Mass Spectrometry of 3,4-Dihydroquinazolin-4-ones of Pharmaceutical Interest. Part 3 [a,b]. Electron Ionization Mass Spectra of 2-Substituted-3-(5′-pyrazolyl)-4(3*H*)-quinazolinones

Mirella Ferrugia*, Maria Luisa Bajardi, Leopoldo Ceraulo and Salvatore Plescia

Dipartimento di Chimica e Tecnologie Farmaceutiche,
Via Archirafi 32, 90123-Palermo, Italy

Received October 17, 1991

The fragmentation reactions induced by electron impact of eighteen title compounds has been investigated with the aid of low beam energy spectra (14 eV, nom. value), metastable ion detection, high resolution measurements and labelling experiments. The loss of the 4-carbonyl oxygen together with the 3-substituent, which constitutes a characteristic fragmentation route of 3-aryl and 3-heteroaromatic substituted-4(3*H*)-quinazolinones, is again observed, but the presence of a carboxyethyl group at the 4′-position of the pyrazole ring is responsible of an anomalous loss of 47 daltons from the molecular ion. Lastly, a comparison with the previously described behaviour of 3-(5′-isoxazolyl) derivatives was carried out.

J. Heterocyclic Chem., **29**, 565 (1992).

Introduction.

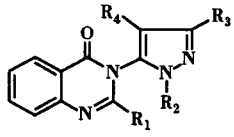
We have previously studied the electron ionization mass spectra (eims) of a series of 3-(5′-isoxazolyl)-3,4-dihydroquinazol-4-ones, which have interesting analgesic activity [4]. The same activity, associated with a lower gastric toxicity, was also found in a series of 3-(5′-pyrazolyl)-3,4-dihydroquinazol-4-ones [5]. Hence it seemed of interest to study these compounds under electron impact in order to evaluate the importance, if there is one, of the type of the heterocycle at the 3 position of quinazolinone ring, as well as that of the presence of a carboxyethyl group at the 5′-position of the pyrazole ring. The study was also carried out with the aid of exact mass measurements, metastable ion research and deuterium labelled compounds. The compounds **1-18** have been investigated.

Results and Discussion.

The 75 eV eims of **1-18** are reported in Table 1.

The molecular ions are always abundant and peaks corresponding to the overall loss of the 3-substituent and of the 4-carbonyl oxygen constitutes a characteristic of these compounds (ion *a* Scheme 1) [1]. The same ion *a* is responsible for the intense peaks in the mass spectra of

Block I



Compound	R_1	R_2	R_3	R_4
1	H	CH_3	H	H
2	H	C_6H_5	CH_3	H
3	CH_3	C_6H_5	CH_3	H
4	C_2H_5	C_6H_5	CH_3	H
5	C_6H_5	C_6H_5	CH_3	H
6	H	CH_3	H	$COOC_2H_5$
7	CH_3	CH_3	H	$COOC_2H_5$
8	C_2H_5	CH_3	H	$COOC_2H_5$
9	C_6H_5	CH_3	H	$COOC_2H_5$
10	H	C_6H_5	H	$COOC_2H_5$
11	CH_3	C_6H_5	H	$COOC_2H_5$
12	C_2H_5	C_6H_5	H	$COOC_2H_5$
13	C_6H_5	C_6H_5	H	$COOC_2H_5$
14	C_6H_4-p-CH_3	C_6H_5	H	$COOC_2H_5$
15	C_6H_4-p-NO_2	C_6H_5	H	$COOC_2H_5$
16	D	CH_3	H	$COOC_2H_5$
17	CD_3	CH_3	H	$COOC_2H_5$
18	CH_3	C_6H_5	H	COOH

Scheme 1

Fragmentation Routes for the Loss of the 3- Substituent and the 4-Oxygen

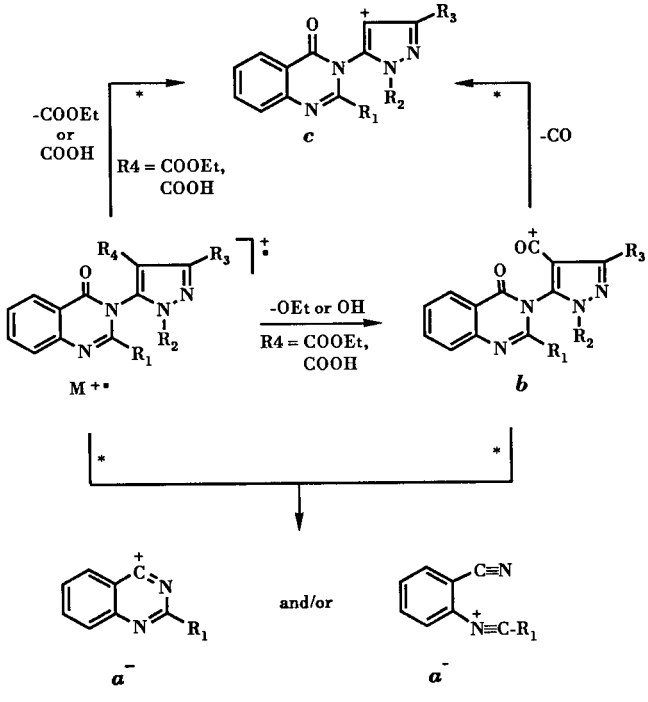


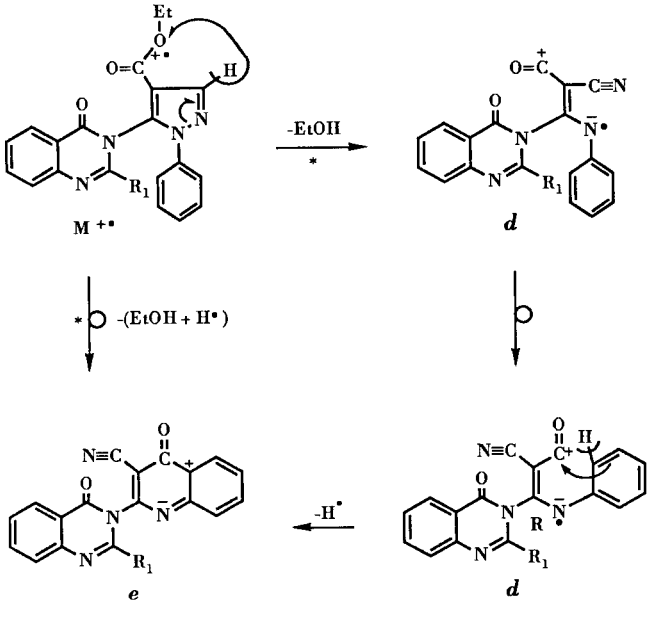
Table 1

Compound	M	a	b	c	d	e
1	226 (15)	129 (19)	–	–	–	–
2	302 (23)	129 (9)	–	–	–	–
3	316 (15)	143 (100)	–	–	–	–
4	330 (82)	157 (87)	–	–	–	–
5	378 (97)	205 (100)	–	–	–	–
6	298 (43) (100)	129 (22)	253 (52) (13)	225 (5)	252 (93) (89)	251 (100) (13)
7	312 (73) (100)	143 (30)	267 (32) (8)	239 (5)	266 (100) (44)	265 (83)
8	326 (76)	157 (33)	281 (36)	253 (19)	280 (100)	279 (65)
9	374 (84) (100)	205 (100)	329 (18)	301 (85) (9)	328 (17) (4)	327 (22)
10	360 (52)	129 (11)	315 (42)	287 (17)	314 (41)	313 (100)
11	374 (61) (100)	143 (44) (63)	329 (28) (23)	301 (22) (15)	328 (56) (72)	327 (44) (25)
12 [a]	388 (67) (100)	157 (16)	343 (24)	315 (15)	342 (62) (17)	341 (24)
13	436 (93)	205 (97)	391 (15)	363 (100)	390 (6)	389 (5)
14	450 (32)	219 (67)	405 (8)	377 (100)	404 (3)	403 (<3)
15	481 (90)	250 (100)	436 (20)	408 (64)	–	–
16	299 (56) (100)	130 (46)	254 (65) (21)	226 (10)	253 (71) (96)	252 (100) (34)
17	315 (58) (100)	156 (57)	270 (17) (4)	242 (4)	269 (31) (16)	268 (100) [b] (64)
18 [a]	346 (56)	143 (36)	329 (7)	301 (18)	328 (28)	327 (32)

The unassigned intensities refer to mass spectra recorded with an ionizing energy of 14 eV. [a] The base peak is at m/z 77. [b] This peak is accompained by one at m/z 267 with the same intensity.

Scheme 2

Proposed Mechanism for the Elimination of Ethanol Followed by Hydrogen Ejection for the *N*-Phenyl-substituted Derivatives **10-15**



several 3-(5′-isoxazolyl)-4-(3*H*)-quinazolinones [3] and it is also present, even if with a lower intensity, in the mass spectra of methaqualone [5,6] and of other related 2-methyl-3-aryl derivatives [6]. For the structure of the ion *a* the opened $a^{\cdot}$ [6,8,9], or an equilibrium between $a^{\cdot}$ and a^{-} [7] structures have been suggested and more recently identical structure or an identical mixture of structures (independently on the precursor) were suggested on the ground of the results of CAD-MIKE analysis [1]. The B^2/E linked scan spectra evidence as the ion *a* is formed exclusively from the molecular ion for the compounds **1-5**, whereas in the case of the carboxyethyl derivative **6-17** and of the carboxylic acid **18** it arises also from ion *b*, formed in turn by α-carbonyl cleavage of M^+. The ion *c*, which is responsible of the base peak of **13** and **14**, is also formed through α-carbonyl cleavage.

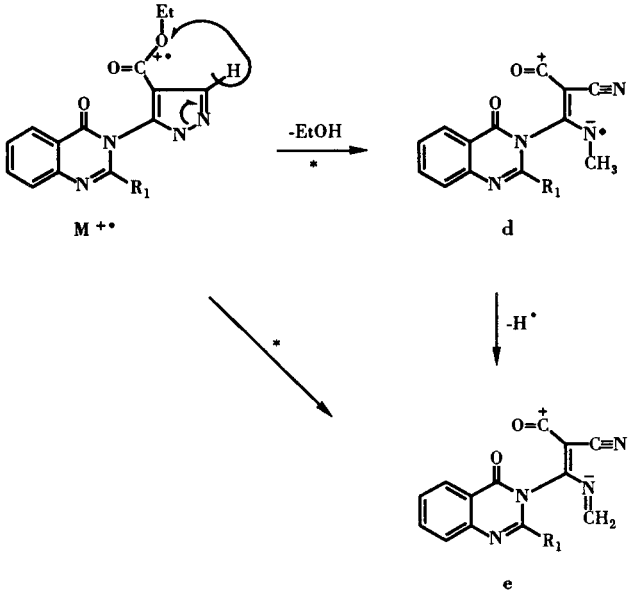
All the carboxyethyl derivatives **6-17** and the carboxylic acid **18** show intense peaks corresponding to ethanol elimination (or water by **18**) (ion *d*) together with peaks at a mass unity below (ion *e*). The B^2/E linked scan spectra indicate that both ions arise from the molecular ion.

The origin of hydrogen atoms involved in this process is

determined by deuterium labelled compounds **16** and **17**. The eims of **16** shows a complete shift of both ions *d* and *e*, that is consistent with hydrogen migration which doesn't involve the hydrogen (or deuterium) atom at C-2. The analysis of the eims results of **17** are complicated as the sample is composed of a mixture of trideuterio, dideuterio, monodeuterio and unlabelled derivatives in the ratio $d_3:d_2:d_1:d_0$ = 1:0.58:0.17:0.04. However, the B/E linked scan spectrum of the Md_3 molecular ion (m/z 315) unequivocally demonstrates that deuterium atoms aren't involved as it loses only 46 and 47 daltons, as the unlabelled compound **7**. These findings, in addition to the fact that both *d* and *e* ions are present in compounds **8, 9, 14** and **15** with aryl substituents at C-2, lead to the suggestion that the hydrogen at the 3-position of the pyrazole ring alone is able to migrate. The subsequent loss of hydrogen, which occurrs in both 1'*N*-phenyl **10-15** (Scheme 2) and 1'*N*-methyl derivatives **6-9, 16, 17** (Scheme 3) to stable ions *e*, must occur very rapidly since a metastable ion for the overall process is observed. The formation of the *d* and *e* ions required a low energy, as it is observed in the 14 eV eims also.

Scheme 3

Proposed Mechanism for the Elimination of Ethanol Followed by Hydrogen Ejection for the N'-Methyl Derivatives 6-9, 16, 17



The eims of the 4'-carboxy derivative **18** is closely similar to those of the corresponding ethyl ester **7**; in the case, of course, the ions *d* and *e* arise from the molecular ion by loss of water and water followed by hydrogen respectively.

Conclusions.

In conclusion, the overall loss of the 4-oxygen and the 3-substituent also in these compounds confirms that this process is characteristic of 3-aryl and 3-heteroaryl-substituted-4(3*H*)-quinazolinones [1,3]. In contrast to the corresponding 3-5'-isoxazolyl derivatives [3], the *a* ion is formed exclusively without ring opening, *i.e.* from M^+ and from the *b* ion. This behaviour is in line with the more favoured N-O bond cleavage under electron impact of isoxazoles [11-14] respect to the *N-N* bond cleavage of pyrazoles [15]. Ring opening of pyrazole ring seems to occur through a concerted process involving 3'-H migration to the oxygen of the 4'-carboxyethyl group, which is responsible of the formation of the *d* and *e* ions.

EXPERIMENTAL

Low resolution mass spectra (75 eV and 14 eV) were measured on a Jeol JMS-01-SG-2 mass spectrometer, which consists of EB (Mattauch-Herzog) geometry. In a typical experiment 3 number of scans were averaged. Ions were generated in the built-in electron impact ionization source (ionization potential 75 eV, total emission current 100 μA). The accelerating voltage was 10kV. The ionization chamber temperature was varied from 100 to 250°. Exact mass measurements were performed at 15,000 resolving power, using a photo-plate detection technique and perfluorokerosene as the standard, and were run out to an accuracy of ± 10 ppm of the theoretical value. First field-free metastable ions were detected by the accelerating voltage scan technique and/or by B/E and B^2/E linked scan spectra. The samples were introduced into the source by a direct inlet system, with a probe temperature of about 130°. The B/E and B^2/E linked scan spectra are recorded on a ZAB 2F instrument.

All the compounds were synthesized according to literature [4,5]; the labelled compounds **16** and **17** were obtained using monodeuterioformic acid and trideuterioacetic acid instead of unlabelled materials as the starting reagents.

Acknowledgment.

The authors thank the M.U.R.S.T. for financial support and Professor S. Foti (Dipartimento di Scienze Chimiche, Catania, Italy) for the B/E and B^2/E linked scan spectra.

REFERENCES AND NOTES

[a] For part **2** see ref [1].

[b] This work constitutes also part **13** of the series Studies in Organic Mass Spectrometry. For part **12** see ref [2].

* Author to whom correspondence should be addressed.

[1] L. Ceraulo, P. Agozzino, M. Ferrugia and S. Plescia, *Rapid Commun. Mass. Spectrom.*, **2**, 223 (1988).

[2] L. Ceraulo, M. Ferrugia and V. Sprio, *Org. Mass Spectrom.*, **27**, 37 (1992).

[3] L. Ceraulo, S. Plescia, G. Daidone and M. L. Bajardi, *J. Heterocyclic Chem.*, **21**, 1209 (1984).

[4] S. Plescia, G. Daidone, L. Ceraulo, M. L. Bajardi and R. Arrigo Reina, *Farmaco, Ed. Sci.*, **39**, 120 (1984).

[5] S. Plescia, M. L. Bajardi, D. Raffa, G. Daidone, M. Matera, A. Caruso and M. Amico-Roxas, *Eur. J. Med. Chem.-Chim. Ther.*, **21**, 291 (1986).

[6] Fr. R. Preuss, H. Hoffmann-Pinther, H. Achenbach and H. Friebolin, *Pharmazie*, **25**, 752 (1970).

[7] S. Pfeier, H. Polmann and R. Kraft, *Pharmazie*, **29**, 765 (1974).

[8] S. C. Pakrashi, J. Bhattacharyya, L. F. Johnson and H. Budzikiewicz, *Tetrahedron*, **19**, 1011 (1963).

[9] M. Luckner, K. Winter, L. Nover and J. Reisch, *Tetrahedron*, **25**, 2575 (1969).

[10] J. G. Liehr, A. G. Brenton, J. H. Beynon and W. J. Richter, *Org. Mass Spectrom.*, **16**, 139 (1981).

[11] A. Selva, R. Stoyanova, V. Vettori and A. Auricchio, *Ann. Chim. (Rome)*, **69**, 81 (1979) and references.

[12] G. Bouchoux and Y. Oppiliard, *Org. Mass Spectrom.*, **16**, 459 (1981).

[13] D. C. Nonhebel, *Org. Mass Spectrom.*, **3**, 1519 (1970).

[14] J. L. Auabagnac and D. Bourgeon, *Org. Mass Spectrom.*, **12**, 65 (1977).

[15] J. van Thuijl, K. L. Klebe and J. J. van Houte, *Org. Mass Spectrom.*, **3**, 1549 (1970).