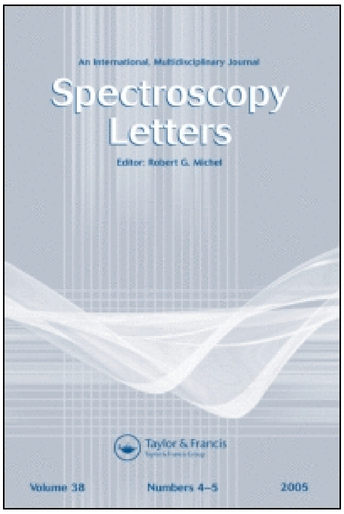

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Identification and Characterization of 4-Hydroxy-2H-1,2-benzothiazine-3-carboxylic Acid 1,1-Dioxide Derivatives by Mass Spectroscopy

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IDENTIFICATION AND CHARACTERIZATION OF 4-HYDROXY-2H-1,2-BENZOTHIAZINE-3-CARBOXYLIC ACID 1,1-DIOXIDE DERIVATIVES BY MASS SPECTROSCOPY

Key words: Electron Impact Mass Spectra, 4-Hydroxy-2H-1,2-benzothiazine-3-carboxylic Acid 1,1-Dioxide Derivatives.

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ABSTRACT

Electron impact mass spectral fragmentation of certain esters and amides derived from 4-hydroxy-2H-1,2-benzothiazine-3-carboxylic acid 1,1-dioxide is described. Common ions to both series may be observed, as well as others allowing them to be differentiated. The method is promissory for identification and analysis of these compounds.

INTRODUCTION

Interest in 4-hydroxy-2H-1,2-benzothiazine-3-carboxylic acid 1,1-dioxide (I, X=OH, R=H) derivatives was enhanced by the discovery of potent anti-inflammatory activity in certain carboxami-

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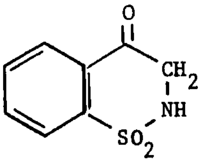
des[1-4]. Both IR and ^{1}H-NMR spectra of several esters[5] and amides[6] were studied and support the enolic structure of these compounds. However, to the best of our knowledge,there has been no systematic study dealing with the electron impact (EI) behaviour of such compounds and only the mass spectrum of Pyroxicam (I, X=NH-2-pyridyl, R=CH_3) has been described so far[7]. In an intent of establish a correlation between mass spectrum and structure of this family, we report here the EI mass spectra of a series of esters and amides derived from the above acid (Table 1) together with that of the unsubstituted compound 15 which, in contrast to the previous ones, possesses ketonic structure[5].



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EXPERIMENTAL

Mass spectra were recorded on a Hewlett-Packard Gas Chromatograph (GC) 5890 Series II with an HP1 active column (12 m x 0.2 mm x 0.33μm) and 5971A mass selective detector, employing 70 eV electron energy and 290°C source temperature. Samples were introduced as methanol solutions through the GC at 250°C with a 2 min. solvent delay. Mass measurements were performed by scanning with a resulting 2306 V voltage.

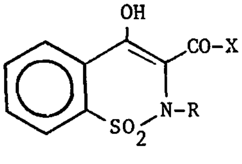
Compounds 1-4[5], 5[1], 6[8], 7[6], 8[6], 9[9], 10[6], 11[6], 13[9] and 15[5] were prepared by procedures described in literature. Compounds 12[1] and 14[1] were obtained by reaction of compounds 7 and 10 respectively with methyl iodide in ethanolic sodium ethoxide. The samples were purified by recrystallization to constant m.p.Purity was ascertained by t.l.c. experiments on Silica Gel GF $_{254}$.

RESULTS AND DISCUSSION

The main fragment ions in the EI mass spectra of compounds 1-15, as well as their relative intensities, are given in Table 2.

TABLE 1

4-Hydroxy-2H-1,2-benzothiazine-3-carboxylic Acid 1,1-Dioxide Derivatives



I

Compound	X	R
1	OCH_3	H
2	OC_2H_5	H
3	$OCH(CH_3)_2$	H
4	$OC(CH_3)_3$	H
5	OCH_3	CH_3
6	NH_2	H
7	$NHCH_3$	H
8	$NHCH(CH_3)_2$	H
9	$N(C_2H_5)_2$	H
10	NHC_6H_5	H
11	$N(CH_3)C_6H_5$	H
12	$NHCH_3$	CH_3
13	$NHCH(CH_3)_2$	CH_3
14	NHC_6H_5	CH_3

A representative mass spectrum is shown in Fig. 1. With the exception of compound 6 all spectra display the molecular ion peak. Ions at m/z 51, 76, 77, 104, 105, 152 and 169 are observed with variable intensity. Typical fragments for esters (compounds 1-5) and amides (compounds 6-14) allowing them to be differentiated are commented afterwards. The possible fragmentation routes are shown in Scheme 1.

TABLE 2

Selected Fragment Ions in the EI Mass Spectra of Compounds 1-15 [m/z (% relative abundance)]

Ion	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
$M^{+\cdot}$	255 (37.3)	269 (57.4)	283 (18.2)	297 (0.5)	269 (15.7)	240 -	254 (33.5)	282 (42.2)	296 (2.8)	316 (68.2)	330 (2.3)	268 (8.4)	296 (37.5)	330 (2.5)	197 (2.4)
[M+1]	256 (3.9)	270 (10.9)	284 (2.3)	298 -	270 (2.2)	241 (54.7)	255 (3.8)	283 (35.5)	297 (1.0)	317 (10.4)	331 -	269 (1.2)	297 (5.6)	331 (0.5)	198 -
[M-64]	191 -	205 -	219 -	233 -	205	176 (18.5)	190 (19.4)	218 (22.6)	232 (8.2)	252 (21.7)	266 (4.6)	204 (3.5)	232 (9.9)	266 (3.8)	133 (5.4)
[CONR'R"]	-	-	-	-	-	44 (a)	58 (52.8)	86 (8.4)	100 (100)	120 (1.0)	134 (0.6)	58 (6.3)	86 (5.4)	120 (0.8)	-
[NR'R"]	-	-	-	-	-	16 (a)	30 (a)	58 (27.5)	72 (68.3)	92 (1.0)	106 (1.7)	30 (a)	58 (19.4)	92 (0.9)	-
[M-CONR'R"]	-	-	-	-	-	196 (1.1)	196 -	196 -	196 -	196 (13.2)	196 (100)	210 -	210 -	210 (5.6)	-
m/z 51	(15.4)	(29.1)	(27.7)	(10.2)	(25.2)	(7.8)	(35.3)	(31.3)	(6.5)	(8.2)	(7.6)	(6.7)	(14.1)	(5.6)	(10.6)
m/z 76	(55.1)	(61.6)	(56.6)	(15.3)	(55.4)	(5.4)	(64.6)	(53.2)	(15.3)	(13.2)	(11.9)	(80.8)	(26.6)	(74.2)	(72.2)
m/z 77	(32.4)	(28.9)	(37.0)	(8.7)	(35.2)	(6.4)	(69.8)	(58.5)	(14.1)	(5.8)	(7.8)	(17.2)	(32.3)	(6.3)	(4.8)
m/z 104	(100)	(100)	(100)	(15.4)	(100)	(46.5)	(87.2)	(70.5)	(11.7)	(6.4)	(16.2)	(100)	(44.7)	(100)	(100)
m/z 105	(42.9)	(43.6)	(44.5)	(17.5)	(24.7)	(100)	(100)	(83.0)	(5.1)	(24.4)	(19.9)	(26.8)	(37.7)	(17.6)	(55.0)
m/z 117	-	-	-	-	(79.7)	-	-	-	-	-	-	(6.8)	(62.1)	(15.4)	-
m/z 152	(5.9)	(14.4)	(4.9)	(3.5)	(4.8)	(5.3)	(6.5)	(9.3)	(3.8)	(9.3)	(2.5)	(69.8)	(6.5)	(69.5)	(1.5)

m/z 168	(13.0)	(18.7)	(28.1)	(7.6)	(12.4)	-	-	-	-	-	-	-	-	-	(3.9)
m/z 169	(9.3)	(13.1)	(14.5)	(3.6)	(7.0)	(4.6)	(8.0)	(9.7)	(5.1)	(3.6)	(16.4)	(22.8)	(3.8)	(24.3)	(5.0)
m/z 223	(8.4)	(20.4)	(46.4)	(24.7)	-	-	-	-	-	-	-	-	-	-	-
m/z 224	(3.2)	(5.0)	(9.5)	(7.2)	-	-	-	-	-	-	-	-	-	-	-
m/z 237	-	-	-	-	(11.8)	-	-	-	-	-	-	-	-	-	-
m/z 238	-	-	-	-	(3.9)	-	-	-	-	-	-	-	-	-	-
m/z 241	-	(11.6)	(80.3)	(100)	-	(54.7)(b)	-	-	-	-	-	-	-	-	-
Other ions (c)	102 (15.1) 103 (20.5) 131 (22.8) 132 (10.0) 148 (27.3) 159 (12.9	102 (20.3) 131 (25.0) 132 (12.3) 149 (37.8) 159 (20.6) 167 (13.2)	102 (12.7) 103 (17.8) 131 (20.3) 149 (20.5) 242 (12.4)	57 (32.5) 242 (11.0)	56 (25.2) 75 (11.3) 118 (10.8) 162 (13.5) 237 (11.8)	103 (17.2) 131 (26.4) 132 (16.9) 148 (42.9) 159 (30.9) 176 (18.5)	85 (85.5) 131 (29.7) 132 (16.0) 159 (22.0) 162 (40.4) 190 (19.4)	60 (39.7) 113 (100) 131 (36.4) 159 (60.7) 190 (23.3) 218 (22.6)	56 (10.2) 196 (14.8)	93 (100) 146 (12.3) 147 (41.3) 159 (16.4) 197 (11.9)	197 (19.4)	118 (16.4)	70 (18.9) 145 (60.4) 149 (13.1) 172 (49.3) 173 (100) 190 (32.1)	91 (10.0) 146 (10.2)	

(a) Ions with m/z <50 are not recorded. (b) Corresponds to [M+1] ion. (c) Peaks greater than 10% are included.

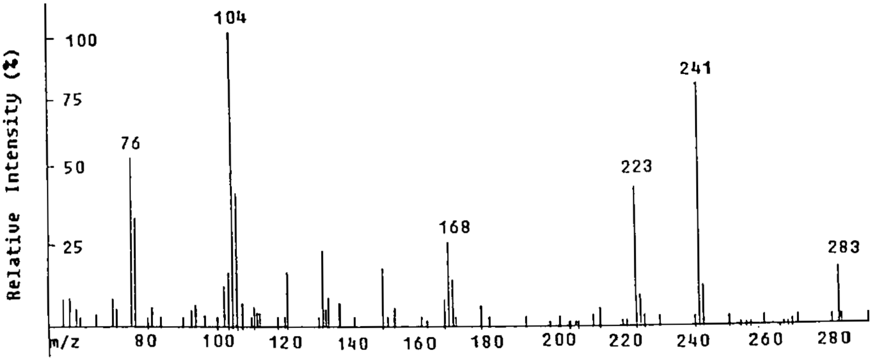
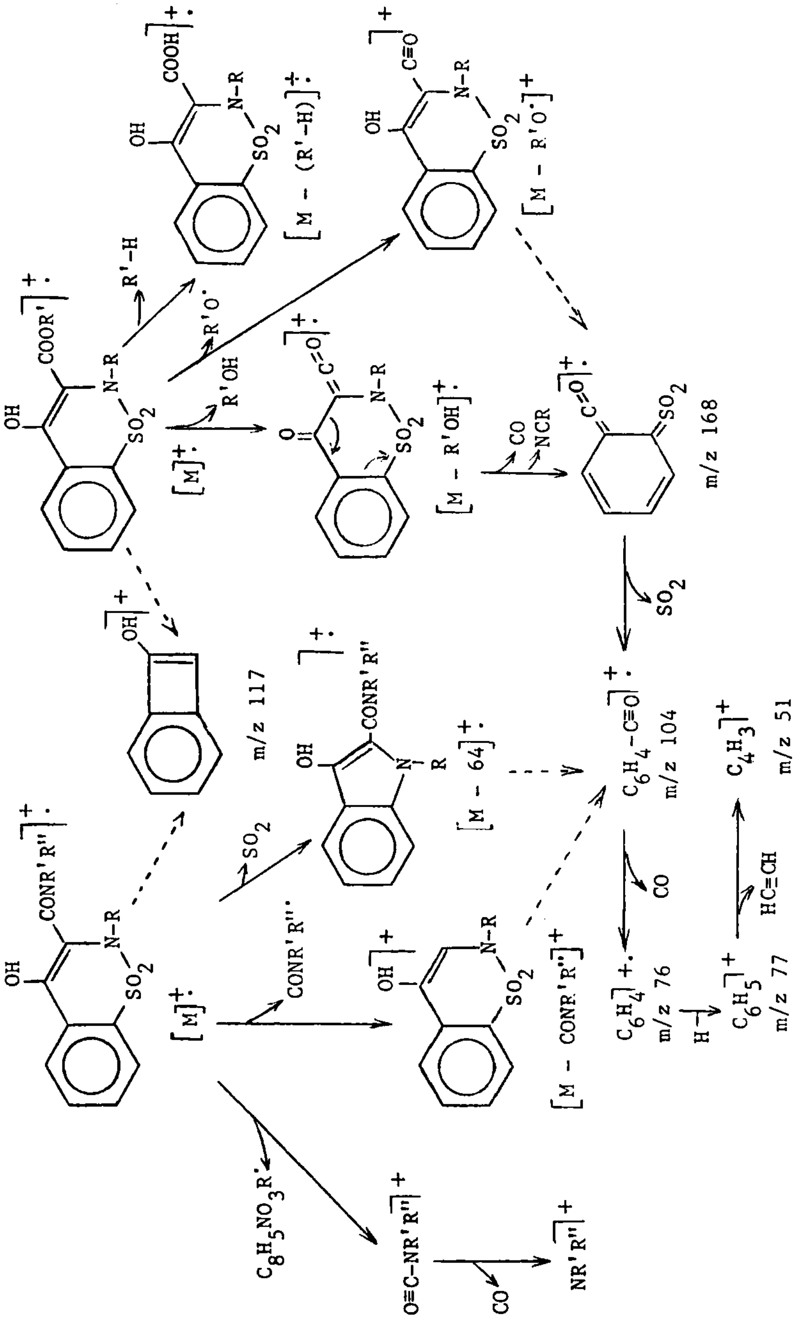


FIG. 1. Mass spectrum of compound 3.

In the alkyl carboxylates (I, X=OR'), while the methyl ester 1 shows a considerable $M^{+\cdot}$ (37.3%), in higher alkyl esters with increasing chain branching of the alcohol, the molecular ion peak becomes progressively smaller and in compound 4 it is virtually negligible (0.5%). Concurrently,the m/z 241 peak$[M-(R'-H)]^{+\cdot}$ probably the carboxylic acid ion which may arise by a McLafferty rearrangement, becomes more significant and is in fact the base peak in t-butyl ester. As may be expected this fragment is absent in the methyl esters 1 and 5 for which the loss of alkene is unavailable.

Fragments appearing in all esters examined are the m/z 168 and those corresponding in composition to the loss of R'OH and R'O˙from the molecular ion (m/z 223 and 224 for compounds 1-4 and m/z 237 and 238 for compound 5). Fragment m/z 168 (Scheme 1) was proposed to demonstrate the ketonic structure of 3-acetyl-4-hydroxy-2H-1,2-benzothiazine 1,1-dioxide (I, X=CH_3, R=H)[8]. However, in our case, this peak appears both in esters whose structure is recognized to be enolic[5], and in the ketonic compound 15 though to a lesser degree (3.9%). The expulsion of SO_2 from this ion probably produces the fragment m/z 104,which is the base peak in the esters except in t-butyl ester 4.


OH
COOR'
N-R
SO2
[M]+·
R'-H
R'O·
R'OH
OH
COOH
N-R
SO2
[M - (R'-H)]+·
OH
C=O
N-R
SO2
[M - R'O·]+
O
C=O
N-R
SO2
[M - R'OH]+·
CO
NCR
C=O
SO2
m/z 168
SO2
OH
m/z 117
OH
CONR'R''
N
R
[M - 64]+·
C6H4-C≡O
m/z 104
CO
C6H4
m/z 76
H
C6H5
m/z 77
HC≡CH
C4H3
m/z 51
OH
CONR'R''
N-R
SO2
[M]+·
SO2
CONR'R''·
OH
N-R
SO2
[M - CONR'R'']+
C8H5NO3R'
O≡C-NR'R''
CO
NR'R''

Scheme 1

As regards the examined amides unsubstituted in the sulphonamidic nitrogen (I, X=NR'R", R=H), the secondary ones (Compounds 7, 8 and 10) present substantially stronger molecular ions (33.5-68.2%) than the tertiary amides(compounds 9 and 11). In the latter, the lower molecular abundance agrees with the lesser chemical stability observed for this amide type[10]. Throughout, N-sulphonamidic methylation decreases molecular ion abundance. Primary amide 6 lacks the molecular ion peak, but like other amides[11] presents a considerable ion(M+1)(m/z 241, 54.7%).

In all examined amides, ions $(M - 64)^{+\cdot}$, corresponding to SO_2 expulsion from the $M^{+\cdot}$, are present with variable intensity (3.5-22.6%), as well as those corresponding to the CONR'R" and NR'R" fragments for N-alkyl amides (m/z 100, base peak in compound 9), and M - CONR'R" fragment for N-aryl amides (m/z 196 base peak in compound 11). In contrast to esters no m/z 168, 223 (or 237), 224 (or 238) and 241 are observed. The base peak has no diagnostic value since it fails to correspond preferentially to any common ion.

Besides the peaks observed in each series, 2-methyl derivatives present a characteristic m/z 117 peak of appreciable intensity. Mihalic et al. proposed the structure shown in Scheme 1 for an ion having this m/z ratio, present in the Pyroxicam spectrum[7].

On the basis of the foregoing results, it is encouraging to point out the usefulness of the mass spectrometry in the identification, structure determination and analysis of 4-hydroxy-2H-1,2-benzothiazine-3-carboxylic acid 1,1-dioxide derivatives.

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REFERENCES

1. Lombardino, J. G., Wiseman, E. H. and McLamore, W. M. J. Medic. Chem. 1971; 14: 1171.

2. Lombardino, J. G. and Wiseman, E. H. J. Medic. Chem. 1972; 15: 848.
3. Zinnes, H., Lindo, N. A., Sircar, J. C., Schwartz, M. L., Shavel, J. Jr. and DiPasquale, G. J. Medic. Chem. 1973; 16: 44.
4. Zinnes, H. Sircar, J. C., Lindo, N. Schwartz, Fabian, A.C., Shavel, J. Jr, Kasulanis, C., Genzer, J. D., Lutomski, C. and DiPasquale, G. J. Medic. Chem. 1982; 25: 12.
5. Schapira, C. B., Perillo, I. A. and Lamdan, S. J. Heterocyclic Chem. 1980; 17: 1281.
6. Perillo, I. A., Schapira, C. B. and Lamdan, S. J. Heterocyclic Chem. 1983; 20: 155.
7. Mihalic, M., Hofman, H., Kajfez, F., Kuftinec, J., Blazevic, N. and Zinic, M. Acta Pharm. Jugosl. 1982; 32: 13.
8. Rasmussen, C. R. J. Org. Chem. 1974; 39: 1554.
9. Schapira, C. B. and Perillo, I. A. J. Heterocyclic Chem. (In press).
10. Perillo, I. A. and Schapira, C. B.. Unpublished results.
11. McLafferty, F. W. Interpretation of Mass Spectra, 3rd ed., University Science Books, Mill Valley, California,1980.

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