Benzothiazole compounds. X. Mannich reaction of 2-mercaptobenzothiazole with primary amines

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A number of derivatives was prepared by Mannich reaction of 2-mercaptobenzothiazole (2-MBT) with primary amines and formaldehyde. The relation between the basicity of amines and the formation of mono- and bisderivatives has been established. The electronic spectra of the products obtained prove the substitution in the position 3 in the molecule of 2-MBT.

Приготовлены производные 2-меркаптобензтиазола реакцией Манниха с первичными аминами и формальдегидом. Обнаружена связь между основностью аминов и образованием моно- и бис-производных. Электронные спектры продуктов подтверждают замещение 2-меркаптобензтиазола в положении 3.

The present data on the Mannich reaction of 2-mercaptobenzothiazole with primary amines do not offer a satisfactory explanation why with some amines monoderivatives and with the others bisderivatives are obtained (Scheme 1). For example, aniline in ethanol at 30°C gives monoderivative, while cyclohexylamine in acetone at 0°C yields a bisderivative [1]. In order to solve this problem, series of experiments with different amines (Table 1) was carried out under identical conditions, *i.e.* at the same temperature, the same equimolar concentration of the starting compounds, and using the same solvent.

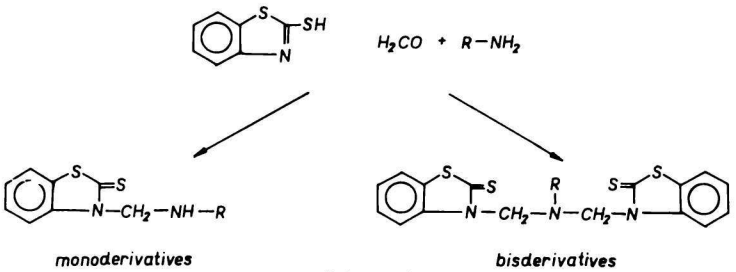
We have found that under these conditions the amines with pK_B around 3—5 (cyclohexylamine, allylamine, benzylamine) afforded only bisderivatives while those with pK_B around 9—14 (aniline, *p*-toluidine, *o*-nitroaniline) gave exclusively monoderivatives. Another group of amines (2-ethylhexylamine, 2-methoxyethylamine, 3-methoxypropylamine, 3-isopropoxypropylamine) with pK_B 3—5 gave, in accordance with the observed rule, only bisderivatives.

Furthermore, cyclohexylamine was tested under conditions described in [1] for the reaction with aniline and, to the contrary, aniline was treated under conditions described for the reaction with cyclohexylamine [1]. It has been found that under these reversed conditions the reactions did not proceed.

In further experiment we tried to change the order of addition of the individual reactants and the solvent in comparison to procedure described in [1]. The modified order: 2-MBT, solvent, cyclohexylamine, formaldehyde did not influence the course of the reaction, the product being always a bisderivative.

Some studies [1, 2] characterize monoderivatives formed on the basis of their identity with the products of the reaction of corresponding amines with 3-hydroxymethyl-2-benzothiazolinethione. Following the procedure described in [1] we have carried out reactions with 3-hydroxymethyl-2-benzothiazolinethione and the amines listed in Table 1. It has been

found that amines with pK_B 9—14 afforded monoderivatives, identical with those prepared by Mannich reaction while amines with pK_B 3—5 did not react under the same conditions. The latter observation is in contradiction with the data in [1] where the reaction with cyclohexylamine is claimed to yield a crystalline compound with m.p. 157—158°C.



Scheme 1

Apparently, this compound is believed to be a monoderivative since the same paper [1] gives for the m.p. of the bisderivative the value of 164—167°C. The assumption that the former product is a monoderivative is supported by [3] where the m.p. value given for monoderivative of cyclohexylamine is 157—158°C. A compound with approximately the same m.p. (156—158 °C) has been obtained when we dissolved cyclohexyl-bis[(2-benzothiazolinethione-3-yl)methyl]amine (*IV*) in benzene and heated the solution to 35—37 °C. Elemental analysis indicated the formation of an addition product of compound (*IV*) with benzene.

Comparison of the yields obtained with cyclohexylamine and aniline under conditions described in [1] and those obtained with our standard procedure showed the conditions described in [1] to be more favourable.

Determination of the site of substitution in the thiazole ring of 2-MBT was performed by measuring the electronic spectra of the prepared derivatives. The corresponding spectral data are given in Table 2. All the investigated spectra exhibited two intensive absorption bands in the ultraviolet region with maxima at 240 and 320 nm. A somewhat different spectrum was obtained with compound *III* where the lower-wavelength maximum was shifted to 230 nm and additional absorption maxima at 278 and 403 nm were observed. In all cases the absorption spectra resembled the absorption spectrum of 2-MBT. The position of the absorption maxima in the spectra of the investigated compounds proves that the chromophore group is located in thiazole parts of their molecules. The obtained values were compared with the spectral values of compounds with dithiocarbamate structure N—(S=C)—S [4] and with the more recent data [3, 5] only for monoderivatives where 2-MBT was substituted in the position 3. The correlation of the spectral data proves that in both types of compounds the molecule of 2-MBT is substituted in the position 3.

Experimental

2-Mercaptobenzothiazole for the experiments was purified as described previously [6].

Absorption spectra in the ultraviolet and visible region were measured using a registration SF-8 spectrophotometer (LOMO, Leningrad). For u.v. spectroscopy ethanol (Lachema, Brno) was used as the solvent which at the same time served as the reference standard.

Table 1

Properties of the synthesized compounds

No.	R	pK_B of amine 25°C	Mono/bis	Formula	*M*	Calculated/found				Yield %	M.p. °C
						% C	% H	% N	% S		
I	CH_3—C_6H_4	8.93	mono	$C_{15}H_{14}N_2S_2$	286.41	62.90 63.35	4.92 5.06	9.77 9.70	22.39 21.96	85	112—114
II	C_6H_5	9.42	mono	$C_{14}H_{12}N_2S_2$	272.38	61.73 61.47	4.44 4.44	10.28 10.24	23.54 23.59	94	105—107
III	NO_2--C_6H_4	14.28	mo	$C_{14}H_{11}N_3S_2$	317.38	52.98 52.97	3.49 3.56	13.23 13.40	20.20 19.75	40	197—199
IV	C_6H_{12}	3.36	bis	$C_{22}H_{23}N_3S_4$	457.70	57.73 57.77	5.08 5.24	9.18 9.40	28.02 27.94	60	164—166
V	CH_2=CH−CH_2	4.20	bis	$C_{19}H_{17}N_3S_4$	415.62	54.90 55.26	4.12 4.18	10.11 9.78	30.85 30.83	53	158—160
VI	C_6H_5—CH_2	4.62	bis	$C_{23}H_{19}N_3S_4$	465.68	59.32 59.29	4.11 4.35	9.02 9.17	27.54 27.60	80	169—171
VII	$CH_3(CH_2)_3CH(C_2H_5)CH_2$	—	bis	$C_{24}H_{29}N_3S_4$	487.77	59.09 59.15	5.99 6.03	8.61 8.80	26.29 25.85	50	89— 91
VIII	$CH_3O(CH_2)_2$	—	bis	$C_{19}H_{19}N_3OS_4$	433.64	52.62 53.07	4.41 4.22	9.69 9.87	29.57 29.30	48	135—137
IX	$CH_3O(CH_2)_3$	—	bis	$C_{20}H_{21}N_3OS_4$	447.66	53.66 53.60	4.72 4.89	9.38 9.63	28.65 28.60	40	114—116
X	$(CH_3)_2CHO(CH_2)_3$	—	bis	$C_{22}H_{25}N_3OS_4$	475.72	55.54 55.68	5.29 5.30	8.83 8.83	26.96 27.00	55	137—139

Table 2

Absorption data of 2-MBT and compounds *I*—*X* in ethanol

Compound	2-MBT	*I*	*II*	*III*	*IV*	*V*	*VI*	*VII*	*VIII*	*IX*	*X*
λ_{max}	238	238	238	232.5	238.5	238.5	239	238.5	238.5	238.5	238.5
	323.5	323	323	278	323	321	323	323	321	321.5	321.5
				326.5							
				403							
log *a*	4.15	4.40	4.37	4.48	4.49	4.44	4.47	4.49	4.49	4.53	4.50
	4.42	4.44	4.42	3.85	4.72	4.68	4.72	4.70	4.71	4.74	4.71
				4.32							
				3.74							

Standard procedure for preparation of derivatives

Formaldehyde (30% solution; 0.05 mole) was added dropwise to amine (0.05 mole) under stirring at 25°C. Immediately after the addition of formaldehyde, acetone (40 ml) was gradually introduced so that the temperature of the reaction mixture did not surpass 25°C. Then after 3 min at the same temperature 2-MBT (0.05 mole) was added. After several minutes the product started to precipitate from the clear solution. After standing for 30 min the product was filtered, washed on the filter with acetone (10 ml) and dried at room temperature.

Monoderivatives I—III

Formaldehyde (5 ml of 30% solution; 0.05 mole) was added dropwise to *p*-toluidine (5.3 g; 0.05 mole) under stirring at 30°C. After formation of a solid white precipitate acetone (40 ml) was added. After vigorous mixing 2-MBT (8.2 g; 0.05 mole) was added in small amounts under continuous stirring. After 10 min the mixture was carefully heated to 50—55°C whereas obtained the yellow solution. After standing for 10 min the solution was cooled to 0°C and diluted with water (60 ml). After several minutes yellowish needles of 3-(*p*-toluidinemethyl)-2-benzothiazolinethione (*I*) crystallized from the solution. After 10 min the crystals were filtered and washed with ethanol. The product was purified by crystallization from ethanol.

The same procedure was used for preparation of 3-(anilinemethyl)-2-benzothiazolinethione (*II*) and 3-(*o*-nitroanilinemethyl)-2-benzothiazolinethione (*III*).

Bisderivatives IV—X

Cyclohexylamine (5 g; 0.05 mole) was cooled to 0°C and 30% formaldehyde (5 ml; 0.05 mole) was added under stirring. Then the mixture was diluted with acetone (40 ml) and 2-MBT (8.2 g; 0.05 mole) was added in small portions under continuous stirring. After several minutes the product, cyclohexyl-bis[(2-benzothiazolinethione-3-yl)methyl]amine (*IV*), started to precipitate from the clear solution. After 30 min the product was isolated by filtration and washed with acetone.

The same procedure was used for preparation of allyl-bis[(2-benzothiazolinethione-3-yl)-methyl]amine (*V*), benzyl-bis[(2-benzothiazolinethione-3-yl)methyl]amine (*VI*), 2-ethylhexyl-bis[(2-benzothiazolinethione-3-yl)methyl]amine (*VII*), 2-methoxyethyl-bis[(2-benzothiazolinethione-3-yl)methyl]amine (*VIII*), 3-methoxypropyl-bis[(2-benzothiazolinethione-3-yl)methyl]amine (*IX*),

and 3-isopropoxypropyl-bis[(2-benzothiazolinethione-3-yl)methyl]amine (*X*). These products precipitated from the solution in the powdered form.

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