SYNTHESIS AND BIOLOGICAL ACTIVITY OF β-(3-METHYL-7-XANTHINYL)PROPIONIC ACID DERIVATIVES

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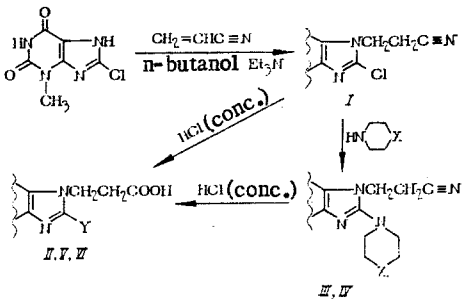
In the present work we continued synthetic investigations based on 3-methyl-8-chloroxanthine with the object of obtaining new biologically active compounds of this series. We previously [1-3] studied alkylation of 3-methyl-8-chloroxanthine by ethylenechlorohydrin, epichlorohydrin, and α-halogenoketones. An attempt to synthesize β-(3-methyl-8-chloro-7-xanthinyl)propionic acid by direct alkylation of 3-methyl-8-chloroxanthine with β-bromo-(chloro)propionic acids, analogously to the method of [4], was unsuccessul. Therefore we developed a method by which reaction of 3-methyl-8-chloroxanthine with acrylonitrile in n-butanol yielded 3-methyl-7-(β-cyanoethyl)-8-chloroxanthine (I). Compound (I) was hydrolyzed to β-(3-methyl-8-chloro-7-xanthinyl)propionic acid (II) by boiling with conc. HCl. It was established that reaction of (I) with piperidine or morpholine in boiling DMF occurs by substitution of the Cl atom with formation of the corresponding 8-N-piperidino- (III) and 8-N-morpholino-(IV) derivatives. Heating the last two with conc. HCl gives β-(3-methyl-8-N-piperidino-7-xanthinyl)propionic acid (V) and β-(3-methyl-8-N-morpholino-7-xanthinyl)propionic acid (VI).



II: Y = Cl; V: Y = piperidino, VI: Y = morpholino; III: X = CH_2; IV: X = O

The structure of the compounds synthesized was confirmed by IR and PMR spectroscopic data. The IR spectra of compounds (II), (V), and (VI) contain marked absorption bands characteristic of the carboxyl group in the region of 3420-3440 cm^{-1} (OH), and 1720-1730 cm^{-1} (C=O). In other respects their IR spectra do not substantially differ from the spectra of the corresponding nitriles (I), (III), and (IV), with the obvious exception of the absence of stretching vibrations of the nitrile group in the region of 2230 cm^{-1}. The chemical shifts of protons of compounds (I)-(VII) are presented in Table 1.

Esterification of the acid (VI) proceeds smoothly on heating it in ethanol in the presence of conc. H_2SO_4. The IR spectrum of ethyl β-(3-methyl-8-morpholino-7-xanthinyl)propionate (VII) reveals the absence of stretching vibrations of the OH group. The PMR spectrum of (VIII) (see Table I) shows additional signals of protons of the ethoxy group in the region δ 1.12 ppm (t, CH_3); protons of the methylene group are registered as a quartet at δ 4.27 ppm. On treatment of (VII) with hydrazine hydrate in ethanol, with brief heating, β-(3-methyl-8-N-morpholino-7-xanthinyl)propionyl hydrazide (VIII) is formed.

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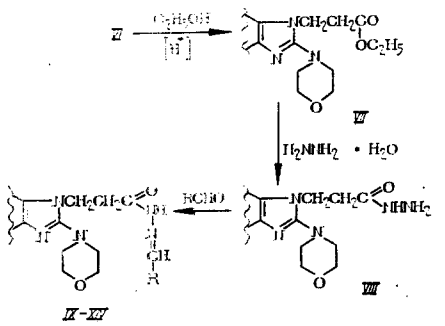
TABLE 1. Chemical Shifts (in ppm) of Protons of Compounds (I)-(VII)

Compound	N(1)-H	N(3)-CH_3	N(7)-CH_2	CH_2-C	H_β of amine	H_α of amine
I	s, 11,32	s, 3,21	m, 4,44			
II	s, 11,18	s, 3,22	t, 4,31	t, 2,69		
III	s, 11,02	s, 3,33	t, 4,22	t, 3,43	br. s, 1,64	br. s 3,22
IV	s, 10,97	s, 3,24	t, 4,23		q, 3,63	q 3,09
V	s, 10,83	s, 3,24	t, 4,17	t, 2,72	br.s 1,54	br.s 3,09
VI	s, 10,83	s, 3,21	t, 4,14	t, 2,71	br.s 3,59	br.s 3,08
VII	s, 10,92 t, 1,12 (CH_3—C)	s, 3,23	t, 4,0	t, 2,87 q, 4,27	br.s 3,7	br.s 3,19



Reaction of the hydrazine (VIII) with aromatic aldehydes proceeds readily in aqueous dioxane or aqueous isopropanol in the presence of catalytic amounts of conc. HCl. The resulting acid hydrazide hydrazones (IX)-(XIV) are brightly colored crystalline substances, poorly soluble in lower alcohols, benzene, and dioxane.

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IR Spectra were recorded on a UR-20 instrument (GDR) using KBr pellets and mineral oil. PMR Spectra were taken on Tesla BS 487 C spectrometer (60 MHz) with DMSO-d_6 as solvent. Chemical shifts are cited in the δ scale relative to HMDS.

3-Methyl-7-(β-cyanoethyl)-8-chloroxanthine (I). A mixture of 4 g (0.02 mole) of 3-methyl-8-chloroxanthine, 6.5 ml (0.01 mole) of acrylonitrile, and 5 ml of triethylamine is boiled in 50 ml of n-butanol for 4 h. After cooling, the residue is filtered off and washed with acetone. Yield of (I) 94%, mp 293-294°C (aqueous DMF). Found, %:C 42.53, H 3.05, Cl 13.87, N 27.43. $C_9H_8ClN_5O_2$. Calculated, %: C 42.61, H 3.18, Cl 13.98, N 27.61.

3-Methyl-7-(β-cyanoethyl)-8-N-piperidinoxanthine (III). A mixture of 5.07 g (0.02 mole) of (I) and 4 ml (0.04 mole) of piperidine is boiled in 50 ml of DMF for 3 h. After filtering hot, the filtrate is diluted with water. The residue is filtered off, washed with water and dried. Yield of (III) 74.1%, mp 228-229°C (aqueous DMF). Found, %: C 55.35, H 5.78, N 27.76. $C_{14}H_{18}N_6O_2$. Calculated, %: C 55.61, H 6.00, N 27.80.

Compound (IV). This is obtained analogously. Yield 28.3%, mp 242°C (aqueous DMF). Found, %: C 51.23, H 5.17, N 27.59. $C_{13}H_{16}N_6O_3$. Calculated, %: C 51.31, H 5.30, N 27.62.

β-(3-Methyl-8-chloro-7-xanthinyl)propionic Acid (II). A solution of 2.5 g (0.01 mole) of (I) is boiled in 20 ml of conc. HCl for 1 h. After cooling, the residue is filtered off, washed well with water, and dried. Yield of (II) 69.1%, mp 275-277°C (from water). Found, %: C 39.55, H 3.21, Cl 12.95, N 20.50. $C_9H_9ClN_4O_4$. Calculated %: C 39.64, H 3.33, Cl 13.01, N 20.55.

Compounds (V) and (VI). These are obtained analogously. (V), Yield 71%, mp 216-218°C (from water). Found, %: C 52.27, H 5.87, N 21.8. $C_{14}H_{19}N_5O_4$. Calculated, %: C 52.33, H 5.96, N 21.80. (VI), Yield 64.2%, mp 228-229°C, (from water). Found, %: C 48.15, H 5.23, N 21.60. $C_{13}H_{17}N_5O_5$. Calculated, %: C 48.29, H 5.30, N 21.66.

Ethyl β-(3-Methyl-8-N-morpholino-7-xanthinyl)propionate (VII). A solution of 3.23 g (0.01 mole) of (VI) in a mixture of 15 ml conc. H_2SO_4 and 50 ml ethanol is boiled for 1.5 h. The mixture is cooled, diluted with water, and left for 24 h at 5°C. The residue is filtered off, washed with ice-water, and dried. Yield of (VII) is 73.7%, mp 187-189°C (from water). Found, %: C 51.15, H 6.00, N 19.88. $C_{15}H_{21}N_5O_5$. Calculated, %: C 51.27, H 6.02, N 19.94.

β-(3-Methyl-8-N-morpholino-7-xanthinyl)propionyl Hydrazide (VIII). A mixture of 2.3 g (6.5 mmoles) of (VII) and 1.9 ml (39 mmoles) of hydrazine hydrate is boiled in 50 ml of ethanol for 30 min. The mixture is left for 24 h at room temperature. The residue is filtered off, washed with water, and dried. Yield of (VIII) 95.5%, mp 186-188°C (from ethanol). Found, %: C 46.20, H 5.58, N 29.00. $C_{13}H_{19}N_7O_4$. Calculated, %: C 46.28, H 5.68, N 29.07.

Hydrazones of β-(3-Methyl-8-N-morpholino-7-xanthinyl)propionyl Hydrazide (IX)-(XIV). A mixture of 1 mmole of (VIII), 1 mmole of appropriate aldehyde, 5 ml of water, 5 ml of dioxane or isopropanol, and 3 drops of conc. HCl is boiled for 40-60 min. After cooling, the residue is filtered off and recrystallized from suitable solvent.

N-(p-Nitrobenzylidene)hydrazide of β-(3-Methyl-8-N-morpholino-7-xanthinyl)propionic Acid (IX). Yield of (IX) 95.7%, mp 182°C (aqueous dioxane). Found, %: C 51.00, H 4.65, N 23.79. $C_{20}H_{22}N_8O_6$. Calculated, %: C 51.06, H 4.71, N 23.82.

N-(m-Nitrobenzylidene)hydrazide of β-(3-Methyl-8-N-morpholino-7-xanthinyl)propionic Acid (X). Yield of (X) 64%, mp 278-280°C (aqueous dioxane). Found, %: C 51.00, H 4.65; N 23.79. $C_{20}H_{22}N_8O_6$. Calculated, %: C 51.06, H 4.71, N 23.82.

N-(p-N,N-Dimethylaminobenzylidene)hydrazide of β-(3-Methyl-N-morpholino-7-xanthinyl) propionic Acid (XI). Yield of (XI) 64.1%, mp 246-248°C (aqueous dioxane). Found, %: C 56.31, H 5.95, N 23.89. $C_{22}H_{28}N_8O_4$. Calculated, %: C 56.40, H 6.02, N 23.92.

N-(2-Indolon-3-ylidene)hydrazide of β-(3-Methyl-8-N-morpholino-7-xanthinyl)propionic Acid (XII). Yield of (XII) 56%, mp 244-246°C (aqueous DMF). Found, %: C 53.97, H 4.70, N 24.00. $C_{21}H_{22}N_8O_5$. Calculated, %: C 54.07, H 4.75, N 24.03.

N-(2,4-Dihydroxybenzylidene)hydrazide of β-(3-Methyl-8-N-morpholino-7-xanthinyl)propionic Acid (XIII). Yield of (XIII) 33%, mp 320°C (with decomposition, from aqueous dioxane). Found, %: C 52.30, H 5.00, N 21.41. $C_{20}H_{23}N_7O_6$. Calculated,%: C 52.51, H 5.07, N 21.44.

N-(5-Bromo-2-hydroxybenzylidene)hydrazide of β-(3-Methyl-8-N-morpholino-7-xanthinyl)propionic Acid (XIV). Yield of (XIV) 50%, mp 312-4°C (aqueous DMF). Found, %: C 46.10, H 4.18, Br 1515, N 18.79. $C_{20}H_{22}BrN_7O_5$. Calculated, %: C 46.16, H 4.26, Br 15.36, N 18.84.

EXPERIMENTAL BIOLOGY

The antimicrobial activity of the synthesized compounds was studied on liquid nutrient medium by the method of twofold serial dilutions with *Staphylococcus aureus* 209P, *Escherichia coli* 675, *Pseudomonas aeruginosa* 165, *Proteus vulgaris* 261, *Bacillus anthracoides* 1312, *Shigella flexneri* 2a 516, *Salmonella typhi* 1196, and *Candida albicans* 624. Investigations showed that the compounds obtained possess weak antibacterial (min. inhibitory concn. = 200-500 μg/ml) and antifungal (min. inhibitory concn. = 200-500 μg/ml) activity.

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