Pyrones

V—The Mass Spectra and Fragmentation Mechanisms of Some 3(5)-Methoxy-4-pyrones

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The mass spectra of methyl kojate (2-hydroxymethyl-5-methoxy-4*H*-pyran-4-one), two deuterated analogues and 14 related 3(5)-methoxy-4-pyrones have been studied. These compounds fragment according to a common mechanism, initiated by primary rearrangement of the molecular ion(s). Guidelines which indicate the presence of 3(5)-methoxy-4-pyrones and allow structural determinations to be made from their mass spectra are presented. For the majority of substituents studied, the nature of the substituent has no major effect upon the fragmentation pattern; the cyano group does. The hydroxy counterparts of the above compounds are readily converted for analysis by simple methylation.

INTRODUCTION

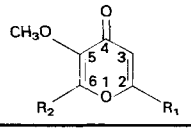
In a recent paper[1] we reported some features of the mass spectral fragmentation mechanisms of methyl maltol (3-methoxy-2-methyl-4*H*-pyran-4-one) and methyl allomaltol (5-methoxy-2-methyl-4*H*-pyran-4-one). Fragmentation is preceded by formation of a rearranged molecular ion, and the base peak is obtained in each case by one of two fragmentation pathways which are initiated by methyl loss and which are structure dependent. For methyl maltol, methyl loss precedes two CO losses yielding the base peak at *m/z* 69, while in the case of methyl allomaltol, methyl loss is followed by loss of CH_2O to yield the base peak at *m/z* 95. These processes are not observed in the corresponding hydroxy compounds.[2]

RESULTS AND DISCUSSION

The mass spectra of the 3(5)-methoxy-4-pyrones shown below have not been reported previously.

The common features present in the 70 eV mass spectra of these compounds are summarized in Table 1.

Table 1. Peak intensities in the mass spectra of some 3(5)-methoxy-4*H*-pyran-4-ones



Compound	R_1	R_2	$[M]^{+\cdot}$	$[M-H]^{+\cdot}$	$[M-18]^{+\cdot}$ [b]	$[M-30]^{+\cdot}$	*m/z* 125	*m/z* 95
1	H	H	100	30	32	34	30[a]	15
2	H	CH_3	100	24	66	16	22	7
6	CH_3	H	72	22	13	40	3	100
4	CH_2OH	H	100	32	27	16	26	100
8	CH_2OCH_3	H	56	12	10	7	28	100
9	CH_2OCOCH_3	H	27	8	3	4	8	100
10	CH_2Cl	H	29	14	3	21	5	100
11	CHO	H	86	21	33	8	59	100
12	CH=NOH	H	44	11	33	8	10	100
13	$COOCH_3$	H	46	15	11	6	22	100
14	$COOCH_2CH_3$	H	39	5	8	11	19	100
15	CN	H	40	9	3	32	0	18
							m/z 203/205	*m/z* 173/175
3	CH_2OH	Br	60	19	6	16	0	100
							m/z 203/205	*m/z* 173/175
4	CH_2OCH_3	Br	37	7	4	6	1	100
							m/z 150	*m/z* 120
5	CH_2OCH_3	CN	34	6	0	0	0	34

[a] For this compound only: *m/z* 125 = $[M-H]^+$.
[b] Metastable ion peaks were detected for this process in each case.

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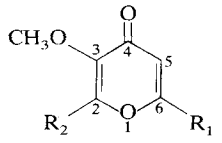
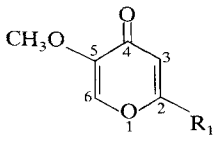


3-Methoxy-4-pyrones

	R_2	R_1
1	H	H
2	CH_3	H
3	Br	CH_2OH
4	Br	CH_2OCH_3
5	CN	CH_2OCH_3



5-Methoxy-4-pyrones

	R_1
6	CH_3
7	CH_2OH
8	CH_2OCH_3
9	CH_2OCOCH_3
10	CH_2Cl
11	CHO
12	CH=NOH
13	$COOCH_3$
14	$COOCH_2CH_3$
15	CN

In order to ascertain whether the same fragmentation mechanisms are occurring in the above compounds as were found for methyl allomaltol,[1] the spectrum of methyl kojate (2-hydroxymethyl-5-methoxy-4*H*-pyran-4-one, **7**) was analysed in detail. A comparison of the mass spectra (of methyl kojate and methyl-d_3 kojate) reveals that in all major daughter ions one deuterium atom is always retained. In the case of water loss, one of the methoxy hydrogen atoms is always involved, and for greater than 95% of the ions, the second hydrogen also comes from the methoxy methyl group. This is identical to the results obtained in the case of methyl allomaltol[1] (that the hydroxyl group at C-2 is not involved in the water loss was confirmed from deuterium exchange experiments).

It is apparent, then, that methyl kojate fragmentation follows a pathway similar to that of methyl allomaltol,[1] viz. production of a rearranged molecular ion by (1, 6)-transfer of a methoxy hydrogen atom to the 4-carbonyl oxygen, with ensuing loss of H_2O, CH_2O, and $R_1\cdot$ (i.e. $\cdot CH_2OH$) occurring as described.[1] These losses are supported by appropriate metastable ion peaks and labelling data.

These processes indeed appear to be common to the 2-substituted-5-methoxy-4-pyrones studied (**3**, **4**, **6**–**14**). (In the compounds **3** and **4**, these peaks are shifted 78 and 80 mass units to higher mass values, since the bromine atoms are retained in the fragments.) The base peak, *m/z* 95, is formed by loss of CH_2O and $R_1\cdot$ (and/or the inverse process) from the rearranged molecular ion (**5**, **15** are exceptions, *vide infra*), and peaks are observed at $[M-30]^{+\cdot}$ (loss of CH_2O) and *m/z* 125 (loss of $R_1\cdot$), the relative abundance of these two latter ions apparently being independent of substituent nature. (There may be a correlation between log ([125]/[$M^{+\cdot}$]) and σ^{+}[3]; data are insufficient for firm conclusions to be drawn.) The only process which does not proceed via the rearranged molecular ion (*a* in Ref. 1) is loss of a methoxy hydrogen directly from the unrearranged molecular ion[1] (in competition with the formation of the rearranged molecular ion), suggested from the observed loss of deuterium, not protium, from methyl-d_3 kojate.

From a consideration of the data of Table 1, several general observations may be made about the fragmentation of 3- or 5-methoxy-4*H*-pyran-4-ones: (i) when the only other substituent is located *para* to the methoxy group, ($R_1 \neq H$), the normal fragmentations (as discussed above) are observed (base peak, or most intense fragment, *m/z* 95); (ii) with substituents *ortho* and *para* to the methoxy group, the *ortho* substituent is always retained and the normal fragmentation is observed; (iii) with no substituent *para* to the methoxy group and an *ortho* substituent present (i.e. **2**), the most intense fragment is produced by loss of the *ortho* substituent and two molecules of CO from the rearranged molecular ion.

A strongly electron-withdrawing substituent can perturb the behaviour: the cyano compounds **5** and **15** differ considerably from the normal pattern. Some of the expected features are indeed present (see Table 1), but the intensities are much reduced. Indeed, for the simple derivative **15**, the most intense ions appear to be formed by the retro Diels-Alder fragmentations (base peak *m/z* 51, C-2—C-3-derived and *m/z* 56, C-5—C-6-derived), which are normally considered to be typical of 4-pyrones.[2] For the derivative **5**, the major alternative processes appear also to be retro Diels-Alder derived (*m/z* 70, C-5—C-6-derived and base peak *m/z* 45).

The cyano group has the most positive σ^{+} value[4] of the substituents in this study, reflecting its largest response to processes involving electron demand. The two fragmentation modes observed here (retro Diels-Alder and 1,6-hydrogen migration-induced pathways) probably differ sufficiently in mechanism such that only the presence of a substituent with a large and positive σ^{+} value ($\sigma^{+} > 0.6$, e.g. CN, $\sigma^{+}0.66$ and possibly NO_2, $\sigma^{+}0.79$) causes the former process to be observed and dominate. Thus, compounds bearing substituents such as Br, COOR, or CH_2X (σ^{+} values *c.* +0.1–+0.4) fragment only by the 'normal' 1,6-hydrogen migration pathways.

Using the trends derived in the preceding discussion, we feel that it is possible to predict the spectrum of a given 3(5)-methoxy-4-pyrone, *or*, given the spectrum, identify the substituent pattern of the pyrone. The analysis of the corresponding hydroxy compounds is achieved after simple methylation as described previously.[1] A summary of our conclusions follows:

Guidelines for interpreting spectra of 3(5)-methoxy-4-pyrones

1. Indications of 3(5)-methoxy-4-pyrones

   (a) $[M-H]^{+\cdot}$ $(M-1)$
   (b) $[M-H_2O]^{+\cdot}$ $(M-18)$
   (c) $[M-CH_2O]^{+\cdot}$ $(M-30)$

2. If the base peak or most intense fragment (MIF) is
   (a) *m/z* 95, then there is no substituent *ortho* to MeO ($R_2 = H$)

   $$\text{mass } R_1 = m/z\ [M]^{+\cdot} - 125$$

   or

   $$\text{mass } R_1 = m/z\ [M-30]^{+\cdot} - 95$$

   (b) greater than *m/z* 95, but not equal to *m/z* $[M-71]^{+}$ then there is a substituent *ortho* to MeO ($R_2 \neq H$)

   $$\text{mass } R_2 = m/z\ [MIF]^{+} - 94$$

and

$$\text{mass } R_1 = m/z\ [M-30]^{+\cdot} - m/z\ [MIF]$$

or

$$\text{mass } R_1 = m/z\ [M]^{+\cdot} - m/z\ [R_2]^{+} - 124$$

(N.B. $m/z\ [M-71]^{+} = m/z\ [M]^{+\cdot} - CH_3 \cdot CO - CO$)

(c) Less than m/z 95 or equal to $m/z\ [M-71]^{+}$, then there is a substituent *ortho* to, but not *para* to, MeO ($R_1 = H$)

$$\text{mass } R_2 = m/z\ [M-71]^{+} - 54$$

It must be emphasized that the presence of these peaks and corresponding fragmentation patterns only suggests the presence of a 3- or 5-methoxy-4*H*-pyran-4-one; their absence does not rule out the possibility.

EXPERIMENTAL

All melting points are uncorrected. Kojic acid was purchased from Aldrich Chemical Co. and recrystallized before use. Preparation of methyl allomaltol (**6**),[1] methyl maltol (**2**)[1] and 5-methoxy-4*H*-pyran-4-one-2-carbonitrile (**15**)[5] have been reported previously. Mass spectra were recorded on an Hitachi RMU-7E double focusing instrument.

2-Hydroxymethyl-5-methoxy-4*H*-pyran-4-one (7). (methyl kojate)

The methyl ether was prepared by methylation of kojic acid with diazomethane; m.p. 160–161 °C (lit.[5] m.p. 161 °C).

5-Methoxy-2-methoxymethyl-4*H*-pyran-4-one (8)

The dimethyl derivative was prepared by reaction of kojic acid with dimethyl sulfate and base, m.p. 89–90 °C (lit.[7] m.p. 90–91 °C).

2-Acetoxymethyl-5-methoxy-4*H*-pyran-4-one (9)

Acetylation of methyl kojate (**7**) with acetyl chloride and pyridine proceeded normally, m.p. 125–126 °C (lit.[8] m.p. 125–126 °C).

2-Chloromethyl-5-methoxy-4*H*-pyran-4-one (10)

Methyl kojate (**7**) was treated with thionyl chloride according to literature procedure[6] to yield **10**, m.p. 117.5–118.5 °C (lit.[6] m.p. 118 °C).

5-Methoxy-4*H*-pyran-4-one-2-carboxaldehyde (11)

The aldehyde was prepared by manganese dioxide oxidation of the above alcohol by standard procedures; m.p. 199.5–200.5 °C (lit.[9] m.p. 202 °C).

5-Methoxy-4*H*-pyran-4-one-2-carbaldoxime (12)

Treatment of the aldehyde (**11**) with methanolic hydroxylamine hydrochloride yielded the oxime, m.p. 130 °C. (Found: C, 49.73; H, 4.45; N, 7.82. $C_7H_7NO_4$ requires C, 49.71; H, 4.17; N, 8.28%).

Methyl 5-methoxy-4*H*-pyran-4-one-2-carboxylate (13)

The methyl ester was prepared by solvolysis of the nitrile (**15**) with methanolic hydrogen chloride, m.p. 200.5–201.5 °C (lit.[10] m.p. 197 °C).

Ethyl 5-methoxy-4*H*-pyran-4-one-2-carboxylate (14)

The ethyl ester was prepared in a manner analogous to that described for the methyl ester, m.p. 155.5–156.5 °C (lit.[10] m.p. 154–155 °C).

2-Bromo-6-hydroxymethyl-3-methoxy-4*H*-pyran-4-one (3)

2-Bromokojic acid (prepared according to Ichimoto,[11] m.p. 165–167 °C) in methanol/ether solution was methylated with diazomethane to yield the methyl ether **3**, m.p. 122–123 °C.

2-Bromo-3-methoxy-6-methoxymethyl-4*H*-pyran-4-one (4)

2-Bromokojic acid[11] was methylated with dimethyl sulfate/KOH according to Thomas's procedure;[7] chromatography produced colourless crystals, m.p. 65 °C.

3-Methoxy-6-methoxymethyl-4*H*-pyran-4-one-2-carbonitrile (5)

Cuprous cyanide and the bromo compound (**4**) were heated in *N*-methylpyrrolidinone at 150 °C for 14 h. Work-up with ferric chloride/aq. HCl and extraction allowed the isolation[12] of the above nitrile as an oil: m/z 195.0536. Calc. for $C_9H_9NO_4$ 195.0531.

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