INVESTIGATIONS IN THE IMIDAZOLE SERIES

XLVIII.* NEW SYNTHESIS OF 2-ACYL- AND 2-ACYL-3-ALKYLTHIAZOLO[3,2-*a*]BENZIMIDAZOLES

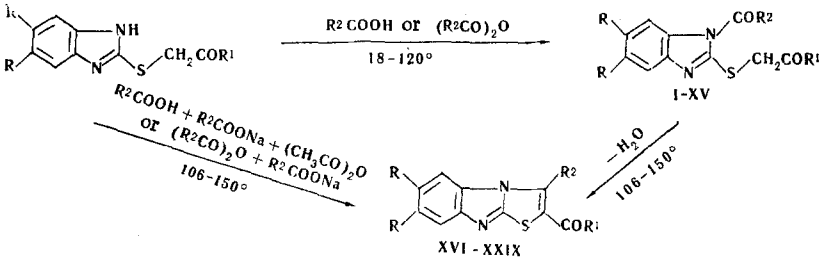
A. N. Krasovskii, P. M. Kochergin, and T. E. Kozlovskaya

UDC 547.785.5'789.6

A new synthesis of 2-acyl- and 2-acyl-3-alkylthiazolo[3,2-*a*]benzimidazoles was realized by the reaction of 2-acylmethylmercaptobenzimidazoles with acylating agents.

Aldehydes and ketones of the thiazolo[3,2-*a*]benzimidazole series have received very little study. Only one compound – 2-acetyl-3-methylthiazolo[3,2-*a*]benzimidazole, previously obtained via the generally accepted scheme for the synthesis of thiazolo[3,2-*a*]benzimidazole derivatives, viz., reaction of 2-mercaptobenzimidazole with 3-chloro-2,4-pentanedione [2-4] – has been reported.

We have found a new, simple method for the preparation of 2-acyl- and 2-acyl-3-alkylthiazolo[3,2-*a*]-benzimidazoles [5]. It consists in the fact that N-acyl derivatives of 2-acylmethylmercaptobenzimidazoles (I-XV, Table 1) rather than O-acyl derivatives of the enol forms of the above-indicated ketones, as is the case with pyridine [2, 3], form by the action of acylating agents [formic acid or carboxylic acid anhydrides (best prepared in the presence of a sodium salt of the corresponding carbylic acids)] on 2-acylmethylmercaptobenzimidazoles [6, 7]. On heating, I-XV readily split out a molecule of water at the expense of the oxygen atom of the N-acyl group and the hydrogen atoms of the active methylene group of the ketone residue in the 2-position of the benzimidazole ring, and the corresponding 2-acyl- and 2-acyl-3-alkylthiazolo-[3,2-*a*]benzimidazoles (XVI-XXIX) are obtained. This synthesis can be carried out in one step without isolation of the intermediate I-XV.



The structures of I-XXIX were confirmed by IR spectra, by the formation of derivatives at the carbonyl group (for example, the p-nitrophenylhydrazone of XXII), and also by the alternative synthesis of XXIII from 2-mercaptobenzimidazole and 3-chloro-2,4-pentanedione [3].

EXPERIMENTAL

1-Acyl-2-acylmethylmercaptobenzimidazoles [(I-XV), Table 1]. A. A previously prepared mixture of 10 ml of 85% formic acid and 10 ml of acetic anhydride was added to 0.01 mole of the 2-acylmethyl-

*See [1] for communication XLVII.

Zaporozhe Medical Institute. S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 393-396, March, 1971. Original article submitted February 9, 1969.

TABLE 1. 1-Acyl-2-acylmethylmercaptobenzimidazoles (I-XV) and 2-Acylthiazolo[3,2-*a*]benzimidazoles (XVI-XXIX)

Compound	R	R¹	R²	Mp (decomp.), °C	ν_{CO}, cm⁻¹ [a]	Empirical formula	Found, %				Calculated, %				Yield, %
							C	H	N	S	C	H	N	S	
I	H	C_6H_5	H	140—141	1700, 1729	$C_{16}H_{12}N_2O_2S$	64,8	3,9	9,5	10,5	64,8	4,0	9,5	10,8	99
II	H	*p*-BrC_6H_4	H	145—146	1693, 1728	$C_{16}H_{11}BrN_2O_2S$ [b]	51,2	2,7	7,7	8,3	51,2	2,9	7,5	8,5	99
III	H	*p*-$O_2NC_6H_4$	H	205—206	1692, 1732	$C_{16}H_{11}N_3O_4S$	56,7	3,4	12,1	9,4	56,3	3,3	12,3	9,4	98
IV	CH_3	C_6H_5	H	164—165	1695, 1720	$C_{18}H_{16}N_2O_2S$	66,6	5,1	8,6	9,7	66,6	5,0	8,6	9,9	97
V	CH_3	*p*-BrC_6H_4	H	155—157		$C_{18}H_{15}BrN_2O_2S$ [c]	53,4	3,6	6,4	7,5	53,6	3,7	6,9	7,9	93
VI	CH_3	*p*-$O_2NC_6H_4$	H	225—226	1690, 1718	$C_{18}H_{15}N_3O_4S$	57,9	3,9	—	8,4	58,5	4,0	—	8,7	97
VII	H	CH_3	CH_3	172—173		$C_{12}H_{12}N_2O_2S$	58,3	5,0	11,6	12,7	58,0	4,9	11,3	12,9	82
VIII	H	C_6H_5	CH_3	155—156	1688, 1710	$C_{17}H_{14}N_2O_2S$	66,2	4,5	9,1	10,6	65,8	4,5	9,0	10,3	92
IX	H	*p*-BrC_6H_4	CH_3	156—157	1695	$C_{17}H_{13}BrN_2O_2S$ [d]	52,2	3,4	7,6	8,3	52,4	3,4	7,2	8,2	99
X	CH_3	CH_3	CH_3	144—145	1710	$C_{14}H_{16}N_2O_2S$	60,6	5,8	10,1	11,8	60,8	5,8	10,1	11,6	95
XI	CH_3	C_6H_5	CH_3	163—164	1690, 1720	$C_{19}H_{18}N_2O_2S$	67,4	5,2	8,0	9,6	67,4	5,3	8,3	9,5	96
XII	H	CH_3	C_2H_5	161—162		$C_{13}H_{14}N_2O_2S$	59,5	5,6	10,7	12,0	59,5	5,4	10,7	12,2	90
XIII	H	C_6H_5	C_2H_5	142—143	1698, 1718	$C_{18}H_{16}N_2O_2S$	67,0	5,0	8,6	9,9	66,6	5,0	8,6	9,9	53
XIV	H	*p*-BrC_6H_4	C_2H_5	178—179		$C_{18}H_{15}BrN_2O_2S$ [e]	—	—	6,8	8,2	—	—	6,9	7,9	75
XV	CH_3	$C(CH_3)_3$	C_2H_5	92—93 and 128—129	1689, 1712	$C_{18}H_{24}N_2O_2S$	64,8	7,2	8,1	9,1	65,0	7,3	8,4	9,6	75
XVI	H	C_6H_5	H	163—164	1635	$C_{16}H_{10}N_2OS$	69,1	3,7	10,0	11,7	69,0	3,6	10,0	11,5	90—93
XVII	H	*p*-BrC_6H_4	H	227—228	1657	$C_{16}H_9BrN_2OS$ [f]	53,5	2,9	7,5	8,8	53,8	2,5	7,8	8,9	93—98
XVIII	H	*p*-$O_2NC_6H_4$	H	277—278	1640	$C_{16}H_9N_3O_3S$	59,6	2,9	12,9	9,9	59,4	2,8	12,9	9,9	90—96
XIX	CH_3	C_6H_5	H	186—187	1630	$C_{18}H_{14}N_2OS$	70,6	4,9	8,8	10,3	70,6	4,6	9,1	10,5	90
XX	CH_3	*p*-BrC_6H_4	H	255—256	1648	$C_{18}H_{13}BrN_2OS$ [g]	56,3	3,5	7,0	8,2	56,1	3,4	7,2	8,3	91—97
XXI	CH_3	*p*-$O_2NC_6H_4$	H	279—280	1651	$C_{18}H_{13}N_3O_3S$	61,4	3,6	12,0	8,9	61,5	3,7	12,0	9,1	91
XXII	H	H	CH_3	227—228	1678	$C_{11}H_8N_2OS$ [h]	61,0	3,7	12,7	15,1	61,1	3,7	12,9	14,8	81
XXIII	H	CH_3	CH_3	163—164	1650	$C_{12}H_{10}N_2OS$ [i]	—	—	—	—	—	—	—	—	96
XXIV	H	*p*-BrC_6H_4	CH_3	217—218	1623	$C_{17}H_{11}BrN_2OS$ [j]	55,1	3,6	7,4	8,9	55,0	3,0	7,5	8,6	86
XXV	CH_3	CH_3	CH_3	229—230	1658	$C_{14}H_{14}N_2OS$	64,8	5,5	10,6	12,3	65,1	5,5	10,8	12,4	85
XXVI	H	*p*-BrC_6H_4	C_2H_5	160—161	1648	$C_{18}H_{13}BrN_2OS$ [k]	56,9	3,4	7,1	8,3	56,1	3,4	7,2	8,3	83—85
XXVII	CH_3	CH_3	C_2H_5	132—133	1650	$C_{15}H_{16}N_2OS$	66,5	5,7	10,4	11,4	66,1	5,9	10,3	11,8	73
XXVIII	CH_3	$C(CH_3)_3$	C_2H_5	161—162	1660	$C_{18}H_{22}N_2OS$	68,9	6,9	9,0	10,3	68,7	7,0	8,9	10,2	80
XXIX	CH_3	C_6H_5	C_2H_5	187—188	1639	$C_{20}H_{18}N_2OS$	71,9	5,7	8,2	9,6	71,8	5,4	8,4	9,6	90

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

[b] Found %: Br 21.6. Calculated %: Br 21.3.

[c] Found %: Br 20.3. Calculated %: Br 19.8.

[d] Found %: Br 20.7. Calculated %: Br 20.5.

[e] Found %: Br 20.1. Calculated %: Br 19.8.

[f] Found %: Br 22.6. Calculated %: Br 22.4.

[g] Found %: Br 21.1. Calculated %: Br 20.7.

[h] p-Nitrophenylhydrazone, mp 250-251° (decomp., from acetic acid). Found %: C 54.9; H 4.4; N 18.7; S 8.3. $C_{17}H_{13}N_5O_2S \cdot H_2O$. Calculated %: C 55.2; H 4.1; N 18.9; S 8.7.

[i] Mp 163-164° [4].

[j] Found %: Br 21.8. Calculated %: Br 21.5.

[k] Found %: Br 21.1. Calculated %: Br 20.7.

mercaptobenzimidazole [7]. The reaction mass was allowed to stand for 24-26 h at 18-20° and poured into water. The precipitate of I-VI was filtered and washed with water until it gave a neutral reaction and was then dried in a vacuum desiccator. This reaction can be carried out in the presence of a solvent [dimethylformamide (10-15 ml)].

B. A solution of 0.01 mole of the 2-acylmethylmercaptobenzimidazole and 10-15 ml of acetic or propionic anhydride was heated for 5 min at 95-100° (to obtain VII, X, and XII), for 30 min at 95-100° (for VIII, IX, XI, XIII, XIV), or for 15-20 min at 115-120° (XV). The mixture was cooled, poured into water, and the precipitate of VII-XI was filtered. To isolate XII and XV the reaction mass was diluted with 15-20 ml of acetone, and the solution was poured into water. The mixture was cooled to 2-5° with stirring, and the precipitate was filtered. Compounds XIII and XIV were isolated by vacuum distillation of propionic anhydride; the residue was triturated with cooled ethanol (10-15 ml), and the crystallized compound was filtered and washed with ether. The products were colorless or yellow (VI) crystalline substances which are readily hydrolyzed by heating in water to the corresponding 2-acylmethylmercaptobenzimidazoles. They must be dried at room temperature in a vacuum desiccator over $CaCl_2$ or H_2SO_4. For analysis the compounds were purified by crystallization from anhydrous ethanol (VII-XI) or by reprecipitation with water in the cold from dimethylformamide (I-IV), methanol (XII), or ethanol (XIII-XV).

2-Acyl- and 2-Acyl-3-alkylthiazolo[3,2-*a*]benzimidazoles [(XVI-XXIX), Table 1]. A. An equivalent amount of sodium formate dihydrate was added to 0.01 mole of the 2-acylmethylmercaptobenzimidazole followed by a mixture of 10-15 ml of 85% formic acid and 10-15 ml of acetic anhydride. The reaction mass was refluxed for 1-2 h, cooled, and poured into water. The precipitate of XVI-XXI was filtered and washed with water. Compounds XVI and XVII were also obtained in the absence of sodium formate dihydrate when the reaction was carried out in dimethylformamide or without a solvent in an autoclave at 150-155° (2-6 h).

B. A mixture of 0.01 mole of the 2-acylmethylmercaptobenzimidazole [6, 7], an equivalent amount of sodium acetate or propionate, and 10-15 ml of acetic or propionic anhydride was refluxed for 30 min (to obtain XXII, XXIII, and XXV), for 2 h (for XXIV), for 1 h at 120-125° (for XXVII), or for 2 h at 140-160° (for XXVI, XXVIII, and XXIX). The mixture was cooled and poured into water. The precipitate of XXIII-XXV was filtered and washed with water. Compounds XXVI-XXVIII were isolated by dilution of the reaction mass with 15-30 ml of acetone and pouring of this mixture into water. Compounds XXII and XXIX were isolated after removal of the acid anhydride by vacuum distillation; the residue was triturated with ethanol, poured into water, neutralized with sodium carbonate, and the precipitate was filtered. Compounds XXIII and XXV were obtained in the absence of sodium acetate.

C. A mixture of 0.005 mole of the 1-acyl-2-acylmethylmercaptobenzimidazole (II, VI, VII, IX, and XIV), an equivalent weight of the sodium salt of the corresponding acid, and 15-20 ml of acetic anhydride (to obtain XVII, XX, XXIII, and XXIV) or 10 ml of propionic anhydride (to obtain XXVI) was stirred with cooling and then refluxed for 30 min (to synthesize XXIII) or for 2 h (in all of the remaining cases). The mixture was then cooled, poured into water, and the precipitate was filtered. Compound XXVI was isolated by dilution of the reaction mass with 30 ml of acetone and subsequent pouring into water. The products were colorless or yellow (XVIII and XXI) crystalline substances which were purified for analysis by crystallization from aqueous ethanol (XVI and XXIII), ethanol (XIX, XXII, XXV, XXVIII, and XXIX), methanol (XXVI and XXVII), butanol (XX and XXI), dioxane (XVIII), aqueous dioxane (XVII), and 1:1 ethanol–butanol (XXIV).

LITERATURE CITED

1. I. A. Mazur, P. M. Kochergin, and V. G. Tromsa, Khim. Geterotsikl. Soedin., 389 (1971).
2. J. J. D'Amico, R. H. Campbell, and E. C. Guinn, J. Org. Chem., 29, 865 (1964).
3. J. J. D'Amico, R. H. Campbell, and E. C. Guinn, US Patent No. 3,225,059; Chem. Abstr., 64, 8198 (1966).
4. A. N. Krasovskii and P. M. Kochergin, Khim. Geterotsikl. Soedin., 321 (1969).
5. P. M. Kochergin and A. N. Krasovskii, USSR Author's Certificate No. 230,823; Byull. Izobr., No. 35, 21 (1968).
6. A. N. Krasovskii and P. M. Kochergin, Khim. Geterotsikl. Soedin., 899 (1967).
7. A. N. Krasovskii and P. M. Kochergin, Khim. Geterotsikl. Soedin., 316 (1969).