Organic Mass Spectrometry, 1971, Vol. 5, pp. 1029 to 1041. Heyden & Son Limited. Printed in Northern Ireland

MASS SPECTRA OF β-QUINUCLIDONES AND β-BENZQUINUCLIDONES

A. I. ERMAKOV, YU. N. SHEINKER, E. E. MIKHLINA, L. I. MASTAFANOVA, V. YA. VOROBJOVA, A. D. YANINA and L. N. YAKHONTOV
S. Ordzhonikidze All Union Chemical-Pharmaceutical Research Institute, Moscow, USSR

and

R. G. KOSTYANOVSKY,
Institute of Chemical Physics, Academy of Sciences of the USSR, Moscow, USSR

(*Received* 20 *March* 1971; *accepted* 22 *April* 1971)

Abstract—The mass spectra of quinuclidone-3, benzquinuclidone-3, 2-azaquinuclidone-3, 2-azabenzquinuclidone-3 and some of their functional substituted derivatives have been investigated. Fragmentation of the compounds investigated has been shown to proceed through the open form of the molecular ion with cleavage of a bridgehead bond containing the carbonyl group and subsequent elimination of carbon monoxide.

THE MASS spectra of some quinuclidones were first investigated[1] from the point of view of relaxation of the amine stabilization in accord with Bredt's rule. Unlike the respective non-bridgehead structures, the mass spectra of quinuclidone, 2- and 4-azaquinuclidones and other similar functional derivatives have been found to exhibit low intensity of the amine fragments [M − 1]. On the other hand in certain cases this does not hold and the peak intensity corresponding to the α-cleavage has been shown to be rather high.[2,3]

A suggestion regarding the formation of such fragments from the open form of the molecular ion has been confirmed by analysis of the low voltage mass spectra, in which the peak intensity corresponding to α-cleavage decreased essentially. At the same time for the non-bridgehead amines the respective fragments remain maximal as the ionizing voltage decreases to 12 eV.[4]

In the present study the fragmentation of quinuclidones-3 and benzquinuclidones-3 was indeed found to occur via the open form of the molecular ion with cleavage of a bridgehead bond containing the carbonyl group. Subsequent elimination of carbon monoxide afforded fragments characteristic of the given class of compounds.

From a comparison of the mass-spectra of quinuclidone-3 (I) and benzquinuclidone-3 (II) (Figs. 1 and 2), it is evident that their fragmentations are similar. The fragments *m/e* 97 and 145 (base peaks), are generated from the molecular ions Ia and IIa by a loss of 28 m.e. From the mass spectra of these compounds labelled with O^{18} it can be concluded that this process is the carbon monoxide elimination (instead of C_2H_4 assumed in ref. 2), which could be described by the open form of the molecular ions *a* and *a'* (Schemes 1 and 2). The structures of generating ions *b* and *b'* explain the formation of the following fragments: *c*, *d m/e* 82, *e m/e* 69, (*m** 49·5) *f m/e* 42, (*m** 18·4) (in quinuclidone spectrum), *c'* *m/e* 130, (*m** 116) and *e'* *m/e* 117, (*m** 94·5), in benzquinuclidone spectrum).

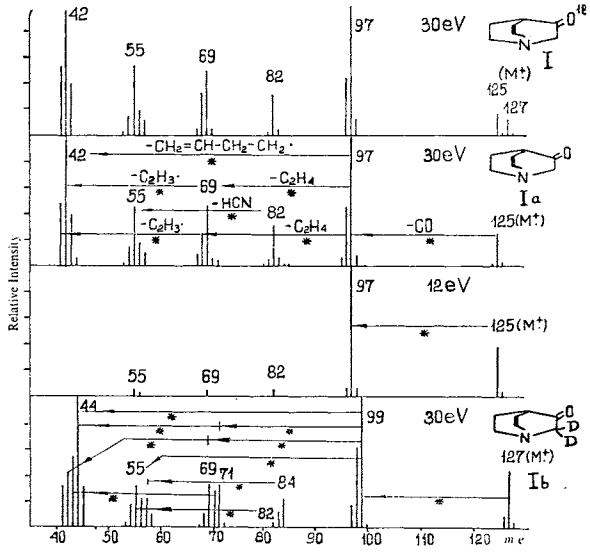


FIG. 1

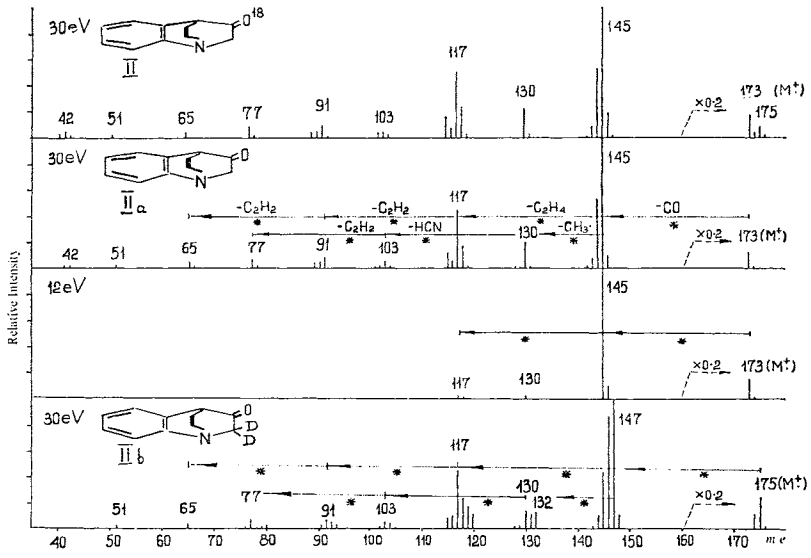


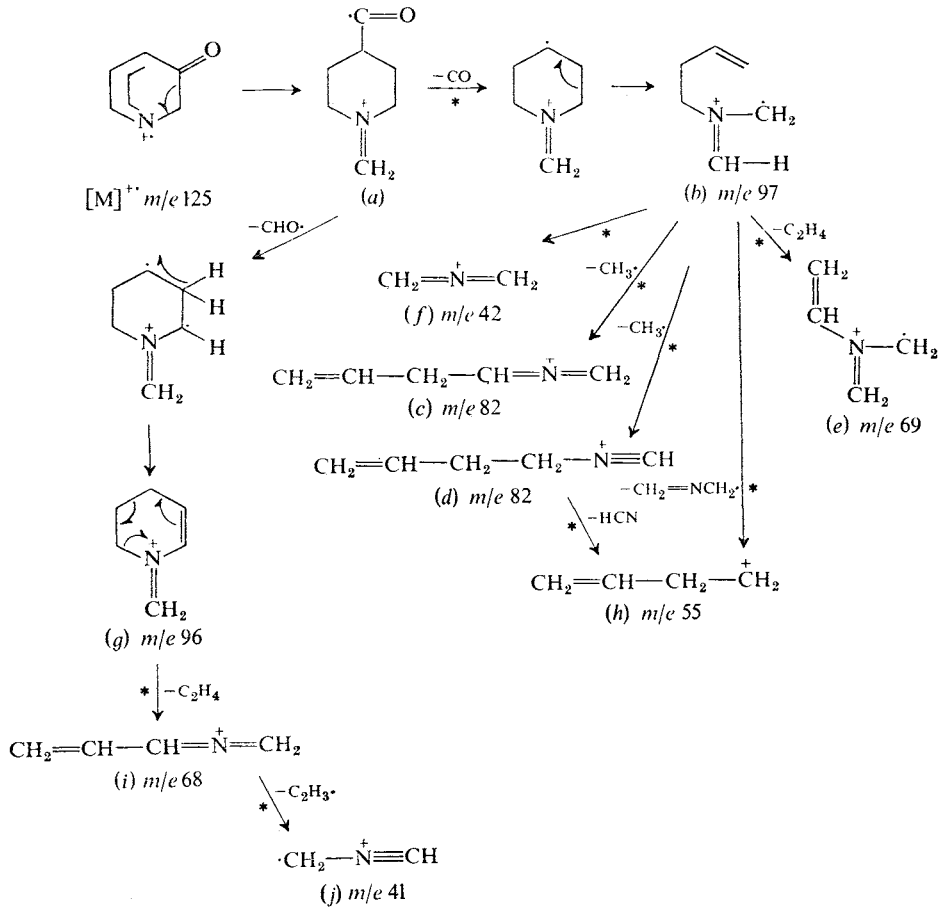
FIG. 2

Elimination of hydrogen cyanide from the fragments *d* and *c'* leads to the hydrocarbon ions *h* and *h'* (*m/e* 55 and *m/e* 103).

The fragments *m/e* 96 and 144, which are abundant in the spectra of I and II (*ca.* 50% Rel. int.) are generated during the formal radical expulsion from the open form of the molecular ion. In this case elimination of the α-hydrogen is most probable.

Owing to a simultaneous hydrogen rearrangement (e.g. from C_3 to the radical centre at C_4† in the ions *a* and *a'*), the fragments *g* and *g'* with partially conjugated

† Hydrogen migration to an adjacent radical centre has been discussed elsewhere.[10]

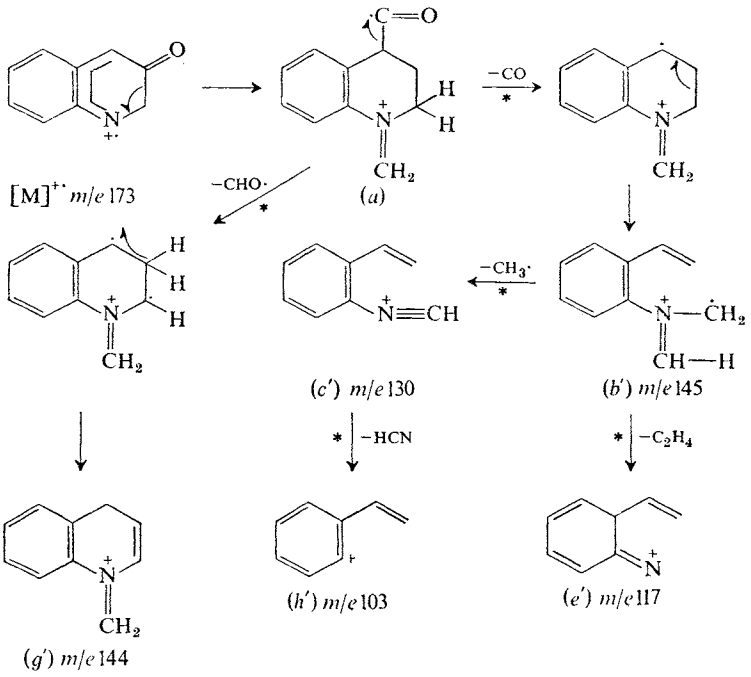


SCHEME 1

bonds are generated. This process agrees with the subsequent decay of the fragment *m/e* 96, confirmed by the 'metastable' peaks of the ions *i*, *m/e* 68, (m^* = 48·0) and *j* *m/e* 41, (m^* 24·5).

The fragmentations of I and II are confirmed by the mass spectra of the compounds labelled with deuterium at C_2, in which the fragments *m/e* 82, 69, 68 and 42 for I, and 130 for II are shifted towards greater mass, which is in agreement with the structures proposed.

The presence of the *m/e* 69 peak, in the mass spectrum of Ib, is explained by CD_2CH_2 expulsion from the fragment *m/e* 99 (m^* 48). This process might be due to an isotope effect.[11] Note that the increase in the total relative peak intensity in the region between *m/e* 67 and 71 in the spectra of Ib with respect to those observed in Ia does not affect the value Σ 67 to71/Σ 40 (where Σ 67 to 71 is the ion current of the group of peaks from *m/e* 67 to 71, Σ 40 is the total ion current), which in both cases is the same.



SCHEME 2

The fragmentations specific to I and II appear also in case of ethyl 3-benzquinuclidone-2-carboxylate acid (III). By analogy with the previous cases, the abundance of the [M — CO] fragment, *m/e* 217 (m^* = 192) generated from the open form of the molecular ion is the base peak (Fig. 3). The presence of metastable ions in the mass spectrum of III which are unequivocally identified allows the proposal of a general scheme of fragmentation of these compounds (Scheme 3). Expulsion of the carboethoxy group from the [M — CO] fragment (m^* = 95·5) produces the fragment *g'*, *m/e* 144, (95%, Rel. int.). As a result of such rearrangement the latter has a structure identical to that of the ion in the fragmentation of II.

Apparently an analogous rearrangement also takes place in the formation of ion *k*, *m/e* 188, which then cleaves to *l*, *m/e* 170 (m^* = 154) and *m*, *m/e* 143 (m^* = 109), the peak of fragment *m/e* 145, in the spectrum of III is explained by expulsion of butyrolactone from the [M — CO] ion. This process is most specific for V and VI.

Complete spectral identity of the ethyl esters of 3- and 5-quinuclidone-2-carboxylic acids (V and VI, Fig. 4) with identical metastable ions is direct evidence of a fragmentation from the open form of the molecular ion. Actually such identity may only be explained via formation of the ions *n* and *g* (Scheme 4).

Expulsion of carbon monoxide from the open form of the molecular ion and a simultaneous cleavage of the C_7—C_8 bond leads to the fragment *n*, *m/e* 169, which is identical for V and VI. The one-step expulsion of butyrolactone from ion *n* (m^* = 56) involves a six-membered transition state and formation of fragment *b*, *m/e* 97,

* A distorted spectrum of this compound as previously reported,[2] might be due to the sample degradation in the metal inlet system.

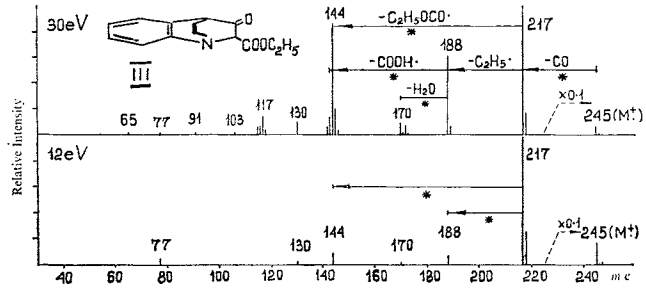
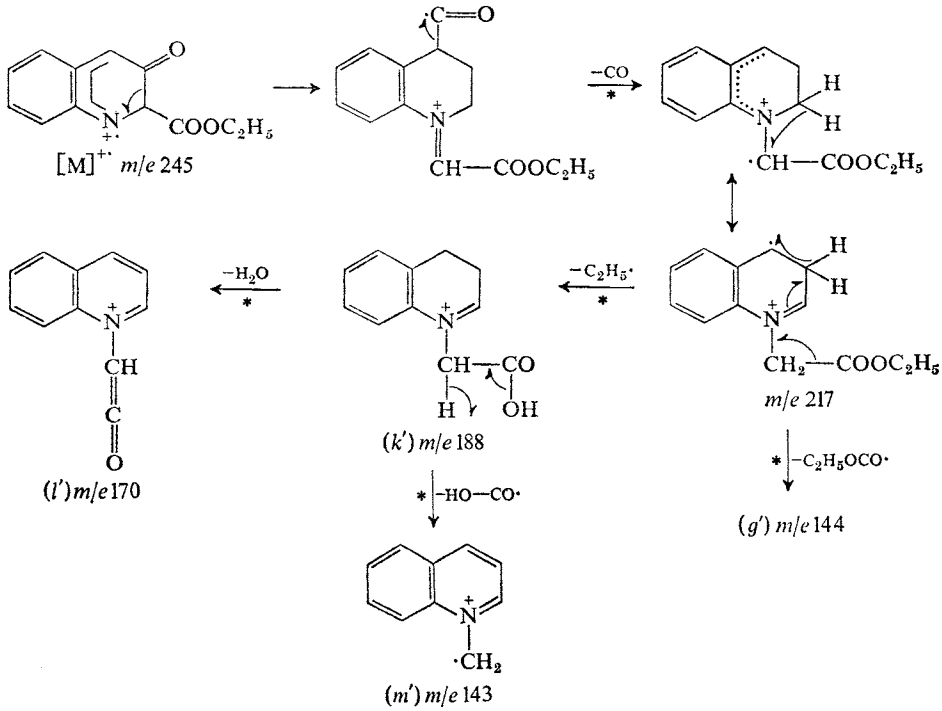


FIG. 3



SCHEME 3

analogous to that formed from I. This process is confirmed by fragmentation of VI deuterated in the ethyl group (Fig. 4); *m/e* 94, is shifted by unity towards higher mass. This is most pronounced at 12 eV. Moreover the higher intensity of the *m/e* 97 peak, in respect to that of *m/e* 96, observed at the lower ionizing voltage is an indication of fragmentation via the six-membered transition state. Subsequent decay of fragment *b* resulting in the ions *m/e* 82, 69, 55 and 45 is shown in Scheme 1. These processes are confirmed by metastable ions. In the mass spectrum of VI deuterated at C_6 the fragment peaks, *m/e* 82 and 42, are shifted towards the greater masses while the *m/e* 55 fragment retains both its abundance and mass number, as has already been observed in decay of Ib compared to that of I.

α-Expulsion of the carboethoxy group from the [M — CO] ions gives the *m/e* 96

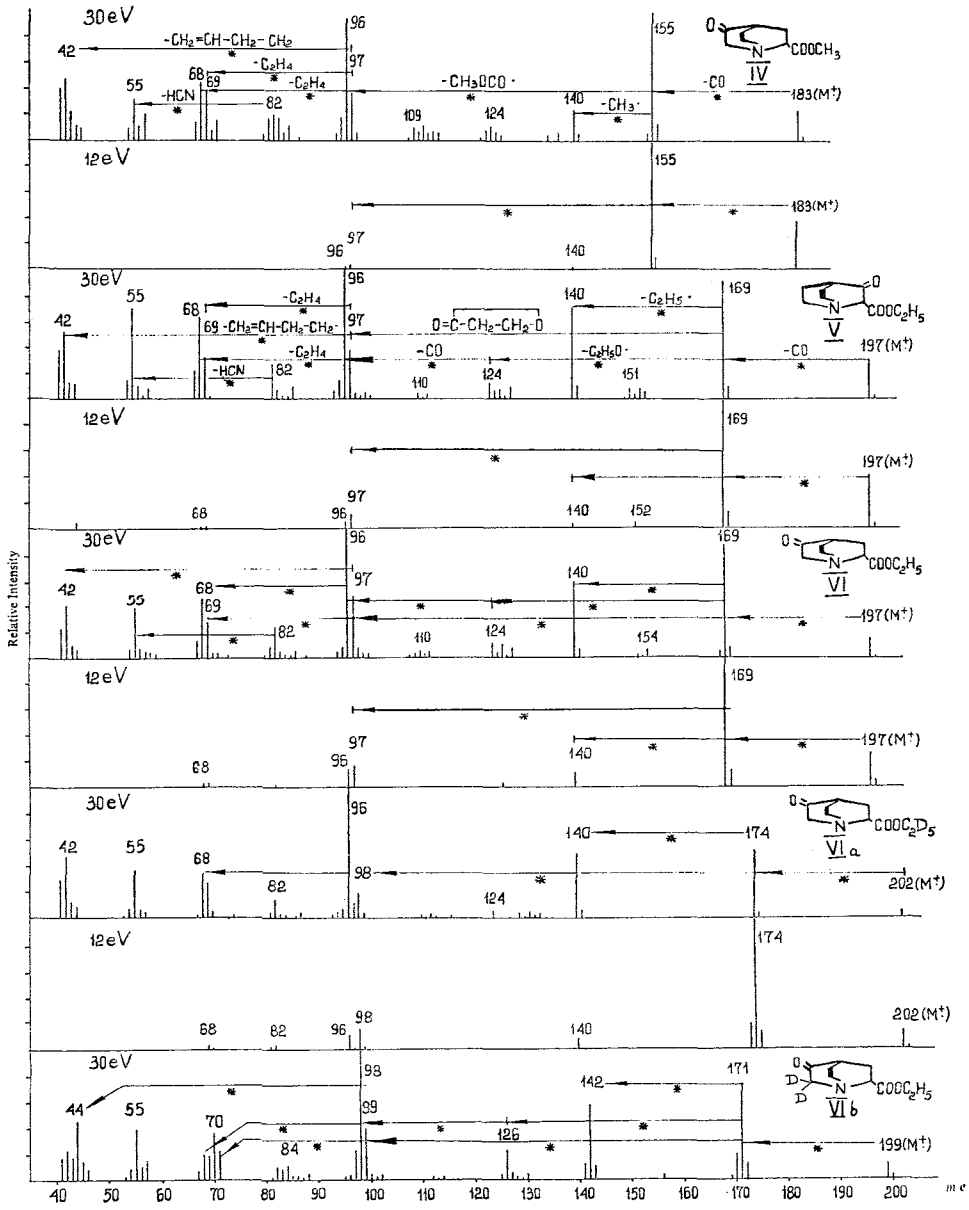
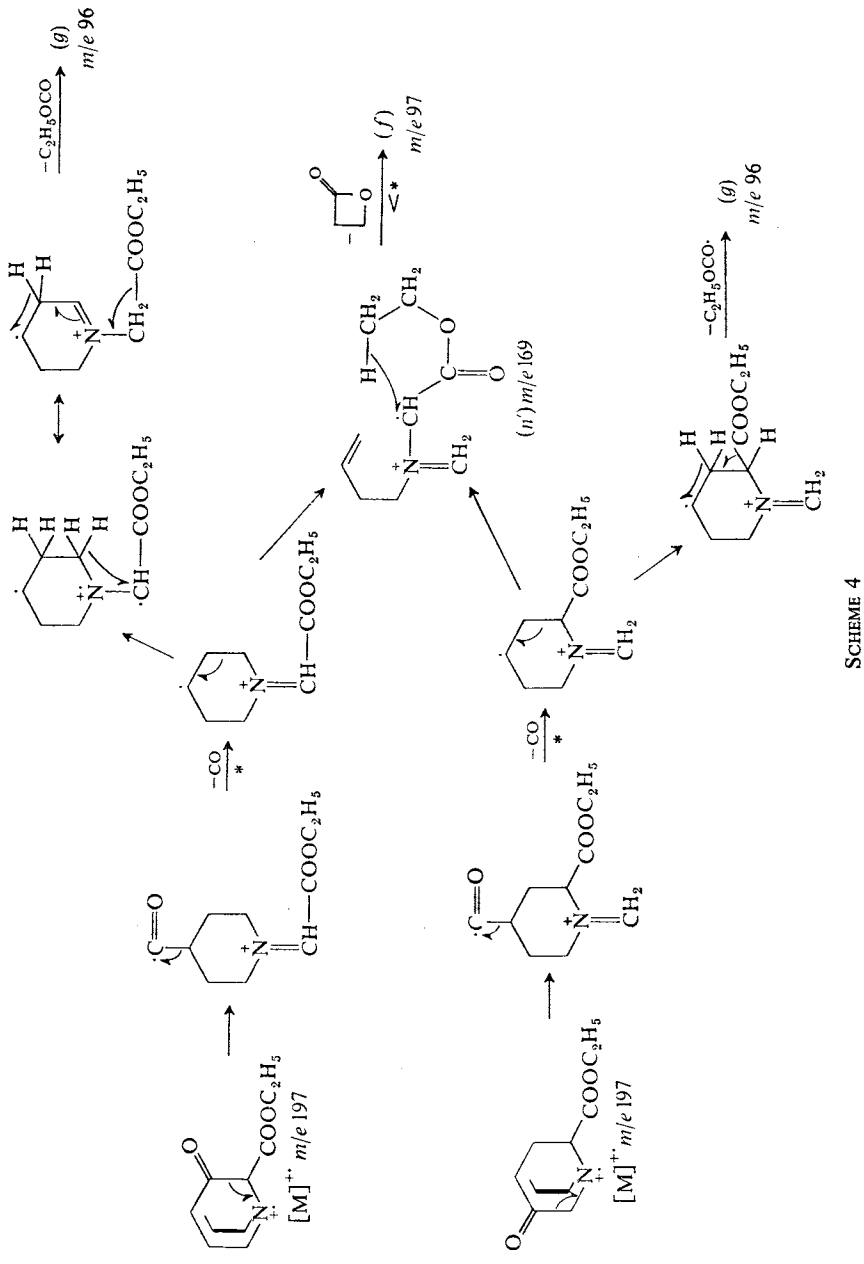


FIG. 4

fragment which is the base peak in the spectra of V and VI. As follows from a comparison of the mass spectra of Ia, Ib, IV, V, VI, VIa and VIb the *m/e* 96 ions of V and VI and the fragment *g* of I should be the same. Hence in this case formation of the *m/e* 96 fragment of V and VI might be again assumed to arise via the rearrangement presented in the Scheme. We note that the mass spectrum of compound IV exhibits the metastable ion, $m^* = 59{\cdot}5$, corresponding to the direct expulsion of CH_3OCO,



SCHEME 4

whereas V and VI also show a consecutive cleavage of C_2H_5O ($m^* = 90$) and CO ($m^* = 74$).

Unlike quinuclidone-2 carboxylic esters, for which α-expulsion of carbalkoxy group occurs from the molecular ion,[2] the mass spectra of IV, V and VI contain almost no $[M - COOR]^{+\cdot}$ fragment because of the CO elimination.

Identity of the spectra of C_2 epimeric 2-benzoyloxymethyl-5-ketoquinuclidones (VII and VIII, Fig. 5) also confirms expulsion from the open form of the molecular ion which does not differ stereochemically for the isomers. Fragmentations of VII and VIII are shown in Scheme 5.

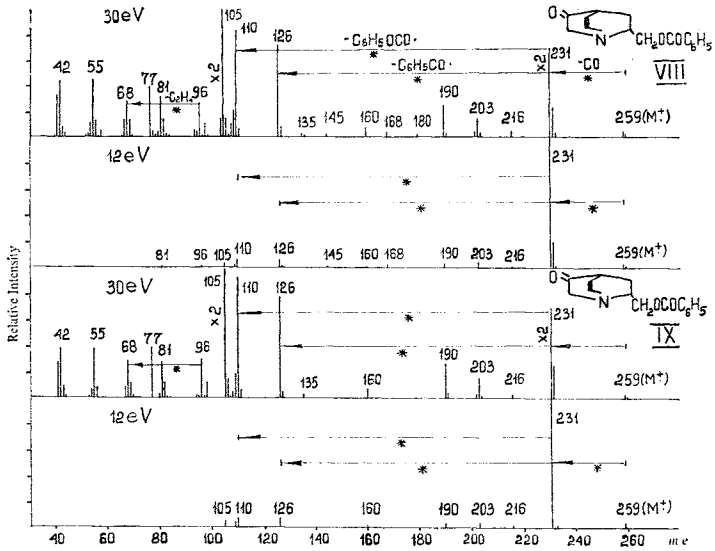
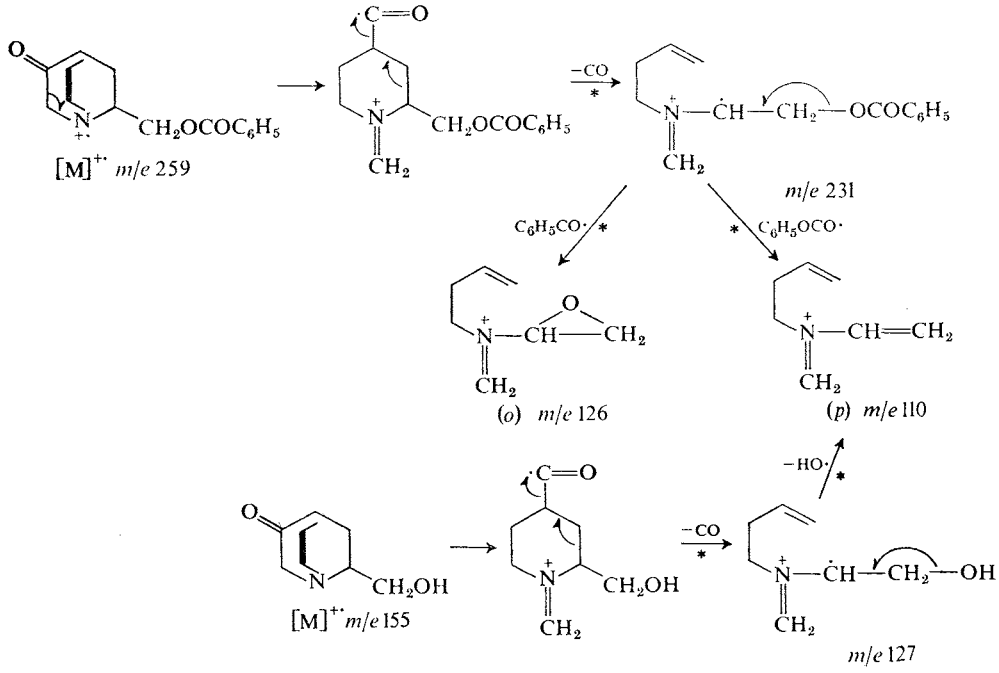


FIG. 5

The bond cleavage of the α-substituent of the [M — CO] fragment leads to the ions *o* and *p*, *m/e* 126 ($m^* = 69$) and 110 ($m = 52$). In the case of 2-oxymethyl-5-ketoquinuclidone (IX, Fig. 6), the fragment *p* results from the expulsion of the hydroxyl radical ($m^* = 95{\cdot}5$) and also from the ion [M — CO]. Fragmentation of 2-azaquinuclidone-3 and 2-azabenzquinuclidone-3 (X and XI, Fig. 7) has some specificity (Schemes 6 and 7).

The peaks of fragments *m/e* 70 and 69 of X are most intense. Their formation may be explained as follows. The peaks of [M — CO — 28] and [M — CO — 29] shift by unit mass in the spectrum of the N deuterated analogues. Thus, based on the structure of the [M — CO] ion, eliminations of C_2H_5 ($m^* = 48$) and C_2H_4 or N = CH_2 groups are most probable. From an analysis of the fragmentation of X and other similar functional derivatives,† the fragments *m/e* 69 and 70 might be assumed to result from $[M - CO]^{+\cdot}$ having the structure *q*. In such cases a labile hydrogen migrates to a radical centre at C_4, thus causing elimination of $C_2H_5\cdot$ and $\cdot N = CH_2$, and formation of fragments *r* and *s*. The hydrocarbon fragment, *m/e* 55, arises from

† For example 3-hydroxyquinuclidones, the mass spectra of which will be reported separately.



SCHEME 5

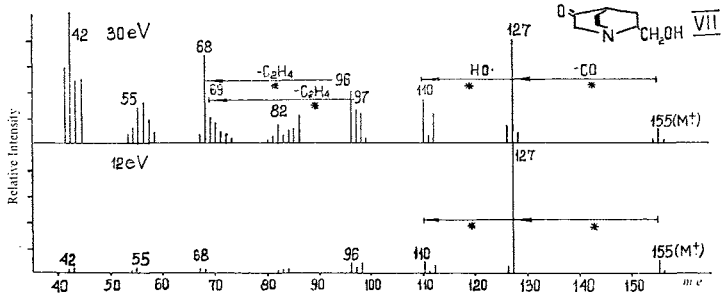


FIG. 6

a consecutive expulsion of the methyl group and a nitrogen molecule from the ion *t*, *m/e* 98.

The fragmentation of XI is interesting because its mass spectrum below *m/e* 117 resembles that of II. This is explained by the fact that the structure of fragment *m/e* 130, in the fragmentation of XI and II is the same.

This process is confirmed by the mass spectrum of the N-deuterated analogue in which the ion *m/e* 130 contains no label. The presence of a metastable ion, $m^* = 95{\cdot}5$, indicates the cleavage of [M − CO], 28 m.e. from the ion and formation of an intense fragment, *m/e* 118. This process may be associated with elimination of N=CH from ion *u*. An analogous phenomenon also takes place in the fragmentation of X. The observed expulsion of 27 m.e. from the ion *v*, *m/e* 118, ($m^* = 70$)

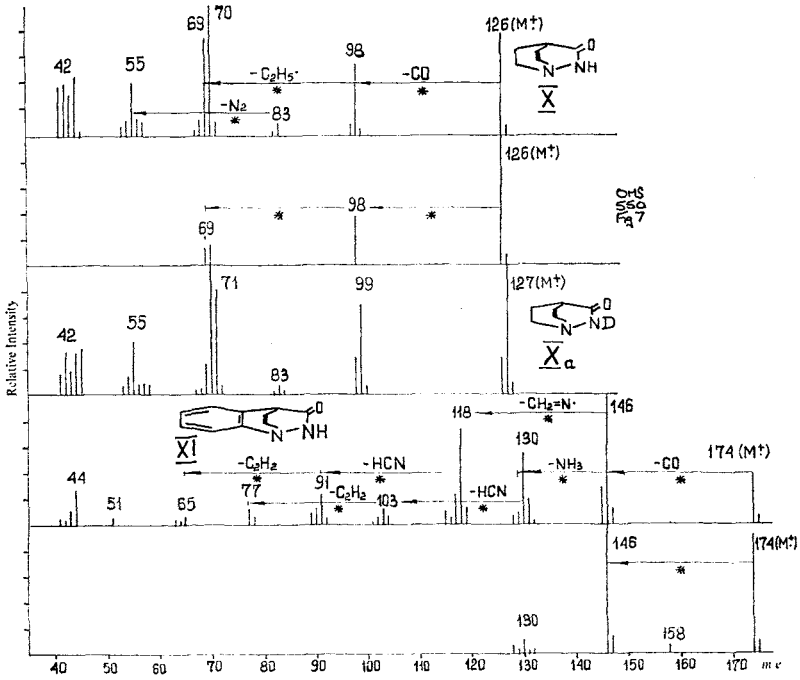
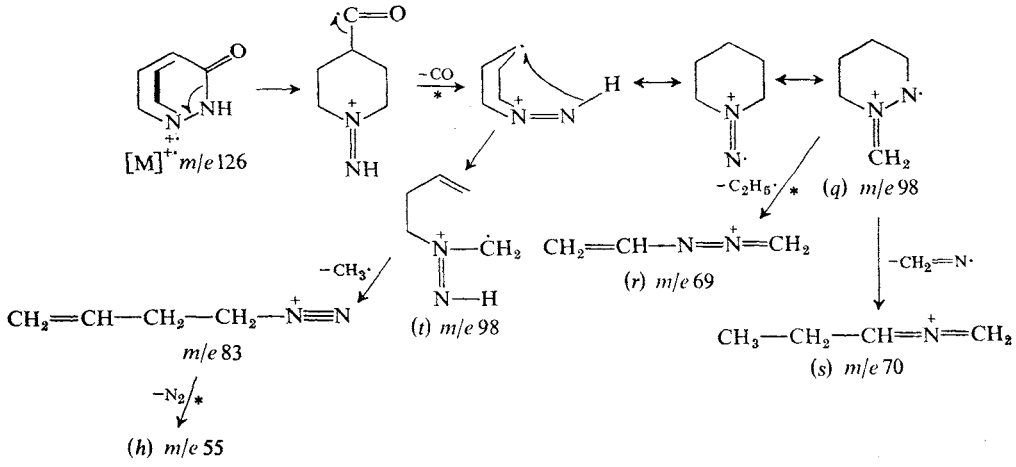


FIG. 7

is a result of HCN elimination and fragment *w* formation, *m/e* 91, whose subsequent degradation is confirmed by metastable ions.

It is interesting that at ionizing voltages below 12 eV the base peak is $[M - CO]^{+\cdot}$ for all the compounds investigated. Apparently the specific behaviour observed for [M − CO] fragments is defined by the stability of the neutral and charged fragments generated, rather than by the low activation energy of CO expulsion.

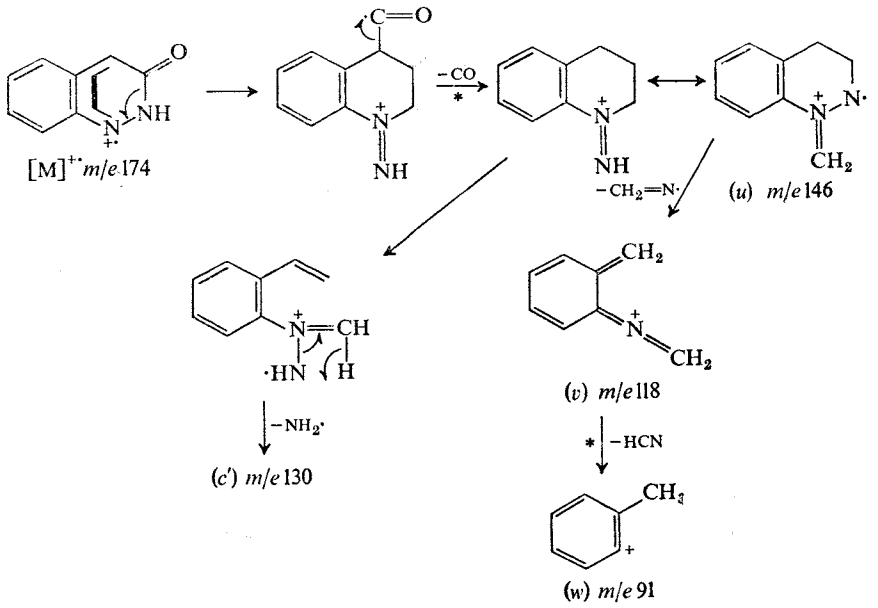
On this view CO elimination is suppressed only in compounds where the substituents facilitate fragmentation into the energy efficient fragments. This is the case



SCHEME 6

for example in the fragmentation of quinuclidones XII, XIII and XIV (Fig. 8 and Scheme 8).

The mass spectrum of 3-quinuclidone-2 carbox pyperidid acid (XII, Fig. 8) is a superposition of the spectra of XII ($[M]^{+\cdot} = 236$) and piperidine ($[M]^{+\cdot} = 85$). The piperidine molecular ion may form by α-hydrogen migration via an intermediate. The efficiency of such a process is determined both by the presence of the second ionization centre in XIII and generation of a neutral fragment in the form of stable structure X. The intensities of the peaks *m/e* 208, 97 and 96 corresponding to a

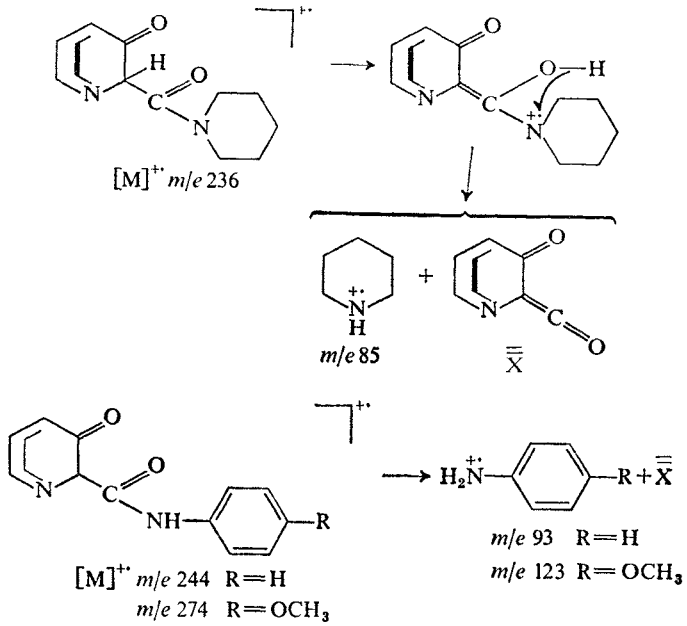


SCHEME 7

quinuclidone decay are still significant in the spectrum of XII, however, while at 12 eV, the [M — CO] ion is one of the intense peaks.

In the mass spectra of 3-quinuclidone-2-carboxylic acid anilides (XIII and XIV), the respective molecular ion peaks of aniline and *p*-anizidine generated analogously to the piperidine fragment of XII are the base peaks at 30 and 12 eV. Unlike the fragmentation of XII, however, in XIII and XIV the aromatic fragment peaks dominate.

Thus, analysis of the data allows us to assume that the quinuclidone and benzquinuclidone fragmentations occur through the open form of the molecular ion, the cleavage of a bridgehead bonding containing the carbonylic group with the subsequent elimination of carbon monoxide. Further bond cleavage in the [M — CO] ion involves formation of the characteristic fragments which determine the subsequent fragmentation steps. With substituents which stimulate more energy efficient competitive reactions (the aromatic fragment formation), a CO expulsion from quinuclidones could be essentially suppressed.



SCHEME 8

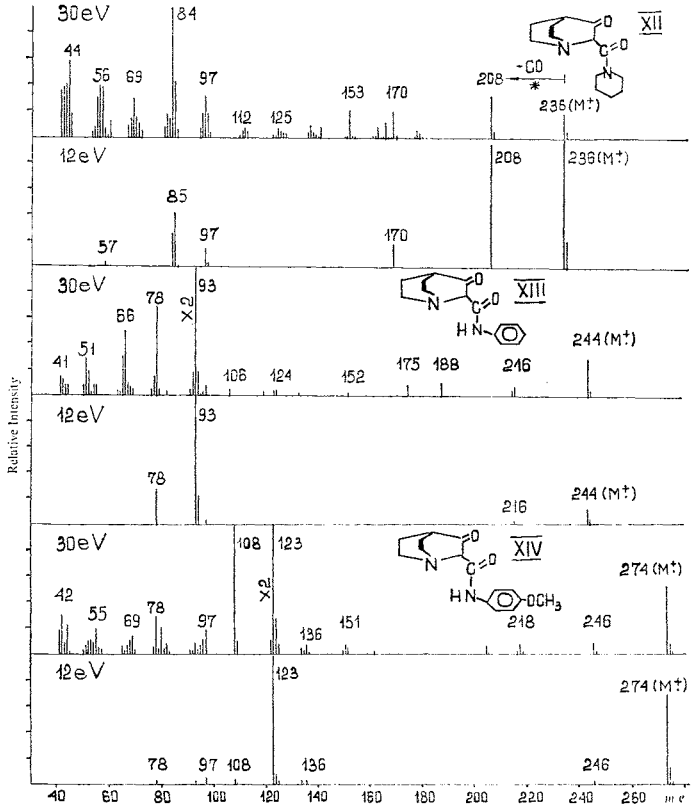


FIG. 8

EXPERIMENTAL

The mass spectra were measured with an MX1303 mass spectrometer at ionizing voltages 50, 30 and 12 eV. Before measuring the spectra, the compounds were purified by distillation or sublimation *in vacuo*. Isotopic labelling in I and II was introduced by refluxing the compounds with H_2O^{18} + 5% KOH. The compounds I and II deuterated at C_2 were prepared by refluxing with D_2O + 5% KOH for 1 hr, while C_6 deuteration was performed by refluxing with C_2H_5OD. For the ethyl group deuteration of VI, use was made of the following procedure: 0·23 g of 5-ketoquinuclidine-2-carboxylic acid hydrochloride, m.p. 297°C, whose substituent configuration corresponds to the quinine series,* was refluxed for 2·5 hrs with 2 ml of C_2D_5OH, under continuous bubbling of hydrogen chloride. The reaction mass was evaporated to dryness and treated with anhydrous benzene (two 2 ml portions) with its subsequent removal *in vacuo*, after which esterification with C_2D_5OH was repeated. The deuterated ketoester base was isolated as previously described.[8]

The syntheses of the following compounds have been reported elsewhere (I[5], II[6], IV[7], V[8], VI[8], X[9]).

Compound III was prepared from 1-ethoxycarbonylmethylen-4-ethoxycarbonyl-1,2,3,4-tetrahydroquinoline, b.p. 155 to 157° (0·8 mm), VII, VIII and IX from IV, for VII m.p. 95 to 96,5°, VIII, m.p. 88 to 89°, IX m.p. 75°, XI was obtained from 1-amino-1,2,3,4-tetrahydrocinchoninic acid, m.p. 186 to 188° (from ethylacetate); XII, XIII and XIV from IV, for XII b.p. 167 to 168° (0·6 mm), for XIII m.p. 229 to 230° (decomp.), for XIV m.p. 228° (decomp.).

Syntheses of compounds III, VII, VIII, IX, XIII and XIV will be reported in a separate communication.

REFERENCES

1. R. G. Kostyanovsky, *Tetrahedron* (1971) in press.
2. R. G. Kostyanovsky, E. E. Mikhlina, E. J. Levkeeva and L. N. Yakhontov, *Org. Mass Spectrom.* **3,** 1023 (1970).
3. E. E. Mikhlina, K. F. Turchin, V. Ya. Vorobjova, A. I. Ermakov, R. G. Kostyanovsky, Yu. N. Sheinker and L. N. Yakhontov, *Proc. Acad. Sci. USSR* **195,** 1347 (1970).
4. R. G. Kostyanovsky, Ch. Chafisov, *Proc. Acad. Sci. USSR* **198,** No. 2 (1971).
5. E. E. Mikhlina and M. V. Rubtsov, *J. Com. Chem. USSR* **29,** 118 (1959).
6. A. D. Yanina, E. E. Mikhlina, K. A. Zaitseva, M. D. Mashkovsky and L. N. Yakhontov, *Chim. Pharm. J. USSR* **8,** 7 (1969).
7. L. N. Yakhontov and M. V. Rubtsov, *J. Com. Chem. USSR* **29,** 2343 (1959).
8. L. N. Yakhontov, L. N. Mastafanova, M. V. Rubtsov, *J. Com. Chem. USSR* **30,** 519 (1960).
9. E. E. Mikhlina, N. A. Komarova and M. V. Rubtsov, *Chem. Heterocyclic Compounds USSR,* 259 (1966).
10. C. Djerassi in *Advances in Mass Spectrometry*, Vol. 4, E. Kendrick (Ed), London, Institute of Petroleum, 1969, pp. 199 to 209.
11. J. H. Beynon, *Mass-Spectrometry and its Applications to Organic Chemistry*, Elsevier, Amsterdam 1960.

* Separation of diastereomers and elucidation of steric configuration for this compound are to be reported.