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SYNTHESIS, TRANSFORMATIONS, AND PHYSICOCHEMICAL PROPERTIES OF 3-(4′-METHYLPHENYL)-8-METHYLXANTHINE DERIVATIVES

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A preparative method for producing of 3-(4′-methylphenyl)-8-methylxanthine, its 7-substituted derivatives, 3-(4′-methylphenyl)-8-methylxanthinyl-7-acetic acid, its ester, amide, hydrazide, ylidenehydrazides, and N*-phenylhydrazinocarbothiamide was developed. The structure of the cyclization product of the last, 3-(4′-methylphenyl)-7-[2-(4″-phenyl-5″-thio-4″*H*-[1″,2″,4″]triazol-3″-yl)methyl]xanthine, was confirmed by elemental analysis and PMR spectroscopy.*

Keywords: xanthines, synthesis, PMR spectroscopy.

3-Methylxanthine derivatives are known to possess various types of pharmacological activity [1–7] that are responsible for their wide range of medical application [8–10]. However, their structural analogs with different substituents in the 3-position of the bicyclic xanthine are insufficiently studied.

The goal of the present work was to elaborate synthetic approaches to the production of previously undescribed 3-(4′-methylphenyl)-8-methylxanthine derivatives and to study their physicochemical properties.

We used the known method of Traube xanthine synthesis to synthesize starting 3-(4′-methylphenyl)-8-methylxanthine (**2**) [11] from 1-(4′-methylphenyl)-5,6-diamino-(1*H*,3*H*)pyrimidine-2,4-dione (**1**) [12], heating of which in an excess of glacial acetic acid with subsequent cyclization of the intermediate in aqueous NaOH produced **2**.

The PMR spectrum of **2** (Table 1) lacked resonances for the amines that were characteristic of **1**. Instead, singlets for NH groups at 13.39 ppm and methyl at 2.35 ppm of the corresponding intensities were observed and proved that the imidazole ring had formed.

We showed earlier [13, 14] that alkylation of 3-arylxanthines in DMF in the presence of an equimolar amount of $NaHCO_3$ occurred at the N atom in the 7-position. We used this feature to produce 7-substituted **3**–**6** by reaction of **2** with halocarbonyl compounds (*α*-bromoacetophenone, chloroacetic acid, *n*-propyl chloroacetate, or chloroacetamide). PMR spectra of synthesized **3**–**6** (Table 1) lacked resonances for imidazole NH groups, which confirmed the substitution, and exhibited 2H singlets for methylenes in the range 5.92–4.91 ppm. Resonances for xanthine protons and substituents in the 3-, 7-, and 8-positions of the bicyclic core were found at the appropriate fields with the corresponding shapes and intensities and proved the structures of **3**–**6**.

3-(4′-Methylphenyl)-8-methylxanthinyl-7-acetic acid (**5**) was produced in high final yield as a result of alkaline hydrolysis of ester **6** or amide **4**. Ester **6** was also synthesized by refluxing **5** in propanol-1 in the presence of dioxane and a catalytic amount of conc. H_2SO_4. Samples of **5** and **6** that were produced by the different methods did not show melting-point depression. Their PMR spectra were identical.

Considering that acid hydrazides are convenient synthons for further structural modification of the acetohydrazide motif, including for the synthesis of various benzylidenehydrazides, potential antioxidants and antimicrobial compounds, **6** was reacted with an excess of hydrazine hydrate in EtOH to produce hydrazide **7** as a precipitate from the reaction mixture after a few minutes of heating. Compound **7** was used in further reactions without additional purification.

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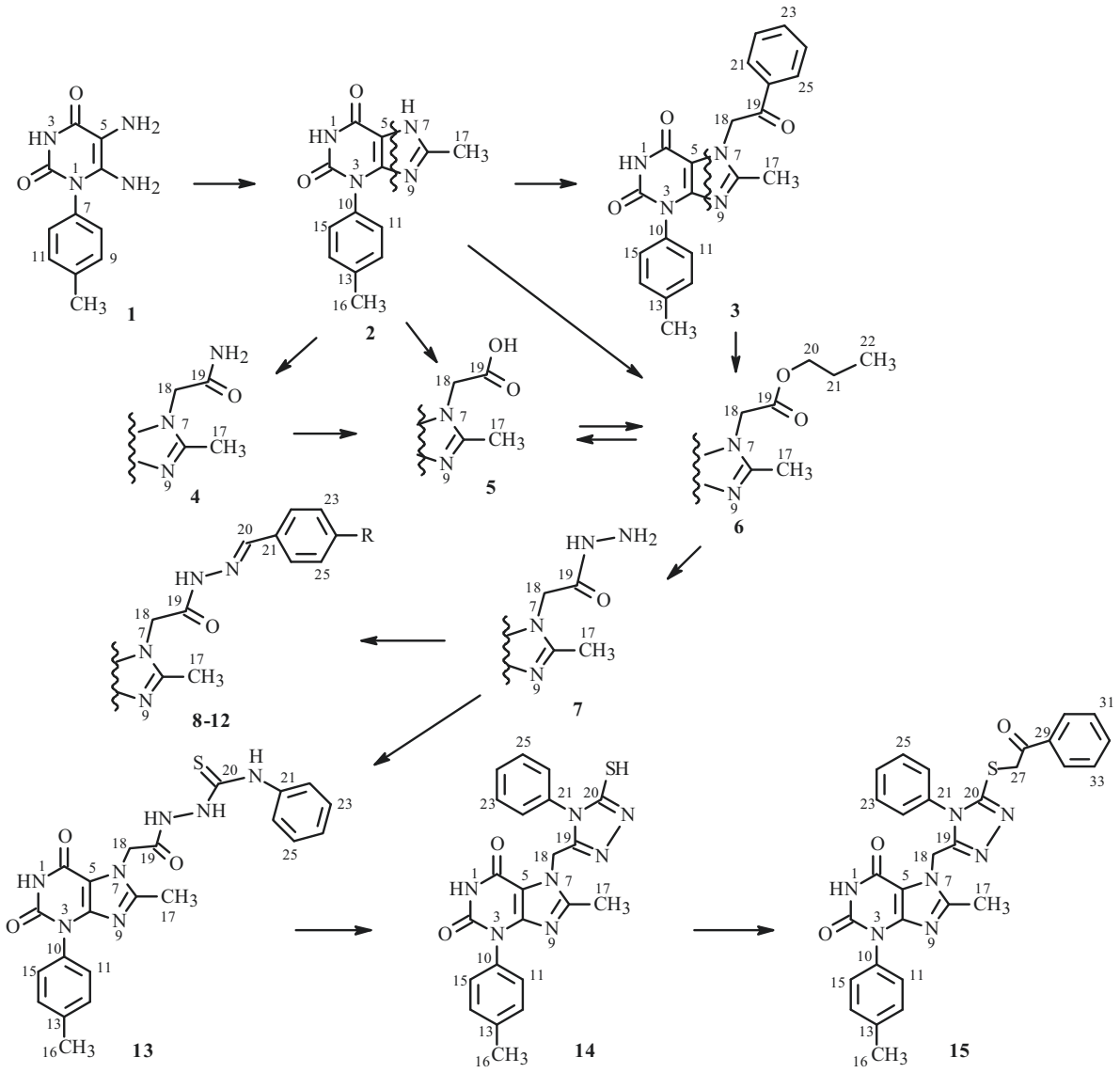

8: R = H; **9:** R = Cl; **10:** R = $N(CH_3)_2$; **11:** R = OH; **12:** R = OCH_3

The PMR spectrum of **7** (Table 1) contained resonances for protons of the acetohydrazide radical as broad singlets at 9.37 (1H, NH) and 4.31 ppm (2H, NH_2). Resonances for methyl and methylene protons of the ester group were missing.

Brief heating of **7** with aromatic aldehydes in aqueous dioxane in the presence of AcOH produced benzylidenehydrazides **8**–**12**. Reaction with phenylisothiocyanate gave *N*-phenylhydrazinocarbothiamide **13**.

PMR spectra of **8**–**12** (Table 1), in contrast with that of starting **7**, showed singlets in the range 8.06–7.89 ppm for resonances of the azomethine protons of the aldehyde group. Resonances for the hydrazide NH protons were shifted to weak field in the range 11.84–11.52 ppm. This was explained by the electron-accepting effect of the N atom. Resonances of other protons corresponded with the structure of the ylidenehydrazine substituents in the 7-position and proved unambiguously their structures (Table 1).

The PMR spectrum of *N*-phenylhydrazinocarbothiamide **13** (Table 1) showed singlets for four NH protons at weak field of 11.36, 10.51, 9.82, and 9.76 ppm. The intensity of the multiplet for the aromatic protons increased to nine units compared with starting hydrazide **7**.

Because 1,2,4-triazoles exhibit broad spectra of biological activity [15] and combination into a single structure of triazole and natural heterocycles is advantageous [16], we synthesized 3-(4′-methylphenyl)-7-[2-(4″-phenyl-5″-thio-4″*H*-[1″,2″,4″]triazol-3″-yl)methyl]-8-methylxanthine (**14**) by heating **13** in basic solution. The PMR spectrum of **14** (Table 1) had a singlet at 13.98 ppm that was due to the resonance of the SH proton and lacked resonances for NH protons of the hydrazinocarbothioamide moiety.

TABLE 1. PMR Spectra of Synthesized compounds **2**–**15** (400 MHz, $CDCl_3$, δ, ppm, J/Hz)

Compound	H-1 (1H, s)	$H_{arom.}$	3H-17 (3H, s)	3H-16 (3H, s)	2H-18 (2H, s)	Other resonances
2	11.22	7.31–7.12 (4H, m, H-11, 12, 14, 15)	2.35	2.18	–	13.39 (1H, s, H-7)
3	11.18	8.22–7.92 (2H, d, H-14, 15); 7.78–7.42 (5H, m, H-21-26); 7.40–7.19 (2H, d, H-11, 12)	2.32	2.20	5.92	–
4	11.12	7.36–7.17 (4H, m, H-11, 12, 14, 15)	2.36	2.19	4.91	7.69 (2H, s, NH_2-19)
5	11.20	7.34–7.19 (4H, m, H-11, 12, 14, 15)	2.38	2.22	5.01	12.61 (1H, s, OH-19)
6	11.21	7.32–7.16 (4H, m, H-11, 12, 14, 15)	2.31	2.19	5.14	4.13 (2H, t, OCH_2-20), 1.54 (2H, m, CH_2-21), 0.82 (3H, t, CH_3-22)
7	11.17	7.30–7.13 (4H, m, H-11, 12, 14, 15)	2.34	2.12	4.93	9.37 (1H, s, NH-19), 4.31 (2H, s, NH_2)
8	11.23	7.71–7.19 (9H, m, H-11, 12, 14, 15, 22–26)	2.37	2.21	5.50	11.82 (1H, s, NH-19), 8.02 (1H, s, CH-20),
9	11.24	7.80–7.62 (2H, d, H-22, 23); 7.53–7.39 (2H, d, H-25, 26); 7.32–7.12 (4H, m, H-11, 12, 14, 15)	2.34	2.21	5.52	11.84 (1H, s, NH-19), 8.06 (1H, s, CH-20)
10	11.17	7.52–7.39 (2H, d, H-22, 23); 7.33–7.18 (4H, m, H-11, 12, 14, 15); 6.79–6.64 (2H, d, H-25, 26)	2.35	2.20	5.43	11.52 (1H, s, NH-19), 7.89 (1H, s, CH-20), 2.98 (6H, s, CH_3-27, 28)
11	11.19	7.59–7.42 (2H, d, H-22, 23); 7.36–7.22 (4H, m, H-11, 12, 14, 15); 6.92–6.75 (2H, d, H-25, 26)	2.39	2.21	4.99	11.60 (1H, s, NH-19), 9.91 (1H, s, OH-24), 7.92 (1H, s, CH-20)
12	11.22	7.71–7.52 (2H, d, H-22, 23); 7.52–7.22 (4H, m, H-11, 12, 14, 15); 7.03–6.89 (2H, d, H-25, 26)	2.36	2.24	5.54	11.71 (1H, s, NH-19), 7.98 (1H, s, CH-20), 3.75 (3H, s, OCH_3-27)
13	11.36	7.58–7.06 (9H, m, H-11, 12, 14, 15, 22-26)	2.38	2.24	5.06	10.51 (1H, s, NH-19), 9.82 (1H, s, NHNH), 9.76 (1H, s, NH-20)
14	11.19	7.62–7.31 (5H, m, H-22–26) 7.11 (4H, m, H-11, 12, 14, 15)	2.38	2.21	5.38	13.98 (1H, s, SH)
15	11.12	7.99–7.04 (14H, m, H-11, 12, 14, 15, 22–26, 30–34)	2.36	2.23	5.54	4.84 (2H, s, CH_2-27)

TABLE 2. Physicochemical Characteristics of Synthesized compounds **2**–**15**

Compound	mp, °C	Empirical formula	Yield, %	Compound	mp, °C	Empirical formula	Yield, %
2	> 300	$C_{13}H_{12}N_4O_2$	76.9	**9**	> 300	$C_{22}H_{19}N_6O_3Cl$	83.8
3	> 300	$C_{21}H_{18}N_4O_3$	75.3	**10**	297–299	$C_{24}H_{25}N_7O_3$	80.4
4	> 300	$C_{15}H_{15}N_5O_3$	82.7	**11**	> 300	$C_{22}H_{20}N_6O_4$	72.8
5	> 300	$C_{15}H_{14}N_4O_4$	*	**12**	> 300	$C_{23}H_{22}N_6O_4$	97.1
6	210–211	$C_{18}H_{20}N_4O_4$	**	**13**	234–236	$C_{22}H_{21}N_7O_3S$	84.1
7	> 300	$C_{15}H_{16}N_6O_3$	83.7	**14**	> 300	$C_{22}H_{19}N_7O_2S$	86.7
8	> 300	$C_{22}H_{20}N_6O_3$	98.4	**15**	160–161	$C_{30}H_{25}N_7O_3S$	64.8

*By method A, yield 35.2%; by method B, 84.8 and 80.2%, respectively; **by method A, yield 75.0%; by method B, 78.3%.

We found that brief heating of **14** with α-bromoacetophenone in basic aqueous EtOH formed 3-(4′-methylphenyl)-7-[5″-(2‴-oxo-2‴-phenylethylthio)-4″-phenyl-4″*H*-[1″,2″,4″]triazol-3″-ylmethyl]-8-methylxanthine (**15**). The resonance of the triazole SH group disappeared in the PMR spectrum of S-substituted **15** (Table 1). However, a singlet for methylene protons appeared and the intensity of the multiplet for the aromatic protons increased. This reaction opens possibilities for further modification of the molecule by adding pharmacophores.

EXPERIMENTAL

Melting points were determined in open capillaries on a PTP apparatus (M). PMR spectra were recorded in DMSO-d_6 or DMSO-d_6:$CDCl_3$ with TMS internal standard on a Bruker SF-400 instrument. Elemental analyses were performed on an Elementar Vario L cube instrument and agreed with those calculated for all compounds. Tables 1 and 2 present the physicochemical properties of the synthesized compounds.

Synthesis of 3-(4′-Methylphenyl)-8-methylxanthine (2). Compound **1** (23.2 g, 0.1 mol) was dissolved in AcOH (60 mL), refluxed for 3 h, cooled, and poured into H_2O. The resulting precipitate was filtered off, washed with H_2O, dried at 80°C, dissolved in NaOH solution (1 N, 200 mL), refluxed for 2.5 h, and filtered hot. The pH was adjusted to 4 using H_2SO_4 solution. The resulting precipitate was filtered off and dried at 100°C.

Synthesis of 3-(4′-Methylphenyl)-8-methylxanthinyl-7-acetic Acid (5). *Method A*. Compound **2** (2.56 g, 0.01 mol) was treated with DMF (15 mL) and $NaHCO_3$ (1.84 g, 0.022 mol), heated for 15 min, treated with chloroacetic acid (1.04 g, 0.011 mol), refluxed for 2 h, and filtered hot. The filtrate was cooled and poured into H_2O (50 mL). The pH was adjusted to 2. The resulting precipitate was filtered off, washed with H_2O, dried at 70°C, and reprecipitated from aqueous $NaHCO_3$.

Method B. Ester **6** (3.56 g, 0.01 mol) or amide **4** (3.13 g, 0.01 mol) was dissolved in aqueous NaOH (90 mL, 0.5 N), refluxed for 2 h, and filtered hot. The filtrate was cooled and neutralized with H_2SO_4 solution (0.1 N) until the pH was 2. The resulting precipitate was filtered off, washed with H_2O, dried at 70°C, and reprecipitated from aqueous $NaHCO_3$.

Synthesis of *n*-Propyl Ester of 3-(4′-Methylphenyl)-8-methylxanthinyl-7-acetic Acid (6). *Method A*. Compound **2** (2.56 g, 0.01 mol) was treated with DMF (15 mL) and $NaHCO_3$ (0.92 g, 0.011 mol), heated for 15 min, treated with *n*-propyl chloroacetate (1.5 g, 0.011 mol), refluxed for 2 h, and filtered hot. The filtrate was cooled and treated with H_2O (50 mL). The resulting precipitate was filtered off, washed with H_2O, dried at 70°C, and recrystallized from propanol-1.

Method B. A mixture of acid **5** (3.14 g, 0.01 mol), propanol-1 (80 mL), and conc. H_2SO_4 (6 mL) was heated and treated with dioxane until the acid dissolved completely. The resulting true solution was refluxed for 5 h, cooled, and poured into H_2O (300 mL). The resulting precipitate was filtered off, washed with H_2O, dried at 70°C, and recrystallized from propanol-1.

3-(4′-Methylphenyl)-7-(2″-phenyl-2″-oxoethyl)-8-methylxanthine (**3**) and the amide of 3-(4′-methylphenyl)-8-methylxanthinyl-7-acetic acid (**4**) [using α-bromoacetophenone (2.19 g, 0.011 mol) and chloroacetamide (1.02 g, 0.011 mol) as the alkylating agent, respectively] were synthesized by method A.

Synthesis of the Hydrazide of 3-(4′-Methylphenyl)-8-methylxanthinyl-7-acetic Acid (7). A suspension of **6** (3.56 g, 0.01 mol) in EtOH (30 mL) was heated for 10 min and treated with hydrazine hydrate (5 mL). The resulting true solution was refluxed for 30 min and cooled. Hydrazide **7** precipitated as crystals that were filtered off, washed with H_2O, and dried at 80–85°C.

Synthesis of Benzylidenehydrazides of 3-(4′-Methylphenyl)-8-methylxanthinyl-7-acetic Acid (8–12). A solution of **7** (3.28 g, 0.01 mol) in aqueous dioxane (70 mL, 1:1) was heated to 50°C, treated with glacial AcOH (3 mL) and the appropriate benzaldehyde (0.011 mol), refluxed for 15–25 min, and cooled. The corresponding ylidenehydrazides precipitated and were filtered off, washed with H_2O and Et_2O, dried at 80–85°C, and recrystallized from aqueous dioxane.

Synthesis of 2-[3-(4′-Methylphenyl)-8-methylxanthin-7-yl]-*N*-[(phenylcarbamothioyl)amino]acetamide (13). Compound **7** (3.28 g, 0.01 mol) was dissolved in dioxane–H_2O (100 mL, 2:1) with heating, treated with phenylisothiocyanate (3 mL), refluxed for 15 min, and cooled. The resulting precipitate was filtered off, washed with H_2O, dried at 80–85°C, and recrystallized from aqueous dioxane.

Synthesis of 3-(4′-Methylphenyl)-8-methyl-7-[2-(4″-phenyl-5″-thio-4″*H*-[1″,2″,4″]triazol-3″-yl)methyl]xanthine (14). Compound **13** (2.31 g, 0.005 mol) was dissolved in NaOH solution (25 mL, 0.25 N), refluxed for 1 h, and filtered hot. The filtrate was cooled and neutralized with H_2SO_4 to pH 4. The resulting precipitate was filtered off, washed with H_2O, dried at 80°C, and recrystallized from aqueous dioxane.

Synthesis of 3-(4′-Methylphenyl)-7-[5″-(2‴-oxo-2‴-phenylethylthio)-4″-phenyl-4″*H*-[1″,2″,4″]triazol-3″-ylmethyl]-8-methylxanthine (15). A mixture of **14** (4.45 g, 0.01 mol) and aqueous NaOH (45 mL, 0.25 N) was heated, treated with a mixture of α-bromoacetophenone (2.19 g, 0.011 mol) and propanol-2 (45 mL), refluxed for 1 h, and filtered hot. The filtrate was cooled and poured into H_2O. The resulting precipitate was filtered off, washed with H_2O, dried at 80°C, and recrystallized from EtOH.

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