s.	N.	Garmash, B.	Α.	Priimenko,	N.	A.	Klyuev,	UDC 547.857.4'859'785.5.07:
N.	I.	Romanenko,	V	A. Golets,	and	т.	A. Kozik	543.51:542.953:535:37

Oxazolo[3,2-f]xanthines were synthesized by the reaction of 7-acylalkyl-8-bromo-3methyl- and -1,3-dimethylxanthines with sodium benzoate in dimethylformamide. Their alkylation with methyl iodine was studied. The reaction of oxazolo[3,2-f]xanthines with primary amines leads to the previously described imidazo[1,2-f]xanthines.

In [1] we described the synthesis of 2-(p-nitrophenyl)-6H-8-methyloxazolo[3,2-f]xanthine by the action of formamide on 7-(p-nitrobenzoyl)methyl-8-bromo-3-methylxanthine. The goal of the present research was to develop methods for the synthesis of derivatives of this system and to study their properties. Depending on the reaction time, the reaction of 1phenacyl-2-bromopyridinium salts with amines leads to oxazolo[3,2-a]- or imidazo[1,2-a]pyridines [2]. Imidazo[1,2-f]xanthine derivatives are formed in the reaction of 7-acylalkyl-8haloxanthines with primary amines, i.e., the formation of an annealated imidazole ring via intramolecular cyclization occurs [3, 4]. It seemed of interest to accomplish the reaction of 7-acylalkyl-8-haloxanthines with other nucleophilic reagents. Oxazolo[3,2-f]xanthines X-XVIII (Table 1) were obtained by refluxing 7-acylalkyl-8-haloxanthines I-IX with an equimolar amount of sodium benzoate in DMF.

Their structures were confirmed by mass spectrometry. A molecular-ion peak (M^{+}) , which has the maximum intensity, is present in the mass spectra of XI-XIII, XV, and XVI. The stabilities with respect to electron impact (W_M) range from 12% to 17%. The peak of a doubly charged molecular ion is detected in each case. The combination of these data constitutes evidence for the existence of a condensed hetaryl system. The presence of a dioxopyrimidine fragment in the structure of the compounds is confirmed by characteristic $[M - R_sNCO]^+$ (a) and $[M - CONR_sCO]^+$ (b) ions, as well as by the $[R_sNCO]^+$ ion; this is typical for annealated derivatives of xanthine, particularly for imidazo[1,2-f]xanthines and thiazolo[3,2-f]xanthines [5-7]. The presence of an oxazole ring is demonstrated by $R^1-C=C-R^2(c)$,

 $R^2-C\equiv C-R^2$ (d), $R^1-C\equiv 0^+$ (e), and R^{1+} (f) ions.



I, XIII $R^1 = C_6H_4 - C_6H_5 - p$; R^2 , $R^3 = H$; II, XII $R^1 = C_6H_4 - CH_5 - p$; R^2 , $R^3 = H$; III, XVII $R^1 = C_6H_4 - CH_3 - p$; $R^2 = H$; $R^3 = CH_3$; IV, XII $R^1 = C_6H_4 - NO_2 - p$; R^2 , $R^3 = H$; V, XIV $R^1 = C_6H_4 - Br - p$; $R^2 = H$; $R^3 = CH_3$; VII, X, XX, XXII, XXIV $R^1 = C_6H_5$; $R^2 = H$; $R^3 = H$; VIII, XV, XIX, XXI, XXII $R^1 = C_6H_5$; $R^2 = H$; $R^3 = CH_3$; XIX, XX $R = C_6H_5$; $R^2 = H$; $R^3 = CH_3$; XIX R $R^1 = C_6H_5$; $R^2 = C_2H_5$; $R^3 = CH_3$; XIX, XX $R = C_6H_5$; XXI, XXII $R = CH_2C_6H_5$; XXII $R = CH_2C_6H_5$; XXII $R = CH_2C_6H_5$; XXII R = CH_2C_6H_5; XXIV R = H

When there is an NO₂ group in substituent R^1 (XII), an $[M - NO]^+$ ion with m/z 297 (35) and an $[M - NO_2]^+$ ion with m/z 281 (38), as well as an ion with m/z 209 (66), which arises in the case of splitting out of NO₂ from ion b [1], are recorded in the mass spectrum.

In the PMR spectra of oxazolo[3,2-f]xanthines (Table 1) the signals of the protons and their integral intensities correspond to the proposed structures.

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or month	ر •		PMR spectrum,	5, ppm•	Fou	nd, %		Email formula	Calc	ula ted,	g/o	Yield.
minoduloo) •dim	N ₈ -CH ₃	C ₃ H	C ₆ H,X	U	н	z	Emprica volution	U	н	z	%
XI	152154				50,8	4,2	19,8	C ₁₇ H ₁₇ BrN ₄ O ₃	50,4	4,2	19,7	78
×x	340-342 > 320	3,18 (s, 3H)	(7,35 (s, 1H)	6,83—7,33 (m, 5H)	60,6	4,6	19,6 19,3	C ₁₄ H ₁₀ N ₄ O ₃ C ₁₅ H ₁₂ N ₄ O ₃	60,8 0,8	3.0 1,4 0,1,0	18,9	16
	>>300	3,56 (s. 3H)	7,89 (s, 1H)	7.19—7.56 (w. m. 9H)	50,9	2,6	21,9 15,8	C1,H9NsOs C26H1,NAO3	67,0	3,9,4	15,6	881
XIX XV	>360 322-324	[3,75 (s, 3H) [3.26** (s, 3H)	7,73 (s, 1H) 8.75 (s, 1H)	7,45 (br. s, 4H) 7.51-7.83 (m. 5H)	46,4 60.7	4 3 8 3 8 3	15,8 18,5	C ₁ ,H ₃ BrN4O ₃ C ₁₅ H ₁₂ N4O ₃	46,6 60,8	4,1	18,9	81
	212214 316318	3,40 (s, 3H) 3,1** (s, 3H)	7,6 (11H)	7,3 (br. s, 5H) Center of an AB system	61,7	4,2	17,2 18,3	C ₁₇ H ₁₆ N ₄ O ₃ C ₁₆ H ₁₄ N ₄ O ₃	63,9 61,9	3,5 4,6	17,6	94 92
IIIVX	>300	3,13** (s 311)	7,86 (s, 1H)	7,0, 4H ($J=8Hz$) 7,1 (br. s, 5H)	48,1	3,2	15,1	C ₁₅ H ₁₁ BrN4O ₃	48,0	3,0	14,9	94
*See [1] fo	or the PMR s	pectrum of	XII.									

TABLE 1. Characteristics of the Synthesized IX-XVIII

*Signal of the PMR spectrum of XII. *Signal of the protons of the N₆-CH₃ group: 3.49 (s, 3H) for XV, 3.26 (s, 3H) for XVIII, and 3.26 (s, 3H) for XVII. for XVII. ***Ethyl substituent attached to $C_{(3)}$: 1.3 (t, 3H), 3.13 (q, 2H), $J_{1,2} = J_{2,1} = 8$ Hz.

The IR spectra of derivatives of 6H-8-methyloxazolo[3,2-f]xanthines and <math>6,8-dimethyl-oxazolo[3,2-f]xanthines X-XVIII differ little from the spectra of derivatives of imidazo[1,2-f]xanthine [3-5, 7] — the absorption bands of the stretching vibrations of the CH₂, C=O, CH_{arom}, C=N, and C=C groups are found in the same regions. Only the absorption bands of the stretching vibrations of the NH group in 6H-8-methyloxazole[3,2-f]xanthines are shifted to the lower-frequency region (3125-3150 cm⁻¹) as compared with the vibrations in the spectra of 6H-8-methylindazo[1,2-f]xanthines.

6,8-Dimethyloxazolo[3,2-f]xanthine derivatives XV-XVIII can be obtained from the corresponding 6H-8-methyloxazolo[3,2-f]xanthines X-XIV by alkylation with methyl iodide in DMF in the presence of anhydrous potassium carbonate. The samples obtained by this method did not depress the melting points of samples obtained by the direct cyclization of 7-acylalkyl-1,3dimethyl-8-bromoxanthines.

The described 6H-8-methyl- and 6,8-dimethylimidazo[1,2-f]xanthines are formed by the action of primary amines on 6H-8-methyl- and 6,8-dimethyloxazolo[3,2-f]xanthines under severe conditions (heating in a high-boiling amine or in a sealed ampul with excess amine at 175-180°C) (see the scheme). The samples of imidazo[1,2-f]xanthines obtained by this method did not depress the melting points of samples obtained by the reaction of 7-acylalkyl-8-haloxanthines with primary amines.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were obtained with a Specord IR-75 spectrometer. The PMR spectra of solutions in d_6 -DMSO and CF₃COOH were obtained with Tesla BS-467 and Bruker M-250 spectrometers with tetramethylsilane as the internal standard. The mass spectra were recorded with a Varian MAT-311A spectrometer with direct introduction of the samples into the ion source at a vaporization temperature of 100-150°C; the accelerating voltage was 3 kV, the cathode emission current was 1 mA, and the ionizing-electron energy was 70 eV.

The characteristics of the synthesized compounds are presented in Tables 1 and 2.

7-Aroylmethyl-8-bromo-3-methyl- and -1,3-dimethylxanthines I-VIII were obtained by the methods in [8, 9].

 $7-\alpha$ -Ethylbenzoylmethyl-8-bromo-1,3-dimethylxanthine (IX). A mixture of 29.7 g (100 mmole) of the potassium salt of 8-bromo-1,3-dimethylxanthine and 22.7 g (100 mmole) of α -bromobutyrophenone was refluxed in 100 ml of DMF for 30 min, after which it was cooled, diluted with 150 ml of water, and allowed to stand for 48 h at 0°C. The resulting precipitate was removed by filtration, washed with water, and dried. A sample for analysis was crystallized from isopropyl alcohol.

<u>6H-8-Methyl- and -6,8-Dimethyloxazolo[3,2-f]xanthines X-XVIII.</u> A mixture of 10 mmole of the corresponding 3-methyl- or 1,3-dimethyl-7-aroylmethyl-8-bromoxanthine I-IX and 1.44 g

Com- pound	m/z values (relative intensities, %)
XI	43 (29), 83 (50), 91 (10) (f), 115 (27), 116 (12) (d), 119 (6) (e), 132 (5) (c), 148 (11), 210 (29), 224 (12), 225 (8) (b), 253 (5) (a), 281 (16), 295
XII	$ \begin{array}{c} (7), \ 296 \ (100), \ 297 \ (17) \\ 43 \ (12), \ 83 \ (66), \ 122 \ (5) \ (f), \ 146 \ (9), \ 147 \ (5) \ (d), \ 150 \ (9) \ (e), \ 163 \ (5) \ (c), \\ 163, 5 \ (5), \ 240 \ (5), \ 254 \ (11), \ 255 \ (18) \ ('bH), \ 284 \ (8) \ (a), \ 312 \ (5), \ 326 \ (5), \\ \end{array} $
XIII	327 (100), 328 (20) 43 (10), 83 (45), 153 (6) (f), 177 (9), 178 (10) (d), 179 (5), 181 (5) (e), 194 (5) (c), 272 (5), 286 (10), 287 (5) (b), 315 (85) (a), 357 (5), 358 (100),
xv	359 (26) 57 (7), 77 (9) (f), 83 (33), 101 (5), 102 (17) (d), 105 (8) (e), 118 (7) (c), 143(8), 196 (5), 210 (22), 211 (7) (b), 239 (6) (a), 281 (5), 295 (10), 296
XVI	$ \begin{array}{c} (100), \ 297 \ (18) \\ 57 \ (15), \ 77 \ (23) \ (f), \ 83 \ (88), \ 105 \ (10) \ (e), \ 129 \ (40), \ 130 \ (12) \ (d), \ 146 \ (5) \\ (c), \ 162 \ (18), \ 224 \ (5), \ 238 \ (7), \ 239 \ (5) \ (b), \ 267 \ (6) \ (a), \ 295 \ (10), \ 309 \ (46), \\ 323 \ (5), \ 324 \ (100), \ 325 \ (22) \\ \end{array} $
*The	peaks of ions with intensities ≥ 5% of the maximum are

TABLE 2. Mass Spectra of XI-XIII, XV, and XVI*

presented.

(10 mmole) of sodium benzoate was refluxed in 70-100 ml of DMF for 40-60 min, after which it was cooled and diluted with 100-250 ml of water. The resulting precipitate was removed by filtration, washed with water and ethanol, and dried. This method was used to obtain X-XVIII. Samples for analysis were crystallized from DMF or acetic acid.

<u>6,8-Dimethyloxazolo[3,2-f]xanthines XV-XVIII.</u> A mixture of 10 mmole of the corresponding 6H-8-methyloxazolo[3,2-f]xanthine X-XIV, 3.0 ml (50 mmole) of methyl iodide, and 1.4 g (10 mmole) of anhydrous potassium carbonate was refluxed for 1-2 h, after which the hot mixture was filtered. The filtrate was cooled and allowed to stand for 12 h, and the resulting precipitate was removed by filtration (where necessary, the reaction mass was diluted with a twofold volume of water), washed successively with water and ethanol, and dried. This method was used to obtain XV-XVIII in 92-98% yields.

<u>6H-8-Methyl- and 6,8-Dimethylimidazo[1,2-f]xanthines XIX-XXIV.</u> A mixture of 10 mmole of the corresponding 6H-8-methyl- or 6,8-dimethyloxazolo[3,2-f]xanthine X-XVIII and 20-40 mmole of the primary amine in 150 ml of ethanol (methanol) was heated in a sealed ampul at 175-180°C for 4-6 h, after which it was cooled and diluted with 200 ml of water. The resulting precipitate was removed by filtration, washed with ethanol, and dried. This method was used to obtain XIX-XXIV.

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