STUDIES IN THE IMIDAZOLE SERIES

XXXVI. 2-β-Oxoalkylthio- and 2-β-Oxoaralkylthiobenzimidazoles*

A. N. Krasovskii and P. M. Kochergin

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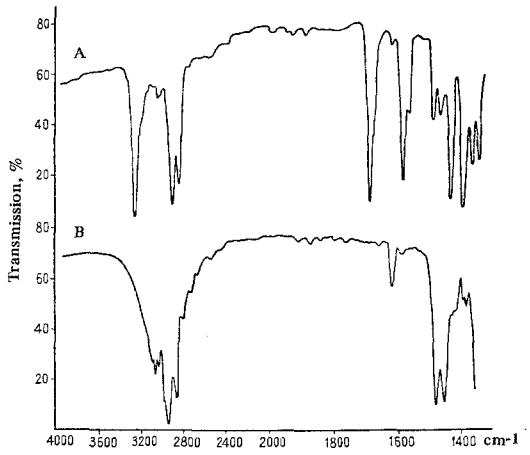
The reaction of 2-mercaptobenzimidazole and 5,6-dimethyl-2-mercaptobenzimidazole with α-halogenoketones has given a series of 2-β-oxoalkylthio- and 2-β-oxoaralkylthiobenzimidazoles—intermediate products for the synthesis of thiazolo[3,2-a]benzimidazoles. The compounds obtained exhibit the phenomenon of ring-chain tautomerism.

2-β-Oxoalkylthio- and 2-β-oxoaralkylthiobenzimidazoles have hardly been studied. Four such compounds



IR spectra: A) 2-(p-bromophenacylthio)benzimidazole (XIII); B) 2-(α-methyl-β-oxobutylthio)benzimidazole (V).

have been described, these having been obtained by the reaction of 2-mercaptobenzimidazole with phenacyl bromide, chloroacetone, 3-chloropentane-2,4-dione, and ethyl α-chloroacetoacetate [1–3]. Nevertheless, substances of this series are of interest for the study of their biological, physicochemical, and chemical properties, in particular for obtaining derivatives of the little-studied tricyclic compound thiazolo[3,2-a] benzimidazole [3–6].

We have made a more detailed study of the reaction of 2-mercaptobenzimidazole and 5,6-dimethyl-2-mercaptobenzimidazole with α-halogenoketones of the aliphatic-acyclic, aliphatic-aromatic, and aliphatic-heterocyclic series. It was found that in ethanolic solution in the presence of an equivalent amount of caustic soda or sodium alkoxide, both at the boil and in the cold, good yields are obtained of the corresponding 2-β-oxoalkylthio- and 2-β-oxoaralkylthiobenzimidazoles (I–XXIX, table). When the reaction is carried out in the absence of an alkaline agent, features of the structure of the halogenoketones and the temperature of the process are of great importance. In the case of aliphatic-aromatic halogenoketones (phenacyl bromide, etc.), even on prolonged boiling in ethanol and butanol the hydrohalides of the corresponding 2-β-oxoaralkylthiobenzimidazoles are obtained. When α-halogenoketones of the aliphatic, aliphatic-heterocyclic, and acyclic series are used, to avoid the possible cyclization of the 2-β-oxoalkylthiobenzimidazoles formed to the corresponding thiazolo[3,2-a]benzimidazoles [3,4], it is desirable not to heat the reaction mixture above 65° C. However, apparently, not all 2-β-oxoalkylthiobenzimidazoles cyclize readily on being heated to 78–80° C. When 2-mercaptobenzimidazole is boiled with bromopinacolone and 2-bromopentan-3-one in ethanol for 4 hr, the hydrobromides of the bases III and V are obtained in good yield.

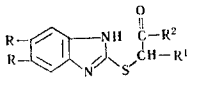
The IR spectra of the majority of the 2-β-oxoalkylthiobenzimidazoles exhibit sharp absorption bands of the CO group in the 1650–1740 cm^{-1} region. However, in the case of IV–VII, X, XI, XVII–XX, XXII, XXIV, XXV, XXVIII, and XXIX, mainly having residues of aliphatic and alicyclic ketones, these bands are absent (compare the IR spectra of V and XIII, Fig. 1) and absorption bands are found in the high-frequency region at 2700–3200 cm^{-1} (frequently in the form of ill-defined shoulders or broad bands in the region of absorption of paraffin oil) apparently due to the stretching vibrations of OH groups. This fact is probably explained by the possibility of the existence of these compounds as tautomeric forms—derivatives of 3-hydroxythiazolino-[3,2-a]benzimidazole—as in the case of benzimidazol-2-yl-thioacetaldehydes [6] and the analogous derivatives of 2-mercapto- and 4(5)-mercaptoimidazole [7, 8]. The IR spectra of the substances were recorded by E. M. Peresleni and Yu. I. Pomerantsev, to whom the authors express their deep gratitude.

EXPERIMENTAL

2-β-Oxoalkylthio- and 2-β-oxoaralkylthiobenzimidazoles (I–XXIX). a) A solution of 0.05 mole of sodium ethoxide in 50 ml of ethanol was treated with 0.05 mole of 2-mercaptobenzimidazole or 5,6-dimethyl-2-mercaptobenzimidazole [6] and then with 0.05–0.055 mole of an α-halogenoketone (for the synthesis of I, IV, VIII, XI, XVI, XXI, XXII, and XXIX the chloroketones were used, and in all the other cases the corresponding bromoketones). The mixture was stirred at 60–65° C for 1 hr and at the boiling point for 10 min (XVII—only 1 hr at 50° C) and cooled, and the precipitates (IV, VIII, XII–XV, XVII, XVIII, XXI) were filtered off and washed with water. For the isolation of VII, XIX, XX, XXII, and XXIV–XXIX, after the end of the reaction the cooled reaction mixture was poured into water and the precipitate was filtered off. Compounds II, III, and VI were extracted with chloroform after dilution of the reaction mixture with water. Compounds I and V were obtained similarly in ethanolic solution of NaOH and KOH, respectively; compounds X and XI were isolated when the

*For part XXXV, see [6].

2-β-Oxoalkylthio- and 2-β-Oxoaralkylthiobenzimidazoles



Compound	R	R¹	R²	Mp, °C (decomp.)	Empirical formula	Found, %				Calculated, %				Yield, %	Mp, °C (1*decomp.) of the picrates (hydrobromides); [hydrochlorides]
						C	H	N	S	C	H	N	S		
I	H	H	CH_3	113—114[3]	$C_{10}H_{10}N_2OS$	—	—	—	—	—	—	—	—	80	133—136, [164—166]
II	H	H	C_3H_7	166—168	$C_{12}H_{14}N_2OS \cdot HCl$[2*]	53.55	5.78	10.13	11.85	53.22	5.58	10.35	11.84	97	
III	H	H	$C(CH_3)_3$	225—226	$C_{13}H_{16}N_2OS \cdot HBr$[3*]	47.61	5.18	8.42	9.77	47.42	5.20	8.51	9.74	96—99	158—159
IV	H	CH_3	CH_3	155—155.5	$C_{11}H_{12}N_2OS$	59.73	5.49	12.51	14.60	59.97	5.49	12.72	14.56	90	236—237
V	H	CH_3	C_2H_5	108—109	$C_{12}H_{14}N_2OS$	61.52	5.86	11.99	13.56	61.51	6.02	11.96	13.68	52—87	142—143
VI	H	C_2H_5	CH_3	128—129	$C_{12}H_{14}N_2OS$	61.94	6.03	11.71	13.64	61.51	6.02	11.96	13.68	93	
VII	H	C_3H_7	CH_3	117—118	$C_{13}H_{16}N_2OS$	62.89	6.50	11.63	13.28	62.87	6.49	11.28	12.91	88	
VIII	H	$COCH_3$	CH_3	183—184[3]	$C_{12}H_{12}N_2O_2S$	—	—	—	—	—	—	—	—	84	
IX	H	H	C_4H_3S[4*]	168—169	$C_{13}H_{10}N_2OS_2$	57.12	3.93	10.21	23.03	56.91	3.67	10.21	23.37	97	(208—209)
X	H		C_5H_7O[5*]	173,5—174,5	$C_{12}H_{12}N_2OS$	61.95	5.12	12.07	13.77	62.04	5.21	12.06	13.80	39—49	188—190
XI	H		C_6H_9O[6*]	136—138	$C_{13}H_{14}N_2OS$	63.01	5.90	11.11	13.14	63.38	5.73	11.37	13.02	78	242—244
XII	H	H	C_6H_5	169—171[7*]	$C_{15}H_{12}N_2OS$	66.82	4.28	10.44	11.65	67.14	4.51	10.44	11.95	98	189.5—190.5, (213—215)
XIII	H	H	p-BrC_6H_4	187—189	$C_{15}H_{11}BrN_2OS$	51.67	3.03	7.84	9.32	51.88	3.19	8.07	9.23	95	187.5—188.5
XIV	H	H	m-$O_2NC_6H_4$	146.5—147.5	$C_{15}H_{11}N_3O_3S$	57.49	3.58	13.55	10.04	57.49	3.54	13.41	10.23	99	186—188
XV	H	H	p-$O_2NC_6H_4$	168—170	$C_{15}H_{11}N_3O_3S$	57.26	3.60	13.68	9.98	57.49	3.54	13.41	10.23	84	184.5—185.5
XVI	H	H	3.4-$(OH)_2C_6H_3$	223—224	$C_{15}H_{12}N_2O_3S$	60.46	4.33	9.18	10.74	59.98	4.03	9.33	10.68	—	199—200, [224—225]
XVII	H	CH_3	C_6H_5	119—120	$C_{16}H_{14}N_2OS$	68.01	4.85	10.02	11.69	68.06	4.99	9.92	11.36	98	
XVIII	H	C_6H_5	CH_3	157—158	$C_{16}H_{14}N_2OS$	67.80	5.00	9.42	11.56	68.06	4.99	9.92	11.36	70	
XIX	H	$C_6H_5CH_2$	CH_3	144—145	$C_{17}H_{16}N_2OS$	68.51	5.40	9.29	10.64	68.89	5.44	9.45	10.82	49	
XX	H	CH_3	p-$C_6H_5C_6H_4$	135—136	$C_{22}H_{18}N_2OS$	73.50	4.92	7.42	9.11	73.71	5.06	7.82	8.95	86	
XXI	H	C_6H_5	C_6H_5	165—167	$C_{21}H_{16}N_2OS$	73.36	4.96	8.53	9.41	73.23	4.68	8.13	9.31	76	
XXII	CH_3	H	CH_3	139—140	$C_{12}H_{14}N_2OS$	61.21	6.02	11.84	13.90	61.51	6.02	11.96	13.68	78	273—275
XXIII	CH_3	H	$C(CH_3)_3$	147—148	$C_{15}H_{20}N_2OS$	65.04	7.09	9.79	11.68	65.18	7.30	10.14	11.60	91	(243—244)
XXIV	CH_3	CH_3	CH_3	167—168	$C_{13}H_{16}N_2OS$	62.85	6.78	11.25	12.77	62.87	6.49	11.28	12.91	89	255—256
XXV	CH_3	CH_3	C_2H_5	126—127	$C_{14}H_{18}N_2OS$	63.24	6.70	10.84	13.07	64.09	6.92	10.68	12.22	76	
XXVI	CH_3	H	C_6H_5	151—152	$C_{17}H_{16}N_2OS$	68.55	5.41	9.50	10.07	68.89	5.44	9.45	10.82	99	191—192
XXVII	CH_3	H	p-BrC_6H_4	164—165	$C_{17}H_{15}BrN_2OS$	54.05	3.92	7.32	8.44	54.40	4.03	7.47	8.54	97	
XXVIII	CH_3	H	p-$O_2NC_6H_4$	150—151	$C_{17}H_{15}N_3O_3S$	59.63	4.54	12.26	8.99	59.81	4.43	12.31	9.40	99	
XXIX	CH_3	C_6H_5	C_6H_5	160—161	$C_{23}H_{20}N_2OS$	73.75	5.35	7.41	8.54	74.16	5.41	7.52	8.61	92	

1*The picrates and hydrohalides were analyzed for nitrogen and halogen, respectively. 2*Found, %: Cl 12.83. Calculated, %: Cl 13.09. The base II was an oily liquid. 3*Found, %: Br. 23.76. Calculated, %: Br 24.27. The base III was an oily liquid. 4*C_4H_3S—2-thienyl. 5*C_5H_7O—cyclopentanon-2-yl. 6*C_6H_9O—cyclohexanon-2-yl. 7*According to the literature [1], mp 120° C, [2], mp 172-173° C.

We express our gratitude to V. V. Kolpakova and her colleagues for performing the analyses.

reaction was carried out in ethanolic NaOH for 12–16 hr at room temperature. Compounds **I**, **V**, and **XI** were extracted with chloroform.

b) A solution of 0.05 mole of 2-mercaptobenzimidazole or 5,6-dimethyl-2-mercaptobenzimidazole and 0.05–0.055 mole of an α-halogenoketone in 50–100 ml of ethanol was stirred at 60–65° C for 1 hr. It was then boiled either for 10 min (**I**, **IX**), 1 hr (**XXIII**), 4 hr (**III**, **V**, **X**), or 5 hr (**XII**) and cooled; the precipitate of the hydrohalide of **III**, **XII**, or **XXIII** was filtered off, or the reaction mixture was poured into water and neutralized with aqueous NH_3 or Na_2CO_3, and the free base **V** or **X** extracted with chloroform. The hydrobromide of **XVI** was obtained by boiling the starting materials in butanol for 6 hr. Compounds **I–XXIX** are colorless, yellow (in the case of the nitro compounds), or pale yellow (thiophene derivatives) crystalline substances (with the exception of **II** and **III**) which are soluble in organic solvents and in mineral acids but insoluble in water and which give the qualitative reactions for a carbonyl group. Analytically pure samples were obtained by crystallizations: from aqueous ethanol (**I**, **II**, **IV–VII**, **IX**, **X**, **XVI–XIX**, **XXI–XXV**), ethanol (**III**, **VIII**, **XIV**, **XX**, **XXVI**, **XXIX**), butanol (**XIII**, **XXVIII**), dimethylformamide–water (1 : 2) (**XI**), ethanol–butanol (2 : 1) (**XII**, **XV**), and dioxane–water (2 : 1) (**XXVII**). The values of ν_{CO} in cm^{-1} in the IR spectra (recorded in paraffin oil on a UR-10 instrument) were: 1727 (hydrochloride of **I**), 1725 (hydrochloride of **II**), 1670 (**IX**), 1655 (hydrobromide of **IX**), 1682 (**XII**), 1692 (**XIII**), 1695 (**XIV**), 1675 (**XV**), 1650 (**XVI**), 1660 (hydrochloride of **XVI**), 1688 (**XXI**), 1705 (**XXIII**), 1702 s and 1704 w (hydrobromide of **XXIII**), 1688 and 1700 (**XXVI**), and 1670 (**XXVII**).

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Zaporozh'e Pharmaceutical Institute

Ordzhonikidze All-Union Chemical and Pharmaceutical Scientific-Research Institute, Moscow