SYNTHESIS AND PROPERTIES OF SOME 5-NITROBENZIMIDAZOLE 2-ALKYLTHIOETHERS

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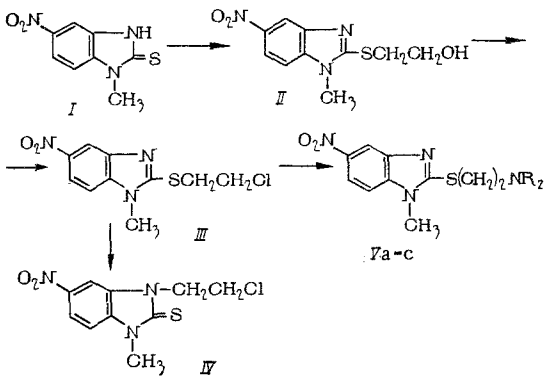
Among the numerous benzimidazole derivatives, di- and trisubstituted benzimidazoles are creating great interest; among these, substances have been found with high pharmacological activity [1, 2]. Many of them belong to the derivatives of 2-benzimidazolethione and have dialkylaminoalkyl groups and substituents in the benzene ring in their structure [3, 4].

With the objective of seeking biologically active compounds, we have synthesized a number of dialkylaminoethyl derivatives of 1-methyl-5-nitro-2-benzimidazolethione and have studied their pharmacological activity. 1-Methyl-2-(β-hydroxyethylmercapto)-5-nitrobenzimidazole (II) was synthesized by condensation of 1-methyl-5-nitro-2-benzimidazolethione (I) with ethylene chlorohydrin in alkaline medium. Replacement of the hydroxy group by chlorine in II by use of thionyl chloride leads to 1-methyl-2-(β-chloroethylmercapto)-5-nitrobenzimidazole (III). On heating a little above its m.p., III undergoes an intramolecular rearrangement to form 1-methyl-3-(β-chloroethyl)-5-nitrobenzimidazole-3-thione (IV). A thermal rearrangement of this type has been noted in the literature for alkoxy and alkylathio derivatives of benzimidazole [5, 6].



The presence of a nitro group in the 5-position of the benzimidazole ring, on one hand, and of a chlorine atom in the alkyl chain, on the other, apparently facilitates breaking of the S-CH_2 bond and assists the occurrence of the rearrangement under milder conditions (a few minutes at 160°). For alkylthiobenzimidazoles, a similar rearrangement takes place at 200° over a period of a few hours [5]. The structure of compounds III and IV was confirmed by spectral evidence. The IR spectrum of compound III differs from that of compound IV in the multiple bond absorption region. Compound III has a series of bands at 1620, 1602, 1470, and 1440 cm^{-1}, which are probably characteristic of the vibrations of C=N and C=C bonds; in IV, absorption in this region is observed at 1613, 1493, and 1429 cm^{-1}. The UV spectrum of III differs appreciably from that of IV. For comparison, we took the spectrum of I as a model. The UV spectra of I and IV almost fully coincided in the intensity and position of the absorption maxima [for I, λ_{max} is 276-280 nm (log ε = 4.38), 355-365 nm log ε = 4.01); for IV, λ_{max} = 278-280 nm (log ε = 4.36), 355-365 nm (log ε = 4.00)], and

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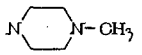
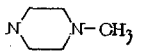
TABLE 1. 1-Methyl-2-alkylmercapto-5-nitrobenzimidazoles

Compound	NR_2	Yield in (%)	Melting point (in deg)
II	—	66	157—8
III	—	80	150—1
Va	$N(C_2H_5)_2$	—	53—4
Va·HCl	$N(C_2H_5)_2$	51	222—3
Vb		82	145—6
Vb·HCl		—	251—2
Vc		80	127,5—8,5
Vc·2HCl		—	258—60 (decomp.)

Compound	Found (in %)			Empirical formula	Calculated (in %)		
	N	S	Cl		N	S	Cl
II	16,65	12,68	—	$C_{10}H_{11}N_3O_3N$	16,60	12,65	—
III	15,38	11,97	13,02	$C_{10}H_{10}ClN_3O_2S$	15,47	11,79	13,07
Va	—	10,48	—	$C_{14}H_{20}N_4O_2S$	—	10,38	—
Va·HCl	15,92	9,26	10,28	$C_{14}H_{20}N_4O_2S·HCl$	16,24	9,28	10,28
Vb	17,30	10,22	—	$C_{14}H_{18}N_4O_3S$	17,39	9,94	
Vb·HCl	15,25	8,96	9,85	$C_{14}H_{18}N_4O_3S·HCl$	15,58	8,94	9,90
Vc	20,84	9,80	—	$C_{15}H_{21}N_5O_2S$	20,89	9,55	—
Vc·2HCl	15,92	7,63	16,15	$C_{15}H_{21}N_5O_2S·2HCl·H_2O$	16,42	7,51	16,65

Note. Compounds II and Vb were crystallized from alcohol; III, from acetone; Va, Vb·HCl, and Vc·2HCl, from aqueous alcohol; Va·HCl, from absolute alcohol; and Vc, from water.

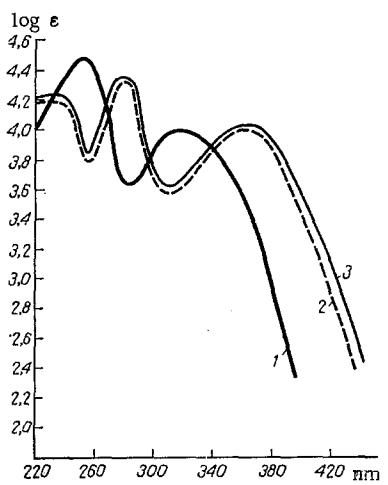


Fig. 1. UV spectra of III (1); IV (2); and I (3).

at the same time they differ from the spectrum of III [λ_{max} 250-254 nm (log ε = 4.45); 312-320 mm (log ε = 4.00)] (see Fig. 1). These data indicate a close similarity in the electronic spectra of these substances.

For pharmacological tests, we synthesized the dialkylaminoalkyl thioethers Va-c by reaction of III with a large excess of the appropriate amines, with heating for 20 h. The compounds obtained were isolated in the form of the bases and the hydrochlorides. Data on the compounds synthesized are given in Table 1. In distinction from III, the aminoalkyl derivatives, V, do not rearrange on heating above 200°. On heating IV with excess of amines, only the starting materials were isolated from the reaction mixture.

Pharmacological study of the compounds synthesized was performed in the laboratory of nerve system pharmacology by N. I. Pryanishnikova. The following were investigated: overall action, toxicity, neurotropic activity, effect on phenamine hyperactivity, potentiation of narcotic action, muscular relaxing action, and anesthetizing activity. It was noted that the 1-methyl-2-(β-dialkylaminoethylmercapto)-5-nitrobenzimidazoles (Va-c) have a high toxicity: their LD_{50} in intraperitoneal use is 170 to 270 mg/kg. Compounds Va and Vb display some neurotropic properties at a dose of 30-50 mg/kg: they depress the motor activity of mice, they reduce the hyperactivity caused by phenamine

(Va, by a factor of 4-6), and they increase the length of thiopental sleep 1.5-2 fold. Compound Vc in a dose of 40-50 mg/kg has an antagonistic effect with respect to phenamine and, at the same time, causes a small increase in the motor activity of mice.

EXPERIMENTAL

The UV spectra of the compounds were taken on an SF-4 spectrophotometer in alcohol at a concentration of 10^{-4} to 10^{-5} mole/liter, d = 1 cm.

1-Methyl-2-(β-hydroxyethylmercapto)-5-nitrobenzimidazole (II). Compound I (3.5 g) was dissolved in an aqueous alkali solution (from 0.7 g of NaOH and 20 ml of water), and to this solution at 40-50° was added 2 g of ethylene chlorohydrin, dropwise; the solution was stirred for 3 h. The precipitate of II which fell was separated, washed with water, and dried.

1-Methyl-2-(β-chloroethylmercapto)-5-nitrobenzimidazole (III). Compound II (2 g) was added in small portions to 8 ml of thionyl chloride, the mixture was heated on a water bath for 10 min, and the excess thionyl chloride was distilled off under vacuum. The residue was treated with a 10% sodium bicarbonate solution. The precipitate of III was filtered off, washed with water, and dried.

1-Methyl-3-(β-chloroethyl)-5-nitrobenzimidazole-2 (IV). Compound III (1 g) was melted and kept at 160-170° for 30 min. The melt was cooled and recrystallized from dimethylformamide or acetone. There was obtained 0.83 g (98%) of product, m.p. 192-193°.

Found %: Cl 12.95; N 15.34; S 11.89. $C_{10}H_{10}ClN_3O_2S$. Calculated %: Cl 13.07; N 15.49; S 11.78.

1-Methyl-2-(β-dialkylaminoethylmercapto)-5-nitrobenzimidazoles (V). A mixture of 2 g of III and 15 ml of diethylamine was heated in a sealed ampoule for 14 h on a boiling water bath; the mixture was cooled, the excess diethylamine was removed, and the residue was treated with water. The mixture was extracted with ether, the ether solution was dried with magnesium sulfate, and it was mixed with an ether solution of hydrogen chloride. The precipitate of Va hydrochloride which separated was filtered off and was washed with a small amount of absolute alcohol. The base Va was liberated by the action of ammonia solution on an aqueous solution of the hydrochloride. Compounds Vb and Vc were prepared by heating III with a 10-15-fold amount of the appropriate amine for 20 h on a water bath, and treatment of the reaction mixture with an excess of water. The hydrochlorides were prepared by mixing warm alcoholic solutions of the bases with an alcoholic hydrogen chloride solution.

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