STUDIES IN THE IMIDAZOLE SERIES

L*. SYNTHESIS OF DERIVATIVES OF THIAZOLO[3,2-a]BENZIMIDAZOLE

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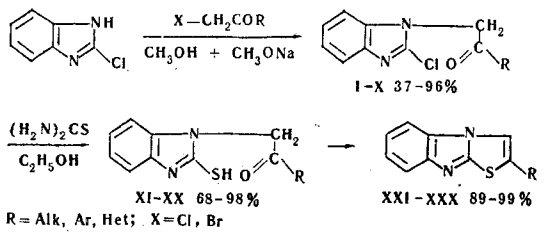
A new synthesis of derivatives of thiazolo[3,2-a]benzimidazoles based on 2-halogenobenzimidazoles has been performed. The reaction of 2-chlorobenzimidazole with α-halogeno ketones and the subsequent heating of the resulting 1-acylmethyl-2-chlorobenzimidazoles with thiourea has given 1-acylmethyl-2-mercaptobenzimidazoles. The cyclization of the latter under the action of mineral acids or water-abstracting agents has given a series of 2-alkyl-, 2-aryl-, and 2-heteryl-substituted thiazolo[3,2-a]benzimidazoles.

The preparation of thiazolo[3,2-a]benzimidazole derivatives by the reaction of 2-mercaptobenzimidazoles with α-halogeno carbonyl compounds [2-10] or alkyl halides [11, 12] and of 2-aminothiazole with p-quinone [13] is known. This method is inconvenient for the synthesis of 2-aryl- and 2-heteryl-substituted thiazolo[3,2-a]benzimidazoles because of the poor accessibility of the arylchloroacetaldehydes, and the corresponding heteryl and bromo compounds, and their acetals.

In development of previous work [14] we have made a more detailed study of a method of synthesizing thiazolo[3,2-a]benzimidazoles from 2-halogenobenzimidazoles. The reaction of 2-chlorobenzimidazole [15, 16] with aliphatic, aliphatic-aromatic, and aliphatic-heterocyclic α-halogeno ketones in methanol in the presence of sodium methoxide has given 1-acylmethyl-2-chlorobenzimidazoles (I-X, Table 1). When these compounds were heated with thiourea in alcohols (ethanol, hexanol) or dimethylformamide, as in the formation of 2-mercaptoimidazole [17] from 2-chlorobenzimidazole, the chlorine was replaced by a mercapto group, giving 1-acylmethyl-2-mercaptobenzimidazoles (XI-XX, Table 2), which, in the solid state, according to their IR spectra (presence of absorption bands of an NH group and not of an SH group), have the structure of 1-acylmethylbenzimidazoline-2-thiones. On treatment with water-abstracting agents ($POCl_3$, conc. H_2SO_4) or on heating with hydrohalic acids, these thiones split out a molecule of water and cyclize to form 2-alkyl-, 2-aryl-, or 2-heteryl-substituted thiazolo[3,2-a]benzimidazoles (XXI-XXX, Table 3).



*For Communication XLIX, see [1].

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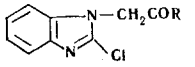
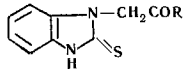
TABLE 1. 1-Acylmethyl-2-chlorobenzimidazoles[a]



Compound	R	Mp, °C	Empirical formula	Found, %				Calculated, %				Yield, %	IR spectrum[b] ν_{CO}, cm^{-1}
				C	H	Cl	N	C	H	Cl	N		
I	CH_3	153—154	$C_{10}H_9ClN_2O$	57,64	4,60	17,10	13,42	57,56	4,39	16,99	13,42	47	1730
II	$C(CH_3)_3$	129—130	$C_{13}H_{15}ClN_2O$	62,50	5,85	14,12	11,30	62,27	6,03	14,14	11,17	50	1718
III	C_6H_5	168—170[c]	$C_{15}H_{11}ClN_2O$	—	—	—	—	—	—	—	—	85	1700
IV	p-ClC_6H_4	168—169	$C_{15}H_{10}Cl_2N_2O$	58,68	3,22	23,51	9,22	59,03	3,30	23,24	9,18	85	1708
V	p-BrC_6H_4	169—170	$C_{15}H_{10}ClBrN_2O$	51,41	2,67	33,39[d]	7,88	51,53	2,88	33,00	8,01	89	1695
VI	p-$CH_3C_6H_4$	158—159	$C_{16}H_{13}ClN_2O$	67,70	4,60	12,62	10,09	67,49	4,60	12,45	9,84	96	1695
VII	p-$CH_3OC_6H_4$	152—153	$C_{16}H_{13}ClN_2O_2$	64,20	4,06	12,02	9,45	63,90	4,36	11,79	9,32	72	1690
VIII	p-$C_6H_5C_6H_4$	191—192	$C_{21}H_{15}ClN_2O$	72,60	4,27	10,07	8,16	72,72	4,36	10,22	8,08	60	1700
IX	$C_{10}H_7$[e]	178—179	$C_{19}H_{13}ClN_2O$	71,12	3,79	11,23	8,92	71,14	4,08	11,05	8,73	79	1698
X	C_4H_3S[f]	132—133	$C_{13}H_9ClN_2OS$	56,20	3,13	13,08	10,13	56,42	3,28	12,81	10,12	37	1680

[a]For analysis, the substances were purified by crystallization: I, III, VII, and IX from methanol; V from 80% methanol; IV and VIII from ethanol; II and X from 50% ethanol. [b]The IR spectra were recorded on a UR-10 instrument in paraffin oil. For the microanalyses of all the compounds and for recording the IR spectra, we thank V. V. Kolpakova, Yu. N. Sheinker, and their colleagues. [c]mp 168-170°C [14]. [d]Total halogen. [e]$C_{10}H_7$ = α naphthyl. [f]C_4H_3S = α thienyl. Found, %: S 11.66. Calculated, %: S 11.59.

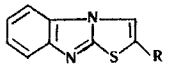
TABLE 2. 1-Acylmethylbenzimidazoline-2-thiones[a]



Compound	R	Mp, °C	Empirical formula	Found, %				Calculated, %				Yield, %	IR spectra[b], cm^{-1}	
				C	H	N	S	C	H	N	S		ν_{CO}	ν_{NH}
XI	CH_3	196—197	$C_{10}H_{10}N_2OS$	58,28	4,90	13,57	15,37	58,27	4,89	13,58	15,54	68	1732	3115, 3150
XII	$C(CH_3)_3$	224—225	$C_{13}H_{16}N_2OS$	62,89	6,47	11,20	12,64	62,87	6,49	11,28	12,91	97	—	—
XIII	C_6H_5	242—243	$C_{15}H_{12}N_2OS$	66,92	4,62	10,71	11,79	67,13	4,51	10,44	11,95	91	1706	3090, 3150
XIV	p-ClC_6H_4	225—226	$C_{15}H_{11}ClN_2OS$	59,61	3,57	9,46	10,84	59,50	3,66	9,15	10,59	96	1690	3115, 3170
XV	p-BrC_6H_4	246—248	$C_{15}H_{11}BrN_2OS$	52,11	3,24	8,45	9,03	51,88	3,19	8,06	9,24	78	1700	3130, 3180
XVI	p-$CH_3C_6H_4$	229—230	$C_{16}H_{14}N_2OS$	67,71	5,36	9,18	10,76	68,06	4,50	9,92	11,36	97	1695	3120, 3160
XVII	p-$CH_3OC_6H_4$	233—234	$C_{16}H_{14}N_2O_2S$	64,65	4,91	9,29	10,50	64,41	4,73	9,39	10,75	97	1688	3120, 3160
XVIII	p-$C_6H_5C_6H_4$	291—292	$C_{21}H_{16}N_2OS$	73,14	4,62	8,14	9,24	73,23	4,68	8,13	9,31	97	—	—
XIX	$C_{10}H_7$[c]	282—283	$C_{19}H_{14}N_2OS$	71,85	4,42	8,58	10,05	71,67	4,43	8,80	10,07	98	1690	3150
XX	C_4H_3S[d]	219—220	$C_{13}H_{10}N_2OS_2$	57,04	3,64	10,67	23,54	56,91	3,67	10,21	23,38	91	1678	3080, 3150

[a]For analysis, the substances were purified by crystallization: XI, XIII-XVII, and XX from ethanol; XI from 50% ethanol; XVIII from ethanol–dioxane (1:2); and XIX from dimethylformamide–ethanol (2:3). [b]UR-10 instrument in paraffin oil. [c]$C_{10}H_7$ = α naphthyl. [d]C_4H_3S = α thienyl.

TABLE 3. 2-Alkyl-, 2-Aryl, and 2-Heterylthiazolo[3,2-a]benzimidazoles[a]



Compound	R	Mp, °C	Empirical formula	Found, %				Calculated, %				Yield, %
				C	H	N	S	C	H	N	S	
XXI	CH_3	157—158[b]	$C_{10}H_8N_2S$	—	—	—	—	—	—	—	—	78
XXII	$C(CH_3)_3$	131—132	$C_{13}H_{14}N_2S$	68,11	6,10	12,06	13,60	67,79	6,13	12,16	13,92	99
XXIII	C_6H_5	166—167[c]	$C_{15}H_{10}N_2S$	—	—	—	—	—	—	—	—	95
XXIV	*p*-ClC_6H_4	225—226	$C_{15}H_9ClN_2S$	63,14	3,40	9,79	11,39	63,26	3,19	9,84	11,26	93
XXV	*p*-BrC_6H_4	222—223	$C_{15}H_9BrN_2S$	54,34	2,69	8,56	9,62	54,72	2,75	8,51	9,74	98
XXVI	*p*-$CH_3C_6H_4$	178—179	$C_{16}H_{12}N_2S$	72,79	4,58	10,39	12,32	72,69	4,58	10,60	12,13	99
XXVII	*p*-$CH_3OC_6H_4$	162—163	$C_{16}H_{12}N_2OS$	68,33	4,51	9,92	11,34	68,54	4,32	9,99	11,44	89
XXVIII	*p*-$C_6H_5C_6H_4$	205—206	$C_{21}H_{14}N_2S$	77,28	4,29	8,39	9,96	77,27	4,32	8,58	9,82	99
XXIX	$C_{10}H_7$[d]	228—229	$C_{19}H_{12}N_2S$	76,33	3,88	9,64	10,88	75,97	4,03	9,33	10,67	93
XXX	C_4H_3S[e]	150—151	$C_{13}H_8N_2S_2$	60,81	3,18	10,97	24,96	60,91	3,15	10,93	25,02	97

[a]For analysis, the compounds were purified by crystallization: XXI from 30% ethanol, XXIII and XXX and XXIV-XXVII from ethanol. [b]Picrate with mp 247-248°C (decomp. from CH_3COOH); according to [8], mp of the base 157-158°C, mp of the picrate 247-248°C. [c]mp 166-167°C [14]. [d]$C_{10}H_7$ = α naphthyl. [e]C_4H_3S = α thienyl.

EXPERIMENTAL

1-Acylmethyl-2-chlorobenzimidazoles (I-X, Table 1). To a solution of 0.05 mole of sodium methoxide in 50 ml of methanol were added 0.05 mole of 2-chlorobenzimidazole [15, 16], and, after this had dissolved, 0.05-0.051 mole of an α-halogeno ketone (for the synthesis of I, either the chloro ketone or the bromo ketone was used, and in all the other cases the corresponding bromo ketones). The reaction mixture was heated to the boil for 3 h (in the preparation of I, II, and VI), 2 h (in the preparation of III, IV, VII, VIII, and X), or 1 h 30 min (in the preparation of IX) and cooled to 4-6°C, and then the precipitate was filtered off and washed with water. For the isolation of II and V, after the end of the reaction and cooling, the reaction mixture was poured into water, and the precipitate was filtered off and washed with water. The reaction mixture was diluted with water, compound X was extracted with chloroform, the chloroform was distilled off, and the residue was washed with acetone–petroleum ether (1:5). Colorless crystalline substances soluble in the majority of organic solvents, insoluble in water; they do not form hydrochlorides and picrates.

1-Acylmethylbenzimidazoline-2-thiones (XI-XX, Table 2). To a solution of 0.01-0.03 mole of a 1-acylmethyl-2-chlorobenzimidazole in 30-100 ml of ethanol (in the preparation of XI-XVI, XIX, and XX) or in 50-100 ml of methanol (in the preparation of XVII and XVIII) was added 0.01-0.03 mole of thiourea. The mixture was heated at 50-52°C for 1 h 30 min (in the preparation of XI) or was boiled for 30 min (XIX), 1 h (XII-XV, XVII), 1 h 30 min (XVI, XX), or 2 h 30 min (XVIII), cooled, poured into water, and neutralized with $NaHCO_3$ solution, and the precipitate was filtered off and washed with water. Before crystallization from a solvent, the crude XI and XII were purified by reprecipitation from 10% KOH or NaOH with dilute CH_3COOH. Compound XIII was also obtained with a yield of 36% by carrying out the reaction in hexanol (boiling for 1 h), and XV with a yield of 94% in dimethylformamide (boiling for 30 min). Colorless crystalline substances soluble in organic solvents and aqueous solutions of caustic alkalis, insoluble in water.

2-Alkyl-, 2-Aryl-, and 2-Heterylthiazolo[3,2-a]benzimidazoles (XXI-XXX, Table 3). a) A solution of 0.005-0.01 mole of a 1-acylmethylbenzimidazoline-2-thione in 10-15 ml of $POCl_3$ was boiled for 1 h (in the preparation of XXI-XXIV and XXVII-XXX), 40 min (XXV), or 25 min (XXVI), and the mixture was cooled to 18-20°C, poured into ice water (when the reactions were carried out on the large scale, the $POCl_3$ was distilled off in vacuum), and neutralized with ammonia solution, and the precipitate was filtered off and washed with water. A mixture of XXI with 2-methylthiazolo[3,2-a]benzimidazole [8] gave no depression of the melting point.

b) A solution of 0.67 g of XIII in 10 ml of conc. H_2SO_4 was left at 18-22°C for 32 h, and was then poured into water and neutralized with ammonia, and the precipitate was filtered off. The yield of XXIII was 0.36 g (57.6%).

c) A mixture of 0.67 g of XIII and 10 ml of 46% HBr was boiled for 2 h, cooled, and treated as described above. The yield of XXIII was 0.62 g (99.2%). Properties of XXI-XXX: colorless crystalline substances soluble in organic solvents and mineral acids, insoluble in water.

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