Mass Spectrometric Investigation of Isomeric 1,2,3,4-Tetrahydro-4-oxoquinazolines

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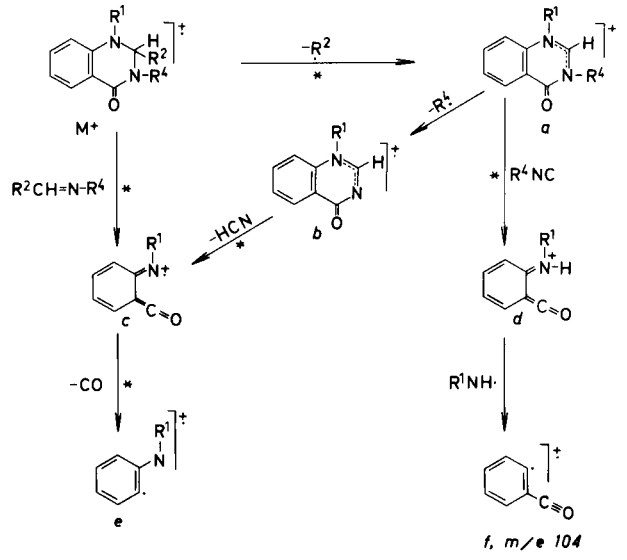
Six isomeric methylphenyl-1,2,3,4-tetrahydro-4-oxoquinazolines have been prepared and their fragmentation patterns upon electron impact studied. Deuterium labelling and high-resolution measurements were performed in order to facilitate the interpretation of the spectra. The dissociation of the molecular ion follows two main routes, the fragmentation being governed by the position of the phenyl group.

In a series of papers, we have reported on the mass spectral behaviour of 3,4-dihydro-4-oxoquinazolines, 1,2,-3,4-tetrahydro-2-oxoquinazolines and 1,2,3,4-tetrahydro-2,4-dioxoquinazolines (1,2,3). It was found that the substituent at the C-2 position of the 3,4-dihydro-4-oxoquinazolines studied greatly influenced the fragmentation pattern of these compounds (1).

No systematic investigation of the 1,2,3,4-tetrahydro-4-oxoquinazolines upon electron impact has, to our knowledge, been performed. We found it interesting to study the mode of fragmentation of this type of compounds, our interest being especially focused on the influence of substituents on the fragmentation pattern. The present paper gives an interpretation of the mass spectra of the



Scheme 1

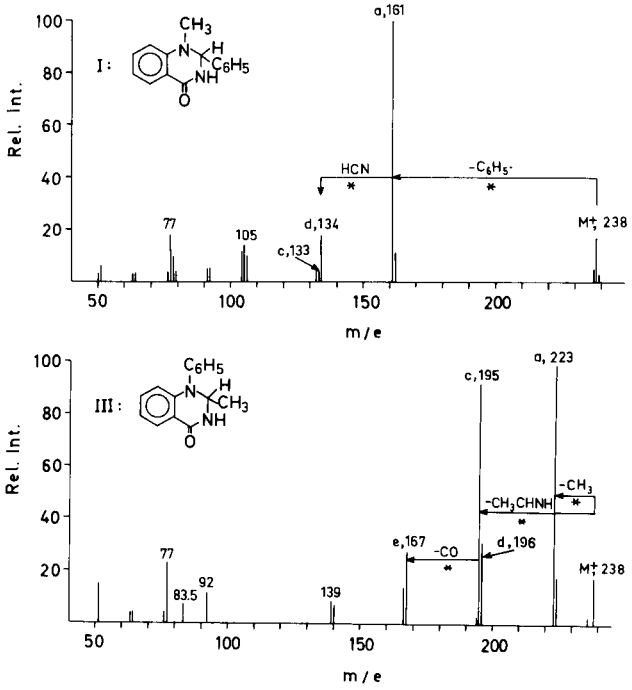


Figure 1. Fragmentation patterns of compounds I and III.

six possible compounds (I-VI) having a methyl and a phenyl group located at two of the positions 1,2 and 3 of 1,2,3,4-tetrahydro-4-oxoquinazoline (*cf.* Table I). Two representative spectra are given in Figure 1. Methyl and phenyl groups were chosen as substituents because of their stability upon electron impact and, consequently, small contribution to the fragmentation pattern.

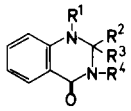
Specifically labelled deuterium compounds were also synthesized (see Table I) and their mass spectra examined. The fragmentation pathways proposed are substantiated by shifts in spectra of labelled compounds (*cf.* Table II).

Further evidence is obtained by appropriate metastable peaks in most of the spectra as indicated by asterisks in Scheme 1.

The base peak in the spectra of compounds I, II, III, V and VI corresponds to *a* (*cf.* Scheme 1 and Table II), formed by loss of the substituent, if any, or hydrogen from the C-2 position of M^+. This cleavage is the main fragmentation pathway, the peak corresponding to *a* dominating the spectra of these compounds. The nature of the group R^2 is also reflected in the intensity of the molecular ion (see Table II). The spectra of compounds II and IV exhibit a strong M^+ due to the small tendency

TABLE I

Structures of the 1,2,3,4-Tetrahydro-4-oxoquinazolines



Compound	R^1	R^2	R^3	R^4
I	CH_3	C_6H_5	H	H
I-2-d	CH_3	C_6H_5	D	H
I-3-d	CH_3	C_6H_5	H	D
II	CH_3	H	H	C_6H_5
II-2,2-d_2	CH_3	D	D	C_6H_5
III	C_6H_5	CH_3	H	H
III-2-d	C_6H_5	CH_3	D	H
IV	C_6H_5	H	H	CH_3
V	H	CH_3	H	C_6H_5
V-2-d	H	CH_3	D	C_6H_5
VI	H	C_6H_5	H	CH_3
VI-1-d	D	C_6H_5	H	CH_3

of the molecular ion to lose a hydrogen atom. In contrast, the other four compounds give rise to a relatively weak molecular ion, since a methyl or phenyl fragment is easily expelled from the C-2 position of M^+ to give *a*.

The fragmentation of *a* follows two pathways (*cf.* Scheme 1). The most important route is an RDA-like fission of the heterocyclic ring involving a hydrogen rearrangement leading to *d*. An abundant peak corresponding to this cleavage is found in all the spectra examined (Table II). The relative intensities of peaks corresponding to *d* depend on the nature of R^1, the peak being most intense in the spectra of compounds III and IV having a phenyl substituent. The origin of the transferred hydrogen in the step $a \rightarrow d$ was established by deuterium-labelling experiments (Table II). The hydrogen rearrangement is not a site-specific reaction and the transferred hydrogen can originate both from the C-2 and N-3 positions depending on where a transferable hydrogen is available. When competition between these two positions is possible, as in I and III, the N-3 hydrogen is almost exclusively preferred.

The odd-electron ion *c* is probably formed directly from the molecular ion by fission of the heterocyclic ring. Its formation seems to be influenced by the structure of R^1. In the spectra of compounds III and IV, where R^1 is C_6H_5, the corresponding peak has a relative intensity of 90-100%, while the analogous peak of I, II, V and VI is only 4-14% of the base peak.

The relative proportions of the odd-electron ion *c* and the even-electron ion *d* in the spectra of I-VI are listed in Table III. Obviously, the hydrogen rearrangement leading to *d* is most favourable in the fragmentation of I. This behaviour is in accord with the fragmentation mode outlined in Scheme 1 and is governed by the following factors: (i) The formation of *a* (precursor of *d*) depends on the nature of the substituent at C-2. The tendency of cleavage with loss of R^2 decreases in the order R^2 = phenyl, methyl, hydrogen. (ii) The transition from M^+ to *c* is favoured by a phenyl group at N-1, stabilizing fragment *c*. (iii) A transferable hydrogen at N-3 favours the rearrangement reaction to *d*.

In the fragmentation of V, the ion represented by *a* is exposed to another type of cleavage with expulsion of the N-3 phenyl group affording *b*. This ion then gives rise to *c* in the normal way. Loss of a phenyl group from *a* is, however, not observed in the spectrum of II. The reason for this is not satisfactorily understood. The further fragmentation of species *c* and *d* gives rise to *e* and *f* and their protonated analogues (not depicted in Scheme 1).

A prominent peak corresponding to *e* is found in the spectra of compounds III-IV and I-II, where R^1 is phenyl or methyl, respectively. Eland and Danby (4) and also Das *et al.* (5) suggested that diphenylamine rearranges to carbazole upon electron impact. The fragmentation of these compounds is characterized by the formation of intense ions at m/e 140 and 139. A very abundant doubly charged molecular ion (m/e 83.5) is also characteristic in the spectrum of carbazole. All these features are found in the spectra of compounds III and IV, indicating rearrangement to carbazole of *e* (R^1 = phenyl). A similar process starting with *e* in the fragmentation of I and II (R^1 = methyl) cannot be excluded.

High-resolution measurements of the peaks m/e 140 and 139 show that the corresponding ions have an elemental composition of $C_{10}H_6N$ and $C_{11}H_8$, respectively, indicating a dual mode of fragmentation for species *e* ($R^1 = C_6H_5$) through loss of C_2H_3 or H_2CN. This is in agreement with the fragmentation pattern found for carbazole (6) and further supports the proposed rearrange-

TABLE II

Relative Intensities (%) of the Principal Peaks in the Mass Spectra of the Isomeric Tetrahydrooxoquinazolines I-VI and Some Deuterated Analogues. The letters refer to the fragments depicted in Scheme 1.

	Compounds											
m/e	I	I-2-d	I-3-d	II	II-2,2-d_2	III	III-2-d	IV	V	V-2-d	VI	VI-3-d
241					13							
240		3			74M^+		3					3
239	3	18M^+	11M^+	10	20		18M^+	8	3	11M^+		11M^+
238	17M^+	6	9	68M^+	100	18M^+	4	49M^+	10M^+	7	10M^+	7
237	5	4	3	100*a*				30*a*	4	4	7	
236				4	4	3	3	3				3
235							17			20		
224						18	96		16	100		
223						100*a*	19		100*a*	49		
197							5					
196						26*d*	24	19*d*				
195						92*c*	100	100*c*				
194						3	7					
168						6	7					
167						28*e*	25	16*e*				
166						14	13	9				
163		12	11									12
162	11	100	100								11	100
161	100*a*	20	60								100*a*	16
148										6		
147									7	49		
146									60*b*	31		
145									4			
140						7	6	4				
139						8	7	5				
135			19		3							
134	18*d*	19	13	4*d*	19							
133	4*c*	5	6	14*c*	21							
132	4	4	6	5	5							
121										7		9
120									8*d*	7	9*d*	8
119									9*c*	10	8*c*	
118									8	10	7	7
117									4			
107		7	9		5							
106	10	5	11	5	7					4		
105	14	18	30	46	60				6	10	4	6
104	12	15	21	25	29				6	4		
93			3		8				4	7		3
92	5	3	7	4	5	11	13	7	8	11	8	8
91	5	3	5	10	8		8		7	6	4	
83,5						7	8	5	4			
79	4	3	6									
78	10	8	12	9	15				4	9		
77	18	15	28	20	21	23	20	15	23	24	8	9
76	4	3	5			4	4		3	4	4	
66									6			3
65									6	6	4	3
64	3	3	5			4	4		3	9		6
63	3	3	5			4	4					
52			3		3							
51	6	5	12	4	8	14	12	8	7	8	4	6
50	3		4				4					

TABLE III

Relative Proportions of Fragments *c* and *d* formed in the Fragmentation of Compounds I-VI.

Compound	*c* m/e	*d* m/e	rel. int. *c* / rel. int. *d*
I	133	134	0.2
II	133	134	3.5
III	195	196	3.5
IV	195	196	5.3
V	119	120	1.1
VI	119	120	0.9

TABLE IV

High Resolution Data of 1,2,3,4-Tetrahydro-4-oxoquinazolines

Compound	Measured Mass	Theoretical	Formula
I	134.0611	134.0606	C_8H_8NO
II	133.0533	133.0528	C_8H_7NO
III	139.0548	139.0548	$C_{11}H_7$
III	140.0503	140.0500	$C_{10}H_6N$
III	167.0732	167.0735	$C_{12}H_9N$
IV	139.0540	139.0548	$C_{11}H_7$
IV	140.0499	140.0500	$C_{10}H_6N$
IV	167.0738	167.0735	$C_{12}H_9N$

ment of ion m/e 167.

In conclusion, this investigation has shown that the fragmentation of the isomeric methylphenyltetrahydro-oxoquinazolines I-VI studied, follows a common pattern, consisting of two main routes of cleavage. The most important step is the dissociation of M^+ with loss of the C-2 group, but a direct fission of the heterocyclic ring is also an important pathway. The fragmentation is, to a great extent, governed by the position of the phenyl group. The compounds having an *N*-1 phenyl group (Nos. III and IV) afford a diphenylamine moiety *e* (m/e 167) which rearranges to a carbazole ion.

EXPERIMENTAL

The mass spectra were recorded on an LKB 9000 mass spectrometer using a direct probe heated to suitable temperature. The ionizing energy was maintained at 70 eV, the temperature of the ion source being kept at 270°. Only peaks equal to or greater than 3% of the base peak are noted in Table II. High-resolution spectra were obtained using an Atlas SM 1 spectrometer. The results are listed in Table IV.

Infrared spectra were routinely recorded in potassium bromide pellets to check the identity of the compounds, a Perkin-Elmer Infracord 337 being used. Melting points were taken in an electrically heated metal block using calibrated Anschütz thermometers. Elementary analyses were obtained from the Max-Planck-Institut für Kohlenforschung, Mülheim, W. Germany.

1,2,3,4-Tetrahydro-1-methyl-4-oxo-3-phenylquinazoline (II).

2-Methylamino-*N*-phenylbenzamide (7) (0.1 g., 4.2 mmoles) was dissolved in 20 ml. of 40% ethanol and, after addition of 1.2 g. of 37% formaldehyde solution (10 mmoles), the solution was refluxed for 1 hour. The compound separated as white flakes upon cooling. It was recrystallized from ethanol-water, yield 85%, m.p. 115-116°; lit. (8) m.p. 115°.

1,2,3,4-Tetrahydro-2-methyl-4-oxo-1-phenylquinazoline (III).

1,4-Dihydro-2-methyl-4-oxo-1-phenylquinazoline (9) (0.5 g., 2.1 mmoles) was reduced with sodium borohydride (0.15 g., 4.2 mmoles) in 6 ml. of methanol, the mixture being refluxed for 2 hours. Water was added and the precipitated product filtered and recrystallized from ligroin, yield 80%, m.p. 150-152°.

Anal. Calcd. for $C_{15}H_{14}N_2O$: C, 75.6; H, 5.92; N, 11.76. Found: C, 75.5; H, 5.86; N, 11.91.

1,2,3,4-Tetrahydro-3-methyl-4-oxo-1-phenylquinazoline (IV).

1,2,3,4-Tetrahydro-4-oxo-1-phenylquinazoline (VIII) (3.0 g., 13 mmoles) was dissolved in 50 ml. of dry DMF. Sodium hydride 50% (0.62 g., 13 mmoles) was added in small portions, a three-necked flask with mechanical stirrer, dropping funnel and calcium chloride tube being used. The mixture was stirred for 30 minutes at room temperature, after which methyl iodide (3.7 g., 26 mmoles) was added. After 15 minutes of stirring, the temperature was increased to 80° for a further 30 minutes. Water was added in order to precipitate the product. After standing overnight, the supernatant was decanted and the residue recrystallized from ligroin, yield 38%, m.p. 75-76°.

Anal. Calcd. for $C_{15}H_{14}N_2O$: C, 75.6; H, 5.92; N, 11.76. Found: C, 75.5; H, 5.90; N, 11.86.

1,4-Dihydro-4-oxo-1-phenylquinazoline (VII).

2-Anilinobenzamide (9) (6 g., 28 mmoles) was refluxed for 5 hours with 25 g. (0.55 mole) of formic acid. The mixture was evaporated to dryness and the product recrystallized from ethanol-water (1+9), yield 65%, m.p. 182-184°.

Anal. Calcd. for $C_{14}H_{10}N_2O$: C, 75.7; H, 4.54; N, 12.60. Found: C, 75.6; H, 4.63; N, 12.64.

1,2,3,4-Tetrahydro-4-oxo-1-phenylquinazoline (VIII).

1,4-Dihydro-4-oxo-1-phenylquinazoline (VII) (0.5 g., 23 mmoles) was dissolved in 6 ml. of methanol and reacted with sodium borohydride (0.17 g., 4.6 mmoles) for 2 hours at 0°. The product was precipitated by addition of 20 ml. of water and 0.1 ml. of 5 *M* hydrochloric acid, yield 90%, m.p. 202-204°.

Anal. Calcd. for $C_{14}H_{12}N_2O$: C, 75.0; H, 5.39; N, 12.49. Found: C, 74.5; H, 5.73; N, 12.39.

1-Methyl-4-oxo-2-phenylquinazoline-2-d (I-2-d).

This compound was obtained by reduction of 1,4-dihydro-1-methyl-4-oxo-2-phenylquinazoline (10) with sodium borodeuteride in methanol. The product was recrystallized from ethanol and water (1+9), m.p. 202-203°; lit. (11) 203° (non-deuterated).

1-Methyl-4-oxo-3-phenylquinazoline-2,2-d_2 (II-2,2-d_2).

This compound was prepared as described for II but with the use of deuterioformaldehyde in deuterium oxide, m.p. 116°.

2-Methyl-4-oxo-1-phenylquinazoline-1-d (III-1-d).

This compound was synthesized as described for III but with the use of sodium borodeuteride, m.p. 148-149°.

2-Methyl-4-oxo-3-phenylquinazoline-2-d (V-2-d).

This compound was obtained according to Okumura *et al.* (12) but with the use of sodium borodeuteride, m.p. 168-169°; lit. (12) 167-169° (non-deuterated). The synthesis of compounds I and VI is described in ref. (11) and compound V in ref. (12).

The labelled compounds I-3-d and VI-1-d were prepared by recrystallization of I and VI in deuterium oxide, the exchange being followed by examination of the ir spectra.

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