STUDIES IN THE IMIDAZOLE SERIES

LV.* SYNTHESIS OF IMIDAZO[1,2-f]XANTHINE DERIVATIVES BASED ON 8-METHYLMERCAPTOTHEOPHYLLINE

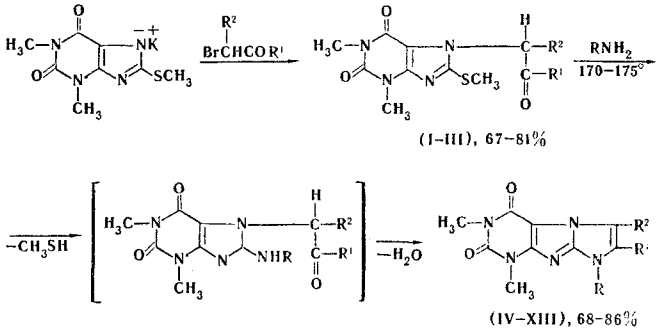
A. A. Tkachenko, P. M. Kochergin, and G. F. Panchenko

UDC 547.785.5'857.4.07

Imidazo[1,2-f]xanthine derivatives were synthesized by the reaction of 8-methylmercaptotheophylline with α-haloketones and subsequent heating of the 7-acylalkyl-8-methylmercaptotheophyllines with ammonia and primary amines.

We have previously described the synthesis of imidazo[1,2-f]xanthine derivatives from 8-amino(alkylamino, arylamino)theophyllines [1] and 8-bromotheophylline [2]. This paper is devoted to the synthesis of imidazo[1,2-f]xanthines [3] based on 8-mercaptoxanthines, since the latter are accessible compounds and can be obtained by direct synthesis from 4,5-diaminouracils [4-8]. Since nucleophilic substitution of a methylmercapto group by an amino(alkylamino) group [9,10] proceeds readily in the 8-methylmercaptopurine series, it may also be expected to be successful in the 8-methylmercaptoxanthine series.

We used 8-methylmercaptotheophylline [11] as the starting material. It was found that its potassium salt readily reacts with α-haloketones in alcohol or in dimethylformamide to form 7-acylalkyl-8-methylmercaptotheophyllines (I-III, Table 1). When I-III are heated with ammonia or primary amines in alcohol at 170-175°, the methylmercapto group is replaced by an amino (alkylamino, arylamino) group, and the intermediate 7-acylalkyl-8-amino(alkylamino, arylamino)theophyllines cyclize simultaneously to give imidazo[1,2-f]xanthine derivatives (IV-XIII, Table 1).



(I-III), 67-81%

(IV-XIII), 68-86%

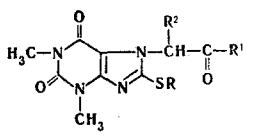
R=H, Alk, Ar; R¹=Alk, Ar; R²=H, Alk

The purity of I-XIII was proved by two-dimensional paper chromatography, while the structures of the three-ringed compounds as 1H-imidazo[1,2-f]xanthine derivatives was proved by the fact that IV, V, IX, and X were identical to compounds previously obtained by cyclization of 7-phenacyl-8-amino(methylamino)-theophyllines [1] or by the reaction of 7-phenacyl-8-bromotheophylline with ammonia and methylamine [1,2].

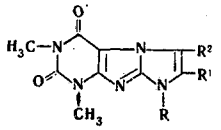
*See [1] for communication LIV.

Zaporozhe Medicinal Institute. S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical-Chemistry Institute, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 686-688, May, 1971. Original article submitted October 28, 1969.

TABLE 1. 7-Acylalkyl-8-methylmercaptotheophyllines (I-III) and Imidazo[1,2-f]xanthine Derivatives (IV-XIII)[a]



I-III



IV-XIII

Comp.	R	R¹	R²	mp (decomp)	Empirical formula	Found, %			Calc., %			Yield, %
						C	H	N	C	H	N	
I[b]	CH_3	CH_3	H	186—187	$C_{11}H_{14}N_4O_3S$[c]	47,0	5,1	19,6	46,8	5,0	19,8	67
II	CH_3	CH_3	CH_3	162—164	$C_{12}H_{16}N_4O_3S$[d]	48,8	5,4	19,1	48,6	5,4	18,9	81
III	CH_3	C_6H_5	H	202—203	$C_{16}H_{16}N_4O_3S$[e]	55,8	4,8	16,1	55,8	4,7	16,3	80
IV	H	CH_3	H	360	$C_{10}H_{10}N_5O_2$[f]	—	—	—	—	—	—	69
V	CH_3	CH_3	H	249—250	$C_{11}H_{13}N_5O_2$[g]	—	—	—	—	—	—	69
VI	CH_2CH_2OH	CH_3	H	252—254	$C_{12}H_{15}N_5O_3$	51,4	5,4	25,0	52,0	5,5	25,3	82
VII	CH_2CH_2OH	CH_3	CH_3	203—206	$C_{13}H_{17}N_5O_3$	53,5	5,9	24,3	53,6	5,9	24,0	68
VIII	n-C_3H_7	CH_3	CH_3	153—155	$C_{14}H_{19}N_5O_2$	58,2	6,4	24,0	58,1	6,6	24,2	71
IX	H	C_6H_5	H	340—345	$C_{15}H_{13}N_5O_2$[h]	—	—	—	—	—	—	70
X	CH_3	C_6H_5	H	235—236	$C_{16}H_{15}N_5O_2$[i]	—	—	—	—	—	—	71
XI	CH_2CH_2OH	C_6H_5	H	236—237	$C_{17}H_{17}N_5O_3$	60,5	5,0	20,5	60,2	5,1	20,6	70
XII	C_6H_{11}	CH_3	CH_3	230—232	$C_{17}H_{23}N_5O_2$	62,2	6,7	21,4	62,0	7,0	21,3	73
XIII	m-C_6H_4-CH_3	CH_3	CH_3	212—214	$C_{18}H_{19}N_5O_2$	64,1	5,5	20,9	64,1	5,7	20,8	86

[a]The compounds were purified for analysis by crystallization: I, II, VIII, and XII from aqueous methanol (1 : 1); III, VI, VII, and XI from methanol; IV, V, and X from ethanol; IX from glacial acetic acid; XIII from acetone–water (1 : 1).

[b]IR spectrum, cm^{-1}: I 1660, 1700, 1730 (CO); II 1655, 1700, 1728 (CO); III 1660, 1695 (CO); IV 1664, 1708 (CO); V 1668, 1700 (CO); VI 1670, 1711 (CO), 3300 (OH); IX 1663, 1695 (CO), 3150 (NH); X 1645, 1707 (CO); XI 1668, 1695 (CO), 3400 (OH); XIII 1666, 1710 (CO). The spectra were obtained from solid suspensions in mineral oil with a UR-10 spectrometer.

[c]Found %: S 11.6. Calculated %: S 11.4.

[d]Found %: S 10.8. Calculated %: S 10.8.

[e]Found %: S 9.2. Calculated %: S 9.3.

[f]Decomposes above 360° [2].

[g]mp 249-250° [2].

[h]Decomposes at 340-345° [1].

[i]mp 235.5-236° [2].

EXPERIMENTAL*

8-Methylmercaptotheophylline. This was obtained by the method in [11], with the difference that the reaction was carried out in 50% methanol rather than in water. The yield of a product with mp 307-310° (decomp., from aqeuous ethanol) was 83%. The potassium salt was obtained by heating 0.02 mole of 8-methylmercaptotheophylline with 0.03 mole of KOH in 35 ml of methanol. The solution was cooled, and the precipitate was filtered and washed with methanol to give 76% of a product with mp 277-280° (decomp., from methanol).

7-Acylalkyl-8-methylmercaptotheophylline (I-III). The α-bromoketone (0.06 mole) was added to a suspension of the potassium salt of 8-methylmercaptotheophylline in 200 ml of hot methanol, and the mixture was refluxed for 2-3 h, filtered, and the filtrate was cooled. The resulting precipitate was filtered and washed with water and ether. In the preparation of II the reaction was carried out in 100 ml of dimethylformamide at the boiling point for 30 min, and the solution was evaporated in vacuo to half its original

*We thank V. V. Kolpakova and Yu. N. Sheinker and their co-workers for performing the microanalyses and obtaining the IR spectra of the compounds.

volume and cooled. The product was a colorless, crystalline substance which was slightly soluble in most organic solvents and insoluble in water.

Imidazo[1,2-f]xanthine Derivatives (IV-XIII). A mixture of 0.025 mole of I-III and 50 ml of 15-25% of alcoholic ammonia, methylamine, or 0.05 mole of another primary amine in 60 ml of methanol was heated for 8 h in an autoclave (0.15 liter) at 170-175°. The mixture was then cooled, and the precipitate was filtered and washed with water and acetone. Evaporation of the mother liquor to a small volume gave an additional amount of compound.

8-Propylaminotheophylline (XIV). A. This was obtained in 92% yield by heating 0.025 mole of 8-bromotheophylline [12] with 0.05 mole of propylamine in 50 ml of methanol at 160° (5-6 h) and had mp 292-295° (from acetic acid). Found %: C 50.8; H 6.1; N 29.3. $C_{10}H_{15}N_5O_2$. Calculated %: C 50.6; H 6.4; N 29.5.

B. A mixture of 0.3 mole of II, 0.06 mole of propylamine, and 60 ml of methanol was heated for 8 h at 185-190°. The mixture was cooled, and the precipitate was filtered and washed with water and ether to give 66% of XIV with mp 292-295°.

C. A solution of 0.01 mole of VIII in 50 ml of methanol was heated and worked up as in experiment B to give 51% of XIV with mp 292-295°.

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