_9O_{14}S$. Calculated: C 31.7; N 22.2; S 5.6%. No melting-point depression was observed for a mixture of this product with the substance obtained by method A.

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