REACTION OF 7-ACYLMETHYL-8-BROMO-3-METHYLXANTHINES WITH

FORMAMIDE

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A method has been developed for the synthesis of imidazo[1,2-f]xanthines and oxazolo[2,3-f]xanthine by the reaction of 7-acylmethyl-8-bromoxanthines with formamide.

In continuation of the investigations of synthesis in the series of annelated xanthine and purine derivatives [1-3], we studied the reaction of 7-acylmethyl-8-bromo-3-methylxanthines (Ia-d) with formamide. Ketones Ia-d were obtained by reacting the potassium salt of 8-bromo-3-methylxanthine [4] with the corresponding α -bromoketones in DMFA, in analogy to [1].



Ia IIa $R=R^1=CH_3$; Ib R=H, $R^1=C_6H_4NO_2-p$; IC II6 R=H, $R^1=C_6H_4Cl-p$; Id II_C R=H, $R^1=C_6H_4Br-p$

In the IR spectra of ketones Ia-d, there are stretching vibration bands of the carbonyl groups in the 1680-1700 cm⁻¹. In the PMR spectrum of 3-methyl-7-p-chlorophenacyl-8-bromo-3-methylxanthine (Ic), the following proton signals were recorded (ppm): $3.20 - \text{NCH}_3$ (s, 3H), $5.53 - N_7\text{CH}_2$ (s, 2H), an AB system with a center at $7.33 - \text{CH}_{\text{arom}}$ (q, 4H).

It is known [5] that heating of formamide with halides leads to the formation of either formylamines or formates, while with hydroxy- or haloketones, formamide forms imidazoles. It was therefore of interest to study the reaction of ketones Ia-d with formamide, as the result of which heteroannelated derivatives of xanthine with one of the above indicated structures could theoretically be formed (see scheme).

We found that, depending on the substituents in the side chain, the reaction of ketones Ia-d proceeds in two directions only. A brief boiling of 3-methyl-7-(1-methyl-2-oxo-1-propyl), 7-p-chlorophenacyl-, and 7-p-bromophenacyl-8-bromoxanthines (Ia,c,d) in excess of formamide leads to substituted imidazo[1,2-f]xanthines (IIa-c). The PMR spectrum of 1,6,7-trimethylamidazo[1,2-f]xanthine (IIa) is characterized by the presence of three

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Com- pound	тр, °С	Found, %			Empirical	Calculated, %			Yield
		с	н	N	formula	с	н	N	*
la Ib Ic Id Ila Ilb Ilc III	$\begin{array}{r} 233 - 235\\ 281 - 282\\ 290 - 292\\ 304 - 305\\ > 330\\ > 330\\ > 330\\ > 330\\ > 330\\ > 330\end{array}$	38,3 41,3 42,3 38,2 51,3 53,5 46,9 50,9	3,4 2,4 2,8 2,4 4,7 3,0 3,0 3,2	17,5 17,3 14,3 12,4 30,0 22,6 19,3 21,7	$\begin{array}{c} C_{10}H_{11}BrN_4O_5\\ C_{14}H_{10}BrN_5O_5\\ C_{14}H_{10}BrCIN_4O_3\\ C_{14}H_{10}Br_2N_4O_3\\ C_{14}H_{10}Br_2O_2\\ C_{14}H_{10}SO_2\\ C_{14}H_{10}CIN_5O_2\\ C_{14}H_{10}BrN_5O_2\\ C_{14}H_{9}N_5O_5 \end{array}$	38,1 41,2 42,3 38,0 51,5 53,3 46,7 51,4	3,5 2,4 2,5 2,3 4,6 3,2 2,8 2,8 2,8	17,8 17,2 14,1 12,7 30,0 22,2 19,4 21,4	41 88 89 76 52 71 75 69

TABLE 1. Characteristics of Synthesized Compounds

TABLE 2. Mass Spectra of Synthesized Compounds*

Compound	Mass spectrum, m/z (intensity, %)						
lla	53 (20), 67 (16), 73 (8), 82 (12), 95 (10), 120 (10), 135 (18), 161 (40), 162 (24) 163 (10) 189 (10) 199 (18) 232 (7) 233 (100) 234 (12)						
Ι ΙЪ	$\begin{array}{c} \textbf{43} (33), \ 75 (20), \ 82 (23), \ 91 (10), \ 101 (15), \ 127 (17), \ 138 (10), \ 182 (12), \ 208 (10), \ 217 (24), \ 219 (8), \ 243 (55), \ 244 (44), \ 246 (40), \ 247 (16), \ 182 (12), \ 218 (10), \ 217 (24), \ 219 (8), \ 243 (55), \ 244 (24), \ 246 (40), \ 247 (16), \ 24$						
Ис	43 (26), 70 (12), 75 (16), 76 (10), 82 (17), 91 (20), 100 (10), 101 (14), 107 (11), 127 (22), 182 (18), 194 (10), 208 (13), 261 (13), 263 (13), 287						
111	(35), 288 (25), 289 (41), 290 (25), 316 (32), 317 (13), 318 (32), 359 (98), 360 (18), 361 (100), 362 (17) 56 (13), 73 (10), 83 (12), 89 (19), 101 (10), 117 (11), 147 (8), 150 (9), 209 (18) 210 (10) 255 (7) 281 (8) 284 (10) 297 (21) 237 (100) 235						
	(17) (10), 210 (10), 230 (1), 261 (6), 264 (10), 251 (21), 521 (100), 526 (17)						

*Given are ion peaks with intensity of \geq 7%. Evaporation temperature of the sample 240°C (for (IIa) and 300°C for(II b, c, III)).

narrow singlets with an intensity ratio of 1:1:1 at 3.27 (N_1CH_3), 2.17 (C_6CH_3) and 1.9 ppm (C_7CH_3). In the mass spectrum of imidazoxanthine(IIa), a peak of M⁺ with m/z 233 is recorded, which corresponds to the calculated molecular weight. The presence of an isotopic peak with m/z 234 and intensity of 12.8% corresponds to the empirical formula of the molecule $C_{10}H_{11}N_5O_2$. The high stability to electron impact ($W_M = 18\%$) confirms the cyclic character of imidazo [1,2-f]xanthine (IIa). The dissociation of M⁺ can be represented by the following ions (m/z): [M - H]⁺ - 232 (a β -dissociation leading to widening of the imidazole ring), [M - NCHO]⁺ - 190 (retrodienic dissociation of the uracil fragment of the molecule), [M - HNCO) - CO]⁺ - 162 and [(M - HCNO) - CO - HCN]⁺ - 135 (ions confirming the structure of the uracil part of the molecule) [6], [(M - HNCO) - H]⁺ - 189, [(M - HNCO) - COH]⁺ - 161, [(M - HCO) - CO - HCN - CH_3]⁺ - 120 (ions confirming the presence of the imidazole fragment in the molecule of IIa). The mass spectra of imidazoxanthines IIa-c are given in Table 2.

Under similar conditions, the reaction of 3-methyl-7-p-nitrophenyl-8-bromoxanthine (Ib) with formamide results in the formation of 2-p-nitrophenyl-6H-8-methyloxazole [2,3-f]xanthine (III), which is a representative of a new heteroaromatic system. In the PMR spectrum of oxazole III there are two singlets at $3.27 - N_8CH_3$ (3H) and 7.67 ppm - C_3H (1H). The proton signals of para-substituted phenyl ring are represented by an AB system with a center at 7.61 ppm (4H). The mass spectrum of oxazole III has a peak of M⁺ with m/z 327. According to high-resolution mass spectrometry data, the empirical formula of the molecule is $C_{14}H_9N_5O_5$ (determined 327.0675, calculated, 327.0655). With the introduction of the nitro group and in the presence of an oxazole ring, the character of the fragmentation of compound III changes substantially in comparison with the case of compounds IIa-c: fragmentary ions with m/z 297 and 281 are observed, characterizing a nitro group in the molecule. The oxazole ring (an α -substitution in it) is confirmed by the presence of an ion with m/z 150-[CO - C_6H_4 - NO_2]⁺. In the mass spectrum of III there are also ions characterizing the uracil fragment of the molecule (Table 2).

All the above data serve to confirm the structure of the compounds obtained.

EXPERIMENTAL

The IR spectra were recorded on an UR-20 spectrophotometer in mineral oil. The PMR spectra were run on a "Tesla BS-467" spectrometer (60 MHz) in CF₃COOH, using HMDS as internal standard. The mass spectra were taken on a "Varian MAT-311A" mass spectrometer with a direct introduction of the sample into the ionic source. Standard measuring conditions were employed: accelerating voltage 3 kW, cathode emission current 30 μ A, ionizing voltage 70 V.

The characteristics of compounds Ia-d, IIa-c and III are given in Table 1.

<u>3-Methyl-7-acylmethyl-8-bromoxanthines (Ia-d).</u> A mixture of 2.83 g (10 mmoles) of potassium salt 3-methyl-8-bromoxanthine [4] and 11 mmoles of the corresponding bromoketone in 30 ml or DMFA is boiled for 1 h to 1 h 30 min, then cooled to 20°C, and diluted with water to 100 ml. The precipitate is filtered, washed with 100 ml of acetone and crystallized from DMFA.

<u>Derivatives of imidazo[1,2-f]xanthine (IIa-c)</u>. A mixture of 0.01 mole of ketone Ia, Ic, or Id is boiled for 15 min with 30 ml of formamide, and then cooled to 20°C. The precipitate is filtered, washed with 200 ml of water and 100 ml of acetone, and crystallized from DMSO.

<u>2-p-Nitrophenyl-6H-8-methyloxazolo[2,3-f]xanthine (III)</u> was obtained in a similar way as IIa-c by reacting 3-methyl-7-p-nitro-8-bromoxanthine (Ib) with formamide.

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