Mass Spectrometry of Onium Compounds

Part III.[1] Studies of Pyridinium-3-oxides

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Simple pyridinium-3-oxides in the mass spectrometer on direct insertion are readily evaporated without any chemical rearrangement. α-3-Hydroxypyridinium-carboxylic acids are *O*-trans-alkylated, decarboxylated and rearranged to aziridopyridines or 2H-azepines before evaporation. A desoxy analogue was partly decarboxylated and rearranged as above, but the major pathway was de-alkylation.
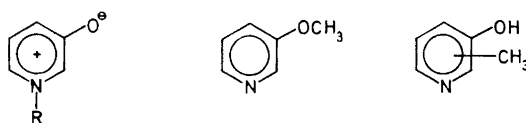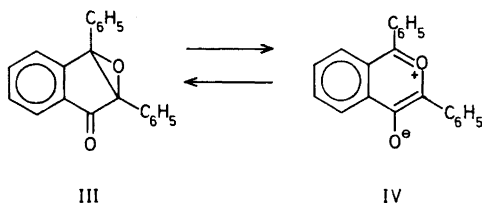
The electron induced fragmentations are discussed and rationalized in terms of the covalent gaseous isomers of the original betaines.

Mass spectrometry of the three isomeric trimethylanilinium-oxides[2] shows that the *m*- and *p*-isomers undergo intermolecular trans-*O*-alkylation to the covalent ether isomers before evaporation in the mass spectrometer. For the *o*-isomer, the experimental evidence favours direct evaporation of the major portion of the molecules without any prior structural changes, and therefore the molecule must have some means for internal charge compensation. In this report we have extended our studies to betaines, which in theory can become covalent through valence isomerism, and in a such way escape the intermolecular electrostatic attraction in the solid state. The models used are *N*-alkyl pyridinium-3-oxides, derived from 3-hydroxypyridines by *N*-alkylation.[3] Despite the fact that these compounds have salt-like character and therefore should not be volatile, their MS spectra recorded with the ion source at about 220° show a strong signal corresponding to the molecular weight. The volatility may be explained by a covalent structure. Also in the gas phase at 10^{-6} torr, a covalent structure would be energetically favoured compared to a salt-like structure, since there are no other molecules available for solvation and charge dispersion. On the other hand, in solution and in the solid state, the properties of these molecules are best explained by a zwitterionic structure. For the simple *N*-alkyl derivatives, the following valence isomerism is possible:

I   II
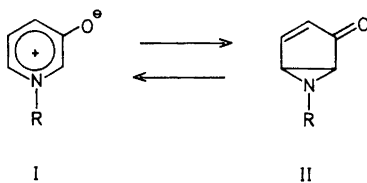
Scheme A.

Mason [4] has investigated such an equilibrium by UV determinations. He states that the "*meta*-quinoid" structure $(R = CH_3)$ cannot predominate in the ground state in view of its salt like character, but the first excited state should be less polar than the ground state. The analogous homocyclic bi-cyclo[3.‌1.0]hexenones on irradiations give aromatic phenols corresponding to the reverse isomerisation.[5] Directly analogous to the pyridinium case is the thermochroism shown by benzpyrylium oxide, which exists in equilibrium with indenone oxide, the equilibrium position being temperature dependent.[6] The equilibrium is also affected by irradiation, and the corresponding 2,4,6-triphenylpyrylium oxide behaves in the same way.[7] The fact that these transitions lie well within the readily accessible thermal region for pyrylium oxides

III   IV

I a) R = CH₃   V   VI

b) R = CH₂C₆H₅

c) R = $\overset{CH_3}{\underset{}{C}}$HCO₂C₂H₅

d) R = $\overset{CH_3}{\underset{}{C}}HON\overset{CH_3}{\underset{CH_3}{}}$

Scheme B.

suggests a similar energy requirement for such transformations in the pyridinium oxide series. This does not exclude the possibility, however, that the betaines, in the absence of a chemical rearrangement, may evaporate in a mesoionic state with a high degree of charge neutralisation through delocalisation of the negative charge of the oxy-group into the azinium ring. No decision between these possibilities is made in the present work. For illustrative purposes, however, the volatile species are drawn in the cyclopentenone form.

The compounds were introduced directly into the ionization chamber. Both betaines and their respective salts with strong acids and hydroxides were studied. Dealkylation is the normal pyrolytic pathway for N-quaternary salts containing a good nucleophilic anion.[2] For the methiodide (Ia) dealkylation accounts for less than 50 % of the volatile product, for the hydrobromide
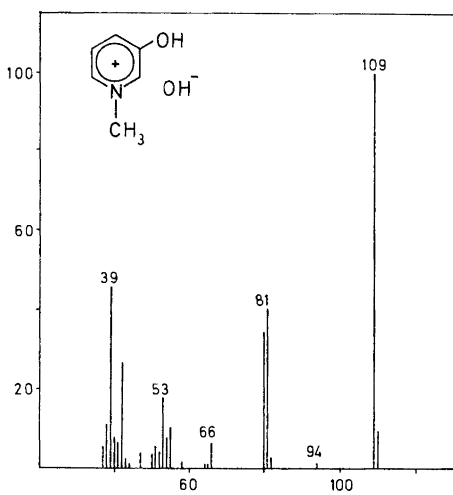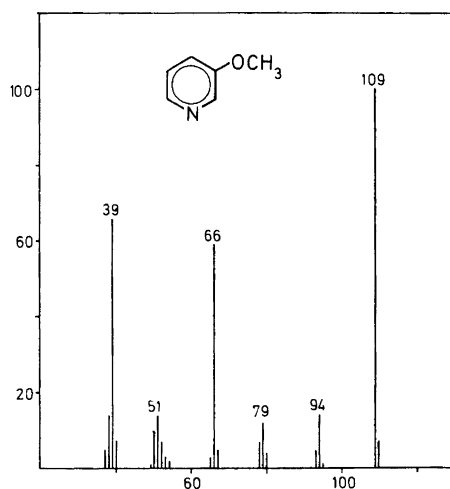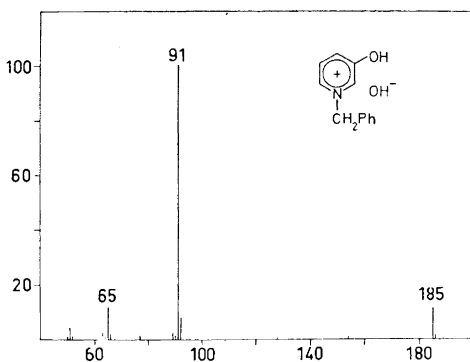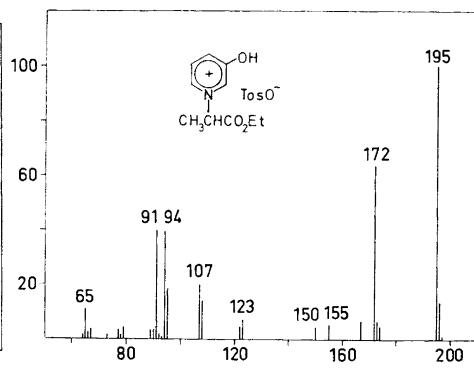

Fig. 1.

Fig. 2.

Fig. 3.

Fig. 4.

of the benzyl derivative (Ib), debenzylation is a minor pathway, for the hydro-bromide of the amide (Id), dealkylation is hardly seen (Fig. 5), and no dealkyla-tion was observed in the tosyl salt of the ester (Ic). Instead, the anion abstracts the proton from the hydroxyl group whereby the zwitterion is liberated and evaporated (Fig. 4). In the mass spectrum, the base peak corresponds to the mass of the zwitterion. The benzyl derivative (Ib) constitutes an exception in this respect due to the more favourable tropylium ion formation (Fig. 3).
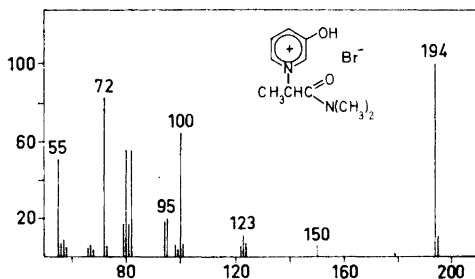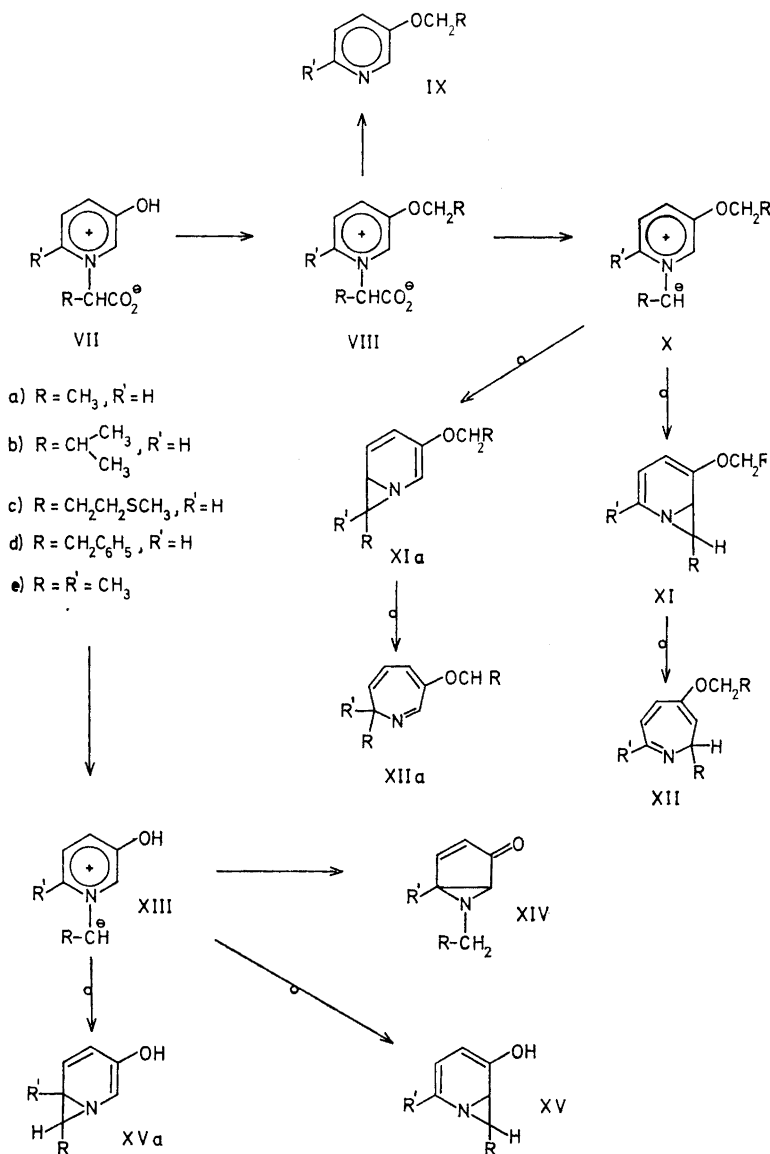

Fig. 5.

The crystal form of the N-methyl (Ia) and N-benzyl (Ib) zwitterions were monohydrated and the water could not easily be removed. In the mass spec-trometer, however, the water molecule is assumed lost, so that the pyridinium derivatives behave like true zwitterions.

Besides an isomeric "*meta*-quinoid" structure, there are other ways by which such betaines could become covalent. Thus transalkylation from the quaternary nitrogen to the phenolic oxygen would seem likely, since a similar mechanism is in operation for anilinium oxides.[2] Therefore the spectrum of 3-methoxypyridine was recorded (Fig. 2). Both analogues have the molecular ion as base peak (m/e 109). While the N-methyl derivative loses CO to give m/e *81*, however, this fragment is absent in the spectrum of the methoxy analogue. The latter loses instead a methyl radical (m/e 94) and formaldehyde (m/e 79).

Migration of the methyl group to the C-2 or C-6 carbon in the pyridine nucleus would also give a covalent molecule. The spectra of 3-hydroxy-6-methylpyridine and 3-hydroxy-2-methylpyridine, however, are characterized [8] by expulsion of a hydrogen radical (M − 1), a fragment not present in the case of the N-methyl derivative. These possibilities are therefore excluded.

The samples were then introduced into the instrument *via* the indirect inlet system, where the pressure requirement is 10^{-2} torr as compared to a pressure of 10^{-6} in the ionization chamber. The higher pressure requirement results in a temperature increase to about 300°, to effect a sufficiently high vapour pressure of the sample in the ionization chamber. The salts now showed a very marked dealkylation tendency. The zwitterions were also largely dealkylated in contrast to the behaviour by direct insertion. In general, the strongest signal from the pyridinium moiety is due to 3-hydroxypyridine (m/e 95) formed by pyrolysis. In the case of the N-methyl derivative (Ia), the

signal intensity from the species corresponding to the molecular weight was about two third of that from 3-hydroxypyridine. Both the m/e 81 (M − CO) and the m/e 79 (M − CH$_2$O) peaks, characteristic for the N-methyl and the O-methyl isomers, respectively, are present, but the intensity of the former is low. Because of the higher temperature required, sufficient energy is supplied

a) $R = CH_3, R' = H$

b) $R = CH\begin{smallmatrix}CH_3\\CH_3\end{smallmatrix}, R' = H$

c) $R = CH_2CH_2SCH_3, R' = H$

d) $R = CH_2C_6H_5, R' = H$

e) $R = R' = CH_3$

Scheme U.

to the molecules for transalkylation to occur. Also present in the spectrum is a peak at (M−H) with intensity about 10 % of the base peak. This could well arise from 2- or 6-methyl-3-hydroxypyridine, formed by a pyrolytic rearrangement of the methyl group.

The benzyl derivative (Ib) behaves as above. In addition, when the temperature was raised gradually to 320° in the indirect insertion system to attain the desired sample vapour pressure, it was found that at about 300° a new peak at m/e 275 started to appear. This peak is probably caused by an N,O-dibenzylated pyrolysis product, which loses a proton followed by some electronic rearrangement to a neutral and volatile molecule. The signal intensity, however, is only about 3−4 %. The tendency for transalkylation, as discussed below, is much more pronounced for carboxylic acid derivatives, and this reaction w ll be discussed more fully for such derivatives.

On direct insertion into the ionization chamber, the carboxylic acids were found to behave differently from the N-alkyl derivatives discussed above. These acids are readily decarboxylated due to the activation by the quaternary nitrogen. The apparent molecular ion is therefore at $M−44$, but in addition, the spectra (Figs. 6−10) exhibit mass fragments at higher mass units. The
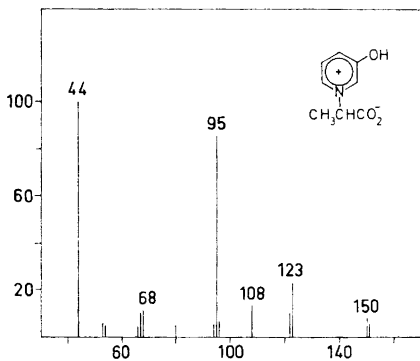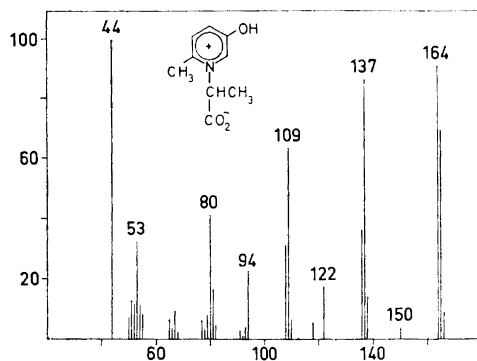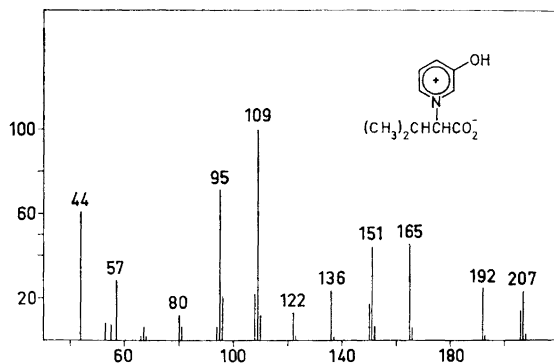

Fig. 6.

Fig. 7.

Fig. 8.

M−44 peak can arise either by direct evaporation of the decarboxylated material *via* the cyclopentenone (XIV), as discussed above, or be a fragment from the transalkylated *N*-quaternary derivative (X), or due to the ether
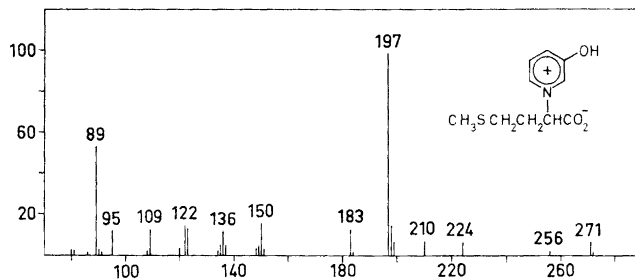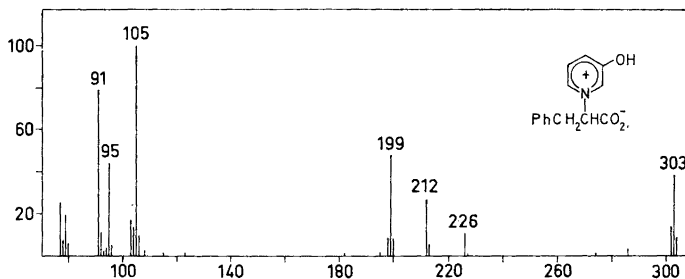

Fig. 9.

Fig. 10.

(1X). The occurrence of transalkylation was proved by recording the mass spectra of mixtures of two different zwitterions. A homogeneous mixture was prepared by evaporation of an aqueous solution of the two zwitterions in the mass spectrometer. The spectra showed the expected three transalkylated "molecular ions", corresponding to X. In two of the molecular species, the alkyl groups were the same, respectively, while in the third species they were different. The third species, of course, consists of two structural isomers with positionally interchanged alkyl groups.

The question now arises as to how the transalkylated and decarboxylated zwitterion (X) is volatilized. A valence isomer as discussed above is no longer applicable. The most likely explanation is a nucleophilic intramolecular attack by the carbanion carbon in the side-chain onto the electropositive α-carbon in the pyridinium ring with the formation of a condenced azirido-pyridine ring system. The latter can well evaporate as such or undergo a further electronic shift to a 2H-azepine. At least after electron impact we will assume a 2H-azepine structure, since such a structure fits well the observed fragmentations. The suggested isomerisation is analogous to the well established photoisomerisation of pyridine *N*-oxides [9] and the photochemical isomerisation of 1-iminopyridinium ylides, which yield 1,2-oxazepines and 1H-1,2-diazepines, respectively.[9,10]

The decarboxylated acid (XIII) can be transformed both to azirido pyridines (XV, XVa) or, like the simple N-alkyl pyridinium oxides, to a cyclopentenone structure (XIV) before evaporation. There is no evidence to decide between these possibilities. Similarly, pyridinium dicyanomethylide gives the azirido-pyridine ring system, when irradiated in benzene.[11]

The carbanion carbon (X) can attack either of the two α-carbons in the pyridinium ring and probably does so. The relative amounts of the isomers formed will depend on steric and electronic factors. Both the 2H-azepines or its precursors on electron impact should fragment very much in the same way. For convenience, therefore, we shall use the isomer XII and its precursor (XI) in our formulation after electron impact, implying also the isomers XIa and XIIa under these formulae.

Strong acid salts of the carboxy-pyridinium derivatives (VII) did not show any tendency to N-dealkylation. The zwitterions and the strong acids were volatilized separately.

The zwitterions on indirect introduction were largely pyrolyzed to 3-hydroxypyridine.

In the pyridinium-3-desoxy derivative (XVI) below (Fig. 11), where O-transalkylation or valence isomerism are excluded, the tosylate anion is
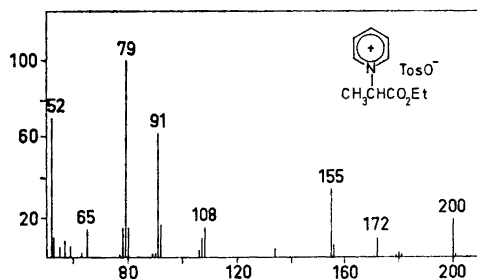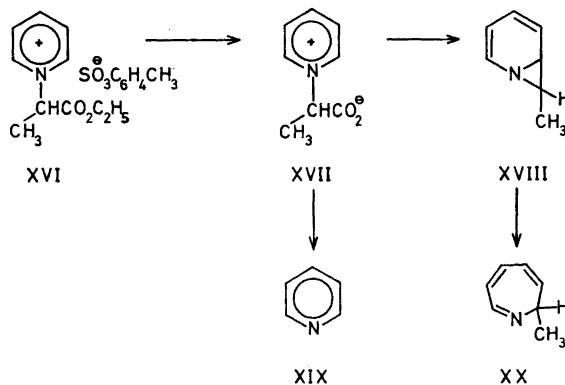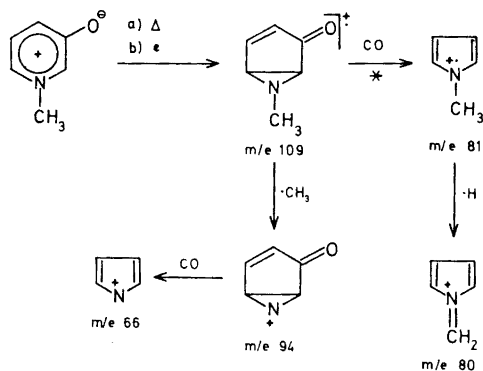

Fig. 11.

Scheme D.

alkylated to ethyl tosylate (*m/e* 200). The pyridinium carboxylate (XVII) formed in this reaction suffers decarboxylation. The resulting zwitterion is either isomerized to (XVIII) or broken further down to pyridine and ethylene.

The major fragmentation pathways after electron impact for the *N*-methyl-pyridinium oxide are as shown (Fig. 1):

Scheme 1.

The molecular ion gives by far the strongest peak in the spectrum after direct introduction of the sample. Loss of CO from the molecular ion is the major pathway (*m/e* 81). The latter can lose a hydrogen to give *m/e* 80. The molecular ion can also lose a methyl group to give *m/e* 94, but this only amounts to about 1 % of the base peak. Cleavage of the C−N bond becomes much more important for larger *N*-substituents. Another important pathway for larger *N*-substituents (Figs. 4 and 5) is a rearrangement process with transfer of hydrogen to the annular nitrogen (*m/e* 95) and expulsion of the side-chain as an olefin. This process does not occur in the case of the *N*-methyl derivative, nor in the case of the *N*-benzyl derivative (see below), so that the hydrogen in that process probably comes from a carbon further away from the nitrogen, presumably a β- or γ-hydrogen.

The M − 15 fragment (*m/e* 94) can go on to lose CO (*m/e* 66). Further fragmentations of these major intermediates lead to small fragments typical for aromatic structures.

The hydroiodide gives the same spectrum as the zwitterion, but super-imposed are the spectra of dealkylated hydroxypyridine (*m/e* 95) and methyl iodide formed (*m/e* 142), as well as iodine (*m/e* 127) and HI (*m/e* 128).

3-Methoxypyridine (Fig. 2) fragments differently from the *N*-methyl analogue. The molecular ion (*m/e* 109) is again the base peak. While the M − 15 peak in anisole only amounts to 1 − 2 % of the height of the base peak, the intensity of the M − 15 fragment (*m/e* 94) in this case is about 20 %. As in the case of anisole, the molecular ion also can lose formaldehyde, to give an ion with mass *m/e* 79 (M − 30). Both the M − 15 and M − 30 ions dissociate further with loss of CO, to give the ions *m/e* 66 and *m/e* 51, respectively.

In the spectrum of the N-benzyl derivative (Fig. 3), after direct introduction of the sample, the base peak is at m/e 91. This peak is due to the tropylium ion, arising by cleavage of the N-benzyl bond. No other fragment has higher intensity than $10-15$ %. The molecular ion at m/e 185 lies in this intensity region. The hydrobromide gave the same spectrum apart from the superimposed spectrum of 3-hydroxypyridine (m/e 95) and of benzyl-bromide (m/e 170, 172).

Indirect insertion leads largely to pyrolysis product. The base peak in the spectrum is due to 3-hydroxypyridine (m/e 95). The latter is largely a pyrolysis product. The transalkylated product is seen at m/e 275. The fragmentation of such structures is more fully discussed under pyridinium acids (see below). It should be pointed out, however, that the m/e 275 ion can lose the phenyl group to attain an azatropylium structure m/e 198 (Scheme 2). The expulsion of a hydrogen is less important than in cases discussed below. The m/e 275 is O-debenzylated, where the charge may reside on the benzyl fragment (m/e 91) or on the heterocyclic fragment (m/e 184). This transition, however, only accounts for part of the signal intensity at m/e 184. A strong metastable peak
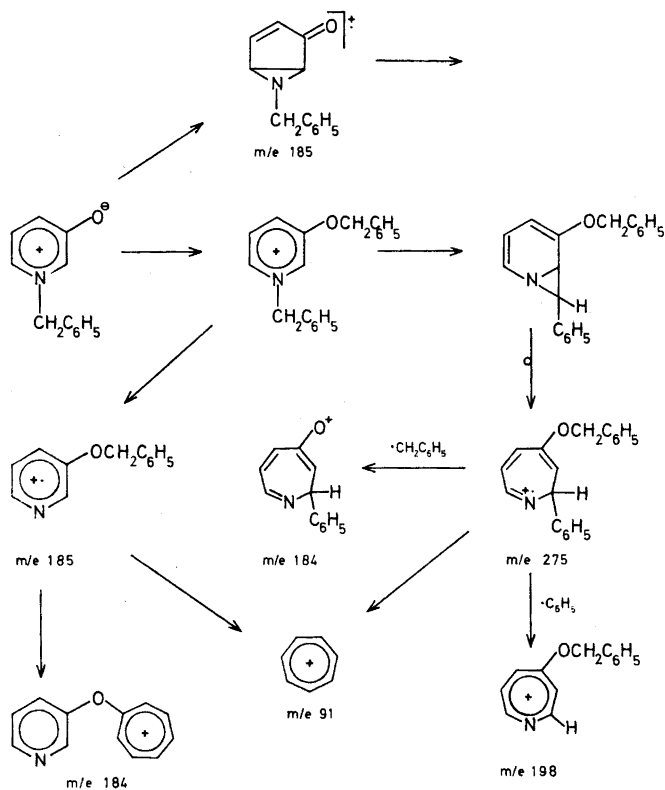
Scheme 2.

corresponds to the m/e 185→m/e 184 transition. The ions giving rise to the m/e 185 signal can only partially arise by direct evaporation of N-benzyl pyridinium-oxide, since this does not give the $M-1$ fragment as discussed above. The most plausible explanation seems to be an O-benzylation-N-debenzylation process to the simple benzylether (m/e 185), which, besides the tropylium ion (m/e 91), also could give rise to the observed $M-1$ peak as indicated.

As discussed above, the α-pyridinium carboxylic acids are decarboxylated and partly transalkylated before evaporation (Figs. 6 – 10).
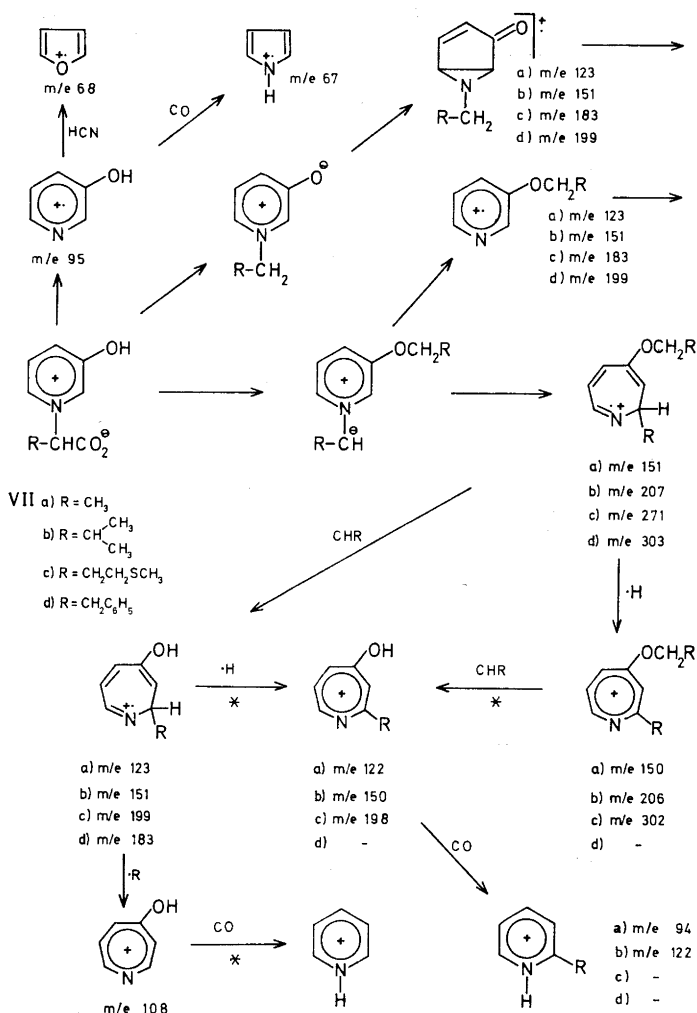
Scheme 3.

The resultant *O*-alkylated 2H-azepine or its azirido-pyridine precursor can lose a hydrogen to form an azatropylium structure. That a hydrogen and not the more stable R radical should be expelled seems rather surprising. Next follows McLafferty rearrangement with expulsion of the *O*-alkyl group as olefin and formation of a hydroxytropylium structure. The opposite sequence order also leads to the same tropylium ion. The M − 44 peak can arise in three ways. Decarboxylation of the acid and evaporation as the covalent α,β-unsaturated ketone (XIV) or the azirido-pyridine (XV) leads to an ion with this mass number. Secondly, the transalkylated product can suffer pyrolytic *N*-dealkylation with formation of the 3-pyridyl ether (IX). Finally, the ion can arise from the transalkylated 2H-azepine (XII) by electron induced McLafferty rearrangement and expulsion of the *O*-alkyl group as olefin. The relative contribution to the signal at this mass number is difficult to assess.

The hydroxy-azepine can lose either hydrogen or the R-radical to arrive at an azatropylium structure in contrast to the behaviour of the corresponding *O*-alkyl derivative, which only would expel a hydrogen and not the R-radical. Thus loss of the R-radical gives the *m/e* 108 ion which further can lose CO to *m/e* 80. The latter ion corresponds to protonated pyridine. The tendency to lose CO from the corresponding R-substituted azatropylium ion seems much less. The 6-methyl homologue (VIIe) fragments very much like VIIa, but with some relative intensity differences (Fig. 7).

Scheme 4.
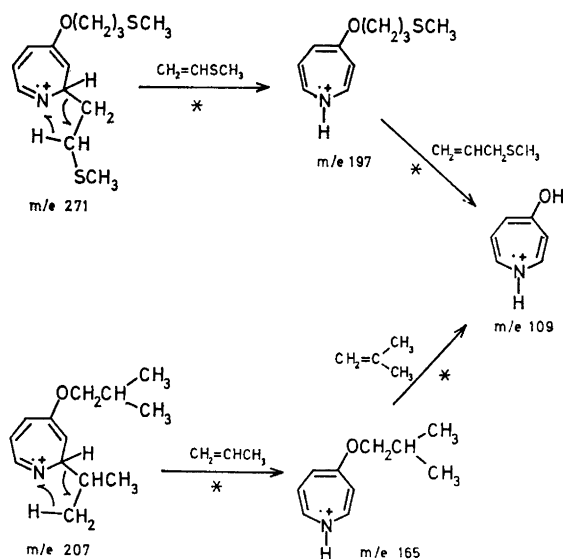
The methionine derivative (Fig. 9) does not show any tendency to attain an azatropylium structure by expulsion of hydrogen or R-radicals. Other competing processes are energetically favoured. The base peak in the spectrum

is at m/e 197. This fragment arises by a proton transfer, presumably from the β-position in the side-chain, to the annular nitrogen with expulsion of the side-chain as an olefin. This is followed by a McLafferty expulsion of the O-alkyl group as olefin (RCH), to give the ion m/e 109. A metastable peak confirms this transition. The loss of the RCH olefin verifies that the initial fragmentation occurred in the side-chain next to the nitrogen. The valine analogue (Fig. 8) is another example in our series with an aliphatic β-hydrogen. The same type of fragmentation is observed for the valine derivative, but is of less importance than in the methionine case.

The sulphur derivative can arrive at an azatropylium structure by a hydrogen shift, coupled with fragmentation of the side-chain.
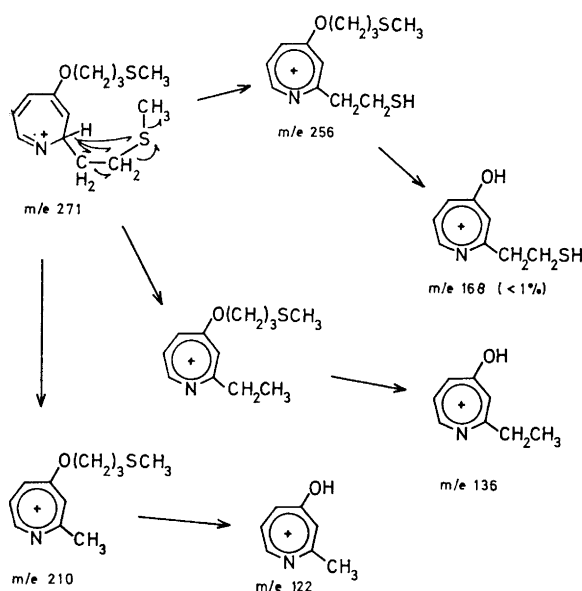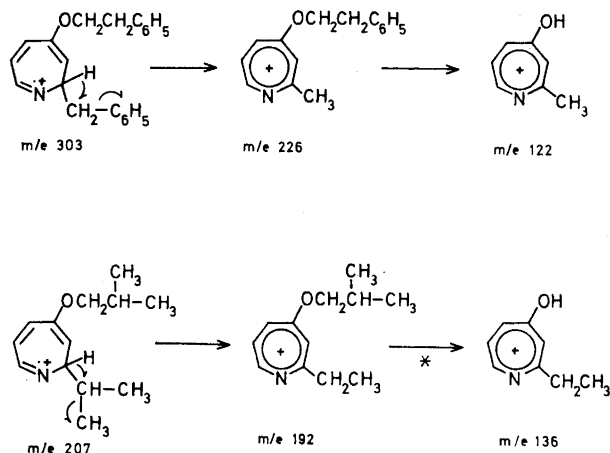

Scheme 5.

Again the McLafferty rearrangements to the corresponding hydroxy derivatives (m/e 122, 136, and 168) confirm the initial fragmentation positions.

The phenyl derivative (Fig. 10) is another example where a good leaving group is attached to the α-carbon of the side-chain. This is shown by the high intensity of the m/e 226 ion, formed by phenyl group expulsion. Similarly, the valine derivative (Fig. 8) loses a methyl group by this route (m/e 192).

In general, a hydrogen radical could also be expelled from a side-chain carbon in the same way as the radicals above. This would not be apparent in the spectrum, however, without appropriate labelling, since the mass of the ion formed is the same as that formed by direct expulsion of hydrogen from the ring.
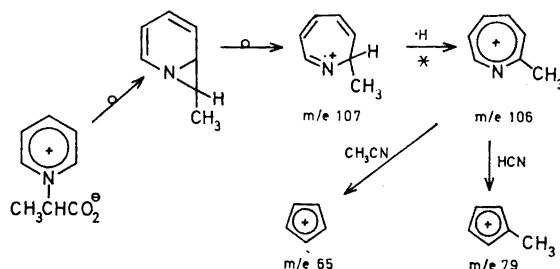
Scheme 6.

In addition to the discussed fragmentation, *O*-alkyl ethers suffer cleavage of the C−O linkage with charge retention on the alkyl group, and this gives rise to the respective ions at m/e 29 (a), m/e 57 (b), m/e 89 (c), m/e 105 (d).

The 2H-azepine from the phenyl derivative can lose the benzyl radical to arrive at an azatropylium structure as discussed above. But on bond cleavage, the charge can equally well reside on the benzyl part due to the stability of the tropylium ion formed (m/e 91). In the other examples above, the charge is largely retained by the hetero-aromatic moiety.

The unsubstituted α-pyridiniumpropionic acid derivative (Fig. 11) could be expected to behave similarly to the pyrolytically formed transalkylated products discussed above. Pyrolysis of the tosyl salt of the ethyl ester, after direct insertion into the ionization chamber, liberates the pyridinium acid with formation of ethyl tosylate by a transesterification process. The spectrum is somewhat complicated by the strong signals from ethyl tosylate (m/e 200) and its fragmentation products. A strong metastable peak shows loss of ethylene from the ester with formation of tosyl acid (m/e 172). The most important fragments from this acid are at m/e 108 ($-SO_2$), at m/e 107 ($-SO_2-H$), at m/e 79 ($-SO_2-H-CO$), at m/e 155 ($-OH$), at m/e 92 ($-SO_3$), and at m/e 91 ($-OH-SO_2$ or SO_3-H).

The pyridinium acid, liberated in the transesterification, is decarboxylated and to a large extent pyrolyzed to pyridine. Thus the base peak in the spectrum is that of pyridine (m/e 79), which is the major contributor to this peak. The pyridine fragment C_4H_4 (m/e 52) is the second most intense peak in the spectrum. Part of the decarboxylated material, however, gives rise to a signal at m/e 107, corresponding to the formation of a 2H-azepine or its azirido-pyridine precursor. The m/e 107 structur can attain a tropylium-like structure by expulsion

of hydrogen (m/e 106), but there was no metastable peak for the expulsion of a methyl group (m/e 92) in agreement with the findings for the O-alkyl-2H-azepines discussed above. The 2-methyl-azatropylium ion can further lose HCN (m/e 79) or CH_3CN (m/e 65). The latter can also arise from azatropylium by HCN expulsion.
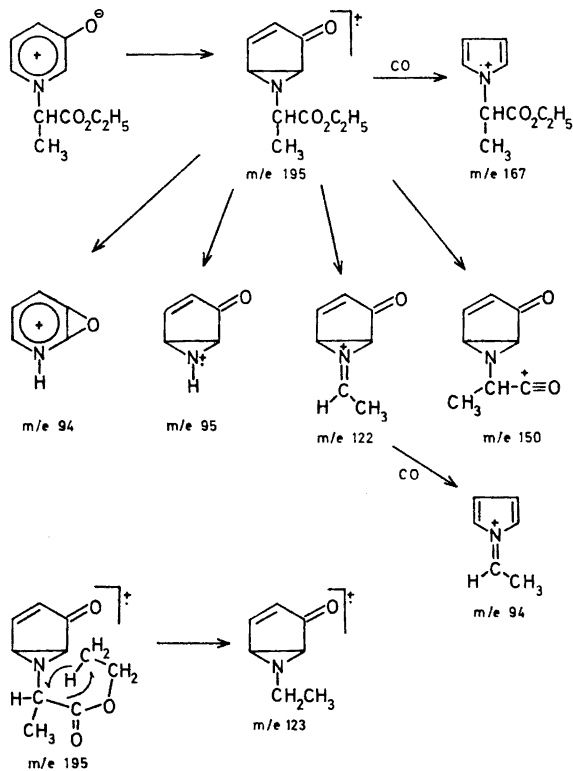

Scheme 7.

No transalkylation to the pyridyl oxygen was seen on direct insertion of the tosylate of the pyridinium ethyl ester (Ic). The ester therefore behaves very much like the simple N-alkyl pyridinium oxides, previously discussed. Nor does any transesterification to ethyl tosylate take place, as was found for the 3-desoxy analogue discussed above. The sulphonic acid is evaporated as such and complicates the spectrum somewhat by its superimposed fragmentation pattern. The base peak in the spectrum, however, is that of the ester zwitterion. The direct evaporation through a covalent isomer such as a cyclopentenone structure is therefore favoured as compared to a transalkylation process. The corresponding 2H-azepine structures could not expel the whole N-propionyl side-chain in one step (m/e 94), and must therefore be excluded, unless both covalent forms are present (m/e 94).

The major fragments arise by loss of CO (m/e 167) and by the expected fragmentation pattern of the N-side-chain. Thus cleavage on both sides of the ester carbonyl gives the ions m/e 150 (M – OEt) and m/e 122 (M – CO_2Et). The latter fragment further contributes to the m/e 94 peak by CO expulsion. The m/e 94 peak also comes from cleavage of the N – C bond in the side-chain. High resolution shows the relative contribution to be 5:1, respectively. The m/e 95 peak corresponds to 3-hydroxypyridine, which could in part arise by pyrolysis. However, electron induced rearrangement with proton transfer to the pyridine and expulsion of the side-chain as olefine seems more likely, since the pyridine signal in the case of N-methyl and N-benzyl derivatives (Ia, Ib) was nearly absent. The best explanation for the m/e 123 peak involves a similar rearrangement process with expulsion of an unstable β-lactone, which well can collapse to ethylene and CO_2.

The higher temperature required by the indirect insertion technique led to a number of pyrolysis products from Ic. Thus ethyl tosylate was formed as in the case of the 3-desoxypyridinium ester (XVI) by direct insertion. 3-

Hydroxypyridine (m/e 95) is the other major pyrolysis product. Only a little of the liberated acid loses CO_2 and evaporates as a covalent isomer.
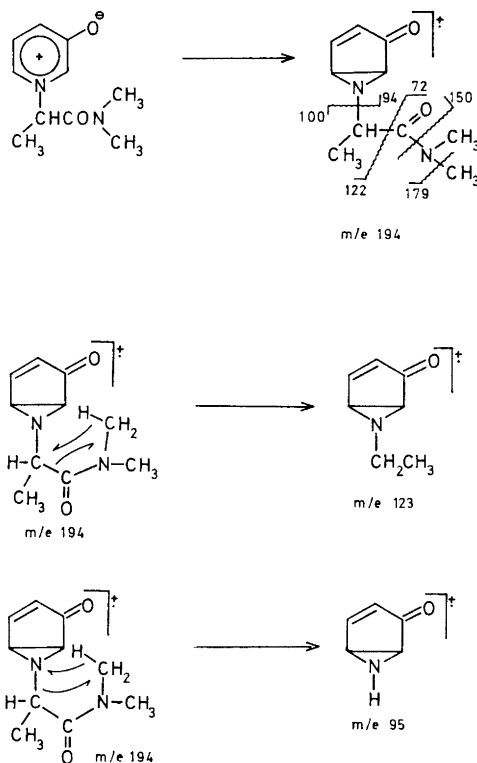

Scheme 8.

The corresponding N,N-dimethylamide (Id) hydrobromide behaves in the same way as the ester. The bromide ion is found as bromine (m/e 79, 81) and HBr (m/e 80, 82). The amide molecular ion is the base peak (m/e 194).
The most important fragments arise by the expected manner from the side-chain. The formation of the ions at m/e 95 and m/e 123 are visualized as taking place by McLafferty rearrangements as indicated.

EXPERIMENTAL

Scheme 9.

Both the methoxy derivative [12] (V) and the simple N-alkyl derivatives [13] (Ia, Ib) were prepared according to the literature. The other compounds were available from other work.[3]

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