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SYNTHESIS AND PHYSICOCHEMICAL PROPERTIES OF IMIDAZO[1,2-*f*]XANTHINE DERIVATIVES

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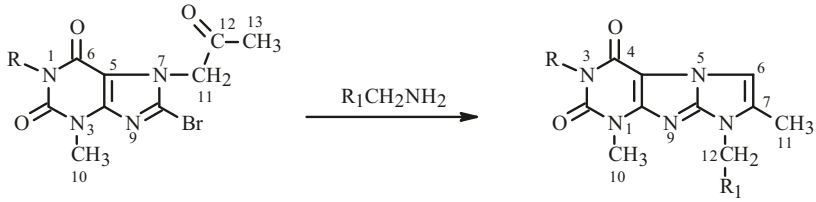
A simple preparative method for the synthesis of imidazo[1,2-f]xanthine derivatives, promising synthons for further modification of the xanthine molecule, was developed. The spectral characteristics of the synthesized compounds were studied.

Keywords: xanthine, synthesis, amines.

Xanthine derivatives that are variously condensed along the "f" edge exhibit a broad spectrum of biological activity [1–4]. Imidazo[1,2-*f*]xanthines are the most studied of these with respect to both chemistry [5–7] and biology [8–11]. The development of simple laboratory synthetic methods for new derivatives of this heteroaromatic system is of great practical and theoretical interest because the xanthine molecule could be substantially modified at the uracil and annelated imidazole cores. Therefore, the library of potential biologically active chemical compounds would be expanded.

Hence, we synthesized previously unknown imidazo[1,2-*f*]xanthine derivatives **3**–**16** by reacting 8-bromo-7-(2-oxopropyl)xanthines (**1** and **2**) [12] with primary aliphatic amines in aqueous dioxane.



1, 2 **3 - 16**

1: R = H; **2:** R = CH_3; **3:** R = H, R_1 = $CH(CH_3)_2$; **4:** R = H, R_1 = *n*-C_4H_9; **5:** R = H, R_1 = *n*-C_5H_{11}
6: R = H, R_1 = $(CH_2)_2$-morpholine-4; **7:** R = CH_3, R_1 = H; **8:** R = CH_3, R_1 = C_2H_5; **9:** R = CH_3; R_1 = *n*-C_3H_7
10: R = CH_3, R_1 = $CH(CH_3)_2$; **11:** R = CH_3, R_1 = *n*-C_4H_9; **12:** R = CH_3, R_1 = *n*-C_5H_{11}; **13:** R = CH_3, R_1 = C_6H_5
14: R = CH_3, R_1 = $CH_2C_6H_5$; **15:** R = CH_3, R_1 = *n*-C_5H_{11}; **16:** R = CH_3, R_1 = $(CH_2)_2OCH_3$

The synthetic method for imidazo[1,2-*f*]xanthines that was proposed by us had important advantages over previously published methods [13, 14]. Water was used as the solvent (dioxane was added for homogenization of the solution). The reaction occurred at 100°C in 1.5-2.0 h. Therefore, this method had more favorable economic factors.

PMR spectra of **3**–**16** (Table 1) had characteristic singlets in the range 7.34–7.24 ppm (1H) and 2.32–1.96 ppm (3H) that were due to resonance of the aromatic proton in the 6-position and methyl protons in the 7-position, respectively, and confirmed unambiguously that an external imidazole ring was present. Methylene proton resonances (2H) of the appropriate shape in the range 4.22–3.78 ppm proved that the alkyl substituent was present in the 8-position.

The benzyl methylene protons were found in the spectrum of **13** as a singlet at weak field of 5.30 ppm. Proton resonances of other substituents in the 8-position of the imidazoxanthine were clearly resolved at the appropriate field with the appropriate shape and intensity (Table 1). The uracil part of **3**–**6** was characterized by singlets in the ranges 10.86–10.69 (1H, N_3H) and 3.40–3.35 ppm (3H, N_1CH_3). Theophylline derivatives **7**–**16** were characterized by two strong singlets in the range 3.45–3.20 ppm that were due to resonance of *N*-methyl protons. These data confirmed convincingly the structures of the synthesized compounds.

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TABLE 1. PMR Spectra of compounds **3**–**16** (δ, ppm)

Compound	NH (1H, s)	H-6 (1H, s)	N_8CH_2 (2H)	N_1CH_3, N_3CH_3 (3H, s)	CH_3-7 (3H, s)	Other resonances
3	10.86	7.34	3.8 d	3.35	2.29	2.24 (1H, m, H-13); 0.88 (6H, d, H-14, 15)
4	10.69	7.24	4.0 t	3.40	2.32	1.79 (2H, m, H-13); 1.36 (4H, m, H-14, 15); 0.91 (3H, t, H-16)
5	10.85	7.31	3.99 t	3.36	2.3	1.76 (2H, m, H-13); 1.28 (6H, m, H-14–16); 0.85 (3H, t, H-17)
6	10.78	7.26	4.05 t	3.36	2.32	3.53 (4H, br.s, H-17, 18); 2.29 (6H, m, H-14–16); 1.95 (2H, m, H-13)
7	–	7.26	–	3.58*; 3.41; 3.24	2.29	–
8	–	7.31	3.96 t	3.41; 3.21	2.3	1.79 (2H, m, H-14); 0.88 (3H, t, H-15)
9	–	7.29	4.01 t	3.45; 3.24	2.32	1.77 (2H, m, H-14); 1.34 (2H, m, H-15); 0.95 (3H, t, H-16)
10	–	7.31	3.78 d	3.39; 3.2	2.29	2.21 (1H, m, H-14); 0.88 (6H, d, H-15, 16)
11	–	7.3	3.97 t	3.40; 3.2	2.3	1.80 (2H, m, H-14); 1.27 (4H, m, H-15, 16); 0.85 (3H, t, H-17)
12	–	7.28	4.0 t	3.44; 3.24	2.32	1.79 (2H, m, H-14); 1.28 (6H, m, H-15–17); 0.86 (3H, t, H-18)
13	–	7.41–7.22 (6H, m, H-6, 15–19)	5.3 s	3.42; 3.21	2.23	–
14	–	7.23–7.1 (6H, m, H-6, 16–20)	4.22 t	3.43; 3.22	1.96	3.08 (2H, t, H-14)
15	–	7.32	4.06 t	3.44; 3.22	2.31	4.66 (1H, t, OH); 3.44 (2H, m, H-15); 1.92 (2H, m, H-14)
16	–	7.32	4.05 t	3.41; 3.21	2.29	3.32 (2H, t, OCH_2-15); 3.23 (3H, s, OCH_3-16); 2.0 (2H, m, H-14)

*Chemical shift of resonances for protons N_1–, N_3–, and N_8–CH_3.

TABLE 2. Physicochemical Data and Yields of compounds **3**–**16**

Compound	mp, °C	Empirical formula	Yield, %	Compound	mp, °C	Empirical formula	Yield, %
3	260–262	$C_{13}H_{17}N_5O_2$	65.5	**10**	167–168	$C_{14}H_{19}N_5O_2$	65.7
4	223–224	$C_{14}H_{19}N_5O_2$	90.0	**11**	181–182	$C_{15}H_{21}N_5O_2$	85.8
5	208–209	$C_{15}H_{21}N_5O_2$	81.8	**12**	176–177	$C_{16}H_{23}N_5O_2$	83.6
6	219–220	$C_{16}H_{22}N_6O_3$	54.6	**13**	219–220	$C_{17}H_{17}N_5O_2$	57.3
7	229–230	$C_{11}H_{13}N_5O_3$	40.4	**14**	223–224	$C_{18}H_{19}N_5O_2$	56.4
8	206–207	$C_{13}H_{17}N_5O_2$	78.5	**15**	248–249	$C_{13}H_{17}N_5O_3$	51.5
9	188–189	$C_{14}H_{19}N_5O_2$	62.3	**16**	178–179	$C_{14}H_{19}N_5O_3$	62.3

EXPERIMENTAL

Melting points were determined in open capillaries on a PTP (M) apparatus. PMR spectra were recorded in DMSO-d_6 or DMSO-d_6 + $CDCl_3$ with TMS internal standard on a Bruker SF-400 spectrometer. Elemental analyses were carried out on an Elementar vario EL cube instrument and agreed with those calculated. Tables 1 and 2 present the physicochemical properties of the compounds.

Synthesis of 3,8-Disubstituted 1,7-Dimethylimidazo[1,2-*f*]xanthines (3-16). A mixture of bromoxanthine (**1** or **2**, 0.01 mol), the appropriate primary amine (0.03 mol; for the syntheses of **7** and **8**, 0.1 mol of 40% methylamine or propylamine was used), H_2O (30 mL), and dioxane (5–10 mL) was refluxed for 1.5–2.0 h and cooled. The precipitate was filtered off, washed with H_2O, and crystallized from aqueous *i*-PrOH (**3**–**12** and **15**), aqueous dioxane (**13** and **14**), or H_2O (**16**).

REFERENCES

1. V. M. Dianov, *Vopr. Biol. Med. Farm. Khim.*, **3**, 55 (2009).
2. N. I. Romanenko, B. A. Samura, I. V. Fedulova, B. A. Priimenko, A. Yu. Chervinskii, and S. N. Garmash, *Khim.-farm. Zh.*, 187 (1986).
3. N. I. Romanenko, I. V. Fedulova, B. A. Priimenko, B. A. Samura, L. M. Kapkan, A. Yu. Chervinskii, T. M. Pekhtereva, and S. N. Garmash, *Khim.-farm. Zh.*, 427 (1986).
4. N. I. Romanenko, I. V. Fedulova, B. A. Priimenko, N. A. Klyuev, T. A. Pereverzeva, B. A. Samura, and E. V. Aleksandrova, *Khim.-farm. Zh.*, 49 (1996).
5. Yu. V. Strokin, B. A. Priimenko, A. K. Sheikman, and N. A. Klyuev, *Khim. Geterotsikl. Soedin.*, 1404 (1979).
6. B. A. Priimenko, B. A. Samura, S. N. Garmash, N. A. Klyuev, and N. I. Romanenko, *Khim.-farm. Zh.*, 32 (1983).
7. S. N. Garmash, B. A. Priimenko, N. A. Klyuev, N. I. Romanenko, and A. K. Sheikman, *Khim. Geterotsikl. Soedin.*, 407 (1984).
8. V. I. Kornienko, B. A. Samura, M. I. Romanenko, and M. V. Glushchenko, *Visn. Farm.*, **57** (1), 67 (2009).
9. B. A. Samura, N. I. Romanenko, and M. V. Glushchenko, *Zaporozh. Med. Zh.*, **52** (1), 89 (2009).
10. V. I. Kornienko, B. A. Samura, N. I. Romanenko, and M. V. Glushchenko, *Probl. Ecol. Med. Genet. Clin. Immunol.*, **90** (3), 180 (2009).
11. I. V. Kireev, *Visn. SumDU, Ser. Med.*, 1, 22 (2009).
12. M. I. Romanenko, T. M. Rak, O. O. Martinyuk, B. A. Samura, V. I. Kornienko, and B. O. Priimenko, *Visn. Farm.*, **65** (1), 67 (2011).
13. P. M. Kochergin, V. I. Linenko, A. A. Tkachenko, B. A. Samura, and M. V. Povstyanoi, *Khim.-farm. Zh.*, 22 (1971).
14. A. A. Tkachenko, P. M. Kochergin, and F. A. Zubkov, *Khim. Geterotsikl. Soedin.*, 682 (1971).