47-1; 1,3-dithiane, 505-23-7; 2-(β-hydroxypropyl)-1,3-dithiane, 14950-49-3; 2-(β-hydroxypropyl)-1,3-dithiane *p*-toluenesulfonate, 14950-42-6; 1,3-propylene dithioacetal of *trans*-2-hydroxy-1-cyclohexanecarboxaldehyde, 14950-43-7; 1,3-propylene dithioacetal of *trans*-2-hydroxy-1-cyclohexanecarboxaldehyde *p*-toluenesulfonate, 14950-44-8; cyclobutanone, 1191-95-3; cycloheptane-1,4-dione, 14950-46-0.

Acknowledgment.—We are indebted to the National Science Foundation and the National Institutes of Health for financial support of this research.

Mass Spectrometry in Structural and Stereochemical Problems. CXLVI.[1] Mass Spectrometric Fragmentations Typical of Sterols with Unsaturated Side Chains[2]

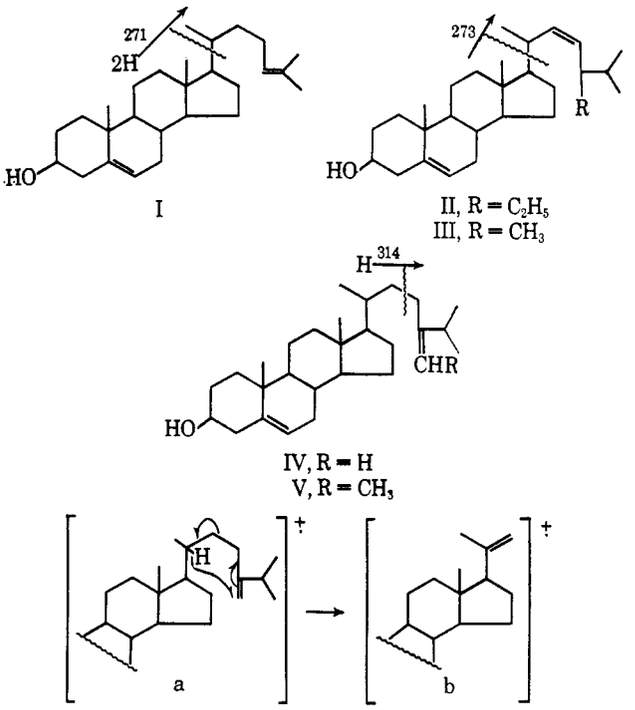
S. G. WYLLIE[3] AND CARL DJERASSI

Department of Chemistry, Stanford University, Stanford, California

Received August 10, 1967

The characteristic mass spectral features associated with the usual saturated side chain of sterols are drastically altered when double bonds are introduced into the side chain. One of the most diagnostic and mechanistically intriguing fragmentations of such unsaturated sterols involves the loss of the entire C-17 substituent together with the rearrangement of two hydrogen atoms. Attention is drawn to the utility of such mass spectral decompositions in structure elucidation of unknown sterols and the nature of the fragmentation processes has been clarified through the use of deuterium-labeled steroids. In that connection several syntheses of Δ^{22}- and Δ^{24}-steroidal olefins were developed.

The mass spectrometric fragmentations of steroids, initiated either by various functional groups or inherent in the steroidal skeleton have been the subject of considerable study[4] in our laboratory both with regard to their use as a structural tool and the elucidation of their mechanism. During the examination of the mass spectra of a number of naturally occurring sterols it became apparent that a diagnostically important and mechanistically interesting cleavage was associated with the presence of a double bond in the side chain. Thus an intense peak at *m/e* 271 appears in the mass spectrum of desmosterol (I), this fragment corresponding to the loss of the side chain together with two hydrogen atoms from the steroid nucleus. Stigmasterol (II) and a number of 6,7-dihydroergosterol (III) derivatives show a similar peak though of reduced intensity owing to the competing allylic cleavage of the 17–20 bond giving an ion of mass 273. Similarly 24-methylenecholesterol (IV) and fucosterol (V) show an *m/e* 271 peak although of low intensity compared with the strong peak at *m/e* 314 which dominates the mass spectra of these compounds. This latter fragment must arise by cleavage of the 22–23 bond together with a one hydrogen transfer from the charge retaining moiety. Mechanistically this decomposition may be rationalized by a "McLafferty" type of rearrangement (a → b), the transferred hydrogen originating from C-20.



Since the outset of our investigation both of the above fragmentations have been noted by a number of workers,[5] but, although the "McLafferty" type of mechanism has been proposed to explain the genesis of the *m/e* 314 peak or its equivalent, no explanation has been forthcoming regarding the formation of the important fragment of mass 271. In view of the generality of this fragmentation, its diagnostic utility for the structural elucidation of new sterols,

(1) Paper CXLV: W. Carpenter, A. M. Duffield, and C. Djerassi, *J. Am. Chem. Soc.*, **89**, 6167 (1967).

(2) Financial assistance by the National Institutes of Health (Grants No. AM-04257 and CA-07195) of the U. S. Public Health Service is gratefully acknowledged.

(3) Postdoctoral Research Fellow, 1965–1967.

(4) (a) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. 2, Holden-Day, Inc., San Francisco, Calif., 1964; (b) R. T. LaLonde, L. Tökés, and C. Djerassi, *J. Org. Chem.*, **32**, 1012 (1967); (c) R. T. LaLonde, L. Tökés, and C. Djerassi, *ibid.*, **32**, 1020 (1967); (d) L. Tökés, G. Jones, and C. Djerassi, in preparation.

(5) (a) P. Eneroth, K. Hellström, and R. Ryhage, *Steroids*, **6**, 707 (1965); (b) J. Bergman, B. O. Lindgren, and C. M. Svahn, *Acta Chem. Scand.*, **19**, 1661 (1965); (c) B. A. Knights, *Phytochemistry*, **4**, 857 (1965); (d) B. A. Knights and W. Laurie, *ibid.*, **6**, 407 (1967); (e) P. Benveniste, L. Hirth, and G. Ourisson, *ibid.*, **5**, 31 (1966); (f) W. Sucrow, *Chem. Ber.*, **99**, 3559 (1966); (g) N. Ikekawa, K. Tsuda, and W. Morisaki, *Chem. Ind.* (London), 1179 (1966); (h) P. J. Flanagan and J. B. Thomson, *Steroids*, **9**, 601 (1967); (i) R. T. Aplin and G. M. Hornby, *J. Chem. Soc., Sect. B*, 1078 (1966); (j) B. A. Knights, *J. Gas Chromatog.*, **5**, 273 (1967); (k) G. Galli and S. Maroni, *Steroids*, **10**, 189 (1967).

and the great rarity[6] of unidirectional double hydrogen transfers in mass spectral fragmentation processes, a detailed investigation of its scope and mechanism has been carried out.

Synthetic Studies.—Our initial synthetic effort was directed toward the preparation of hitherto undescribed "naked" steroidal olefins having the double bond in various positions in the side chain. Δ^{24}-5β-Cholestene (VIII) was prepared by an unexceptional route. Cholan-24-ol (VI) on Moffatt oxidation[7] gave cholan-24-al (VII)[7] which when subjected to the Corey modification[8] of the Wittig reaction with the appropriate reagent gave Δ^{24}-5β-cholestene (VIII). The synthesis of Δ^{23}-5β-cholestene (XII) utilized the same starting material. On conversion to the iodide and dehydrohalogenation, Δ^{23}-cholene (IX) was obtained. Epoxidation gave 23,24-oxidocholane (X) which on treatment with periodic acid in acetone gave 24-norcholan-23-al (XI) directly. This method for the cleavage of olefins has since been reported[9] and appears to be of considerable utility for the synthesis of aldehydes and/or degradation of olefins. Wittig reaction on the aldehyde gave Δ^{23}-5β-cholestene (XII). In this case only the compound having a *cis* double bond could be detected. Δ^{22}-5α-Cholestene (XVI) was prepared from Δ^{22}-5α-cholesten-16β-ol (XIV) obtained by cleavage of 5α-furanostan (XIII) after the method of Djerassi, *et al.*[10] Δ^{22}-5α-Cholesten-16β-ols having both *cis* and *trans* double bonds as indicated by their infrared spectra were isolated. Jones oxidation[11] followed by electrolytic reduction[12] gave the *cis*- and *trans*-Δ^{22}-5α-cholestenes.

24-Methyl-Δ^{24}-5β-cholestene (XVIII) was synthesized from cholanic acid by treatment with methyllithium giving 26,27-bisnor-5β-cholestan-24-one (XVII) which on Wittig reaction gave the required olefin.

Since the hydrogen atoms transferred during the rearrangement appeared most likely to originate from ring D, intermediates suitable for labeling these positions with deuterium were also synthesized.

5α-Etianic acid (XIX) on treatment with the lithium alkenyl derived[13] from 5-chloro-2-methyl-pent-2-ene gave in moderate yield 21-nor-Δ^{24}-5α-cholesten-20-one (XX). Electrolytic reduction[12] gave 21-nor-Δ^{24}-5α-cholestene (XXI). Standard base-catalyzed deuterium exchange followed by separation of the C-17 isomers by thin layer chromatography and electrolytic reduction gave 17,22,22-d_3-21-nor-Δ^{24}-5α-cholestene (XXII).

1,4-Addition of the Grignard reagent prepared from 5-bromo-2-methyl-pent-2-ene[14] to $\Delta^{17(20)}$-5α-pregnen-16-one (XXIII) in the manner already described[15] gave Δ^{24}-5α-cholesten-16-one (XXIV) as an inseparable mixture of epimers at C-20. Electrolytic reduction furnished Δ^{24}-5α-cholestene (XXV) whose mass spectrum was very similar to that of Δ^{24}-5β-cholestene (VIII) thus demonstrating that the stereochemical difference did not affect the mass spectral fragmentation. The usual deuterium exchange of the ketone followed by electrolytic reduction provided 15,15,17-d_3-Δ^{24}-5α-cholestene (XXVI) while electrolytic reduction in the presence of deuterium oxide and deuteriosulfuric acid gave 16,16-d_2-Δ^{24}-cholestene (XXVII).

Apocholic acid[16] on Jones oxidation followed by modified Wolff–Kischner reduction[17] led to $\Delta^{8(14)}$-cholenic acid (XXVIII) which on treatment with hydrogen chloride in chloroform gave a mixture of the $\Delta^{8(14)}$ and Δ^{14} isomers. Without further purification this mixture was reduced with lithium aluminum hydride and deuterioborated utilizing the procedure of Sondheimer, *et al.*,[18] but using lithium aluminum deuteride in place of lithium aluminum hydride. Protonolysis[19] of the resulting organoborane with propionic acid gave a mixture of $\Delta^{8(14)}$-cholen-24-ol (XXVIIIa) and 14α-d_1-cholan-24-ol (XXIX), the $\Delta^{8(14)}$ double bond being unaffected during this sequence. Careful chromatography gave 14α-d_1-cholan-24-ol (XXIX) which on Moffatt oxidation[7] and Wittig reaction gave 14α-d_1-Δ^{24}-5α-cholestene.

In order to label C-12 the ethylene ketal of methyl 12-ketocholanate[20] on reduction with lithium aluminum hydride and Moffatt oxidation gave cholan-12-one-24-al 12-ethylene ketal (XXX), which was transformed by Wittig reaction and acid treatment to Δ^{24}-5β-cholesten-12-one (XXXI). Electrolytic reduction in deuterium oxide–deuteriosulfuric acid gave 12,12-d_2-Δ^{24}-5β-cholestene (XXXII). For this compound the electrolytic reduction proceeded very slowly and the isotopic purity of the product was not high.

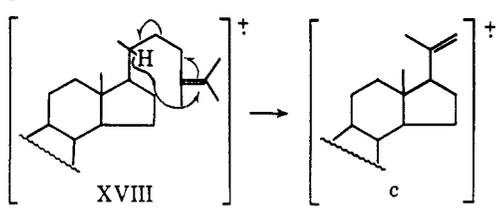
Δ^{22}-5α-Cholesten-16-one (XV) prepared as described above gave by similar methods 15,15,17-d_3-Δ^{22}-5α-cholestene (XVIa) and 16,16-d_2-Δ^{22}-5α-cholestene (XVIb). The ketone having the *cis* Δ^{22} double bond being available in greater amount was used in these preparations. 12,12-d_2-5α-Pregnan-20-one[21] (XXXIII) on reaction with dimethyl sulfonium methylide[22] gave 12,12-d_2-20-methyl-20,21-oxido-5α-pregnane (XXXIV). This compound was subjected to treatment with boron trifluoride in benzene to give 12,12-d_2-20-formyl-5α-pregnane (XXXV). Wittig reaction with the appropriate reagent then led to 12,12-d_2-Δ^{22}-5α-cholestene (XXXVI) which was probably a mixture of isomers at both C-20 and the double bond. The mass spectrum of the mixture obtained from unlabeled pregnan-20-one was essentially identical with that of the pure isomers described above except for some intensity differences. The synthesis of 14α-d_1-Δ^{22}-5α-cholestene (XXXVIII) involved exactly the same reaction sequence, the

(6) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1967.
(7) R. B. Moffatt and K. Pfitzner, *J. Am. Chem. Soc.*, **87**, 5661 (1965).
(8) E. J. Corey, M. Chaykovsky, and R. Greenwald, *J. Org. Chem.*, **28**, 1128 (1963).
(9) G. Maerker and E. T. Haeberer, *J. Am. Oil Chemists' Soc.*, **43**, 97 (1966).
(10) C. Djerassi, O. Halpern, G. R. Pettit, and G. H. Thomas, *J. Org. Chem.*, **24**, 1 (1959).
(11) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).
(12) L. Throop and L. Tökés, *J. Am. Chem. Soc.*, **89**, 4789 (1967).
(13) J. W. Cornforth, R. H. Cornforth, and K. K. Mathew, *J. Chem. Soc.*, 2539 (1959).
(14) M. Julia, S. Julia, and R. Guegan, *Bull. Soc. Chim. France*, 1072 (1960).
(15) C. Beard, J. M. Wilson, H. Budzikiewicz, and C. Djerassi, *J. Am. Chem. Soc.*, **86**, (1964).
(16) A. W. Devor and H. W. Marlow, *ibid.*, **68**, 2101 (1946).
(17) Huang-Minlon, *ibid.*, **68**, 2487 (1946).
(18) F. Sondheimer, M. Nussim, and Y. Mazur, *J. Org. Chem.*, **29**, 1120 (1964).
(19) H. C. Brown and K. Murray, *ibid.*, **26**, 631 (1961).
(20) J. Barnett and T. Reichstein, *Helv. Chim. Acta*, **21**, 926 (1938).
(21) L. Tökés, R. T. LaLonde, and C. Djerassi, *J. Org. Chem.*, **32**, 1020 (1967).
(22) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1353 (1965).

starting material in this case being 14α-d_1-5α-pregnan-20-one (XXXVII).[23]

Discussion of Mass Spectral Fragmentation Processes

The mass spectra of the "naked" steroidal olefins are shown in Figures 1–5. They resemble in most aspects those of the analogous sterols[5j] (I–V). The most significant peaks are markedly different from those observed[4d] with sterols possessing a saturated side chain (*e.g.*, cholestane) thus showing the important influence of unsaturation in the side chain. The base peak in the spectrum (Figure 1) of Δ^{24}-5β-cholestene (VIII) is at *m/e* 257 (*i.e.*, loss of the side chain plus two hydrogens corresponding to *m/e* 271 in desmosterol (I)) and the favorable nature of this rearrangement is demonstrated by the fact that this peak is the only one of any intensity remaining at low electron voltages. Δ^{23}-5β-Cholestene (XII) also shows (Figure 2) an intense ion at *m/e* 257 but in this case allylic cleavage of the 20–22 bond gives rise to a strong *m/e* 287 peak. At lower electron voltages however *m/e* 257 becomes the base peak of the spectrum. The fragment of mass 257 in the spectrum (Figure 3) of Δ^{22}-5α-cholestene (XVI) is much less intense than that of mass 259 arising by allylic cleavage of the 17–20 bond. The abundant *m/e* 286 ion must be produced by cleavage of the 20–22 bond together with a one hydrogen transfer from the charge retaining fragment. At lower electron voltages this peak becomes the base peak in the spectrum. 21-Nor-Δ^{24}-5α-cholestene (XXI) has a very similar spectrum (Figure 4) to that (Figure 1) of Δ^{24}-5β-cholestene (VIII) the 21-methyl group, as expected, having little effect on the fragmentation. The base peak in the spectrum (Figure 5) of 24-methyl-Δ^{24}-5β-cholestene (XVIII) occurs at *m/e* 300 possibly owing to a McLafferty rearrangement as represented in eq 1. The validity of this proposal however remains to be proven by deuterium labeling.



(1)

Below we discuss in detail the origin of the most important peaks in the light of the peak shifts observed with the various deuterated compounds.

Peak *m/e* 257.—The peak shifts found in the various labeled olefinic steroids are shown in Table I. In the Δ^{24} series the peak at *m/e* 257 in the spectrum (Figure 4) of 21-nor-Δ^{24}-5α-cholestene (XXI) is not shifted in that of its 17,22,22-d_3-derivative (XXII). Therefore, the C-17 hydrogen must be completely transferred from the nucleus during the rearrangement. This is confirmed by the shifts observed in the spectrum of 15,15,17-d_3-Δ^{24}-5β-cholestene (XXVI) in which one deuterium is completely lost from the charge retaining moiety since the original *m/e* 257 peak now appears at *m/e* 259. One of the two hydrogen atoms transferred during the double hydrogen rearrangement giving rise to the *m/e* 257 peak therefore originates from C-17.

(23) B. Zeeh, G. Jones, and C. Djerassi, *Chem. Ber.*, in press.

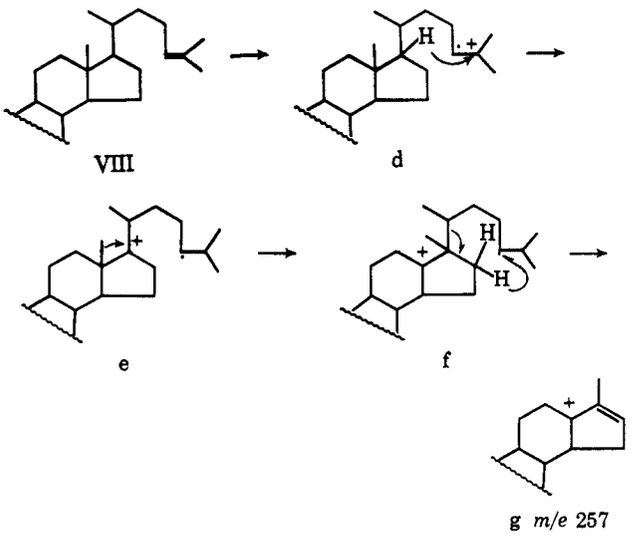
TABLE I
SHIFTS[a] IN THE PRINCIPAL PEAKS (*m/e*) IN THE MASS SPECTRA OF DEUTERATED CHOLESTENES

Compd	M$^+$ [b]	*m/e* 286 (%)	*m/e* 257 (%)
Δ^{24}-5β-Cholestene (VIII) (Figure 1)	370		257
			257 (10)
14α-d_1-Δ^{24}-5β-Cholestene (VIIIa)	371		258 (90)
			258 (35)
12,12-d_2-Δ^{24}-5β-Cholestene (XXXII)	372		259 (65)
			258 (25)
16,16-d_2-Δ^{24}-5α-Cholestene (XXVII)	372		259 (75)
15,15,17-d_3-Δ^{24}-5α-Cholestene (XXVI)	373		259
21-Nor-Δ^{24}-5α-Cholestene (XXI) (Figure 4)	356		257
17,22,22-d_3-21-Nor-Δ^{24}-5α-cholestene (XXII)	359		257
Δ^{22}-5α-Cholestene (XVI) (Figure 3)	370	286	257
12,12-d_2-Δ^{22}-5α-Cholestene (XXXVI)	372	288	259
16,16-d_2-Δ^{22}-5α-Cholestene (XVIb)	372	288	259
		288 (30)	
15,17,17-d_3-Δ^{22}-5α-Cholestene (XVIa)	373	289 (70)	259
			257 (55)
14α-d_1-Δ^{22}-5α-Cholestene (XXXVIII)	371	287	258 (45)

[a] Reported shifts are corrected where possible for isotopic impurity as well as ^{13}C contributions and are greater than 90% unless otherwise indicated. [b] See relevant Experimental Section for isotopic compositions.

The shifts observed in the 12,12-d_2 (XXXII), 14-d_1 (VIIIa), and 16,16-d_2 (XXVII) Δ^{24} olefins show that 35% of the second hydrogen involved in the transfer arises from C-12, 10% for C-14, and 25% from C-16. These results (calculated to the nearest 5%) enable us to account for 1.7 of the two hydrogens transferred and since an isotope effect may well be operating in the transfer of the second hydrogen only some 20% of the second hydrogen source is unknown. The rearrangement typical of Δ^{24} sterols is therefore characterized by one site specific (C-17) hydrogen transfer with the second itinerant hydrogen originating from a number of positions.

Mechanistically the movement of the hydrogen from C-17 poses some difficulty since it requires that during the rearrangement two bonds attached to the same carbon atom are broken, a situation which is not usually observed in mass spectrometric fragmentations.[6] In fact such a situation is strongly indicative of a skeletal rearrangement and we propose that the C-18 methyl group migrates to the electron-deficient site at C-17 left by the departing hydrogen atom. Abstraction of the second hydrogen atom followed by homolysis of the 17–20 bond would then give rise to the allylically stabilized *m/e* 257 ion g. For the sake



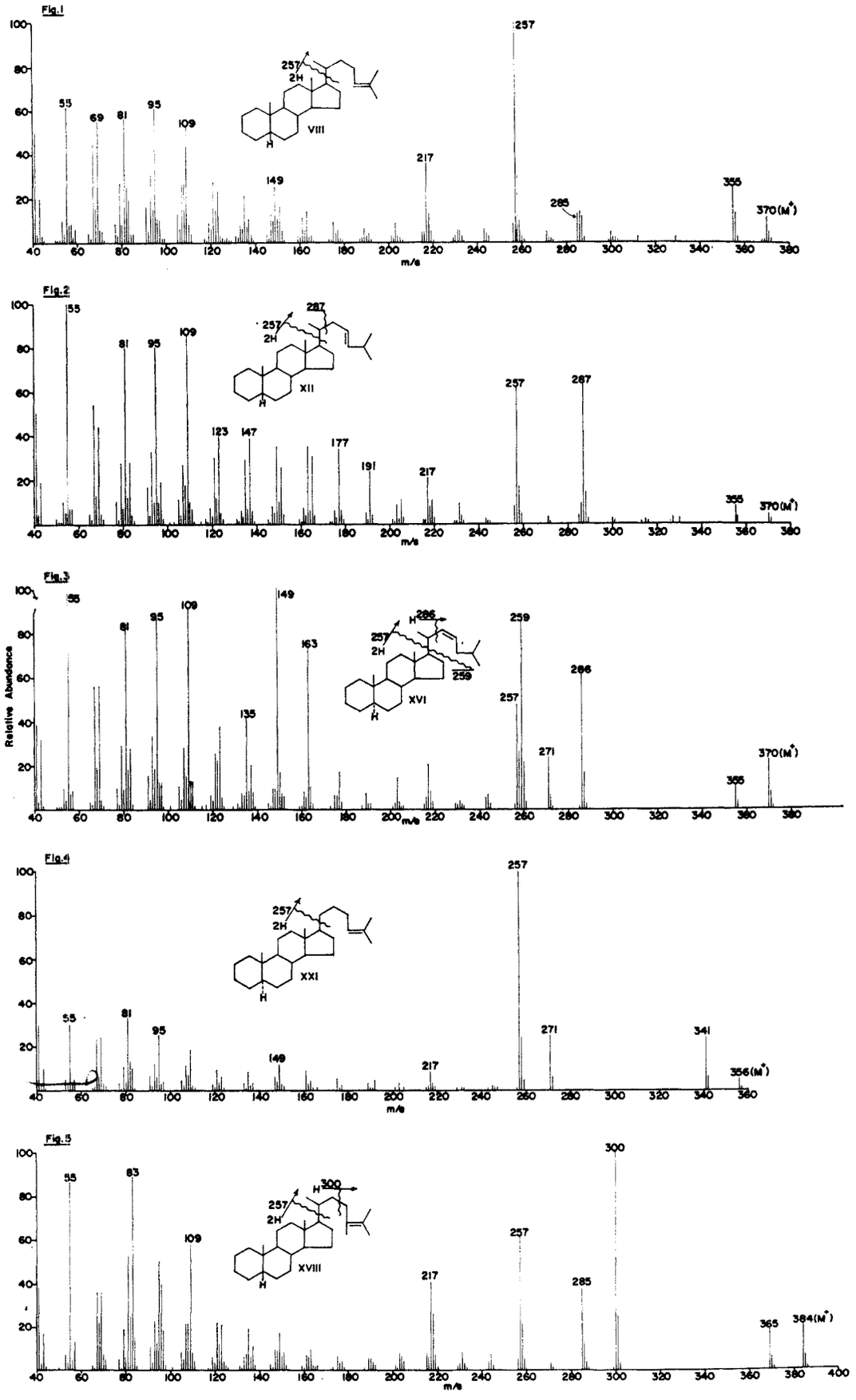


Figure 1.—Mass spectrum of Δ^{24}-5β-cholestene (VIII).
Figure 2.—Mass spectrum of Δ^{23}-5β-cholestene (XII).
Figure 3.—Mass spectrum of Δ^{22}-5α-cholestene (XVI).
Figure 4.—Mass spectrum of 21-nor-Δ^{24}-5α-cholestene (XXI).
Figure 5.—Mass spectrum of 24-methyl-Δ^{24}-5β-cholestene (XVIII).

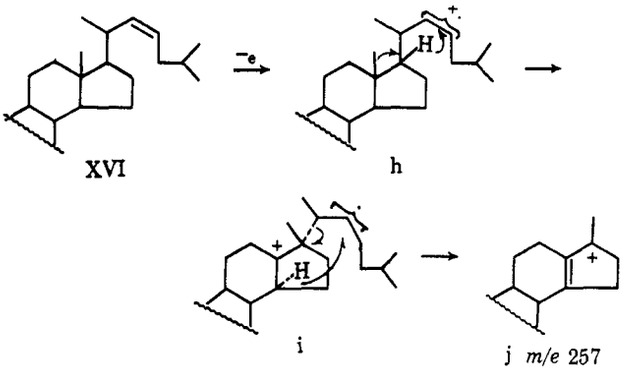
of clarity the reaction sequence is depicted in a stepwise manner and is assumed to be initiated by preferential charge localization at the site of the original double bond. This explains why the usual ring D cleavage of saturated sterols[4d] is greatly repressed.

Methyl migrations have been shown to occur in a number of cases[24] and have been invoked in a number of others to explain the facility of formally unlikely cleavages. Some supporting evidence for this mechanism comes from consideration of the various sites from which the second hydrogen atom migrates. Hydrogen is transferred only from those positions (C-12, C-14, C-16) which can give rise to an allylically stabilized ion of the type g. On these grounds the source of the hydrogen transfer as yet unaccounted for may be the hydrogens of the C-18 methyl group.

It is noteworthy that this fragmentation must involve hydrogen transfers through seven- or eight-membered rings rather than the more usually favored six-membered ones. However, it has been shown[15] in the case of cholestan-16-one that seven-, eight-, and nine-membered rings are involved in hydrogen transfers of a similar nature to those described above.

It is apparent from the results shown in Table I that, although the genesis of the m/e 257 peak in Δ^{22} olefins is superficially similar to that for the Δ^{24} compounds, significant differences exist between their detailed mechanisms. In the spectrum of 15,15,17-d_3-Δ^{22}-5α-cholestene (XVIa) a shift corresponding to the loss of one deuterium atom from the nucleus is observed. One of the hydrogen atoms transferred during the rearrangement leading to an ion of mass 257 therefore originates from either C-15 or C-17, with that on C-17, by analogy with the Δ^{24} series, being the most likely source. The majority of the second hydrogen atom transferred arises from C-14, the spectrum of 14α-d_1-Δ^{22}-5α-cholestene (XXXVIII) showing that some 55% comes from this position. No significant transfer from either C-12 or C-16 could be detected. In contrast, in the Δ^{24} olefins, C-14 provides only 10% of the second hydrogen atom transferred while C-12 and C-16 both make significant contributions.

The major difference between the pathways for the production of the ion of mass 257 in the Δ^{22} and Δ^{24} olefins therefore lies in the transfer of the second hydrogen atom. A number of reasons can be advanced to explain the greater site specificity encountered in the Δ^{22} compounds. The combination of the abstraction of an energetically favored tertiary hydrogen atom with movement through a six- or seven-membered ring makes the hydrogen atom on C-14 a particularly suitable candidate for transfer in the Δ^{22} series (see h → i → j). The similar situation in the Δ^{24} olefins requires an eight-membered ring although, since the transfer of a C-12 hydrogen atom already shown to occur requires this ring size, some other factors, probably steric, must also be operating. From models it can be seen that, if the integrity of the ring system is maintained, the side chain must assume the 17α configuration to allow it to approach the 14α hydrogen atom sufficiently closely for transfer to take place (see h → i → j). This fact provides some indirect support for the methyl migration postulated above since this would lead to inversion of the C-17 stereochemistry thus imparting the required 17α stereochemistry to the side chain.



The present studies on the origin of the m/e 257 peak in the Δ^{22} and Δ^{24} steroidal olefins point again to the subtle factors which may govern hydrogen rearrangement. They also offer an instructive example of how deuterium labeling can provide indirect evidence for otherwise undetectable skeletal rearrangements within a given ion.

Peak Group at m/e 285–287.—The peaks in this group arise by cleavage of the 20–22 bond both with and without hydrogen transfer. The mass spectrum (Figure 1) of Δ^{24}-5β-cholestene (VIII) exhibits three peaks at m/e 285, 286, and 287, but their low intensity precluded any study of the shifts in the deuterated compounds.

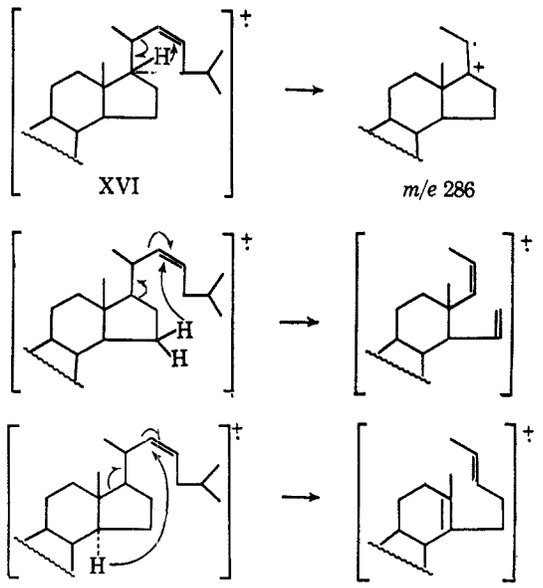
The intense peak at m/e 287 in the spectrum (Figure 2) of Δ^{23}-5β-cholestene (XII) arises by allylic cleavage and occasions no further comment. In the case of Δ^{22}-5α-cholestene (XVI) the peak at m/e 286 represents an interesting and characteristic fragmentation, formally a very unfavorable vinylic cleavage together with a one hydrogen transfer. The importance of this fragmentation at low electron voltages has already been mentioned. Examination of the spectra of the deuterated compounds (Table I) shows that m/e 286 is shifted completely to m/e 288 in 16,16-d_2-Δ^{22}-5α-cholestene (XVIb) and in 12,12-d_2-Δ^{22}-5α-cholestene (XXXVI) while in 15,15,17-d_3-Δ^{22}-5α-cholestene (XVIa) 70% is shifted to m/e 289 and 30% to m/e 288. Thirty per cent of the hydrogen transferred during the cleavage therefore originates from either C-15 or C-17. Plausible mechanisms giving rise to favorably stabilized ions of mass 286 can be drawn with the transferred hydrogen originating from a number of sites. Several of these are shown in Scheme I.

As shown above the presence of a double bond in the side chain gives rise to new peaks, not encountered in the mass spectra of the saturated analogs, which can be very useful in structural studies notably of plant and marine sterols. In our hands, most of the naturally occurring sterols of marine origin—reported as pure compounds in the literature—were proved by mass spectrometry to be mixtures of two to ten components. The increasing use[5j] of combined glpc–mass spectrometric techniques may thus simplify greatly the analysis of such mixtures.

Application to Structural Elucidation of Unsaturated Sterols.—The presence of a major peak at m/e 271

(24) For a review of electron-impact induced rearrangements, see P. Brown and C. Djerassi, *Angew. Chem., Intern. Ed. Engl.*, **6**, 477 (1967).

SCHEME I



(corresponding to m/e 257 in Figures 1–5) in the spectrum of an unknown sterol indicates that the compound probably has the usual sterol nucleus (Δ^5-3-ol moiety) together with a double bond in the side chain. Further inspection of the spectrum may quickly lead to the assignment of the center of unsaturation. The presence of a Δ^{22} double bond is indicated by the allylic cleavage peak at m/e 273 (corresponding to m/e 259 in Figure 3) and a strong peak at m/e 300 (corresponding to m/e 286 in Figure 3). Although we have no spectra of sterols containing a Δ^{23} double bond, by analogy with the olefin spectra (Figure 2), compounds having a double bond in this position should be readily distinguished from the other double-bond isomers by the presence of a major peak at m/e 301 (corresponding to m/e 287 in Figure 2). Compounds having a Δ^{24} double bond are characterized by a triplet of low intensity peaks at m/e 299, 300, and 301 (see m/e 285, 286, and 287 in Figure 1).

An intense peak at m/e 314 indicates that the "McLafferty" type of rearrangement (a → b) is operating and there is present a double bond of the type found in fucosterol (V), 24-methylenecholesterol (IV), or 24-methyldesmosterol (XXXIX). Indeed the spectra of these latter two compounds are virtually identical and cannot be used to distinguish between these isomers. Bergman, *et al.*,[5b] report peaks at m/e 271 and 314 in the spectrum of $\Delta^{7,25}$-5α-stigmastadien-3β-ol which indicates that the "McLafferty" rearrangement also operates in the Δ^{25} series.

It seems likely that the ion of mass 271 in the spectra of sterols having a strong m/e 314 peak is generated, at least in part, by a different sequence from that found in the case of substances where the m/e 314 peak is weak or nonexistent. That the m/e 271 ion arises directly from the molecular ion in the case of demosterol (I) is shown by the presence of a metastable peak at m/e 191.5. A similar observation has been made in the case of $\Delta^{7,25}$-5α-stigmastadien-3β-ol.[5f] However, a metastable peak at m/e 248.5 in the spectrum of fucosterol (V) indicates that at least a portion of the ion of mass 271 is formed by decomposition of a 314 precursor. It has been suggested[5b] that this step, which corresponds to the loss of an isopropylidene group together with two hydrogen atoms, is analogous to the M − 43 ions found[25a] in the mass spectra of $\Delta^{20(29)}$ lupene derivatives. However, the M − 43 ion in the recently measured spectrum of 20-methylene-5α-pregnan-3β-ol (XL)[25b] is very weak.

Examination of the numerous sterol spectra measured in our laboratory and those published[5] shows that in a number of instances the position of the nuclear double bond(s) has some influence on the fragmentations induced by the side-chain double bond. For example the 8,9 double bond in zymosterol (XLI) suppresses the formation of the m/e 271 peak almost completely. Also in sterols having a strong m/e 314 peak (b) in their spectra due to a McLafferty rearrangement (a → b) the intensity of this ion relative to that of mass 271 appears to be controlled by the position of the double bond. Thus, in all the examples we have examined or that have been reported,[5] the m/e 271 peak is more intense than that at m/e 314 if the sterol has a Δ^7 double bond while the reverse situation exists in the case of the Δ^5 isomers.

Finally, it has been our experience that much more information can be garnered from the mass spectrum of the free sterol rather than that of derivatives such as acetates or trimethylsilyl ethers since, in general, although the fragmentations discussed above are still operative in these cases, their lower intensity makes interpretation more difficult.

Experimental Section[26]

Δ^{24}-5β-Cholestene (VIII).—Cholan-24-al (VII, 600 mg)[6] in tetrahydrofuran (5 ml) and dimethyl sulfoxide (5 ml) was added to the isopropylidenetriphenylphosphorane prepared from isopropyltriphenylphosphonium iodide (3.46 g) and sodium hydride (144 mg) by the method of Corey.[7] After 3 hr water (20 ml) was added and the product isolated by hexane extraction. Chromatography on alumina gave Δ^{24}-5β-cholestene (VIII, 100 mg) which on recrystallization from methanol had mp 45.5–46°; nmr signals appeared at δ 0.65 (3 H, singlet, CH_3), 0.92 (3 H, singlet, CH_3), 1.60 (3 H, singlet, olefinic CH_3), 1.68 (3 H, singlet, olefinic CH_3), and 5.08 (1 H, multiplet, olefinic H). Like desmosterol (I),[27] the compound decomposed after standing in air.

Anal. Calcd for $C_{27}H_{46}$: C, 87.57; H, 12.43; mol wt, 370. Found: C, 87.26; H, 12.39; mol wt (mass spectroscopy), 370.

23,24-Oxidocholane (X).—Δ^{23}-Cholene[28] (IX, 1.4 g) in chloroform was stirred with *m*-chloroperbenzoic acid (0.85 g) for 18 hr at room temperature. Dilution with water and ether extraction gave 23,24-oxidocholane (X, 1.38 g) which on recrystallization from methanol afforded an analytical sample with mp 104–105° and $[\alpha]^{27}D$ +18.9° (*c* 1.0).

---

(25) (a) H. Budzikiewicz, J. M. Wilson, and C. Djerassi, *J. Am. Chem. Soc.*, **85**, 3688 (1963). (b) F. Sondheimer and R. Mechoulam, *ibid.*, **80**, 3087 (1958). We are indebted to Professor Mechoulam for a sample of this compound.

(26) Melting points (uncorrected) were determined on the Kofler block. Infrared spectra were measured as 'Nujol' mulls except where indicated; optical rotations were determined in chloroform and nmr spectra in deuteriochloroform. The optical rotatory dispersion measurements, performed by Mrs. R. Records, were obtained with a Durrum-JASCO Model ORD-5 spectropolarimeter. Thin layer chromatography (tlc) was performed on silica gel G (E. Merck, A. G. Darmstadt). Spots or bands were developed with iodine vapor or spraying with 2% ceric sulfate in 2 *N* sulfuric acid and heating for optimum development of colored spots. Mass spectra were determined with an A.E.I. MS-9 or Atlas CH-4 mass spectrometer using the direct inlet technique. The spectra were obtained by Drs. J. K. MacLeod, A. M. Duffield, and Mr. R. G. Ross. All microanalyses are by E. Meier and J. Consul.

(27) M. J. Thompson, J. N. Kaplanis, and H. E. Vroman, *Steroids*, **5**, 551 (1965).

(28) F. C. Chang and N. F. Wood, *J. Org. Chem.*, **30**, 2055 (1965).

Anal. Calcd for $C_{24}H_{40}O$: C, 83.72; H, 11.63; mol wt, 344. Found: C, 83.55; H, 11.72; mol wt (mass spectroscopy), 344.

24-Norcholan-24-al (XI).—Periodic acid (1.73 g) in water (4 ml) and acetone (10 ml) was added to a solution of 23,24-oxidocholane (X, 1.0 g) in acetone (100 ml) and the mixture heated under reflux for 0.5 hr. Concentration of the solution followed by dropwise addition of water till turbidity and cooling gave crystalline 24-norcholan-24-al (XI, 0.93 g), mp 110–111°. Recrystallization from aqueous acetone led to an analytical sample: mp 112–113°; ORD in isooctane (*c* 0.05), $[\Phi]_{589}$ +102°, $[\Phi]_{335}$ −1018°, $[\Phi]_{330}$ −813°, $[\Phi]_{324}$ −1195°, $[\Phi]_{315}$ −254°, $[\Phi]_{312}$ −406°, $[\Phi]_{275}$ −2315°.

Anal. Calcd for $C_{24}H_{40}O$: C, 83.64; H, 11.52; mol wt, 330. Found: C, 83.42; H, 11.67; mol wt (mass spectroscopy), 330.

Δ^{23}-5β-Cholestene (XII).—A procedure virtually identical with that described for the preparation of Δ^{24}-5β-cholestene (VIII) was used to synthesize Δ^{23}-5β-cholestene (XII) from 24-norcholan-24-al (XI, 0.65 g) and isobutyltriphenylphosphonium iodide (3.36 g). Chromatography of the product on alumina gave *cis*-Δ^{23}-5β-cholestene (XII, 0.59 g) which on recrystallization from methanol–chloroform had mp 81–82°; $[\alpha]^{26}D$ +8.2° (*c* 1.0); ν_{max}^{KBr} 716 cm^{-1}; nmr, δ 0.65 (3 H, singlet, CH_3), 0.93 (6 H, doublet, *J* = 7 cps, CH_3CH), 0.92 (3 H, singlet, CH_3), 5.21 (2 H, doublet, olefinic H).

Anal. Calcd for $C_{27}H_{46}$: C, 87.57; H, 12.43; mol wt, 370. Found: C, 87.50; H, 12.36; mol wt (mass spectroscopy), 370.

Δ^{22}-5α-Cholesten-16-one (XV).—5α-Furanostan[9] (XIII, 1.3 g) in acetic anhydride (50 ml) was heated under reflux with *p*-toluenesulfonic acid (0.7 g) for 2 hr. The mixture was poured onto ice and kept overnight. Ether extraction gave an oil which was chromatographed on alumina (120 g, activity II). Benzene–hexane (1:9) eluted *cis*-Δ^{22}-5α-cholesten-16β-ol acetate (127 mg), mp 98–100° (lit.[9] mp 88–89° was shown by examination of the original compound to be reported incorrectly). The acetate (120 mg) in ether was refluxed with lithium aluminum hydride (200 mg) for 4 hr. The usual work-up gave *cis*-Δ^{22}-5α-cholesten-16β-ol (XIV), mp 146–147°, mol wt (mass spectroscopy) 386.

Jones oxidation[11] of XIV (110 mg) gave after recrystallization from methanol *cis*-Δ^{22}-5α-cholesten-16-one (XV): mp 97–98°; nmr, δ 0.76 (3 H, singlet, CH_3), 0.8 (3 H, singlet, CH_3), 0.9 (6 H, doublet, *J* = 7 cps), 1.09 (3 H, doublet, *J* = 7.5 cps), 5.36 (2 H, multiplet); ORD in methanol (*c* 0.024), $[\Phi]_{589}$ −400°, $[\Phi]_{326}^{trough}$ −10,800°, $[\Phi]_{284}^{peak}$ +9000°.

Anal. Calcd for $C_{27}H_{44}O$: C, 84.37; H, 11.46; mol wt, 384. Found: C, 84.08; H, 11.30; mol wt (mass spectroscopy), 384.

Δ^{22}-5α-Cholestene (XVI).—Electrolytic reduction[12] at a lead cathode of Δ^{22}-5α-cholesten-16-one (XV, 15 mg) in dioxane (70%) and 10% sulfuric acid (30%) for 8 hr gave after recrystallization from methanol *cis*-Δ^{22}-5α-cholestene (XVI, 10 mg), mp 96.5–97.5°.

Anal. Calcd for $C_{27}H_{46}$: C, 87.57; H, 12.43; mol wt, 370. Found: C, 87.38; H, 12.61; mol wt (mass spectroscopy), 370.

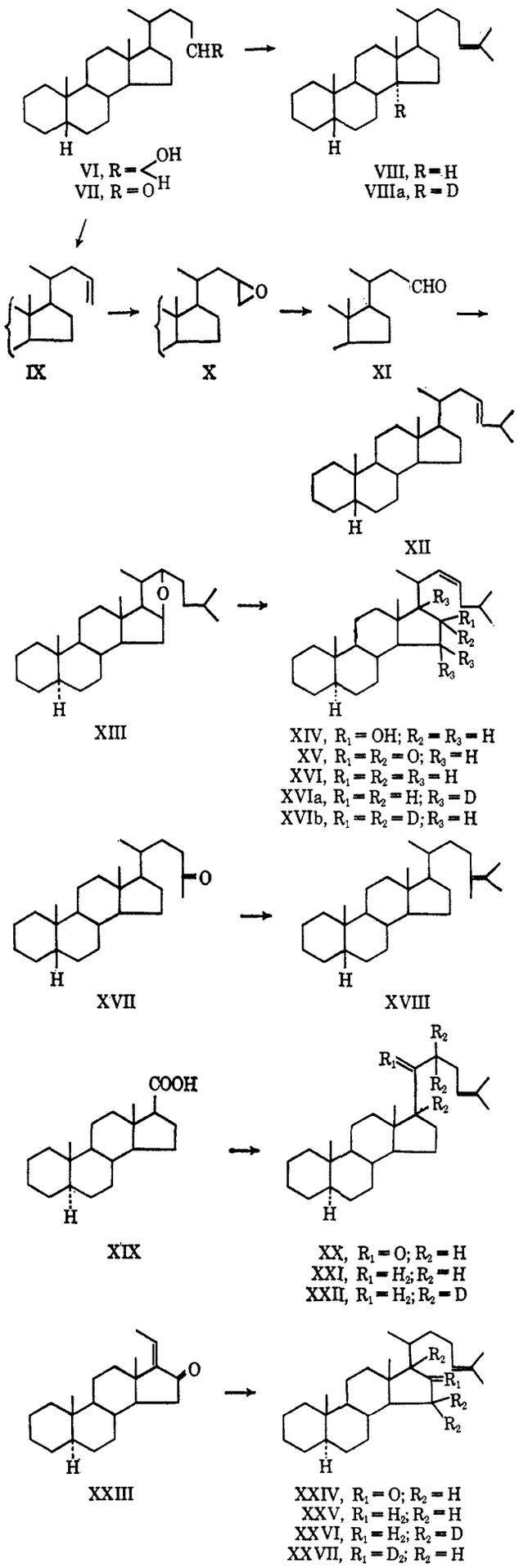
Base-catalyzed deuterium exchange of XV (15 mg) for 48 hr in refluxing deuteriomethanol followed by electrolytic reduction as described above gave 15,15,17-d_3-Δ^{22}-5α-cholestene (XVIa, 9 mg), mp 96–97°; the isotopic composition was 5% d_2 and 95% d_3.

Electrolytic reduction of XV (10 mg) in dioxane (70%) and 10% deuteriosulfuric acid in deuterium oxide (30%) for 8 hr gave 16,16-d_2-Δ^{22}-5α-cholestene (XVIb, 5 mg), mp 96–97°; the isotopic composition was 7% d_1, 90% d_2, and 3% d_3.

24-Methyl-Δ^{24}-5β-cholestene (XVIII).—Methyllithium (4 m*M*) in ether was added to a stirred solution of cholanic acid (1 g) in ether (100 ml) in a nitrogen atmosphere. After 1 hr water was added dropwise. Ether extraction followed by chromatography of the residue on alumina gave 26,27-bisnor-5β-cholestan-24-one (XVII, 255 mg), mp 115–116°.

Anal. Calcd for $C_{25}H_{42}O$: C, 83.8; H, 11.73; mol wt, 358. Found: C, 83.67; H, 11.65; mol wt (mass spectroscopy), 358.

Treatment of the ketone XVII (200 mg) with isopropylidenetriphenylphosphorane prepared from isopropyltriphenylphosphonium iodide (740 mg) and sodium hydride (50 mg) as described above for Δ^{24}-5β-cholestene (VIII), gave, after alumina chromatography, 24-methyl-Δ^{24}-5β-cholestene (XVIII, 110 mg) which on recrystallization from ethanol–chloroform had mp 106–107°; $[\alpha]^{27}D$ +19.8° (*c* 1.0); nmr, δ 0.66 (3 H, singlet, CH_3), 0.92 (3 H, singlet, CH_3), 1.64 (9 H, singlet, olefinic CH_3).



Anal. Calcd for $C_{28}H_{48}$: C, 87.50; H, 12.50; mol wt, 384. Found: C, 87.39; H, 12.60; mol wt (mass spectroscopy), 384.

21-Nor-Δ^{24}-5α-cholesten-20-one (XX).—5-Chloro-2-methylpent-2-ene[13] (2 g) in dry hexane was added dropwise to a stirred dispersion of lithium (250 mg) in hexane (50 ml) under an argon atmosphere. After 10 hr, 5α-etianic acid (XIX, 500 mg) in ether (40 ml) was added and the mixture stirred overnight. Addition of water followed by ether extraction gave the crude product which was chromatographed on silica gel (50 g). Benzene eluted the required ketone (250 mg) which on purification by preparative thin layer chromatography and recrystallization from methanol–chloroform gave an analytical sample of 21-nor-Δ^{24}-5α-cholesten-20-one (XX, 100 mg): mp 62.5–64.5°; ORD in methanol (*c* 0.076), $[\Phi]_{589}$ +194°, $[\Phi]_{310}^{peak}$ +8836°, $[\Phi]_{270}^{trough}$ −9418°; nmr, δ 0.58 (3 H, singlet, CH_3), 0.77 (3 H, singlet, CH_3), 1.60 (3 H, broad singlet, olefinic CH_3), 1.65 (3 H, broad singlet, olefinic CH_3), 5.07 (1 H, multiplet, olefinic H).

Anal. Calcd for $C_{26}H_{42}O$: C, 84.32; H, 11.35; mol wt, 370. Found: C, 84.38; H, 11.43; mol wt (mass spectroscopy), 370.

21-Nor-Δ^{24}-5α-cholestene (XXI).—Electrolytic reduction of 21-nor-Δ^{24}-5α-cholesten-20-one (XX, 20 mg) as described for Δ^{22}-5α-cholestene (XVI) gave, after recrystallization from methanol–chloroform, 21-nor-Δ^{24}-5α-cholestene (XXI, 10 mg), mp 44.5–45.5°.

Anal. Calcd for $C_{26}H_{44}$: C, 87.64; H, 12.36; mol wt, 358. Found: C, 87.41; H, 12.24; mol wt (mass spectroscopy), 358.

Base-catalyzed deuterium exchange of the ketone XX (25 mg) in refluxing deuteriomethanol for 24 hr gave, after separation of the resultant C-17 isomers by thin layer chromatography followed by electrolytic reduction, 17,22,22-d_3-21-nor-Δ^{24}-5α-cholestene (XXII, 10 mg); the isotopic composition was 2% d_1, 16% d_2 and 82% d_3.

Δ^{24}-5α-Cholesten-16-one (XXIV).—$\Delta^{17(20)}$-5α-Pregnen-16-one[15] (XXIII, 420 mg) in ether (10 ml) was added slowly to the Grignard reagent prepared from 5-bromo-2-methyl-pent-2-ene[14] (1.75 g) and magnesium (750 mg) and containing cuprous chloride (50 mg). On completion of the addition (0.5 hr) the mixture was heated under reflux for 6 hr then stirred at room temperature for a further 8 hr. Dilution of the reaction mixture with saturated ammonium chloride and ether extraction gave an oil which was chromatographed on alumina (50 g, activity II). Hexane slowly eluted the ketone which was further purified by preparative thin layer chromatography. Recrystallization from methanol gave Δ^{24}-5α-cholesten-16-one (XXIV, 100 mg), mp 44–48°, as an inseparable mixture of 20α and 20β isomers; nmr signals appeared at δ 0.79 (3 H, singlet, CH_3), 0.95 (3 H, singlet, CH_3), 1.06 (3 H, doublet, J = 7 cps, CH_3CH), 1.60 (3 H, singlet, olefinic CH_3), 1.68 (3 H, singlet, olefinic CH_3), 5.1 (1 H, multiplet, olefinic H).

Anal. Calcd for $C_{27}H_{44}O$: mol wt, 384. Found: mol wt (mass spectroscopy), 384.

Base-catalyzed deuterium exchange followed by electrolytic reduction of XXIV (10 mg) in the manner described for Δ^{22}-5α-cholestene (XVI) yielded 15,15,17-d_3-Δ^{24}-5α-cholestene (XXVI) (20α and 20β), as an oil which showed two poorly resolved peaks on gas phase chromatography (SE-30 column at 255°). The isotopic composition was 16% d_2 and 84% d_3.

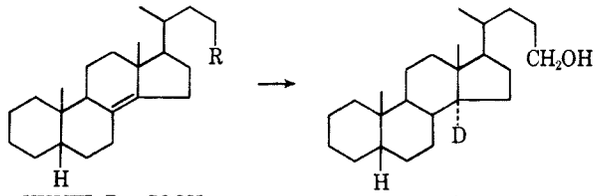
Electrolytic reduction of XXIV (15 mg) in dioxane–deuteriosulfuric acid (see preparation of XVIb) furnished 16,16-d_2-Δ^{24}-5α-cholestene (XXVII) (20α and 20β) as an oil. The isotopic composition was 4% d_1, 65% d_2, 12% d_3, and 8% d_4.

14α-d_1-Δ^{24}-5β-Cholestene (VIIIa).—Apocholic acid[15] (4.2 g) on Jones oxidation[11] and modified Wolff–Kischner reduction[17] gave $\Delta^{8(14)}$-cholenic acid (XXVIII, 2.3 g), mp 128–131°. Recrystallization from methanol gave an analytical sample with mp 132–133° and $[\alpha]^{27}D$ +36.5° (*c* 1.0, ethanol).

Anal. Calcd for $C_{24}H_{38}O_2$: C, 80.45; H, 10.61. Found: C, 80.17; H, 10.63.

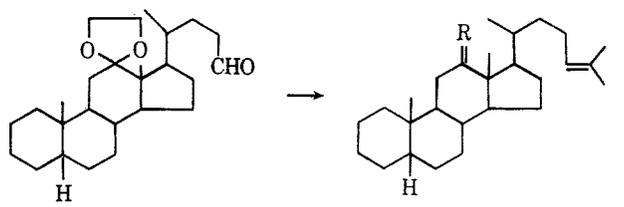
$\Delta^{8(24)}$-Cholenic acid (XXVIII, 2 g) in chloroform (25 ml) at 0° was treated with dry hydrogen chloride for 2 hr. The product was shown by nmr to contain approximately equal amounts of the $\Delta^{8(14)}$ and Δ^{14} isomers. The mixture was methylated with ethereal diazomethane and reduced with lithium aluminum hydride (1.5 g) to give a mixture of $\Delta^{8(14)}$-cholen-24-ol (XXVIIIa) and Δ^{14}-cholen-24-ol. Without further purification the mixture in tetrahydrofuran (50 ml) and boron trifluoride etherate (8 g) was cooled to 0° and lithium aluminum deuteride (1 g) in tetrahydrofuran added dropwise over 1 hr. After stirring for a further 2 hr at room temperature, propionic acid was added cautiously until all reaction ceased. The tetrahydrofuran was removed *in vacuo*, additional propionic acid (40 ml) added, and the mixture refluxed for 19 hr. Dilution with water and ether extraction gave the crude product which was refluxed with lithium aluminum hydride (2 g) in ether for 8 hr. The product, isolated in the usual manner, was chromatographed on alumina (60 g, activity II). Hexane–benzene (6:4) eluted first $\Delta^{8(14)}$-cholen-24-ol (XXVIIIa) followed by 14α-d_1-5β-cholan-24-ol (XXIX, 101 mg), mp 123–124°, mol wt (mass spectroscopy) 347; the isotopic composition was 8% d_0, 91% d_1, and 1% d_2.

Oxidation of XXIX by the Moffatt procedure[6] followed by Wittig reaction on the resulting 14α-d_1-5β-cholan-24-al which was not isolated gave 14α-d_1-Δ^{24}-5β-cholestene (VIIIa) (45 mg) which after several recrystallizations from methanol–chloroform



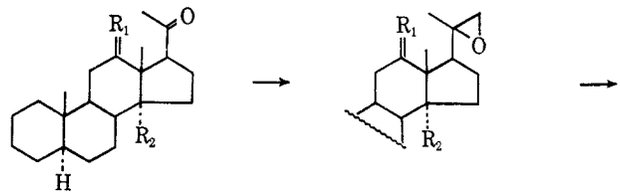
XXVIII, R = COOH
XXVIIIa, R = CH_2OH

XXIX



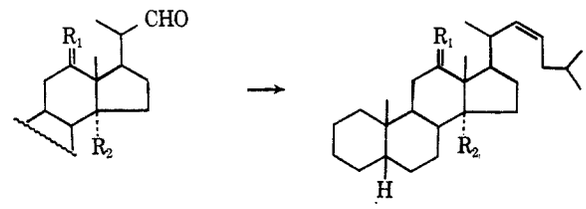
XXX

XXXI, R = O
XXXII, R = D_2



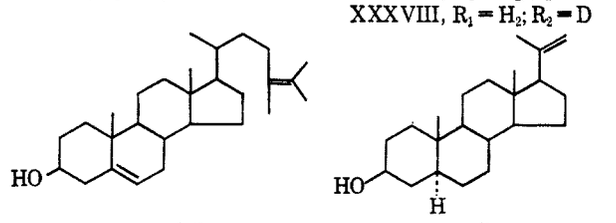
XXXIII, $R_1 = D_2$; $R_2 = H$
XXXVII, $R_1 = H_2$; $R_2 = D$

XXXIV, $R_1 = D_2$; $R_2 = H$



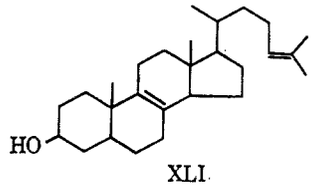
XXXV, $R_1 = D_2$; $R_2 = H$

XXXVI, $R_1 = D_2$; $R_2 = H$
XXXVIII, $R_1 = H_2$; $R_2 = D$



XXXIX

XL



XLI

had mp 44–44.5°; the isotopic composition was 8% d_0, 91% d_1, and 1% d_2.

12,12-d_2-Δ^{24}-5β-Cholestene (XXXII).—Methyl 12-ketocholanate (1 g) was heated under reflux with ethylene glycol (200 mg) and *p*-toluenesulfonic acid (50 mg) in benzene for 24 hr using a water separator. The crude ketal was taken up in ether and then heated under reflux with lithium aluminum hydride (500 mg) for 4 hr. Work-up in the usual manner gave 12-ketocholan-24-ol ethylene ketal which was homogeneous by thin layer chromatography. Moffatt oxidation[6] of this compound gave 12-ketocholan-24-al ethylene ketal (ν_{max} 3.7 and 5.8 μ (–CHO)) which was immediately subjected to the Wittig reaction as described above. Chromatography on silica gel gave the crude Δ^{24}-5β-cholesten-12-one ethylene ketal (220 mg) which was taken up in ethanol and stirred with *p*-toluenesulfonic acid (50 mg) for 3 hr. Dilution with water and ether extraction gave after recrystallization from methanol–chloroform, Δ^{24}-5β-cholesten-12-one (XXXI, 200 mg) with mp 116–118° and $[\alpha]^{25}D$ +101 (*c* 1.0).

Anal. Calcd for $C_{27}H_{44}O$: C, 84.38; H, 11.46; mol wt, 384. Found: C, 84.34; H, 11.54; mol wt (mass spectroscopy), 384.

Electrolytic reduction of a 10-mg sample in dioxane–deuteriosulfuric acid gave 12,12-d_2-Δ^{24}-5β-cholestene (XXXII) whose isotopic composition was 4% d_0, 27% d_1, 66% d_2, and 3% d_3.

12,12-d_2-Δ^{22}-5α-Cholestene (XXXVI).—A stirred dispersion of sodium hydride (20 mg) in dimethyl sulfoxide (5 ml) was heated at 70–75° for 45 min. The resulting solution was cooled to room temperature, tetrahydrofuran (5 ml) added and the mixture cooled further in an ice–salt bath. Trimethyl sulfonium iodide (145 mg) in dimethyl sulfoxide (2 ml) was added followed by 12,12-d_2,5α-pregnan-20-one[20] (XXXIII, 148 mg) in tetrahydrofuran (3 ml). After 1.5 hr at room temperature, dilution with water and ether extraction gave crude 12,12-d_2-20-methyl-20,21-oxido-5α-pregnane (XXXIV) which after recrystallization from methanol had mp 116–117°; ν_{max} 11.6, 12.2 μ; mol wt (mass spectroscopy) 316.

The epoxide (XXXIV, 140 mg) in benzene (5 ml) was stirred with boron trifluoride etherate (6 drops) for 10 min. Saturated sodium carbonate (5 ml) was then added and the organic layer separated and dried. Evaporation of the solvent gave crystalline 12,12-d_2-20-formyl-5α-pregnane (XXXV) (ν_{max} 3.7 and 5.8 μ) which was treated immediately with the phosphorane prepared from isoamyltriphenylphosphonium iodide (1.16 g) and sodium hydride (60 mg). Chromatography of the product on alumina gave an oil (117 mg) which on recrystallization from methanol gave 12,12-d_2-Δ^{22}-5α-cholestene (XXXVI), mp 52–56° (probably a mixture of isomers at C-20 and at the double bond); the isotopic composition was d_0 2%, d_1 20%, d_2 55%, d_3 18%, and d_4 4%.

14α-d_1-Δ^{22}-5α-Cholestene (XXXVIII).—14α-d_1-5α-Pregnan-20-one (XXXVII, 30 mg)[23] was treated with dimethyl sulfonium methylide[22] prepared from trimethyl sulfonium iodide (326 mg) and sodium hydride (39 mg) in dimethyl sulfoxide (3 ml) and tetrahydrofuran (4 ml) as described above for the preparation of 12,12-d_2-Δ^{22}-5α-cholestene (XXXVI). Without isolation the resulting epoxide, in benzene, was treated with boron trifluoride etherate (6 drops) and the aldehyde produced subjected immediately to the Wittig reaction. Chromatography on alumina gave 14α-d_1-Δ^{22}-5α-cholestene (XXXVIII, 18 mg) as an oil; its isotopic composition was 14% d_0 and 86% d_1.

Registry No.—VIII, 14949-23-6; VIIIa, 14949-24-7; X, 14949-25-8; XI, 4877-66-1; XII, 14949-12-3; XIV, 14949-11-2; XV, 14949-13-4; XVI, 15076-93-4; XVIa, 14949-14-5; XVIb, 14949-15-6; XVII, 14949-16-7; XVIII, 14949-17-8; XX, 14949-18-9; XXI, 14949-19-0; XXII, 14949-20-3; XXIV, 14949-21-4; XXVI, 14949-22-5; XXVII, 14949-26-9; XXVIII, 14949-27-0; XXIX, 14949-28-1; XXXI, 14949-29-2; XXXII, 14949-55-4; XXXIV, 15077-14-2; XXXVI, 14949-56-5; XXXVIII, 14949-57-6.

Ozone Oxidation of Primary Amines to Nitroalkanes

G. BRYANT BACHMAN AND K. G. STRAWN[1]

Department of Chemistry, Purdue University, Lafayette, Indiana

Received February 10, 1967

Ozonation of primary amines produces nitroalkanes in modest yields (25–53% optimum), which are dependent on the structure of the amine, the solvent, and the temperature. About 3 mole equiv of ozone are required and the probable intermediates are N-alkylhydroxylamines and nitrosoalkanes. By-products include aldehydes, ketones, acids, and amides in relative amounts which also depend on the structure of the amine. N-Alkylhydroxylamines are ozonated to nitroalkanes in better yields (43%). Ketimines derived from primary amines give nitroalkanes in poorer yields (15%). Oximes do not yield nitroalkanes on ozonation. Ozone compares favorably with other oxidizing agents for converting primary amines into nitroalkanes, especially when the amine group is attached to a primary alkyl group.

Various oxidizing agents convert primary aliphatic amines into nitroalkanes, but ozone is reported to give other products but not nitroalkanes. Long[2] states that primary amines do not react with ozone, while Bailey[3] reports that methylamine gives formaldehyde, methyl nitrite and nitrate, and ammonium nitrite and nitrate. Florentine[4] claims the production of carboxylic acids by ozonation of primary amines in the presence of water and a Japanese patent[5] describes the production of 9-aminononanoic acid by ozonation of oleylamine, indicating preferential attack on the double bond rather than on the amino group by the ozone.

With the thought that the reported failures to ozonize primary amines to nitroalkanes may have depended on the N–H bonds present in such amines, we decided to attempt the ozonation of ketimines, $R^1R^2C{=}NR^3$, instead. Previous work in this area has been concerned primarily with Schiff bases in which R^3 is aromatic and R^2 is hydrogen. Bailey[6] reports traces of nitrobenzene from N-benzylideneaniline, while Miller[7] reports a 10% yield of *p*-chloronitrobenzene from N-benzylidene-*p*-chloroaniline and a 14% yield of 1,4-dinitrobenzene from N-benzylidene-*p*-nitroaniline. Belew and Person[8] obtained an oxa-

(1) Commercial Solvents Corp. Research Assistant, 1965.
(2) L. Long, Jr., *Chem. Rev.*, **27**, 437 (1940).
(3) P. S. Bailey, *ibid.*, **58**, 925 (1958).
(4) F. P. Florentine, Jr., U. S. Patent 2,793,221 (May 21, 1957); *Chem. Abstr.*, **51**, 17982*g* (1957).
(5) H. Otsuki and H. Funahashi, Japanese Patent 4117 (1956); *Chem. Abstr.*, **60**, 16522*b* (1957).
(6) A. H. Riebel, R. E. Erickson, C. J. Abshire, and P. S. Bailey, *J. Am. Chem. Soc.*, **82**, 1801 (1960).
(7) R. E. Miller, *J. Org. Chem.*, **26**, 2327 (1961).
(8) J. S. Belew and J. T. Person, *Chem. Ind.* (London), 1246 (1959).