Mass Spectra of Azabicyclospirohydantoins

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The mass spectra of some *N*-substituted nortropane and granataninespirohydantoins are compared with those of *N*-substituted 3-azabicyclo[3.2.1]octane-8-spiro-, 3-azabicyclo[3.3.1]nonane-9-spiro-, 8-azabicyclo-[4.3.1]decane-10-spiro- and 3,7-diazabicyclo[3.3.1]nonane-9-spiro-5'-hydantoins. Mass spectra data of monothio- and dithio-tropanespirohydantoins are also included. Mass fragmentation and structure relationships of these molecules have been established.

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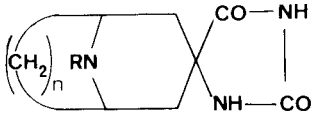
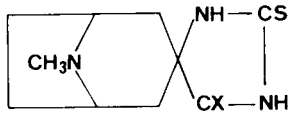
Compounds I, II, III and IV (Tables I-III) have been obtained by the Bucherer-Bergs synthesis from the corresponding azabicycloalkanones (1-5). The stereochemistry has been determined by ^1H and ^{13}C nmr (2-4,6) and X-ray diffraction data (7-10).

Table I



I



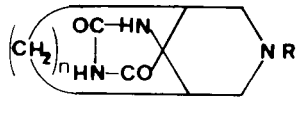
II

1, n = 2; R = H
2, n = 2; R = Me
3, n = 2; R = Et
4, n = 2; R = *n*-Pr
5, n = 2; R = *n*-Bu
6, n = 2; R = *i*-Pr
7, n = 2; R = EtOH
8, n = 2; R = Ph
9, n = 2; R = CH_2Ph
10, n = 2; R = $(CH_2)_2Ph$

11, n = 3; R = H
12, n = 3; R = Me
13, n = 3; R = Et
14, n = 3; R = *n*-Pr
15, n = 3; R = *n*-Bu
16, n = 3; R = *i*-Pr
17, n = 3; R = EtOH
18, n = 3; R = Ph
19, n = 3; R = CH_2Ph
20, n = 3; R = $(CH_2)_2Ph$

21, X = O
22, X = S

Table II

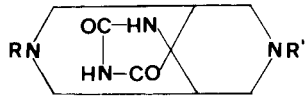


III

23, n = 2; R = Me; R' = H
24, n = 2; R = Et; R' = H
25, n = 2; R = *n*-Pr; R' = H
26, n = 2; R = *i*-Pr; R' = H
27, n = 3; R = Me; R' = H
28, n = 3; R = Et; R' = H
29, n = 3; R = *n*-Pr; R' = H
30, n = 3; R = *i*-Pr; R' = H
31, n = 3; R = *n*-Bu; R' = H
32, n = 4; R = Me; R' = H
33, n = 4; R = Et; R' = H
34, n = 4; R = *n*-Pr; R' = H
35, n = 4; R = *i*-Pr; R' = H
36, n = 4; R = *n*-Bu; R' = H

37, n = 2; R = Me; R' = $(CH_2)_2NMe_2$
38, n = 2; R = Me; R' = $(CH_2)_2NEt_2$
39, n = 2; R = Et; R' = $(CH_2)_2NMe_2$
40, n = 2; R = Et; R' = $(CH_2)_2NEt_2$
41, n = 2; R = *n*-Pr; R' = $(CH_2)_2NMe_2$
42, n = 2; R = *n*-Pr; R' = $(CH_2)_2NEt_2$
43, n = 2; R = *i*-Pr; R' = $(CH_2)_2NMe_2$
44, n = 2; R = *i*-Pr; R' = $(CH_2)_2NEt_2$
45, n = 3; R = Me; R' = $(CH_2)_2NMe_2$
46, n = 3; R = Me; R' = $(CH_2)_2NEt_2$
47, n = 3; R = Et; R' = $(CH_2)_2NMe_2$
48, n = 3; R = Et; R' = $(CH_2)_2NEt_2$
49, n = 3; R = *n*-Pr; R' = $(CH_2)_2NMe_2$
50, n = 3; R = *n*-Pr; R' = $(CH_2)_2NEt_2$
51, n = 3; R = *i*-Pr; R' = $(CH_2)_2NMe_2$
52, n = 3; R = *i*-Pr; R' = $(CH_2)_2NEt_2$

Table III



IV

53, R = R' = Me
54, R = Me; R' = Et
55, R = Me; R' = n-Pr
56, R = Me; R' = *i*-Pr
57, R = Me; R' = *n*-Bu
58, R = Me; R' = cyclohexyl

M$^+$-1 Peak.

The situation of the piperidine nitrogen atom attached to both bridgehead carbon atoms in compounds I and II, makes impossible the presence of the M$^+$-1 peak, which appears in compounds III and IV according to previous references (11).

Base Peak.

The base peak of most of the compounds are in agreement with the results found in the corresponding azabicyclic systems (11-15) and are a consequence of the preferred α-cleavage with respect to the piperidine nitrogen atom (16) Figure 1).

The relative abundance of fragments **59, 60, 61** and **62** (Figure 1) depends on the kind of *N*-substituent. For alkyl (others than methyl) or arylalkylsubstituents of compounds I and III, the nature of the base peaks is shown in Figure 3. These base peaks can be originated by an α-cleavage on the side chain. This feature is not observed in compounds **3** and **13** (*N*-ethyl), and their base peaks are identified with the fragments **59** and **61** respectively, in the same way as in the case of compounds **2** and **12** (*N*-methyl).

Compounds IV show a base peak m/e 58 (**63**) which takes place from the fragmentation of both *N*-methyl- and *N*-alkylpiperidine rings. The last cleavage gives the fragment **64** which leads to **63** (Figure 2) as it was previously reported (15). In the case of compound **58** (Table III), the

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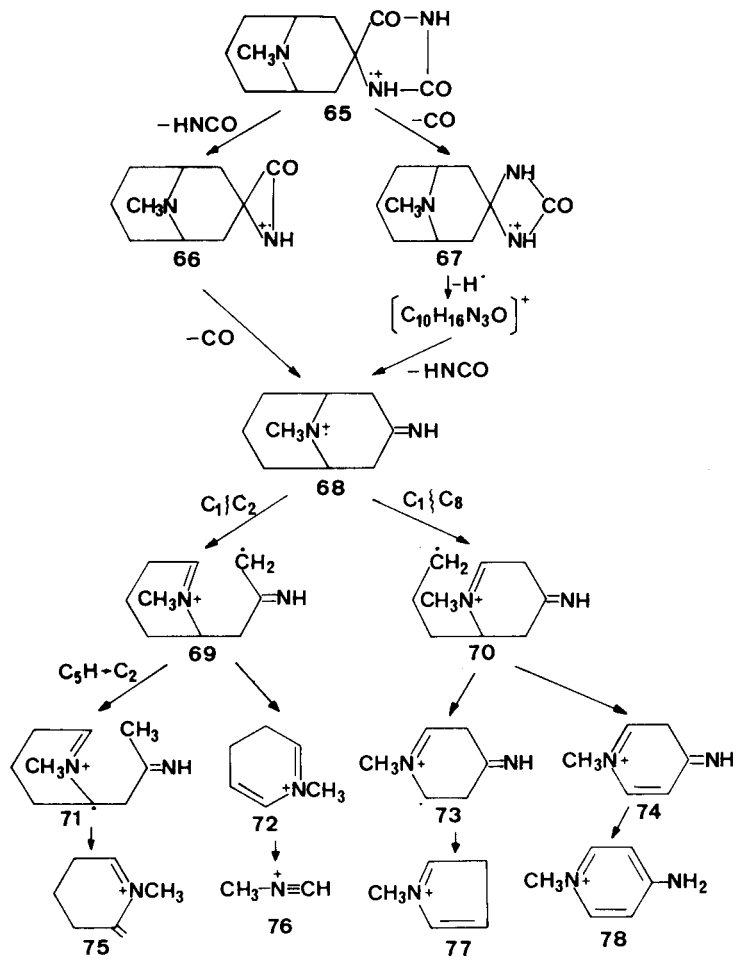
Scheme I



fragment **64** cannot originate **63** and so the base peak is m/e 222 instead of m/e 58 (**63**).

The absence of fragment **63** in compound **53** (Table III) might be explained as a consequence of the stability of azabicyclic support. Thus, the base peak observed is m/e 84 (**100**) (Figure 9) which is originated from a hydantoin ring fragmentation and it will be discussed later.

The behaviour of compound **22** (Table I) is similar to that of compounds I (n = 2). Although the base peak is apparently m/e 83 (Figure 7), its intensity is due to an addition of two different species **82** and **84** (Scheme IV).

General Fragmentation.

Regarding the general fragmentation schemes only the *N*-methyl derivatives of compounds I, II and III are analyzed. The difference found for *N*-substituted compounds have already been mentioned and/or will be discussed later.

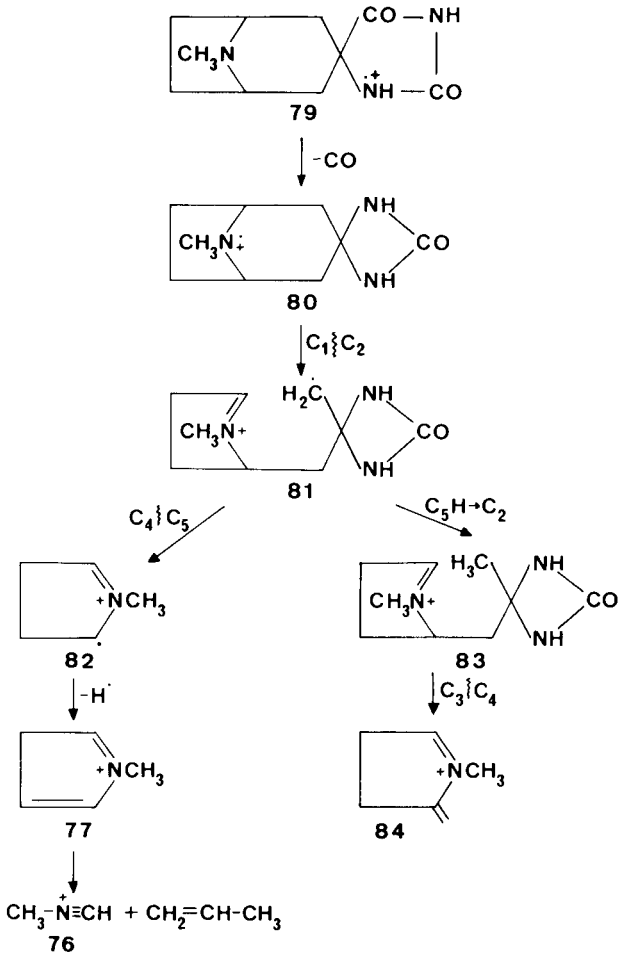
The preferred fragmentation pathway of compound **12** is shown in Scheme I. The molecular ion **65** is formed on the N_1' nitrogen atom from which an imine fragment **68** is originated through several previous cleavages in a similar way to that described by Locock and coworkers (18). The fragmentation pattern from this intermediate is similar to that proposed for pseudopelletierine (14).

In compound **18** (Table I), the M^+ peak is increased as should be expected (17), and the base peak has the structure **60** (Figure 1) in accordance with the conclusions deduced for pseudopelletierine by Guthrie and coworkers (14).

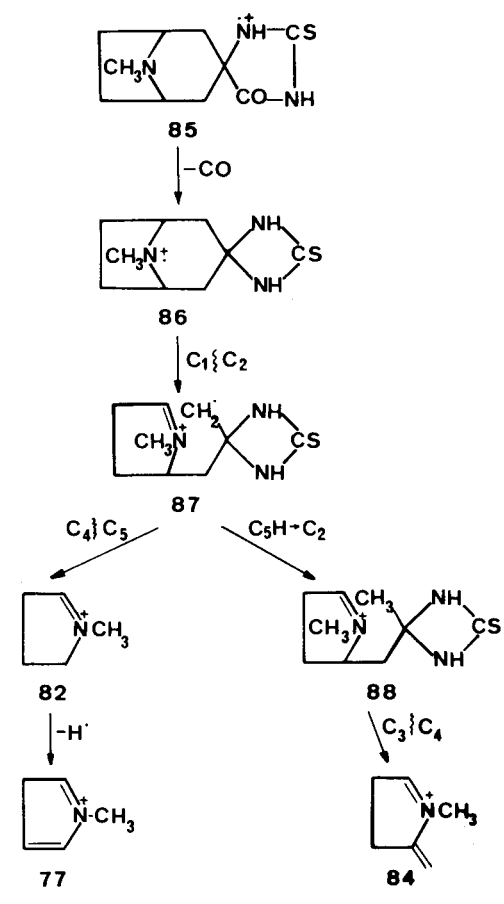
Compound **2** originates fragment **80** by loosing of carbon monoxide. This fragment **80** undergoes subsequent fragmentation in a similar way as fragment **68**. The diazetidone ring stability of fragment **80**, in the nortropane system, can be explained in terms of the absence of the transannular effect of granatanine C_7 in methylene group.

In compound **21** the molecular ion has an abundance of 94% which is due to the stabilizing effect of the C=S group as it was described for analogous compounds (19). The general pathway of fragmentation is similar to that described for compound **2** as is shown in Scheme III.

Scheme II



Scheme III



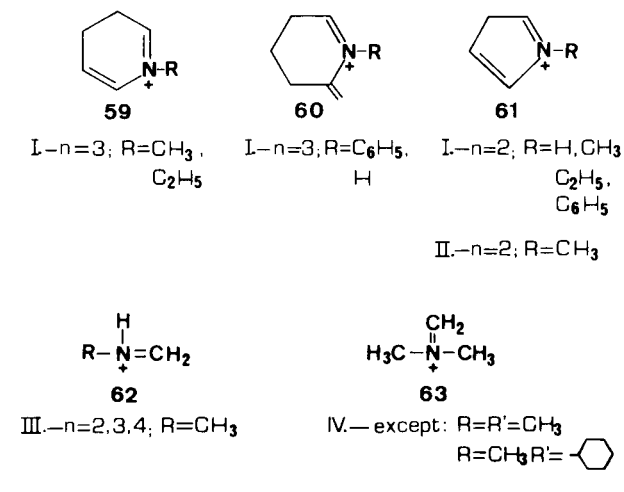


Figure 1. Main Base Peaks for Compounds I-IV

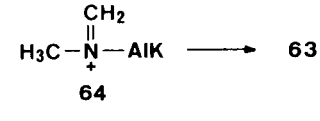


Figure 2. Base Peak for Compounds IV (R' = Alkyl)

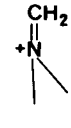
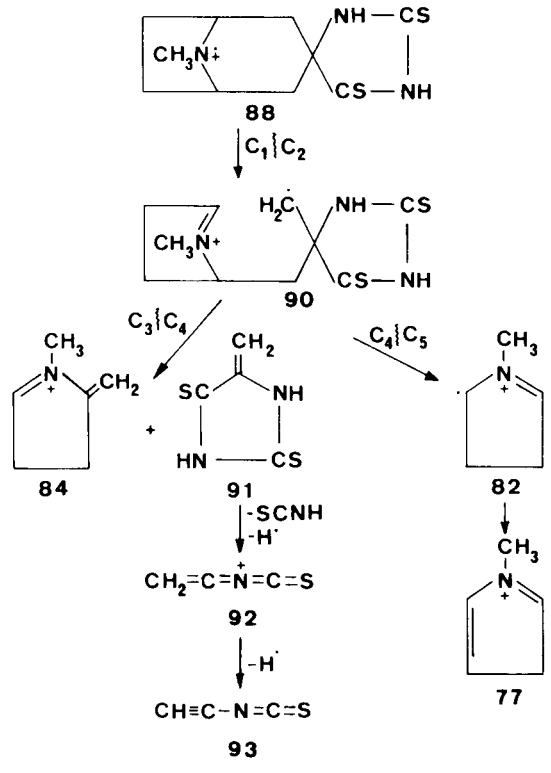
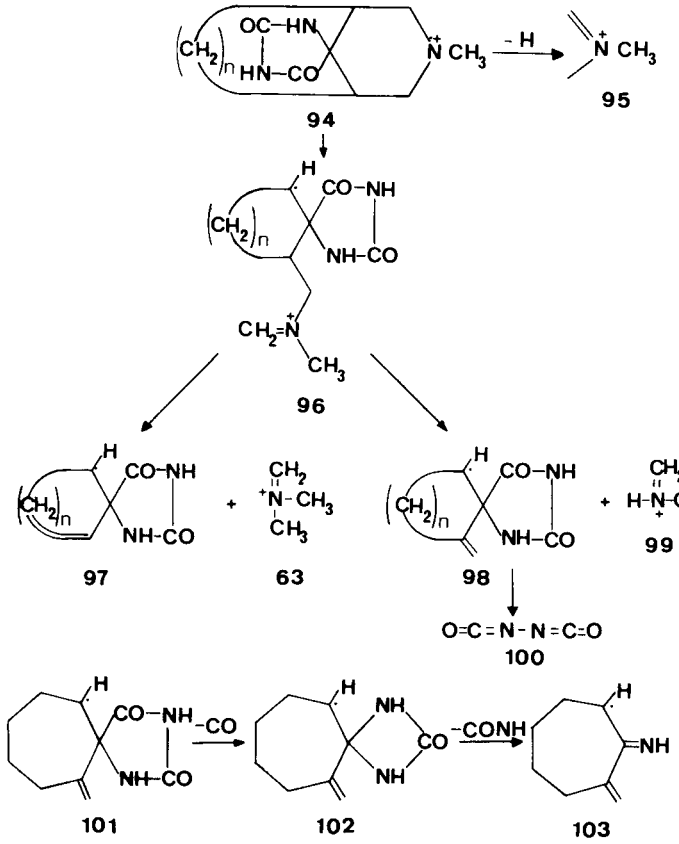


Figure 3. Base Peak for Compounds I and III (R = Alkyl)

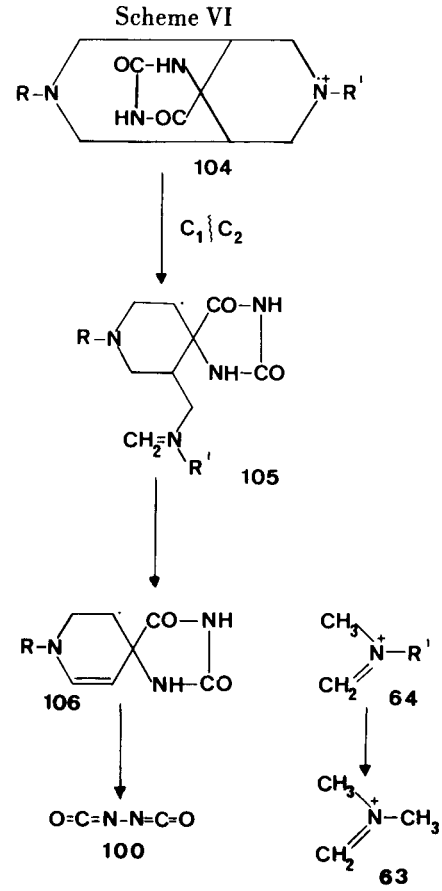
Scheme IV



Scheme V



Scheme VI



The presence of two sulphur atoms in compound **22** increases the stability of the hydantoin ring and the fragmentation starts by the azabicyclic support (Scheme IV).

Scheme V shows the fragmentation pathway of compounds III *N*-methyl substituted. In contrast with compounds I, the hydantoin ring is more stable than the azabicyclic system. No partial fragmentation of the hydantoin ring is observed, but the hydantoin ring rearranges to originate the fragment **100** (m/e 84).

In compound **32**, the fragment **101** may follow a fragmentation pathway in a similar way to that described in Scheme I (Scheme V).

In compounds I, II and III with *N*-substituents other than methyl, the preferred fragmentation pathway is the α-cleavage of the *N*-substituent (Figure 12).

In compounds **37-52** the main fragmentation occurs in the α-position of the dialkylaminoethyl chain (Figure 13).

Scheme VI shows the fragmentation pathway proposed for compounds IV, this scheme is similar to that of compounds III. Compound **53** is an exception and has already been discussed.

Finally, regarding the results mentioned above for the studied *N*-methylderivatives, we can conclude that the

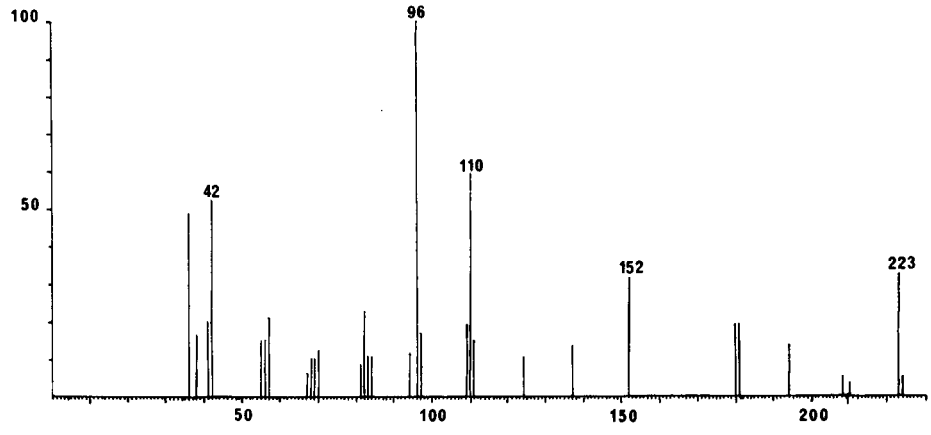


Figure 4. Mass Spectrum of Compound **12**

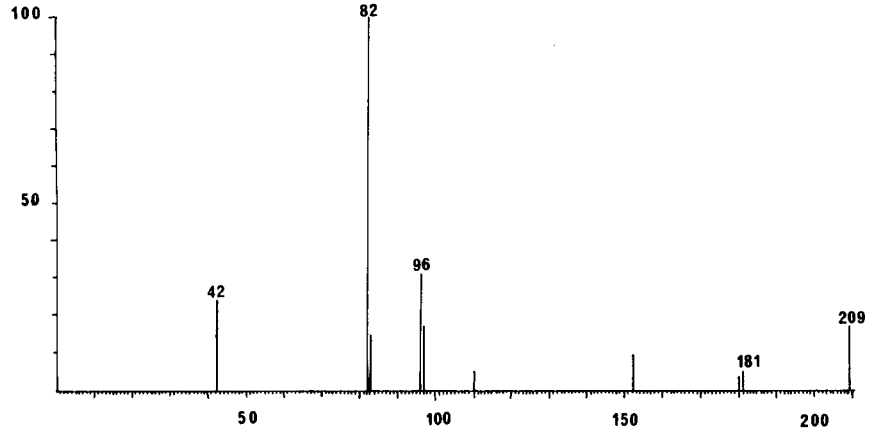


Figure 5. Mass Spectrum of Compound **2**

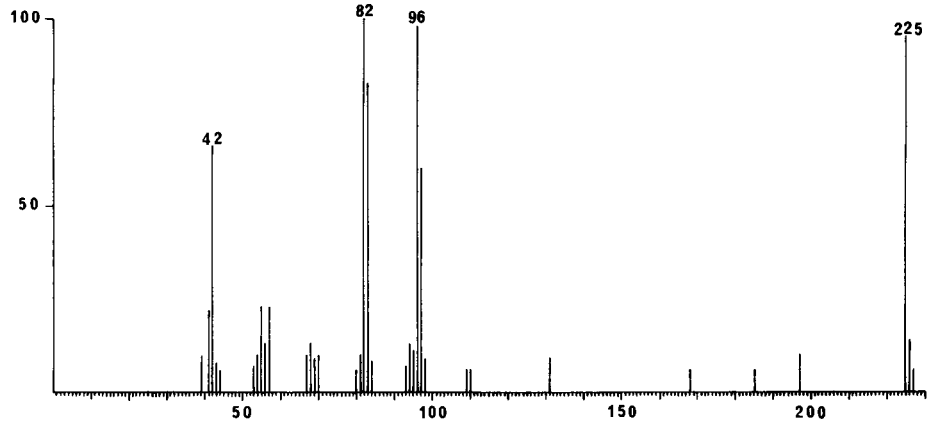


Figure 6. Mass Spectrum of Compound **21**

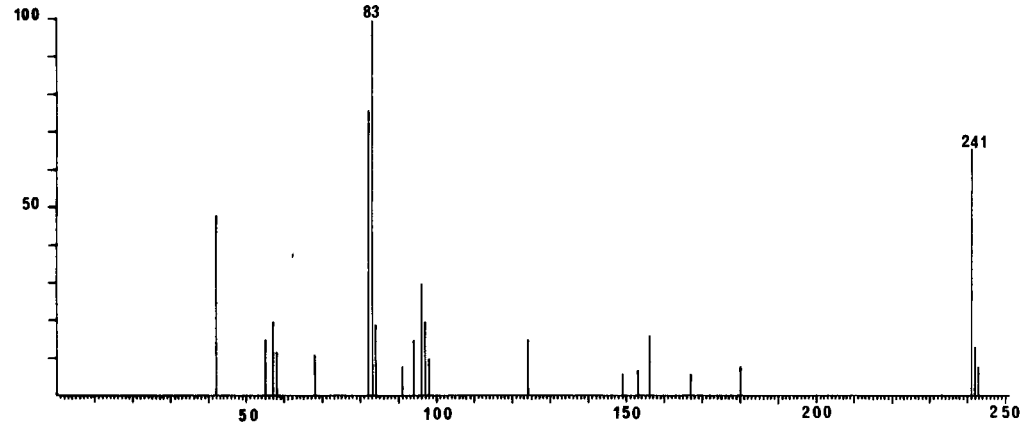


Figure 7. Mass Spectrum of Compound **22**

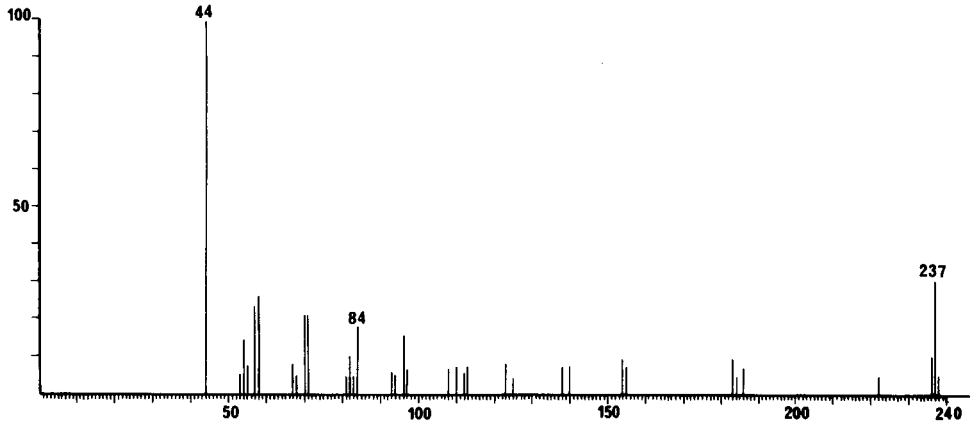


Figure 8. Mass Spectrum of Compound **32**

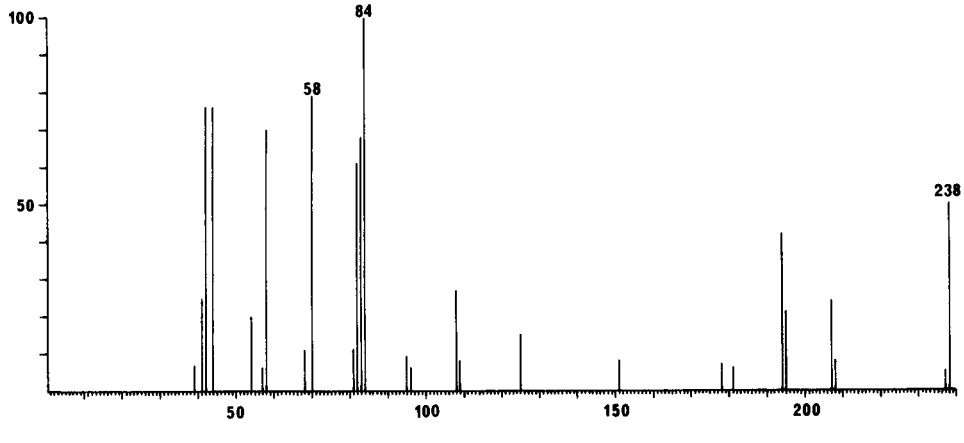


Figure 9. Mass Spectrum of Compound **53**

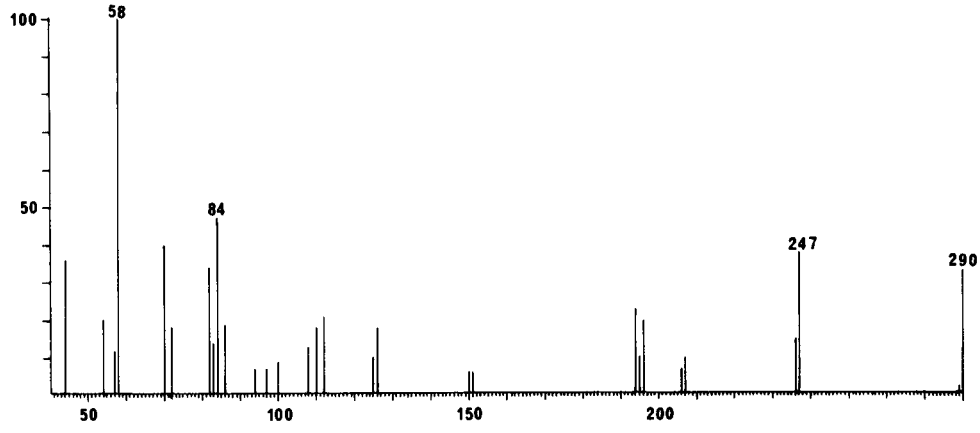


Figure 10. Mass Spectrum of Compound **57**

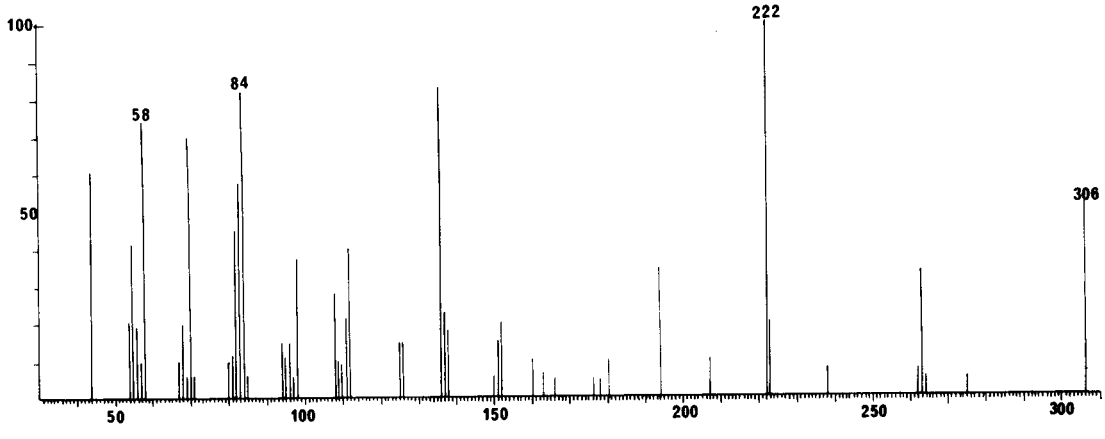


Figure 11. Mass Spectrum of Compound **58**

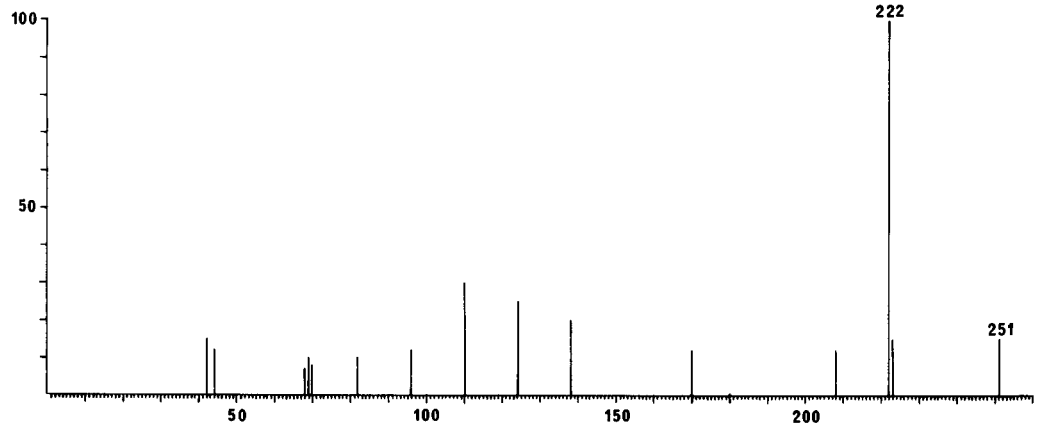


Figure 12. Mass Spectrum of Compound **14**

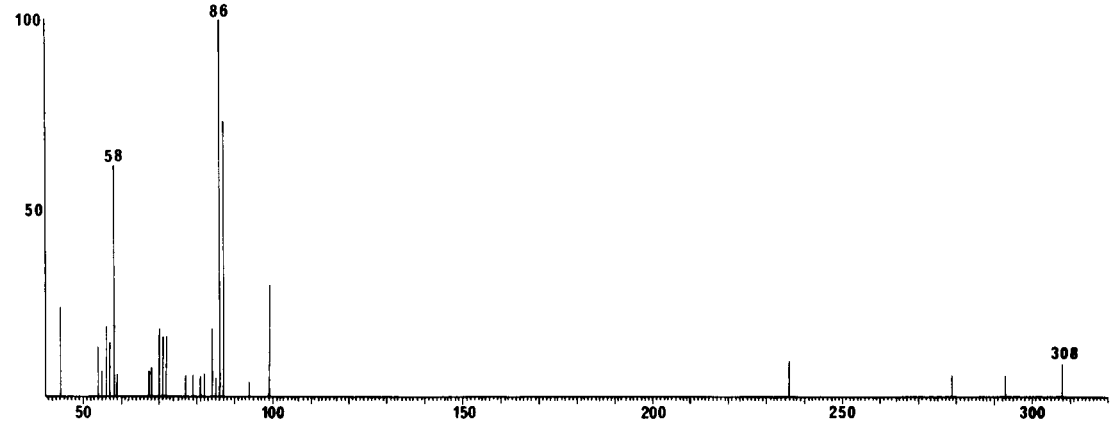


Figure 13. Mass Spectrum of Compound **38**

stability of the hydantoin ring depends on steric requirements. The polymethylene chain steric hinderance in compounds I makes the hydantoin ring less stable to the electronic impact than the azabicyclic system. On the other hand the hydantoin ring is more stable than the azabicyclic system in compounds III and IV because of the absence of this steric hinderance and their fragmentation patterns are similar to those of spirohydantoins previously described in the literature (20).

EXPERIMENTAL

The mass spectra were recorded in a Hitachi Perkin-Elmer RMU-SMG spectrometer. All spectra were determined at 75 eV and heated to the minimum temperature necessary to produce a spectrum.

In the line drawings (Figures 4-13), peaks whose intensities were less than 5% of the base peak were not plotted unless they appeared to have special significance.

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