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SYNTHESIS AND SOME PROPERTIES OF 6-β-OXOALKYL(ARALKYL, HETARALKYL, CYCLOALKYL)THIOPURINES

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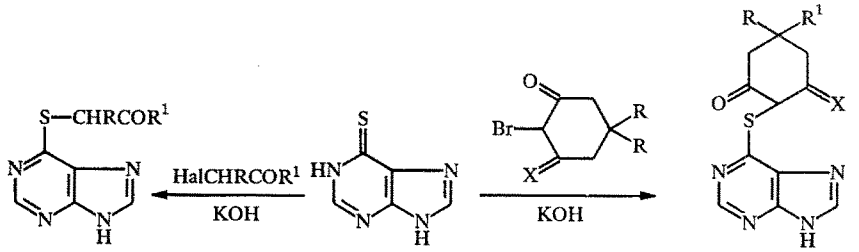
The reaction of 6-purinethione with α-haloketones has given a series of new 6-β-oxoalkyl(aralkyl, hetaralkyl, cycloalkyl)thiopurines. Their alkylation in position 9 and acid hydrolysis to hypoxanthine and its 9-alkyl derivatives has been studied. The hydrolysis of the acetals of 6-formylmethylthiopurine and the oxidation of 6-(2,3-dihydroxypropyl)thiopurine leads to 6-formylmethylthiopurine, which shows a ring-chain tautomerism and exists in the form of 7-hydroxy-7,8-dihydrothiazolo[2,3-i]purine.

In continuation of investigations, the results of which have been reported in [1], we considered it to be expedient to prepare a series of new 6-β-oxoalkyl(aralkyl, heteralkyl, cycloalkyl)thiopurines which are of interest as potential biologically active substances [2] and as intermediate products in the synthesis of derivatives of thiazolo[2,3-i]purine [3, 4] and 7,8-dihydrothiazolo[2,3-i]purine [3].

We have thoroughly investigated the reaction of 6-purinethione with primary and secondary α-chloro(bromo)ketones of the aliphatic, aliphatic–aromatic, alicyclic, and heterocyclic series. The process proceeds easily in aqueous alcoholic solution in the presence of potassium hydroxide at 20-60°C and leads to a series of new S derivatives of 6-purinethione (Table 1, II, III, V-XIII).



I - XI Hal = Cl, Br XII, XIII

I, II, IV, VI—XII R = H; III, V, XIII R = CH_3; I, III R^1 = CH_3; II R^1 = C_2H_5; IV, V R^1 = C_6H_5; VI R^1 = $C_6H_4C_6H_{11}$-*p*; VII R^1 = $C_6H_4C_6H_5$-*p*; VIII R^1 = 3-acetoxymethyl-4-acetoxyphenyl; IX R^1 = C_6H_4Cl-*p*; X R^1 = $C_6H_4NO_2$-*m*; XI R^1 = 2-C_5H_4N; XII X = H_2; XIII X = O

The individual character and purity of compounds I-XIII have been confirmed by elemental analysis and TLC and their structure by IR, UV, and PMR spectroscopy, and mass spectrometry.

The IR spectra of ketones I-XI contain absorption bands which are characteristic for the stretching vibrations of the carbonyl group in the region 1680-1715 cm^{-1}. Their PMR spectra (Table 2) contain a singlet of the methylene group (4.33-5.07

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ppm) or a signal of the methine proton (4.95-6.06 ppm), depending on the presence of a substituent at the α-C atom and singlets of the protons of the purine ring in the region 8.42-8.68 ppm. The signals of the purine system protons have been identified on the basis of [5]. These data show unambiguously that the ketones I-XI are present solely in the open-chain form in solutions as well as in the solid state.

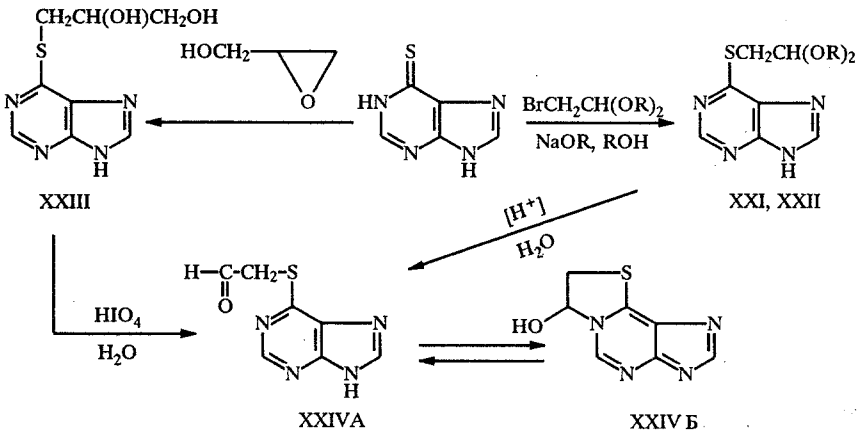
The mass spectra of compounds I-XIII record the peak of the molecular ion which corresponds to the calculated molecular mass.

We have also investigated some properties and conversions of the compounds of this series. The alkylation of 6-acetonyl- and 6-phenacylthiopurines (I, IV) with alkyl halides in DMSO in the presence of anhydrous potassium carbonate gave the 9-methyl and 9-ethyl derivatives of the initial purines XVI and XVII. The structure of compounds XVI and XVII was established by their UV spectra, from the absence of a shift of the absorption maximum in comparison with the spectra of the initial compounds [6], and also by hydrolytic splitting to the 9-derivatives of hypoxanthine XIX and XX by heating in 5 N hydrochloric acid, as described for other 9-alkyl-6-alkyl(heteryl)thiopurines [7, 8].

The 6-β-oxoalkylthiopurines I-XIII are very weak bases. They are only soluble in concentrated mineral acids; when the solutions are diluted with water they are precipitated as the free bases. Only the ketone XI, which contains the pyridine ring, is a relatively strong base and forms salts with mineral as well as with organic acids (hydrochloride, succinate).

The compounds I-XIII are unstable in solutions of acids and alkali at 90-100°C. In concentrated alkali solutions degradation of the purine ring takes place and in 5 N hydrochloric and in glacial acetic acids hydrolytic splitting to hypoxanthine XVIII.

Of particular interest were the synthesis of 6-formylmethylthiopurine and the study of its ring-chain tautomerism, as demonstrated earlier on the examples of the formylmethylthio derivatives of imidazole [9, 10] and its annelated systems [11].



XXI R = Et; XXII R = Bu

6-Formylmethylthiopurine(7-hydroxy-7,8-dihydrothiazolo[2,3-i]purine) XXIV was obtained by two methods: by acid hydrolysis of the diethyl(dibutyl) acetals XXI and XXII and by the oxidation of 6-(2,3-dihydroxypropyl)thiopurine (XXIII) with periodic acid.

A characteristic property of compound XXIV, in distinction from the ketones I-XI, is the presence of ring-chain tautomerism. Compound XXIV manifests the properties of an aldehyde (XXIV A) and gives qualitative reactions for the carbonyl group; for instance, it forms the thiosemicarbazone XXV and the 2,4-dinitrophenylhydrazone XXVI. On the other hand the IR and PMR spectra show that in the solid state and in some solvents (DMSO) it is present in the form of the tricyclic tautomer XXIV B.

In the IR spectrum of the compound XXIV the carbonyl band is missing, while a broad absorption band is present in the region 3070-3200 cm^{-1}, which can be attributed to the absorption of the hydroxime group.

The question, whether the compound XXIV has the open (A) or cyclic (B) structure, was answered by analyzing its PMR spectrum. If the compound XXIV had the open structure XXIV A, the PMR spectrum should contain a doublet of the protons of the methylene group and a triplet of the proton of the aldehyde group. However, in our instance the PMR spectrum of compound XXIV contains a multiplet of protons of the methylene group and singlets of the protons of the purine ring, which is in agreement only with the cyclic structure of compound XXIV.

TABLE 1. Physicochemical Properties of 6-Purinethione Derivatives (I-XIII)

Compound	Empirical formula	T_{mp} °C	IR spectrum, ν, cm^{-1}		Yield, %
			C=O	NH	
I	$C_8H_8N_4OS$	184...185*	1715	3105	87
II	$C_9H_{10}N_4OS$	192...194	1715	3100	81
III	$C_9H_{10}N_4OS$	188...190	1715	3090	86
IV	$C_{13}H_{10}N_4OS$	170...171**	1690	3100	86
V	$C_{14}H_{12}N_4OS$	198...200	1690	3100	78
VI	$C_{19}H_{20}N_4OS$	201...202	1690	3110	84
VII	$C_{19}H_{14}N_4OS$	197...198	1695	3100	83
VIII	$C_{18}H_{16}N_4O_5S$	202...204	1735...1725, 1680	3100	85
IX	$C_{13}H_9ClN_4OS$	186...187	1685	3100	83
X	$C_{13}H_9N_5O_3S$	174...176	1690	3095	79
XI	$C_{12}H_9N_5OS$	182...184	1690	3095	68
XII	$C_{11}H_{12}N_4OS$	175...177	—	—	74
XIII	$C_{13}H_{14}N_4O_2S$	238...239	—	—	63

*mp = 184.5° according to [12].
**mp = 170°C according to [12].

TABLE 2. PMR and UV Spectra of 6-Purinethione Derivatives (II-V, VII)

Compound	PMR spectrum, δ, ppm (DMSO-D6)	UV spectrum, λ_{max} (log ε), nm (ethanol)
II	1,18 (3H, t, CH_3), 2,56 (2H, qn CH_2), 4,45 (2H, s, S—CH_2), 8,42 (1H, s, 8-H), 8,59 (1H, s, 2-H)	216,0 (4,07), 281,3 (4,2)
III	1,51 (3H, d, CH_3), 2,28 (3H, s, CH_3CO), 4,95 (1H, qn, S—CH), 8,44 (1H, s, 8-H), 8,67 (1H, s, 2-H)	216,0 (4,09), 280,7 (4,2)
IV	5,00 (2H, s, S—CH_2), 7,7...8,1 (5H, m, C_6H_5), 8,47 (1H, s, 8-H), 8,60 (1H, s, 2-H)	247,2 (4,1), 284,8 (4,25)
V	1,63 (3H, d, CH_3), 6,06 (1H, qn, S—CH), 7,39...8,11 (5H, m, C_6H_5), 8,42 (1H, s, 8-H), 8,64 (1H, s, 2-H)	248,1 (4,14), 284,3 (4,24)
VII	5,07 (2H, s, S—CH_2), 7,44...8,25 (9H, m, $C_6H_4C_6H_5$), 8,44 (1H, s, 8-H), 8,59 (1H, s, 2-H)	246,5 (4,4), 288,5 (4,4)

An analogous picture is also obtained in the IR spectrum of 6-(2-oxocyclohexyl)thiopurine (XII). In the solid state this compound probably exists as the cyclic tautomer, the hydroxy derivative tetranydrobenzothiazolino[2,3-i]purine; in solution, however, it manifests the properties of a ketone and forms the 2,4-dinitrophenylhydrazone XV.

EXPERIMENTAL

The IR spectra were taken on a Specord IR-75 spectrometer (in vaseline oil), the UV spectra on a Perkin–Elmer 402 spectrometer. The PMR spectra were recorded on a Tesla BS-587 AC spectrometer with a working frequency of 80 MHz. TMS served as the internal standard. The mass spectra were obtained on an MS-132IA spectrometer, using direct injection of the sample into the ion source. The ionizing voltage was 70 eV, the temperature of the ionization chamber was about 170°C.

The progress of the reaction and the purity of the compounds were checked by chromatography on Silufol UV-254 plates in the systems: a) n-butanol–water–acetic acid (5:3:2) and b) isopropanol–water–25% aqueous ammonia solution (15:4:1). The spots were revealed in UV light or by exposure to iodine vapors.

The elemental analysis data for C, H, N, S, and Cl corresponded to the calculated data. 6-Purinethione hydrate was used as a preparation of pharmacopoeia purity.

6-β-Oxoalkyl(aralkyl, hetaralkyl, cycloalkyl)thiopurines (I-XIII, Table 1). A suspension of 17 g (0.1 mole) of 6-purinethione in 100 ml water is treated with stirring with a solution of 5.8 g KOH (0.1 mole) in 70 ml water. The obtained solution is treated with a solution of 0.1-0.11 mole α-haloketone in 200 ml ethanol. The mixture is stirred for 3 h in the preparation of V-IX, XI, XIII, XVI, 7 h for X, XII, XIV, XV, and 12 h for XVII at 20-30°C. When necessary, the solution was heated to 50-60°C. The end of the reaction was established by TLC from the absence of the initial thione. The reaction mixture was evaporated in vacuum to half the original volume and cooled for 10-12 h at 4-6°C. The precipitate is filtered off, washed with cooled 50% ethanol, and dried. For analysis the compounds were purified by crystallization from aqueous ethanol (I-IV, XI), ethanol (V, IX, XIII), aqueous acetone (VI, VIII, XII), isopropanol (XIII), or aqueous DMFA (X).

2,4-Dinitrophenylhydrazone of 6-(α-methylphenacyl)thiopurine (XIV, $C_{20}H_{16}N_8O_4S$) was prepared by heating the ketone III and 2,4-dinitrophenylhydrazine in glacial acetic acid; mp 164-165°C (from CH_3COOH).

2,4-Dinitrophenylhydrazone of 6-(2-oxocyclohexyl)thiopurine (XV, $C_{17}H_{16}N_8O_4S$) was obtained from 6-(2-oxocyclohexyl)thiopurine (XII) in the same way as the hydrazone XIV; mp 153-154°C (from CH_3COOH).

Succinate of 6-[(2-pyridyl-2)-2-oxoethyl)]thiopurine, Hydrate (XIa, $C_{12}H_9N_4OS \cdot C_4H_6O_4 \cdot H_2O$); mp 134-136°C (from water).

9-Methyl-6-acetonylthiopurine (XVI, $C_9H_{10}N_4OS$). A solution of 2.1 g (0.01 mole) of ketone I in 15 ml DMSO is treated with 1.5 g finely ground anhydrous potassium carbonate and 2.8 g (0.02 mole) methyl iodide. The mixture is stirred for 15 h at 80°C, the solvent is stripped off in vacuum; the residue is washed with 1 N sodium hydroxide solution, then with ice water. The residue is dried and crystallized from acetone–ether (5:1), then from acetone. Yield 1.6 g (7.3%) of compound XVI; mp 142-144°C (from acetone). IR spectrum: 1715 cm^{-1} (CO). UV spectrum (in ethanol), λ_{max} (log ε): 280.9 nm (4.21).

9-Ethyl-6-phenacylmethylthiopurine (XVII, $C_{15}H_{14}N_4OS$) was obtained in the same way as compound XVI from the ketone IV and ethyl iodide. Yield of compound XVII 67%; mp 157-159°C (from acetone). IR spectrum: 1690 cm^{-1} (C=O).

Hypoxanthine (XVIII, $C_5H_4N_4O$). A. A suspension of 2.7 g ketone IV in 20 ml 5 N hydrochloric acid is boiled for 30 min, the solution formed is filtered and neutralized with sodium carbonate to pH 6-7. The precipitate formed is washed with water and acetone, and dried. Yield 0.9 g (63%) of compound XVIII; mp > 330°C. IR spectrum: 1725 (CO), 3080, 3140 cm^{-1} (NH). According to [13] mp > 350°C.

B. A solution of 2.7 g ketone IV in 50 ml 99% acetic acid is heated on a boiling water bath for 3 h. After clarification with active carbon the solvent is stripped off in vacuum, the residue is crystallized from aqueous ethanol. Yield 0.4 g (28%) of compound XVIII; mp > 330°C.

C. A solution of 2.0 g ketone III in 25 ml acetic acid is heated and treated as described in method B. Yield of compound XVIII 0.3 g (23%); mp > 330°C. The samples of hypoxanthine XVIII, obtained by methods A, B, and C, do not give a melting point depression when mixed with each other and with a sample of known purity.

9-Methylhypoxanthine (XIX, $C_6H_6N_4O$). A sample of 2.2 g ketone XVI in 25 ml 5 N hydrochloric acid is boiled for 1 h. The solution is neutralized to pH 6 with a soda solution, clarified with active carbon, and evaporated to a small volume in vacuum. The precipitate is filtered off and washed with water and acetone. Yield 0.65 g (49%) of compound XIX; mp > 330°C (decomposes, from water) (according to [14] mp 390°C (decomposes)). IR spectrum: 1730 (C=O), 3300 cm^{-1} (NH).

9-Ethylhypoxanthine (XX, $C_7H_8N_4O$) was obtained by hydrolysis of the ketone XVII in 5 N HCl with a yield of 33%; mp 262-263°C (from aqueous ethanol). According to [15] mp 263-265°C.

The diethylacetal of 6-formylmethylthiopurine (XXI) was obtained according to [16].

Dibutylacetal of 6-Formylmethylthiopurine (XXII, $C_{15}H_{24}N_4O_2S$) was prepared in the same way, with the difference that the reaction was carried out in absolute butanol. Yield of acetal XXII 8%; mp 110-112°C (from a butanol–hexane mixture 1:1). IR spectrum 3080 cm^{-1} (NH).

6-(2,3-Dihydroxypropyl)thiopurine (XXIII, $C_8H_{10}N_4O_2S$). A suspension of 17.0 g (0.1 mole) of 6-purinethione, dissolved in a solution of 5.8 g (0.1 mole) potassium hydroxide in 500 ml 95% ethanol was treated with 7.8 g (0.105 mole) of freshly distilled glycidol. The mixture was stirred for 3 h, acidified with 2% hydrochloric acid to pH 5 and cooled. The precipitate is filtered off, washed with water, and dried. Yield 18.7 g (76%) of the diol XXIII; mp 196-197°C (from water) (according to [17] mp 196-197°C). M^+ 226. IR spectrum: 3100, 3150-3300 cm^{-1} (NH, OH).

7-Hydroxy-7,8-dihydrothiazolo[2,3-i]purine (XXIV, $C_7H_6N_4OS$). A. A solution of 3.0 g (13 mmoles) of compound XXIII in 120 ml water is treated in portions with stirring by 3.75 g (22 mmoles) periodic acid dihydrate. The mixture is stirred for 30 min, neutralized with sodium bicarbonate to pH 5 and cooled; the precipitate is filtered off and washed with water. Yield 2.2 g (87%) of compound XXIV; mp 189-190°C (from aqueous acetone). M^+ 194. IR spectrum: 3200-3070 (OH), 1610, 1555

(C=C, C=N) cm^{-1}. PMR spectrum (DMSO-D_6): 8.75 (1H, s, 2-H), 8.63 (1H, s, 5-H), 6.39 (1H, m, 7-H) 3.81-3.53 ppm (2H, m, $C_{(8)}H_2$).

B. A sample (1.0 g) of acetal XXI or XXII in 10 ml 2% hydrochloric acid is heated for 30 min on a boiling water bath. The solution is neutralized with sodium bicarbonate to pH 5-6 and cooled to 0-2°C; the precipitate is filtered off and crystallized successively from water and aqueous acetone. Yield 0.2 g (26%) of thiazolinopurine XXIV; mp 189-190°C. Mixing with the sample obtained by Method A does not depress the melting point.

Thiosemicarbazone of 6-Formylmethylthiopurine (XXV, $C_8H_9N_7S_2$) was obtained by heating of compound XXIV with thiosemicarbazide in aqueous ethanol solution; mp 88-89°C (from ethanol).

2,4-Dinitrophenylhydrazone of 6-Formylmethylthiopurine (XXVI, $C_{13}H_{10}N_8O_4S$) was obtained by heating of compound XXIV with 2,4-dinitrophenylhydrazine in glacial acetic acid; mp 243-244°C (from CH_3COOH).

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