INVESTIGATIONS IN THE IMIDAZOLE SERIES

XLVII.* 2-ACYL- AND 2-ACYL-3-ALKYL-SUBSTITUTED IMIDAZO[2,1-b]-THIAZOLE AND IMIDAZOLINO[2,1-b]THIAZOLE

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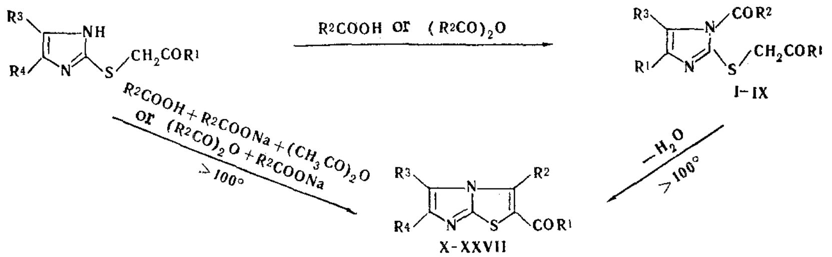
A number of 2-acyl(2-acyl-3-alkyl)imidazo[2,1-b]thiazoles and previously unknown 2-acyl-(2-acyl-3-alkyl)imidazolino[2,1-b]thiazoles were obtained by the reaction of 2-acylmethylmercapto derivatives of imidazole and imidazoline with acylating agents.

In developing the research in [2] it was of interest to elucidate whether the reaction of 2-acylmethylmercaptoimidazoles with acetic anhydride is a special case of the formation of 2-acyl-3-methylimidazo-[2,1-b]thiazoles or if it is general in character and can be used for the synthesis of the difficult-to-obtain or previously unknown aldehydes and ketones of the imidazo[2,1-b]thiazole and imidazolino[2,1-b]thiazole series.

We established that 2-acylmethylmercaptoimidazoles [1,3,4], as in the case of acetic anhydride, also form the corresponding N-acyl derivatives (I-IX, Table 1) by reaction with formic acid or propionic anhydride. Compounds I-IX readily split out a water molecule and are converted to 2-acyl- and 2-acyl-3-alkyl-substituted imidazo[2,1-b]thiazoles (X-XXVII, Table 1).

A simpler, one-step method for obtaining aldehydes and ketones of the imidazo[2,1-b]thiazole series is the reaction of 2-acylmethylmercaptoimidazoles with formic acid in the presence of sodium formate and acetic anhydride or with carboxylic acid anhydrides in the presence of sodium salts of the corresponding acids.



We synthesized a number of previously unknown 2-acyl(2-acyl-3-alkyl)imidazolino[2,1-b]thiazoles (XXX-XXXIII) via a similar scheme from the accessible 2-acylmethylmercaptoimidazolines [5].

The structures of the compounds obtained were confirmed by IR spectra, reactions at the carbonyl group, and the alternative synthesis of 2-acetyl-3-methyl-5,6-diphenylimidazo[2,1-b]thiazole (XXI) from 4,5-diphenyl-2-mercaptoimidazole with 3-chloro-2,4-pentanedione [1].

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*See [1] for communication XLVI.

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TABLE 1. 1-Acyl-2-acylmethylmercaptoimidazoles (I-IX) and 2-Acylimidazo[2,1-b]thiazoles (X-XXVII)

Compound	R^1	R^2	R^3	R^4	Mp, °C	ν_{CO}, cm^{-1}[a]	Empirical formula	Found, %				Calculated, %				Yield, %
								C	H	N	S	C	H	N	S	
I	CH_3	H	p-$NO_2C_6H_4$	H	152—154	—	$C_{13}H_{11}N_3O_4S$	—	—	13,5	10,3	—	—	13,8	10,5	82
II	C_6H_5	H	p-$NO_2C_6H_4$	H	141—142	1690, 1747	$C_{18}H_{13}N_3O_4S$	59,2	3,6	11,5	8,6	58,9	3,6	11,4	8,7	92
III	p-BrC_6H_4	H	p-$NO_2C_6H_4$	H	119—120	1676, 1735	$C_{18}H_{12}BrN_3O_4S$[b]	48,6	3,0	9,2	7,0	48,4	2,7	9,4	7,2	90
IV	CH_3	C_2H_5	C_6H_5	H	167—169	1727	$C_{15}H_{16}N_2O_2S$	62,4	5,6	9,7	11,2	62,5	5,6	9,7	11,1	60
V	C_6H_5	C_2H_5	C_6H_5	H	174—175	1688, 1780	$C_{20}H_{18}N_2O_2S$	68,9	5,1	7,9	9,1	68,6	5,2	8,0	9,1	43
VI	p-BrC_6H_4	C_2H_5	C_6H_5	H	173—175	1692, 1738	$C_{20}H_{17}BrN_2O_2S$[b]	56,5	3,9	6,3	7,5	56,9	4,0	6,5	7,5	60
VII	CH_3	C_2H_5	p-$NO_2C_6H_4$	H	210—212	1729	$C_{15}H_{15}N_3O_4S$	54,3	4,4	12,4	9,5	54,0	4,5	12,6	9,6	82
VIII	C_6H_5	C_2H_5	p-$NO_2C_6H_4$	H	196—198	1698, 1737	$C_{20}H_{17}N_3O_4S$	61,1	4,0	10,4	8,4	60,8	4,3	10,6	8,1	87
IX	p-BrC_6H_4	C_2H_5	p-$NO_2C_6H_4$	H	197—198	1695, 1741	$C_{20}H_{16}BrN_3O_4S$[b]	50,9	3,4	8,6	6,5	50,6	3,4	8,9	6,8	75
X	C_6H_5	H	H	H	112—113	1633	$C_{12}H_8N_2OS$	62,9	3,6	12,0	14,2	63,1	3,5	12,3	14,1	84
XI	p-$NO_2C_6H_4$	H	H	H	208—209	1650	$C_{12}H_7N_3O_3S$	52,7	2,6	15,5	11,6	52,7	2,6	15,4	11,7	68
XII	C_6H_5	H	C_6H_5	H	126—127	1630	$C_{18}H_{12}N_2OS$	70,9	4,3	8,8	10,8	71,0	4,0	9,2	10,5	82
XIII	p-BrC_6H_4	H	C_6H_5	H	256—257	1632	$C_{18}H_{11}BrN_2OS$[b]	56,7	2,8	7,2	8,5	56,4	2,9	7,3	8,4	96
XIV	p-$NO_2C_6H_4$	H	C_6H_5	H	258—261	1640	$C_{18}H_{11}N_3O_3S$	61,6	3,2	11,7	9,3	61,9	3,2	12,0	9,2	85
XV	CH_3	H	p-$NO_2C_6H_4$	H	192—195	1630	$C_{13}H_9N_3O_3S$	—	—	14,6	11,4	—	—	14,6	11,2	77—98
XVI	C_6H_5	H	p-$NO_2C_6H_4$	H	162—164	1670	$C_{18}H_{11}N_3O_3S$	62,1	3,6	11,9	9,2	61,9	3,2	12,0	9,2	90—93
XVII	CH_3	H	C_6H_5	C_6H_5	226—227	1675	$C_{19}H_{14}N_2OS$	71,7	4,6	9,0	10,2	71,7	4,4	8,8	10,1	91
XVIII	p-BrC_6H_4	H	C_6H_5	C_6H_5	194—195	1630	$C_{24}H_{15}BrN_2OS$[b]	62,7	3,2	6,1	6,9	62,7	3,3	6,1	7,0	93
XIX	p-$NO_2C_6H_4$	H	C_6H_5	C_6H_5	167—169	—	$C_{24}H_{15}N_3O_3S$	67,4	3,8	9,8	7,4	67,7	3,6	9,9	7,5	94
XX	H	CH_3	C_6H_5	C_6H_5	228—229	1668	$C_{19}H_{14}N_2OS$[c]	71,9	4,4	8,6	10,2	71,7	4,4	8,8	10,1	72
XXI	CH_3	CH_3	C_6H_5	C_6H_5	190—191	1648	$C_{20}H_{16}N_2OS$[d]	—	—	—	—	—	—	—	—	52
XXII	p-BrC_6H_4	CH_3	C_6H_5	C_6H_5	175—176	1631	$C_{25}H_{17}BrN_2OS$[b]	63,4	3,6	6,2	6,8	63,4	3,6	5,9	6,8	94
XXIII	H	C_2H_5	C_6H_5	C_6H_5	181—183	1671	$C_{20}H_{16}N_2OS$	72,3	4,9	8,3	9,9	72,3	4,8	8,4	9,7	96
XXIV	p-BrC_6H_4	C_2H_5	C_6H_5	H	161—163	1650	$C_{20}H_{15}BrN_2OS$[b]	58,0	3,4	6,9	7,9	58,4	3,6	6,8	7,8	76—80
XXV	CH_3	C_2H_5	p-$NO_2C_6H_4$	H	210—212	1650	$C_{15}H_{13}N_3O_3S$	57,4	4,4	12,9	10,2	57,1	4,2	13,3	10,2	63
XXVI	C_6H_5	C_2H_5	p-$NO_2C_6H_4$	H	218—220	1639	$C_{20}H_{15}N_3O_3S$	63,5	3,8	11,3	8,5	63,7	4,0	11,1	8,5	42—55
XXVII	p-BrC_6H_4	C_2H_5	C_6H_5	C_6H_5	170—173	1658	$C_{26}H_{19}BrN_2OS$	64,3	4,2	5,4	6,8	64,1	3,9	5,7	6,6	85

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

[b] The Br content was determined and agreed with the calculated value within the limits of the error in the determination.

[c] p-Nitrophenylhydrazone with mp 254-255° (decomp., from ethanol–dioxane). Found %: C 63.9; H 4.4; N 14.8; S 6.4. $C_{25}H_{19}N_5O_2S \cdot H_2O$. Calculated %: C 63.6; H 4.5; N 14.4; S 6.8.

[d] Mp 190-191° [1].

EXPERIMENTAL

1-Formyl-2-acylmethylmercaptoimidazoles (I-III). A previously prepared and cooled mixture of 10 ml of 85% formic acid in 20 ml of acetic anhydride was added to 0.01 mole of 2-acylmethylmercaptoimidazole, and the reaction mass was allowed to stand for 18 h at 18-20° and poured into water (with cooling). The precipitate was filtered, washed with water, dried in a vacuum desiccator over $CaCl_2$, and purified by reprecipitation with water from dimethylformamide.

1-Propionyl-2-acylmethylmercaptoimidazoles (IV-IX). A solution of 0.01 mole of 2-acylmethylmercaptoimidazole in 10-20 ml of propionic anhydride was heated at 135-140° (bath temperature) for 10 min (to obtain IV), 40 min (for V-VII), and for 1 h (for VIII-IX). The mixture was cooled, and the precipitate was filtered, washed with ether, and crystallized from ethanol (IV), butanol (V-VII), dioxane (VIII), or ethanol–dioxane (IX).

2-Acyl(2-acyl-3-alkyl)imidazo[2,1-b]thiazoles (X-XXVII). A. An equivalent quantity of sodium formate dihydrate and 20-30 ml of a mixture prepared from 85% formic acid and acetic anhydride (1 : 2) were added to 0.01 mole of the 2-acylmethylmercaptoimidazole. The reaction mass was refluxed for 1 h (to obtain XII), for 1.5 h (XV), 2 h (X, XIII-XVI, XVIII, XIX), 3 h (XI), or for 4 h (XVII), cooled, poured into water, and the resulting precipitate was filtered and washed with water.

B. A mixture of 0.01 mole of 2-acylmethylmercaptoimidazole, an equivalent amount of sodium acetate or propionate, and 15-40 ml of acetic or propionic anhydride was refluxed for 20 min (to obtain XXI, XXII, XXV, and XXVII), for 30 min (XXIV), or for 1 h (XX, XXIII, and XXVI) and cooled. The resulting precipitate was filtered and washed with ether and water; XXII was isolated by elution of the reaction mass with water, while XX, XXIII, and XXIV were isolated after dilution of the reaction mass with water and subsequent neutralization with ammonium hydroxide. The precipitate of XX was removed by filtration, while XXIII and XXIV were extracted with chloroform.

C. A mixture of 0.01 mole of VI-VIII, an equivalent amount of sodium propionate, and 10-15 ml of propionic anhydride was refluxed for 20 min (to obtain XXIV and XXV) or for 1 h (XVI), cooled, and worked up as described in experiment B. Compounds XV and XVI were similarly obtained from I and II by heating in acetic anhydride in the presence of sodium formate for 3 h at 95-100°. For analysis, the compounds were purified by crystallization from 60% ethanol (X and XVI), butanol (XI, XIV, XVIII, and XXV), ethanol (XII, XVII, XIX, XX, and XXIV), ethanol–dioxane (XIII and XXVI), propanol (XV), ethanol–butanol (XXI, XXII, XXVII), or methanol (XXIII).

1-Acetyl-2-phenacylmercaptoimidazoline (XXVIII). 2-Phenacylmercaptoimidazoline (2 g) was added with cooling to 30 ml of acetic anhydride, the solution was allowed to stand for 4 h at 15-20°, and 50 ml of ether was added. The precipitate was filtered and washed with ether to give 1.8 g (77%) of a product with mp 142-143° (decomp., from ethanol). IR spectrum: 1679 cm^{-1} (CO). Found %: C 59.6; H 5.3; N 10.7; S 12.1. $C_{13}H_{14}N_2O_2S$. Calculated %: C 59.5; H 5.4; N 10.7; S 12.2.

1-Acetyl-2-(p-bromophenacyl)mercaptoimidazoline (XXIX). This was similarly obtained in 88% yield and had mp 155-156° (decomp., from butanol). IR spectrum: 1680 cm^{-1} (CO). Found %: C 45.7; H 3.6; N 8.1; S 9.5. $C_{13}H_{13}BrN_2O_2S$. Calculated %: C 45.7; H 3.8; N 8.2; S 9.4.

2-Benzoylimidazolino[2,1-b]thiazole (XXX). A mixture of 10 ml of 85% formic acid and 20 ml of acetic anhydride was added to 2 g of 2-phenacylmercaptoimidazoline and 2 g of sodium formate, and the resulting solution was heated for 2 h at 55-60°, cooled, and poured into water. The mixture was neutralized with ammonium hydroxide, extracted with chloroform, and base XXX was converted to 2.1 g (86%) of the hydrochloride with mp 251-253° (decomp., by precipitation with ether from absolute ethanol) by the action of alcoholic HCl. IR spectrum: 1630 cm^{-1} (CO). Found %: C 53.9; H 4.3; Cl 13.3; N 10.6; S 12.3. $C_{12}H_{10}N_2OS \cdot HCl$. Calculated %: C 54.0; H 4.2; Cl 13.3; N 10.5; S 12.0.

2-(p-Bromobenzoyl)imidazolino[2,1-b]thiazole (XXXI). This was obtained in the same way as XXX but with the difference that the reaction mass was heated at 95-100°. The hydrobromide was obtained in 70% yield and had mp 286-287° (decomp., by precipitation from ethanol with ether). IR spectrum: 1637 cm^{-1} (CO). Found %: C 36.6; H 2.8; Br 41.0; N 7.0; S 8.0. $C_{12}H_9N_2OS \cdot HBr$. Calculated %: C 36.9; H 2.6; Br 41.0; N 7.2; S 8.2.

2-(p-Nitrobenzoyl)imidazolino[2,1-b]thiazole (XXXII). This was obtained in the same way as XXX (with heating at 95-100° for 2 h). The hydrochloride was obtained in 68% yield and had mp 236-238° (decomp., by precipitation with ether from absolute ethanol). Found %: C 46.5; H 3.5; Cl 11.8; N 13.7; S 10.6. $C_{12}H_9N_3O_3S \cdot HCl$. Calculated %: C 46.2; H 3.2; Cl 11.4; N 13.5; S 10.3.

2-(p-Bromobenzoyl)-3-methylimidazolino[2,1-b]thiazole (XXXIII). A mixture of 2.2 g of XXIX, 2.2 g of sodium acetate, and 15 ml of acetic anhydride was heated for 45 min at 95-100° and worked up as described for XXX to give 86% of hydrobromide with mp 269-270° (decomp., by precipitation with ether from methanol). IR spectrum: 1725 cm^{-1} (CO). Found %: C 38.6; H 3.0; N 7.1; S 8.0. $C_{13}H_{11}BrN_2OS \cdot HBr$. Calculated %: C 38.8; H 3.0; N 6.9; S 7.9.

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