IDENTIFICATION OF ISOMERIC 2-DIALKYLAMINOETHYLTHIO-THIENO [2,3-*c*] AND [3,2-*d*] ISOTHIAZOLES WITH ANTIFUNGINE ACTIVITY BY ELECTRON IMPACT MASS SPECTROMETRY[1]

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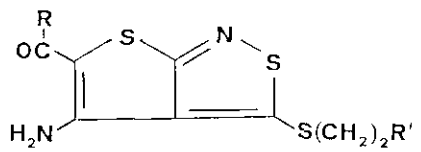
Abstract - The EI mass spectra of sixteen title compounds were studied. The 5-acyl and the 2-dialkylaminoethylthio substituents are responsible of the main fragmentation processes of thieno [2,3-*c*] and thieno [3,2-*d*] isothiazoles. An easy criterion of distinction between the two types of heterocyclic compounds results from the comparison of the relative abundances of some ionic species.

Recently we reported a preparation route for an unambiguous synthesis of isomeric thieno [2,3-*c*] and thieno [3,2-*d*] isothiazoles[2]. Using such a way, the 2-dialkylaminoethylthio derivatives 1a-h and 2a-h were prepared[3], and the 5-benzoyl derivatives of both series (1 and 2 from g to h) evidenced interesting fungicida propierties versus *Candida tropicalis*, *Candida albicans* and *Candida parapsilosis*[3].



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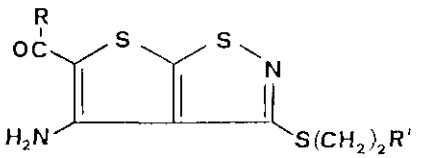
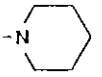
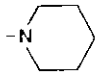
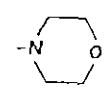


2

COMP.	R	R'	COMP.	R	R'
a	CH_3	$-N(CH_3)_2$	e	C_6H_5	$-N(CH_3)_2$
b	CH_3		f	C_6H_5	
c	CH_3		g	C_6H_5	
d	CH_3		h	C_6H_5	

As extention of our studies on mass spectrometry[4], and particularly on its application for identifying isomeric compounds of pharmaceutical interest[5], we examined and compared the mass spectra of these compounds.

RESULTS AND DISCUSSION

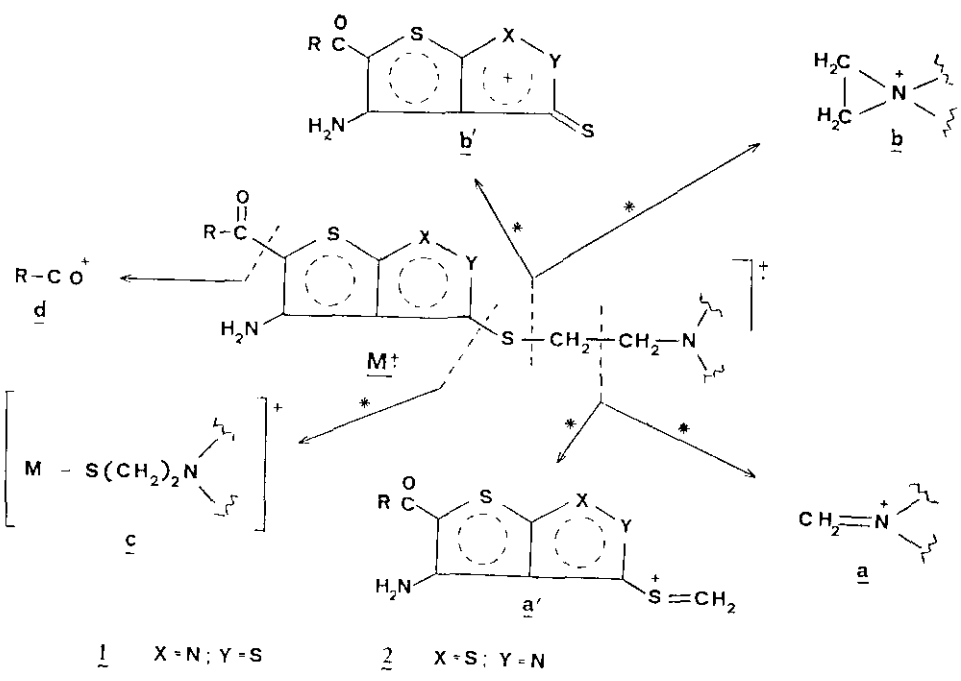
The significant peaks of the 75 eV mass spectra of 1a-h and 2a-h are reported in table 1, and the metastable supported transitions were indicated by an asterisk on the arrows in the schemes.

The molecular ion peaks are always observed and those of 1a-h are more intense with respect to the corresponding 2a-h isomers. The main fragmentation processes involve either the dialkylaminoethyl group linked to the exocyclic sulphur atom or the 5-acyl group. In particular 1a-h and 2a-h evidence the base peak corresponding to the immonium ion *a*, arising by the energetically favoured cleavage of the dimethylenic bond (scheme 1). The same fragmentation affords *a'*, in smaller amounts, with charge retention on the heterocyclic moiety.

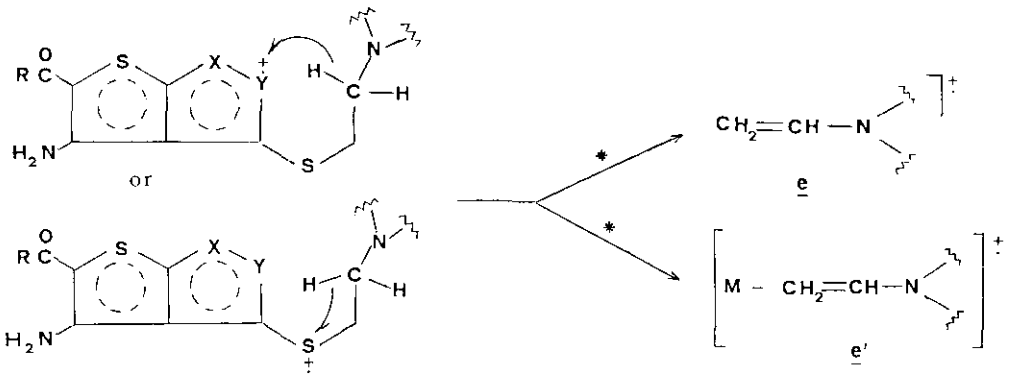
The loss of the whole dialkylaminoethyl group was also observed indipendently on the heterocyclic structure 1 or 2 ; this is line with the losses of both alkyl radicals occurring in a series of 3,5-bisalkylthio isothiazoles[6]. In this process also the charge was mainly mantained by the dialkylaminoethyl moiety, which should be stabilized by formation of the cyclic ammonium ion *b*.

Finally the loss of the whole dialkylaminoethylthio radical gives the slightly abundant ion *c*, while the alpha cleavage at the carbonyl group yields the acylium ion *d*.

SCHEME 1 - Simple bond cleavage reactions



SCHEME 2 - Proposed mechanisms for the main rearrangement process.

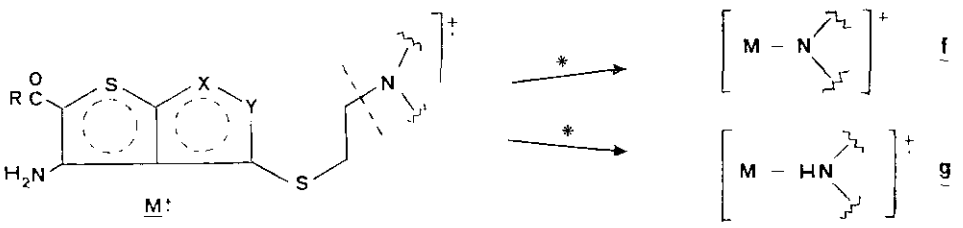


1 X=N; Y=S 2 X=S; Y=N

Also the rearrangement process involving a hydrogen migration, similar to a McLafferty reaction, with charge retention mainly in the enamine moiety (ion *e*), constitutes an important common fragmentation pathway (scheme 2) ; in this respect it must be noticed that, while hydrogen trasfering reactions on the nitrogen of the isothiazole ring are well known[6,7], the occurrence of an analoguous process involving sulphur atom has not been reported. In our compounds an alternative mechanism, proceeding through a hydrogen migration on the exocyclic sulphur atom via a four-membered cyclic transition state, cannot be excluded *a priori* . However, composite metastable peaks for $M^{+\cdot} \rightarrow e$ reactions are not observed even under conditions of high energy resolution. This suggests that ion *e* was not formed by two competitive mechanisms[8].

Other processes occurring in lower extent, involve the loss of the amino group as radical or as molecule (scheme 3, ions *f* and *g* respectively).

SCHEME 3 -- Loss of the dialkylamino group



1 X=N; Y=S 2 X=S; Y=N

TABLE 1 : m/z Values and Relative Abundances (in parenthesis) of the Characteristic Ions of 1a-h and 2a-h (75 eV)[a]

COMP. \ IONS[b]	M	*a*	*a'*	*b* [c]	*b'*	*c*	*d*	*e*	*e'*	*f*	*g*
1a	301(62)	58(100)	243(5)	72(99)	229(10)	197(3)	43(84)	71(46)	230(30)	257(4)	256(14)
2a	301(6)	58(100)	243(7)	72(70)	229(6)	197(6)	43(75)	71(95)	230(9)	257(3)	256(3)
1b	327(18)	84(100)	243(2)	98(44)	229(2)	197(2)	43(25)	97(17)	230(4)	257(1)	256(6)
2b	327(3)	84(100)	243(2)	98(10)	229(2)	197(2)	43(21)	97(55)	230(2)	257(1)	256(1)
1c	341(13)	98(100)	243(2)	112(42)	229(2)	197(2)	43(33)	111(10)	230(2)	257(1)	256(5)
2c	341(3)	98(100)	243(4)	112(6)	229(2)	197(3)	43(24)	111(24)	230(1)	257(1)	256(1)
1d	343(10)	100(100)	243(3)	114(48)	229(3)	197(2)	43(25)	113(8)	230(7)	257(1)	256(6)
2d	343(2)	100(100)	243(5)	114(10)	229(3)	197(3)	43(30)	113(30)	230(5)	257(1)	256(1)
1e	363(10)	58(100)	305(3)	72(70)	291(4)	259(2)	105(22)	71(7)	292(9)	319(3)	318(3)
2e	363(1)	58(100)	305(3)	72(13)	291(3)	259(3)	105(18)	71(30)	292(3)	319(2)	318(1)
1f	389(7)	84(100)	305(3)	98(35)	291(2)	259(3)	105(20)	97(13)	292(3)	319(2)	318(3)
2f	389(2)	84(100)	305(3)	98(10)	291(3)	259(6)	105(24)	97(40)	292(2)	319(1)	318(1)
1g	403(7)	98(100)	305(3)	112(40)	291(3)	259(2)	105(18)	111(9)	292(4)	319(2)	318(4)
2g	403(2)	98(100)	305(2)	112(9)	291(2)	259(3)	105(38)	111(27)	292(2)	319(1)	318(1)
1h	405(11)	100(100)	305(5)	114(40)	291(5)	259(4)	105(35)	113(5)	292(10)	319(1)	318(3)
2h	405(8)	100(100)	305(3)	114(70)	291(13)	259(30)	105(50)	113(94)	292(18)	319(2)	318(2)

a-The complete 75 eV mass spectra have been sent to the"Mass Spectrometry Data Center" Nottingham NGD 2RD,England.

b-For ion assignements see either Schemes 1, 2, 3 or the text.

c-The relative intensity was uncorrected from isotopic contribution of *e*.

The characteristic breakdown processes involving isothiazole ring cleavage through endocyclic N-S and/or S-C bond fission[6,7,9-11] are completely quenched by the occurrence of the energetically more favourable fragmentations due to the presence of the 5-dialkylaminoethylthio group; this makes the mass spectra of 1a-h and 2a-h very similar. However, a comparative analysis of the relative intensities evidences that the rearrangement reaction affording *e* occurs to a lower extent, with respect to the simple bond cleavage reactions, in 1a-h compounds. In particular, the relative abundance ratio $|e|/|b|$ constitutes an important and immediate analytical tool to distinguish between the two series. In fact its values are found in the ranges from to 0.10 to 0.45 for the thieno[2,3-*c*]isothiazoles (1a-h) and from 1.35 to 5.45 for the thieno[3,2-*d*]isothiazoles (2a-h). Such a difference makes unnecessary the availability of both terms of the isomeric couples; this appears of interest since the other commonly used instrumental techniques give incomplete informations in this respect. In fact the ^{1}H nmr spectra show the S-CH_2 signals of the type 1 derivatives upfield with respect to those of the corresponding 2 isomers[2], but the differences in chemical shifts are very small (<0.2 ppm). On the other hand, both ir[2,3] and uv[3] data lead to discriminate between the heterocyclic ring 1 or 2, but these give not information on the 2-dialkylaminoethylthio group.

EXPERIMENTAL

The compounds were prepared as in ref. 3. Low resolution mass spectra were run on a Jeol JMS-01-SG-2 double focussing mass spectrometer, with an electron beam energy of 75 eV, an accelerating voltage of 5 KV and an electron current of 100 μA. The samples were introduced by a direct inlet system (with a probe) into the ion source at about 200 °C. First field-free region metastable ions were detected by the accelerating voltage scan technique.

ACKNOWLEDGMENT

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REFERENCES AND NOTES

1. This work constitutes part 5 in the series "Studies in Organic Mass Spectrometry"; for part 4 see ref. 4.
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