972. *The Acid-catalysed Rearrangement of 3-Methylenecholestane.*

By R. C. Cookson, D. P. G. Hamon, and R. E. Parker.

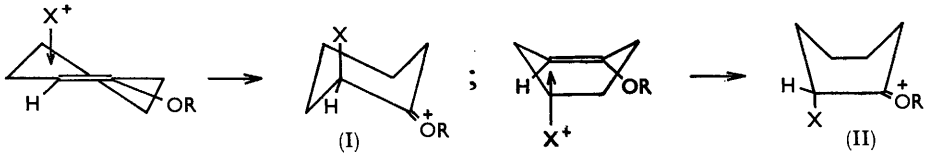
The rates of acid-catalysed rearrangement of 3-methylenecholestane and of its 2α- and 2β-deutero- and 2,2,4,4-tetradeutero-derivatives to 3-methylcholest-2-ene in slightly aqueous dioxan are identical within experimental error. The deuterium contents of the products of the reactions in the aqueous dioxan and in chloroform–acetic acid (after correction for isotope exchange with the solvent) show a preference for loss of an equatorial rather than an axial hydrogen atom.

The results are consistent with the intermediate formation of the 3-methyl-3-cholestanyl cation.

During the last decade there has been much interest in the stereochemistry of keto–enol reactions. Although modified slightly in points of detail,[1-3] Corey's theory,[4,5] that (in the absence of strong, opposing steric repulsion) the transition state for axial addition to an enol is favoured because of better orbital overlap, is still valid. According to the theory, a half-chair enol should give as initial product mainly the axial chair ketone (I), and a half-boat enol mainly the axial boat ketone (II) (which may be stable or may pass into a more stable equatorial chair ketone). The course of the reaction is determined by the balance between this stereoelectronic preference for axial gain or loss of an electrophile, and the steric repulsion [2] that usually opposes it. In the particular case of 3-hydroxy- and 3-acetoxy-cholest-2-ene [partial formula (V), YZ = OH or OAc], kinetically controlled bromination in fact yields the equatorial 2α-bromo-ketone (III; X = α-Br, Y = O),

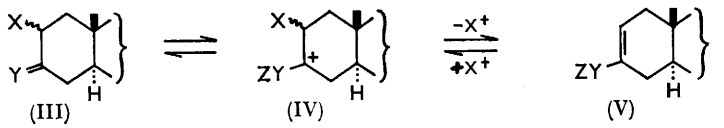
[1] Cookson and Dandegaonker, *J.*, 1955, 352.
[2] Zimmerman and Mais, *J. Amer. Chem. Soc.*, 1959, **82**, 3644, and earlier papers.
[3] Djerassi, Finch, Cookson, and Bird, *J. Amer. Chem. Soc.*, 1960, **82**, 5488; Villotti, Ringold, and Djerassi, *ibid.*, p. 5693, and references cited there.
[4] Corey, *Experientia*, 1953, **9**, 329; *J. Amer. Chem. Soc.*, 1953, **75**, 2301; 1954, **76**, 175.
[5] Corey and Sneen, *J. Amer. Chem. Soc.*, 1956, **78**, 6269.

although in the absence of the angular 10-methyl group the main product is the expected axial 2β-bromo-ketone.[3] Evidently the energy of the transition state for axial 2β-addition in the first case is raised by repulsion from the axial methyl group, so that α-addition

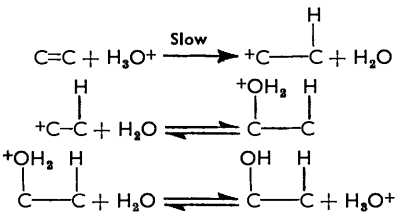


supervenes, whether by direct equatorial attack, axial attack on a distorted boat conformation, or rearrangement of an α-bromonium ion.

The mechanism of acid-catalysed hydration of olefins and the reverse reaction have also excited interest. The kinetics require a multi-stage mechanism involving a carbonium



ion, and the dependence of rate on H_0 has led Taft and his collaborators [6] to favour a mechanism in which the slow step is the rearrangement of the π-protonated olefin to a loosely, but specifically, hydrated (" encumbered ") carbonium ion. Recently, however, Bunnett [7] has applied to the reaction his new acidity function,* the use of which seems to have resolved most of the conflicts caused by the old Hammett–Zucker theory [8] of H_0-dependence. Pointing out that the reaction has the w-value near zero, characteristic of reactions involving slow transfer of a proton to a hydrocarbon, he argues persuasively in favour of the simpler mechanism also considered by Taft:



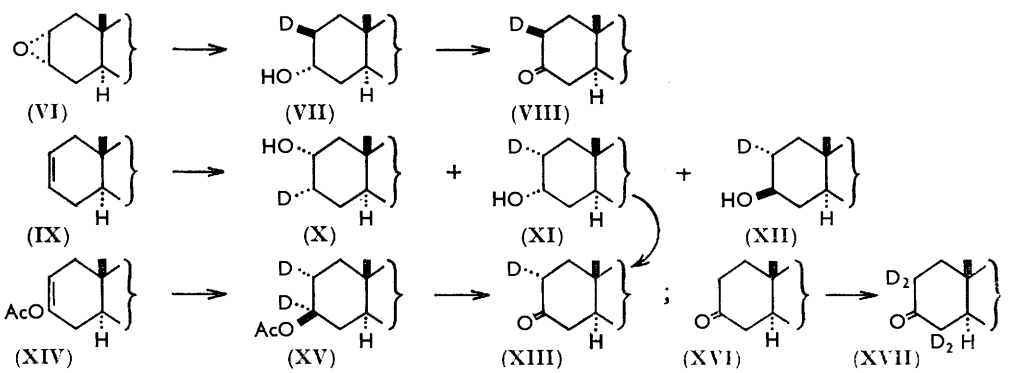
We hoped to throw further light on the mechanism of such reactions by examining the stereospecificity of proton loss from a suitable carbonium ion, again choosing ring A of cholestane as a system of well-known conformation. The acid-catalysed rearrangement [9] of 3-methylenecholestane to 3-methylcholest-2-ene is virtually irreversible, and the reaction can be followed by the change in optical rotation. The deuterium contents were measured of the 3-methylcholest-2-ene from rearrangement of specifically deuterated samples of 3-methylenecholestane, both for reaction in wet dioxan (about 2% of water) and in chloroform–acetic acid. The hydrocarbons were too insoluble in solvents containing enough water to allow a correlation of rate with acidity function.

The various deuterated 3-methylenecholestanes were prepared from the corresponding deuterated cholestan-3-ones by the Wittig reaction.[9] Treatment of 2α,3α-epoxycholestane (VI) with lithium aluminium deuteride was assumed to give the diaxial product

* The w-value of a reaction is defined as the slope of (log k + H_0) plotted against log a_{H_2O}, where k is the apparent first-order rate constant. A w-value of 0 thus signifies a horizontal line.

[6] Boyd, Taft, Wolf, and Christman, *J. Amer. Chem. Soc.*, 1960, **82**, 4729, and references cited there.
[7] Bunnett, *J. Amer. Chem. Soc.*, 1961, **83**, 4978.
[8] Hammett, " Physical Organic Chemistry," McGraw-Hill, New York, 1940, p. 273.
[9] Barton, Campos-Neves, and Cookson, *J.*, 1956, 3500.

(VII), which was oxidised to 2β-deuterocholestan-3-one (VIII). Reaction of cholest-2-ene (IX) with deuterated diborane and subsequent treatment with alkaline hydrogen peroxide gave the two expected alcohols, 3α-deuterocholestan-2α-ol (X) and 2α-deuterocholestan-3α-ol (XI), together with (rather surprisingly) 2α-deuterocholestan-3β-ol (XII). Oxidation



of alcohol (XI) gave 2α-deuterocholestan-3-one (XIII). An alternative route to this compound, by deuteration of 3-acetoxycholest-2-ene (XIV) over a rhodium catalyst to 3β-acetoxy-2α,3α-dideuterocholestane (XV) and subsequent hydrolysis and oxidation to 2α-deuterocholestan-3-one (XIII), gave a product which, after conversion into the deuterated 3-methylenecholestane, proved to be a mixture of approximately equal amounts of 2α-deutero-3-methylenecholestane and a 4-deutero-3-methylenecholestane (Compound A, p. 5019); the double bond in the acetate (IX) presumably migrated on the rhodium–alumina catalyst. 2,2,4,4-Tetradeuterocholestan-3-one (XVII) was prepared from cholestan-3-one (XVI) by exhaustive deuteration with deuterium oxide in dioxan containing a little sodium.

Experimental

Infrared spectra in the carbon–deuterium stretching region were measured for carbon tetrachloride solutions on a Unicam S.P. 100 spectrophotometer fitted with a grating. Other spectra were measured for Nujol mulls. Except where otherwise stated, optical rotations were measured for chloroform solutions.

Materials.—*3-Methylenecholestane.* Treatment of cholestan-3-one [10] with methylenetriphenylphosphorane in dry ether [9] gave 3-methylenecholestane, m. p. 64—65° (from ethyl acetate–methanol), $\nu_{max.}$ 895, 1650, and 3050 cm.$^{-1}$.

2β-Deutero-3-methylenecholestane. Cholestan-3-one was brominated in acetic acid,[11] and the resulting 2α-bromocholestane-3-one was reduced with sodium borohydride [12] to a mixture of 2α-bromocholestan-3α- and -3β-ol. Methanesulphonyl chloride (50 ml.) was added to a solution of the mixed epimers (76 g.) in dry pyridine (250 ml.) (cf. Rodger [13]), and the mixture was set aside overnight. After removal of pyridine under reduced pressure, the crude product was treated with zinc and acetic acid. Working up in the usual way and chromatography on alumina gave cholest-2-ene (37·5 g.), m. p. 73—74° (from ethyl acetate–methanol), $[\alpha]_D$ +68° (*c* 1·25).

Treatment of cholest-2-ene with perbenzoic acid [14] gave 2α,3α-epoxycholestane, m. p. 101—103° (from ether–ethanol), [α] +37° (*c* 0·84). A mixture of 2α,3α-epoxycholestane (5·5 g.) and lithium aluminium deuteride (1·17 g.) was heated under reflux in purified dioxan for 90 hr. Working up in the usual way and chromatography on silica gave 2β-deuterocholestan-3α-ol (4·15 g.), m. p. 184—186° (from ethanol), $[\alpha]_D$ +28° (*c* 0·53), $\nu_{max.}$ 1010, 2155, and 3270 cm.$^{-1}$

[10] Bruce, *Org. Synth.*, 1937, **17**, 43.
[11] Butenandt and Wolff, *Ber.*, 1935, **68**, 2091.
[12] Fieser and Huang, *J. Amer. Chem. Soc.*, 1953, **75**, 4837.
[13] Rodger, Ph.D. Thesis, Glasgow, 1960.
[14] Fürst and Plattner, *Helv. Chim. Acta*, 1949, **32**, 275.

Heterogeneous oxidation of this alcohol in benzene [15] with a mixture of sodium dichromate, chromium trioxide, and acetic acid gave 2β-deuterocholestan-3-one, m. p. 128—129° (from light petroleum), $\nu_{max.}$ 1715 and 2140 cm.$^{-1}$. Conversion of the ketone by the method used for the undeuterated analogue gave 2β-deutero-3-methylenecholestane, m. p. 64—65°, $[\alpha]_D$ +26° (*c* 0·28), containing 0·99 atom of deuterium per molecule.

2α-*Deutero*-3-*methylenecholestane*. Powdered lithium aluminium deuteride (0·90 g.) was added during 3 hr. to a solution of cholest-2-ene (15 g.) and boron trifluoride–ether complex (30 ml.) in dry ether (150 ml.), through which nitrogen was bubbled, and the resulting mixture was left overnight. The ethereal solution was washed with aqueous sodium sulphate solution and dried (Na_2SO_4), and the ether removed. The resulting white gum was dissolved in dioxan and the solution was made alkaline by the addition of ethanolic sodium hydroxide. A large excess of hydrogen peroxide (100-vol.; 60 ml.) was added and the mixture was warmed for a few minutes on the steam-bath. The product was worked up in the usual way and chromatographed on alumina (13·2 g. of product in 1 : 1 benzene–light petroleum). Elution with 1 : 1 benzene–light petroleum gave cholest-2-ene (1·8 g.), m. p. and mixed m. p. 72° (from ethyl acetate–methanol); elution with 3 : 2 benzene–ether gave first 2α-deuterocholestan-3α-ol (3·5 g.), m. p. and mixed m. p. with epicholestanol 184—186° (from ethanol), $\nu_{max.}$ 1010, 1030, 2145, and 3270 cm.$^{-1}$, and, secondly, 3α-deuterocholestan-2α-ol (2·0 g.), m. p. 177—180° (from ethanol), $\nu_{max.}$ 1020, 1030, 2150, and 3270 cm.$^{-1}$; elution with 98 : 2 ether–ethyl acetate gave 2α-deuterocholestan-3β-ol (1·1 g.), m. p. and mixed m. p. with cholestan-3β-ol 140—141° (from ethanol), $\nu_{max.}$ 1020, 1030, 2160, and 3350 cm.$^{-1}$. Oxidation of the last alcohol gave a deuterocholestan-3-one, the infrared spectrum of which in the C–D stretching region was identical with that of 2α- and different from that of 2β-deuterocholestan-3-one. The remainder of the material on the column was recovered in the form of impure intermediate fractions.

2α-Deuterocholestan-3-one, prepared by oxidation of 2α-deuterocholestan-3α-ol under the same conditions as for the production of 2β-deuterocholestan-3-one, was converted into 2α-deutero-3-methylenecholestane by the method used for the undeuterated analogue. The product had m. p. 64—65°, $[\alpha]_D$ +26° (*c* 0·28), and contained 1·03 atoms of deuterium per molecule.

2,2,4,4-*Tetradeutero*-3-*methylenecholestane*. Cholestan-3-one (11 g.) was heated under reflux for 1 hr. in dioxan (100 ml.) containing deuterium oxide (3 ml.) in which a small pellet of sodium had been dissolved. A 30-ml. portion was removed; the remainder was evaporated to dryness and the residue heated under reflux for 1 hr. with fresh dioxan (70 ml.) and deuterium oxide (2·2 ml.). A further portion was removed and the process repeated with the remainder. The resulting products were three samples of cholestan-3-one that had been subjected to increasing amounts of exchange. The first sample was shown to be incompletely deuterated, by the presence of an infrared band at 1420 cm.$^{-1}$. The third sample, 2,2,4,4-tetradeuterocholestan-3-one, m. p. 128—129° (from light petroleum), showed no such band and was converted into 2,2,4,4-tetradeutero-3-methylenecholestane, m. p. 64—65°, $[\alpha]_D$ +25° (*c* 0·28), containing 4·08 atoms of deuterium per molecule.

Attempted preparation of 2α-*deutero*-3-*methylenecholestane*. Cholestan-3-one (40 g.), acetyl chloride (80 ml.), and acetic anhydride (200 ml.) were heated under reflux for 5 hr. The cooled solution was poured into water, and the product separated by filtration. Working up in the usual way and chromatography on silica gave 3-acetoxycholest-2-ene [16] (33 g.), m. p. 90—93° (from ethanol), $[\alpha]_D$ +59° (*c* 1·05).

Preliminary studies with hydrogen showed that, whereas hydrogenation of the enol acetate in ethyl acetate over Adams catalyst caused only hydrogenolysis, hydrogenation in ethyl acetate over a catalyst consisting of rhodium (5%) on alumina gave a smaller amount of hydrogenolysis product and some of the required cholestan-3β-yl acetate. The following procedure was, therefore, adopted.

3-Acetoxycholest-2-ene (33 g.) in ethyl acetate (500 ml.) containing rhodium catalyst (5 g.) was treated with deuterium (generated by electrolysis of deuterium oxide containing phosphorus pentoxide) at room temperature and atmospheric pressure until the uptake of gas (*ca.* 30 ml. hr.$^{-1}$) slowed appreciably (*ca.* 5 days). Solvent was removed from the filtered solution, and the residue was chromatographed on silica. Elution with light petroleum gave

[15] Corey, Howell, Boston, Young, and Sneen, *J. Amer. Chem. Soc.*, 1956, **78**, 5036.
[16] Rubin and Armbrecht, *J. Amer. Chem. Soc.*, 1953, **75**, 3513.

deuterated cholestane, m. p. 80—81°, $[\alpha]_D$ +27° (*c* 1·14). Elution with 3 : 2 light petroleum–benzene gave a mixture, the infrared spectrum of which indicated the presence of both enol acetate and acetate (bands at 1745 and 1760 cm.$^{-1}$). This mixture (23 g.) was hydrolysed by being heated under reflux with potassium hydrogen carbonate (23 g.) in a mixture of dioxan, methanol, and water for 3 hr. and the product was worked up in the usual way and chromatographed on alumina. Elution with 3 : 2 light petroleum–benzene gave cholestan-3-one, m. p. and mixed m. p. 127—128°. Elution with 4 : 1 benzene–ethyl acetate gave deuterated cholestan-3β-ol (10·5 g.), m. p. and mixed m. p. 140—142°.

This supposed 2α,3α-dideuterocholestan-3β-ol was converted into the ketone and thence into supposed 2α-deutero-3-methylenecholestane (Compound A) by the methods used for the production of 2β-deutero-3-methylenecholestane. Compound A had m. p. 64—65°, $[\alpha]_D$ +27° (*c* 0·28), and contained 1·02 atoms of deuterium per molecule. Experiments on the constitution of this compound are described below.

Attempted preparation of 2,2-dideutero-3-methylenecholestane. Bromination [17] of 2α-bromocholestan-3-one in anhydrous acetic acid buffered with potassium acetate at 90° gave 2,2-dibromocholestan-3-one, m. p. 149—152° (decomp.), $\nu_{max.}$ 1735 cm.$^{-1}$. Zinc dust was added slowly during 30 min. to a solution of 2,2-dibromocholestan-3-one in boiling *O*-deuteroacetic acid and the mixture was heated under reflux for 3 hr. The deuteroacetic acid was removed under reduced pressure and the residue was chromatographed on silica. Elution with 9 : 1 light petroleum–benzene gave 3-acetoxy-2-bromocholest-2-ene, m. p. 87—90°, $\nu_{max.}$ 1210, 1220, and 1760 cm.$^{-1}$. Elution with 4 : 1 light petroleum–benzene gave deuterated cholestan-3-one, m. p. and mixed m. p. 128—129°, $\nu_{max.}$ 1715 and 2100—2300 cm.$^{-1}$. The deuterated 3-methylenecholestane prepared from this ketone contained only 0·49 atom of deuterium per molecule.

3-Methylcholest-2-ene. Cholestan-3-one (5·2 g.) was treated with methylmagnesium iodide in ether, to give a mixture of the two epimeric 3-methylcholestan-3-ols.[9] A solution of the mixed epimers in acetic acid containing a few drops of 70% perchloric acid was heated on a steam-bath for 30 min. Working up in the usual way and chromatography on alumina gave 3-methylcholest-2-ene (4·0 g.), m. p. 82—83° (from ethyl acetate–methanol).

Dioxan. Commercial dioxan was purified with hydrochloric acid and stannous chloride [18] and had b. p. 102°/770 mm.

Acetic acid. " AnalaR " acetic acid was heated under reflux for several hours with acetic anhydride and a few drops of sulphuric acid and then distilled through a Vigreux column. The middle fraction had b. p. 118—119°/760 mm.

Chloroform. " AnalaR " chloroform was used without further purification.

Dioxan–water solvent. Reactions in aqueous dioxan were started by mixing 20 ml. of a solution of the reactant in dioxan containing 1·25% v/v water with 5 ml. of a solution made by diluting 1 ml. of 12·02N-perchloric acid (*d* 1·685) to 10 ml. with pure dioxan. The final solution was, therefore, 0·24N with respect to perchloric acid and contained 1·95% w/v water (1·09M). The initial concentration of 3-methylenecholestane was about 6×10^{-3}M.

Acetic acid–chloroform solvent. An anhydrous solution of perchloric acid in acetic acid was prepared by adding the calculated quantity of acetic anhydride to a solution of 10 ml. of aqueous 12·20N-perchloric acid in acetic acid, keeping the mixture for 24 hr., and then diluting it to 100 ml. with acetic acid; 1 ml. of this solution was then diluted to 100 ml. with acetic acid, giving a solution 0·012N with respect to perchloric acid. The reactions were started by adding 5 ml. of this solution to a solution of the reactant in a mixture of chloroform (20 ml.) and acetic acid (100 ml.), and the final solution was, therefore, 0·00048N in perchloric acid and contained 16% v/v chloroform and 84% acetic acid.

Rate Measurements.—Rates of rearrangement. A standard solution of the reactant (3-methylenecholestane or one of its deuterated derivatives) in dioxan containing 1·25% v/v of water was prepared at the temperature of the thermostat-bath and the rotation of the solution was determined in a thermostat-controlled polarimeter tube. The reaction was started by mixing 20 ml. of this solution with 5 ml. of an acid solution (prepared by diluting 1 ml. of aqueous 12·02N-perchloric acid to 10 ml. with dioxan, at the temperature of the thermostat-bath) and quickly transferring the mixture to a thermostat-controlled 4 dm. polarimeter tube. Readings of rotation were taken at appropriate intervals to cover the first 70% of the reaction, and a final reading was taken after not less than twenty times the half-life of the reaction.

[17] Crowne, Evans, Green, and Long, *J.*, 1956, 4351.
[18] Cavell, Chapman, and Johnson, *J.*, 1960, 1413.

Rates of exchange. For measurements of the rates of exchange in aqueous dioxan, the reactions were carried out in the way described above, except that the reaction mixture was not transferred to a polarimeter tube. At known intervals aliquot parts were withdrawn and added to an excess of aqueous sodium hydroxide solution. The mixture was extracted with ether, and the ethereal extract washed several times with water and dried (Na_2SO_4). After removal of ether, the product was purified by chromatography on alumina and its deuterium content determined (see below).

The reactions in acetic acid–chloroform were started by adding 5 ml. of 0·012N-perchloric acid in acetic acid to a solution of the reactant in a mixture of chloroform (20 ml.) and acetic acid (100 ml.). Aliquot parts were withdrawn at intervals and the product was isolated as above. The deuterium content of the product was determined by a simplified procedure in these cases (see below).

Deuterium Analyses.—The various deuterated 3-methylenecholestanes and the deuterated 3-methylcholest-2-enes isolated from reactions in aqueous dioxan were analysed for deuterium by combustion of the sample in a combustion train and measurement of the intensity of the peak at 2490 cm.$^{-1}$ (HOD fundamental band) in the infrared spectrum of the water produced.[19] The whole procedure is based on that used by Dr. G. Eglinton of Glasgow University and we are very grateful to him for the use of facilities in his laboratory before the setting up of our own apparatus.

For each determination the sample of deuterated compound was mixed with a sufficient quantity of undeuterated parent compound so that the water produced on combustion contained about 1·0—1·5 atoms % of deuterium. Enough mixture was burnt to produce about 30 mg. of water and this was transferred to a cell made by cementing a quartz microscope slide to either side of a lead spacer (0·075 mm. thick). The optical density at 2490 cm.$^{-1}$ was then determined and the method was calibrated against standard D_2O–H_2O mixtures, containing 0—2% w/w of D_2O (with H_2O in the reference cell). A plot of optical density against amount of D_2O was almost linear over this range, all the deuterium being present as HOD. (Above about 6% of D_2O complications occur, due to the presence of D_2O as well as HOD molecules.)

For the products obtained from the reactions in acetic acid–chloroform a simplified method of deuterium analysis was used. The deuterated 3-methylcholest-2-enes were isolated as before, but their deuterium contents were determined by measurement of the area under the peak in the C–D stretching region of the infrared spectrum. The method was standardised with samples of product, whose deuterium contents had been determined by the combustion method.

Experiments with Compound A.—Compound A was isomerised to deuterated 3-methylcholest-2-ene under the same conditions as for 3-methylenecholestane and its other deuterated derivatives, and the rate of isomerisation was found to be the same as that for all these compounds (see below). However, whereas the product of isomerisation of 2β-deutero-3-methylenecholestane had only one peak (2230 cm.$^{-1}$) in the 2000—2300 cm.$^{-1}$ region of its infrared spectrum, the product of isomerisation of compound A had an additional peak at 2135 cm.$^{-1}$. Although this peak is not present in the spectrum of compound A itself, its presence in the spectrum of the isomerisation product suggests that some of the deuterium is present elsewhere than in the 2-position.

To determine whether this differently situated deuterium was present in compound A itself or whether it had arisen by migration of deuterium during the isomerisation, we prepared the isomerisation product by an alternative method unlikely to allow migration of deuterium. The ketone precursor of compound A (supposed 2α-deuterocholestan-3-one) was treated with methylmagnesium iodide to give a mixture of the deuterated 3-methylcholestan-3-ols. The deuterated 3β-methylcholestan-3α-ol was separated from this mixture by chromatography on silica and dehydrated to deuterated 3-methylcholest-2-ene (compound B) by the action of phosphorus oxychloride in pyridine. The infrared spectrum of compound B contained peaks at both 2230 and 2135 cm.$^{-1}$ and it was, therefore, concluded that compound A itself contained some of its deuterium elsewhere than in the 2-position.

Treatment of compound A with a concentration of acid higher than that used in the rate measurements resulted in a complete loss of the 2230 cm.$^{-1}$ band in the spectrum of the product and a considerable reduction in intensity of the 2135 cm.$^{-1}$ band. This is consistent with

[19] Keston, Rittenberg, and Schoenheimer, *J. Biol. Chem.*, 1937, **122**, 227; Gaunt, *Analyst*, 1954, **79**, 580.

assuming the contaminant in compound A to be a 4-deutero-3-methylenecholestane, since 2,2,4,4-tetradeutero-3-methylenecholestane has been shown to lose more than two atoms of deuterium per molecule on long contact with acid (see below).

When the isomerisation of compound A was carried out under the conditions of the rate measurements, the product contained 0·7 atom of deuterium per molecule (see below), *i.e.*, 0·3 atom of deuterium per molecule was lost during isomerisation. If it is assumed that the deuterium is lost entirely from the 2-position, then it follows that the difference in areas under the 2230 cm.$^{-1}$ peaks in the spectrum of compound B and of the isomerisation product of compound A corresponds to 0·3 atom of deuterium per molecule. Hence it is possible to calculate the amount of deuterium in the 2-position of compound A and, by difference, the amount in the 4-position. On this basis compound A appears to be an approximately equimolar mixture of 2α- and a 4-deutero-3-methylenecholestane.

The 4-deutero-3-methylenecholestane must have arisen in the deuteration of the supposed 3-acetoxycholest-2-ene, either because the latter is a mixture of 3-acetoxycholest-2- and -3-ene, or because some 3-acetoxycholest-2-ene isomerises to 3-acetoxycholest-3-ene on the deuteration catalyst. To decide between these alternatives, we treated the supposed 3-acetoxycholest-2-ene with bromine in acetic acid containing sodium acetate and dehydrobrominated [20] the product with a mixture of lithium bromide and lithium carbonate in dimethylformamide. Under these conditions 3-acetoxycholest-2-ene and 3-acetoxycholest-3-ene would be expected to produce the readily distinguishable cholest-1- and cholest-4-en-3-one, respectively. In fact, chromatography and ultraviolet spectroscopy showed that the product was cholest-1-en-3-one, containing (if any) not more than 5% of cholest-4-en-3-one. It follows, therefore, that the supposed 3-acetoxycholest-2-ene is substantially pure (at least 95%) and that 3-acetoxycholest-3-ene must have been formed from it by isomerisation on the catalyst used for the deuteration. Since the 3-ene is less stable than the 2-ene, it must be reduced more quickly, to explain the production of roughly equal amounts of 2- and 4-deutero-product.

Results

Kinetic Experiments.—The first-order rate constants k_1 for the rearrangement of 3-methylenecholestane and its deuterated derivatives were obtained from plots of $\log_{10}(\alpha_\infty - \alpha)$ against t, where α is the observed optical rotation at time t and α_∞ is the rotation after " infinite " time (at least twenty times the half-life), the slope of the line being equal to $-k_1/2{\cdot}303$. All the reactions went to completion, as shown by the rotation at " infinite " time. The measured rate constants for all the reactions and the Arrhenius parameters and entropy of activation for the reaction of 3-methylenecholestane are collected in Table 1. The rate constants are accurate to ±4%, E to ±0·7 kcal. mole^{-1}, $\log_{10} A$ to ±0·4, and $\Delta S^\ddagger$ to ±1·9 cal. mole^{-1} deg.$^{-1}$.

In the case of 2,2,4,4-tetradeutero-3-methylenecholestane, the plot of $\log_{10}(\alpha_\infty - \alpha)$ against t was not a straight line and the value of k_1 given in Table 1 for the reaction of this compound was determined from the initial slope. The gradual decrease in rate for the tetradeutero-compound remains puzzling.

The reaction of 3-methylenecholestane was of the first order in the methylene compound, since variation of the initial concentration of methylene compound did not alter the first-order rate constant. This reaction was also carried out with different initial concentrations of perchloric acid and of water and, by application of the differential method of determining reaction orders,[21] was shown to be of order +5·3 in perchloric acid and −5·0 in water.

Exchange Experiments.—For the exchange reaction of 2β-deutero-3-methylenecholestane in aqueous dioxan, a plot of log (atoms of deuterium per molecule of isolated product) against time gave a line which was straight after an initial steep portion. The steep part of the line corresponds to loss of deuterium in the isomerisation and the straight part to loss of deuterium by exchange from the product of isomerisation. Extrapolation of the straight part of the line to a point corresponding to the time of half-reaction of the isomerisation gave the amount of deuterium in the product of the isomerisation reaction. The amounts of deuterium in the products of isomerisation of the other deuterated 3-methylenecholestanes were determined

[20] Joly and Warnant, *Bull. Soc. chim. France*, 1958, 367.
[21] Laidler, " Chemical Kinetics," McGraw-Hill, New York, 1950, p. 14.

similarly and the results are shown in Table 2. The latter part of the plot for 2,2,4,4-tetradeutero-3-methylenecholestane was not exactly linear (and would not be expected to be) and extrapolation in this case was only approximate.

TABLE 1.

Measured rate constants, Arrhenius parameters, and entropy of activation for isomerisations in aqueous dioxan.

(k_1 and A in sec.$^{-1}$; E in kcal. mole^{-1}; $\Delta S^{\ddagger}$ in cal. mole^{-1} deg.$^{-1}$.)

Compound	Temp.	$10^5 k_1$	E	$\log_{10} A$	$\Delta S^{\ddagger}$
3-Methylenecholestane	20·1°	3·75	24·0	13·4	+0·7
	30·2	15·2			
	40·4	53·3			
2β-Deutero-3-methylenecholestane	30·2	15·5			
2α-Deutero-3-methylenecholestane	30·2	14·7			
Compound A	30·2	14·9			
2,2,4,4-Tetradeutero-3-methylenecholestane	30·2	15 (from initial rate)			

TABLE 2.

Amounts of deuterium lost in the isomerisation reactions (deuterium contents in atoms of deuterium per molecule).

3 Methylenecholestane derivative	Deuterium content of reactant	Deuterium content of product in aqueous dioxan	Deuterium content of product in acetic acid–chloroform
2β-Deutero-	0·99	0·91	0·99
2α-Deutero	1·03	0·65	0·56
2,2,4,4-Tetradeutero-	4·08	*ca.* 3.	

DISCUSSION

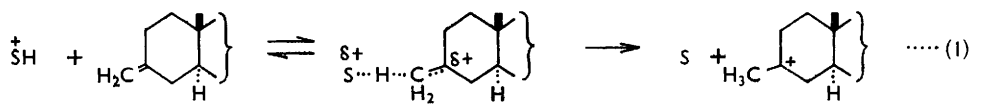
Application of Curtin and Kellom's method [22] to the figures for the amount of deuterium lost in the isomerisation of 2β- and 2α-deutero-3-methylenecholestane (Table 2) allows the total effect to be separated into an isotope effect I (a measure of the isotopic discrimination in the absence of a steric effect) and a stereospecific effect S (a measure of the stereospecificity in the absence of an isotope effect), on the assumption that the isotope effect is the same for loss of axial and equatorial atoms. For the reactions in aqueous dioxan, $I = 4{\cdot}4$ (in favour of loss of protium rather than deuterium) and $S = 2{\cdot}6$ [in favour of loss of equatorial (α) rather than axial (β) hydrogen]. For the reactions in chloroform–acetic acid, 2β-deutero-3-methylenecholestane appears to lose no deuterium during isomerisation, so values for I and S cannot be calculated; but the greater loss of deuterium from 2α-deutero-3-methylenecholestane in chloroform–acetic acid than in aqueous dioxan implies an even greater preference for equatorial loss in the former solvent ($S > 2{\cdot}6$).

The magnitude of the isotope effect ($I = 4{\cdot}4$) for the reactions in aqueous dioxan indicates appreciable stretching of the carbon–hydrogen bond in the transition state [23] where the products diverge. However, the results in Table 1 show that the rate constants for the reactions of 3-methylenecholestane and its 2α- and 2β-deutero-derivatives are identical within experimental error (*i.e.*, there is no kinetic isotope effect). The rate-determining step and the step leading to the products cannot, therefore, be the same and the mechanism must consist of at least two stages, with at least one intermediate, and the final stage cannot be rate-determining.

That 3-methylcholest-3-enes are not intermediates can be inferred from the fact that the product from the reaction of 2,2,4,4-tetradeutero-3-methylenecholestane after about thirty half-lives still contained 2·5 atoms of deuterium per molecule. If 2,2,4-trideutero-3-methylcholest-3-ene had been intermediate, the product could not have contained more than 2 atoms of deuterium per molecule.

[22] Curtin and Kellom, *J. Amer. Chem. Soc.*, 1953, **75**, 6011.
[23] Westheimer, *Chem. Rev.*, 1961, **61**, 265.

The reaction probably proceeds, therefore, by the slow transfer of a proton from the solvent to the olefin. The intermediate carbonium ion is then rapidly converted into the products.[6,7] The high entropy of activation (+0·7 cal. mole^{-1} deg.$^{-1}$) suggests that the transition state for the slow step is less solvated than the initial state, as required by a mechanism with the charge dispersed in the transition state (S usually dioxan):



Transition state

The present results provide no evidence for or against the formation of a π-complex [6,24] (or of another kind of " freer " proton [25]) in an initial fast equilibrium, followed by slow conversion into the carbonium ion: nor do they exclude the unlikely possibility that the methylene compound itself is in equilibrium with the carbonium ion, or the rather more likely one that the carbonium ion is in equilibrium with the tertiary alcohols [26] or the corresponding dioxan oxonium salts.

The actual magnitudes of the orders in perchloric acid (+5·3) and in water (−5·0) can hardly be taken as reflecting directly the change in average numbers of molecules involved in going from the initial to the transition state, but must be due to more general changes in the nature of the solvent. Water is a stronger base than dioxan,[27,28] and addition of small proportions of water to dioxan causes a large fall in acidity function.[27] The increase in dielectric constant produced by addition of water should also shift the equilibrium away from the transition state (with its dispersed charge) toward the initial state (with its more concentrated charge). Consideration of probable kinds of molecular solvation point in the same direction as the macroscopic dielectric constant. In water the proton exists as $H_3O^+(H_2O)_3$,[29] which is more weakly bound to about six other water molecules.[30] From crude calculations based on change in standard partial molar free energy with change in solvent composition for solutions of perchloric acid in 50% aqueous dioxan Grunwald *et al.*[31] suggested that the proton exists, on average, in the form H_3O^+-(dioxan)$_3$. While that would indicate less preferential solvation by water than one would have expected, the large organic cation * may even have some preference for solvation by dioxan.[31] Perchloric acid probably exerts its additional accelerating effect by removing free water from the solution as solvated hydroxonium ions. Perchlorate ions, like other inorganic anions, are also probably preferentially solvated by water.[31]

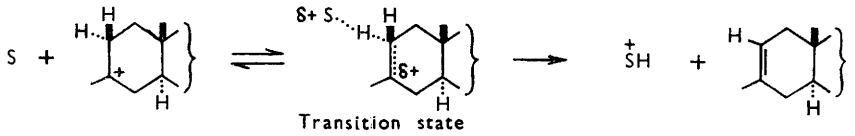
Although its rate was not measured, there is no reason to doubt that the reaction in chloroform–acetic acid has the same mechanism (1), where S now represents acetic acid instead of dioxan.

The second stage of the reaction, removal of a proton (or deuteron) from the carbonium ion, requires a molecule of base, which in aqueous dioxan will be a molecule of water, as

* Grunwald *et al.*[31] interpreted their measurements on salt solutions as showing that large organic cations, such as tetramethylammonium, were solvated much like hydrocarbons. The same might not apply to a carbonium ion with its vacant orbital and less shielded centre of charge.

[24] Hammond and Collins, *J. Amer. Chem. Soc.*, 1960, **82**, 4323; *J. Org. Chem.*, 1960, **25**, 911.
[25] de la Mare, Hughes, Ingold, and Pocker, *J.*, 1954, 2930.
[26] Dostrovsky and Klein, *J.*, 1955, 791.
[27] Braude and Stern, *J.*, 1948, 1976.
[28] Lemaire and Lucas, *J. Amer. Chem. Soc.*, 1951, **73**, 5198; Arnett and Wu, *ibid.*, 1960, **82**, 4999.
[29] Wicke, Eigen, and Ackermann, *Z. phys. Chem.* (*Frankfurt*), 1954, **1**, 340; Beckey, *Z. Naturforsch.*, 1959, **14**, 712.
[30] Hasted, Ritson, and Collie, *J. Chem. Phys.*, 1948, **16**, 1; Ackermann, *Discuss. Faraday Soc.*, 1957, **24**, 180.
[31] Grunwald, Baughman, and Kohnstam, *J. Amer. Chem. Soc.*, 1960, **82**, 5801.

the strongest base. The mechanism of the second step (for α-attack) can therefore be written:



(where S is usually H_2O, no doubt further hydrogen-bonded to the solvent).

The isotope effect ($I = 4{\cdot}4$) indicates considerable stretching of the C–H bond in the transition state, which must, therefore, be fairly similar to the olefin (cf. the theoretical maximum at 30·2° of 6·7). The stereospecific effect ($S = 2{\cdot}6$ in favour of α-attack) can be divided into two factors. The first of these, the steric effect, takes account of the total energy of repulsion between unbound or partly bound atoms in the transition state (compared with alternative transition states), both within the carbonium ion and between it and the partly solvated proton. The second, the stereoelectronic effect, arising from orbital-overlap,[4,5] is at a maximum when the partially formed or broken C–H bond is at right angles to the nodal plane of the empty *p*-orbital of the carbonium ion and at a minimum when it is in the plane.

Our results with olefins invite comparison with those on ketones. The most obvious of the many changes produced in the system, (III ⟶ V) (X = Z = H, Y = O or CH_2), by substituting O for CH_2 are:

(1) The olefin (III; X = H, Y = CH_2) can accept a proton only through its π-electrons (whether *via* a complex or directly to the carbonium ion), whereas the ketone (III; X = H, Y = O) can take up a proton reversibly because of the unshared electrons on oxygen.

(2) Correspondingly, the protonated ketone (IV; X = Z = H, Y = O) is much more stable relative to the enol (V; Y = O, Z = H) than is the carbonium ion (IV; X = Z = H, Y = CH_2) relative to the olefin (V; Y = CH_2, Z = H), because of the greater conjugation of the *p*-electrons of OH than hyperconjugation of CH_3 with the vacant orbital. In addition the enol can form a hydrogen bond to the solvent.

(3) The equilibrium lies in favour of compound (III) for the ketone but compound (V) for the olefin.

The effect of (2) and (3) must be to move the transition state for the step (IV ⟶ V) nearer to (V) for enolisation than for olefin isomerisation. Assuming that the reactions take place by analogous mechanisms, one would, therefore, expect in the same solvent a greater isotope effect (*I*) and a lower stereoelectronic effect for enolisation than for olefin isomerisation. In fact, for enolisation of 3β-acetoxycholestan-7-one catalysed by hydrogen bromide in chloroform Corey and Sneen [5] observed an isotope effect of 7·4, considerably greater than our value of 4·4 for olefin isomerisation catalysed by perchloric acid in aqueous dioxan (a more basic solvent, which should shift the transition state towards IV).

On the other hand, the 7-ketone lost the axial 6β-proton in preference to the equatorial 6α-proton ($S = 0{\cdot}8$—$0{\cdot}7$ for HBr in chloroform, and less than 0·1 in the less acidic solvent, acetic acid), while the 3-methylenecholestane lost the equatorial 2α-proton preferentially ($S = 2{\cdot}6$ in aqueous dioxan). One explanation of this reversal of expected behaviour would be to suppose that the effective size of the base in the former reaction (Br^- or HBr_2^-) is much less than in the latter (H_2O, 2 dioxan). It is more probably, however, largely a property of the molecular environment, for kinetically controlled bromination of the ketones provides a precisely analogous contrast: 3β-acetoxycholest-6-en-7-ol gives mainly the axial 6β-bromo-7-one,[5] whereas cholest-2-en-3-ol or its acetate (V; Y = O, Z = H or Ac) gives almost entirely the equatorial 2α-bromo-3-one [3] (III; X = Br, Y = O).*

The reason probably lies in the well-known flexibility of ring A compared with the

* Chlorination, however, gives the 6α-chloro-7-one.[5]

other rings of the cholestane nucleus. If the other rings remain chairs the only alternative to the chair conformation of ring B in cholestan-7-one is a strained and distorted half 7,10-boat,* the full boat conformation being prevented by the fusion with ring C. The transition state of lowest energy for enolisation must then be intermediate between the chair conformation of the 7-ketone and the half-chair conformation of the Δ^6-enol, which is quite rigid and inflexible. The 3-ketone or carbonium ion (IV), on the other hand, as well as the chair conformation considered so far, can adopt the 3,10- or the 2,5-boat conformation, or the twisted conformation [32,33] intermediate between the last two. Pseudo-rotation of the boat conformation of cyclohexane itself [32] causes no angle-strain in the ring. The twisted-boat conformation of (IV), however, seems to involve a very slight widening of endocyclic angles: it offers, nevertheless, some of the advantages [32, 33] of the twisted-boat cyclohexane and also staggers the methylene groups at positions 2 and 11. Since the 7-ketone undergoes unambiguous axial bromination (and deprotonation) in spite of the angular methyl group, it is tempting to assume that the stereo-electronic effect still compels axial attack on the enol of the 3-ketone, which must then go through a boat form.

The axial transition state intermediate between the 2,5-boat (IV; X = Z = H, Y = CH_2; or X = Br, Y = O, Z = H) and the half-chair 2-ene (V; YZ = CH_3 or OH) would suffer from, *inter alia*, serious interaction between the solvated 2α-proton (or $\overset{\delta+}{Br}$) and the 5α-hydrogen atom, and need not be considered further. The two alternatives, therefore, are (*a*) the transition state intermediate between the chair carbonium ion [or protonated enol (IV)] and the half-chair 2-ene (V), and (*b*) the one intermediate between the 3,10-boat (or twisted boat—a very fine distinction) and the half-chair 2-ene. At the price of slightly more internal repulsion energy within the molecule, transition state (*b*) has the minimum repulsion for axial (α) gain or loss of the solvated electrophile, compared with (*a*) which, of course, suffers particularly from the interaction of the electrophile with the axial 10-methyl group. (In the absence of the latter the 3-ketone yields mainly axial 2β-bromide.[3])

To decide through which of the four transition states, axial or equatorial of type (*a*) or (*b*), a particular reaction will proceed is a complex question, requiring analysis of entropy changes as well as of transition-state energies, but it seems reasonable that, for reactions where the transition state is not too far from (IV) and Corey's stereo-electronic factor is important, the axial transition state (*b*) should be preferred, leading to overall β-equatorial gain or loss. We think, therefore, that the change (IV) ⟶ (V) probably goes through a boat-like transition state (*b*).

The greater loss of an α-proton from the carbonium ion in chloroform–acetic acid than in dioxan–water still calls for comment. The stereo-electronic effect will certainly be smaller because acetic acid is a weaker base than water (or dioxan), and hence the transition state should be nearer to the products for reaction in chloroform–acetic acid. It cannot be assumed that this change is enough to allow reaction through the equatorial, chair transition state, because the differential solvation of the reactants and transition states as well as the relative sizes of the bases are hard to estimate (a molecule of acetic acid hydrogen-bonded to at least one other molecule, against a molecule of water hydrogen-bonded to one or probably two molecules of dioxan).

We thank Dr. J. Hudec for helpful advice. This research was supported by a grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is hereby made to the donors of the Fund.

THE UNIVERSITY, SOUTHAMPTON. [*Received, June 6th*, 1962.]

* The numbers denote the bow and stern of the boat.

[32] Hendrickson, *J. Amer. Chem. Soc.*, 1961, **83**, 4537.
[33] Johnson, Bauer, Margrave, Frisch, Dreger, and Hubbard, *J. Amer. Chem. Soc.*, 1961, **81**, 606.