INVESTIGATIONS IN THE IMIDAZOLE SERIES

XXXVII. Thiazolo[3, 2-a]benzimidazoles*

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Cyclization of 2-β-oxoalkylthio- and 2-β-oxoaralkylthiobenzimidazoles and the reaction of 2-mercaptobenzimidazoles with α-halogenoketones in the absence of bases has given a number of derivatives of thiazolo[3, 2-a]benzimidazole, cyclopentenothiazolo[3, 2-a]benzimidazole, and tetrahydrobenzothiazolo[3, 2-a]benzimidazole.

Synthesis of derivatives of thiazolo[3, 2-a]benzimidazoles from 2-mercaptobenzimidazoles and α-halogenoketones has been inadequately studied [1–5].

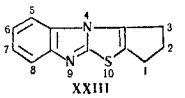
To obtain compounds of this series, which are of interest for biological investigations, we have made a detailed study of the cyclization of the 2-β-oxoalkylthio- and 2-β-oxoaralkylthiobenzimidazoles obtained previously [6]. It has been established that these compounds, like the 2-β-oxoalkylthio- and 2-β-oxoaralkylthioimidazoles [7] readily undergo dehydration on being boiled with phosphorus oxychloride, being converted into the corresponding thiazolo[3, 2-a]benzimidazoles (V, IX–XVI, XX, XXI, XXIII). An exception is formed by 2-pinacolonothiobenzimidazole, which undergoes no change even on being boiled with phosphorus oxychloride for 20 hr, this apparently being explained by steric hindrance.

Unlike the 2-β-oxoaralkylthiobenzimidazoles, the 2-β-oxoalkylthiobenzimidazoles readily cyclize even on treatment with H_2SO_4 in the cold and on heating with H_3PO_4, HCl, and CH_3COOH, while their hydrochlorides cyclize on being boiled with water and ethanol (IV).

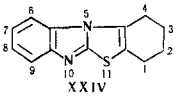
The substituted thiazolo[3, 2-a]benzimidazoles can also be obtained in one stage—by heating 2-mercaptobenzimidazoles with α-halogenoketones in organic solvents. This reaction does not always take place unambiguously, and its results depend on the structural features of the halogenoketone and the temperature and time of the process. Thus, on being boiled with 2-mercaptobenzimidazoles in ethanol for 4–5 hr, the α-halogenoketones of the aliphatic and acyclic series (apart from bromopinacolone and 2-bromopentan-3-one) form the hydrohalides of tri- and tetracyclic bases (I–IV, VI–VIII, XVII, XVIII, XXIV, XXV). In the case of the aliphatic aromatic halogenoketones, the reaction can be carried out (cf. IX, XIII, XIX, XXII) only in high-boiling solvents (dimethylformamide, hexyl alcohol); when these compounds are boiled in ethanol and butanol the hydrohalides of the corresponding 2-β-oxoaralkylthiobenzimidazoles are formed [6].

The derivatives of cyclopentenothiazolo[3, 2-a]benzimidazole (XXIII) and of tetrahydrobenzothiazolo[3, 2-a]benzimidazole (XXIV, XXV) that we have synthesized have been obtained for the first time. Only octahydrobenzothiazolo[3, 2-a]benzimidazole is known in the literature [2].

The structure of all the tri- and tetracyclic compounds was confirmed by their IR spectra, which lacked absorption bands of NH, OH, and CO groups (with the exception of VIII).

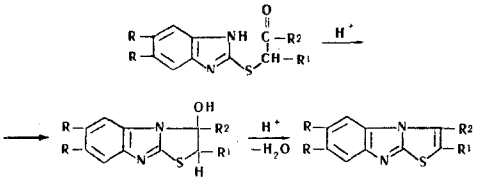


XXIII



XXIV

Information on the synthesis of thiazolo[3, 2-a]benzimidazoles obtained previously [6, 8] and in this work permit the conclusion that the closure of the thiazole ring takes place, as in the case of the imidazo[2, 1-c] thiazoles [9], in the following way:



The reaction is catalyzed by acids. Thus, 2-acetonylthiobenzimidazole (XXVII) undergoes no change on being boiled in ethanol (4 hr) while the hydrochloride of this compound is converted into I in high yield under the same conditions.

EXPERIMENTAL

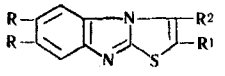
Thiazolo[3, 2-a]benzimidazole derivatives. a) A mixture of 0.01 mole of a 2-β-oxoalkylthio- or 2-β-oxoaralkylthiobenzimidazole [6] and 20–50 ml of $POCl_3$ was boiled for 1 hr (V), 4 hr (XV), 10 hr (IX, XIII, XVI, XX), 12 hr (XII), 16–18 hr (X, XXI), or 22 hr (XI). The solvent was distilled off in vacuum, and the residue was decomposed with water and neutralized with NH_3 or Na_2CO_3, and the precipitate was filtered off and washed with water. In the isolation of XVI, after cooling, the reaction mixture was poured onto ice and neutralized with KOH solution and then with $NaHCO_3$ to pH 8, and the precipitate was filtered off.

b) A solution of 0.01 mole of 2-(α-methylacetonylthio)benzimidazole (XXVI) [6] in 10 ml of concentrated H_2SO_4, in 10 ml of 85–89% H_3PO_4, or in 15 ml of galcial CH_3COOH was kept at, respectively, 18–20° C for 24 hr, 95–100° C for 1 hr, or at the boil for 4 hr. The reaction mixture was poured into water and neutralized with NH_3, or the solvent CH_3COOH was distilled off in vacuum, and the residue was washed with water. This gave IV in 89, 99, and 96.5% yield, respectively.

c) A solution of 0.01 mole of XXVII [6] in 20 ml of concentrated HCl or in 20 ml of ethanol with the addition of 2–3 drops of concentrated HCl was boiled for 4 hr, the solvent was distilled off in vacuum, and the residue was dissolved in water and neutralized with NH_3. This gave I with yields of 96 and 78%, respectively. When the hydrochlo-

*For part XXXVI, see [6].

Thiazolo[3, 2-a]benzimidazoles



Compound	R	R¹	R²	Mp, °C (decomp.)	Empirical formula	Found, %				Calculated, %				Yield, %	Mp, °C (decomp.) of the picrate (hydrobromide)*
						C	H	N	S	C	H	N	S		
I[1, 3–5]	H	H	CH_3	161—162	$C_{10}H_8N_2S$	64.07	4.33	14.76	16.81	63.80	4.28	14.88	17.03	73	241—242
II	H	H	C_2H_5	227—228	$C_{11}H_{10}N_2SHBr$	46.41	4.25	9.54	11.42	46.65	3.91	9.89	11.32	72	221—222
III	H	H	C_3H_7	76—77	$C_{12}H_{12}N_2S$	66.61	5.70	12.91	15.16	66.63	5.59	12.95	14.82	65	248—250 (226—228)
IV[2]	H	CH_3	CH_3	151—152	$C_{11}H_{10}N_2S$	65.56	5.10	14.04	16.32	65.31	4.98	13.85	15.85	89—99	233—234 (267—268)
V	H	CH_3	C_2H_5	127—128	$C_{12}H_{12}N_2S$	66.43	5.30	12.79	14.71	66.63	5.59	12.95	14.82	93	227—228
VI	H	C_2H_5	CH_3	107—108	$C_{12}H_{12}N_2S$	66.50	5.78	12.94	14.93	66.63	5.59	12.95	14.82	93	224—226 (227—229)
VII	H	C_3H_7	CH_3	237—238	$C_{13}H_{14}N_2SHBr$	49.80	4.83	8.90	10.33	50.16	4.86	9.00	10.30	76	212—213
VIII[4]	H	$COCH_3$	CH_3	163—164	$C_{12}H_{10}N_2OS$	62.52	4.37	11.77	13.79	62.58	4.38	12.17	13.92	95	—
IX	H	H	C_6H_5	139.5—140.5	$C_{15}H_{10}N_2S$	71.93	4.33	11.44	12.86	71.97	4.03	11.19	12.81	94	242—243
X	H	H	p-BrC_6H_4	200.5—201	$C_{15}H_9BrN_2S$	54.43	2.71	8.62	9.67	54.72	2.76	8.51	9.74	97	264—266
XI	H	H	m-$O_2NC_6H_4$	196.5—197	$C_{15}H_9N_3O_2S$	61.19	3.01	14.07	10.76	61.00	3.07	14.23	10.86	87	244—245
XII	H	H	p-$O_2NC_6H_4$	230—231	$C_{15}H_9N_3O_2S$	61.01	3.42	14.26	11.06	61.00	3.07	14.23	10.86	89	268—270
XIII	H	CH_3	C_6H_5	179—180	$C_{16}H_{12}N_2S$	72.46	4.51	10.66	12.29	72.69	4.58	10.60	12.13	92	—
XIV	H	C_6H_5	CH_3	131—132	$C_{16}H_{12}N_2S$	72.34	4.45	10.80	11.99	72.69	4.58	10.60	12.13	91	231—232
XV	H	$C_6H_5CH_2$	CH_3	122—123	$C_{17}H_{14}N_2S$	73.35	5.06	9.75	11.21	73.35	5.07	10.06	11.52	79	—
XVI	H	C_6H_5	C_6H_5	193—194	$C_{21}H_{14}N_2S$	77.11	4.44	8.72	9.83	77.27	4.32	8.58	9.82	98	215—216
XVII	CH_3	H	CH_3	205—206	$C_{12}H_{12}N_2S$	66.84	5.69	12.93	14.90	66.63	5.59	12.95	14.82	98	285—286 [263—266]
XVIII	CH_3	CH_3	CH_3	162—164	$C_{13}H_{14}N_2S$	68.13	6.31	12.08	13.57	67.79	6.13	12.16	13.92	—	259—260 (308—309)
XIX	CH_3	H	C_6H_5	192—193	$C_{17}H_{14}N_2S$	73.72	5.02	9.68	11.76	73.35	5.07	10.06	11.52	40	263—264
XX	CH_3	H	n-BrC_6H_4	265—266	$C_{17}H_{13}BrN_2S$	57.39	3.81	8.06	8.77	57.15	3.67	7.84	8.97	98	—
XXI	CH_3	H	n-$O_2NC_6H_4$	305—306	$C_{17}H_{13}N_3O_2S$	63.09	4.07	12.80	9.89	63.14	4.05	12.99	9.92	60	—
XXII	CH_3	C_6H_5	C_6H_5	225—226	$C_{23}H_{18}N_2S$	78.35	5.18	8.23	9.31	77.93	5.12	7.90	9.05	51	—

*The picrates and hydrohalides of the crystalline bases were analyzed for their contents of nitrogen and halogen, respectively.

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

ride of **XXVII** was boiled in water (20 ml) and the solution was then neutralized with NH_3, **I** was obtained with a yield of 95%.

d) A solution of 0.05 mole of 2-mercaptobenzimidazole or 5,6-dimethyl-2-mercaptobenzimidazole [8] in 50–70 ml of ethanol was treated with 0.05–0.051 mole of an α-halogenoketone, the mixture was boiled for 4 hr and cooled, and the precipitate was filtered off and washed with water. The ethereal-ethanolic mother solutions were evaporated and an additional amount of the substance was obtained. In this way, the hydrohalides of **II–IV, VI, VII, XVII,** and **XVIII** were obtained with yields of 72, 65, 42, 93, 76, 98, and 88%, respectively. The bases were isolated from the hydrochlorides in the usual way. In the preparation of **I** and **VIII**, after cooling, the reaction mixture was poured into water and neutralized with NH_3 or $NaHCO_3$, giving yields of 73 and 95%, respectively. Compounds **IX, XIX**, and **XXII** (yields 40, 39, 51%, respectively) were obtained by performing the reaction in hexyl alcohol (boiling for 6 hr, distillation of the solvent in vacuum, neutralization of the residue with aqueous ammonia), and **XIII** (yield 20%) in dimethylformamide (boiling for 5 hr, pouring of the solution into water, neutralization with NH_3, extraction with chloroform). The chloroketones were used for the synthesis of **I, VIII, XVII,** and **XXII**, and the bromoketones for all the other compounds.

Cyclopentenothiazolo[3,2-a]benzimidazole (XXIII). A mixture of 2.32 g of 2-(α-cyclopentanonylthio)benzimidazole [6] and 20–25 ml of $POCl_3$ was boiled for 20 min and cooled, and the viscous mass was poured onto ice and treated as described for **XIV** (a). This gave 2.05 g (95.7%) of a substance with mp 178–180° C. Colorless elongated prisms with mp 181–182° C (from ethanol). Found, %: C 67.50; H 4.74; N 13.11; S 14.98. Calculated for $C_{12}H_{10}N_2S$, %: C 67.26; H 4.70; N 13.07; S 14.96. Picrate with mp 236–238° C (decomp., from glacial CH_3COOH).

1,2,3,4-Tetrahydrobenzothiazolo[3,2-a]benzimidazole (XXIV). A solution of 0.03 mole of 2-mercaptobenzimidazole in 50 ml of ethanol was cooled to 20–40° C and treated with a solution of 0.03 mole of 2-bromocyclohexanone in 10 ml of methanol; then the mixture was boiled for 4 hr and was worked up as described for the preparation of I (d). The yield of hydrobromide was 5.54 g (92.6%). Colorless prisms with mp 273–275° C (decomp., from ethanol). Found, %: Br 25.96. Calculated for $C_{13}H_{12}N_2S \cdot HBr$, %: Br 25.84. The base **XXIV** was isolated from the hydrobromide by the usual method. Colorless leaflets with mp 144–145° C (from ethanol–water, 1 : 2). Found, %: C 68.53; H 5.32; N 12.36; S 13.99. Calculated for $C_{13}H_{12}N_2S$, %: C 68.38; H 5.30; N 12.27; S 14.04. Picrate, mp 246–248° C (decomp., glacial acetic acid).

7,8-Dimethyl-1,2,3,4-tetrahydrobenzothiazolo[3,2-a]benzimidazole (XXV). This was obtained from 2-mercapto-5,6-dimethylbenzimidazole and 2-bromocyclohexanone in a similar manner to **XXIV**. The yield of the hydrobromide was 64%. Colorless prisms with mp 306–307° C (decomp., from ethanol–water, 1 : 1). Found, %: Br 23.98. Calculated for $C_{15}H_{16}N_2S \cdot HBr$, %: Br 23.70. The base **XXV** was obtained by the decomposition of the hydrobromide. Colorless crystals with mp 207–208° C (from ethanol–water, 2 : 1). Found, %: C 70.49; H 6.31; N 10.88; S 12.79. Calculated for $C_{15}H_{16}N_2S$, %: C 70.27; H 6.29; N 10.93; S 12.51. Picrate, mp 262–263° C (decomp., glacial acetic acid).

Properties of compounds **I–XXV**: white or yellow (in the case of the nitro compounds) crystalline substances of a basic nature, soluble in organic solvents and mineral acids, insoluble in water. The analytically pure substances were obtained by crystallization from: methanol (**XXII**), anhydrous ethanol (**VII**), ethanol (**VIII**), aqueous ethanol (**I, III, IV, V, VI, XIII, XIV, XV, XVII, XVIII, XIX**), butanol (**X, XII, XVI**), dioxane–water, 1 : 1 (**IX**), dimethylformamide–water, 2 : 1 (**XI**), and dimethylformamide (**XX, XXI**). The bases **II** and **VII** formed oily liquids.

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