STUDIES IN THE IMIDAZOLE SERIES

LVII.* SYNTHESIS OF 6,7-DIMETHYLBENZIMIDAZO[2,1-b]-THIAZOLID-3-ONE AND ITS DERIVATIVES WITH RESPECT TO THE METHYLENE GROUP

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6,7-Dimethylbenzimidazo[2,1-b]thiazolid-3-one was synthesized, and its reactions with aldehydes, isatin, nitroso compounds, and arene diazonium salts were studied. As a result, ylidene and imino derivatives and azo coupling products were obtained. According to the IR spectra, the azo coupling products have 6,7-dimethylbenzimidazo[2,1-b]thiazolidine-2,3-dione 2-arylhydrazone structures.

Various derivatives with respect to the methylene group of benzimidazo[2,1-b]thiazolid-3-one [1-10] and 6(7)-aminobenzimidazo[2,1-b]thiazolid-3-one [11], which are of interest as dyes and biologically active substances, are described in the literature. However, 6,7-dialkylbenzimidazothiazolid-3-ones and their derivatives are unknown.

As a further development of the research in [12, 13], we have accomplished the synthesis of 6,7-dimethyl- and 2,6,7-trimethylbenzimidazo[2,1-b]thiazolid-3-ones (VI and VII) and have studied the reactions of the former at the methylene group. The starting materials were 5,6-dimethyl-2-benzimidazolylmercaptoacetic (II) [14, 15] and α-(5,6-dimethyl-2-benzimidazolyl)mercaptopropionic (III) [15] acids, which we prepared by a simpler method – by heating 2-mercapto-5,6-dimethylbenzimidazole (I) [14] with chloro(bromo)acetic and α-bromopropionic acids in glacial acetic acid. An attempt to obtain acid II by heating I with bromoacetic acid in methanol yielded primarily its methyl ester (IV), the structure of which was confirmed by alternative synthesis from I and methyl bromoacetate.

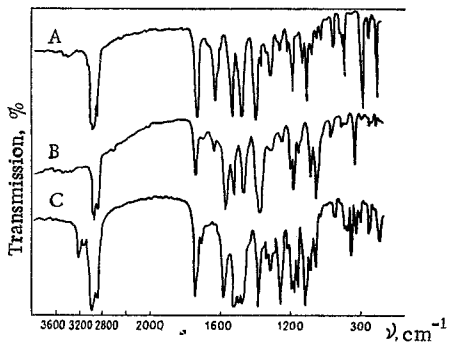

Fig. 1. IR spectra: A) 2-benzylidene-6,7-dimethylbenzimidazo[2,1-b]thiazolid-3-one (VIII); B) 2-(p-dimethylaminophenylimino)-6,7-dimethylbenzimidazo[2,1-b]thiazolid-3-one (XVII); C) 2-(p-methoxyphenylhydrazone) of 6,7-dimethylbenzimidazo[2,1-b]thiazolidine-2,3-dione (XVIII).

The formation of ester IV by the reaction of I with bromoacetic acid in methanol is explained by the ease of esterification of acid II in the presence of hydrogen bromide. A similar course for the reaction was previously observed in the reaction of 8-mercaptopurine [16] and 2-mercaptoimidazole [17-19] derivatives with chloro- and bromoacetic acids in alcohols.

Acids II and III, on refluxing in acetic anhydride in the absence of pyridine, which is recommended in [2,3,5,9, 10] for the synthesis of benzimidazo[2,1-b]thiazolid-3-one, are readily cyclized to lactams VI and VII. Under similar

*See [1] for communication LVI.

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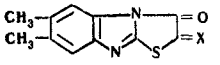
TABLE 1. 6,7-Dimethylbenzimidazo[2,1-b]thiazolid-3-one 

Compound	X	mp (dec.)[a]	Empirical formula	Found %				Calculated %				Yield %	IR spectrum[b] ν_{CO}, cm^{-1}
				C	H	N	S	C	H	N	S		
VIII	C_6H_5CH	254—255	$C_{18}H_{14}N_2OS$	69,90	4,68	9,42	10,86	70,56	4,61	9,14	10,47	80	1725
IX	p-$CH_3OC_6H_4CH$	238—239	$C_{19}H_{16}N_2O_2S$	67,58	4,60	8,41	9,52	67,83	4,79	8,33	9,53	49	1713
X	p-$(CH_3)_2CHC_6H_4CH$	225—226	$C_{21}H_{20}N_2OS$	72,53	5,65	8,00	9,51	72,38	5,79	8,04	9,20	80	1725
XI	o-$O_2NC_6H_4CH$	246—247	$C_{18}H_{13}N_3O_3S$	61,89	3,84	12,28	9,50	61,52	3,73	11,96	9,13	70	1728
XII	m-$O_2NC_6H_4CH$	259—260	$C_{18}H_{13}N_3O_3S$	61,58	3,68	11,97	9,41	62,52	3,73	11,96	9,13	72	1730
XIII	p-$O_2NC_6H_4CH$	318—319	$C_{18}H_{13}N_3O_3S$	61,48	3,84	11,85	9,18	62,52	3,73	11,96	9,13	60	1726
XIV	2-Furfurylidene	260—261	$C_{16}H_{12}N_2O_2S$	64,67	4,00	9,60	10,53	64,85	4,08	9,46	10,82	76	1725
XV	5-Nitro-2-furfurylidene	274—276	$C_{16}H_{11}N_3O_4S$	56,03	2,98	12,91	9,18	56,30	3,25	12,31	9,39	67	1728
XVI	3-Isatinylidene	344—345	$C_{19}H_{13}N_3O_2S$	65,95	3,98	11,78	9,47	65,69	3,77	12,09	9,23	92	1710 1625 w
XVII	p-$(CH_3)_2NC_6H_4N$	300—302	$C_{19}H_{18}N_4OS$	65,37	4,91	15,77	9,38	65,12	5,18	15,99	9,15	39	1735
XVIII	p-$CH_3OC_6H_4NHN$	228—229	$C_{18}H_{16}N_4O_2S$	61,41	4,64	16,11	9,36	61,34	4,58	15,90	9,10	24	1732[c]
XIX	p-BrC_6H_4NHN	262—263	$C_{17}H_{13}BrN_4OS$[d]	50,95	3,53	14,04	8,26	50,88	3,27	13,96	7,99	56	1740[e]

[a]The compounds were purified for analysis by crystallization: from n-propanol (IX), glacial acetic acid (VIII, X-XII, XIV-XVI), dioxane (XVIII), and dimethylformamide (XIII and XIX), and by reprecipitation by the addition of ethanol to dichloroethane–chloroform solutions (1 : 1) (XVII).

[b]The IR spectra of mineral oil suspensions were recorded with a UR-10 spectrometer.

[c]IR spectrum: 3190 cm^{-1} (ν_{NH}).

[d]Found %: Br 20.30. Calculated %: Br 19.91.

[e]IR spectrum: 3180 cm^{-1} (ν_{NH}).

conditions, ester IV, like esters of imidazole-2-mercaptoacetic acids [12], forms only an N-acetyl derivative (V).

Lactam VI, which has an active methylene group between the sulfur and carbonyl group, readily reacts with aldehydes, isatin, nitroso compounds, and arenediazonium borofluorides to form ylidene (VIII-XVI, Table 1) and imino derivatives (XVII), as well as azo coupling products (XVIII) and XIX). Lactam VII, despite the presence of a methylidyne group, does not react with borofluorides.

The structures of the compounds (VI-XIX) that we synthesized were confirmed by their IR spectra (Fig. 1),* in which one observes the bands of the valence vibrations of the CO group. It is interesting to note that the azo compound structure was assigned [9-11] to the products of the azo coupling of benzimidazo[2,1-b]thiazolid-3-one with diazonium salts, while the products that we obtained (XVIII and XIX) and the products of the azo coupling of imidazo[2,1-b]thiazolid-3-ones [13] are, judging from their IR spectra (from the presence of an NH group absorption band at 3180-3190 cm^{-1}), the 2-arylhydrazones of 6,7-dimethylbenzimidazo[2,1-b]thiazolidine-2,3-dione.

EXPERIMENTAL

5,6-Dimethyl-2-benzimidazolylmercaptoacetic Acid (II). Chloroacetic acid [1.14 g (0.011 mole)] or bromoacetic acid [1.53 g (0.011 mole)] was added to a solution of 1.78 g (0.01 mole) of I [14] in 25 ml of acetic acid, the mixture was refluxed for 10-12 min, and 1.63 g (0.012 mole) of sodium acetate trihydrate was added to the hot solution. The mixture was then poured into water, and the precipitate was filtered to give 2.2 g (93%) of a product with mp 208-209° (decomp., from ethanol) (mp 208-209° [14], mp 207-208° [15]).

α-(5,6-Dimethyl-2-benzimidazolyl)mercaptopropionic Acid (III). This was similarly obtained in 86% yield by heating I with α-bromopropionic acid and had mp 208-209° (from acetic acid) (mp 208-210° [15]).

Methyl 5,6-Dimethyl-2-benzimidazolylmercaptoacetic Acid (IV). A. A mixture of 1.78 g (0.01 mole) of I and 1.39 g (0.01 mole) of bromoacetic acid in 15 ml of anhydrous methanol was refluxed for 1 h, cooled, poured into water, and neutralized with sodium bicarbonate solution. The precipitate was filtered and washed with water to give 2.25 g (90%) of IV with mp 111-112° (from CCl_4). IR spectrum: 1740 cm^{-1} (CO). Found %: C 57.28; H 5.66; N 11.08; S 12.77. $C_{12}H_{14}N_2O_2S$. Calculated %: C 57.57; H 5.64; N 11.19; S 12.81. Acidification of the filtrate with acetic acid gave 0.2 g (8.4%) of II with mp 208-209° (decomp., from ethanol).

B. A solution of 1.78 g (0.01 mole) of I and 1.55 g (0.01 mole) of methyl bromoacetate in 20 ml of anhydrous methanol was refluxed for 1 h, the solvent was removed by vacuum distillation, and the residue was triturated with ethyl acetate. The resulting crystals were filtered and washed with ethyl acetate and ether to give 3.21 g (97%) of the hydrobromide of IV with mp 174-174.5° (reprecipitation by ether from methanol). Found %: Br 24.56. $C_{12}H_{14}N_2O_2S \cdot HBr$. Calculated %: Br 24.13. Neutralization of the hydrobromide with aqueous sodium bicarbonate gave base IV with mp 111-112°. This product did not depress the melting point of the substance obtained by method A.

Methyl 1-Acetyl-5,6-dimethyl-2-benzimidazolylmercaptoacetate (V). A solution of 0.85 g of IV in 5 ml of acetic anhydride was refluxed for 4-5 min, cooled, and 20 ml of acetone was added. The solution was poured into water, and the precipitate was filtered to give 0.95 g (60%) of a product with mp 148-148.5° [from ethanol–acetic anhydride (10:1)]. IR spectrum: 1690, 1730 cm^{-1} (CO). Found %: C 57.95; H 5.68; N 9.94; S 10.79. $C_{14}H_{16}N_2O_3S$. Calculated %: C 57.51; H 5.52; N 9.58; S 10.97.

6,7-Dimethylbenzimidazo[2,1-b]thiazolid-3-one (VI). A solution of 2.36 g of II in 6 ml of acetic anhydride was refluxed for 4-5 min and cooled. The precipitate was filtered and washed with 5 ml of anhydrous ethanol and then with ether. Evaporation of the mother liquors gave an additional quantity of this substance. The overall yield of product with mp 175-176° (decomp., from anhydrous ethanol) was 1.74-1.78 g (80-82%). IR spectrum: 1736 cm^{-1} (CO). Found %: C 60.65; H 4.75; N 12.73; S 14.95. $C_{11}H_{10}N_2OS$. Calculated %: C 60.53; H 4.62; N 12.84; S 14.69.

2,6,7-Trimethylbenzimidazo[2,1-b]thiazolid-3-one (VII). A solution of 5 g of III in 6 ml of acetic anhydride was refluxed for 7-8 min and then cooled to 0-4°. The precipitate was filtered and washed with petroleum ether and then with ligroin to give 4.58 g (99%) of a product with mp 123-124° (from ligroin). IR

*We thank Yu. N. Sheinker, V. V. Kolpakova and co-workers for recording the IR spectra and performing the microanalyses.

spectrum: 1738 cm^{-1} (CO). Found %: C 62.27; H 4.95; N 12.43; S 13.49. $C_{12}H_{12}N_2OS$. Calculated %: C 62.04; H 5.21; N 12.06; S 13.80.

Ylidene Derivatives of 6,7-Dimethylbenzimidazo[2,1-b]thiazolid-3-one (VIII-XVI). A. A 0.0105-mole sample of aldehyde and three to four drops of piperidine were added to a solution of 0.01 mole of VI in 50 ml of anhydrous ethanol. The solution was refluxed for 1-2 h and cooled. The precipitate (VIII, IX) was filtered and washed with ethanol. Evaporation of the mother liquor gave an additional amount of substance.

B. A 0.0105-mole sample of aldehyde or isatin was added to a solution of 0.01 mole of VI in 30 ml of acetic acid, and the mixture was refluxed for 20 min (XV and XVI), 30 min (XIII), or 1 h (VIII, X-XII, and XIV), after which it was worked up as described above. In the isolation of X, the reaction mass, after cooling upon completion of the reaction, was poured into water, and the precipitate was filtered. The yellow (VIII-X and XII-XIV), orange (XI), dark-brown (XV), or dark-red (XVI) crystals were only slightly soluble in ethanol and most of the other organic solvents.

2-(p-Dimethylaminophenylamino)-6,7-dimethylbenzimidazo[2,1-b]thiazolid-3-one (XVII). A 0.01-mole sample of p-nitrosodimethylaniline and five to six drops of piperidine were added to a solution of 0.01 mole of VI in 60 ml of anhydrous ethanol, and the mixture was refluxed for 2 h and cooled. The precipitate was filtered and washed with ethanol to give dark-rose needles that were soluble in chloroform and dichloroethane, slightly soluble in ethanol, and insoluble in ether and water.

6,7-Dimethylbenzimidazo[2,1-b]thiazolidine-2,3-dione 2-Arylhydrazones (XVIII and XIX). A suspension of 0.01 mole of arenediazonium borofluoride in a mixture of 50 ml of anhydrous methanol and 5 ml of acetic anhydride was added to a solution (cooled to 10-15°) of 0.01 mole of VI and 2 g of anhydrous sodium acetate in a mixture of 45 ml of acetic acid and 10 ml of acetic anhydride. The mixture was allowed to stand in a dark place at 18-20° for 18-20 h (XIX) or for 46-48 h (XVIII), and the resulting precipitate was filtered. The orange (XVIII) or light-orange (XIX) crystals were slightly soluble in most organic solvents and insoluble in water.

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