Skeletal Rearrangement of α-Hydroxy-ketones upon Electron Impact

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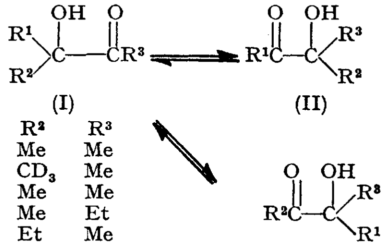
A skeletal rearrangement induced by electron impact in a number of α-hydroxy-ketones has been studied. Methyl, ethyl, and possibly hydrogen undergo ready 1,2-shifts. The rearrangement is not brought about by thermal excitation and is analogous to the acid-catalysed acyloin transformation described by Favorskii. Evidence is presented that the electron-impact induced transformation proceeds by rearrangement of the molecular ions, and the possibility of determining migratory aptitudes is discussed.

It has recently been realised that electron-impact induced rearrangements of groups other than hydrogen occur quite frequently. Such skeletal rearrangements occur in various types of compound.[1] A rationalisation [2] of these migrations has been given, which, while not making possible the *a priori* prediction of the structures of the rearranged molecular ions and their principal fragments, defines the type of molecule in which electron-impact induced rearrangements are most likely to be observed and thus makes the task of structure assignment less difficult. Further exploration of rearrangement phenomena is interesting not only in its own right but because of possible analogies with both thermal and acid-catalysed carbonium ion rearrangements. It is with the latter that we are concerned here.

Few of the rearrangements observed appear to have thermal or acid-catalysed analogues, although thermal rearrangements occurring in the heated inlet of the mass spectrometer have not always been rigorously excluded. Precautions are usually taken with heat-sensitive compounds but occasionally unexpected thermal reactions occur, for example, in the case of semicarbazones.[3] Aryl migration induced both thermally and by electron impact occurs in certain phenylhydrazones.[4] There seems to be only one authentic instance of a classical carbonium ion rearrangement taking place in the mass spectrometer. This is the recently reported analogue of the pinacol–pinacolone rearrangement.[5] We report here the electron-impact induced analogue of the acid-catalysed acyloin transformation of α-hydroxy-ketones.

This rearrangement (II) $\rightleftharpoons$ (I) $\rightleftharpoons$ (III) was first described by Favorskii [6] and occurs when α-hydroxy-ketones and -aldehydes are heated in solution with a trace of mineral acid. We have found that unsymmetrically substituted α-hydroxy-ketones appear to isomerise


(I) (II) (III)

	R¹	R²	R³
(1)	Me	Me	Me
(2)	Me	CD_3	Me
(3)*	Me	Me	Me
(4)	Me	Me	Et
(5)	Me	Et	Me
(6)	Et	Et	Me
(7)	Ph	Me	Ph
(8)	Me	H	Me
(9)	Ph	H	Ph

* 21·76% ^{18}OH-labelled.

Table 1

Mass spectra of compounds (1)—(7) and (10)

(1)	*m/e*	28	29	31	41	42	43	44	45	58
	I(%)	12	3	27	18	7	39	8	3	7
	m/e	59	60	69	84	87	102			
	I(%)	100	4	4	2	4	0·8			
(2)	*m/e*	27	28	29	30	31	32	33	39	40
	I(%)	2	7	3	2	20	18	10	4	4
	m/e	41	42	43	44	45	46	59	60	61
	I(%)	13	6	41	11	6	20	37	10	11
	m/e	62	63	87	90	105				
	I(%)	100	16	2	4	0·6				
(3)	*m/e*	28	29	31	33	41	42	43	44	45
	I(%)	10	4	25	6	17	8	40	8	6
	m/e	58	59	60	61	69	87	102	104	
	I(%)	7	100	4	12	4	4	0·9	0·2	
(4)	*m/e*	27	28	29	31	39	41	43	45	55
	I(%)	4	5	7	15	2	8	17	2	7
	m/e	57	59	60	73	87	116			
	I(%)	4	100	5	12	3	1·3			
(5)	*m/e*	26	27	28	29	31	39	41	42	43
	I(%)	3	16	6	19	20	9	17	5	72
	m/e	44	45	55	57	59	60	69	72	73
	I(%)	3	18	62	8	80	3	7	2	100
	m/e	74	87	98	116					
	I(%)	5	10	2	0·6					
(6)	*m/e*	27	28	29	31	39	41	43	44	45
	I(%)	9	7	17	7	4	12	36	15	40
	m/e	53	55	56	69	72	73	74	83	87
	I(%)	2	47	3	9	3	100	5	3	26
	m/e	101	130							
	I(%)	7	0·2							
(7)	*m/e*	26	27	28	32	39	40	41	42	43
	I(%)	3	5	18	2	5	3	8	5	87
	m/e	44	50	51	76	77	78	91	96	97
	I(%)	9	5	18	3	49	9	5	2	7
	m/e	98	105	106	118	120	121	122	165	167
	I(%)	9	74	7	15	6	100	17	2	4
	m/e	182	183	184	208	226				
	I(%)	5	16	2	3	0·35				
(10)	*m/e*	27	28	29	39	41	43	45	55	56
	I(%)	4	8	19	6	25	2	2	3	8
	m/e	57	58	59	87	102				
	I(%)	100	4	2	4	6				

All ions greater than 2% of the base peak (arbitrarily 100%) are recorded. The molecular ions of lesser intensity are also included.

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[1] P. Brown and C. Djerassi, *Angew. Chem. Internat. Edn.*, 1967, **79**, 481.

[2] R. G. Cooks, J. Ronayne, and D. H. Williams, *J. Chem. Soc.* (*C*), 1967, 2601.

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[4] W. D. Crow, J. L. Occolowitz, and R. K. Solly, *Austral. J. Chem.*, 1968, **21**, 761.

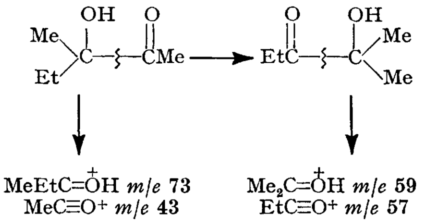
[5] K. G. Das, C. A. Chinchwadkar, and P. S. Kulkarni, *Chimia* (*Switz.*), 1968, **22**, 88.

[6] A. E. Favorskii, *Bull. Soc. chim. France*, 1926, **39**, 216.

upon electron impact to give fragments characteristic both of the original and of the rearranged α-hydroxy-ketones and that such fragments carry a large proportion of the total positive ion current. This contrasts with the rearrangement fragments of the pinacols,[5] which were of fairly low intensity (12% of the base peaks).

The mass spectra of the compounds (1)—(9) and pivalic acid, $Me_3C{\cdot}CO_2H$ (10) have been obtained. Those of (1)—(7) and (10) are recorded in Table 1. Acetoin (8) and benzoin (9) are not included since their spectra are described elsewhere.[7] The spectrum of 3-hydroxy-3-methylbutan-2-one (1) is included as it shows considerable differences from the published spectrum [7] in the intensities of individual fragments; there are no major differences in the fragment distribution.

The skeletal rearrangement ions in the spectra of (1), (2), and (4)—(7) are summarised in Table 2 and compared with the corresponding unrearranged ones. Thus, for example, major fragmentation modes for (5) appear to involve the processes shown in Scheme 1.



SCHEME 1

TABLE 2

Relative abundance of the rearranged and corresponding unrearranged ions in the spectra of (1), (2), and (4)—(7)

	$R_2C{=}\overset{+}{O}H$				$RC{\equiv}\overset{+}{O}$			
	Rearr.		Unrearr.		Rearr.		Unrearr.	
	m/e	*I*(%)	*m/e*	*I*(%)	*m/e*	*I*(%)	*m/e*	*I*(%)
(1)	*a*		59	100	*a*		43	38·5
(2)	59	37	62 [a]	100	46	20	43 [a]	40·5
(4)	73	12	59	100	43	16·5	57	4
(5)	59	80	73 [a]	100	57	8	43 [a]	72
(6)	73	100	87	25·5	57	3·5	43	36 [b]
(7)	183	16	121 [a]	100	43	86·5	105 [a]	73·5

[a] Rearranged and unrearranged fragments are identical. [b] Doublet consisting of 36% $C_2H_3O^+$ and 16% $C_3H_7^+$.

TABLE 3

Oxygen-18 content of important ions in the spectra of (3) and (1)

	Ratio of intensities (%) of *m/e*		
	104/102	61/59	45/43
$Me_2C(^{18}OH){\cdot}COMe$ (3) ...	22·3	12·45	16·05 *
$Me_2C(OH){\cdot}COMe$ (1)	0·2	0·32	6·85 *

* These values do not represent the actual ^{18}O content but are probably due to an additional species.

Table 3 shows for comparison the oxygen-18 content of important ions in the spectra of (3) and (1).

That the rearrangement of the hydroxy-ketones in the mass spectrometer is not due to a thermal reaction is shown by the following evidence. Compounds (1)—(3), (5), and (6) were purified by preparative g.l.c., which involved vaporisation at 200—220°, and were in fact recovered pure (n.m.r.). Methyl benzoin (7) was kept at 145° for 20 min. under nitrogen in a sealed tube filled with glass beads to increase the surface area. The n.m.r. spectrum of recovered material was identical with that of the starting material. Compounds (2) and (6) were studied for possible variations of the mass spectra with time under normal recording conditions. Five min. after admitting a sample of (2) to the source chamber through the heated inlet (160°) the spectrum was very similar to that shown in Table 1. After a further 10 min. in the source the same sample was re-scanned, and showed an unaltered spectrum. A sample of (6) was heated for 3 hr. in the ' hot box ' of the MS9 heated inlet system before being admitted to the source. Relative to *m/e* 73 as base peak the peaks at *m/e* 87, 55, 45, and 43 declined by 4, 1, 7, and 6% respectively, compared with the values shown in Table 1. These differences are probably within the range of reproducibility of the instrument.[8] In addition, the spectrum of (7) was determined by the direct insertion technique at low temperature. At 60—70° a partially scanned spectrum showed the presence of the rearrangement fragment at *m/e* 183 ($Ph_2C{=}\overset{+}{O}H$) and at 90—110° a fully scanned spectrum showed the presence of this ion with an intensity of 5% relative to the unrearranged fragment, *m/e* 121 ($PhMeC{=}\overset{+}{O}H$), as base peak.

The changes in the spectrum of (7) caused by reduced electron-beam energies were studied. As the energy was reduced from 70 to nominal 11 ev, the ions *m/e* <105 almost disappeared but the peaks *m/e* ⩾105 were unchanged except for minor variations in intensities. The percentage of the ion current carried by the skeletal rearrangement fragment *m/e* 183 ($Ph_2C{=}\overset{+}{O}H$) did not decrease but rather increased from 16 to 30%, and the ion *m/e* 208 $(M - 18)^+$ became more noticeable than at 70 ev. This showed that the most probable reason for the low intensity of *m/e* 183 relative to the other rearrangement fragments (Table 2) is its instability towards further fragmentation at high electron-beam energies.

These results show that in the compounds studied the rearrangements must be due essentially to electron impact and probably involve the high energy non-bonding pair of electrons of the carbonyl oxygen.

The general features of the mass spectra, apart from the presence of rearrangement ions, are consistent with a combination of those of tertiary alcohols and ketones.[9] In all cases the molecular ions and $M - H_2O$ peaks are extremely weak, characteristic of tertiary alcohols, but the peaks due to M — Me, or in the cases of (6) and (7) M — Et and M — Ph respectively, are weak or absent in

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[7] A. Cornu and R. Massot, ' Compilation of Mass Spectral Data,' Heydon and Son Ltd., London, 1966.

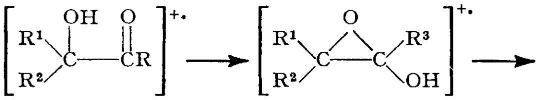
[8] P. C. Haake and M. J. Frearson, unpublished work.

[9] H. Budzikiewicz, C. Djerassi, and D. H. Williams, ' Interpretation of Mass Spectra of Organic Compounds,' Holden-Day, San Francisco, 1964.

contrast with those alcohols which tend to cleave next to the carbon carrying the hydroxy-group to form alkyl radicals. The principal fragments are in fact formed by cleavage α to the carbonyl group to give simple spectra comparable to those of ketones. McLafferty rearrangement, which is possible in (5) and (6) and would lead to $M - C_2H_4$ peaks, is not observed, although these spectra do contain low-abundance $M - 29$ ions.

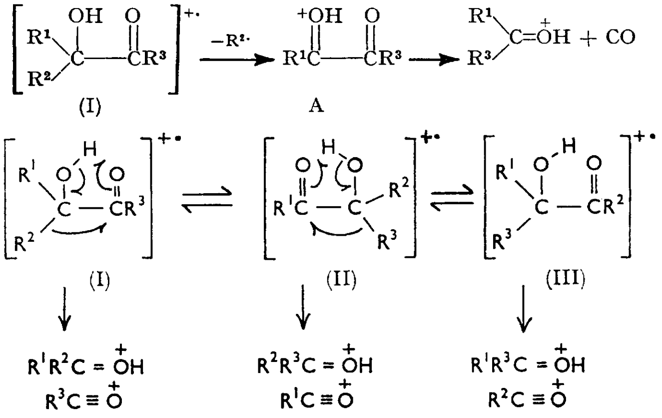
The identities of the rearrangement ions are mostly self-evident. In the spectrum of (6), the ion *m/e* 73, which might have been derived from the molecular ion by successive loss of Et and $CH_2{=}CH_2$, was shown to be C_4H_9O, not $C_3H_5O_2$, by high resolution mass measurement. We have considered three mechanisms for their formation.

The first, corresponding to the postulated mechanism of the acid-catalysed rearrangement, involves the formation of the isomeric hydroxy-epoxide (IV) followed by the 1,2-shift of either an R or a hydroxy-group. Thus the molecular ions of (I) would lead, by way of intermediates of the type (IV) to the molecular ions of (I), (II), (III), and of the trisubstituted acetic acid. The work of Audier and his co-workers[10] on the electron-impact induced rearrangement of epoxides leads to the expectation that 1,2-alkyl or -aryl shifts will be easy and that of Williams *et al.*[11] shows that 1,2-hydroxy-group shifts can occur. However, the spectrum of pivalic acid (10) (Table 1) gives no important fragment ions in the mass spectrometer, apart from *m/e* 41, in common with its isomer (1). In particular, the base peak of the pivalic acid spectrum, *m/e* 57, is absent from that of (1) and an intense metastable peak at *m/e* 29·5 shows that the *m/e* 41 species is derived from this ion by loss of methane. This argues strongly against the hydroxy-epoxide mechanism.



Molecular ions derived from (I), (II), (III), and $R^1R^2R^3C\cdot CO_2H$

The two other mechanisms envisaged are A and B (Scheme 2). So far as the former is concerned, analogies for the loss of an alkyl or aryl radical, followed by extrusion of carbon monoxide, with migration, are available.[2] This mechanism would thus account for the appearance of the rearrangement ions $R^1R^3C{=}\overset{+}{O}H$, though not satisfactorily for the complementary ions, *e.g.* $R^2\overset{+}{C}O$. Metastable peaks corresponding to molecular ion fragmentations are not observable in the normal spectra of (1)—(7). However, study of (7) by metastable defocussing[12] showed a weak transition corresponding to *m/e* 266 ⟶ 183 and no evidence for the transition *m/e* 211 ⟶ 183. Thus in the case of (7) the formation and fragmentation of the rearranged molecular ion, $[Ph_2C(OH)\cdot COMe]^{+\cdot}$, as in B is established.



SCHEME 2

Other evidence also favours mechanism B. It should first be noted that repeated 1,2-shifts lead to the formation of (I), (II), and (III) from the initial ionisation of (I) and, in general, equilibration of either (I), (II), or (III) is possible to give a distribution of the three molecular ions which is to some extent statistical and also must depend on the relative thermodynamic stabilities of the ions. The similarity of the mass spectra of isomeric compounds has been taken as good evidence for equilibration of the molecular ions.[2,13] Since the average time spent by a positive ion in the source of a mass spectrometer is 1—5 μsec.,[14] complete equilibration implies that the 1,2-shifts have very large rate constants.

The extent of rearrangement of (1) may be judged from the spectra of (2) and (3) on the assumption that secondary isotope and steric effects (as between CH_3 and CD_3 [15]) are within the experimental error of the instrument. The 2 : 1 ratio expected for complete equilibration of the deuteriated compound (2) is shown almost exactly by the *m/e* 43 and 46 peaks and the ratio *m/e* 62 : *m/e* 59 is in fair agreement (Table 2). Complete randomisation of the methyl groups in (3) labelled with 22·3% oxygen-18 would lead to 11·15% oxygen-18 in the derived $Me_2C{=}\overset{+}{O}H$ ion. The experimental value of 12·45% (Table 3) is in reasonable agreement. A species other than $CH_3\cdot C^{18}O^+$ must be contributing to *m/e* 45 in both (1) and (3) so that the ratio *m/e* 43 : *m/e* 45 cannot accurately reflect the amount of rearrangement.

Complete equilibration of the molecular ions of (4) and (5) would be expected to lead to similar spectra and proportions of the ions of *m/e* 73 and 59. Tables 1 and 2 show that the spectra are considerably different and

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[10] H. E. Audier, J. F. Dupin, M. Fétizon, and Y. Hoppilliard, *Tetrahedron Letters*, 1966, 2077.

[11] D. H. Williams, R. G. Cooks, J. H. Bowie, P. Madsen, G. Schroll, and S. O. Lawesson, *Tetrahedron*, 1967, **23**, 3173.

[12] K. R. Jennings, *J. Chem. Phys.*, 1965, **43**, 4176.

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[15] K. Mislow, R. Graeve, A. J. Gordon, and G. H. Wahl, *J. Amer. Chem. Soc.*, 1963, **85**, 1199; H. C. Brown and G. J. McDonald, *ibid.*, 1966, **88**, 2514; H. C. Brown, M. E. Azzaro, J. G. Koelling, and G. J. McDonald, *ibid.*, 1966, **88**, 2520.

randomisation of the alkyl groups cannot have occurred. Metastable transitions are found in both spectra for the loss of water from the $R^1R^2C{=}\overset{+}{O}H$ ions and the intensities of the fragments of *m/e* 58 and 41, respectively, bear a fairly constant ratio to those of the parent ions, *e.g. m/e* 73 : 55 is 1·7 : 1 in the spectrum of (4) and 1·6 : 1 in that of (5). This indicates that the energies of these ions in the two spectra are approximately equal.

Other evidence against complete equilibration of the kind represented in the proposed mechanism is found in the spectrum of (6). The rearrangement ion $EtMeC{=}\overset{+}{O}H$ (the base peak) is almost four times as intense as the unrearranged ion, $Et_2C{=}\overset{+}{O}H$; this ratio is far greater than the value of 2 : 1 expected to result from equilibration. It may be, however, that with increasing complexity, the $R_2C{=}\overset{+}{O}H$ ions become significantly less stable. Indirect evidence which supports this can be seen in the intensity of the complementary ion, $MeC{\equiv}O^+$. In most of the compounds in which this is a possible acyl fragment it is less intense than the corresponding $R_2C{=}\overset{+}{O}H$ ion (Table 2). In the case of (6) the opposite is true, and comparison with (2), where *m/e* 43 is of a similar intensity, points to the ease of fragmentation of $Et_2C{=}\overset{+}{O}H$ relative to $EtMeC{=}\overset{+}{O}H$ being the real reason for its low intensity.

Finally, and perhaps most important, the mass spectra of acetoin (8) and benzoin (9) show no ions due to rearrangement; this shows either that hydrogen migrates much more readily than either Me or Ph, or that no rearrangement takes place. We favour the former explanation, in agreement with the recent finding [4] that in phenylhydrazones migration of hydrogen is much easier than that of a phenyl group in the mass spectrometer. In the acid-catalysed rearrangement of unsymmetrical acyloins it was observed that the isomeric acyloin, not the hydroxy-aldehyde, was formed by a 1,2-hydrogen shift; [6] this reinforces the analogy between the acid-catalysed and the electron-impact induced rearrangements.

Other workers [10,16] have raised the question of the possibility of determining relative migratory aptitudes in rearrangements such as this. The foregoing remarks indicate that this will not in general be straightforward.[4] If it could be assumed that a certain fraction of the molecular ions rearranged once and once only in the general structures (I), (II), or (III), and that the six possible primary fragments were equally stable to further fragmentation then it would be possible to determine approximate ratios of rearrangement to non-rearrangement, and migratory aptitudes. However, this will represent an extremely favourable case. In general it will be necessary to determine the extent to which equilibration of the molecular ions is taking place, by double labelling with oxygen-18 and deuterium, or to examine all the possible isomeric hydroxy-ketones in conjunction with low voltage studies, before any such results become useful. It is also an open question whether the concept of migratory aptitudes is meaningful in the context of a highly energetic equilibrating molecular ion.[14] We hope to report such studies in due couse.

EXPERIMENTAL

Mass spectra were obtained with an A.E.I. MS9 instrument operating at 70 ev by use of a heated inlet system at 180—200° and a source temp. of 150—160°, unless otherwise stated. All compounds were purified before use.

α-Bromo-ketones.—These were prepared from the appropriate ketone by reaction with *N*-bromosuccinimide in carbon tetrachloride,[17] and hydrolysed to the corresponding α-hydroxy-ketones.[18]

α-Hydroxy-ketones.— 3-Hydroxy-3-methylbutan-2-one (1) had b.p. 41—43°/14 mm., n_D^{20} 1·4155 (lit.,[19] n_D^{18} 1·417). 3-Ethyl-3-hydroxypentan-2-one (6), b.p. 63°/21 mm. was further purified by g.l.c.; n_D^{25} 1·4235 (lit.,[20] n_D^{25} 1·4231). 2-Hydroxy-2-methylpentan-3-one (4) had n_D^{20} 1·4193 (lit.,[21] $n_D^{14·5}$ 1·4238). 3-Hydroxy-3-methylpentan-2-one (5), prepared from methyl magnesium iodide and biacetyl had b.p. 46—50°/14 mm. (lit.,[21] 52°/17 mm.) and was further purified before use by g.l.c. 2-Hydroxy-2,3-diphenylpropan-3-one (7) had m.p. 66—67° (lit.,[22] 67—68°).

3-Hydroxy-3-trideuteriomethylbutan-2-one.—A solution of trideuteriomethylmagnesium iodide (5 mmoles) in ether was slowly added to a solution of biacetyl (5 mmoles) in ether, cooled to 0°, under dry nitrogen. After hydrolysis with ammonium chloride solution the product was extracted with ether and purified by preparative g.l.c. (12 ft. 20% LAC on silazined 60—80 Celite at 70°). A second separation (7 ft. Apiezon L at 75°) gave a colourless liquid (56 mg., 11%) (Found: C, 57·1. $C_5H_7D_3O_2$ requires C, 57·2%), τ (CCl_4) 8·67 (3H, s), 7·78 (3H, s), and 6·40 (1H, s).

[Hydroxy-^{18}*O]-3-hydroxy-3-methylbutan-2-one*.—3-Bromo-3-methylbutan-2-one was hydrolysed, by a modification of the procedure of Aston and Greenberg,[18] in a dioxan–sodium–[^{18}O]water system labelled with 21·76% ^{18}O (Yeda Research and Development Co. Ltd., Rehovoth, Israel) and the hydroxy-ketone was separated by g.l.c. Oxygen-18 in the carbonyl group was reduced to the natural abundance by equilibration in 0·1N-potassium hydroxide and the product was re-separated by preparative g.l.c The isotopic purity and absence of impurities were established by mass spectrometry (Found: *m/e* 104 : 102, 22·3. Calc. 21·96%).

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