Mass Spectrometry of 'Onium Compounds. Part XIV.[1] Methiodides of Methyl Pyridylacetates

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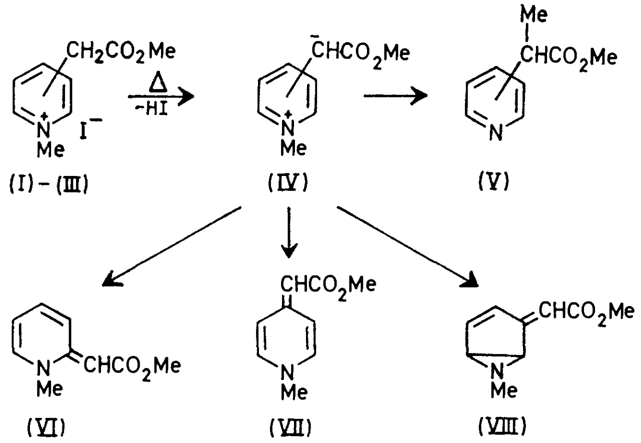
Methiodides of the three isomeric methyl pyridylacetates have been investigated by mass spectrometry. Thermal loss of hydrogen iodide with formation of the volatile anhydro-base was an important process for the 2- and 4-isomers. The 3-isomer underwent a redox process to give a volatile dihydropyridine whose structure was confirmed by separate synthesis of the 1,4-dihydro-derivative. Demethylation was shown by deuteriation to take place mainly from the ester group. Ionization potential values have been determined and used in structural deductions. The major electron-induced fragmentation pathways are discussed.

ZWITTERIONS are liberated from simple 3-hydroxypyridinium salts in the mass spectrometer and are not structurally rearranged to covalent molecules before evaporation.[2,3] Proton elimination from substituent other than the hydroxy-group may also lead to zwitterion formation. In this work the methiodides of methyl 2-pyridyl- (I), 3-pyridyl- (II), and 4-pyridyl- (III) acetates have been investigated together with their *N*-trideuteriomethyl analogues [1-*Me*-$^2H_3$]-(I—III).

These compounds possess a strongly activated methylene group attached to the pyridine nucleus. It is known that the 2- and 4-isomers readily eliminate a proton to give the corresponding anhydro-base.[4] Removal of a methylene proton from the 3-isomer might, by analogy to the 3-hydroxypyridinium system,[2] give rise to a volatile mesoionic structure or possibly a valence isomer (VIII). Alternatively the zwitterions can be transalkylated to tertiary pyridines (V). These possibilities are indicated in Scheme 1.



SCHEME 1

The mass spectra obtained from the 2- and 4-isomers (Figures 1 and 2) indicated that proton elimination had taken place with formation of the volatile anhydro-bases (VI) and (VII) (*m/e* 165). Confirmation followed from the spectra of authentic samples of (VI) and (VII) which were similar with respect to relative peak intensities and the shape of the metastable peaks (Figures 3 and 4). The spectra of the salts, however, have additional peaks due to methyl iodide (*m/e* 142) and other less important pyrolytic products. Additional evidence for the anhydro-base follows from the appearance potential for the formation of the *m/e* 165 ion from the salts (I) and (III) which were close to the ionization potential (IP) values for the corresponding anhydro-bases (Table). Comparison of these values, *ca.* 7 eV, with that, 9·5 eV, found for the pyridylacetates, excludes the presence of the transalkylated product (V) as a major component in the gas phase.

Ionization potentials

Compound	(I)	(II)	(III)	(VI)	(VII)	(XVII)	(IX)	(X)	(XI)
Ion (*m/e*)	165	167	165	165	165	167	151	151	151
IP (eV)	7·10	6·82	6·94	7·02	6·82	6·94	9·40	9·52	9·62

The 3-isomer (II) behaved differently. No peak due to loss of hydrogen iodide was seen (Figure 5). Instead intense peaks appeared at one and two mass units higher. High resolution of the *m/e* 167 species gave the composition $C_9H_{13}NO_2$, which is one double bond equivalent less than required for the anhydro-bases. A metastable peak shows a transition from *m/e* 167 to 166. In the deuteriated compound (Figure 6) the peaks had been shifted to *m/e* 170 and 169. Thermally-induced reduction to a volatile dihydropyridine has thus taken place prior to evaporation. The characteristic fragmentation of such a structure is loss of the sp^3 substituent to reform the stable aromatic pyridinium cation.[5,6] Thermal disproportionation in the mass spectrometer has been described for some *N*-quaternary compounds[7-9] and other examples are also known.[10] Oxidized products are not always seen[11,12] probably because of polymerization to nonvolatile components. The fragmentation pattern of the

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3-isomer is consistent with a 1,4- or 1,2-dihydro-derivative. The former was therefore synthesized and its spectrum found to be very similar to that from the salt (II). The latter has some additional peaks in the spectrum, however, due to other pyrolytic processes (Figures 5 and 7). The two possible dihydro-isomers would be expected to give closely similar spectra, and therefore no conclusion can be drawn as to which isomer is formed. Theoretical calculations have shown that the energy of the highest occupied π-electron orbital is higher for 1,2-dihydropyridine than for the corresponding 1,4-isomer.[13] The IP should therefore be higher for the latter. The value for the 1,4-isomer (XVII) was 6·94 eV (Table). Unfortunately the IP for the 1,2-isomer is not known. The IP for the *m*/*e* 167 species from the salt (II) was *ca*. 0·1 eV lower than for (XVII). From these results it is tentatively concluded that the reduced species in the gas phase from the salt (II) is the 1,2-dihydro-isomer or a mixture of the 1,2- and 1,4-isomers.

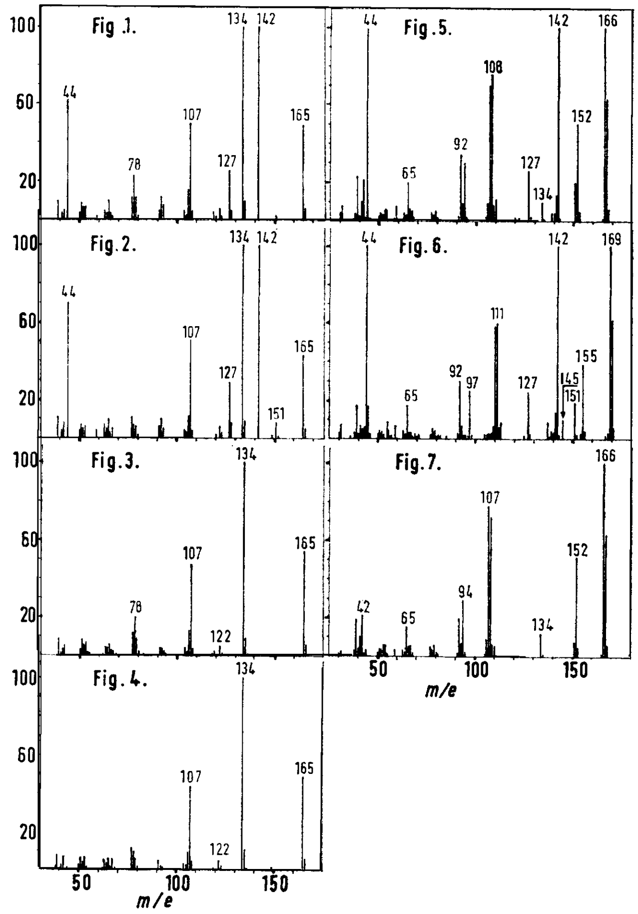


FIGURE 1 Fragmentation pattern of the methiodide of methyl 2-pyridylacetate (I). The peak due to methyl iodide has been reduced from 130 to 100%

FIGURE 2 Fragmentation pattern of the methiodide of methyl 4-pyridylacetate (III). The peak due to methyl iodide has been reduced from 130 to 100%

FIGURE 3 Fragmentation pattern of methyl 1,2-dihydro-1-methylpyridin-2-ylideneacetate (VI)

FIGURE 4 Fragmentation pattern of methyl 1,4-dihydro-1-methylpyridin-4-ylideneacetate (VII)

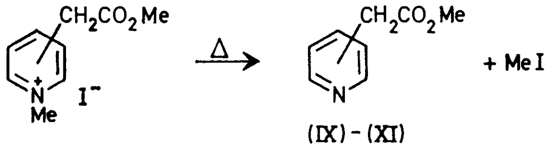
FIGURE 5 Fragmentation pattern of the methiodide of methyl 3-pyridylacetate (II). Peaks due to methyl iodide and carbon dioxide have been reduced from 300 and 200 respectively to 100%

FIGURE 6 Fragmentation pattern of the trideuteriomethiodide of methyl 3-pyridylacetate [1-*Me*-$^2H_3$]-(II). Peaks due to methyl iodide and carbon dioxide have been reduced from 300 and 200 respectively to 100%

FIGURE 7 Fragmentation of methyl 1,4-dihydro-1-methyl-3-pyridylacetate (XVII)

The loss of resonance energy in the dihydropyridine is closely reflected in the IP value (6·94 eV) which should be compared with 9·52 eV for the corresponding pyridylacetate (X) (Table). The IP values for the anhydro-bases (VI) and (VII) (7·02 and 6·82 eV) are also low compared to the corresponding pyridylacetates (IX) and (XI) (9·40 and 9·62 eV). Loss of the pyridine aromaticity in the case of the anhydro-bases is probably the major reason for the marked decrease in ionization potential.

The spectra from the salts (Figures 1, 2, and 5) show intense signals due to methyl iodide (*m*/*e* 142) and carbon dioxide (*m*/*e* 44). Peaks corresponding to the tertiary pyridines (*m*/*e* 151) formed by *N*-demethylation (Scheme 2) were of low intensities. The reason for this was evident from the spectra of the corresponding trideuteriomethiodides [1-*Me*-$^2H_3$]-(I—III) which showed that most of the demethylation was from the ester function (Figure 6). This pyrolytic process bears some resemblance to the ether cleavage on pyrolysis of an ethoxypyridinium bromide in the mass spectrometer.[14] The iodide ion is a poor nucleophile with respect to a carbonyl carbon atom, but an excellent nucleophile with respect to an sp^3 carbon atom. The activated esters above suffer attack first on the ester methyl group with *O*-demethylation followed by decarboxylation. For the 2- and 4-isomers, covalent structures may be written for the decarboxylated product. A covalent structure for the 3-isomer requires rearrangement exemplified by the azepine (XVI) (Scheme 3), or possibly transalkylation to 3-ethylpyridine. The signal at *m*/*e* 107 corresponding to the compounds (XIV)—(XVI) were of medium intensities and were greatly reduced at low voltages. The major contribution therefore comes from electron-induced fragmentations. This conclusion is supported by the relative peak intensities both in the spectra of the



SCHEME 2

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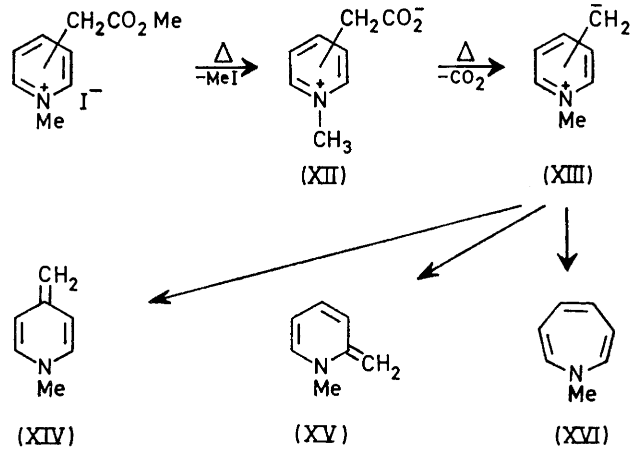
anhydro-bases (VI) and (VII) and the 1,4-dihydropyridine (XVII).

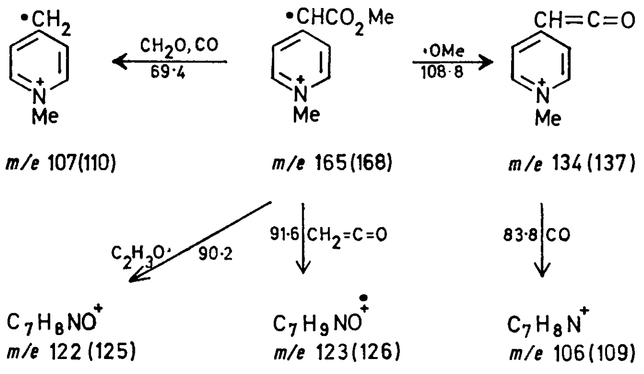
Further information about the behaviour of the carboxylate zwitterion (XII) in the mass spectrometer was desirable. The ester function of the 4-isomer was



SCHEME 3

therefore hydrolysed in aqueous alkali [4] and the solution evaporated in the mass spectrometer. The intensity of the m/e 107 species corresponding to the pyridone methide (XIV) was low compared with m/e 44 (CO_2) even after prolonged heating. The highly reactive decarboxylated product therefore must decompose to less volatile compounds (polymers).

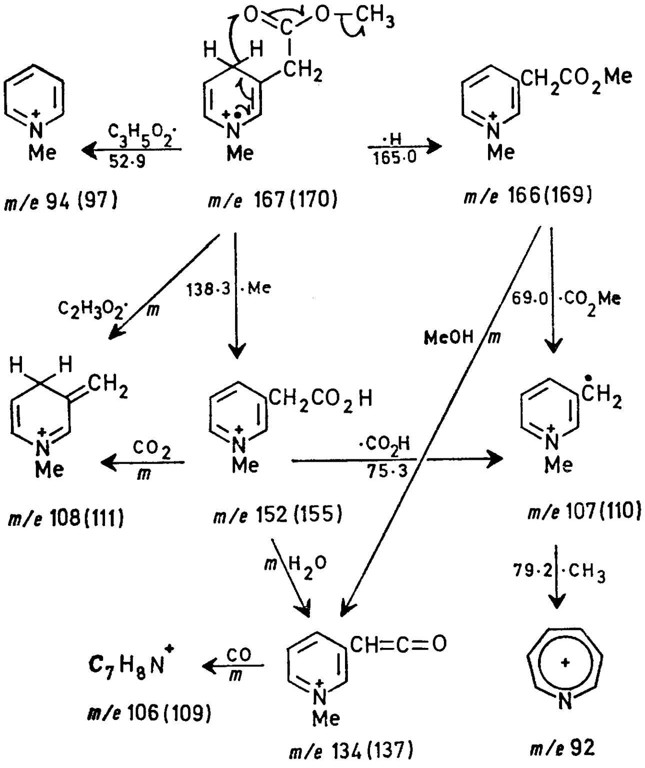
Electron-induced Fragmentation.—The fragmentation processes discussed are based on high resolution and metastable defocusing.[15] In the Schemes the position of the ordinary metastable peak in the spectrum is given. When the transition was found only by metastable defocusing, this is indicated by a '*m*'. The numbers given in brackets refer to the corresponding deuteriated compounds.



SCHEME 4

The mass spectra of the methiodides of methyl 2- and 4-pyridylacetates (Figures 1 and 2) are very similar (Scheme 4). Of special interest is the formation of m/e 107 by loss of $C_2H_2O_2$ from the molecular ion. The process must involve migration of one methyl hydrogen atom from the ester group and is probably induced by the radical located on the methine carbon atom. An analogous process is known from derivatives of furan with an ester group at C-2.[16]

The spectrum of the 3-isomer [(II); Figure 5] shows the presence in the gas phase of small amounts of the *N*-demethylated pyridine (m/e 151). The latter fragments mainly by cleavage β to the pyridine ring and further loss of HCN to the peaks at m/e 92 and 65 respectively. The fragmentation of the reduced salt is discussed in terms of the 1,4-dihydro-derivative (Scheme 5). The specific fragmentation reactions



SCHEME 5

of the 3-substituent appears to be due to an *ortho*-effect from the neighbouring sp^3 hydrogen atom in the ring. Formation of a stable pyridinium ion by cleavage of the sp^3 carbon–hydrogen bond is suggested as the driving force. An interesting reaction is the loss of the ester methyl group (m/e 152). This is normally an unfavourable process, but is observed in certain esters of furan-,[16] thiazole-,[17] and pyrrole-carboxylic acids [18] with a neighbouring XH substituent. The mechanism is analogous to that suggested above.

Syntheses.—The anhydro-bases (VI) and (VII) were readily prepared from the corresponding pyridinium methiodides by treatment with alkali. The methiodides

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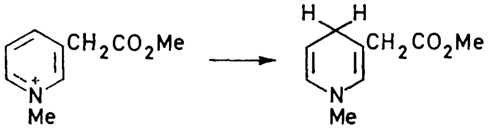
are available in 90% yield from the pyridylacetates simply by treatment with methyl iodide in cold acetone. Heating the reactants together in alcohol as reported[4] was found to give lower yields and inferior products because of decomposition.



(XVII)

Scheme 6

The 3-isomer (II) has been reported to react with sodium borohydride in dilute methanol to give the tetrahydro-compound.[19] Dithionite was therefore tried in our reactions. From the reaction in cold aqueous sodium hydrogen carbonate spectroscopic data showed the product to be a mixture of the tetra- and hexahydro-derivatives. The pure piperidine was obtained by reaction at 70 °C for 15 min. Such a reduction should be stepwise. It has been found that an electron-withdrawing substituent in the 3-position of the pyridine ring stabilizes the dihydro-step while an electron-donating substituent has the opposite effect.[13] A dihydro-derivative of compound (II) would therefore readily undergo further reduction. We succeeded, however, in removing the dihydro-compound as formed from the aqueous reaction medium by using a two-phase system with chloroform and vigorous mechanical stirring. The ring methylene protons in a 1,2-dihydro-isomer should appear as a singlet in the n.m.r. spectrum while these protons in a 1,4-structure would be coupled to the vicinal vinyl proton. The latter was the case for the product obtained, the coupling constant being 4 Hz. The chemical shift for the methylene protons was τ 7·10 which can be compared with τ 7·02 for 1,4-dihydro-1-phenylpyridine and 5·74 for the 1,2-isomer.[20] The dihydro-compound is thus the 1,4-isomer.

EXPERIMENTAL

N.m.r. spectra were recorded on a Varian A-60A instrument. Mass spectra were recorded on an AEI MS902 mass spectrometer attached to an AEI DS30 data system. Both high and low resolution data were processed on a computer.

The pyridinium compounds (I)—(III) were introduced by the heated direct insertion probe at 155 °C. The anhydro-bases (VI) and (VII) and the 1,4-dihydropyridine (XVII) were introduced through the heated inlet system at 190 °C. During all experiments the source temperature was 225 °C and the electron energy was 70 eV unless otherwise stated. At low resolution the ionizing current was 100 μA, and at high resolution (RP = 10,000) 500 μA was used. Perfluorokerosene served as the reference compound.

During ionization potential measurements the ionizing current was 20 μA and the repeller was at cage potential. Xenon was the reference gas. The system for automatic recording of ionization efficiency curves is described elsewhere.[21] The *I–E* curves were interpreted by the semi-log plot method.[22] The recorded IP values are the average of three determinations. The deviation is ±0·02 eV for compounds (VI), (VII), (IX)—(XI), and (XVII) and *ca.* ±0·05 eV for the pyridinium compounds (I)—(III).

Synthesis of Methiodides (I)—(III).—The methyl pyridylacetates and an equivalent amount of methyl iodide were dissolved in acetone and the solution was left in the dark at room temperature overnight. The methiodides were precipitated in *ca.* 90% yield. The deuteriomethiodides were similarly prepared with trideuteriomethyl iodide. 2-Methoxycarbonylmethyl-1-methylpyridinium iodide (I) was precipitated as a dark oil from the reaction mixture. Crystallization was unsuccessful. The compound was purified by precipitation several times from methanolic solution by the addition of chloroform. The oil was dried at 50 °C over P_2O_5 in vacuum (Found: C, 37·1; H, 4·4. Calc. for $C_9H_{12}INO_2$: C, 36·9; H, 4·1%). 3-Methoxycarbonylmethyl-1-methylpyridinium iodide (II) formed pale yellow crystals from methanol, m.p. 96—97 °C [19] (Found: C, 37·0; H, 4·1%). 4-Methoxycarbonylmethyl-1-methylpyridinium iodide (III) formed yellow crystals from methanol, m.p. 145—146 °C [4] (Found: C, 36·9; H, 4·5%).

Synthesis of the Anhydro-bases (VI) *and* (VII).—The 2- and 4-methiodides were dissolved in 1N-NaOH and the solution was extracted rapidly several times with ether. Methyl 1,2-dihydro-1-methylpyridin-2-ylideneacetate (VI) gave intense yellow crystals (80%) from ether–light petroleum (1 : 1), m.p. 96·5—97·0 °C (Found: C, 65·4; H, 6·7. Calc. for $C_9H_{11}NO_2$: C, 65·4; H, 6·7%). Methyl 1,4-dihydro-1-methylpyridin-4-ylideneacetate (VII) gave pale yellow needles (73%) from ether. The compound was further purified by sublimation at 60 °C and 0·05 Torr. It is sensitive to oxygen and moisture, m.p. 112·0—112·5 °C (Found: C, 65·5; H, 6·9%).

Methyl 1,4-*Dihydro*-1-*methyl*-3-*pyridylacetate* (XVII).—A two-phase system was prepared from chloroform (100 ml) and a solution of compound (II) (6·0 g, 0·02 mol) in water (30 ml) to which had been added sodium hydrogen carbonate (11 g). The mixture was vigorously stirred under oxygen-free nitrogen for a few min before sodium dithionite (7·0 g, 0·04 mol) was added. Upon addition the mixture became orange-red. The stirring was continued for 2 h under nitrogen at room temperature, the chloroform layer was separated, washed, dried, and the solvent was evaporated. Distillation at 78 °C and 0·2 Torr of the residual orange-red liquid gave a pale orange liquid (0·22 g, 7%). All operations were performed under nitrogen. Most of the product decomposed to polymeric materials during distillation. The product thus isolated, turned red immediately on exposure to atmospheric oxygen. Under nitrogen it became dark after a few h at room temperature (Found: C, 64·5; H, 7·9. Calc. for $C_9H_{13}NO_2$: C, 64·6; H, 7·8%), τ ($CDCl_3$) 7·30 (3H, NMe), 7·17 (2H, CH_2CO), 7·10 (2H, d, 4-H_2, $J_{4,5}$ 4 Hz), 6·31 (3H, OMe), 5·60 (1H, 2 × t, 5-H, $J_{5,6}$ 8 Hz), and 4·30 (1H, 2 × d, 6-H, $J_{2,6}$ 1 Hz) with a partly superimposed signal at 4·36 (1H, d, 2-H, $J_{2,6}$ 1 Hz).

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