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THE SYNTHESIS OF COMPOUNDS WITH ANTITHYROID ACTIVITY

VII. S- and N-Acyl Derivatives of 2-Mercaptoimidazoles (Imidazole-2-thiones)*

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N-Acyl derivatives of imidazole-2-thione and its derivatives were obtained by the reaction of imidazole-2-thione and its derivatives with aliphatic anhydrides and with benzoyl chloride in pyridine. The hydrochlorides of 1-methyl and 4 (5)-methyl-S benzoylimidazole-2-thione were obtained by the reaction of 1-methyl- and 4(5)-methylimidazole-2-thione with benzoyl chloride in dry ethanol. The acylation of imidazole-2-thione and of some of its derivatives was investigated with the aid of their IR spectra, and the importance of the medium in the formation of N- and S-acyl derivatives was shown, as well as the possibility of the migration of substituents from the S- to the N atom under its influence.

The introduction of the ethoxycarbonyl group into 1-methyl-2-mercaptoimidazole is shown to increase the activity of the latter somewhat (the new derivative was erroneously characterized as 1-methyl-2-ethoxycarbonylthioimidazole (Neomercazole) [2], and was later shown to possess the structure 1-methyl-3-ethoxycarbonyl-2-thioimidazole [3]).

It was thus of interest to synthesize other acylated imidazole-2-thiones and their alkyl- and aryl-derivatives. For this purpose, we used compounds which we had prepared previously [1, 4, 5]. Thus, acylation of imidazole-2-thione and its 1-methyl-, 1-ethyl-, 1-phenyl-, and 4-methyl derivatives with acetic, propionic, butyric, and isobutyric anhydrides, and with benzoyl chloride, in slight excess, in pyridine with heating (except for benzoylation), gave the corresponding N acylated imidazole-2-thiones: 1-acylimidazole-2-thiones (I-III); 1-methyl-3-acylimidazole-2-thiones (IV-VI); 1-ethyl-3-acylimidazole-2-thiones (VIII-IX); 1-phenyl-3-acylimidazole-2-thiones (X-XIII); 1-acyl-4(5)-methylimidazole-2-thiones (XV-XVII).

Constants for the compounds prepared are given in the table. Acylation of 1-methyl- and 4(5)-methylimidazole-2-thione with benzoyl chloride in dry ethanol gave the S-acylated imidazole-2-thione as the hydrochloride. These derivatives are unstable, rearranging readily on standing, or on treatment with pyridine, to the stable N-isomers. All the acyl derivatives were recrystallized from benzene, acetone, ethanol, or dry ether (they are readily hydrolyzed in presence of moisture). The IR spectra of compounds IV, XIV, I, VII, and XVIII were obtained (see figure, curves 1-5) in order to confirm their structures. We wish to thank Prof. Yu. N. Sheinker for the spectrographic investigations. In the crystalline state, compounds I, IV, VII, and XIV possess the thione structure, since their IR spectra possess the band at 1560-1480 cm^{-1} characteristic of the $> N-C=S$ group. The spectrum of XVIII, on the other hand, does not show the band corresponding to the thioamide group, which confirms its sulphide structure. Derivatives of imidazole-2-thione are thus capable of reacting in two ways, depending on the solvent in which the acylation is carried out, to give N- or S-derivatives. Comparison of the spectra of VII and XVIII (Figure, curves 4 and 5) reveals a clear structural difference between them. At the same time, the general shape of the curve of the product obtained by treating compound XVIII with pyridine is identical with that of compound VII (Figure, curves 4 and 6), which shows the possibility of the migration of the benzoyl group from the S- to the N-position under certain conditions. The IR spectra of all the compounds show absorption bands characteristic of the amide $C=O$ stretching frequency at 1724-1695 cm^{-1}.

Experimental

1-Acetyl-4(5)-methylimidazole-2-thione (XIV). Acetic anhydride (0.015 mole) was added to a solution of 4(5)-methylimidazole-2-thione (0.01 mole)[6] in pyridine (15 min), and the mixture heated on a water-bath for 2 hr. The solvent was vacuum-distilled off, and the residue recrystallized from benzene. Mp 200°-202° C [7]. The remaining N-acyl derivatives of imidazole-2-thione were prepared similarly (I-XVII), except for compound VII.

1-Methyl-3-benzoylimidazole-2-thione (VII). 1-Methylimidazole-2-thione (0.01 mole) was dissolved in 15 ml of pyridine, and benzoyl chloride (0.015 mole) added. The mixture became warm, and compound VII separated as a yellow oil which crystallized on addition of ether. Crystallization from dry ethanol, then from ether, gave material mp 98°-100° C (lit. [3] mp 102°).

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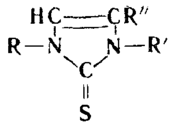
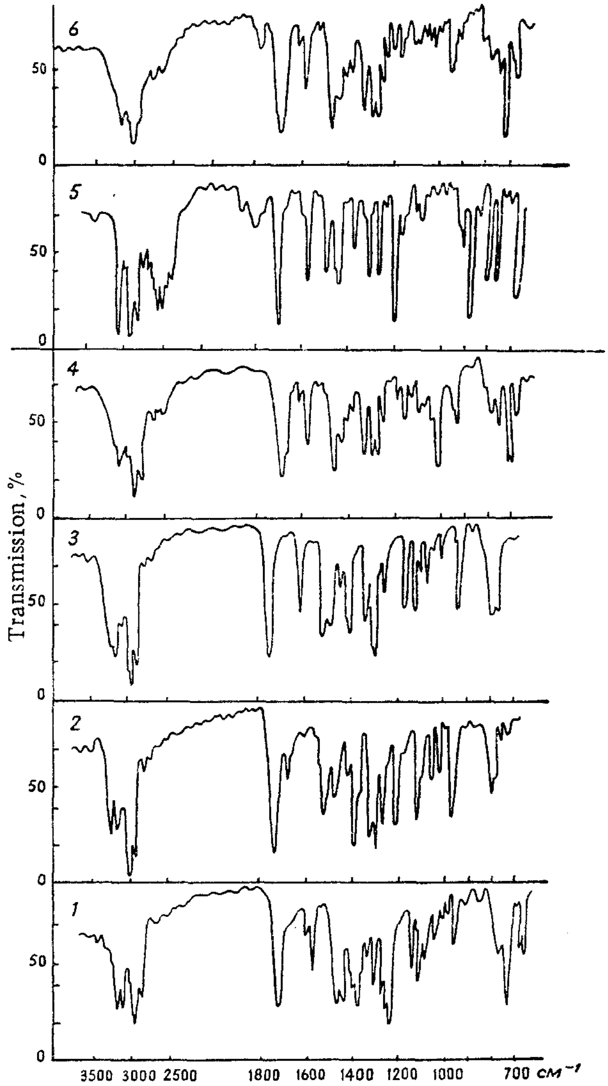
* For part VI see [1].

N-Acyl Derivatives of Imidazole-2-thiones



Compound number	R	R′	R″	Mp, °C	Formula	N, %		Crystalline form	Yield %
						Found	Calculated		
I	CH_3CO	H	H	141—143	$C_5H_6N_2OS$	19.95; 19.72	19.71	Colorless needles	60
II	C_2H_5CO	H	H	142—144	$C_6H_8N_2OS$	18.24; 18.45	17.95	" "	33
III	C_3H_7CO	H	H	80—82	$C_7H_{10}N_2OS$	16.35; 16.50	16.47	Shining needles	52
IV	CH_3	CH_3CO	H	72—74	$C_6H_8N_2OS$	17.45; 17.99	17.95	Slender needles	50
V	CH_3	C_2H_5CO	H	84—86	$C_7H_{10}N_2OS$	16.11; 16.50	16.47	Colorless plates	44
VI	CH_3	C_3H_7CO	H	59—61	$C_8H_{12}N_2OS$	15.67; 15.72	15.21	Colorless needles	56
VII	CH_3	C_6H_5CO	H	98—100	$C_{11}H_{10}N_2OS$	—	—	Yellow needles	54
VIII	C_2H_5	CH_3CO	H	64—66	$C_7H_{10}N_2OS$	16.52; 16.79	16.47	Colorless needles	45
IX	C_2H_5	C_2H_5CO	H	48—50	$C_8H_{12}N_2OS$	14.47; 14.76	15.21	" "	48
X	C_6H_5	CH_3CO	H	117—119	$C_{11}H_{10}N_2OS$	12.62; 12.97	12.84	Colorless plates	70
XI	C_6H_5	C_2H_5CO	H	142—144	$C_{12}H_{12}N_2OS$	11.57; 11.85	12.07	" "	45
XII	C_6H_5	C_3H_7CO	H	92—93	$C_{13}H_{14}N_2OS$	11.63; 11.74	11.38	" "	56
XIII	C_6H_5	*i*-C_3H_7CO	H	97—99	$C_{13}H_{14}N_2OS$	11.67; 11.70	11.38	" "	60
XIV	CH_3CO	H	CH_3	200—202[7]	$C_6H_8N_2OS$	—	—	Small clusters of needles	54
XV	C_2H_5CO	H	CH_3	194—196	$C_7H_{10}N_2OS$	16.67; 16.72	16.47	Colorless needles	94
XVI	C_3H_7CO	H	CH_3	172—174	$C_8H_{12}N_2OS$	15.18; 15.20	15.21	" "	96
XVII	*i*-C_3H_7CO	H	CH_3	155—157	$C_8H_{12}N_2OS$	15.69; 15.75	15.21	" "	98



IR spectra: 1) 1-Methyl-3-acetylimidazole-2-thione; 2) 1-acetyl-4(5)-methylimidazole-2-thione; 3) 1-acetylimidazole-2-thione; 4) 1-methyl-3-benzoylimidazole-2-thione; 5) 1-methyl-S-benzoylimidazole-2-thiol hydrochloride.

1-Methyl-S-benzoylimidazole-2-thiol hydrochloride (XVIII). 0.015 mole of benzoyl chloride was added to a solution of 1-methylimidazole-2-thione (0.01 mole) in 10 ml of dry ethanol. A colorless, crystalline precipitate separated, mp 181°–183° C (from dry ethanol) [3]. Found: N 11.77, 11.26%. Calculated for $C_{11}H_{10}N_2OS:HCl$, N 11.01%. This compound, on treatment with pyridine, gave a yellow crystalline compound, mp 98°–100°, which gave no depression of mp on admixture with compound VII).

4(5)-Methyl-S-benzoylimidazole-2-thiol hydrochloride (XIX). To a solution of 4(5)-methylimidazole-2-thione (0.01 mole) in 10 ml of dry ethanol was added 0.015 mole of benzoyl chloride. The mixture was kept for three days, the solvent vacuum-distilled off, and the residue washed with ether. It was then dissolved in dry ethanol and precipitated with ether. Colorless plates, mp 161°–163° C (from a mixture of ether and ethanol), yield 90%. Found N 10.84, 11.26%. Calculated for $C_{11}H_{10}N_2OS \cdot HCl$; N 11.01%.

The IR spectra of compounds I, IV, XIV, and XVIII were obtained with an IKS-14 spectrometer, and of compound VII with an UR-10 instrument, in the crystalline state as a paste with vaseline oil, using a NaCl prism.

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