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SYNTHESIS OF DERIVATIVES OF 1-AMINOBENZIMIDAZOLINE-2-THIONE

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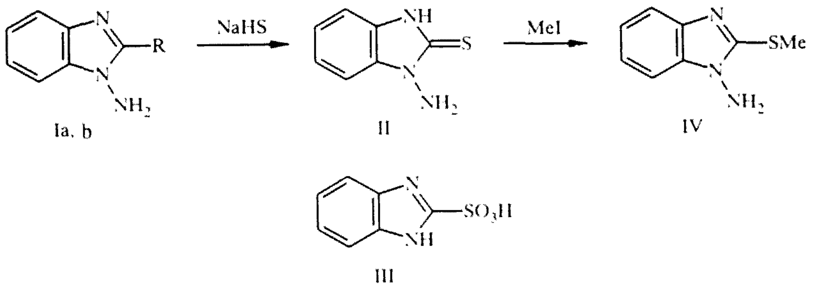
A new method for producing 1-aminobenzimidazoline-2-thione by the reaction of 1-amino-2-chloro-benzimidazole or 1-aminobenzimidazole-2-sulfonic acid with sodium hydrosulfide is proposed. The pathways of synthesis of N-acylamino-2-methylthiobenzimidazoles were studied.

Recently we reported on the synthesis and cardiotonic activity of a number of 2-alkylthio-1-acylbenzimidazoles [1, 2]. Continuing these investigations, we were interested in synthesizing some representatives of hitherto unknown 1-acylamino- and 1-ureido-2-methylthiobenzimidazoles. The reaction of 1-amino-2-methylthiobenzimidazole with the corresponding acylating agents or isocyanates can be a convenient method for synthesizing these compounds. It is advisable to use 1-aminobenzimidazoline-2-thiol as the starting material; as noted in [3], its synthesis involves definite difficulties. According to our data, only two methods of producing 1-amino-2-methylthiobenzimidazole have been published. These are the direct thiolation of N-amino derivatives of benzimidazole [3, 4] and the cyclization of *o*-aminophenylhydrazones with carbon disulfide [3]. In both methods, the N-amino group in the initial compounds must be protected for the successful synthesis of 1-aminobenzimidazoline-2-thione, which usually leads to supplementary steps of the synthesis. Therefore we decided to use nucleophilic substitution of 2-sulfo- or 2-chloro groups in 1-aminobenzimidazoles Ia,b by the mercapto group as a possible alternative method for producing 1-aminobenzimidazoline-2-thione (II). The substitution was performed by heating the benzimidazoles Ia,b in an aqueous solution of sodium hydrosulfide. The yield of compound II was 31 and 39%, respectively. It should be mentioned that in the reaction of 1-aminobenzimidazole-2-sulfonic acid (Ia) with sodium hydrosulfide, we isolated the deamination product — benzimidazole-2-sulfonic acid (III) — from the reaction mixture in a yield of 15%. In the case of 1-amino-2-chlorobenzimidazole (Ib), no other reaction products could be isolated. Competing reactions are unquestionably the cause of the moderate yields, which could not be increased by varying the temperature and duration of the reaction.

Scheme 1



I a R = SO$_3$H, b R = Cl

The acylation of 1-amino-2-methylthiobenzimidazole (IV), produced by methylation of the thione II according to the method of [3], was studied using various reagents. Thus, when compound IV was boiled with acetic anhydride, we obtained

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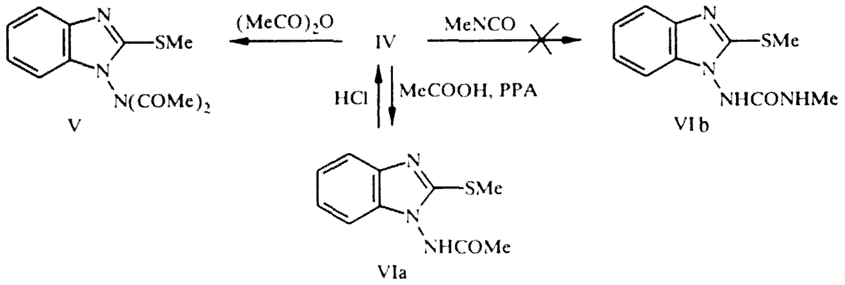
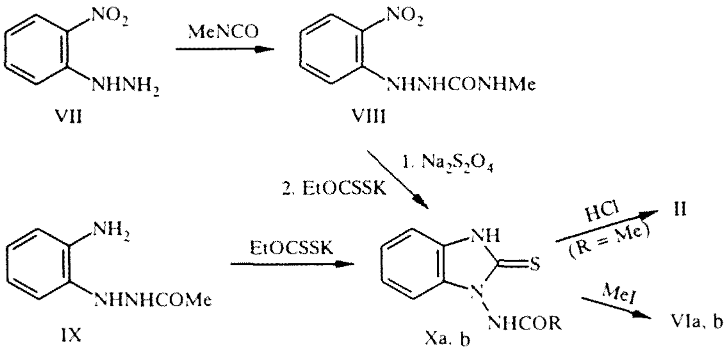
a 64% yield of 1-diacetylamino-2-methylthiobenzimidazole (V). Heating of compound IV with acetic acid in PFK leads to the formation of a monoacetyl derivative VIa. However, the acetylation of the benzimidazole IV with acetyl chloride in the presence of triethylamine did not give positive results.

Scheme 2



In an attempt to produce 1-(3-methylureido)-2-methylthiobenzimidazole (VIb) by the reaction of compound IV with methyl isocyanate, only the original compound IV was isolated from the reaction mixture. Therefore, for the synthesis of the compounds VIa,b we developed a different method, using the approach proposed in [3] for the production of 1-aminobenzimidazoline-2-thiol, i.e., they were produced by cyclization of 1-substituted 2-(2-aminophenyl)hydrazines with potassium ethylxanthogenate, followed by S-methylation of the 1-acylaminobenzimidazoline-2-thiols Xa,b formed with iodomethane. 4-Methyl-1-(2-nitrophenyl)semicarbazide VIII was produced by the reaction of methylisocyanate with 2-nitrophenylhydrazine (VII).

Scheme 3



X a R = Me. b R = NHMe

It was established that hydrolysis of the acetyl derivatives VIa and Xa does not occur during 24 h boiling in a 5% aqueous solution of sodium hydroxide, but in 5 h heating with concentrated hydrochloric acid in 2-propanol the corresponding 1-aminobenzimidazoles IV and II were obtained. Hydrolysis of compounds VIb and Xb does not occur under these conditions.

In the IR spectra of 1-aminobenzimidazoles VIa,b and Xa,b, absorption bands are observed in the regions 3296-3136 and 1680-1528 cm^{-1}, due to the stretching and deformational vibrations of the N—H bond, and the absorption band of the carbonyl group at 1712-1672 cm^{-1}. In the IR spectrum of 1-diacetylamino-2-methylthiobenzimidazole (V), absorption bands of the carbonyl group are observed at 1728 and 1699 cm^{-1}, and in the PMR spectrum of this compound there is a singlet of both methyl groups at 2.36 ppm. In the PMR spectra of the synthesized compounds VIa,b, the signal of the methylthio group is observed at 2.65 and 2.72 ppm, which agrees with the data of the previously synthesized 2-methylthiobenzimidazoles [1, 2]. The protons of the methyl group of compounds VIII, Xb, and VIb resonate in the region of 2.58-3.05 ppm in the form of a doublet.

TABLE 1. Characteristics of Compounds V, VIa,b, VIII, and Xa,b

Compound	mp °C (solvent)	IR spectrum, cm^{-1}	PMR spectrum,* δ, ppm	Yield, %
V	93...95 (EtOH)	1728 (CO), 1699 (CO	2,36 (6H, s, CH_3), 2,78 (3H, s, SCH_3), 7,28...7,41 (4H, m, ArH)	63
VIa	198,5...199,5 (Chloroform)	3168 (NH), 1712 (CO), 1648...1680 (NH)	2,10 (3H, s, CH_3), 2,65 (3H, s, SCH_3), 7,11...7,62 (4H, m, ArH)	53 (A) 86 (B)
VIb	251,5...252 (EtOAc)	3296 (NH), 1700 (CO), 1528 (NH)	2,72 (3H, s, CH_3), 3,05 (3H, d, J = 6 Hz, CH_3), 6,03 (1H, s, NH), 7,15...7,25 (2H, m, ArH)	53
VIII	203,5...204,5 (MeOH)	3320 (NH), 1699 (CO), 1640 (CO)	2,68 (3H, d, J = 4 Hz, CH_3), 6,87 (1H, d. t, J = 7 and 2 Hz, ArH), 7,35 (1H, d. t, J = 8 and 2 Hz, ArH), 7,50 (1H, d. d, J = 8 and 7 Hz, ArH), 7,82 (1H, d. d, J = 8 and 2 Hz, ArH), 9,02 (1H, s, NH)	65
Xa	283...284 (EtOH)	3264 (NH), 1688 (CO)	2,10 (3H, s, CH_3), 7,17...7,22 (4H, m, ArH), 11,04 (1H, s, NH)	65
Xb	240...242 (PrOH)	3312, 3136 (NH), 1672 (CO), 1580 (NH)	2,58 (3H, d, J = 6 Hz, CH_3), 7,16 (4H, s, ArH), 9,10 (1H, s, NH)	37

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*The PMR spectra of compounds VIa and Xa,b were obtained in $(CD_3)_2SO$, V and VIb in $CDCl_3$, and VIII in $(CD_3)_2CO$.

TABLE 2. Data of Elementary Analysis of the Compounds Synthesized

Compound	Gross formula	Found, % / calculated, %		
		C	H	N
V	$C_{12}H_{13}N_3O_2S$	54,74 54,70	4,94 4,97	15,91 15,95
VIa	$C_{10}H_{11}N_3OS$	54,29 53,98	5,01 4,91	18,99 18,73
VIb	$C_{10}H_{12}N_4OS$	50,49 50,83	5,21 5,12	23,79 23,71
VIII	$C_8H_{10}N_4O_3$	46,54 46,22	4,95 4,75	26,73 26,70
Xa	$C_9H_9N_3OS$	52,51 52,16	4,66 4,38	20,05 20,27
Xb	$C_9H_{10}N_4OS$	48,47 48,63	4,44 4,54	25,09 25,21

EXPERIMENTAL

The IR spectra were recorded in liquid petrolatum on a Specord M-80 instrument. The PMR spectra were obtained on a Tesla BS-587 A spectrometer (80 MHz), with internal standard TMS. The course of the reaction and the purity of the compounds obtained were monitored by thin-layer chromatography on Silufol UV-254 plates, developed with UV light and iodine vapors.

The data of elementary analysis of the compounds V, VIa,b, VIII, and Xa,b for C, H, and N correspond to the calculated values.

1-Aminobenzimidazoline-2-thione (II). A. A large excess of hydrogen sulfide was passed through a solution of 8.2 g (200 mmoles) of sodium hydroxide in 20 ml of water for 2 h. Then 15.9 g (75 mmoles) of compound Ia [5] was added, and the reaction mixture was brought to boiling. After the mixture was allowed to cool to room temperature, it was acidified with dilute (1:1) acetic acid to pH 6; the precipitate was filtered off, washed with water, and recrystallized, and 3.8 g (31%) of compound II was obtained. The filtrate was acidified with conc. HCl to pH 1; the crystals that precipitated were filtered off and washed with water. After purification by dissolving in an aqueous solution of sodium bicarbonate, filtration, and acidification with conc. HCl, 2.2 g (15%) of benzimidazole-2-sulfonic acid (III), mp 368-369°C (lit. mp 365-368°C [6]), was obtained. The structure of this compound was also confirmed by the identity of the IR spectra and the absence of depression of the melting point of a mixed sample.

B. An excess of hydrogen sulfide was passed through a solution of 0.32 g (14 mmoles) of sodium hydroxide in 15 ml of water for 2 h, then 0.4 g (2.4 mmoles) of compound Ib [7] and 5 ml of 2-propanol were added, and the mixture was boiled for 24 h. 2-Propanol was distilled off, and the residue was acidified with dilute (1:1) acetic acid to pH 6; the precipitate was filtered off, washed with water, recrystallized, and 0.1 g (39%) of compound II was obtained.

C. We added 3 ml of conc. HCl to a solution of 0.3 g (1.4 mmoles) of compound IXa in 25 ml of 2-propanol and boiled for 4 h, then cooled; the precipitate was filtered off, washed with water, and recrystallized, yielding 0.15 g (63%) of compound II. In all cases mp 212-213°C (from ethanol) (lit. mp 212-213°C [3]).

1-Amino-2-methylthiobenzimidazole (IV). It was synthesized analogously to compound II according to method C from the compound IVa. Yield of compound IV 73%, mp 209-210°C (lit. mp 208-209°C [3]).

1-Diacetylamino-2-methylthiobenzimidazole (V). A solution of 0.5 g (2.8 mmoles) of compound IV in 1 ml of acetic anhydride was boiled for 1 h. Then acetic anhydride was distilled off under vacuum, and the residue was diluted with water; the precipitate was filtered off, recrystallized, and compound V was obtained (Table 1).

1-Acetylamino-2-methylthiobenzimidazole (VIa). A. A. A mixture of 0.5 g (2.8 mmoles) of compound IV and 1.2 ml (20.3 mmoles) of glacial acetic acid in 6 g PFK was heated with mixing for 2.5 h at 130°C. After cooling the reaction mixture was diluted with water and neutralized with aqueous ammonia; the precipitate was filtered off, washed with water, and recrystallized, yielding compound VIa (Table 1).

B. A 0.7 g portion of iodomethane (23 mmoles) was added with mixing to a solution of 1.9 g (20 mmoles) of compound Xa and 0.41 g (21 mmoles) of sodium hydroxide in 40 ml of a mixture of 2-propanol with water (1:1), cooled to 15°C, and the mixture was boiled with a reflux condenser for 1 h. Then it was cooled; the crystalline precipitate was filtered off, washed with water, and recrystallized, yielding compound VIa.

2-Methylthio-1-(3-methylureido)benzimidazole (VIb). It was synthesized from compound Xb analogously to compound VIa according to procedure B, giving compound VIb (Table 1).

4-Methyl-1-(2-nitrophenyl)semicarbazide (VIII). A mixture of 1 g (6.5 mmoles) of compound VII, 0.38 g (6.5 mmoles) of methyl isocyanate, 7.5 ml of anhydrous acetonitrile, and 3.25 ml of anhydrous DMFA was exposed at room temperature for 24 h, then poured out into water; the precipitate was filtered off, washed with water, recrystallized, and compound VIII was obtained (Table 1).

1-Acetylaminobenzimidazoline 2-thione (Xa). A solution of 0.4 g (2.4 mmoles) of compound IX [8] and 0.46 g of potassium ethylxanthogenate (2.9 mmoles) in 5 ml of water and 10 ml of 2-propanol was boiled for 3 h. Then the 2-propanol was distilled off and the residue was acidified with dilute (1:1) acetic acid to pH 6; the precipitate was filtered off, washed with water, and recrystallized, yielding compound Xa (Table 1).

1-(3-Methylureido)benzimidazoline-2-thione (Xb). Sodium dithionite was added in portions with mixing at room temperature to a violet solution of 5.2 g (25 mmoles) of compound VIII in 20 ml of 25% aqueous ammonia and 50 ml of 2-propanol until a yellow suspension was obtained. The crystals were filtered off, and 5.1 (32 mmoles) of potassium ethylxanthogenate was added to the filtrate. After 30 h of boiling, the solution was concentrated to 1/3 volume and acidified with dilute (1:1) acetic acid to pH 6. The precipitate was filtered off, washed with water, and recrystallized, yielding compound Xb (Table 1).

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