TECHNICAL NOTE

Adam Vincze,[1] *Ph.D.; Leon Gefen;*[1] *Abraham Fisher,*[1] *Ph.D.; and Peter Bel,*[1] *D.Sc.*

Low Resolution Electron Impact Mass Spectra of Some Quinuclidine and *N*-Methylpiperidine Glycolates

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ABSTRACT: Quinuclidine and *N*-methylpiperidine glycolates of the general formula PhC(OH)(R)COOR', where Ph is phenyl, R is phenyl or alkyl, and R' the cyclic amine moiety, are known antidepressant and hallucinogenic compounds. Mass spectra of these are scarcely described in the literature and are the subject of this communication. Low resolution electron impact spectra were studied at 70 and low electron volts. The main fragmentation patterns and rearrangements, supported by study of deuterated analogs, are described. Determination of M^+ and two other characteristic ions gives a good knowledge of the compound at hand while recognition of a few more fragments is necessary for an exact knowledge of the specific structure. The spectra and availability of deuterated analogs may lead to development of specific, sensitive methods of analysis for these biologically active compounds.

KEY WORDS: toxicology, spectroscopic analysis, glycolates

The glycolates *N*-methylpiperidine and quinuclidine esters of phenylglycolic (mandelic) acid of the formula PhC(R)(OH)COOR' (where Ph is phenyl, R is phenyl, alkyl, or cycloalkyl, and R' is quinuclidyl-3,*N*-methylpiperidyl-4 or *N*-methylpiperidyl-3) produce a host of pharmacological effects that can be ascribed to both peripheral and central muscarinic receptor blockage [*1-3*]. They have been studied since the early 1950s for their antispasmodic [*4-5*], anticonvulsant [*6*], antidepressant [*7,8*], and antiparkinsonian [*9*] effects. Unfortunately, the central activity is associated with psychotomimetic effects [*10*]. Being psychotomimetric, they have drug abuse potential as hallucinogens and it has indeed been reported that members of the class have entered the street drug scene [*11*].

Dependable, rapid, and sensitive identification and quantitation are prerequisites for further study of pharmacokinetics and for combating drug abuse in both the forensic science and emergency toxicology aspects. Surprisingly, enough data concerning identification of glycolates are rather scarce and quantitation is virtually nonexistent. Only comparatively recently did four communications appear concerning the use of mass spectra of some

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[1]Head, Analytical Chemistry; chemical technician; biomedical research chemist; and mass spectrometrist; respectively, Israel Institute for Biological Research, Ness-Ziona, Israel.

glycolates [*11-14*]. Since apart from the toxicological and forensic science aspects there is also theoretical interest in fragmentation patterns, we chose electron impact ionization first.

Experimental Procedure

Spectra were recorded on a low-resolution double-focusing reversed-geometry mass spectrometer, a Varian MAT 112. For ionization, 70-eV, 1.5-mA or 20- to 25-eV, 300-μA currents were used. Introduction of sample was mostly through direct probe in disposable aluminum crucibles. Alternatively, gas chromatography/mass spectrometry was used. The mandelates usually chromatograph well on weakly polar silicon phases; however, that procedure will not be included in the present report.

All the glycolates used in this study are known compounds and were prepared according to accepted methods (Table 1).

Results and Discussion

The mass spectra of all compounds listed in Table 1 are to be found in Figs. 1 through 13 in form of bar plots, while the main fragmentations common to them all are depicted in Fig. 14.

All the spectra studied have some common features; individual members of the group, however, do have fragments characteristic to them that serve to identify them at a glance. All glycolates studied have molecular ions well discernible even at 70 eV. There is always a prominent ion, henceforth referred to as Ion *a*, the origin of which is the heterocyclic moiety and has the mass of ionized quinuclidine or *N*-methylpiperidine.

Another prominent ion is the phenyl-alkyl-carbinyl ion seemingly arising from fission of the C-C bond between the carbonyl and α-carbon atoms. This ion we shall refer to as Ion *b*.

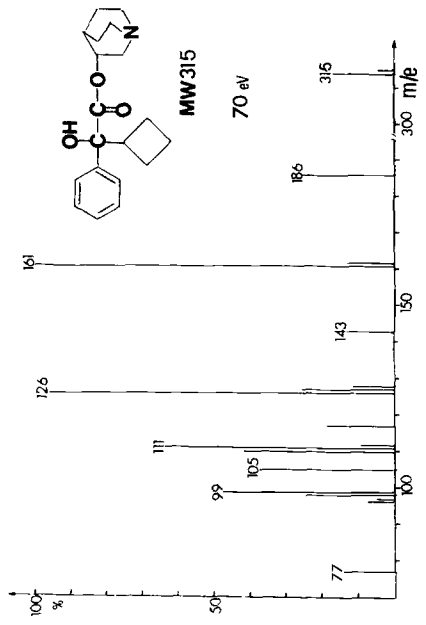
Since all compounds investigated have at least one α-phenyl group, abundant $[PhCO]^+$ and $[Ph]^+$ fragments are found. The first of these is in considerable abundance and sometimes is the base peak but, of course, it is of little value for identification within a group of glycolates. Knowledge of M^+, Ion *a*, and Ion *b* describes the molecule almost completely except for the position of the ester bond on the *N*-methylpiperidine.

A third ion, Ion *c*, has its origin most probably in fission of the C-0 linkage between carbonyl and the oxygen of the heterocyclic moiety yielding the configuration shown in Fig. 15. Proof for these fragmentations and rearrangements from metastable transitions is available in form of DADI (MIKE) spectra.

TABLE 1—*Glycolates used in this study.*[a]

Glycolate	R	R′	Reference
I	phenyl	quinuclidyl	*16*
II	cyclopentyl	quinuclidyl	*17*
III	cyclobutyl	quinuclidyl	*18*
IV	phenyl	*N*-methylpiperidyl-4	*19*
V	cyclopentyl	*N*-methylpiperidyl-4	*18, 20*
VI	cyclobutyl	*N*-methylpiperidyl-4	*21*
VII	isopropyl	*N*-methylpiperidyl-4	*22*
VIII	phenyl	*N*-methylpiperidyl-3	*23*
IX	cyclopentyl	*N*-methylpiperidyl-3	*23*
X	phenyl	3-deutero-quinuclidyl	...
XI	...	$Ph_2C(OD)COO$-quinuclidyl	...
XII	...	PhC(iPr)(OD)COO-*N*-methylpiperidyl-4	...
XIII	...	Ph_2CHCOO-quinuclidyl	*16*

[a]Where Ph = phenyl; D = deuterium; and iPr = isopropyl.



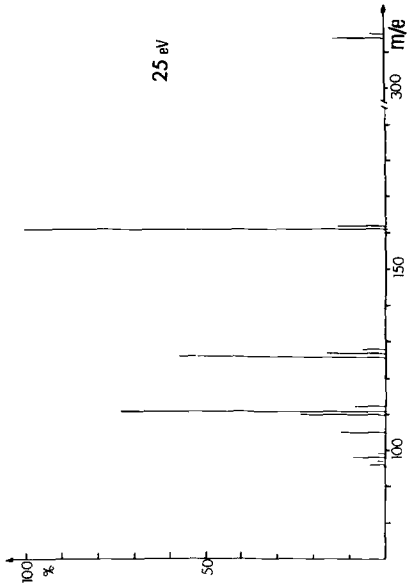
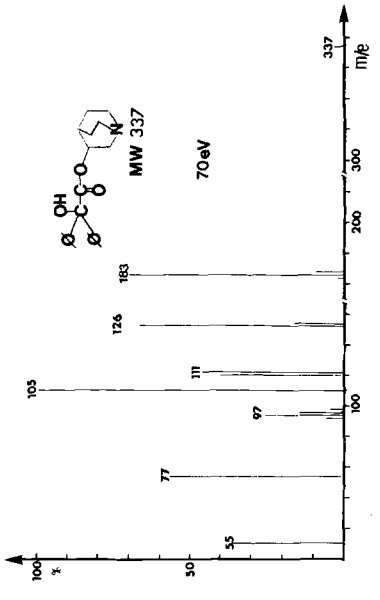


FIG. 2—*Mass spectra of Glycolate II.*



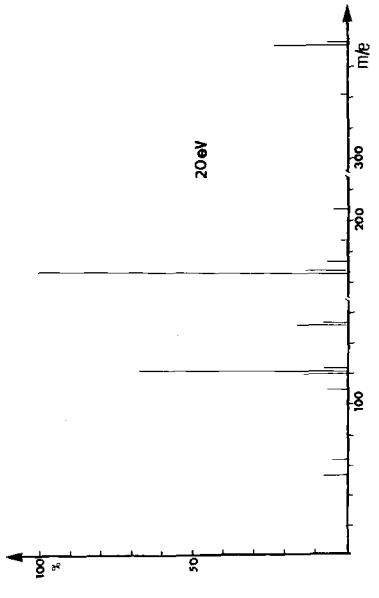


FIG. 1—*Mass spectra of Glycolate I.*

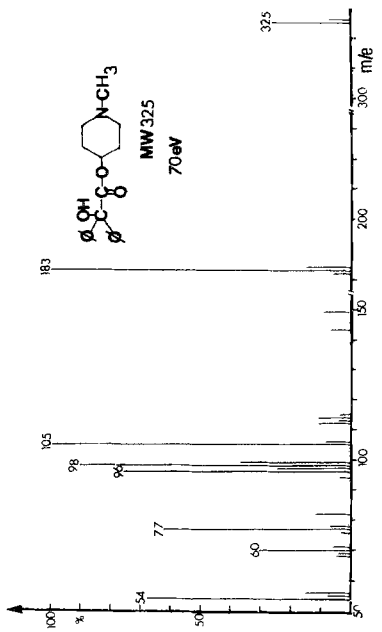


FIG. 4—*Mass spectra of Glycolate IV.*

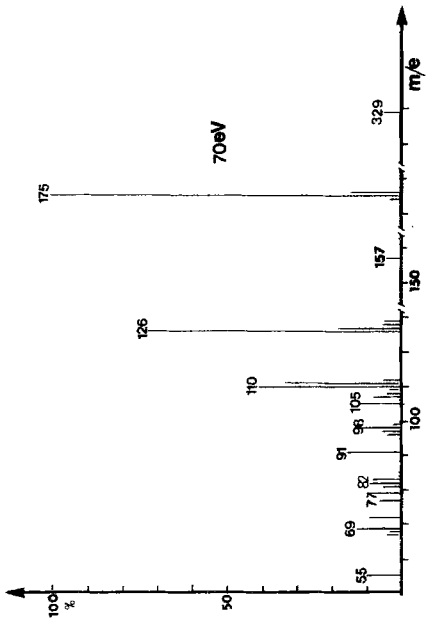


FIG. 3—*Mass spectra of Glycolate III.*

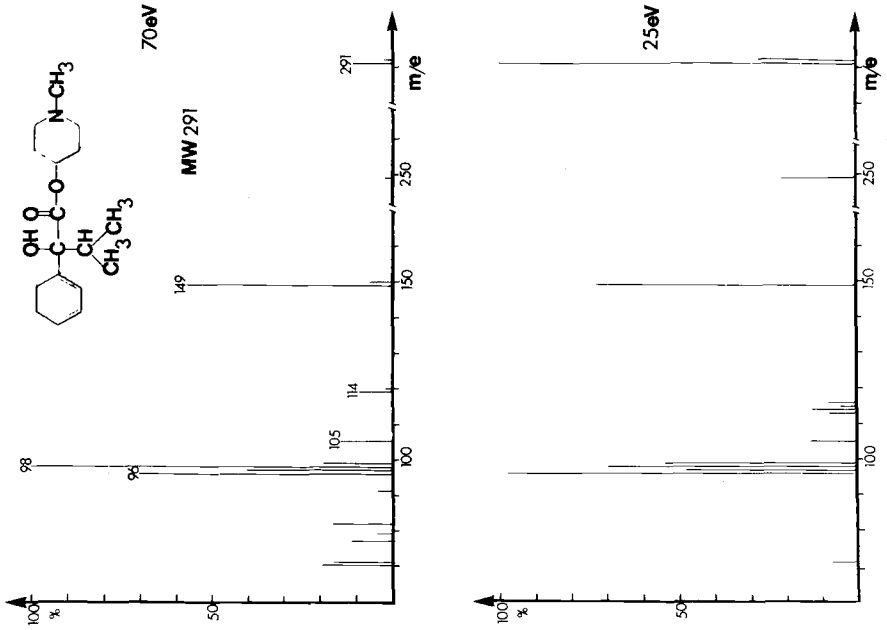


FIG. 5—*Mass spectra of Glycolate V.*

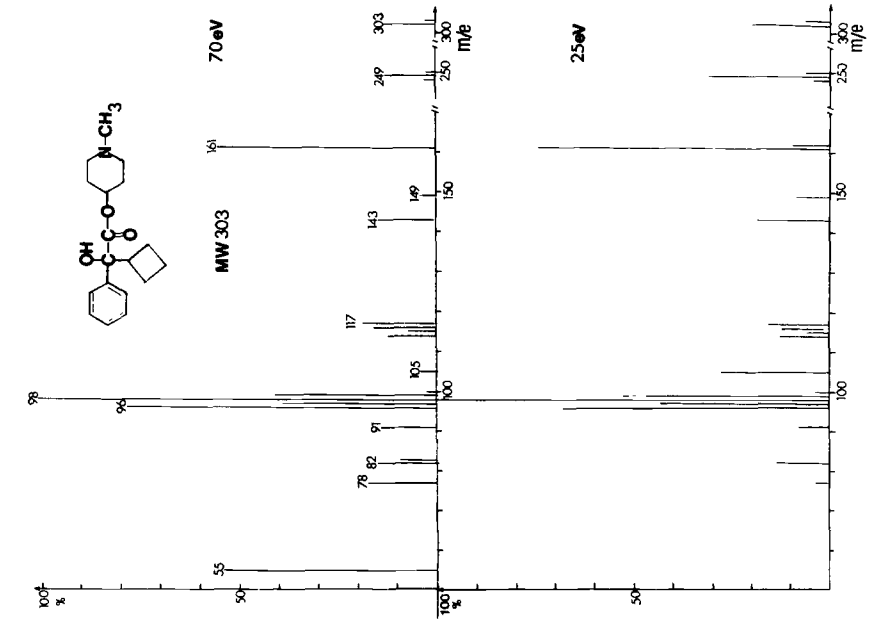


FIG. 6—*Mass spectra of Glycolate VI.*

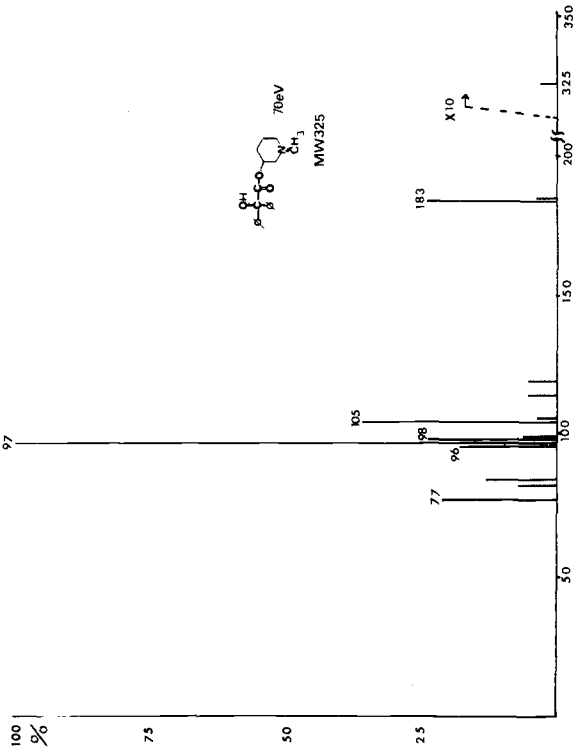


FIG. 8—*Mass spectrum of Glycolate VIII.*

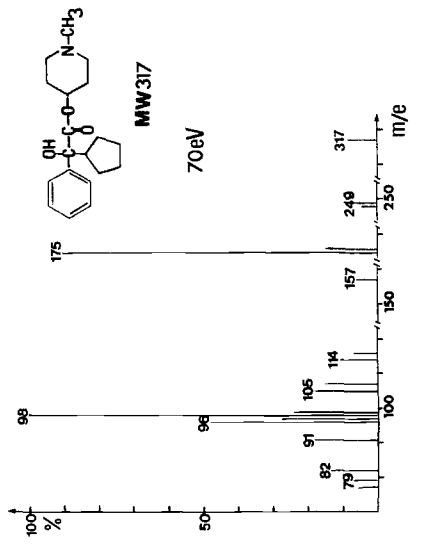
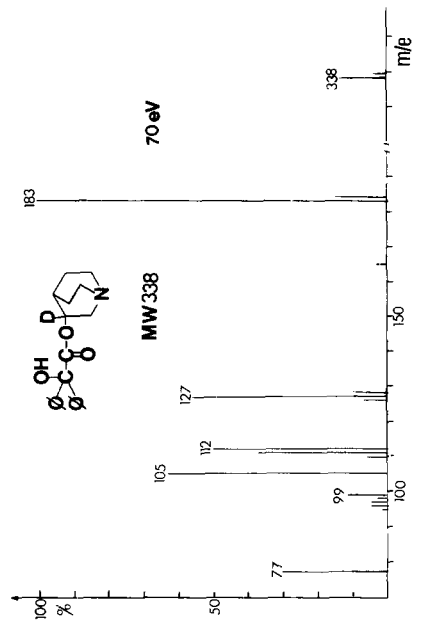


FIG. 7—*Mass spectra of Glycolate VII.*



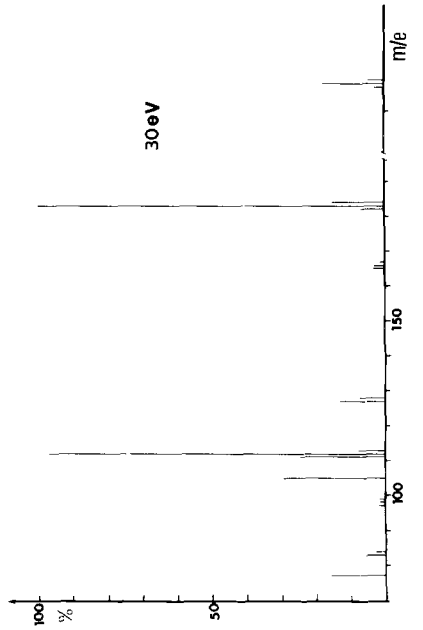
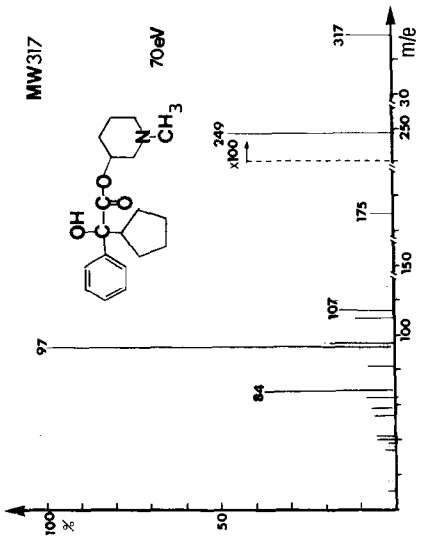


FIG. 10—*Mass spectra of Glycolate X.*



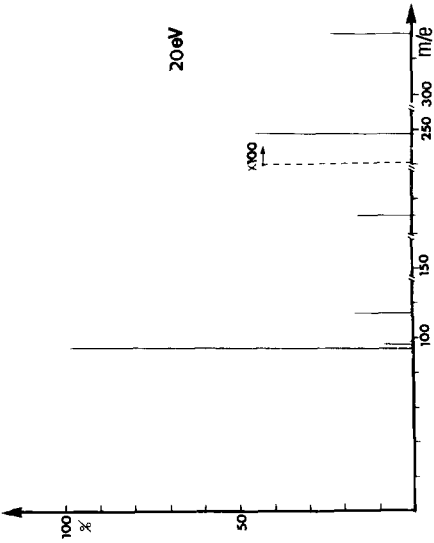


FIG. 9—*Mass spectra of Glycolate IX.*

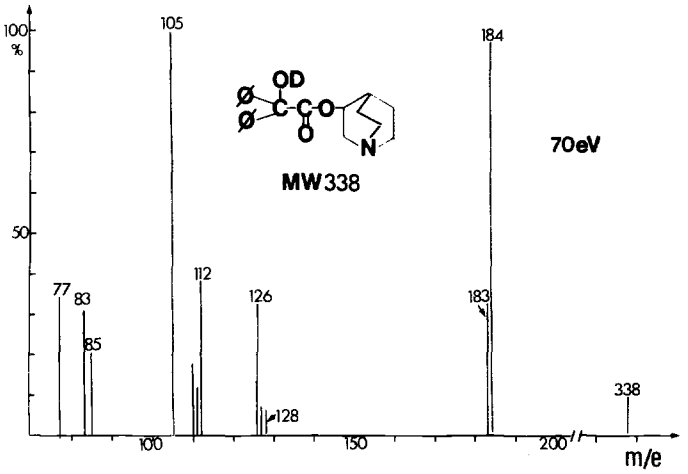


FIG. 11—*Mass spectrum of Glycolate XI.*

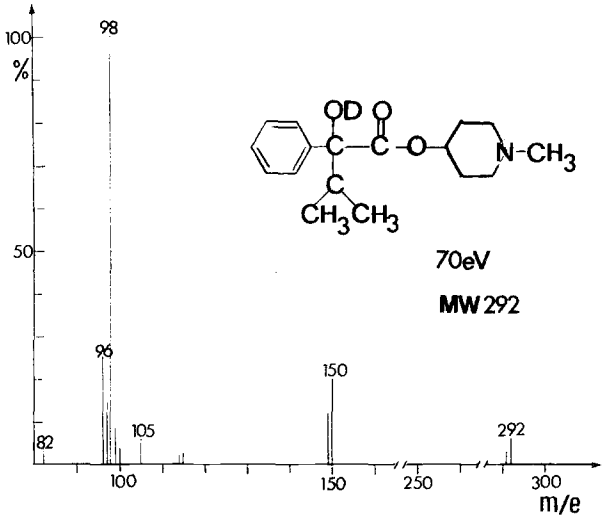


FIG. 12—*Mass spectrum of Glycolate XII.*

The mass spectrum of 3-quinuclidylbenzilate (Fig. 1) has a molecular ion, with a mass to charge ratio m/z of 337, of 10% relative abundance at 70 eV and about 20% at 20 eV (Fig. 1). The base peak in the 70-eV spectrum is $[PhCO]^+$ m/z 105, while Ion *b* is the next most prominent, reaching 70% relative intensity. In this instance it is $[Ph_2C = OH]^+$ m/z 183 and has also been observed by others [*11*] in several benzilates. Ion *a* in the mass spectrum of quinuclidylbenzilate is m/z 110 and has a relative intensity of 30%, while the $a+1$ ion m/z 111 is of 40% abundance in the 70-eV spectrum. A parallel is found in the case of Ion *c*, m/z 126 in benzilates, where m/z 127 is at least twice as abundant as the isotope peak resulting from ^{13}C alone. (No high resolution measurements were performed to distinguish between this isotope peak and $[C+H]^+$ rearrangement peaks.)

These are rearrangement ions, and some insight into their formation was gained by study of the hydroxyl deuterium exchanged molecule, as in Figs. 16 and 17, where the respective

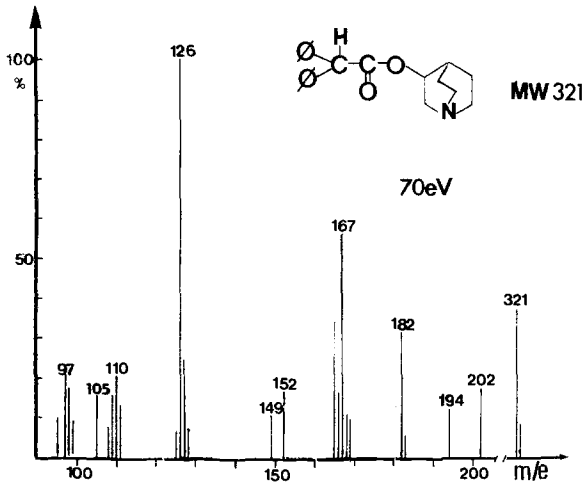


FIG. 13—*Mass spectrum of Glycolate XIII.*

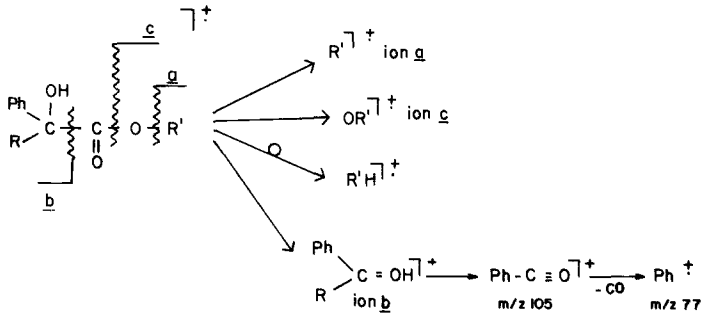


FIG. 14—*Main fragmentations common to Glycolates I through XIII.*

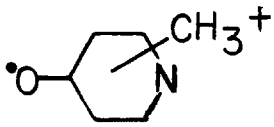


FIG. 15—*Configuration of Ion* c.

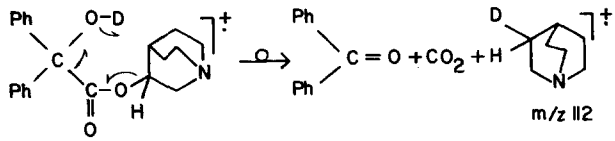


FIG. 16—*Hydroxyl deuterium exchanged molecule with ion at* m/z *112.*

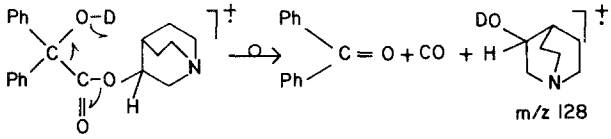


FIG. 17—*Hydroxyl deuterium exchanged molecule with ion at* m/z *128.*

ions appear at *m/z* 112 and 128. The first rearrangement, where the hydroxyl hydrogen is transferred to the heterocycle, is the favored one, and thus *m/z* 111 $(a+H)^+$ eventually becomes the most prominent of the whole spectrum at low ionization energy, which is to be expected of such rearrangements according to the Quasi-Equilibrium Theory [*15*]. No $a-1$ ion was found in analogy with the base peak of spectra described by Sullivan [*12*], where the molecular ion undergoes a McLafferty rearrangement with a transfer of a hydrogen atom in the opposite direction.

The most obvious differences between spectra of benzilates and those of phenylcycloalkyl glycolates of *N*-methylpiperidine, and especially between the latter and 3-quinuclidylbenzilate, are that *m/z* 105 is of comparatively low abundance (15%) and the base peak is *m/z* 98, the *N*-methylpiperidyl ion. Fragments *m/z* 97 and 96 ($a-1$ and $a-2$) arise from loss of one and two hydrogen atoms, respectively. These ions are present in all spectra of *N*-methylpiperidyl glycolates. Mechanisms for their formation were proposed by Petersen [*11*]. Hydrogen was transferred from the hydroxyl of the glycolic acid moiety to the piperidine, giving rise to an *m/z* 99 peak much larger than the ^{13}C isotope peak of *m/z* 98 (the latter should be only 6%). One finds *m/z* 100 in the deuterated compound. The mechanism we propose for this fragmentation is a rearrangement analogous to the one shown in Fig. 16.

It should be pointed out that although fragments in the *m/z* 98 region are found in quinuclidine derivatives as well, the grouping *m/z* 96 to 99 serves to identify an *N*-methylpiperidine derivative. Moreover, the particular pattern enables one to distinguish between three and four substituted *N*-methylpiperidines. Two weak, but not inconspicuous, fragments are *m/z* 248 and *m/z* 249. These are easy to discern since they are in an empty region of the spectrum. The fragmentations leading to these ions are loss of the α-alkyl substituent from the molecular ion and loss of cycloalkenyl with concomitant transfer of a hydrogen atom by a McLafferty-type rearrangement, respectively. This has been described for some other glycolates [*11*]. It is noteworthy that this latter fragmentation is peculiar to α-phenyl, α-cycloalkyl glycolates only.

Conclusions

We believe that the patterns obtained by electron impact ionization enable one to recognize glycolate esters of quinuclidine and *N*-methylpiperidine and to classify them rather accurately by use of the patterns and correlations discussed. This should be a welcome step towards the analysis of these compounds for both biomedical and forensic science purposes.

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Address requests for reprints or additional information to
Adam Vincze
Israel Institute for Biological Research
P.O. Box 19
Ness-Ziona 70400, Israel