ORGANIC MASS SPECTROMETRY, VOL. 25, 517–521 (1990)

Mass Spectra of Heterocyclic Compounds

VI.† 3,4-Dihydro-1*H*-2,3-benzothiazine 2,2-Dioxides

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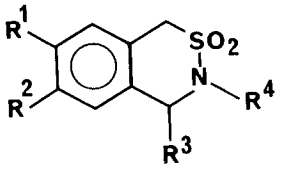
The mass fragmentation behaviour of 3,4-dihydro-1*H*-2,3-benzothiazine 2,2-dioxides was studied. The rationalizations suggested are supported by accurate mass measurements, metastable evidence and deuterium labelling.

INTRODUCTION

As part of our studies on the mass spectrometry of heterocyclic compounds, we report here the analysis of the fragmentation of 3,4-dihydro-1*H*-2,3-benzothiazine 2,2-dioxides under electron impact (EI) conditions. The synthesis of this class of compounds through an intramolecular sulphonylamidomethylation reaction proceeds with good yields and has been previously reported.[2] No reports of previous studies of the behaviour of this type of compounds by mass spectrometry have been found, but Puzo *et al.*[3] suggested that related structures are formed as a result of a rearrangement of an imidosulphite under electron impact. In this study we examined compounds **1**–**14**.



	R^1	R^2	R^3	R^4
1	H	H	H	H
2	H	H	H	CH_3
3	H	H	H	C_2H_5
4	H	H	H	n-C_6H_{13}
5	H	H	H	$Ph(CH_2)_4$
6	H	H	H	$PhCH_2$
7	CH_3	H	H	H
8	AcNH	H	H	H
9	AcNH	H	H	CH_3
10	H	Cl	H	H
11	H	Cl	H	CH_3
12	H	NO_2	H	H
13	H	H	p-$NO_2C_6H_4$	H
14	H	H	Cl_3C	H

† For Part V, see Ref. 1.

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0030–493X/90/100517–05 $05.00

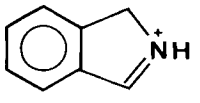
RESULTS AND DISCUSSION

The mass spectra of **1**–**14** are given in Table 1 and some general fragmentations resulting from their analysis are shown in Scheme 1.

The fragmentation processes studied are based on high-resolution mass measurements supporting elemental fragment compositions and on the presence of metastable peaks, which agree with the calculated values. Further, a good correlation is found between the spectrum of **1** and that of its trideutero derivative **1**-d_3 (Fig. 1); the shifts of the m/z values of the ions are in agreement with those predicted from their formation modes.

The molecular ion $M^{+\cdot}$ is of medium or low intensity and is absent in compound **14** because the substituent is easily lost. In most of the examples, the abundance of ion *a* is low in comparison with that of ion *b*, which is the base peak, or is the second in abundance, except when the rupture of the substituent predominates (e.g. loss of ketene from compound **8**).

A common fragment of these compounds is ion *e* (m/z 118), which, although possibly having an identical structure, may have different origins. It is coincident with ion *b* in the fragmentation of the unsubstituted parent derivative **1**, whereas in **2**, **7**, **10** and **12** its formation is interpreted as being due to substituent cleavage from ion *a*; in **3**, **4** and **5** ion *e* is derived from ion *b* by the loss of the nitrogen substituent. Finally, the origin of *e* in **6** (and similarly in **13** and **14**) is shown later in Scheme 3.



e, m/z **118**

For a better description of the fragmentation, it seems appropriate to consider three groups of derivatives: substituted on the N atom, on the benzene ring and on the heterocyclic ring.

Substitution on the N atom

The fragmentation of **2** is analogous to that of unsubstituted **1**. In addition, the loss of a methyl radical

Received 7 March 1990
Revised manuscript received 12 June 1990
Accepted 13 June 1990

Table 1. Mass spectral data for compounds 1–15

		m/z (relative intensity, %)											
Compound	$M^{+\cdot}$	*a*	*b*	*c*	*d*	*e*[a]	*f*	*g*	*h*	*i*[a]	*j*[a]	*k*[a]	Remaining peaks[b]
1	183[c]	119[d]	118[c,d]	91[c,d]	65[d]								117[c] (46); 116[c] (8); 104[c] (9); 92[c,d] (6); 90[c,d] (20); 89[c,d] (17); 64 (9); 63 (11);51 (8)
	(5)	(12)	(100)	(19)	(6)								
1-d_3	186	122	121	93	65								120 (54); 119 (15); 94 (12); 92 (10); 91 (7); 60 (7); 59 (6); 40 (7)
	(7)	(18)	(100)	(17)	(5)								
2	197[c]	133	132[c]	91[c]	65	118[c]		105					196[c] (9); 131 (16); 117[c] (37); 116[c] (6); 104 (13); 103 (12); 90[c] (10); 89[c] (16); 78 (10);
	(47)	(34)	(100)	(19)	(15)	(11)		(11)					77 (13); 66 (12); 63 (12); 51 (13); 42 (55)
3	211[c]	147[c]	146[c,d]	91[c,d]	65[c]	118[c]	132[c,d]	105[d]					196 (37); 117[c] (18); 104 (13); 103 (11); 90 (8); 89[c] (10); 78 (9); 77 (11); 66 (8); 64 (6);
	(26)	(8)	(79)	(15)	(10)	(21)	(100)	(47)					63 (7); 56 (22); 52 (8); 51 (11)
4	267[c]	203[c]				118[c]	132[c]	105[c]					196[c] (34); 104[c] (9); 103 (6); 91[c] (6)
	(4)	(4)				(8)	(100)	(35)					
5	315	251	250	91[d]	65	118	132[d]	105[d]					196[d] (19); 174 (13); 146 (20); 134 (28); 117 (9); 104[d] (46); 103 (10); 78 (9); 77 (8)
	(2)	(68)	(67)	(41)	(8)	(23)	(100)	(63)					
6	273[c]	209[d]	208[c]	91[c,d,e]	65[d]	118[c,d]	132[c,d]	105[c,d]	182[c,d]				104[c,d] (14); 103[c] (8); 92[c] (32); 90[c,d] (6); 89[c,d] (7); 78[c,d] (8); 77[c,d] (8); 43 (10)
	(0.2)	(4)	(29)	(100)	(20)	(32)	(5)	(31)	(47)				
7	197	133	132	105	79	118							149 (7); 130(7); 117 (38); 113 (8); 103 (7); 99 (10); 97 (12); 93 (12); 91 (14); 85 (19);
	(15)	(15)	(100)	(6)	(6)	(10)							81 (14); 77 (10); 71 (31); 70 (8); 69 (32); 65 (7); 57 (55); 56 (7); 55 (17); 43 (38); 41 (19)
8	240	176	175			118		105		198	134[d]	133[d]	132 (15); 119 (14); 117 (11); 116 (10); 107 (14); 106[d] (26); 104 (12); 91 (7);79 (14);
	(21)	(15)	(21)			(13)		(6)		(15)	(38)	(100)	78 (8); 77 (17); 65 (7); 52 (7); 51 (11); 43 (71)
9	254[c]	190[c]	189[c]	148[d,f]		118				212	148[d,f]	147[c,d]	175[c] (10); 149 (7); 146 (13); 145 (6); 133 (12); 132 (24); 131 (13); 120 (8); 119[d] (18);
	(21)	(7)	(69)	(10)		(10)				(2)	(10)	(100)	107 (18); 106[c] (7); 104[c] (6); 91 (8); 77 (7); 43 (36); 42 (25)
10	217[c]	153	152[c]	125		118							154 (14);117[c] (64); 91 (12); 90 (7); 89 (19); 63 (8); 59 (10); 57 (7)
	(28)	(10)	(100)	(7)		(9)							
11	231	167	166		65								168 (8); 131 (67); 130 (7); 89 (16); 77 (10); 63 (10); 51 (8); 42 (28)
	(13)	(5)	(100)		(15)								
12	228	164	163	91	65	118							147 (10); 146 (9); 117 (67); 116 (7); 90 (18); 89 (20); 77 (7); 63 (11);51 (6)
	(5)	(58)	(100)	(12)	(6)	(10)							
13	304	240	239	91	65	118			182				223 (62); 193 (62); 192 (15); 191 (7); 178 (13); 177 (13); 165 (19); 152 (7); 149 (25);
	(10)	(7)	(100)	(26)	(9)	(95)			(27)				117 (34); 116 (6); 103 (11); 92 (20); 90 (19); 89 (20); 76 (11); 63 (10); 51 (7); 50 (6)
14						118[c]			182[c]				164 (6); 130 (6); 128 (7); 117 (27); 91 (17); 90 (10); 89 (13); 64 (6); 63 (6); 57 (6)
						(100)			(41)				
15[g]	147					118	132	105					146 (100); 145 (6); 130 (6); 117 (26); 103 (7); 91 (12); 90 (9); 89 (10); 77 (7); 66 (7);
	(31)					(28)	(57)	(29)					65 (8)

[a] For the origin of ions *e* and *i–k*, see text.

[b] Greater than 5%; satellite peaks are not included.

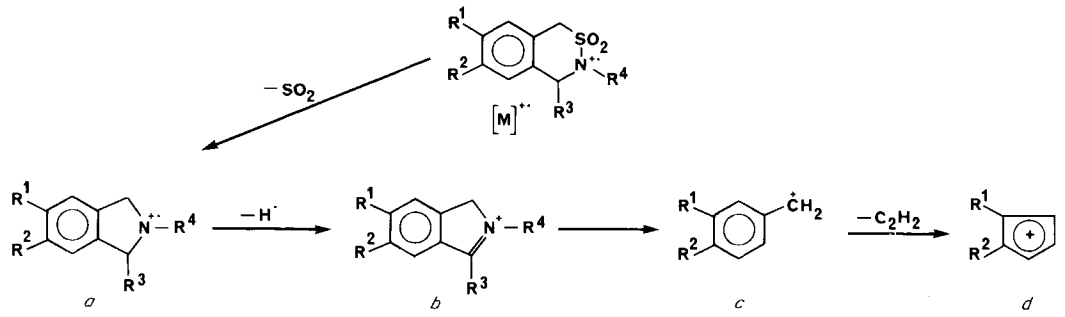
[c] High-resolution measurements.

[d] Metastable ions for fragmentations in Scheme 1–3.

[e] Also generated as Scheme 3.

[f] *m/z* corresponds to ions *c* and *j*.

[g] *N*-Ethylisoindoline included for comparison, see text.



Scheme 1

from ions *a* and *b* gives ions of *m/z* 118 (11%) and *m/z* 117 (37%), respectively. A significant scission of ion *a* results in the elimination of the benzyl radical, yielding a peak of *m/z* 42 (55%).[4] This process is common to the *N*-methyl derivatives **9** (25%) and **11** (28%). The presence and stability of species of *m/z* 42 have been indicated previously for other series of derivatives.[1] Accordingly, the *N*-ethyl derivative **3** yields the homologous ion of *m/z* 56 (22%).

Compounds bearing an RCH_2CH_2—substituent (R = H, alkyl or arylalkyl) on the nitrogen show the common features of Scheme 1. In addition, ion *b* decomposes as expected for properly substituted secondary and tertiary amines[5] by loss of the substituent yielding fragment *e* (*m/z* 118), from which ions *c* and *d* are obtained.

The base peak for **3** (R = H), **4** (R = *n*-Bu) and **5** (R = $PhCH_2CH_2$) is the ion *f* (*m/z* 132). Its formation can be interpreted as being initiated by a prominent *β*-cleavage of the N-substituent of ion $M^{+\cdot}$ (Scheme 2).[6]

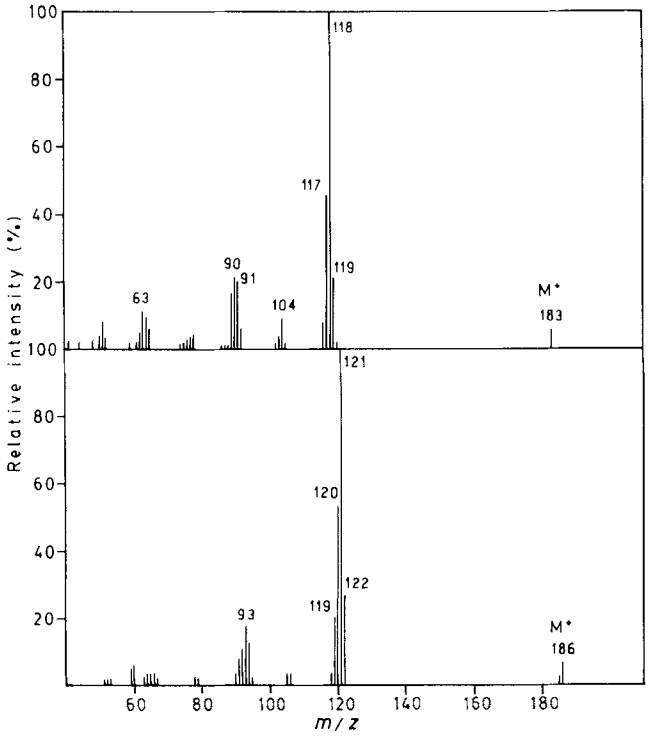
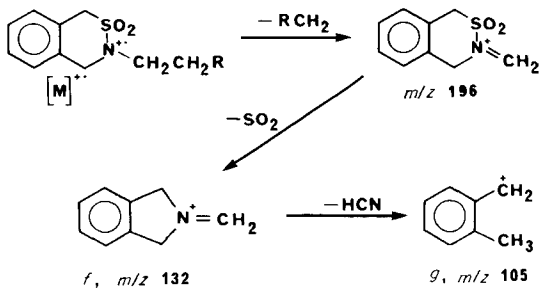


Figure 1. Mass spectra of 3,4-dihydro-1*H*-2,3-benzothiazine 2,2-dioxide (top) and of 3,4-dihydro-1,1,3-trideutero-1*H*-2,3-benzothiazine 2,2-dioxide (bottom) at 70 eV.



Scheme 2

The mass spectrum of **3** (R = H) was compared with that of the *N*-ethylisoindoline **15**. Both spectra are remarkably similar, but in the latter the base peak is at *m/z* 146 ($[M - 1]^+$) instead of ion *f* (*m/z* 132). This result supports the suggestion that, as shown in Scheme 2, ion *f* is derived from a substituent *β*-cleavage as the initial step rather than scission of ion *a*. Ion *f* decomposes further, yielding the abundant ion *g* of *m/z* 105 (47% in **3**; 35% in **4**; 77% in **5**).

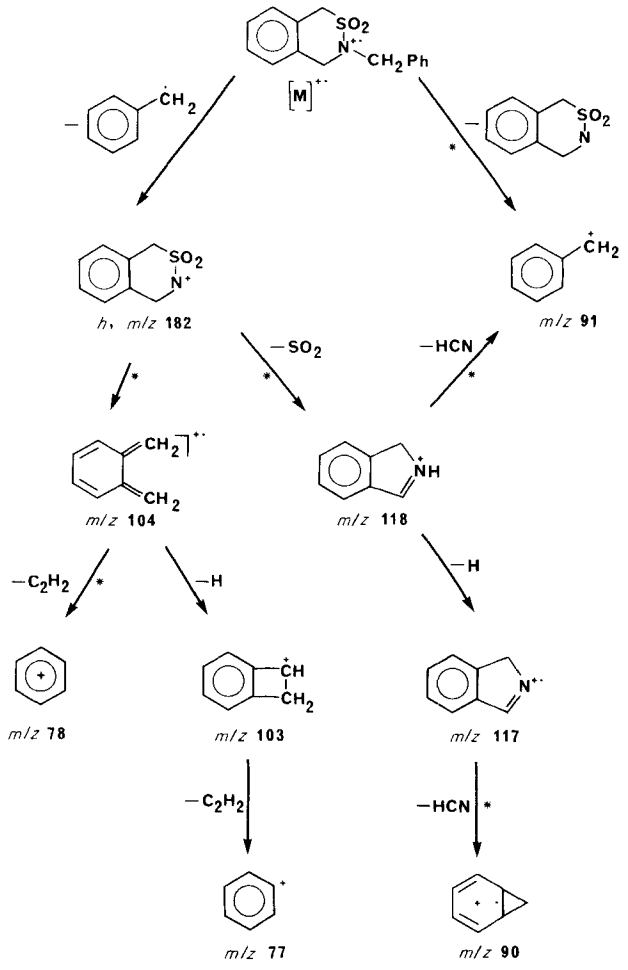
The mass spectrum of **6** shows the general pathway (Scheme 1) from $M^{+\cdot}$, which has a very low abundance. However, the benzyl group determines some characteristic fragmentations, as supported by high-resolution analysis and metastable peaks. The loss of this substituent occurs as the most significant scission giving an ion of *m/z* 91 (also being ion *c*), the base peak of the spectrum. Similar behaviour has been noted with other derivatives.[1]

The elimination of the benzyl group as a radical provides ion *h* of *m/z* 182 (47%) which is further decomposed as shown in Scheme 3. Other intense peaks worth mentioning are ion *g* of *m/z* 105 (31%) and *m/z* 92 (32%; high-resolution analysis $[C_7H_8]$).

Substitution on the benzene ring

The fragmentation pattern of **7**, with a methyl group in position 7, shows the expected peaks in agreement with Scheme 1. The cleavage of the methyl radical from ion *a* yields ion *e* (*m/z* 118) of low abundance (10%) and from ion *b* an ion of *m/z* 117 (38%).

Compounds **8** and **9** have an acetylamino group as a nuclear substituent. There is competition between the fragmentation process in Scheme 1 and the elimination of ketene from the acetyl group of ions $M^{+\cdot}$, *a* and *b* to generate fragments *i*, *j* and *k*, respectively;[7] in both



Scheme 3

compounds the base peak is *k*. On the other hand, the high-resolution analysis of the fragment of *m/z* 148 in **9** shows the contribution of ion *c* [$C_9H_{10}NO$] (45%) and ion *j* [$C_9H_{12}N_2$] (55%). Another common fragment is that of *m/z* 119. Its structure (high-resolution analysis indicates [C_8H_9N]) agrees with that of *m/z* 104 (Scheme 3) plus the amino group as nuclear substituent, and its formation might be rationalized by successive elimination of $RNSO_2$ and CH_2CO from the molecular ion.

As expected, when $R_4 = CH_3$ (**9**), cleavage of the methyl radical from several fragments occurs, e.g. ion *a* gives *m/z* 175 (10%), *j* gives *m/z* 133 (12%) and *k* gives *m/z* 132 (25%).

For nuclear substituents in position 6 (**10** and **11**, $R_2 = Cl$ and **12**, $R_2 = NO_2$) the base peak is ion *b*. Further decomposition of *b* through the elimination of the substituent predominates over that of the pathway in Scheme 1. Thus, in **10**, *b* gives *m/z* 117 (64%), in **11** *m/z* 131 (67%) and in **12** *m/z* 117 (67%). Subsequently these ions lose HCN as the general cleavage from *b* to *c*. Ion *a* undergoes the same sequence of fragmentations but with a much lower abundance of the products.

With **12**, ion *b* loses an oxygen atom from the nitro group to give *m/z* 147 (11%). The presence of chlorine in **10** and **11** is indicated by the typical pattern of one chlorine atom in the peaks $M^{+\cdot}$, *a* and *b*.

Substitutions on the heterocyclic ring

Fragmentation of **13** (R_3 = *p*-nitrophenyl) follows the general pattern (base peak ion *b*). In addition it shows some features common with those of **6**. The substituent cleavage of $M^{+\cdot}$ gives ion *h*, which is further decomposed according to Scheme 3.

The most intense peaks in the spectrum may be interpreted as being derived from ion *b*. In this way, ions of *m/z* 223 (−O; 62%), *m/z* 193 (−NO_2, 62%) and *m/z* 117 (−$C_6H_4NO_2$, 34%) are formed; further scission of the second ion generates an ion of *m/z* 165 (18%).[8]

The high lability of the trichloromethyl group in **14** ($R_3 = CCl_3$) precludes the appearance of the molecular ion. Nevertheless, it is proved by chemical ionizations (I^+ shows $[MH]^+$ and I^- shows $[MH]^-$). The isotopic distribution of these ions is in agreement with the presence of three chlorine atoms.

The fragmentation of ion *h* ($[M - CCl_3]^+$) by elimination of a molecule of sulphur dioxide gives ion *e* (*m/z* 118), the base peak.

EXPERIMENTAL

Mass spectra were taken using the general conditions described in previous papers.[1] Low-resolution mass measurements were recorded on an AEI MS-9 spectrometer (Chemistry Department, Stanford University, USA) and on a Finnigan-MAT 8230 spectrometer (Dortmund University, FRG) at 70 eV (also at 15 eV for **1**, **7**, **9** and **10**) by a direct insertion technique.

Values of the metastable ions were within ±0.2 mass units of the calculated ones; for **3** linked scans at constant *B/E* and B^2/E were used (Varian-MAT 112 S; LEA, Universidad de San Luis, Argentina).

Most of the high-resolution measurements were performed on an AEI MS-30 spectrometer by using an automatic computerized technique (Shrader Analytical Consulting Laboratories, Detroit, USA).

Typical experimental conditions were: source temperature 200 °C, electron energy 70 eV, trap current 300 μA, accelerating voltage 4 kV and resolution 10000. Some other data were obtained on a Finnigan MAT 8230 instrument by the peak matching method relative to perfluorokerosene, resolution 5000. In each instance the measured mass was within 5 ppm of the expected exact mass.

Most of the derivatives examined have been described previously;[2] **4** and **9** are new and were prepared using the same general method by cyclization of the corresponding sulphonamides **16** and **17**. The new compound **5** was obtained by reaction of 4-phenylbutyl bromide and the sodium derivative of the parent compound **1** in anhydrous *N*,*N*-dimethylformamide. Data for the new derivatives are included in Table 2. *N*-Ethylisoindoline was prepared following the literature[9] and purified through its picrate. All the samples used in the measurements were recrystallized to constant melting points.

Table 2. Characterization of new compounds

Compound[a]	Yields (%)	M.p (°C)[b]	ν_{max}(cm^{-1}) (Nujol) NH	SO_2	δ (ppm)[c]
4	81[d]			1340; 1130	0.88 (3H, distorted t, CH_3); 1.06–1.82 (8H, m, four CH_2); 3.15 (2H, t, NH_2C); 4.27 (2H, s, SCH_2); 4.56 (2H, s, $ArCH_2N$); 6.85–7.30 (4H, m, aromatic)
5	65	64–65 (Et_2O)[e]		1335; 1135	1.44–1.90 (4H, m, two CH_2); 2.65 (2H, distorted t, $PhCH_2$); 3.16 (2H, distorted t, NCH_2C); 4.26 (2H, s, SCH_2); 4.51 (2H, s, $ArCH_2N$); 6.90–7.49 (9H, m, aromatic)
9	66	165–166 (alcohol)	3340[f]	1320; 1160	2.17 (3H, s, $COCH_3$); 2.88 (3H, s, NCH_3); 4.25 (2H, s, SCH_2); 4.49 (2H, s, $ArCH_2N$); 4.59 (1H, s, NH); 7.0–7.46 (3H, m, aromatic)
16	83	95–96 (i-Pr_2O)	3240	1305; 1135	0.88 (3H, distorted t, CH_3); 1.09–1.50 (8H, m, four CH_2); 2.98 (2H, q, NCH_2C); 4.00 (1H, broad s, NH); 4.24 (2H, s, SCH_2); 7.38 (5H, s, aromatic)
17		196–197 (alcohol)[e]			2.06 (3H, s, $COCH_3$); 4.21 (2H, s, SCH_2); 6.6–8.3 (4H, m, aromatic); 9.86 (1H, s, NH)

[a] Compound **16**, *N*-*n*-hexylbenzylsulphonamide; **17**, *m*-acetylamino-*N*-methylbenzylsulphonamide. All the compounds were analysed (UMYMFOR, University of Buenos Aires, Argentina) for all the elements except oxygen, giving results within ±0.3% of the calculated values.
[b] Crystallization solvent in parentheses.
[c] ^{1}H NMR spectra in deuterochloroform, except compound **17** (DMSO-d_6), at 80 MHz with tetramethylsilane as internal standard.
[d] Oil, purified by repeated column chromatography (SiO_2).
[e] Crystallized after sublimation; compound **5** at 120 °C/0.7 Pa and **17** at 215 °C/0.14 Pa.
[f] From acetylamino group; $\nu_{C=O}$ 1690 cm^{-1}.

Deuteration of 3,4-dihydro-1*H*-2,3-benzothiazine 2,2-dioxide (1)

The parent compound **1** (10 mg) was dissolved at 90 °C in D_2O (0.8 ml; 99% purity) and the solution was heated for a further 5 h in a tightly stoppered tube. The labelled compound crystallized after cooling in a refrigerator; its melting point was that of the undeuterated compound.

Acknowledgements

We are indebted to Prof. C. Djerassi (Stanford University, USA), Prof. W. P. Neumann and Dr H. Hillgaertner (Dortmund University, FRG) and Dr J. Kavka and Dr F. H. Guidugli (LEA, Universidad de San Luis, Argentina) for their help with mass spectral measurements. We are also grateful to Prof. M. Gonzalez Sierra (Universidad de Rosario, Argentina) for some NMR spectra and SECYT and CONICET (Argentina) for research grants.

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