Electrophilic Substitution with Rearrangement. Part VI.[1] Bromination of 3-Acetoxycholesta-3,5-diene

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Knowledge of the range of conditions and reagents through which 3-acetoxycholesta-3,5-diene (1) is brominated to give 6β-bromocholest-4-en-3-one has been extended. Intermediate adducts involving the 5,6-double bond have been shown to be components of the reaction mixture from (1) and bromine in acetic acid. Acid-catalysed isomerisation and rearrangements of the kinetically controlled products, and dibromination, can be avoided by careful choice of the conditions of bromination and work-up. Complications associated with the reaction paths have been partly elucidated. Some other sources of electrophilic bromine give smooth bromination to the 6β-bromo-derivative.

THE enol acetates of ketones usually react rapidly with carriers of electrophilic bromine to give the corresponding bromo-ketones [equation (1)].[2]

$$R_2C{:}C(R)OAc + BrX \longrightarrow BrCR_2{\cdot}C(R){:}O + AcX \quad (1)$$

The related vinylogous process involving an extended conjugated system is well known also; thus 3-acetoxycholesta-3,5-diene (1) reacts with bromine,[3] or with *N*-bromosuccinimide [4] to give 6β-bromocholest-4-en-3-one (2) (see Scheme).

The principles which govern the orientation of initial electrophilic attack on such compounds have been discussed.[5] It is generally accepted [5,6] that axial attack by bromine is normally preferred, even when steric influences seem to favour the alternative mode, but that isomerisation catalysed by hydrogen bromide is an important secondary reaction, which thus could, for example, lead to the conversion of (2) into its geometric isomer, 6α-bromocholest-4-en-3-one (3), or might give more extensive rearrangement.

Despite these and other related investigations, the details of the reaction paths involved in these brominations are not by any means clear. For some of the reactions,[2,3] routes of various kinds involving addition–elimination sequences have been postulated. Jones and his co-workers,[7,8] however, have suggested that in some cases a cyclic transition state may be involved, since even under conditions of kinetic control (when the subsequent isomerisation is not significant), some enol esters give products both of equatorial and axial attack by electrophilic bromine. In other cases,[9] the reaction conditions are such that an external nucleophile might contribute significantly to the removal of the acetyl group, as in some reactions in the aromatic series reported by us.[10]

The many workers who have used these reactions preparatively have carried out brominations of enol esters with various substrates in a number of solvents and with several sources of electrophilic bromine. It seemed useful, as part of our search for conditions in which a bromodeacylation with rearrangement can be followed kinetically and hence its mechanism defined more precisely, to establish for a single substrate (1) whether there is any significant change in the position

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[6] D. N. Kirk and M. P. Hartshorn, 'Steroid Reaction Mechanisms,' Elsevier, Amsterdam, 1968, pp. 183 ff, 385 ff.
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and stereochemistry of electrophilic attack as the reagent is changed and as the solvent is changed. To be sure of kinetic control of the primary process it was necessary to establish the conditions necessary for the 6β ⇌ 6α isomerisation (2) ⇌ (3). Previous work in this area, though extensive, has been mainly with reference to other compounds. Hydrogen bromide has often been found to be an excellent catalyst, not only for such geometrical isomerisations,[11-13] but also for the rearrangement [14,15] involving migration of bromine often observed in these systems. Hydrogen chloride has sometimes been recorded as being a possible catalyst,[16] though it is generally considered to be much less effective than hydrogen bromide.[13] Our detailed findings relating to these matters will be presented separately.

EXPERIMENTAL

Materials and Methods.—Some of the materials and methods have been described elsewhere.[1,17,18] ^{1}H N.m.r. spectra were recorded by using a Varian T60 spectrometer, the solvent normally being $CDCl_3$, with Me_4Si as internal reference. I.r. spectra were measured by using a Perkin-Elmer 237 instrument; CCl_4 was the solvent except where otherwise stated. Silica gel (Kieselgel S 31614) was used for column chromatography; for t.l.c., Kieselguhr PF254 or PF366 was used. M.p.s were determined by using a Köfler block. Light petroleum had b.p. 50—70°. Cholest-4-en-3-one was purified by crystallisation from acetone, and had m.p. 81—82° (lit.,[19] 79·5—80·5°). 3-Acetoxycholesta-3,5-diene was prepared by heating cholest-4-en-3-one (15 g) with isopropenyl acetate (50 ml) and toluene-*p*-sulphonic acid (0·015 g) for 72 h at reflux temperature. The crude product after removal of excess of isopropenyl acetate was dissolved in benzene and chromatographed on silica gel (300 g). Elution with benzene gave 3-acetoxycholesta-3,5-diene (12 g), which crystallised from methanol as needles, m.p. 79—80° (lit.,[3] 81°), $\nu_{max.}$ (CS_2) 1755 (OAc) and 1635 (C=C) cm^{-1}, τ 9·34 (3H, s, 18-H_3), 9·05 (3H, s, 19-H_3), 7·88 (3H, s, 3-OAc), 4·72 (1H, m, 6-H), and 4·40 (1H, m, 4-H).

5α,6β-Dibromocholestan-3-one was prepared from the appropriate cholesterol dibromide; m.p. 71—73° (lit.,[20] 73—75°), τ 9·25 (3H, s, 18-H_3), 8·37 (3H, s, 19-H_3), 7·12 and 6·25 (2H, 2d, $J_{4,4}$ 16 Hz, 4-H_2), 5·22 (1H, m, 6α-H).

4-Bromocholest-4-en-3-one was obtained for reference by chromatography of the mixture obtained by allowing excess of bromine to react with cholest-4-en-3-one in a mixture of ether, acetic acid, and collidine,[21] m.p. 115—117° (lit.,[21] 117—118°), $\nu_{max.}$ (CS_2) 1690 (C=O) and 1412 (CH_2CO) cm^{-1}, τ 9·27 (3H, s, 18-H_3), 8·73 (3H, s, 19-H_3), and 6·70 (1H, d, $J_{6,6}$ 14 Hz, 6α-H).

4,6β-Dibromocholest-4-en-3-one was obtained from the above reaction mixture, and had m.p. 165—167° (decomp.) [lit.,[22] 165—167° (decomp.)], $\nu_{max.}$ (CS_2) 1690 (C=O) and 1412 (CH_2CO) cm^{-1}, τ 9·20 (3H, s, 18-H_3), 8·44 (3H, s, 19-H_3), and 4·30 (1H, m, 6α-H).

The 6-bromo- and 2α,6-dibromo-cholest-4-en-3-ones were obtained in the following way. A solution of 3-acetoxycholesta-3,5-diene (3 g) in acetic acid (70 ml) was stirred, and to it was added a solution (140 ml) of bromine (0·075M; 1·5 equiv.) in acetic acid at 20°. After 30 min, the solvent was removed under reduced pressure, leaving the crude product as a brown solid, the ^{1}H n.m.r. spectrum of which was used to estimate the proportions (given in brackets as percentages by weight here, as elsewhere in this paper) of the four major components. Chromatography of a portion (3 g) of the crude product enabled the separation of these components. Elution with a mixture (3 : 2) of benzene and light petroleum gave the epimeric 2α,6-dibromocholest-4-en-3-ones which were separated by preparative t.l.c., a similar solvent system being used. 2α,6β-Dibromocholest-4-en-3-one (28%) after recrystallisation from acetone had m.p. 160—162° (lit.,[23] 162—163°), $\nu_{max.}$ 1692 (C=O) and 1612 (C=C) cm^{-1}, τ 9·22 (3H, s, 18-H_3), 8·37 (3H, s, 19-H_3), 7·63 (1H, 2d, $J_{1,1}$ 11, $J_{1,2}$ 14 Hz, 1α-H), 7·35 (1H, 2d, $J_{1,1}$ 11, $J_{1,2}$ 5 Hz, 1β-H), 5·15 (1H, 2d, $J_{1,1}$ 14, $J_{1,2}$ 5 Hz, 2β-H), 5·02 (1H, m, 6α-H), and 4·05 (1H, s, 4-H). 2α,6α-Dibromocholest-4-en-3-one (22%) was recrystallised similarly, m.p. 127—128° (lit.,[16] 129°), $\nu_{max.}$ 1692 (C=O) and 1616 (C=C) cm^{-1}, τ 9·20 (3H, s, 18-H_3), 8·70 (3H, s, 19-H_3), 7·65 (1H, 2d, $J_{1,1}$ 11, $J_{1,2}$ 14 Hz, 1α-H), 7·37 (1H, 2d, $J_{1,1}$ 11, $J_{1,2}$ 5 Hz, 1β-H), 5·15 (2H, m, 2β- and 6β-H), and 3·50 (1H, d, $J_{4,6}$ 1·8 Hz, 4-H). Further elution with benzene then gave the epimeric 6-bromocholest-4-en-3-ones, which were separated similarly. 6β-Bromocholest-4-en-3-one (25%) crystallised from acetone as needles, m.p. 128—131° (lit.,[24] 134—135°), $\nu_{max.}$ 1680 (C=O), 1625 (C=C), and 1422 (CH_2CO) cm^{-1}, τ 9·22 (3H, s, 18-H_3), 8·44 (3H, s, 19-H_3), 5·04 (1H, m, 6α-H), 4·16 (1H, s, 4-H). The isomeric 6α-bromocholest-4-en-3-one (25%) crystallised similarly as needles, m.p. 109—111° (lit.,[23] 113°), $\nu_{max.}$ 1681 (C=O), 1627 (C=C), and 1421 (CH_2CO) cm^{-1}, τ 9·30 (3H, s, 18-H_3), 8·80 (3H, s, 19-H_3), 5·20 (1H, 2d, $J_{6,7}$ 14, $J_{6,7}$ 6 Hz, 6β-H), 3·73 (1H, d, $J_{4,6}$ 1·8 Hz, 4-H).

Similar product mixtures were obtained from reactions using equimolecular concentrations of reagents in acetic acid, in acetic acid containing 0·1M-lithium bromide, in nitromethane, and in dioxan, work-up in all these cases being by evaporation of solvent from the mixture.

The development of hydrogen bromide *via* the acetyl bromide produced in the bromo-deacylation would have encouraged geometric isomerisation to equilibrium mixtures of 6-substituted isomers; but the formation of substantial amounts of dibrominated products was unexpected for reactions in which the reactants were in equimolecular amounts. By the use of excess of bromine, it was established that one molecular equivalent was used up very rapidly but the second much more slowly; however, with a

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two-fold excess of bromine, a rapid consumption of *ca.* 5% more than one molecular equivalent of bromine occurred before the very much slower autocatalytic reaction became established.

These results suggest that under these conditions most of the diene goes rapidly to a monobrominated material, and a small part goes rapidly to a dibrominated material; either or both of the products can slowly and autocatalytically be brominated further. 6β-Bromocholest-4-en-3-one is brominated only slowly under these conditions, and is clearly one of the products present when the initial phase of reaction is complete; but other products must be present also, since dibromocholestenones were apparent in the reaction mixtures in which equimolecular concentrations of reagents were used. We showed also that by including water (4%) in the solvent and working-up the product rapidly by very fast evaporation of the solvent under high vacuum we obtained only 6β-bromocholest-4-en-3-one, though when the reaction mixture was poured into water and extracted with ether, the 6β-bromocholest-4-en-3-one was contaminated with much product of rearrangement to an aromatic structure.

The presence of adducts in the reaction mixture from bromination in acetic acid after completion of the initial phase of the reaction was confirmed by allowing the diene (0·025M) to react with bromine (0·025M) in acetic acid. Reaction was visibly complete within a few seconds, and after *ca.* 10 s a portion was poured into a mixture of aqueous potassium iodide and sodium thiosulphate. The organic product was extracted into ether; the solution was washed with water and dried (Na_2SO_4); and the ether was removed *in vacuo*. The ^1H n.m.r. spectrum showed that the only recognisable bromocholestenone was the 6β-derivative, but a product of hydrolysis (a broad signal at τ 6·6 which exchanges with D_2O and hence represents a hydroxy-group) was present. When the mixture was allowed to stand for 20 s, the same result was obtained; when allowed to stand for 12 h before being worked-up, the product was a mixture of the 6β-, 6α-bromo and the 2α,6β-, and 2α,6α-dibromo-derivatives, together with some hydroxy-containing material; the contour of the broad hydroxy-signal in the ^1H n.m.r. spectrum was not identical with that observed by the similar treatment of the samples taken earlier in the reaction.

In a separate experiment, the diene (0·05M) in acetic acid was placed in an n.m.r. tube, and to it was added one mol. equiv. of a concentrated solution of bromine in acetic acid. The ^1H n.m.r. spectrum was then scanned at intervals. Intermediate development of the clearly recognisable signals of the 4- and 6α-protons of 6β-bromocholest-4-en-3-one was noted. The latter signal (a multiplet centred at τ 5·04) was augmented in intensity, probably because of contribution from the multiplet centred at *ca.* τ 5·13, from the 6α-proton of 5α,6β-dibromocholestan-3-one. A doublet centred at τ 6·25 (J 16 Hz) corresponding to one of the 4-protons was also recognisable in the spectrum when it was scanned repeatedly, but other peaks corresponding with the presence of other adducts were also present, including some in the region of 4-H of the acetoxydiene. The spectrum changed with time, first rapidly by isomerisation of 6β-bromocholest-4-en-3-one to equilibrium with its 6α-isomer; then by disappearance of the subsidiary 4-H signals, and finally by changes in the τ 5—7 region, as the adducts slowly decomposed.

Full characterisation of the components of the reaction mixture is made difficult by the limited solubility of the diene in acetic acid, and by obscuring signals, including satellite signals, of the solvent. In a further experiment, the acetoxydiene (0·025M) was allowed to react with bromine (0·075M) in acetic acid. After 60 s, the mixture was concentrated under high vacuum, to leave a pale brown oil, the ^1H n.m.r. spectrum of which in deuteriochloroform was examined in successive scans. The first scan showed the presence of signals characteristic of 6β-bromocholest-4-en-3-one, 6α-bromocholest-4-en-3-one, and 2α,6β-dibromocholest-4-en-3-one in the ratio 3 : 2 : 1. The presence of small amounts of 2α,6α-dibromocholest-4-en-3-one and of 4,6β-dibromocholest-4-en-3-one was also recognisable. The spectrum further showed the presence of a number of adduct materials, one of which was characterised by a sharp singlet of τ 4·2 in the region of the signals of vinylic protons. Successive scans showed progressive changes in the spectrum, and the nature of these changes could not be analysed fully because of the complexity and because of overlapping signals. The signal at τ 4·2, however, rapidly disappeared, and after a number of scans a signal at τ 3·8 appeared. During that time the proportion of 2α,6-dibromocholest-4-en-3-ones increased; a small amount of 4,6β-dibromocholest-4-en-3-one was formed also. The proportion of 6α-bromocholest-4-en-3-one also increased; its signal at τ 3·5 was apparently not overlapped by any extraneous signals, and the height of this doublet first increased to a value slightly greater than that which was attained in the relatively stable spectrum reached after *ca.* 1 h, when the equilibrium between 6β- and 6α-bromocholest-4-en-3-one was fully established. In this spectrum a further adduct peak at τ 5·0 enhanced the height of the peak characteristic of 6α-H present in both 6β-bromocholest-4-en-3-one and in 2α,6β-dibromocholest-4-en-3-one.

On the addition of 2M-NaOMe (0·05 ml) to the mixture in the ^1H n.m.r. tube, the signals attributable to adducts disappeared, with the appearance (apparently nearly quantitatively) of resonances characteristic of cholest-4-en-3-one.

Both 4,6β-dibromocholest-4-en-3-one and cholest-4-en-3-one were identified by subsequent preparative t.l.c. We estimate from the ^1H n.m.r. spectrum of the isolated material that the final proportions of products in the alkali-treated mixture was as follows: cholest-4-en-3-one, 6%; bromocholest-4-en-3-ones, 6β-, 29%; 6α-, 29%; dibromocholest-4-en-3-ones, 2α,6β-, 14%; 2α,6α-, 14%; 4,6β-, 8%.

This experiment was repeated starting with the acetoxydiene and bromine in equal concentrations. The results, though not identical in detail, were similar. The major components of the final product were again recognisable: 6β-bromocholest-4-en-3-one first present in more than its equilibrium proportion; then 6α-bromocholest-4-en-3-one increasing in amount to more than its equilibrium proportions; 2α,6-dibrominated products increasing in amount through the reaction; and a number of signals attributable to adducts or derived materials. The major groups of these were (i) a singlet at τ 4·35, relatively constant over 1·5 h but ultimately (after several days) disappearing, (ii) a multiplet at τ 3·8, still possibly present at the end of the reaction, and (iii) a very complex multiplet apparent first at *ca.* τ 4·6 and shifting in position until after 1·5 h it appeared to be centred at τ 3·7 and finally altering in shape to include a sharp signal at τ 3·8.

The decomposition of 5α,6β-dibromocholestanone in acetic acid was examined separately. It decomposed auto-

catalytically and quite rapidly to give mainly 6β-bromocholest-4-en-3-one, a little of the 6α-isomer being obtained by geometric isomerisation before the first observation was made.

If the acetoxydiene was allowed to react with bromine in acetic acid in the presence of collidine (1·0M), the reaction mixture could be worked-up after 30 min to give a nearly quantitative yield of 6β-bromocholest-4-en-3-one.

Bromination with N-*Bromosuccinimide in Acetic Acid*—A solution of *N*-bromosuccinimide (0·84 g) in acetic acid (9·3 ml) was added to a stirred solution of 3-acetoxycholesta-3,5-diene in acetic acid (9·3 ml) at 20°. After 2 min, the solvent was removed *in vacuo*; the ^{1}H n.m.r. spectrum of the crude product showed that the starting materials had been converted completely into succinimide and 6β-bromocholest-4-en-3-one; no other products were detected by t.l.c.

Bromination with Hypobromous Acid in 75% *Acetic Acid*.—A solution of hypobromous acid (8·3 ml, 0·03M) in acetic acid (20·3 ml) was added to a stirred solution of 3-acetoxycholesta-3,5-diene (0·1 g) in acetic acid (4·6 ml) at 20°. After 5 min, the solvent was removed *in vacuo*, leaving the crude product which was shown similarly to be 6β-bromocholest-4-en-3-one. Any heating of the partly evaporated material resulted in some isomerisation.

The results of these brominations are summarised in the Table.

Chlorination of 3-*Acetoxycholesta*-3,5-*diene in Anhydrous Acetic Acid*.—3-Acetoxycholesta-3,5-diene (0·23 g) in acetic acid (10·7 ml) was added to a stirred solution of chlorine (0·053M) in acetic acid (10·7 ml) in the dark at 20°. After 2 min, the solvent was removed *in vacuo* to give the crude product (0·24 g) which was chromatographed on silica gel (11 g). Elution with a mixture (7 : 3) of benzene and light petroleum gave 6β-chlorocholest-4-en-3-one (0·21 g) which crystallised from ethyl acetate–methanol, m.p. 125—127° (lit.,[21] 129—130°), $\nu_{max.}$ 1678 (C=O), 1618 (C=C), and 1320 (CH_2CO) cm^{-1}, τ 9·22 (3H, s, 18-H$_3$), 8·52 (3H, s, 19-H$_3$), 5·24 (1H, m, 6α-H), and 4·10 (1H, s, 4-H).

A similar experiment, with reactants initially *ca.* 0·05M, gave a product which contained about 10% of the 6α-isomer; the slow isomerisation of the 6β- to the 6α-isomer could be observed by following the ^{1}H n.m.r. spectrum over the course of some hours.

DISCUSSION

The physical properties and ^{1}H n.m.r. spectra of the products of bromination of 3-acetoxycholesta-3,5-diene allow their clear identification; some of the ^{1}H n.m.r. spectral information has been reported by other workers [25,26] and is in good agreement with our results.

Proportions of products formed in the bromination of 3-acetoxycholesta-3,5-diene at 20°

Medium	[3-Acetoxycholesta-3,5-diene]/M	Reagent/M	Reaction time/min	Proportions of bromocholestenones 6β	6α	2α,6β	2α,6α	Other products: Rearranged aromatic	Other products: Starting material or cholest-4-en-3-one	Work-up method
HOAc	0·033	Br_2 (0·05)	30	0·25	0·25	0·28	0·22			*a*
HOAc	0·05	Br_2 (0·05)	3	0·36	0·36	0·14	0·14		Some	*a*
HOAc–0·1M-LiBr	0·025	Br_2 (0·025)	30	0·41	0·39	0·10	0·10		Some	*a*
HOAc	0·025	Br_2 (0·025)	2	0·50	0·30	0·17	0·03	Some	Some	*a*
$MeNO_2$	0·05	Br_2 (0·05)	30	0·37	0·37	0·13	0·13		Some	*a*
Dioxan	0·05	Br_2 (0·05)	30	0·40	0·40	0·12	0·08		Some	*a*
HOAc–1·0M-collidine	0·025	Br_2 (0·025)	30	1·00						*b*
HOAc–4% H_2O	0·025	Br_2 (0·025)	1	1·00						*c*
HOAc–4% H_2O	0·025	Br_2 (0·025)	3	1·00				Much		*d*
HOAc	0·025	Br_2 (0·025)	0·15	1·00						*e*
HOAc	0·025	Br_2 (0·025)	0·3	1·00						*e*
HOAc	0·025	Br_2 (0·025)	720	0·50	0·40	0·07	0·03		Trace	*e*
HOAc	0·025	NBS[f] (0·025)	2	1·00						*a*
HOAc–75% H_2O	0·008	BrOH (0·008)	5	1·00						*a*

[a] By removal of solvent under reduced pressure (*ca.* 5 min). [b] By adding to water, extracting with ether, and washing the extract with aqueous $NaHCO_3$. [c] By removal of solvent under high vacuum (*ca.* 1 min). [d] By adding reaction mixture to water and extracting with ether. [e] By adding reaction mixture to excess of aqueous KI and $Na_2S_2O_3$ and extracting with ether. [f] *N*-bromosuccinimide.

Measurements of this kind allow also the approximate quantitative determination of some of the components of the crude reaction mixtures, within the limits of error of the instrument, probably in most cases ±2%. Some difficulty exists, however, in recognising the presence of small amounts of 4,6β-dibromocholest-4-en-3-one, since its ^{1}H n.m.r. spectrum is not clearly resolved from those of some other components.

The results summarised in the Table and described above show that the bromination of 3-acetoxycholesta-3,5-diene with molecular bromine can be carried out in such a way as to give 6β-bromocholest-4-en-3-one as the major product. The reaction path is, however, very complicated; depending on the exact conditions of reaction and of work-up, other products can be obtained including 6α-bromocholest-4-en-3-one, 2α,6β- and 2α,6α-dibromocholest-4-en-3-one, and rearranged aromatic material. If excess of bromine is used, all these products and 4,6β-dibromocholest-4-en-3-one can be formed. A number of unstable intermediates are also present in the reacting mixtures, and their transformations in part determine the nature of the final product mixtures.

In the Scheme, we set out details of the main reaction

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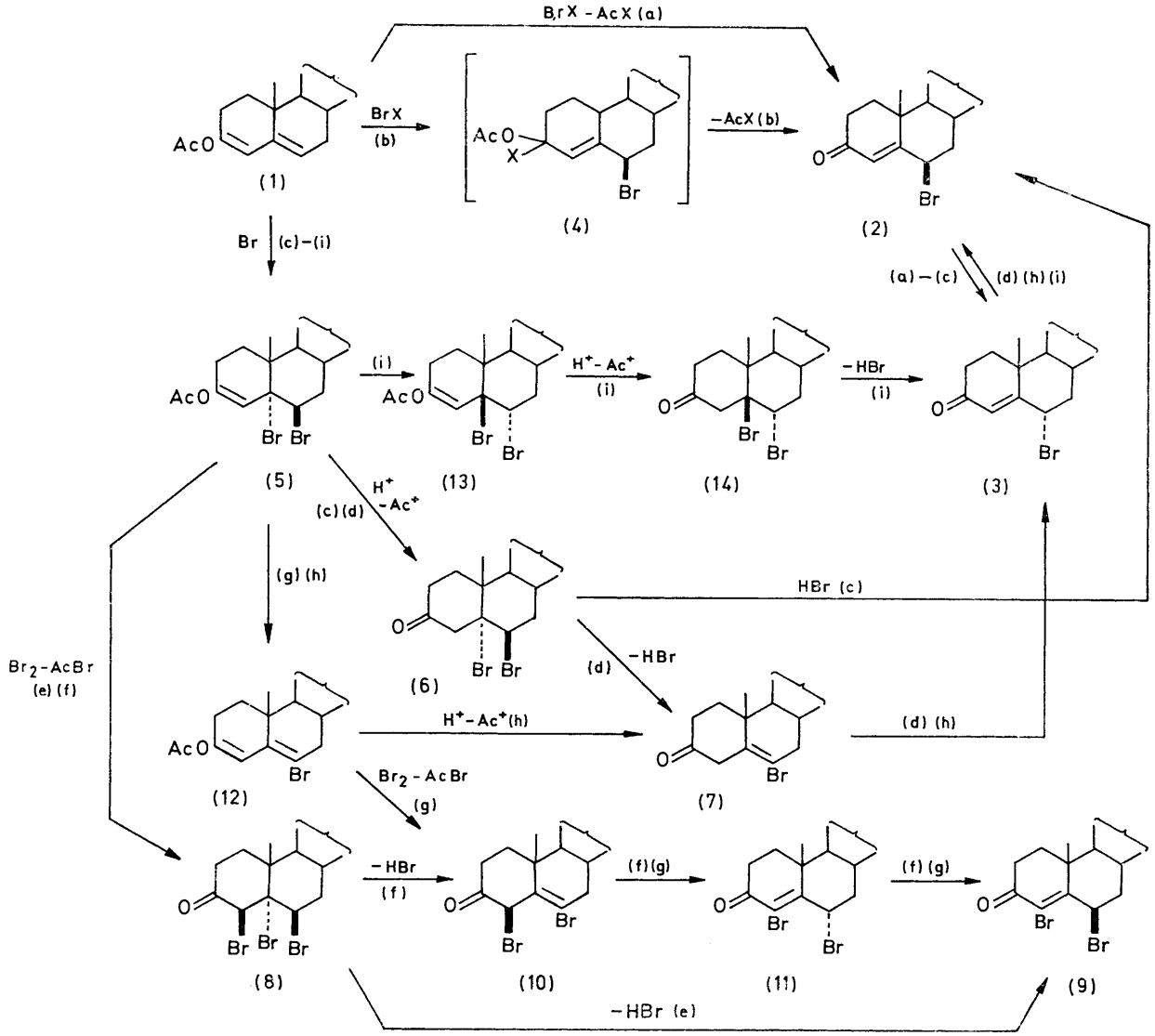
[26] P. L. Julian, L. Bauer, C. L. Bell, and R. E. Hewitson, *J. Amer. Chem. Soc.*, 1969, **91**, 1690.

paths which we think are likely to be contributing to the formation of the 6-bromocholest-4-en-3-ones and of 4,6β-dibromocholest-4-en-3-one, with footnotes indicating side-reactions including those leading to the 2α,6-dibromocholest-4-en-3-ones.

hypobromous acid in aqueous acetic acid (where the active reagent is probably bromine acetate [27]) or with *N*-bromosuccinimide in acetic acid. One possible route for these reactions is the ' conventional ' S_E2' path (a), which would probably require elaboration to include the



SCHEME Probable and possible reaction paths in the bromination of 3-acetoxycholesta-3,5-diene. X = Br, OAc, $\overset{\text{N}}{\text{CO}\cdot(\text{CH}_2)_2\cdot\text{CO}}$, or OH. Routes (a)—(d), (h), and (i), lead to 6-bromocholest-4-en-3-ones. Routes (e)—(g) lead to 4,6β-dibromocholest-4-en-3-one, important only with excess of bromine

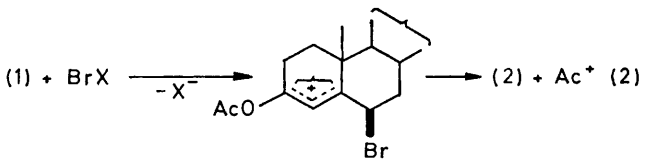
Side reactions

A $AcBr + HOAc \longrightarrow HBr + Ac_2O$
B (5) or (6) or (8) or (12) or (13) + (2) or (3) or (7) ⟶ cholestenone + 2α,6-dibromocholest-4-en-3-one
C (5) or (6) or (8) or (13) or (14) + $H_2O \longrightarrow$ HBr + bromohydrin
D Conversion of components of the reaction mixture into aromatic products of rearrangement

With all the brominating agents studied, the first attack by the reagent occurs axially at the 6-position, giving almost exclusive β-orientation of the entering bromine. No evidence for the intervention of paths involving adducts was found for the reactions with successive stages of co-ordination and heterolysis [equation (2)], as for example in the ' conventional ' S_E2 aromatic substitutions.

[27] P. B. D. de la Mare and J. L. Maxwell, *J. Chem. Soc.*, 1962, 4829.

The alternative, for which no positive evidence can be adduced except the analogy with the 6,5-additions



established for reaction with molecular bromine (see below), is that path (b) is adopted, the 6,3-adduct (4) being too unstable to be detectable, and so decomposing by loss of AcX. Formally such a reaction could be called S_E2', but conventional categorisations are not satisfactory for multi-stage sequences, as is evident from various semantic arguments about related cases.[28,29]

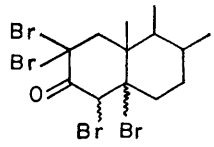
The subsequent geometrical isomerisation of 6β- to 6α-bromocholest-4-en-3-one (2) ⇌ (3) which will be described in more detail in another paper, is acid catalysed; so, though it can occur in acetic acid, the use of a brominating agent BrX which does not give a strong acid, HX, when acting as a source of electrophilic bromine minimises this complication. So does the inclusion of water in the solvent; but this has other side-effects, as will be seen, when certain types of adducts are involved in the reaction sequence.

The development of (2) from (1) by reaction with molecular bromine is so rapid that we believe that path (a) or path (b) contributes substantially to this reaction also. An accompanying process, however, is evident. The reaction mixture immediately after the initial rapid disappearance of bromine clearly contains adduct material, which we believe must initially have as one component the dibromide (5) produced by *trans*-6,5-addition. Several fates are possible for this intermediate. One involves proto-deacylation to give the cholestanone (6). This is a known compound, which we have shown to decompose in acetic acid to give a mixture of (2) and (3). Either route (c) or (d) is theoretically possible for this reaction.

Another possible fate for (5) is its reaction with a further molecule of bromine to give the tribromocholestanone (8). That (5) can be trapped through such a route is indicated by the fact that, with excess of bromine, more than one molecular equivalent is used up rapidly before the subsequent autocatalytic bromination can set in. It is this route, in our view, which leads to the small proportion of 4,6β-dibromocholest-4-en-3-one (9) which we isolated from reaction with excess of bromine. Either route (e) or (f) could be concerned; 4,6α-dibromocholest-4-en-3-one (11) is expected to be thermodynamically unstable relative to its 6β-isomer (9) because of steric interaction between the halogen atoms, and the conversion of (11) to (9) would be expected to be rapid.

A third possible fate for any of the 5-bromocholestane derivatives (5), (6), or (8) involves solvolysis of the tertiary bromine. This reaction clearly is not particularly important in acetic acid, nor indeed in aqueous acetic acid nor with *N*-bromosuccinimide; but when reaction mixtures from treatment of the acetoxydiene with bromine are poured into water, the resulting mixture of products can be recovered and still contain adduct material. This gives a broad ^1H n.m.r. signal which disappears on treatment with D_2O, so clearly some intermediate has undergone solvolysis to give a bromohydrin.

A fourth possible fate for either of the dibromides (5) or (6), or for the tribromide (8), or perhaps even for the 4,6-dibromo-derivatives (10), (11), (13), or (14) is that they may act as sources of positive bromine to give di- or tri-bromo-substituted cholest-4-en-3-ones and the unsubstituted compound. We have established that such reactions can occur, since the initial reaction mixture can be decomposed, different methods of work up being used, giving either 6β-bromocholest-4-en-3-one or a mixture of this, its α-isomer, and the 2α,6-dibromocholest-4-en-3-ones. Shoppee and his co-workers[30] established an analogous reaction path for the decomposition of the tetrabromide (15).



(15)

The experiments involving isolation of products, and those involving ^1H n.m.r. spectral observations in acetic acid, could probably be interpreted in the above terms without further elaboration. The changes that occur in the product when it is recovered immediately after completion of the initial bromination and is then observed in deuteriochloroform suggest that an additional process or processes need to be considered.

Since in this case the initial reaction had been carried out in the presence of excess of bromine, one of these processes probably is the decomposition of the tribromide (8), to give ultimately 4,6β-dibromocholest-4-en-3-one (9) [routes (e) or (f)]. But the appearance of a new, relatively stable signal at τ 3·8, from a compound which with water gives an alcohol, and with alkali gives cholest-4-en-3-one, suggest the presence of an isomeric dibromide. We suggest, therefore, that (5) can undergo an axial–equatorial rearrangement to give (13), which then by loss of HBr and proto-deacylation can give (3) and (2) (route i). Evidence that routes (d) or (i) make some contribution to the reaction sequences is provided by details of the changes in the ^1H n.m.r. spectrum in the region of the absorptions attributable to the vinylic 4-H. In successive scans of the changing spectrum of the product dissolved in chloroform, the signal for 4-H of

[28] P. B. D. de la Mare and C. A. Vernon, *J. Chem. Soc.* (*B*), 1971, 1699.

[29] P. B. D. de la Mare and B. E. Swedlund, in 'The Carbon–Halogen Bond,' ed. S. Patai, Wiley, New York, 1973.

[30] C. W. Shoppee, R. E. Lack, and J. Scott, *J. Chem. Soc.*, 1962, 2233.

6α-bromocholest-4-en-3-one first increased in absolute magnitude and in proportion to the total signals in this region and then decreased to the value expected for an equilibrium mixture with its 6β-isomer. This result suggests strongly that a route or routes leading directly to the 6α- rather than to the 6β-isomer are significant.

A subsidiary set of routes (g) and (b) *via* 3-acetoxy-6-bromocholesta-3,5-diene (12) have been included in the Scheme for completeness. Of the compounds included in the rather complicated set of sequences, those which would be expected to include in their ^{1}H n.m.r. spectra signals at τ *ca.* 4 [apart from the known compounds (1)—(3)] are (5), (13), (8), and (12); the first three of these would have hydrolysable bromine. All could be contributing to the complicated, rapidly occurring changes in the ^{1}H n.m.r. spectrum of initial products dissolved in deuteriochloroform. The acetoxy-singlets that normally would be helpful in identifying intermediates of this kind are obscured by the steroid envelope of signals, though changes in the region of τ 7 were noted, and were consistent with the presence of acetoxy-containing intermediates in the mixtures.

These do not exhaust the possibilities for intermediates contributing to these reactions; for example, the 5β,6β-analogue of (5) could also be present in the mixtures. We have not included 5-acetoxy-6-bromides since we did not obtain any evidence for their intervention in the reactions of *N*-bromosuccinimide or of bromine acetate with the acetoxydiene.

4,6β-Dibromocholest-4-en-3-one in our hands had m.p. 164—166°; its 2α,6β-isomer had m.p. 160—162°. In admixture, the m.p. was depressed. Both have been shown to be formed (the latter in larger amount) in the bromination of 3-acetoxycholesta-3,5-diene with excess of bromine. It was originally thought by Inhoffen [3] that his dibromocholest-4-en-3-one, m.p. 162°, obtained from the acetoxydiene with bromine in a mixture of ether and acetic acid was the former isomer; but, since he found no depression of m.p. when this compound was mixed with a compound obtained by bromination of 6β-bromocholest-4-en-3-one or by dibromination of cholest-4-en-3-one, and since these reactions are now known to give the 2α-isomer,[31] it must be considered that Inhoffen converted the acetoxydiene into this material rather than into the 4,6β-compound.

Although, as far as we are aware, this is the first occasion when 5,6-adducts have been implicated in the bromination of 3-acetoxycholesta-3,5-diene, the similar addition of *m*-chloroperbenzoic acid has been reported by Kirk and Wiles,[32] and the addition of fluorine (supplied by CF_3OF) to steroidal 3,5-dienes has been described by Barton and his co-workers.[33] 1,4-Addition to an analogous system has been described by Hartshorn.[9]

We have not elucidated the way or ways in which the products of reaction can be converted into aromatic products of rearrangement; these are side reactions which can consume much of the starting material, but likewise can be avoided by careful choice of the method of work-up of the reaction mixtures.

The chlorination of 3-acetoxycholesta-3,5-diene has been investigated only sufficiently to confirm that the product mixture from reaction in acetic acid can be converted in reasonable yield into 6β-chlorocholest-4-en-3-one, and that its isomerisation to the 6α-isomer in the reaction mixture is slower than that of its 6β-bromo-analogue. This reaction was more rapid with HBr than with HCl, and resulted in no incorporation of halogen into the steroid nucleus.

We are indebted to Dr. J. W. Barnett for assistance.

[3/070 *Received*, 12*th January*, 1973]

[31] L. F. Fieser and M. Fieser, ' Steroids,' Reinhold, New York, 1959, pp. 288 ff.

[32] D. N. Kirk and J. M. Wiles, *Chem. Comm.*, 1970, 518.

[33] D. H. R. Barton, L. S. Godinho, R. H. Hesse, and M. M. Pechet, *Chem. Comm.*, 1968, 804.