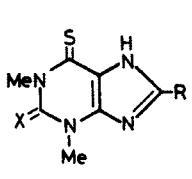
Comparison of the Mass Spectra of 6-Thiotheophyllines and 6-Sulfinyltheophyllines

Felix Bergmann, Miriam Rahat and Arie Frank
Department of Pharmacology, The Hebrew University-Hadassah Medical School, Jerusalem, Israel

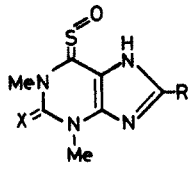
Joseph Deutsch
Department of Pharmaceutical Chemistry, School of Pharmacy, Jerusalem, Israel

Under electron impact, 6-thiotheophyllines eliminate various fragments from the pyrimidine moiety. In a retro Diels-Alder reaction, they lose the fragment X=C=NCH$_3$ from positions 1 and 2 of the pyrimidine ring. In 6-sulfinyltheophyllines, the sulfinyl group is the main target for fragmentation; it can lose either oxygen or sulfur, and the abundance of [M−16]$^+$ and [M−32]$^+$ is much higher than the abundance of the molecular ion. Elimination of the sulfur atom of the 6-sulfinyl substituent, *with retention of its oxygen*, may be explained by intermediate formation of a  **ring. All further fragmentations of the 6-sulfinyl derivatives proceed by a primary loss of oxygen or sulfur, followed by elimination of fragments from the pyrimidine moiety, similar to the primary processes, observed in the mass spectra of the 6-thiotheophyllines.**

Oxidation of 6-thioxanthines to the corresponding 6-sulfinyl derivatives was first described by Walter *et al.*[1] We reported some years ago that stable 6-sulfinylpurines can be obtained only from 6-thiotheophyllines (**1**), However, even compounds **2** lose oxygen easily from the 6-S=O substituent, either by the action of mild reducing agents or simply by heating their solutions in protic solvents.[2] We show here that the instability of the 6-sulfinyl group also finds a characteristic expression in the mass spectra, as evidenced by comparison of the behaviour of compounds of type **1** and **2** under electron impact.



1



2

a: X=O ; R=H
b: X=S ; R=H
c: X=O ; R=C_6H_5
d: X=S ; R=C_6H_5

Mass spectra of 6-thiotheophyllines (1a–1d)

In the series **1a–1d** fragmentation under electron impact involves mainly the pyrimidine moiety. For compound **1a**, the following fragmentations are observed (Fig. 1 and Table 1(a)): expulsion of N=CH_2 and NCH_3 radicals produces the ions *m/z* 168 and 167, (**1b** and **1d** do not contain oxygen so losses of 28 and 29 u can not be due to CO and CHO); elimination of sulfur or of an SH radical yields *m/z* 164 and 163, respectively; expulsion of CS (44 u) gives *m/z* 152, this ion being accompanied by small abundances of *m/z* 151 and 150, representing loss of CSH$^\cdot$ and CSH_2. Similar fragmentations are observed in the spectra of **1b–1d** (Table 1 (a and b)). It is found that **1c** behaves similarly to **1a** and that **1d** resembles **1b**. Clearly, the imidazole ring, with or without the 8-phenyl substituent, is quite resistant to fragmentation under electron impact.

An important process in the mass spectrum of **1a** involves formation of the ions [M−56]$^+$, [M−57]$^{+\cdot}$ and [M−58]$^+$. These have their counterparts in the fragments [M−72]$^+$, [M−73]$^{+\cdot}$ and [M−74]$^+$, formed from **1b**. In the latter molecule, the 2-carbonyl is replaced by a thiocarbonyl group. Therefore, the difference of 16 u between these two triads indicates that position 2 is involved in the expulsion of the neutral fragment O=C=NCH_3 from **1a** and of S=C=NCH_3 from **1b** (Scheme 1). The analogous processes are encountered in the fragmentation of the 8-phenyl derivatives **1c** and **1d** (see Table 1 (b)). The ions *a*, obtained from all four members of series **1**, are

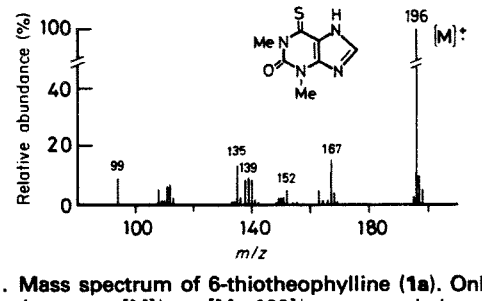


Figure 1. Mass spectrum of 6-thiotheophylline (**1a**). Only fragments in the range [M]$^{+\cdot}$ to [M−100]$^+$ are recorded.

CCC-0030–493X/82/0017–0565$02.00

Table 1. Mass spectra of 6-thiotheophyllines (1a–1d)

(a) 6-Thio- (**1a**) and 2,6-dithiotheophylline (**1b**)

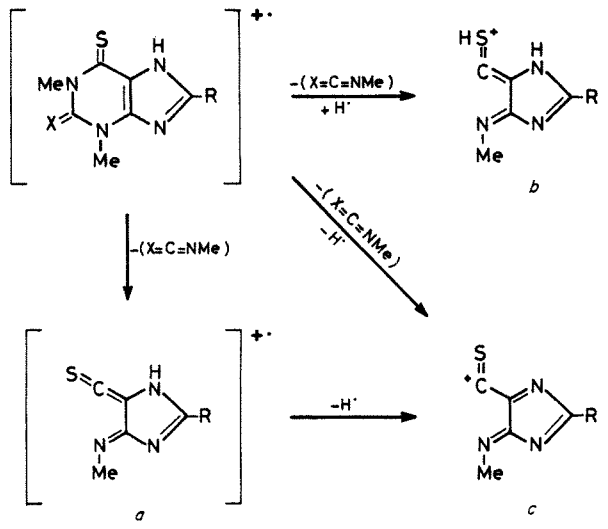
Compound 1a			Compound 1b		
Ion[a] composition	m/z	Relative abundance[b] (%)	Ion composition	m/z	Relative abundance (%)
(M+1)	197	10	$[M]^{+\cdot}$	*212*	100
$[M]^{+\cdot}$	*196*	100	(M−15)	197	5
(M−1)	195	2.9	(M−28)	184	7
(M−28)	168	4	(M−44)	168	13
(M−29)	167	15.3	(M−45)	167	33
(M−32)	164	2	(M−46)	166	19
(M−33)	163	4.4	(M−60)	152	4
(M−44)	152	5	(M−61)	151	4
(M−45)	151	2	(M−64)	148	4
(M−46)	150	2	(M−72)	140	6
(M−56)	140	8.6	(M−73)	139	10
(M−57)	139	9.3	(M−74)	138	6
(M−58)	138	8.6	(M−79)	133	8
(M−60)	136	2.9	(M−100)	112	9
(M−61)	135	17	(M−101)	111	7

(b) 8-Phenyl-6-thio-(**1c**) and 2,6-dithiotheophylline (**1d**)

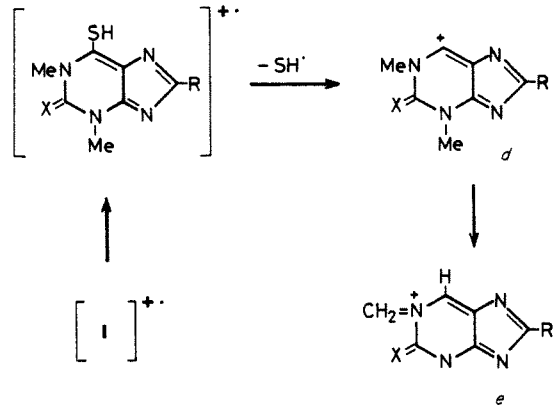
Compound 1c			Compound 1d		
Ion composition	m/z	Relative abundance (%)	Ion composition	m/z	Relative abundance (%)
$[M]^{+\cdot}$	*272*	100	$[M]^{+\cdot}$	*288*	100
(M−28)	244	7.2	(M−33)	255	6.3
(M−29)	243	10	(M−44)	244	5.5
(M−32)	240	4.3	(M−45)	243	15.5
(M−33)	239	3	(M−46)	242	19
(M−56)	216	5.7	(M−72)	216	3.1
(M−57)	215	5.7	(M−73)	215	5.2
(M−58)	214	5.7	(M−74)	214	8.2
(M−61)	211	5.7	(M−79)	209	5.5

[a] Fragments are recorded for the range $[M]^{+\cdot}$ to $[M-100]^{+}$. Only fragments with a relative abundance of at least 2% are included in the tables.

[b] Abundances are expressed as percent base peak which in compounds **1a–1d** is the molecular ion.



Scheme 1



Scheme 2

accompanied by ions *b* and *c*, formed by rearrangements which cause loss or addition of a hydrogen atom. The ions *c* may also be formed from *a* by subsequent loss of hydrogen (see Scheme 1).

The process, represented in Scheme 1, parallels the retro Diels-Alder reaction, observed in the mass spectrum of xanthine,[3] hypoxanthine and guanine.[4]

The 6-thiocarbonyl may undergo enolization with the hydrogen of the 7-NH group, as shown in Scheme 2. The thioenolate then may lose the radical SH· to form the ion $[M-33]^{+}$ (see Table 1). The resulting ion *d* may be stabilized by tautomerism to *e* (see Scheme 2).

Further fragmentations are not discussed here, as our main purpose is comparison of the mass spectra of **1** and **2**.

Mass spectra of 6-sulfinyltheophyllines (2a–2d)

The instability of the 6-sulfinyl group is demonstrated by the low abundance of the molecular ions and by the high abundance of the fragment $[M-16]^{+\cdot}$ (Fig. 2 and Table 2). In view of the lability of the sulfinyl oxygen, it is probable that further fragmentations involve the primary elimination of this oxygen, followed by reactions similar to those observed in series **1**. For instance, in the spectrum of **2a** (Fig. 2) the ions represented by *m/z* 168 and 167 are formed in two-step processes, i.e. removal of oxygen and subsequent elimination of $N{=}CH_2$ and NCH_3 radicals, respectively. Similarly, the ion $[M-60]^{+\cdot}$ is obtained by elimination of oxygen, followed by loss of CS (44 u). In an analogous way, the retro Diels-Alder reactions take place after elimination of oxygen. In the spectrum

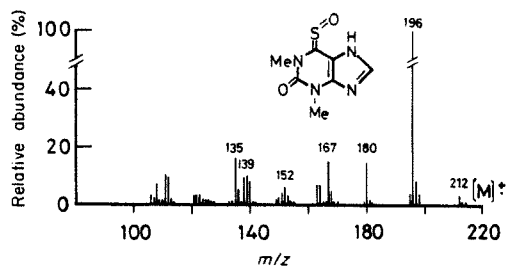


Figure 2. Mass spectrum of 6-sulfinyltheophylline (**2a**). Only fragments in the range $[M]^{+\cdot}$ to $[M-100]^{+}$ are recorded.

Table 2. Mass spectra of 6-sulfinyltheophyllines (2a–2d)

(a) 6-Sulfinyltheophylline (**2a**) and 6-sulfinyl-2-thiotheophylline (**2b**)

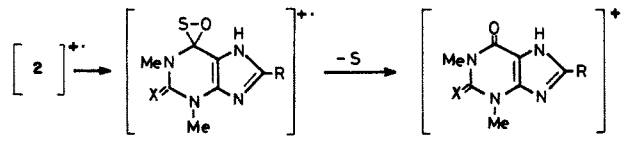
Compound **2a**			Compound **2b**		
Ion composition	m/z	Relative abundance (%)	Ion composition	m/z	Relative abundance (%)
$[M]^{+\cdot}$	212	3	$[M]^{+\cdot}$	228	6
(M−15)	197	8.6	(M−16)	*212*	100
(M−16)	*196*	100	(M−32)	196	20
(M−17)	195	3.8	(M−48)	180	6
(M−32)	180	14.3	(M−49)	179	6.7
(M−44)	168	4.3	(M−60)	168	12.7
(M−45)	167	15	(M−61)	167	26
(M−48)	164	7	(M−62)	166	17.4
(M−49)	163	6	(M−76)	152	4
(M−60)	152	6.2	(M−77)	151	6
(M−61)	151	4	(M−78)	150	4.7
(M−62)	150	2.4	(M−80)	148	4
(M−72)	140	8	(M−88)	140	10
(M−73)	139	10	(M−89)	139	18
(M−74)	138	9	(M−102)	126	2.6
(M−76)	136	4.3	(M−103)	125	4
(M−77)	135	16	(M−104)	124	4
(M−89)	123	3.5	(M−105)	123	4
(M−90)	122	3	(M−107)	121	5
(M−91)	121	3	(M−116)	112	10
(M−100)	112	9			
(M−101)	111	10.3			
(M−104)	108	7			

(b) 8-Phenyl-6-sulfinyltheophyllines (**2c** and **2d**)

Compound **2c**			Compound **2d**		
Ion composition	m/z	Relative abundance (%)	Ion composition	m/z	Relative abundance (%)
$[M]^{+\cdot}$	288	6	$[M]^{+\cdot}$	304	28
(M−16)	*272*	100	(M−16)	*288*	100
(M−32)	256	37.8	(M−32)	272	41
(M−48)	240	53.7	(M−48)	256	38
(M−49)	239	5.8	(M−60)	244	14.8
(M−59)	229	3.6	(M−61)	243	44
(M−60)	228	3.5	(M−62)	242	41.5
(M−61)	227	4.1	(M−76)	228	9.2
(M−72)	216	6.5	(M−77)	227	9.8
(M−77)	211	5.1	(M−78)	226	11.8
(M−78)	212	24.4	(M−80)	224	10.5
(M−89)	199	5.1	(M−90)	214	22
			(M−94)	210	8.7
			(M−95)	209	15.5
			(M−105)	199	6.3

of **2a** and **2c**, this leads to the ions $[M-73]^{+\cdot}$ and their companions $[M-72]^{+}$ and $[M-74]^{+}$, while from **2b** and **2d** the ions $[M-89]^{+\cdot}$ or their companions are formed. All these sequences were confirmed by the method of metastable defocusing.

The most intriguing fragmentation in the mass spectra of compounds **2** involves loss of sulfur from the 6-CSO group, *with retention of the oxygen*. Evidence for the localization of this process derives from the spectra of **2a** and **2c**, since these two derivatives bear a single sulfur atom at position 6. We assume that first a cyclic intermediate is formed (*f* in Scheme 3) which then loses sulfur or an SH radical to yield the



f 3

Scheme 3

theophyllines **3**. Related rearrangements, responsible for replacing CSO bonds by COS linkages, have been reported for sulfones.[5,6]

By metastable defocusing, we have found that removal of SO to give the ion $[M-48]^{+\cdot}$ (Table 2) occurs by sequential loss of oxygen and sulfur. Similarly, the ions $[M-77]^{+\cdot}$ are formed in a 3-step process, viz. by sequential elimination of oxygen, followed by sulfur and finally by NCH_3. However, in view of the considerable abundance of the ions $[M-32]^{+}$, two-step fragmentations involving the primary splitting off of sulfur may also be expected. Indeed, the ion $[M-89]^{+\cdot}$ is formed from **2a** and **2c** by primary loss of sulfur, followed by elimination of $O{=}C{=}NCH_3$. The formation of this ion from **2a** and **2c** differs from the process, yielding $[M-89]^{+\cdot}$ from **2b** and **2d** (see above). However, in the case of **2b**, we have observed the analogous sequence of elimination of sulfur, followed by loss of $S{=}C{=}NCH_3$ to give the ion $[M-105]^{+\cdot}$.

We conclude that in the series **2** the primary step always involves the 6-sulfinyl group. Further fragmentations occur by processes similar to those observed in the mass spectra of the corresponding compounds **1**.

The thermal stability of the sulfines (2a–2d)

In general purines are characterized by high thermal stability. We have shown here that 6-sulfinyltheophyllines lose oxygen under electron impact. However, in the mass spectrometer, these compounds are exposed to high inlet temperatures. Therefore we have determined whether simple heating of the solid materials will cause loss of oxygen. Furthermore, the finding that compounds **2** may also eliminate sulfur, raises the question whether this occurs only under electron impact or perhaps also in a thermal process.

Heating was performed in the presence or absence of oxygen to test whether elimination of sulfur is a truly intramolecular process. The reaction products were analysed by thin-layer chromatography (TLC). Since identical products were formed with and without exclusion of oxygen, the intramolecular character of the rearrangement of the 6-sulfinyl group is confirmed. Table 3 shows that compounds **2a** and **2b** eliminate sulfur to a small extent upon heating, yielding **3a** and **3b**. However, heating of the 8-phenyl derivatives **2c** and **2d** caused loss of oxygen, but no trace of the dethiated derivatives **3a** and **3d** could be detected. We conclude that the purines **2c** and **2d** yield the corresponding theophyllines **3** only under electron impact, but in the case of **2a** and **2b** dethiation is also greatly enhanced by electron impact.

Table 3. Thermal degradation of 6-sulfinyltheophyllines 2[a]

Compound No.	M.p. (°C)	reaction temp. (°C)	Solvent for TLC	R_f of standards				Presence of 3	
				Theophylline	1	2	3	Thermal	Mass spectrum
2a	230	150	acetone–methanol 4:1, v/v	0.50	0.56	0.06	0.50	+	+
2b	210	150	$CHCL_3$–methanol–25% NH_3, 8:4:1	0.61	0.66	0.70	0.54	+	+
2c	300	210	$CHCl_3$–ethyl acetate, 4:1	0.04	0.49	0.23	0.33	–	+
2d	250–253	120	$CHCl_3$–ethyl acetate, 9:1	0.05	0.85	0.54	0.49	–	+

[a] A small amount of solid material was heated in a glass capillary for 5 min, at the reaction temperature shown in column 3. The material was then dissolved in DMF and subjected to TLC on silica. Theophylline, compounds **1** and **2** and the corresponding 6-oxo derivatives **3** were used as standards.

EXPERIMENTAL

Sources and/or methods of synthesis for compounds **1a–1d** and **2a–2d** have been reported previously.[2]

Mass spectra were measured with a LKB 2091 mass spectrometer at 70 eV; ion source temperature 250 °C. The samples were heated externally until a reasonable mass spectrum was obtained. Metastable defocusing was performed with a Varian MS-311 double focusing mass spectrometer.

Acknowledgement

The authors are grateful to Professor Chava Lifschitz for the metastable defocusing measurements.

REFERENCES

1. W. Walter, J. Voss and J. Curts, *Liebigs Ann. Chem.* **695**, 77 (1966).
2. F. Bergmann, A. Frank, H. Weiler-Feilchenfeld and I. Tamir, *J. Org. Chem.* **42**, 2470 (1977).
3. G. Spiteller and M. Spiteller-Friedmann, *Monatsh. Chem.* **93**, 632 (1962).
4. J. M. Rice and G. O. Dudek, *J. Am. Chem. Soc.* **89**, 2719 (1967).
5. S. Meyerson, H. Drews and E. K. Fields, *Anal. Chem.* **36**, 1294 (1964).
6. F. Bergmann and D. Diller, *Org. Mass Spectrom.* **12**, 338 (1977).

Received 30 April 1982; accepted 5 June 1982