6-Sulfinyl Derivatives of Xanthines

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Received November 1, 1976

6-Thiopurines are oxidized by hydrogen peroxide or by perbenzoic acid to 6-sulfinylpurines. In general, these compounds are unstable and only a number of theophylline derivatives have been obtained in pure form. In this series only the isomers in which the 6-sulfinyl group is directed toward 7-NH are formed, since they are stabilized by an intramolecular hydrogen bridge. Their structure has been derived from dipole moments and from the chemical shift of the 1-methyl substituent. The 2-thiocarbonyl group in 2-thiotheophyllines is not attacked by the oxidants used. The latter convert 6-selenoxanthines directly into the corresponding xanthines.

In 1966, Walter et al. described the 6-sulfinyl derivative **2c** (Table I) of theophylline, obtained by oxidation of 6-thiotheophylline **2b** with hydrogen peroxide.[1] We have observed that **2c** can be prepared more conveniently by treating a suspension of **2b** in chloroform with perbenzoic acid. The reaction takes place instantaneously and produces a clear solution of **2c**, the color changing from slightly yellowish to intense green-yellow.

We have studied the generality of this reaction both with aqueous hydrogen peroxide and with solutions of perbenzoic acid in organic solvents. Most of the 6-thiopurines tested were attacked, since their solutions changed color to intense yellow, orange, or green (see footnote to Table I), but the sulfinyl derivatives formed were rather unstable. Isolation of pure 6-sulfinyl derivatives succeeded only in a few cases, notably the theophylline derivatives **2c–5c** (Table I). Heating solutions of the latter in protic organic solvents was sufficient to convert them back to the 6-thiopurines **2b–5b.** Likewise, aqueous hydrogen sulfide or sodium bisulfite reduced the sulfinyl group instantaneously to 6-thiocarbonyl.

Certain 6-SMe purines undergo thiohydrolysis, i.e., the 6-SMe substituent is replaced by SH.[2] However, such a reaction is possible only for univalent SR groups.[3] Therefore it appears improbable that an SH group could substitute directly for SOH, especially in view of the easy reduction of the sulfinylpurines by bisulfite or protic solvents.

The facile reduction of the sulfines by chemical means finds its counterpart in the formation of $[M - 16]^+$ under electron impact. In the mass spectrum of **2c** and **3c**, this ion shows the highest peak, followed by $[M - 48]^+ = [M - SO]^+$. Loss of oxygen from sulfoxides under electron impact is well known.[4] However, splitting off of SO appears to be specific for the sulfinyl derivatives studied here.

It should be noted that the oxidants used did not attack a 2-C=S group (see **3c** and **5c** in Table I).

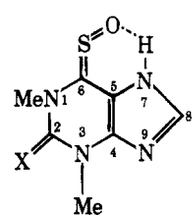
All sulfinylpurines formed complexes with ferric chloride, with characteristic colors (Table IV). Formation of complexes with Cu^{II}, Ni^{II}, and Hg^{II} was recognized by changes in the UV spectrum.

We have also tried to prepare 6-selenoxides by oxidation of 6-selenoxanthines. However, the latter lost elementary selenium and were rapidly converted to the corresponding xanthines.

The relevant physical properties of xanthines, 6-thioxanthines, and their 6-sulfinyl derivatives are compared in Tables I and II. The following statements are pertinent.

1. In the neutral forms of the xanthines **1a–5a** thiation at position 6 causes a bathochromic shift of λ_{max} of 55–75 nm, while introduction of a 2-C=S group has a much weaker influence.[5] The 6-C=S=O substituent further displaces λ_{max} to longer wavelengths by 28–35 nm. Therefore the total shift for the transformation 6-C=O → 6-C=S=O is 80–100 nm.

2. Anion formation in the 6-sulfinyl derivatives **2c–5c** takes place at a higher pK than in the corresponding thioxanthines **2b–5b.** Presumably the 7-NH group is stabilized by hydrogen bonding to 6-S=O (see structure I). The opposite effect is observed for the theobromine derivative **1c** (see structure III). In the latter, the pK for dissociation of the 1-NH group is 1.7



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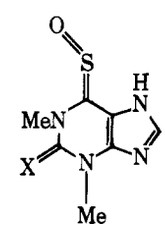

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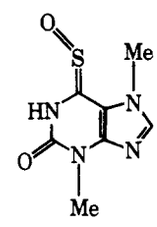

III

units *lower* than for 6-thiotheobromine **1b,** i.e., the sulfinyl group—by virtue of its electron-attracting character—enhances the acidity of the neighboring NH. In **2c–5c,** this effect is overshadowed by the stabilizing influence of the hydrogen bridge, shown in I.

3. The NMR signals of the 8 substituents are only little influenced by changes at position 6. For example, the 8-H band in series **1–3** shifts slightly downfield when one proceeds from 6-C=O to 6-C=S=O. Likewise the 8-phenyl signals are practically identical in the three derivatives **a–c** of series **4** and **5** (see Table II).

The 3-methyl band is displaced to lower field by 0.3–0.45 ppm, when 2-C=O is exchanged by 2-C=S,[6] but the different substitutions at C-6 alter its position only little.

Replacement of either 2- or 6-C=O by thiocarbonyl shifts the 1-methyl signal downfield by 0.4–0.5 ppm. These shifts are additive,[6] i.e., simultaneous thiation at positions 2 and 6 displaces the 1-methyl band by 0.87 ppm (compare the pairs **2a, 3b** and **4a, 5b** in Table II).

In contrast, introduction of a 6-sulfinyl group causes a marked upfield shift of the 1-methyl signal; the latter is now shielded even relative to the corresponding signal in the xanthines **2a–5a** [$\Delta\delta_{1\text{-Me}}$ (**a–c**) 0.12–0.17 ppm].

Although two geometrical isomers of 6-sulfinylpurines (I and II) are possible,[7] only a single compound was isolated in

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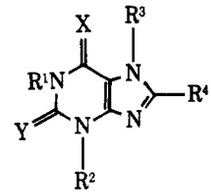
Table I. pK Values and UV Absorption Spectra of Xanthines, 6-Thioxanthines, and the Corresponding 6-Sulfinyl Derivatives[a,c]



Series no.		(a) Xanthines (X = O) pK	(a) λ_{max}, nm N	A	C	(b) 6-Thioxanthines (X = S) pK	(b) λ_{max}, nm N	A	C	(c) 6-Sulfinyl derivatives (X = S=O) pK	(c) λ_{max}, nm N	A	C
1	$R^2 = R^3 = Me$ $R^1 = R^4 = H$ Y = O	+0.3 11.0	273	275	265	+0.3 8.8	347	325	333	+0.4[b] 7.1	376	367	346
2	$R^1 = R^2 = Me$ $R^3 = R^4 = H$ Y = O	+0.7 8.5	272	275	266	+0.4 8.2	343	340	329	+1.0 8.9	377	373	343
3	$R^1 = R^2 = Me$ $R^3 = R^4 = H$ Y = S	−0.3 8.6	284	290	284	−1.0 7.8	348	349	352	0 8.1	383	378	366
4	$R^1 = R^2 = Me$ $R^3 = H$; $R^4 = C_6H_5$ Y = O	+0.1 7.4	306	313	307	+0.9 8.9	364	381	354	−0.3 10.8	392	398	363
5	$R^1 = R^2 = Me$ $R^3 = H$; $R^4 = C_6H_5$ Y = S	−0.5 7.3	320	328	323	−0.5 7.9	375	388	371	−1.5 10.6	403	407	391

[a] In the following cases, formation of the 6-sulfinyl derivatives was established by the color change of the solution and eventually by the bathochromic shift of λ_{max} (values in brackets), but the oxidation products could not be isolated because of their instability: 3,7-dimethyl-6-thiopurine (color change from yellow to green); 3-methyl-8-phenyl-6-thiopurine (from yellowish to intense yellow); 3-methyl-6-thioxanthine (372 nm at pH 8); 6-thiocaffeine (375 nm in ethanol); and 6-thioisocaffeine (375 nm in ethanol). [b] This compound was not obtained in analytically pure form, but was sufficiently stable to permit spectral measurements. [c] N, neutral form; A, anion; C, cation.

Table II. NMR Spectra and R_f Values of Xanthines, 6-Thioxanthines, and the Corresponding 6-Sulfinyl Derivatives

No.	Substituent	δ_{ppm}[a] (a)	(b)	(c)	Solvent	R_f values[b] and fluorescence[c] (a)	(b)	(c)
1	(3-Me)	3.52	3.52	3.56	(1)	0.51 violet	0.73 yellow	0.44 violet
	(7-Me)	4.00	4.15	3.82	(2)	0.66	0.71	0.14
	(8-H)	8.00	8.00	8.10	(3)	0.63	0.68	0.51
2	(1-Me)	3.42	3.83	3.30	(1)	0.68 violet	0.81 yellow	0.67 sky-blue
	(3-Me)	3.62	3.66	3.66	(2)	0.68	0.72	0.58
	(8-H)	8.16	8.20	8.28	(3)	0.68	0.71	0.63
3	(1-Me)	3.85	4.29	3.68	(1)	0.76 violet	0.82 yellow	0.70 black
	(3-Me)	4.02	3.99	4.00	(2)	0.72	0.76	0.69
	(8-H)	8.21	8.23	8.26	(3)	0.71	0.74	0.64
4	(1-Me)	3.46	3.84	3.33	(1)	0.95 radiant	0.98 rose	0.92 violet
	(3-Me)	3.68	3.79	3.74	(2)	0.79 violet	0.82	0.80
	(8-C_6H_5)	7.58[d] 8.19	7.56 8.23	7.57 8.24	(3)	0.76	0.77	0.77
5	(1-Me)	3.91	4.33	3.75	(1)	0.93 light blue	0.82 orange	0.82 dark blue
	(3-Me)	4.13	4.08	4.12	(2)	0.81	0.86	0.86
	(8-C_6H_5)	7.60[d] 8.30	7.58 8.27	7.58 8.27	(3)	0.73	0.79	0.82

[a] All measurements in CD_3COOD at 30 °C. For the symbols (a), (b), (c), see Table I. [b] (1), (2), and (3) indicate the solvents used for paper chromatography (see Experimental Section). [c] Under a Mineralight UV lamp, λ ~254 or 366 nm. [d] The values of δ 7.5–7.6 integrate for 3 protons and represent the multiplet for meta, parahydrogens of the phenyl ring. The signals at δ 8.20–8.30 ppm integrate for two protons and represent the orthohydrogens.

all cases. **3c** and **5c** gave single spots on chromatograms in a variety of solvents (Table II). With **2c** and **4c** a second spot was observed, but was identified as **2b** and **4b**, respectively, resulting from reduction of the sulfinyl group by the paper. Thus the question arises: Does structure I or II represent the single isomer found?

Dipole Moments. We first computed the dipole moments by the CNDO/2 method.[8] The theoretical values for **2a, 3a,** and **2b** were in reasonable agreement with the experimental results.[5] However, unexpected difficulties arose in the calculation of the dipole moments of **3b, 2c,** and **3c.** After a few converging iterations, the energies either oscillated between two slowly-changing limits or they diverged. The results were not improved by small modifications of the geometry of the C=S or C=S=O groups. Similar difficulties have been reported by Cignitti and Paolini.[9] Therefore the moments of structures I and II were calculated by vector addition, assuming the 6-C=S=O group to lie in the plane of the imid-

Table III. Dipole Moments[a]

No.	α'	β'	P_{200}	MR[b]	μ, D	μ, calcd for I[c]	μ, calcd for II[c]
2b	20.06	−1.80	321.4	49.2	3.7		
2c	11.78	−0.83	211.1	60.4	2.7	2.6	5.2
3b	32.28	−0.98	506.1	57.0	4.7		
3c	17.38	−0.57	304.0	68.1	3.4	3.5	6.1
4b	30.67	−0.65	509.9	72.5	4.6		
4c	11.91	−0.75	234.9	83.6	2.7		
5b	45.64	−1.08	721.5	80.1	5.6		
5c	18.20	−0.64	333.5	91.2	3.5		

[a] In dioxane (AR, dried over sodium metal) at 30 °C. [b] Calculated from bond electronic polarizations.[19] [c] See structural formulas.

azole ring. The vector of the 6-carbonyl group was subtracted from the known dipole moments of the xanthines **2a** and **3a**.[5] Then the moment of the sulfinyl group[10] was added in two opposite directions, as indicated by structures I and II. Since all possible mesomeric effects were neglected, the calculations are necessarily crude. Nevertheless, the differences predicted for the moments of I and II are large enough to permit unequivocal assignment of structure I to **2c** and **3c**, by comparison of calculated and experimental values (see Table III).

Introduction of an 8-phenyl substituent does not alter the dipole moment of **2c** and **3c**, respectively, suggesting that **4c** and **5c** are also represented by structures like I.

It should be noted that the dipole moments of the 6-sulfinyl derivatives are considerably smaller than those of the corresponding 6-thioxanthines (see Table III).

Shielding of the 1-Methyl Group by the 6-Sulfinyl Substituent. The most important effect of the 6-sulfinyl group consists in the upfield shift of the 1-methyl signal (Table II). Calculations show that this peculiar shift supports further the assignment of structure I to the sulfines **2c–5c**. The direct electrostatic contribution of a dipolar substituent like C=S=O to the shielding of the protons of the adjacent 1-methyl group can be obtained with the aid of the equation of Schweizer et al.[11] This equation evaluates the effect of a dipolar group by assigning partial charges, equivalent to the group dipole moment, on both sides of a given bond. The figures so obtained differ considerably for $\delta_{1\text{-Me}}$ in I and II. For I, we calculate that the 6-sulfinyl group shields the protons of the 1-Me substituent, while in II it causes a marked shift to lower field, relative to the corresponding signals in the **b** derivatives.

Although the sulfine **1c** could not be isolated in pure form, its NMR spectrum was clearly separated from that of the accompanying **1b**. In **1c** we observe a marked upfield shift of the 7-Me signal, relative to its position in **1b**. By analogy to the structure, assigned to **2c–5c** on the basis of $\delta_{1\text{-Me}}$, this observation suggests that **1c** possesses structure III, in which the sulfinyl group is directed away from position 7. Here again we have calculated the influence of the C=S=O dipole[10] on the two possible isomers of **1c**. In structure III, this dipole causes marked shielding of the 7-Me signal, while in the isomer corresponding to I this signal would be shifted strongly to *lower* field.

It should be noted that the stable H-bonded structure in I is six membered. In III, a hydrogen bridge between the sulfinyl oxygen and the 1-NH group would create a five-membered ring. Therefore the tendency to hydrogen bonding in III—if present at all—is much weaker than in I.

Stability of the 6-Sulfinyl Derivatives to pH Changes. The hydrogen bond in I is broken by anion formation. Therefore alkalinization and reacidification of an aqueous solution of I may yield some of the isomer II. However, from such cycles only the pure isomers I were recovered.

Experimental Section

Melting points were determined with a Fisher-Johns apparatus and are uncorrected. Microanalyses were performed by M. Goldstein, Jerusalem. UV spectra were measured on a Varian Techtron Model 635 or a Cary 14 spectrophotometer, and NMR spectra on a JEOL MH-100 instrument, using tetramethylsilane as internal standard. pK values were derived from plots of λ_{max} or of optical density as function of pH.

For paper chromatography by the descending method, Whatman paper No. 1 was used with the following solvents: (1) 1-butanol–acetic acid–water (12:3:5 v/v), (2) 2-propanol–dimethylformamide–ammonia (d 0.88) (13:5:2 v/v), (3) ethanol–dimethylformamide–water (3:1:1 v/v). Theophylline (R_f 0.68 in all solvents) served as standard for evaluation of R_f values. Spots were located by their fluorescence under a Desaga MinUvis ultraviolet lamp (λ ~254 and 366 nm).

Known Compounds. The following purines were synthesized by known methods: **3a**,[12] **4a**,[13] **1b**,[12] **2b**,[12] **3b**,[14] **1c**.[1] The following pyrimidines are known: 5,6-diamino-1,3-dimethyluracil[15] and its 2-thio derivative.[12]

General Synthetic Procedures. 1. Thiation of Xanthines 4a and 5a. A suspension of a xanthine (1 g) and phosphorus pentasulfide (4 g) in β-picoline (20 mL) was refluxed for 3 h. The solvent was removed in vacuo and the residue treated with boiling water for 15 min. After cooling, the 6-thioxanthine was filtered off and dissolved in hot sodium hydroxide, and the solution was decolorized with charcoal and filtered. The 6-thioxanthines were then precipitated by acidification with acetic acid. For further purification see Table IV.

2. Oxidation of 6-Thioxanthines with Perbenzoic Acid. The 6-thioxanthine was suspended in chloroform or dissolved in methanol; at 0 °C a solution of 1.1 equiv of perbenzoic acid in chloroform was added under continuous stirring. If the product crystallized directly, it was filtered off and purified (Table IV, procedure 2a). If the product remained in solution, the latter was extracted with aqueous sodium bicarbonate. The organic layer was dried over sodium sulfate and the solvent removed in vacuo (procedure 2b).

3. Oxidation of 6-Thioxanthines with H_2O_2. The 6-thioxanthine was dissolved in a mixture of ethanol–chloroform (1:1), containing 1% triethylamine. The solution was stirred and warmed to 50 °C. Hydrogen peroxide (30%, 1.1 equiv) was added dropwise. The mixture was brought to dryness in vacuo and the residue was purified (Table IV).

8-Phenyl-2-thiotheophylline (5a). An intimate mixture of 5,6-diamino-1,3-dimethyl-2-thiouracil sulfate (6.3 g), benzamidine hydrochloride (8.1 g), and anhydrous sodium acetate (3.6 g) was heated to 185 °C for 10 min. The cake was treated with 75 mL of hot water and the mixture filtered. The insoluble product 5a (yield quantitative) was purified as described in Table IV.

6-Selenotheophylline. A. 1,3-Dimethyl-6-methylthio-2-oxopurine.[2] S-Methylation of **2b** was carried out by a modification of the procedure of Neiman et al.[2] A mixture of methyl iodide and of the sodium salt of **2b** was stirred at 4 °C for 48 h. The precipitate formed was recrystallized repeatedly from benzene, mp 189–191 °C, yield 60%.

B. 6-Selenotheophylline. A solution of the foregoing thioether in ethanol was stirred at room temperature, while hydrogen selenide was bubbled through for 30 min.[16] The precipitate formed was recrystallized from ethanol. From concentrated solutions, the product crystallized in square yellow plates, from dilute solutions in yellow needles: yield 76%; mp >300 °C dec; pK −0.5, 7.4; λ_{max} (N) 290, 368 nm; (A) 363 nm; (C) 364 nm; R_f (solvent 1) 0.77; (2) 0.70; (3) 0.69; fluorescence, yellow-gray at 254 nm, orange at 366 nm; $\delta_{1\text{-Me}}$ 3.94; $\delta_{3\text{-Me}}$

Table IV. Preparation and Analysis of New Purines

No.	Mp or dec p, °C	Solvent for crystn	Crystal form and color	Procedure used[a]	Yield, %	Color of complex with $FeCl_3$
			I. Xanthines			
5a	>300	Dioxane	Colorless prisms	*a*	Quant	
			II. 6-Thioxanthines			
4b	257–258	Acetic acid	Yellow, hairlike needles	(1)	95	
5b	284–285	Benzene	Fluffy yellow needles	(1)	Quant	
			III. 6-Sulfinyl Derivatives			
1c	287–290	Ethanol[b]	Stars of yellow needles	(2a)	36	Green
2c	241–244	2-Propanol	Stars of greenish needles	(2b, 3)	50	Dark blue
3c	244–245	1-Butanol	Intense yellow needles	(2a)	93	Green
4c	218–219	Ethanol	Hairlike orange needles	(3)	Quant	Orange
5c	>300	Ethanol	Hairlike orange needles	(3)	Quant	Brown

[a] For procedures used, see Experimental Section. [b] This compound was not obtained in analytically pure form. Satisfactory C, H, N, and S values were obtained for all other compounds.

3.58; $\delta_{8\text{-H}}$ 8.32 ppm (acetic acid). Anal. Calcd for $C_7H_8N_4OSe$: C, 34.6; H, 3.3. Found: C, 35.0; H, 3.3.

6-Selenotheobromine. Through a refluxing solution of 3,7-dimethyl-6-methylthio-2-oxopurine[17] in ethanol, hydrogen selenide was passed for 15 min. The precipitate (yield quantitative) crystallized from ethanol in long, yellow needles: mp 269–272 °C; pK <−2, 8.8; λ_{max} (N) 372 nm; (A) 348 nm; (C) 360 nm; R_f (solvent 1) 0.68; (2) 0.70; (3) 0.68; fluorescence at 366 nm orange; $\delta_{3\text{-Me}}$ 3.47; $\delta_{7\text{-Me}}$ 4.21; $\delta_{8\text{-H}}$ 8.25 ppm (acetic acid). Anal. Calcd for $C_7H_8N_4OSe$: C, 34.6; H, 3.3. Found: C, 34.85; H, 3.1.

Oxidation of 6-Selenoxanthines. When a solution of a 6-selenoxanthine in chloroform was treated at room temperature with perbenzoic acid in chloroform, a red precipitate appeared immediately. After evaporation of the solvent, the organic residue was identified as the corresponding xanthine. With aqueous hydrogen peroxide, the precipitation of selenium was much slower, but again the xanthines were the end products.

Measurement of Dipole Moments. The compounds studied are practically insoluble in nonpolar solvents. Therefore we have used dioxane, although dipole moments in this solvent are somewhat higher than those measured in truly nonpolar solvents.[18] Even in dioxane the maximal concentration of all sulfinyl derivatives amounted to less than 10^{-3} molar fraction. Therefore the moments bear a relatively large error of 0.1–0.2 D. Because of limited solubility, we did not attempt to obtain the molar refractions from the refractive indices of the dioxane solutions, but calculated them from the bond electronic polarizations.[19]

Details of the experimental procedure have been given previously;[5] calculations were performed by the method of Halverstadt and Kumler.[20]

Registry No.—**1a,** 83-67-0; **1b,** 38759-03-4; **1c,** 62006-24-0; **2a,** 58-55-9; **2b,** 2398-70-1; **2c,** 62006-25-1; **3a,** 6603-63-0; **3b,** 6501-94-6; **3c,** 62006-26-2; **4a,** 961-45-5; **4b,** 62006-27-3; **4c,** 62029-53-2; **5a,** 62029-54-3; **5b,** 62006-28-4; **5c,** 62006-29-5; 5,6-diamino-1,3-dimethyl-2-thiouracil sulfate, 62006-30-8; benzamidine hydrochloride, 1670-14-0; 6-selenotheophylline, 62006-31-9; 1,3-dimethyl-6-methylthio-2-oxopurine, 62006-32-0; 6-selenotheobromine, 62006-33-1.

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