Ortho Effect in the Fragmentation of 2-Acetoxychalcones under Electron Impact

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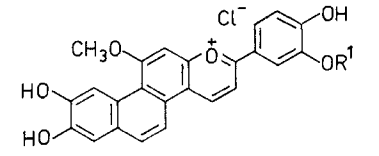
2-Acetoxychalcones decompose under electron impact conditions by loss of an acetoxy fragment to form flavylium ions. The effect is restricted to the *ortho* position and is reduced after hydrogenation of the chalcone double bond. The intense flavylium ion originates—as shown by specific labelling with ^{18}O—from two different fragmentation lines: (a) direct loss of an acetoxy radical by cleavage of the phenolic Ar—O bond and (b) sequential elimination of ketene and a hydroxy radical.

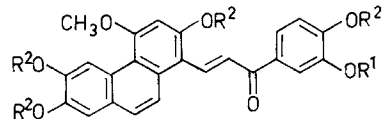
In natural product chemistry acetylation is frequently used for derivatization of phenolic compounds. Under electron impact conditions the resulting phenyl acetates usually eliminate ketene to form phenol ions.[1] An unusual fragmentation was detected recently in the course of structure elucidation of the red cell wall pigments of peat mosses (Sphagnaceae). The acetylated products[2] **2a** and **2b** (obtained by reaction of Sphagnorubin B(**1a**) and Sphagnorubin C (**1b**), respectively, with acetic anhydride in pyridine) decompose under electron impact conditions by losing an acetoxy radical from the molecular ions ($[M-59]^+$) followed by four (**2a**) and three (**2b**) ketene eliminations, respectively. The expected ketene fragmentation pattern ($[M-42]^{+\cdot}$) proved to be a minor process (Table 1).

We found this preferred loss of an acetoxy fragment to be common to 2-acetoxychalcones (Table 1, Fig. 1)



1a: $R^1=H$
1b: $R^1=CH_3$

$(CH_3CO)_2O$ / Pyridine

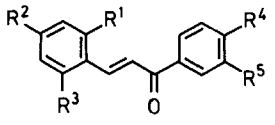


2a: $R^1=R^2=COCH_3$
2b: $R^1=CH_3$, $R^2=COCH_3$

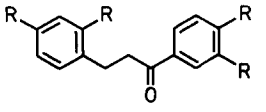
and restricted to the *ortho* position of the substituent. Metastable peaks of the $[M-59]^+$ ions proved the phenolic Ar—O bond to be cleaved. In the case of the isomeric 4-acetoxychalcone (**3b**) the usual ketene elimination, $[M-42]^{+\cdot}$, predominates (Fig. 2). Hydrogenation of the central double bond, e.g. in the 2,3′,4,4′-tetraacetoxydihydrochalcone (**4**), reduces the *ortho* effect; here, the $[M-42]^{+\cdot}$ ion is favoured (Table 1).

Table 1. Abundance of $[M-59]^+$ and $[M-42]^{+\cdot}$ ions in the EI spectra of acetoxychalcones and acetoxydihydrochalcones

Compound		$[M-59]^+$	$[M-42]^{+\cdot}$	Ratio $[M-59]^+/[M-42]^{+\cdot}$
Sphagnorubin B-acetate	(2a)	96	14	6.9
Sphagnorubin C-acetate	(2b)	75	7	10.7
2-Acetoxychalcone	(3a)	87	61	1.4
4-Acetoxychalcone	(3b)	8	100	0.1
2-Acetoxy-4,4′-dimethoxychalcone	(3c)	100	10	10.0
2,3′,4,4′-Tetraacetoxychalcone	(3d)	100	38	2.6
2,3′,4′-Triacetoxy-4-methoxychalcone	(3e)	100	21	4.8
2,3′,4,4′,6-Pentaacetoxychalcone	(3f)	94	10	9.4
2-Acetoxy-3′,4,4′,6-tetramethoxy chalcone	(3g)	100	3	33.3
2,3′,4,4′-Tetraacetoxydihydrochalcone	(4)	27	48	0.5



	R^1	R^2	R^3	R^4	R^5
3a	OAc	H	H	H	H
3b	H	OAc	H	H	H
3c	OAc	OCH_3	H	OCH_3	H
3d	OAc	OAc	H	OAc	OAc
3e	OAc	OCH_3	H	OAc	OAc
3f	OAc	OAc	OAc	OAc	OAc
3g	OAc	OCH_3	OCH_3	OCH_3	OCH_3
3h	OH	OCH_3	H	OCH_3	H



4: R = OAc

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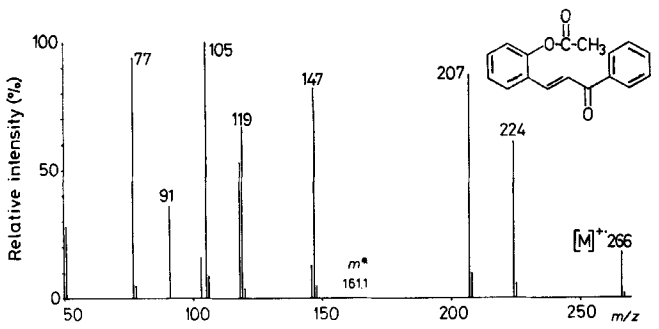


Figure 1. Electron impact mass spectrum of 2-acetoxychalcone (**3a**).

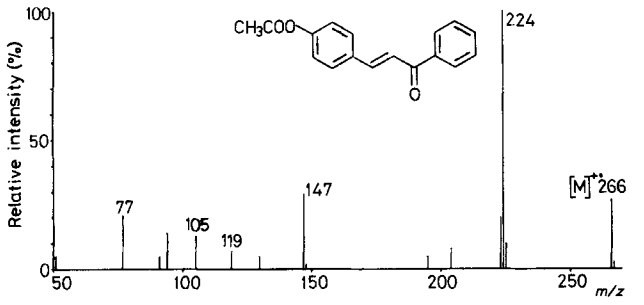


Figure 2. Electron impact mass spectrum of 4-acetoxychalcone (**3b**).

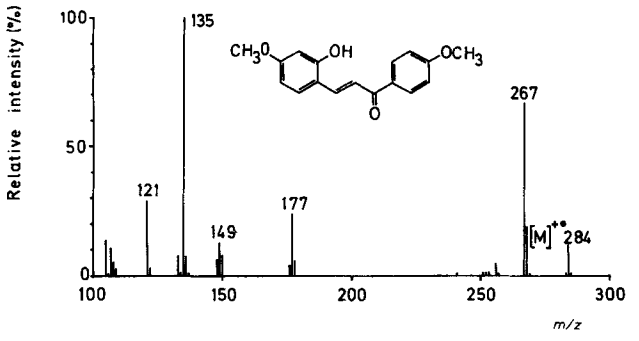


Figure 3. Electron impact mass spectrum of 2-hydroxy-4,4'-dimethoxychalcone (**3h**).

In the 2-hydroxychalcones we found a similar *ortho* effect. For example, 2-hydroxy-4,4'-dimethoxychalcone (**3h**) decomposes mainly by loss of a hydroxy radical from the molecular ion to form the flavylium ion (*m/z* 267); the more typical phenol fragments[1] ($[M-CO]^{+\cdot}$ or $[M-CHO]^{+}$) are minor products (Fig. 3).

This means that in the fragmentation of 2-acetoxychalcones the generation of the flavylium ion could as well be explained by the sequence

$$[M]^{+\cdot} \xrightarrow{-C_2H_2O} [M-42]^{+\cdot} \xrightarrow{-OH\cdot} [M-59]^{+}$$

To distinguish between these alternatives two chalcones were specifically ^{18}O-labelled: [2-^{18}O]2-acetoxychalcone representing aryl-oxygen labelling and [*carbonyl*-^{18}O]2-acetoxy-4,4'-dimethoxychalcone representing carbonyl labelling. The electron impact spectrum of the [2-^{18}O]2-acetoxychalcone (Table 2) shows the same $^{18}O/^{16}O$ ratio for the aryl oxygen (58:42) in the molecular ion and in the $[M-ketene]^{+\cdot}$ fragment ion. In the $[M-acetoxy]^{+}$ fragment, however, the ^{18}O content is reduced from 58% to 39% which means that approximately $\frac{2}{3}$ of the label is retained; therefore the $[M-59]^{+}$ ion cannot originate by cleavage of the aryl-oxygen bond only. This result is supported by the mass spectrum of the *carbonyl*-^{18}O-labelled 2-acetoxy-4,4'-dimethoxychalcone (Table 2). From the isotope abundances it can be seen that it contains 64% labelled and 36% unlabelled carbonyl oxygen. This $^{18}O/^{16}O$ ratio is found unchanged in the $[M-ketene]^{+\cdot}$ fragment ion, but is reduced to 28:72 in the $[M-59]^{+}$ fragment ion. The loss of more than half of the label indicates that there is a second process involving the carbonyl oxygen and a consecutive loss of ketene and a hydroxy radical. This assumption is in accord with the mass spectrum of the corresponding [*carbonyl*-^{18}O]2-hydroxy compound **3h** which shows an almost complete loss of the heavy oxygen in the transition from the molecular ion to the flavylium ion (Table 2).

DISCUSSION

The intense $[M-59]^{+}$ fragment ion in the mass spectra of 2-acetoxychalcones obviously results from cyclization to the stable flavylium ion. Intramolecular aromatic substitutions of this kind are well known in mass spectrometric fragmentations and represent one type of the numerous *ortho* effect reactions,[3] i.e. *ortho*-substituted styryl ketones specifically lose the *ortho* group to form stable benzopyrylium ions.[4] On the other hand compounds unsubstituted in the 2-position expel hydrogen from the styryl ring and yield oxonium ions. As was shown by Williams *et al.*[5] the intense $[M-1]^{+}$ peak found in the mass spectra of chalcones partly derives from this cyclization.

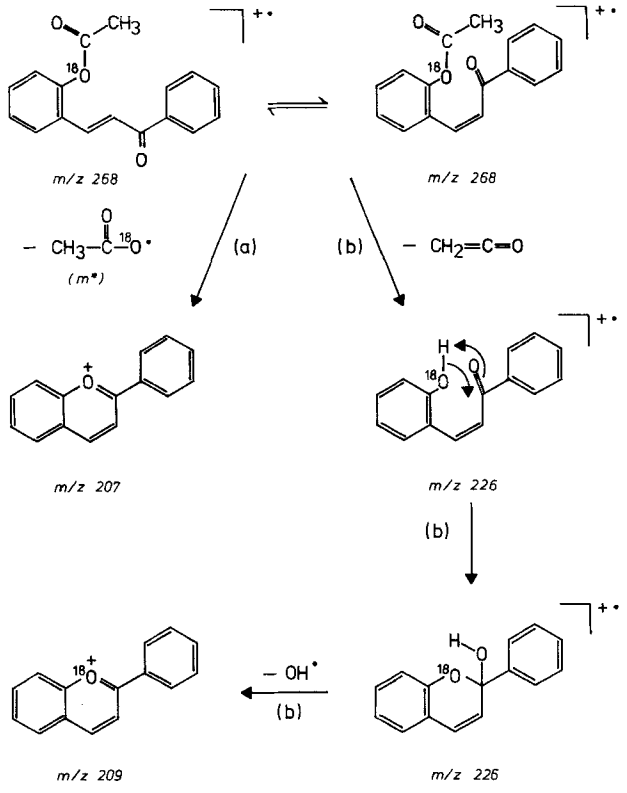
The fragmentation of 2-acetoxychalcones to form flavylium ions has not yet been reported. Since the oxygen of the pyrylium ring originates partly from the aryl oxygen and partly from the chalcone oxygen, as shown by specific ^{18}O labelling, the formation of the flavylium ion under electron impact must follow two different pathways.

(a) In the first fragmentation process the direct cleavage of the Ar—OAc bond is accompanied by ring closure and by retaining the oxygen of the carbonyl group. This pathway is proven by metastable transitions for the $[M-59]^{+}$ ions and the partial loss of the heavy oxygen in the case of the [2-^{18}O]2-acetoxychalcone (**3a**).

(b) The second fragmentation process can be explained by the sequence $[M]^{+\cdot}-[ketene]-[hydroxy\ radical]$ as shown in the mass spectrum of the chalcone **3c**, ^{18}O-labelled in the carbonyl group. This pathway is supported by the fact that the $[M-ketene]$ product itself, the 2-hydroxychalcone **3h**, fragments with preferential loss of a hydroxy radical yielding the identical flavylium ion, and that in this case the carbonyl oxygen of the chalcone is almost completely lost. This fragmentation process is easily explained by an intermediate formation of a flav-3-en-ol (Scheme 1) followed by the elimination of the hydroxy group of the half-acetal.

Table 2. $^{18}O/^{16}O$ ratio of fragment ions (corrected for natural ^{13}C contribution) of [2-^{18}O]2-acetoxychalcone ([2-^{18}O]3a), [*carbonyl*-^{18}O]2-acetoxy-4,4'-dimethoxychalcone ([*carbonyl*-^{18}O]3c) and [*carbonyl*-^{18}O]2-hydroxy-4,4'-dimethoxychalcone ([*carbonyl*-^{18}O]3h)

	2-Acetoxychalcones					2-Hydroxychalcones	
	[2-^{18}O]3a		[carbonyl-^{18}O]3c			[carbonyl-^{18}O]3h	
Ion	m/z	$^{18}O/^{16}O$	m/z	$^{18}O/^{16}O$	Ion	m/z	$^{18}O/^{16}O$
$[M]^{+\cdot}$	268/266	58/42	328/326	64/36			
$[M-ketene]^{+\cdot}$	226/224	58/42	286/284	64/36	$[M]^{+\cdot}$	286/284	59/41
$[M-acetoxy]^{+}$ (=flavylium ion)	209/207	39/61	269/267	28/72	$[M-Hydroxy]^{+}$ (=flavylium ion)	269/267	12/88
Ar—CH=CH—C≡O$^+$	149/147	55/45	177	0/100	Ar—CH=CH—C≡O$^+$	177	0/100
Ar—CH=CH	121/119	59/41	149	0/100	Ar—CH=CH	149	0/100
Ar'—C≡O$^+$	105	0/100	137/135	63/37	Ar'—C≡O$^+$	137/135	59/41



Scheme 1. Mechanisms of flavylium ion formation under electron impact for 2-acetoxychalcones. The fragmentation of [2-^{18}O]2-acetoxychalcone ([2-^{18}O]3a) is depicted for the scheme (see also Fig. 1 and Table 2).

EXPERIMENTAL

The 70 eV mass spectra were obtained with a CH 4 (Atlaswerke Bremen) and a Varian MAT 445 mass spectrometer coupled to a Varian Spectro Spin MAT 200 data processing system (ion source temp. 200 °C).

The sphagnorubin acetates (**2a, b**) were obtained as described elsewhere;[2] the chalcones (**3a–g**) were prepared by the condensation procedure described below for 2-acetoxy[2-^{18}O]chalcone, starting from the corresponding benzaldehydes and acetophenones. All compounds were checked by IR and NMR spectroscopy; details are reported elsewhere.[2]

[2-^{18}O]2-Acetoxychalcone([2-^{18}O]3a). 480 mg (5.1 mmol) phenol-^{18}O (57.8% ^{18}O; Volk AG, FRG) were refluxed for 1 h with 2.0 g NaOH in 2 ml H_2O and 2 ml chloroform. After acidification with 5 M sulphuric acid, the [2-^{18}O]2-hydroxybenzaldehyde was extracted with ethyl acetate (5×3 ml) and purified by chromatography on silica gel (40 cm×2 cm column) with dichloromethane as eluent, (yield 135 mg, 22%). Transformation to the acetate was achieved by incubation (24 h, 20 °C) with 0.5 ml acetic anhydride and 0.5 ml pyridine, evaporation and crystallization from ether/hexane, m.p. 37 °C (yield 126 mg, 85%). Finally, this acetate (66 mg, 0.4 mmol) was refluxed for 24 h with 2-(triphenylphosphoranyliden)acetophenone[6] (171 mg, 0.45 mmol) in 5 ml dry acetonitrile. After evaporation, 70 mg (66%) [2-^{18}O] **3a** was crystallized twice from ethanol, m.p. 67 °C (68–69 °C for the unlabelled compound **3a**[7]).

[*Carbonyl*-^{18}O]2-acetoxy-4,4'-dimethoxychalcone ([*carbonyl*-^{18}O]3c). 163 mg (0.5 mmol) 2-acetoxy-4,4'-dimethoxychalcone (**3c**) were refluxed for 12 h with 3 ml trimethyl orthoformate, 2 ml methanol and 0.1 g acidic ion exchanger (Dowex 50-WX-2, H^+-form, 100–200 mesh). After filtration and evaporation, the dimethyl ketal was stirred for 3 h with 0.30 ml $H_2{}^{18}O$ (95% ^{18}O; Merck, Sharp and Dohme, Montreal, Canada) and 5 μl formic acid in 2 ml dioxane. After evaporation, the [*carbonyl*-^{18}O]-labelled chalcone **3c** was crystallized twice from methanol, m.p. 134 °C; IR (KBr) chalcone C=^{18}O 1640 cm^{-1} as compared with C=^{16}O 1655 cm^{-1}.

2-Hydroxy-4,4'-dimethoxychalcone (3h). This was prepared from **3c** by saponification with 10% ammonia/methanol (1:1, by vol.) for 5 h at 20 °C in argon atmosphere. After evaporation in vacuum (0.01 Torr) the hydroxychalcone **3h** was crystallized twice from water/methanol (10:1), pale yellow crystals, m.p. 111 °C (decomp.).

[*Carbonyl*-^{18}O]2-hydroxy-4,4'-dimethoxychalcone ([*carbonyl*-^{18}O]3h). The compound was obtained from the labelled acetoxycompound (**[*carbonyl*-^{18}O]3c**) as described above for the unlabelled hydroxychalcone, yellow crystals, m.p. 111 °C (decomp.); IR (KBr): chalcone C=^{18}O 1620 cm^{-1} as compared with C=^{16}O 1630 cm^{-1}.

2,3',4,4'-Tetraacetoxydihydrochalcone(4).[2] This was generated from 440 mg (1.0 mmol) 2,3',4,4'-tetraacetoxychalcone (**3d**) by catalytic hydrogenation with 20 mg PtO_2 in 50 ml ethyl acetate for 1 h at 25 °C. After filtration and evaporation, the product crystallized from methanol in colourless needles (m.p. 134 °C); yield 290 mg (66%) **4**. $C_{23}H_{22}O_9$ (442.4): calc. C 62.44 H 5.01, found C 62.08 H 5.00 UV(CH_2Cl_2): $\lambda_{max}(\log \varepsilon) = 247$ (3.89), 288 nm sh (2.79). ^{1}H-NMR($CDCl_3$): $\delta = 2.28$–2.31 (4 s; 12 H, 4 $ArOCOCH_3$), 3.10 (m; 4 H, $ArCH_2CH_2CO$—), 6.96–7.95 (m; 6 H, aryl H).

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