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Mass Spectrometry in Structural and Stereochemical Problems. 250.[1] Characteristic Fragmentations of Cholesterol Acetate[2]

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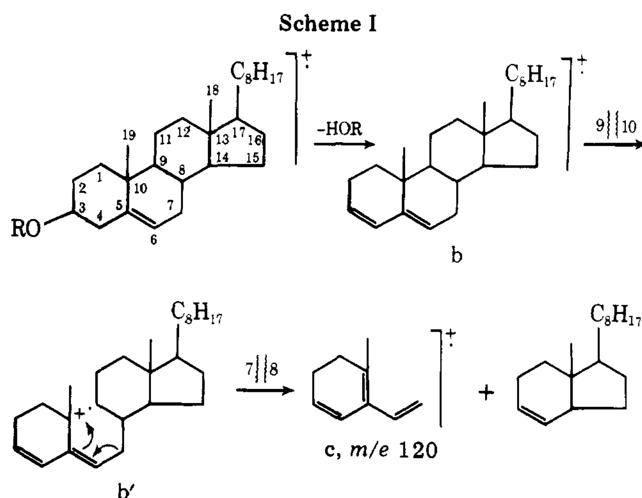
Through the use of extensive deuterium labeling, the structure and origin of the diagnostic fragments of cholesterol acetate have been clarified. Deuterium labels at carbon atoms 9, 11, 12, 14, and 19 which have not previously been reported for cholesterol itself provide information on the genesis of the characteristic $M^+ - 168$ (*m/e* 260) and $M^+ - 181$ (*m/e* 247) fragments of the acetate as well as on the more common loss of acetic acid (*m/e* 368), ring D fragmentation (*m/e* 213), and the proposed retro-Diels–Alder fragment (*m/e* 120). The mass spectra of cholesterol acetate and the free sterol are compared, and further information is provided on the fragments of mass 247, 231, and 213 in cholesterol.

The Δ^5-steroidal olefins and especially those with 3β-hydroxyl substituents and their esters are among the most common naturally occurring steroids. It is not surprising, therefore, that sterols have been the subject of numerous studies attempting to identify them by their characteristic electron impact induced fragmentation. The mass spectrum of cholesterol acetate (Figure 1) is quite different from that of cholesterol (Figure 2) but surprisingly has hardly been examined critically even though sterol acetates are frequently derivatives which are employed in separation schemes of naturally occurring sterol mixtures (e.g., from marine sources). The origins of the major electron impact induced fragments of cholesterol have been established in two recent papers,[4,5] and we have now utilized a number of new labeled cholesterols synthesized in this laboratory during our recent study[1] of the ring D fragmentation of some steroidal olefins to provide information on the acetate.

The characteristic $M^+ - 85$ (*m/e* 301) and $M^+ - 111$ (*m/e* 275) peaks in the mass spectrum of cholesterol (Figure 2) have no analogue in that (Figure 1) of the acetate. A fragment of mass 260 is unique to the latter while *m/e* 247 is present in both spectra as is a small peak at *m/e* 120. Zaretskii[6a] suggested that perhaps the most characteristic peak of the Δ^5-steroids is *m/e* 247, which is present in both cholesterol acetate and the free sterol. Friedland et al.[7] proposed the structure for this fragment shown in (a) which was examined by Knights[8] in his study of Δ^5-3β-hydroxyl sterols who also proposed (a) as the most likely cleavage. However, Budzikiewicz and Ockels[4] found that in their androst-5-en-3β-ols, labels at C-15 and C-16 which would be completely retained in structure (a) were retained only to the extent of 70% in *m/e* 135 (analogous to *m/e* 247 in a steroid with no C-17 substituent). The authors pointed out that while (a) could be established as the major source of *m/e* 135, there must be other contributing fragments. Consistent with this, metastable defocusing showed a number of progenitor ions for that peak in their androstenols. Budzikiewicz and Ockels[4] did note a large apparent transfer from C-8 and C-9 indicating that these sites are the origin of the shifted protons.

A peak at *m/e* 120 was reported in $\Delta^{3,5}$-cholestadiene and cholesterol acetate by Galli and Maroni[9] who proposed its formation in the thermally disallowed retro-Diels–Alder fragmentation of the 3,5-dienyl system (Scheme I). These

Scheme I



authors suggested that this fragment (c) or its analogue should be present in the mass spectrum of a Δ^5-steroid and might be the most characteristic type of fragmentation for such an olefin. This proposal has been questioned by Zaretskii,[6a] who pointed out that since the actual origin of *m/e* 120 was not known and since a wide range of steroidal olefins show a group of peaks of similar intensity in that mass range, more careful study of the origin of this peak would be necessary before it

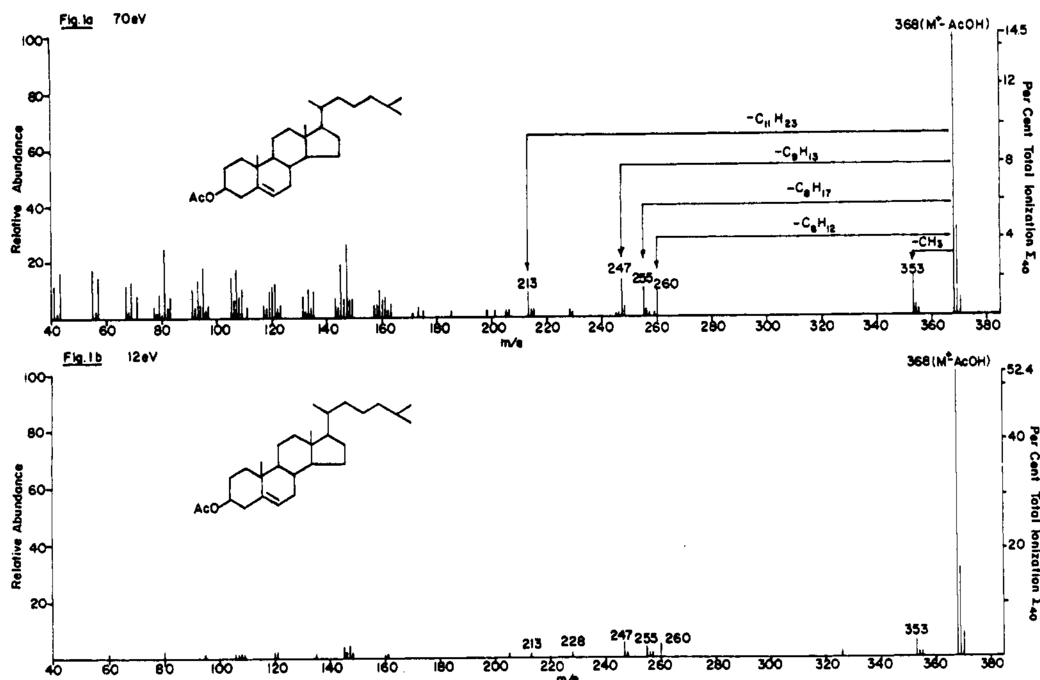


Figure 1. Mass spectra of cholesterol acetate (**1b**): (a) 70 eV; (b) 12 eV.

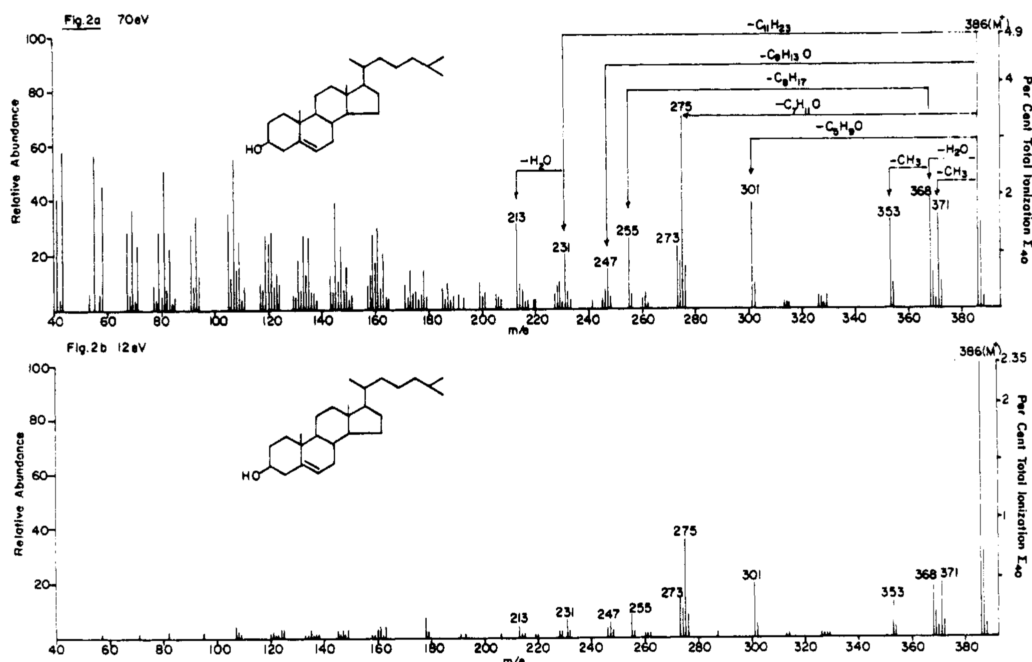
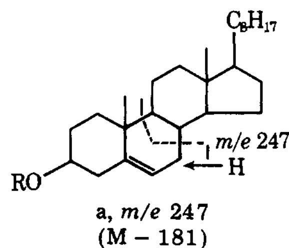


Figure 2. Mass spectra of cholesterol (**1a**): (a) 70 eV; (b) 12 eV.

could be considered characteristic of any particular class of steroids.



a, *m/e* 247
(M − 181)

Results and Discussion

Since the mass spectrum of cholesterol-*2,2,4,4-d*$_4$ acetate (**11b**) (Table I) shows no more than three deuterium labels in the $M^+ - 60$ peak, virtually all of the acetic acid loss must involve adjacent carbon atoms, presumably the allylically activated C-4. Consistent with this observation is the fact that no detectable transfer was observed (Table I) from the other labeled acetates. Zaretskii[6b] has speculated that the absence of a molecular ion peak in the mass spectra of the Δ^5-steroidal 3β-acetates reported by Galli and Maroni[9] could have been due to the high temperatures used in that study. However, we have found that no molecular ion is visible in the mass spectrum of the acetate even if the samples are run using a direct insertion probe. Because of this facile 1,2-elimination of acetic acid, the mass spectrum of cholesterol acetate is quite different from that of cholesterol and must be explained in terms of fragmentation of a $\Delta^{3,5}$-cholestadiene (or isomeric diene) species (*m/e* 368, $M^+ - 60$) which is the largest fragment in the spectrum.

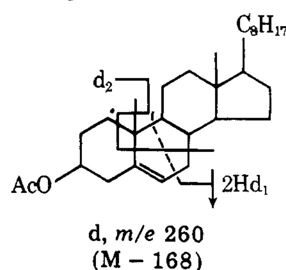
Table I. Shifts[a] of Mass Spectral Peaks of Deuterated Cholesterol Acetates

Registry no.	Compd	Label	Isotope composition, %	$M^+ - AcOH$	$M^+ - CH_3 - AcOH$	$M^+ - C_8H_{12} - AcOH$	$M^+ - C_8H_{17} - AcOH$	$M^+ - C_9H_{13} - AcOH$	$M^+ - C_{11}H_{23} - AcOH$
604-35-3	**1b**		Cholesterol acetate	368	353	260	255	247	213
62743-51-5	**12b**	*3α-d_1*	2 d_0 98 d_1	369	354	260	256	247	214
62743-52-6	**10b**	*1β-d_1*	23 d_0 73 d_1 4 d_2	369	354	260	256	247	214
62743-53-7	**11b**	*2,2,4,4-d_1*	3 d_0 3 d_1 8 d_2 29 d_3 54 d_4 3 d_5	371	356	260	258	247	216
62743-54-8	**13b**	*7,7-d_2*	4 d_0 6 d_1 90 d_2	370	355	260 (26%) 261 (62%) 262 (12%)	257	247	214 (26%) 215 (74%)
62743-55-9	**14b**	*8β-d_1*	3 d_0 96 d_1 1 d_2	269	354	261	256	247 (47%) 248 (53%)	213 (11%) 214 (89%)
62743-56-0	**2b**	*9α-d_1*	12 d_0 88 d_1	369	354	260 (6%) 261 (94%)	256	247 (9%) 248 (91%)	213 (25%) 214 (75%)
62743-57-1	**3b**	*11,11-d_2*	4 d_1 96 d_2	370	355	261 (4%) 262 (96%)	257	249	215
62743-58-2	**4b**	*12,12-d_2*	28 d_1 72 d_2	370	355	262	257	249	215
62743-59-3	**9b**	*14α-d_1*	4 d 96 d_1	369	354	260 (45%) 261 (55%)	256	247 (26%) 248 (74%)	213 (25%) 214 (75%)
62743-60-6	**5b**	*19-d_1*	9 d_0 91 d_1	369	353 (67%) 354 (33%)	260	256	247	213 (9%) 214 (91%)
62743-61-7	**15b**	*26,26,26,-27,27,27-d_6*	2 d_2 4 d_3 9 d_4 24 d_5 61 d_6	374	359	266	255	253	213

[a] The shift values have been corrected for ^{13}C contributions and effects due to isotope composition. The spectra were measured at 70 eV.

Loss of a methyl group from $M^+ - 60$ in cholesterol acetate or from M^+ in the free sterol results in both cases in a 67% loss of the C-19 label (Tables I and II). These figures are in fair agreement with those of the 19-labeled pregnenediol analogue used by Wyllie et al.[5] which showed a 58% loss of C-19 in the $M^+ - 15$ peak. The quantitative differences are probably due to the different steroid models rather than to the different instruments used to measure the mass spectra. For instance, in Δ^7-steroids considerable variation in the ratio of loss of the C-18 and C-19 angular methyl groups with variation of the length of the C-17 side chain has been observed.[1] Loss of water and methyl radical in the spectrum of cholesterol to give *m/e* 353 resulted in 77% loss of C-19, and the presence of metastable peaks at *m/e* 336 (371 → 353) and *m/e* 339 (368 → 353) shows that either loss of H_2O from M^+ (*m/e* 368) or loss of methyl from M^+ (371) can precede the formation of *m/e* 353. It is evident that initial loss of water from M^+ in cholesterol must have a significant effect on the expulsion of C-19 over C-18 whereas the loss of acetic acid from cholesterol acetate does not. This is in good agreement with the proposal[5] that loss of water from M^+ in cholesterol is preceded to a large extent by skeletal cleavages.

The data in Table I indicate complete loss of the label on carbon atoms 1, 2, 3, 4, and 19 and retention at positions 8, 12, 26, and 27 for the ion of mass 260. The retention of C-7 which would differentiate between fragments d_1 and d_2 cannot be established directly from the mass spectrum of the C-7 labeled cholesterol acetate (**13b**) since one of the C-7 labels is lost cleanly while the second is retained to the extent of 74%. This could be due to contribution by a species arising from complete loss of C-7 after proton exchange with the charge retaining fragment (d_2) or to stepwise transfer of one or both of the C-7 protons to the portion of the molecule lost in d_1.



d, *m/e* 260
(M − 168)

Partial retention of the label at C-7 in d_2 would most likely involve abstraction of one of the allylic C-7 protons by a radical somewhere in the charge retaining portion of the molecule followed by abstraction of another proton by the radical at C-7 which the data in Table I indicate would originate mostly from C-14. Since transfer to the hypothetical radical at C-7 would proceed through a 1,3 shift from C-14 rather than a 1,2 shift from C-8, a rationalization of d_2 would have to include activation of the C-14 proton for transfer as well as removal of the availability of the C-8 proton. Furthermore, since both the angular methyl group (C-19) and the skeletal fragment are lost, metastable defocusing would be expected to show cleavage d_2 to proceed through a stepwise loss of these unconnected fragments; however, this is not the case. The only parent seen (Table III) for *m/e* 260 (in the first field-free re-

Table II. Shifts[a] of Mass Spectral Peaks of Deuterated Cholesterols

Registry no.	Compd	Label	Isotope composition, %	M^+	$M^+ - CH_3$	$M^+ - H_2O$	$M^+ - CH_3 - H_2O$	$M^+ - C_5H_9O$	$M^+ - C_7H_{11}O$	$M^+ - C_8H_{17}$	$M^+ C_8H_{17} - H_2O$	$M^+ - C_9H_{15}O$	$M^+ - C_{11}H_{23}$	$M^+ - C_{11}H_{23} - H_2O$
57-88-5	**1a**	Cholesterol		386	371	368	353	301	275	273	255	247	231	213
7604-	**11a**	*2,2,4,4-*	3 d_0	390	375	372	357	301	275	277	259	247	235	217
91-3		d_4	3 d_1											
			8 d_2											
			29 d_3											
			54 d_4											
			3 d_5											
62743-	**2a**	*9α-d_1*	12 d_0	387	372	368	353	301	276	274	255	247	231	213
62-8						(19%)	(12%)	(11%)			(14%)	(25%)	(8%)	(29%)
			88 d_1			369	354	302			256	248	232	214
						(81%)	(88%)	(89%)			(86%)	(75%)	(92%)	(71%)
62743-	**3a**	*11,11-d_2*	4 d_1	388	372	370	355	303	277	275	257	248	232	215
63-9												(5%)	(3%)	
			96 d_2									249	233	
												(95%)	(97%)	
62743-	**4a**	*12,12-d_2*	28 d_1	388	373	370	355	303	277	275	257	248	232	214
64-0												(5%)	(2%)	(1%)
			72 d_2									249	233	215
												(95%)	(98%)	(99%)
62743-	**9a**	*14α-d_1*	4 d_0	387	372	369	354	301	276	274	256	247	231	213
65-1								(22%)				(26%)	(37%)	(26%)
			96 d_1					302				248	232	214
								(78%)				(74%)	(63%)	(74%)
62743-	**5a**	*19-d_1*	9 d_0	387	371	369	353	302	276	274	256	247	231	213
66-2					(67%)		(77%)						(17%)	(28%)
			91 d_1		372		354						232	214
					(33%)		(23%)						(83%)	(72%)

[a] The shift values have been corrected for ^{13}C contributions and effects due to isotopic composition. The spectra were measured at 70 eV.

gion) is m/e 368 ($M^+ - 60$); therefore, any rationalization of this cleavage would also necessarily include migration of the C-19 angular methyl group to the expelled portion of the molecule. Because of these requirements any mechanistic rationalization of d_2 becomes unfavorably long and complex.

Absolute differentiation between d_1 and d_2 would require ^{13}C labeling. However, since d_1 can be rationalized most believably using standard techniques, it would seem to be the most favorable possibility. The formal vinylic cleavage and additional loss of both protons from C-7 required in d_1 necessitate a mechanism which would include isomerization of the double bond and several successive proton shifts; because of the complex nature of these processes, any rationalization should be considered highly speculative.

In contrast to the multiple progenitor ions reported by Budzikiewicz and Ockels[4] in their discussion of the peak analogous to m/e 247 in the study of Δ^5-androstenols, metastable defocusing work done in this study (Table III) on cholesterol acetate shows that the expected parent m/e 368 ($M^+ - 60$) is virtually the only source of this peak. It is notable that since the model compounds used by Budzikiewicz and Ockels[4] possessed no side chain, the corresponding fragment was of significantly lower mass and therefore appeared in a portion of the mass spectrum which is much more likely to contain fragments from a multitude of different pathways.

The deuterium labeling data in Table I show that the fragment at mass 247 in cholesterol acetate has the schematic structure shown in (a), the same as established by Wyllie et al.[5] for the free sterol. The transferred deuterium originates at C-8 (47%) and C-14 (26%) with some transfer from C-9 (9%). Wyllie et al.[5] established that in cholesterol major portions (55%) of the transferred hydrogen originate at C-8. Using a Δ^5-cholen-3β-ol model compound labeled at C-9 they reported that transfer from this position appeared to be of equal importance. However, neither of the previous studies[4,5] included sterols labeled at C-14, and our work (Table II) indicates that in cholesterol transfer from C-9 and C-14 are of approximately equal importance (25 and 26%, respectively). A mechanism which would provide a route to the desired fragment is shown in Scheme II (b → e → f) for the ionized diene species b presumed to be the major constituent of m/e 368 in cholesterol acetate. This mechanism allows access by the C-7 carbonium to positions 8 and 9 as well as 14 as does the mechanism proposed by Wyllie et al.[5] for the free sterol, and either of these

Scheme II

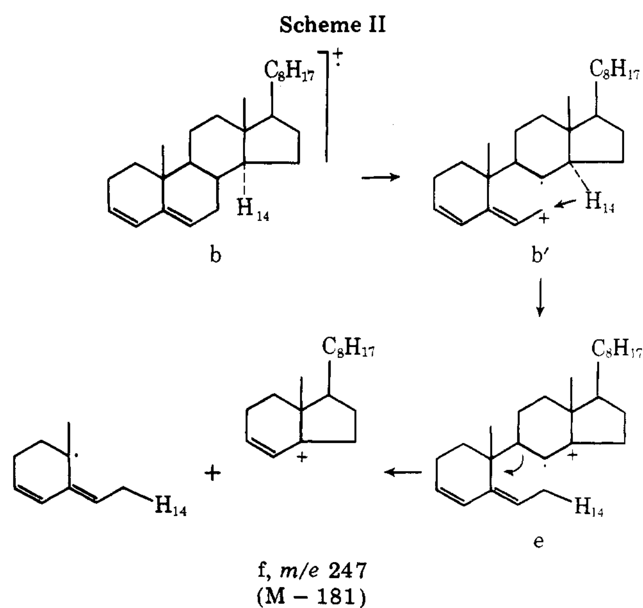


Table III. Cholesterol Acetate Metastable Defocusing[a] Data

Daughter ion	Parent ion	% area
260	368 (M^+ − AcOH)	100
247	368	>95
	354	<5
246	368	>95
	261	<5
213	368	35
	353	<5
	326	<5
	255	<5
	228	55
121	368	30
	247	20
	206	20
	191	<5
	177	10
	163	5
	149	5
	136	5
120	368	50
	260	10
	228	5
	214	5
	202	5
	176	<5
	162	5
	148	5
	135	5
119	368	5
	353	10
	255	5
	215	5
	201	5
	187	<5
	175	5
	161	15
	147	25
	134	20

[a] Values are given in terms of relative percent area of the parent peak in the defocused spectrum and are accurate to ±5%. Measurements were made on an AEI MS-9 double focusing mass spectrometer.

rationalizations is equally valid for cholesterol or the acetate.

The ion of mass 213 in cholesterol acetate can be seen to occur via the usual ring D cleavage involving loss of carbon atoms 15, 16, and 17 together with their substituents and one additional hydrogen atom.[1,10] The proton transferred to this fragment originates (Table IV) from positions 7, 9, and 14 (29, 27, and 27%, respectively) in approximately equal amounts with some transfer also from C-8 (12%). These values have been corrected for the existence of an unrelated fragment at *m/e* 213 which is the product of loss of carbons 16 and 17 and their substituents followed by expulsion of C-19 (Tables I and III) as described previously for the unsaturated steroids and steroidal olefins.[1,10]

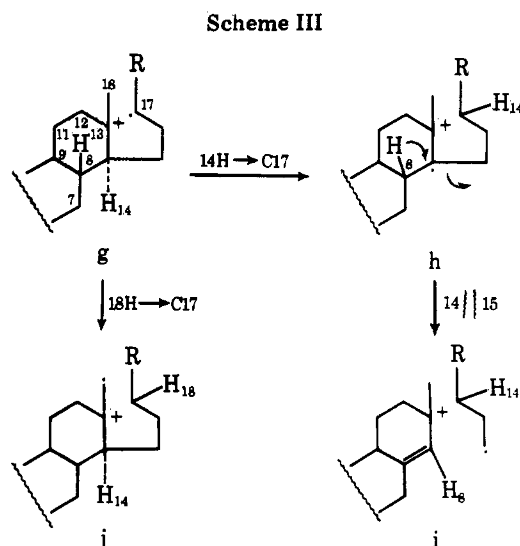
In cholesterol the ring D fragmentation with or without loss of the 3β substituent occurs with hydrogen transfer originating much more specifically from C-14 (45% in the formation of *m/e* 231 and 36% in 213), the second largest site of transferred hydrogen being C-8 in the formation of *m/e* 231 (20%) with most of the remaining transfer from carbon atoms 7 and 9. The ion of mass 213 shows considerably more transfer from C-9 (40%) although some of this [19% in the case of *m/e* 368 (M^+ − 18), Table II] is due to loss of the label at C-9 in the expulsion of the 3β-hydroxyl substituent. The fragmentation pathway (g → h → i) would be expected to be exactly analogous to the one proposed for the corresponding cleavage in saturated steroids[10] and steroidal olefins[1] and is discussed in greater detail in those papers. In the Δ^5-steroids as established for the other steroidal olefins,[1] abstraction from C-18 to form a primary radical j is expected to be much less favorable than in the saturated steroids[10] due to the availability of allylically activated C-7 protons.

Table IV. Deuterium Transfer (%)[a] in the Ring D Cleavage of Labeled Cholesterols and Cholesterol Acetates

	Labeled position						Total,
	14	12	11	9	8	7	%
	Cholesterols						
m/e 231	45	2	4	10	20[b]	8[b]	89
m/e 213	36	1	0	40	7	14	98
	Cholesterol acetates						
m/e 213	27	0	0	27	12	29	95

[a] These values have been corrected for ^{13}C contributions, isotopic composition, and the presence of fragments originating from other cleavage patterns involving loss of C-19 as described in the text. [b] Data from ref 13.

Scheme III



The labeling data presented in Table V indicate that the *m/e* 120 peak of cholesterol and cholesterol acetate is shifted by the presence of deuterium on carbons 1–7 and on C-19, supporting the proposal of Galli and Maroni[9] that some or all of this peak is due to a retro-Diels–Alder type fragmentation of the presumed $\Delta^{3,5}$-dienyl system resulting from the loss of the 3β substituent (Scheme I). The fragment represented by structure c is then probably a major contributor to *m/e* 120; however, Table V also shows that the peaks at *m/e* 119 and 121 are not shifted cleanly by the deuterium labels and are therefore the result of multiple fragmentation pathways. This is as expected since these peaks are visible in the mass spectra of a wide variety of steroids; their presence makes the exact total composition of *m/e* 120 difficult to elucidate and virtually eliminates the diagnostic utility of the *m/e* 120 peak. The metastable defocusing data of Table III show that in the first field-free region the largest portion of the peak at *m/e* 120 originates directly from *m/e* 368 as would be expected for the RDA fragment c. Both *m/e* 119 and 121 show three major progenitor ions and numerous minor ones supporting the idea that these peaks are composed of a variety of fragments.

In summary, due to the facile 1,2-elimination of acetic acid, the mass spectrum of cholesterol acetate exhibits no molecular ion and the most characteristic peaks in the spectrum, *m/e* 260

Table V. Mass Spectral Peaks[a] of Labeled Cholesterols and Cholesterol Acetates in the Region of *m/e* 120

Labeled position	Peak 117	118	119	120	121	122	123	124	125
				Cholesterols					
(d_0)	39	23	100	87	97	23	45	26	32
$9(d_1)$	26	20	74	100	67	50	41	37	21
$11(d_2)$	18	16	51	100	95	48	64	40	47
$12(d_2)$	33	29	82	100	45	40	53	36	41
$14(d_1)$	38	39	80	100	65	41	27	31	26
$19(d_1)$	25	17	57	60	100	58	32	15	27
				Cholesterol Acetates					
(d_0)	39	23	80	90	100	28	40	0	0
$1(d_1)$	31	20	54	31	100	50	45	13	0
$2,2,4,4(d_4)$[b]	19	18	53	19	71	21	100	39	16
$3(d_1)$	31	29	65	49	100	45	27	2	0
$7(d_2)$	25	33	89	66	100	85	25	19	1
$8(d_1)$	39	36	60	100	55	57	28	15	8
$9(d_1)$	29	35	54	100	86	49	32	25	0
$11(d_2)$	19	17	45	100	85	28	43	14	26
$12(d_2)$	29	26	55	100	71	30	34	21	23
$14(d_1)$	31	28	58	100	66	28	22	18	0
$19(d_1)$	22	13	44	48	100	64	30	10	0
$26,27(d_6)$	41	23	82	100	98	25	47	0	0

[a] See footnote *a*, Table I. [b] After loss of AcOD, this compound is labeled with three remaining deuterium atoms.

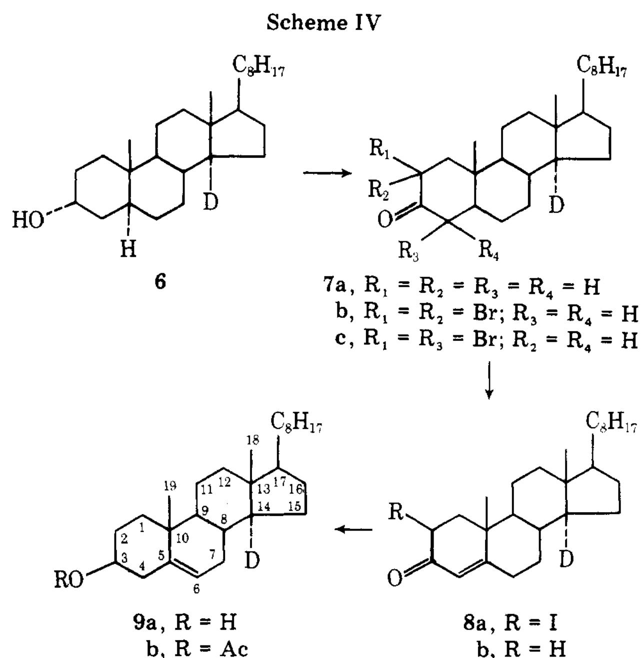
($M^+ - 168$) and 247 ($M^+ - 181$), appear to originate from *m/e* 368 ($M^+ - 60$). Elimination of the 3β substituent in the free sterol proceeds through an entirely different route[5] and the major peaks in its spectrum, *m/e* 301 ($M^+ - 85$) and 275 ($M^+ - 111$), are absent from that of the acetate. These characteristic peaks are of great diagnostic utility and the mechanistic origins of them have proven extraordinarily complicated and virtually unprecedented. This affords another example of the importance of deuterium labeling in unraveling fragmentation mechanisms.

Synthesis

The benzoate esters of cholesterol (**1a**) labeled at carbon atoms 9, 11, 12, and 19 were intermediates in the recently reported[1] synthesis of the correspondingly labeled Δ^7-cholestenes, and hydrolysis provided cholesterol-*9α*-d_1 (**2a**), cholesterol-*11,11*-d_2 (**3a**), cholesterol-*12,12*-d_2 (**4a**), and cholesterol-*19*-d_1 (**5a**). Cholesterol-*14α*-d_1 (**9a**) was accessible through the known cholestan-3α-ol-*14α*-d_1 (**6**)[1] which was oxidized to the ketone (**7a**) and converted to cholest-4-en-3-one-*14α*-d_1 (**8b**) (Scheme IV) by successive dibromination[11] to **7b**, rearrangement to **7c**, sodium iodide treatment to **8a**, and chromous chloride reduction.[12] Conversion of the Δ^4-3-ketone **8b** to cholesterol-*14α*-d_1 (**9a**) was effected by the method of Dauben and Eastham.[13] The syntheses of the remaining compounds [cholesterol-*1β*-d_1 (**10a**),[5] cholesterol-*2,2,4,4*-d_4 (**11a**),[14] cholesterol-*3α*-d_1 (**12a**),[5] cholesterol-7,7-d_2 (**13a**),[15] cholesterol-*8β*-d_1 (**14a**),[5] and cholesterol-*26,26,-26,27,27,27*-d_6 (**15a**)][5] have been reported in the literature and their respective acetates **1b, 2b, 3b, 4b, 9b, 10b, 11b, 12b, 13b, 14b,** and **15b** were available by acetic anhydride treatment.

Cholest-4-en-3-one-*14α*-d_1 (8b). Cholestan-3α-ol-*14α*-d_1[1] (**6**, 400 mg) was oxidized in acetone (40 mL) using an excess of Jones reagent. Extraction into ether and evaporation of the combined extracts provided cholestan-3-one-*14α*-d_1 (**7a**), mp 127–129 °C (lit.[11] 128–130 °C), which was converted to **8b** in the same way as described for the unlabeled compound.[11] Successive dibromination, rearrangement in acetic acid, and dehydrobromination with sodium iodide followed by chromous chloride reduction[12] gave **8b** contaminated with some starting material **7a** which was removed by chromatography on silica. Elution with 30% ether/hexane gave 230 mg of **8b**:

Scheme IV



mp 82–83.5 °C (lit.[11] 79–81 °C); δ 5.59 (s, 1 H, vinyl), 1.19 (s, 3 H, C-19 calcd[16] 1.19), 0.72 (s, 3 H, C-18 calcd. 0.72); M^+ *m/e* 385.

Cholesterol-*14α*-d_1 (9a). Cholest-4-en-3-one-*14α*-d_1 (**8b**, 48 mg) was stirred at room temperature under N_2 in 10 mL of dry dimethylformamide until dissolved. Potassium *tert*-butoxide (90 mg) was added and the reaction mixture was stirred under N_2 for 2 h and poured into a briskly stirred solution of 500 mg of $NaBH_4$ in 20 mL of 10% aqueous methanol.[13] The mixture was stirred for another 15 min, then extracted into ether, evaporated, and recrystallized from methanol to produce pure cholesterol-*14α*-d_1 (**9a**): 27 mg; mp 145 °C (lit.[1] 145 °C); NMR identical with that of unlabeled material; M^+ *m/e* 387.

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Registry No.—**6**, 62777-57-5; **7a**, 62743-67-3; **8b**, 62743-68-4.

References and Notes

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(2) Taken in part from the Ph.D. Dissertation of L. G. Partridge, 1977.
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Reactions of New Organocuprates. 2.[1] Substitution Reactions of Alkyl, Cycloalkyl, and Aryl Halides with $LiCu_2(CH_3)_3$, $Li_2Cu(CH_3)_3$, and $Li_2Cu_3(CH_3)_5$

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The new cuprates $LiCu_2(CH_3)_3$, $Li_2Cu(CH_3)_3$, and $Li_2Cu_3(CH_3)_5$ in Et_2O and THF have been compared to $LiCu(CH_3)_2$ and CH_3Li in their reaction toward alkyl, cycloalkyl, and aryl halides (where halogen = I, Br, Cl, F). In most cases the new cuprate $Li_2Cu(CH_3)_3$ was superior to all other reagents and in some cases the superiority was substantial.

We have recently obtained evidence for the existence of the new organocuprate species, $LiCu_2(CH_3)_3$ and $Li_2Cu(CH_3)_3$ in THF and $Li_2Cu(CH_3)_3$ and $Li_2Cu_3(CH_3)_5$ in Et_2O.[2] We have also reported the reactions of these new organocuprates with enones in order to compare their regioselectivity and reaction rate with $LiCu(CH_3)_2$.[1] Owing to the current interest in substitution reactions using organocopper reagents,[3] we have now evaluated these new cuprates in their reaction with alkyl, cycloalkyl, and aryl halides and have noted some interesting and important observations.

Results and Discussion

The organic halides were allowed to react with the new organocuprates and $LiCu(CH_3)_2$ in THF and Et_2O in order to compare the reactivity of the new cuprates and the yields of the reactions. Since $Li_2Cu(CH_3)_3$ is in equilibrium with $LiCu(CH_3)_2$ and CH_3Li, the reaction of CH_3Li in each case is also compared. Each reaction was carried out using excess reagent (10:1 molar ratio of active methyl:halide), room temperature, and two solvents (THF and Et_2O). Since $LiCu_2(CH_3)_3$ is insoluble in Et_2O and $Li_2Cu_3(CH_3)_5$ is insoluble in THF, studies of these cuprates were not involved in these particular solvents. The results of these reactions are shown in Table I.

In the reactions of 1-iododecane (expt 1–7), each organocuprate reagent reacted similarly to produce the substitution product, *n*-undecane, in high yield. The earlier reaction time (10 min) indicated that $Li_2Cu(CH_3)_3$ in THF reacted more rapidly than any other reagent. The metal–halogen exchange to form 50% *n*-decane in the reaction of CH_3Li with 1-iododecane suggests that in reactions involving $Li_2Cu(CH_3)_3$, the reactive species is $Li_2Cu(CH_3)_3$ and not one of its equilibrium components (e.g., CH_3Li). Our previous studies have shown that $Li_2Cu(CH_3)_3$ forms an equilibrium mixture in THF and Et_2O as described by eq 1.

$$Li_2Cu(CH_3)_3 \rightleftharpoons CH_3Li + LiCu(CH_3)_2 \quad (1)$$

Methyllithium as well as the cuprates also reacted with 1-bromodecane to form undecane. The yields in THF were quantitative after just 1 h reaction time (expt 8–14), although the yields were considerably lower (42–61%) in ether solvent. The reactione of1-chlorodecane (expt 15–21) illustrate the superiority of $Li_2Cu(CH_3)_3$ over $LiCu(CH_3)_2$ or $LiCu_2(CH_3)_3$ in THF or Et_2O in the substitution of chlorine for methyl. A quantitative yield was obtained with $Li_2Cu(CH_3)_3$, whereas with $LiCu(CH_3)_2$ in THF only 22% yield was observed and in the case of CH_3Li in THF, no reaction at all was observed under the same conditions. Although yields are low in all other cases studied involving reaction of the new cuprates and CH_3Li with 1-fluorodecane, a quantitative yield of *n*-undecane was observed when $Li_2Cu(CH_3)_3$ in ether was the reagent. It is interesting to note that whereas $Li_2Cu(CH_3)_3$ in THF is a superior reagent for chlorine displacement, the same reagent in Et_2O is superior for fluorine displacement (expt 22–28).

The reactions of 6-bromo-1-hexene and 6-chloro-1-hexene behaved similarly to 1-bromodecane and 1-chlorodecane (expt 29–40). In general, THF solvent is more suitable than Et_2O for organocuprate substitution reactions of alkyl iodides, bromides, and chlorides and the relative reactivity of the cuprates is $Li_2Cu(CH_3)_3 > LiCu(CH_3)_2$, $LiCu_2(CH_3)_3$, and $Li_2Cu_3(CH_3)_5$, although $Li_2Cu(CH_3)_3$ in Et_2O was superior to THF in its reaction with 1-fluorodecane (expt 26, 96%). Although CH_3Li also produced good yields of substitution products with the iodides and bromides, no reaction took place between CH_3Li and the chlorides and fluorides. In most cases the yield of substitution products is better using the new cu-