# Electrophilic Substitution with Rearrangement. Part VII.[1] Reaction Paths in the Bromination of Cholest-4-en-3-one

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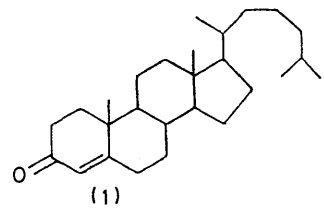
The bromination of cholest-4-en-3-one can occur by a number of reaction paths. Conditions under which reaction can be established as occurring in part by electrophilic attack on (a) cholesta-3,5-dien-3-ol, (b) cholesta-2,4-dien-3-ol or its anion, and (c) cholest-4-en-3-one have been identified; among the products can be included 2α-, 4-, 6β-, and 6α-bromocholest-4-en-3-one; 2α,6β-, 2α,6α-, and 4,6β-dibromocholest-4-en-3-one; and 2α,4,6β-tribromocholest-4-en-3-one. Unstable adducts involving the 4,5-double bond are implicated in a number of cases. Preliminary studies of the bromination of cholest-5-en-3-one also indicate complexities, some of which involve addition to the 5,6-double bond. The rates and mechanism of reversible isomerisation of 6β- to 6α-bromocholest-4-en-3-one, and of 2α,6β- to 2α,6α-dibromocholest-4-en-3-one, have been partly elucidated.

THE reactions of unsaturated steroidal ketones with electrophiles are well understood in principle.[2-4] They become complicated because various tautomeric forms of the substrate are susceptible to electrophilic attack, and because the mesomeric anions produced from them by strong bases are also very reactive. Furthermore, the products first formed are often capable of further reactions which render it difficult to establish kinetic control of the products. Thus for cholest-4-en-3-one (1), all the tautomers (2)—(5) are in principle available and may be relatively easily interconverted: under base catalysis, through the anions (6)—(8), and under acid catalysis, through the conjugate acids (9) and (10). Of the species susceptible to attack by electrophiles, (1) would be expected to be attacked preferentially at 4- or O; (2) at 6- or O; (3) at 2-; (4) at 2-; (5) at 4- or 6-; (6) at 2- or O; (7) at 2- or O; and (8) at 4-, 6-, or O. The position adopted by the entering electrophile does not, therefore, identify the reaction path; and the formation of intermediate adducts is also only partially helpful, since 4,5-adducts could be derived from (1) or (3), and 5,6-adducts from (2), (4), or (5). The orientation of attack likewise is not of great diagnostic value, since axial attack can in principle be initiated on either face of the double-bond system, and predictions concerning the balance between the steric and stereoelectronic effects which influence whether the α- or β-face is preferred in any individual case can be quite difficult.

The bromination of cholest-4-en-3-one has been investigated by many workers, and two main reaction paths have been identified. The first, generally considered to involve axial attack on the enol (5), leads first to 6β-cholest-4-en-3-one, and thence to isomeric and dibrominated products; reaction mixtures tend to be difficult to separate. Acetic acid has often been used as the solvent,[2,5,6] but in acetic acid containing 2% acetic anhydride, a good yield of the 6β-monobromo-derivative has been reported.[7] The second, involving bromination in the presence of proton acceptors (*e.g.* in a mixture of acetic acid, diethyl ether, and collidine), gives 4-bromocholest-4-en-3-one, and evidence favouring a contribution from a 4,5-addition–elimination sequence has been adduced.[4,8]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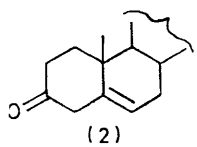
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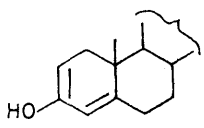
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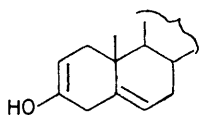
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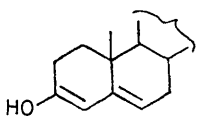
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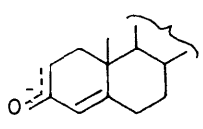
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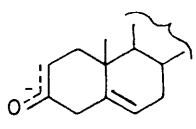
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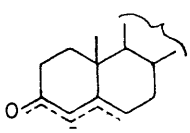
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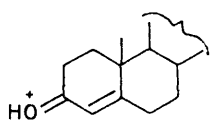
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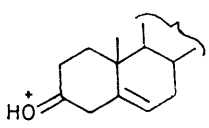
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The present investigation was undertaken as background to our studies of bromodeacylations from un-

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[7] C. F. Boehringer and Sons, G.P. 712,256 (*Chem. Zentralblatt*, 1942, I, 1162).

[8] D. N. Kirk, D. K. Patel, and V. Petrow, *J. Chem. Soc.*, 1956, 627.

saturated systems (*cf.* ref. 1, and earlier papers in this series). In it, we believe we have thrown some new light on the ramifications of the reaction paths, and defined more clearly the conditions needed for preparation of some of the reference materials. It has also been necessary to elucidate the nature of the acid-catalysed geometrical isomerisations of 6β- to 6α-substituted bromocholest-4-en-3-ones.

## EXPERIMENTAL

Many of the materials and methods have been described or referred to in the previous paper,[1] where details relating to 4-, 6β-, and 6α-bromocholest-4-en-3-one, to 2α,6β-, 2α,6α-, and 4,6β-dibromocholest-4-en-3-one, and to 6β-chlorocholest-4-en-3-one are given. The following are details of a preparative bromination under basic conditions.[8]

To cholest-4-en-3-one (3·0 g) in anhydrous ether (30 ml) and collidine (10 ml) was added a solution (30 ml) of bromine (1·05M) in acetic acid. The mixture was set aside in the dark at 20° for 7 days and was then poured into water and extracted with ether. The ether extract was washed (aqueous HCl, then aqueous $NaHCO_3$) and dried ($MgSO_4$). Removal of the ether *in vacuo* gave the crude product (3·6 g), 3 g of which was chromatographed on silica gel (90 g). Elution with benzene–light petroleum (3 : 2) gave first 2α,4,6β-*tribromocholest-4-en-3-one* * (27%, from the $^1H$ n.m.r. spectrum of the mixture), which crystallised from acetone as needles, m.p. 179—182° (Found: C, 52·3; H, 6·6; Br, 38·8. $C_{27}H_{41}BrO_3$ requires C, 52·2; H, 6·6; Br, 38·6%), $\nu_{max.}$ ($CS_2$) 1703 (C=O) $cm^{-1}$, τ 9·22 (3H, s, 18-$H_3$), 8·39 (3H, s, 19-$H_3$), 7·63 (1H, 2d, $J_{1.1}$ 12, $J_{1.2}$ 14 Hz, 1α-H), 7·36 (1H, 2d, $J_{1.1}$ 12, $J_{1.2}$ 6 Hz, 1β-H), 5·02 (1H, 2d, $J_{1,2}$ 14, $J_{1.2}$ 6 Hz, 2β-H), and 4·37 (1H, m, 6α-H). Further elution gave 4,6β-dibromocholest-4-en-3-one (47%) which crystallised from acetone as needles, m.p. 164—166° (decomp.). Elution with benzene then gave mainly 4-bromocholest-4-en-3-one (23%), which crystallised from ethanol as needles, m.p. 115—117°, $\nu_{max.}$ 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, m, 6α-H). The mother liquors from the above crystallisation (3%) consisted largely of hydrocarbon material (probably rearranged aromatic steroids); the presence of traces of 6α- and 6β-bromocholest-4-en-3-one were also indicated by $^1H$ n.m.r. spectroscopy and by t.l.c.

To obtain 2α-bromocholest-4-en-3-one, a solution (10·4 ml) of bromine (0·05M) in anhydrous acetic acid was added to a solution of cholest-4-en-3-one (0·2 g) and pyridine (0·32 ml) in anhydrous acetic acid (10·1 ml) at 20°. After 13 days, the mixture was poured into water and extracted with diethyl ether. The ether extract was washed (aqueous HCl, then aqueous $NaHCO_3$) and dried ($MgSO_4$). Removal of the solvent *in vacuo* gave the crude product (0·24 g) which was chromatographed on silica gel (6·0 g). Elution with benzene–light petroleum (b.p. 50—70°) (2 : 3) gave first a little by-product and then 2α-bromocholest-4-en-3-one (10%) which crystallised from ethanol as needles, m.p. 116—117° (lit.,[2,10] 117—119, 134—135°), $\nu_{max.}$ 1692 (C=O) and 1620 (C=C) $cm^{-1}$, τ 9·28 (3H, s, 18-$H_3$), 8·73 (3H, s, 19-$H_3$), 7·86 (1H, t, $J_{1.1}$ 13, $J_{1.2}$ 13·1 Hz, 1α-H), 7·38 (1H, 2d, $J_{1.1}$ 13, $J_{1.2}$ 6·5 Hz, 1β-H), 5·20 (1H, 2d, $J_{1.2}$ 13·1, $J_{1.2}$ 6·5 Hz, 2β-H), and 4·17 (1H, s, 4-H). 4-Bromocholest-4-en-3-one (20%) and 6β-bromocholest-4-en-3-one (*ca.* 2%) were then eluted and identified by $^1H$ n.m.r. spectroscopy and by t.l.c. Further elution with benzene–$Et_2O$ (1 : 1) gave starting material (68%). A trace of a polybromo-derivative was also detected.

2,2,6β-Tribromocholest-4-en-3-one was prepared by adding gradually a solution of bromine (0·2M) in acetic acid to 6β-bromocholest-4-en-3-one (0·55 g) in ether (25 ml) containing hydrogen bromide (8·65M, *ca.* 0·1 g) until the colour of bromine just persisted. The mixture was set aside at room temperature for 8 h. The precipitate was then filtered off and was recrystallised from ethanol as plates of 2,2,6β-tribromocholest-4-en-3-one (0·5 g), m.p. 185° (decomp.) (lit.,[4] 185—186°), $\nu_{max.}$ 1690 (C=O) and 1610 (C=C) $cm^{-1}$, τ 9·24 (3H, s, 18-$H_3$), 8·20 (3H, s, 19-$H_3$), 7·14 and 6·76 (2H, 2d, $J_{1.1}$ 16 Hz, 1-$H_2$), 5·16 (1H, m, $W_{\frac{1}{2}}$ *ca.* 7 Hz, 6α-H), and 4·10 (1H, s, 4-H).

Cholest-5-en-3-one, m.p. 124°, was prepared by the usual method.[11]

*Bromination of Cholest-4-en-3-one under Conditions conducive to 4-Substitution by Way of an Addition–Elimination Sequence.*—It had been suggested [8] that reactions under the basic conditions described for the preparative bromination of cholest-4-en-3-one above might include a contribution from an addtion–elimination sequence. The use of a more reactive electrophile, together with a nucleophilic component of the solvent, was therefore explored. A solution of hypobromous acid (28·3 ml, 0·046M) was added to a stirred solution of cholest-4-en-3-one (0·5 g) in acetic acid (84·9 ml) at 25°. After the mixture had been stirred vigorously for 2 min, the precipitate which had formed was filtered off and dissolved in light petroleum (b.p. 40—60°). The solution was washed with water and dried and the solvent was removed under reduced pressure to give a solid. This was shown from its i.r. spectrum to be an approximately equimolar mixture of 4-bromocholest-4-en-3-one and various adducts; a broad carbonyl absorption principally at 1725 $cm^{-1}$ was distinct from that of 4-bromocholest-4-en-3-one. The $^1H$ n.m.r. spectrum of this crude material also gave evidence for the presence of adduct materials; a series of signals was observed in the region τ 4·4—6·4 together with an acetyl proton singlet at τ 8·03 and a 19-$H_3$ singlet at τ 8·97.

These materials readily underwent spontaneous decomposition *in vacuo* at room temperature to form mainly (*ca.* 95%) 4-bromocholest-4-en-3-one. Decomposition also in acetic acid, in acetic acid containing perchloric acid, or in acetic acid containing sodium acetate gave similar results. If the reaction mixture was worked up by evaporation of the solvent, the paths taken in the decomposition were more complex; a little 6α- and 6β-bromocholest-4-en-3-one were formed, and some rearranged aromatic product was obtained also.

The reaction was carried out also in deuterioacetic acid with [$^2H$]hypobromous acid; no change in the spectra of either the intermediate adducts or of the decomposition products was detected.

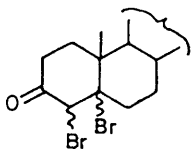
The adducts formed under the above conditions were

* This substance, the structure of which is established by its $^1H$ n.m.r. spectrum, is probably identical with a compound previously obtained by other workers by a different route, and variously described as 2,2,4- or as a 2,4,6-tribromocholest-4-en-3-one.[4,9] Coupling constants recorded for this and the other compounds have been estimated by inspection of the spectra.

[9] H. H. Inhoffen and W. Becker, *Chem. Ber.*, 1952, **85**, 181.
[10] B. Ellis and V. Petrow, *J. Chem. Soc.*, 1956, 1179.
[11] *Org. Synth.*, 1955, **35**, 43.

apparently mainly acetoxy-bromides and bromohydrins. Evidence for the formation of dibromides in the reactions involving molecular bromine proved elusive because of decomposition occurring either before isolation or during work-up. Thus very little adduct was identified from the $^1$H n.m.r. spectrum of the product of reaction of cholest-4-en-3-one (0·025M) with bromine (0·025M) in acetic acid containing 0·5M-collidine; the main product was the 4-bromo-, with smaller amounts of the 2α- and 6β-bromo-derivatives.

Reaction under similar conditions in the presence of pyridine likewise gave no adduct, and by conventional procedures of work-up gave much rearranged aromatic steroid. Work-up by pouring the reaction mixture into excess of aqueous potassium iodide and sodium thiosulphate, followed by extraction into ether, washing with water, and careful evaporation under vacuum at low temperature, however, prevented decomposition to rearranged products, and the $^1$H n.m.r. spectrum of the recovered product showed the presence of a new component having a broad singlet at τ 5·0. Rather little of this material was present in this mixture, and still less from a mixture formed from reaction in the presence of pyridine and lithium bromide; but reaction in the presence of sodium acetate (0·1 or 0·2M) when worked-up similarly gave more. The i.r. spectrum of the crude product had a peak at 1725 cm$^{-1}$ on the side of the main carbonyl band, consistent with the presence of some component containing a saturated carbonyl group. Decomposition of this material [called 'adduct' in the Tables, and regarded as being a 4,5-dibromo-cholestan- or -coprostan-3-one (11)] in warm acetic acid gave 4-bromocholest-4-en-3-one, as judged by changes in its $^1$H n.m.r. spectrum.




(11)

Bromination of cholest-4-en-3-one (0·2 g) with *N*-bromosuccinimide (NBS) (0·093 g) in acetic acid gave after 7 days unchanged starting material (60%), 4-bromocholest-4-en-3-one (17%), 6α-bromocholest-4-en-3-one (8%), 6β-bromocholest-4-en-3-one (8%), and 2α-bromocholest-4-en-3-one (7%).

Bromination with NBS in acetic acid in the presence of sodium acetate was also slow, and gave mainly 4-bromocholest-4-en-3-one (55%), together with a little 2α-bromocholest-4-en-3-one (5%). Reaction with hypobromous acid in alkaline methanol was rapid and gave much rearranged aromatic material, but no products of substitution could be isolated, presumably because these had undergone dehydrobromination.

*Bromination of Cholest-4-en-3-one under Acidic Conditions conducive to Formation of 6-Bromo-substituted Cholest-4-en-3-ones.*—The reaction of cholest-4-en-3-one with bromine in acetic acid was characterised by an initial small uptake of bromine, and then an induction period, followed by completion of the reaction in a very rapid autocatalytic process. Similar behaviour was noted for reaction in nitromethane and in dioxan. Uncontrolled reaction under these conditions, followed by removal of the solvent *in vacuo*, gave mixtures very similar in composition to those obtained similarly from bromine and cholesta-3,5-dienyl 3-acetate.[1]

Reaction with NBS in acetic acid in the presence of perchloric acid (0·5M) gave only 6α- and 6β-bromocholest-4-en-3-one.

The conditions and results of the above experiments are summarised in Tables 1 and 2.

*Bromination of Cholest-5-en-3-one.*—Reaction mixtures obtained in the absence of added substances, or with water, were worked-up by evaporation under high vacuum; benzene was then added and removed under high vacuum. The remainder of these reactions were worked up by adding the mixture to water, followed by extraction into ether, washing with water, and careful removal of the solvent at low temperature. The products are as shown in Table 3.

*Geometrical Isomerisation of the Halogenocholest-4-en-3-ones.*—(a) *6β-Bromocholest-4-en-3-one with* HBr *in acetic acid and in deuterioacetic acid.* In order to estimate more quantitatively the solvent deuterium isotope effect on the rate of isomerisation of the 6β- to the 6α-isomer, which was quite fast in acetic acid, a solvent containing 2·0% of water was used. The signals of 4-H in the 6α- and the 6β-bromo-isomers were separate and distinct; that for the former being a doublet [τ 4·0 ($J$ 1·8 Hz)], and for the latter being a sharp singlet (τ 5·6). Consequently the relevant part of the $^1$H n.m.r. spectrum was examined at intervals of 1 min, and the integrals of the relevant signals were used to estimate the rate of the isomerisation.

For a reaction in which a solution of hydrogen bromide (0·012 ml, 8·77M) and water (0·011 ml) was added to a solution (1 ml, 0·1M) of 6β-bromocholest-4-en-3-one in acetic acid, the half-life for the isomerisation was 19 min. For the corresponding reaction in deuterioacetic acid with deuterium bromide and deuterium oxide, the signal for the 6α-isomer did not appear, and the half-life for the disappearance of the signals for 4- and 6α-H of the 6β-isomer was 5·3 min.

To check whether any isomerisation of 6β- to 6α-bromocholest-4-en-3-one could have occurred by removal of $Br_2$, aqueous HBr [0·006 ml, containing HBr ($5·2 \times 10^{-5}$ mol)] was added to a solution of 6β-bromocholest-4-en-3-one (0·028 g) and phenol (0·007 g) in acetic acid (1 ml). Possible cross-bromination of phenol was sought by examining the mixture at intervals, t.l.c., $^1$H n.m.r. spectroscopy, and g.l.c. being used. For g.l.c., the analysis was performed on a Varian 1400 instrument initiated at 90° and rising to 200°. A 150 cm × 0·3 cm column packed with 3% SE 30 on a Varaport support was used; authentic 4-bromophenol was easily resolved from the other components of the mixture, in which it was found to be absent after several days, in which time the isomerisation of the 6β- to its equilibrium mixture with the 6α-isomer was complete.

(b) *6β-Bromocholest-4-en-3-one with perchloric acid.* The corresponding reaction catalysed by perchloric acid was slow; in 94% acetic acid containing *ca.* 2M-perchloric acid, 10% of the α-isomer was formed after 50 min; and after several days the equilibrium mixture of geometrical isomers had been formed.

(c) *6β-Chlorocholest-4-en-3-one with hydrogen bromide in acetic acid.* Equal volumes of a solution of 6β-chlorocholest-4-en-3-one (0·05M) and HBr (0·5M) in acetic acid were mixed, and the progress of reaction was followed by $^1$H n.m.r. spectroscopy. Some 20% of the 6α-chloro-isomer had been formed by the time that the first measurement was made (*ca.* 2 min), and the equilibrium position (*ca.* 75% α-chloro-isomer) had been reached within 40 min. No evi-

dence was obtained for the incorporation of bromine into the steroid nucleus; addition of the 6β-bromo-analogue to the reaction mixture obscured the spectra of the chloro-compounds, and its presence would therefore have been apparent. The crude product, which contained some rearranged aromatic steroid, was recovered; on chromatography, it gave 6α-chlorocholest-4-en-3-one, which was crystallised from methanol–ethyl acetate, m.p. 120—122° (lit.,[12] 123—125°), $\nu_{max.}$ 1685 (C=O), 1620 (C=C), and 1418 ($CH_2CO$) $cm^{-1}$, τ 9·27 (3H, s, 18-$H_3$), 8·77 (3H, s, 19-$H_3$), 5·32 (1H, 2d, $J_{6,7}$ 10, $J_{6,7}$ 4 Hz, 6β-H), 3·61 (1H, d, $J_{4,6}$ 1·6 Hz, 4-H).

Slower isomerisation was observed when the corresponding solution of hydrogen chloride in acetic acid was used as catalyst.

(d) *4-Bromocholest-4-en-3-one with hydrogen bromide in acetic acid.* Aqueous hydrobromic acid [0·005 ml, containing HBr ($4·3 \times 10^{-5}$ mol)] was added to a solution of 4-bromocholest-4-en-3-one (6·9 mg) in acetic acid (0·50 ml) at 20°. The consequent slow rearrangement, in which significant change was observed only after *ca.* 7 days, was followed by t.l.c. The main products were the epimeric 6-bromocholest-4-en-3-ones, and an unidentified aromatic steroidal ketone. The formation of a trace of 2α-bromocholest-4-en-3-one was also detected.

(e) *2α-Bromocholest-4-en-3-one with hydrogen bromide in acetic acid.* Aqueous hydrobromic acid [0·005 ml, containing HBr ($4·3 \times 10^{-5}$ mol)] was added to a solution of 2α-bromocholest-4-en-3-one (6·0 mg) in acetic acid (0·50 ml) at 20°. Again the main products, formed very slowly, were the epimeric 6-bromocholest-4-en-3-ones and an unidentified aromatic steroidal ketone. A similar reaction, carried out in the presence of pyridine (0·2M) to simulate the conditions in which cholest-4-en-3-one is brominated to give *inter alia* the 2α-isomer, showed that none of the latter compound would be destroyed under the conditions of the bromination.

TABLE 1

Experimental conditions for bromination of cholest-4-en-3-one at 20°

| Expt. no. | Solvent | Added substances | Reagent | Ratio of reactants | Reaction time | Work-up |
|---|---|---|---|---|---|---|
| 1 | 75% HOAc | | BrOH | 1 | 1 min | Filter off adduct |
| 2 | 75% HOAc | | BrOH | 1 | 1 min | Evap. |
| 3 | HOAc | NaOAc, 0·2M | NBS | 1 | 7 days | $H_2O$–$Et_2O$ |
| 4 | HOAc–$Et_2O$ | Collidine, 1·1M | $Br_2$ | 4 | 7 days | $H_2O$–$Et_2O$ |
| 5 | HOAc | Collidine, 0·5M | $Br_2$ | 1 | 112 h | aq. KI, $Na_2S_2O_3$–$Et_2O$ |
| 6 | HOAc | Pyridine, 0·18M | $Br_2$ | 1 | 44 h | aq. KI, $Na_2S_2O_3$–$Et_2O$ |
| 7 | HOAc | Pyridine, 0·18M LiBr, 0·2M | $Br_2$ | 1 | 7 days | aq. KI, $Na_2S_2O_3$–$Et_2O$ |
| 8 | HOAc | NaOAc, 0·10M | $Br_2$ | 1 | 41 h | aq. KI, $Na_2S_2O_3$–$Et_2O$ |
| 9 | HOAc | NaOAc, 0·23M | $Br_2$ | 1 | 42 h | aq. KI, $Na_2S_2O_3$–$Et_2O$ |
| 10 | HOAc | | $Br_2$ | 1 | 3 min | Evap. |
| 11 | HOAc | $HClO_4$, 0·5M | $Br_2$ | 1 | 3 min | $H_2O$–$Et_2O$ |
| 12 | $MeNO_2$ | | $Br_2$ | 1 | 3 min | Evap. |
| 13 | Dioxan | | $Br_2$ | 1 | 3 min | Evap. |
| 14 | HOAc | LiBr, 0·21M | $Br_2$ | 1 | 3 min | aq. KI, $Na_2S_2O_3$–$Et_2O$ |
| 15 | HOAc | | NBS | 1 | 7 days | $H_2O$–$Et_2O$ |
| 16 | HOAc | $HClO_4$, 0·5M | NBS | 1 | 48 h | $H_2O$–$Et_2O$ |

TABLE 2

Proportions of components in the reaction mixtures from the bromination of cholest-4-en-3-one at 20°

| | Substituted cholest-4-en-3-ones | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Expt. no.* | Starting material | 2α-Br | 4-Br | 6β-Br | 6α-Br | 2α,6β-$Br_2$ | 2α,6α-$Br_2$ | 4,6β-$Br_2$ | 2α,4,6β-$Br_3$ | Adduct | Aromatic steroid |
| 1 | | | >0·95 | 0·01 | 0·01 | | | | | | |
| 2 | | | 0·80 | 0·02 | 0·02 | | | | | | 0·16 |
| 3 | 0·50 | 0·02 | 0·18 | | | | | | | | 0·30 |
| 4 | | | 0·23 | Trace | Trace | | | 0·47 | 0·27 | | 0·03 |
| 5 | 0·47 | 0·08 | 0·41 | 0·04 | | | | | | Trace | |
| 6 | 0·34 | 0·05 | 0·53 | 0·03 | | | | | | 0·05 | |
| 7 | 0·54 | 0·11 | 0·35 | | | | | | | | |
| 8 | 0·61 | 0·04 | 0·13 | 0·04 | | | | | | 0·18 | |
| 9 | 0·41 | 0·04 | 0·35 | 0·06 | | | | | | 0·14 | |
| 10 | 0·29 | | | 0·26 | 0·26 | 0·10 | 0·09 | | | | |
| 11 | 0·56 | 0·05 | | 0·22 | 0·12 | 0·05 | Trace | | | | |
| 12 | 0·53 | | | 0·19 | 0·19 | 0·06 | 0·03 | | | | |
| 13 | 0·10 | | | 0·33 | 0·33 | 0·13 | 0·11 | | | | |
| 14 | 0·30 | | | 0·23 | 0·27 | 0·09 | 0·11 | | | | |
| 15 | 0·60 | 0·07 | 0·17 | 0·08 | 0·08 | | | | | | |
| 16 | 0·33 | | | 0·08 | 0·09 | | | | | | |

* For experimental conditions, see Table 1.

## DISCUSSION

Most of the final products of bromination of cholestenone which we have encountered in this work can be separated by chromatography. They have been identified by their known physical properties and through their

[12] Huang-Minlon and Shan-Wei Chin, *Hua Hsueh Hsueh Poh*, 1965, **31** (2), 141 (*Chem. Abs.*, 1965, **63**, 13,353h).

$^1$H n.m.r. spectra. The $^1$H n.m.r. spectrum of the tribromo-compound of m.p. 179—182° establishes that it is 2α,4,6β-tribromocholest-4-en-3-one through the observation of (i) a high value for $J_{1\beta,2\alpha}$, indicating an axial disposition for 2-H and (ii) low, not fully resolved couplings for $J_{6,7}$, indicating an equatorial disposition of 6-H.

Product proportions, estimated from integration of the appropriate signals in the $^1$H n.m.r. spectra, are of course approximations; they probably show relative amounts reasonably satisfactorily, and in representative cases it has proved possible to isolate similar proportions of the major substituted components by chromatography. The proportions of the adducts and other unstable components of the reaction mixture indicated in certain experiments are, however, very approximate and are presented for illustration only; they represent components not fully identified, some of which are rather unstable.

*Bromination of Cholest-4-en-3-one; Addition–Elimination Routes leading to 4-Bromocholest-4-en-3-one.*—Kirk, *et al.*[8] speculated, and various authors have accepted,[3,4] that their preparative procedure leading from cholest-4-en-3-one to its 4-bromo-derivative in a mixture of acetic acid, ether, and collidine proceeded at least in part through a 4,5-dibromide formed by addition to the enone. The corresponding dichlorides were isolated [13] and shown to be converted readily into the 4-substituted products; they were, however, stable to dimethylformamide and to ethylene and propylene oxide, so it was concluded that chlorination could proceed also by direct substitution.

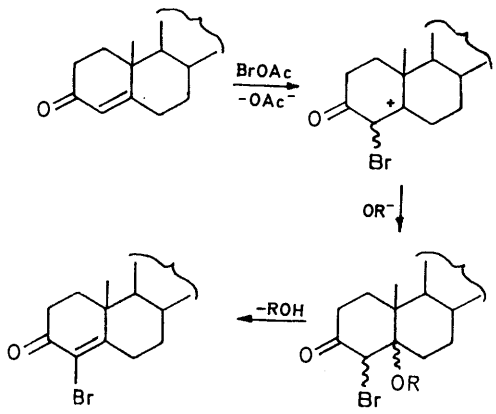
The uncatalysed bromination of cholest-4-en-3-one by bromine in acetic acid is relatively slow, so the behaviour of a more reactive electrophile was investigated. A solution of hypobromous acid in acetic acid has been shown to serve as a source of bromine acetate,[14] which reacts with aromatic compounds much more rapidly than bromine does. Reaction with cholest-4-en-3-one gave a precipitate which comprised a mixture of adducts which readily underwent decomposition under a number of conditions, giving with appropriate precautions almost exclusively 4-bromocholest-4-en-3-one (Table 1; experiments 1, 2).

We believe that by this procedure we have encouraged almost exclusive reaction by addition to the double bond of cholest-4-en-3-one, followed by elimination of acetic acid or of water from the rather labile adduct (Scheme 1). The initial reaction probably involves the cholest-4-en-3-one molecule itself, rather than any derived form.

Repetition of bromination with excess of bromine under the conditions of ref. 8 (Table 1; experiment 4) gave 4-bromocholest-4-en-3-one and products of further bromination. Whether reaction under these conditions involves direct 4-bromination is not known, but significant contributions from addition–elimination sequences are to be expected.

[13] D. N. Kirk, D. K. Patel, and V. Petrow, *J. Chem. Soc.*, 1956, 1184.

*Bromination of Cholest-4-en-3-one under Basic Conditions; Formation of 2α-Bromocholest-4-en-3-one.*—It is clear that, under neutral or basic conditions, direct attack on the cholest-4-en-3-one molecule is slow. With sufficiently strong proton acceptors, two enolate ions (6) and (8) can be expected to be formed. Of these, the latter is thermodynamically the more stable, and could in principle react with an electrophile to give the product of 4- or 6-substitution. The former appears generally to be formed from cholest-4-en-3-one more rapidly,[15] and gives the product of 2-substitution by capture of an electrophile. Malhotra and Ringold's work shows also [15] that the kinetically controlled protonation of (8) in acetic




SCHEME 1

acid occurs preferentially in the 4-position, whereas the corresponding reaction of the derived enol occurs in the 6-position.

A possible limiting type of base-catalysed bromination would involve kinetically controlled liberation of the two enolate ions (6) and (8), followed by their immediate reaction with the electrophile, so that 2-substitution would predominate because (6) is formed more rapidly. Alternatively, if the equilibrium mixture of enols could be produced in bulk concentration prior to addition of the electrophile, 6-substitution would predominate; and if in sufficiently basic solution, the equilibrium mixture of the enolate ions in bulk concentration was obtained, these then would be expected to give predominantly 4-substitution, by analogy with the results for protonation.[15]

The experiments with equimolecular concentrations of reagents in basic solution (Table 1; experiments 5—9), do not correspond with any of these situations. The reactions were slow, so the bulk of the organic compound was not present as an enol or enolate ion; and 4-substitution always predominated in the final product. We obtained clear evidence for the formation of adducts which decomposed on heating in acetic acid to give 4-bromocholest-4-en-3-one. We suggest, therefore, that reaction under this type of condition is composed of a

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

[15] S. K. Malhotra and H. J. Ringold, *J. Amer. Chem. Soc.*, 1962, **84**, 3402; 1963, **85**, 1538.

non-catalysed bromination by way of the formation of a 4,5-adduct [*e.g.* (11)], together with a base-catalysed process of the type mentioned above, leading predominantly to 2α-bromocholest-4-en-3-one *via* the enolate ion (6), and responsible for up to *ca.* 20% of the bromine consumed. The adducts are labile in the presence of base; pyridine, collidine, and lithium bromide all tend to promote elimination and reduce the amount of adduct detectable in the reaction product. We have not excluded the possibility that a small proportion of reaction can involve the enol or other tautomeric forms of the starting material.

*Bromination of Cholest-4-en-3-one catalysed by Hydrogen Bromide.*—When cholest-4-en-3-one and bromine are allowed to react in an organic solvent, the reaction is autocatalysed by the hydrogen bromide produced. The products (Table 1; experiments 10—14) are a mixture of 6β- and 6α-bromocholest-4-en-3-one, together with 2α,6β- and 2α,6α-dibromocholest-4-en-3-one, each pair being obtained in approximately the proportion expected at equilibrium between the two isomers. These product mixtures resemble those from cholesta-3,5-dienyl acetate,[1] but it is not by any means clear how they are formed. One possibility is that acid-catalysed formation of the enol (5) is followed by rapid further bromination at the 6-position. The possibility that these autocatalysed brominations are in part free-radical processes cannot be discounted, however. Disubstituted products probably come from adducts which can act as sources of positive bromine.[1]

*Bromination of Cholest-4-en-3-one catalysed by Perchloric Acid.*—Reaction of cholest-4-en-3-one with bromine in acetic acid containing perchloric acid (Table 1, experiment 11) gave 6β-bromocholest-4-en-3-one as the major product, together with a smaller proportion of the 6α-isomer, some of which would have been obtained by isomerisation of the former compound. The still smaller amounts of the 2α,6β- and 2α,6α-dibromo-derivatives probably come by the HBr-catalysed route, and the trace of the 2α-bromo-isomer may come *via* the enol (3).

The slower reaction of cholest-4-en-3-one with NBS in acetic acid containing perchloric acid (Table 2, experiment 16) gave an equilibrium mixture of the 6β- and 6α-bromo-derivatives.

These two reactions probably present the most convincing examples which we can give of conditions in which the main path involves acid-catalysed formation of the enol (8) followed by 6β-bromination of the double-bond with rearrangement (as in the corresponding reaction of cholesta-3,5-dienyl acetate), followed by geometric rearrangement of the 6β- to the 6α-bromo-isomer.

*Bromination of Cholest-4-en-3-one with NBS in Neutral or Basic Conditions.*—These reactions (Table 1; experiments 3, 15) were slow and gave some 2α-substitution. As with bromine, therefore, they probably involve in part the enolate ion (6) and in part the neutral molecule.

*Bromination of Cholest-5-en-3-one.*—The reaction of cholest-5-en-3-one with bromine in acetic acid has been described in the patent literature[16] as giving 5α,6β-dibromocholestan-3-one, m.p. 80°. Many authors, including ourselves[1] had obtained this compound also by the oxidation of cholesterol 5α,6β-dibromide. Its possible mutarotation in chloroform, which might give the 5β,6α-isomer, was sought by Barton and Miller,[17] but polarimetric investigation was prevented by decomposition. We have found[1] that it loses hydrogen bromide relatively rapidly in acetic acid, to give 6β-bromocholest-4-en-3-one as the product first formed.

Results of our preliminary studies of the products of bromination of cholest-5-en-3-one are recorded in Table 3. The experiments were designed largely to follow the conditions used for cholest-4-en-3-one; they are evidently complicated by concomitant rearrangement to the more stable, fully conjugated isomer. The main substituted products are derivatives of cholest-4-en-3-one, as is expected because of their relatively high thermodynamic stability. The proportions differ from those found in the bromination of the 4-enone, however. Two major differences are established by the results shown in Table 3. First, we obtained evidence, particularly for reactions in basic conditions, for the intermediacy of mixtures of unstable products of addition.

TABLE 3

Proportions of components in the reaction mixtures from bromination of cholest-5-en-3-one (0·005M) with bromine (0·005M) in acetic acid at 25°

| | | | Component proportions | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Substituted cholest-4-en-3-ones | | | | | |
| Expt. no. | Added substances | Reaction time | Starting material | Cholest-4-en-3-one | 4-Br | 6β-Br | 6α-Br | 2α,6β-$Br_2$ | 2α,6α-$Br_2$ | Adducts and other substances |
| 1 | | 5 min | 0·03 | 0·15 | | 0·36 | 0·37 | 0·05 | 0·04 | Trace [a] |
| 2 | LiBr, 0·20M | 44 h | | 0·37 | | 0·20 | 0·25 | 0·07 | 0·10 | Trace [a] |
| 3 | $H_2O$, 2·2M | 5 min | | | | 0·46 | 0·54 | | | |
| 4 | NaOAc, 0·20M | 44 h | 0·07 | 0·05 | 0·06 | 0·35 | 0·35 | | | 0·12 [b] |
| 5 | Pyridine, 0·18M; LiBr, 0·20M | 44 h | Trace | 0·08 | | 0·35 | 0·42 | 0·06 | 0·10 | Trace [a] |

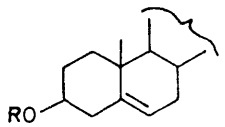
[a] Various n.m.r. signals in the vinyl and alicyclic region. [b] A variety of n.m.r. signals in the region τ 6—7.

[16] Schering-Kahlbaum A.G., G.P. 198,836 (*Chem. Zentralblatt*, 1939, I, 2642).

[17] D. H. R. Barton and E. Miller, *J. Amer. Chem. Soc.*, 1950, **72**, 1066.

Secondly, 6α-bromocholest-4-en-3-one was formed under basic conditions in which it had been shown (*cf.* Table 2) that no isomerisation of 6β- to 6α-bromocholest-4-en-3-one would occur. The starting material (2) would be expected to be brominated much more rapidly than its conjugated isomer (1) and this result establishes that entering halogen can become located to a very significant (perhaps a preponderant) extent at the 6α-position of (2). 5α,6β-Dibromocholestan-3-one is not very easily characterised unambiguously in small amounts in our reaction mixtures, partly because of the weakness of the split signals and partly because of overlap. It is certainly, however, not the only nor even a major part of the adduct material present in our isolated mixtures; and, since it decomposes either in acetic acid (see above) or with alkali [18] to give predominantly 6β-bromocholest-4-en-3-one, it is unlikely to be the source of much of the 6α-bromocholest-4-en-3-one detected in our product mixtures.

*Comparison with the Bromination of Cholesterol.*—It is interesting to compare the above descriptions of the bromination of cholesta-3,5-dien-3-ol (5), its *O*-acetyl derivative,[1] and cholest-5-en-3-one (2) with accounts of the bromination of cholesterol and its *O*-derivatives (12).[3,19] In the reactions of (5) and its derivatives,




(12)

it is generally believed, and is borne out by experience, that as far as the 6-position is concerned, the β-face is the more susceptible to electrophilic attack. For the cholest-5-en-3-one, we have evidence that suggests that the electrophile can become attached at the 6-position in either the α- or the β-situation. For cholesterol and its derivatives, it would seem likely that the α-face is attacked selectively by the electrophile; the group attaching itself kinetically to the 6-position is probably the nucleophile, which displaces bromine from a bromonium ion formed by 6α-attack, thus giving a 5α,6β-adduct. Only by subsequent diaxial–diequatorial rearrangement is the 5β,6α-adduct obtained. Our experiments clearly give only a partial description of the bromination of the 5-enone; we hope to elucidate this and other uncertainties relating to the equilibrium between this and its 4-enone isomer by further investigations including kinetic studies.

*Geometrical Isomerisation of 6β-Bromocholest-4-en-3-one.*—6β-Bromocholest-4-en-3-one undergoes geometrical isomerisation when treated with hydrogen bromide in acetic acid, in dioxan, or in nitromethane. The reaction is very fast in anhydrous acetic acid, but is reduced in rate by the presence of added water. Hydrogen chloride as a catalyst is less effective than hydrogen bromide, and perchloric acid is even less effective. The reaction can be carried to equilibrium without the formation of any 2- or 4-substituted isomers; but, though we did not succeed in cross-brominating phenol by carrying out the rearrangement in the presence of the latter substance, it seemed normal to obtain some 2α,6-dibromocholest-4-en-3-ones also.

These results establish that the major route for geometical isomerisations of these bromo-ketones involves acid-catalysed deprotonation, rather than acid-catalysed removal of electrophilic bromine (as has been established also for some monocyclic systems) [20] and that the effective order of nucleophiles in acetic acid is $Br^- > Cl^- > HOAc$, as is found in other systems.[21,22]

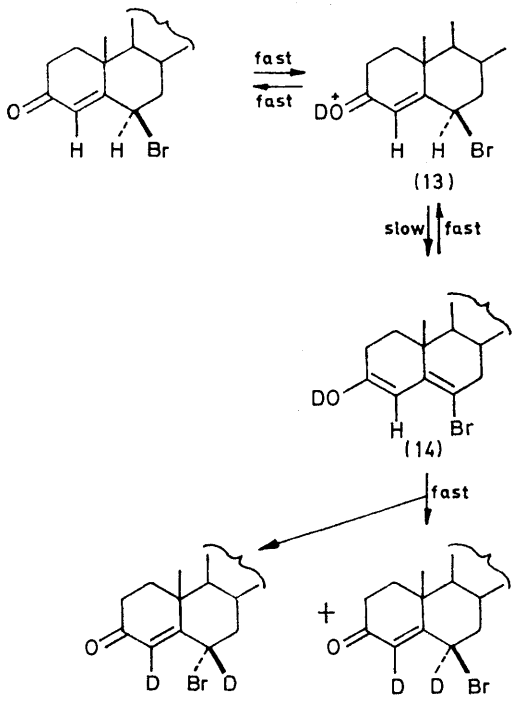
In confirmation of this conclusion, we have shown that the rate of geometrical isomerisation of 6β-chlorocholest-4-en-3-one could be effected by using hydrogen bromide in acetic acid. No bromine was introduced into the steroid nucleus by this procedure, and no isomerisation to 4- or 2-substituted isomers was detected. We have checked that 4- and 2α-bromocholest-4-en-3-one are both stable under the conditions used for the various brominations of cholest-4-en-3-one, though both can undergo very slow subsequent reactions to give complex mixtures of products of rearrangement.

The equilibrium mixture contained a greater proportion of the 6α-isomer than in the case of the bromo-analogue; the rates of attainment of equilibrium in the two systems were similar. These results cannot be interpreted in terms of a mechanism involving dehalogenation, first, because chlorine is known to be removed as a positive species much less readily than bromine, and secondly, because its removal as chlorine bromide would give an electrophilic brominating agent, which would then introduce bromine into the steroid nucleus.

The results obtained by use of deuterioacetic acid as solvent are satisfactorily interpreted (Scheme 2) by assuming that the first-order rate of incorporation of deuterium into the 4-position measures in fact the rate of slow proton-loss (13) ⟶ (14) from the 6-position following a proton pre-equilibrium. The dienol (14) then incorporates deuterium or hydrogen rapidly at the 6-position to give isomerisation, measured in aqueous acetic acid, and rapidly also at the 4-position, measured in the corresponding deuteriated medium. The latter rate is faster than the former, because the common measured process follows the proton pre-equilibrium, and consequently is subject to the usual reverse deuterium solvent isotope effect. The magnitude of this is here

[18] L. Ruzicka, U.S.P., 2,085,474 (*Chem. Abs.*, 1937, 5950).
[19] P. B. D. de la Mare, *Progr. Stereochem.*, 1954, **1**, 90; D. H. R. Barton, E. Miller, and H. T. Young, *J. Chem. Soc.*, 1951, 2598; J. B. Ziegler and A. C. Shabica, *J. Amer. Chem. Soc.*, 1952, **74**, 4891.
[20] P. Moreau, A. Casadevall, and E. Casadevall, *Bull. Soc. chim. France*, 1971, 3973.
[21] C. A. Bunton, P. B. D. de la Mare, and J. G. Tillett, *J. Chem. Soc.*, 1958, 4754.
[22] P. B. D. de la Mare, A. Singh, J. G. Tillett, and M. Zeltner, *J. Chem. Soc.* (*B*), 1971, 1122; P. B. D. de la Mare and A. Singh. *J.C.S. Perkin II*, 1972, 1801.

found to be 3·6; a value of *ca.* 4 has been recorded in other systems.[22,23] The mechanism of 4-deuteriation is not further elucidated by the experiments; either a

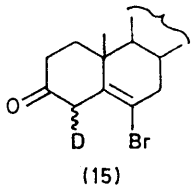



SCHEME 2

one- or a two-stage mechanism is possible, the latter involving the rearranged enone (15).

The influence of added water, which reduces both the rate of isomerisation and the rate of deuterium exchange, confirms that the acid catalysis involves a proton pre-equilibrium.

The debromination–rebromination sequence for geometrical isomerisation catalysed by hydrogen bromide, suggested by Fishman [24] for the geometrical isomerisation of 3β-acetoxy-15β-bromo-5α-androstan-16-one, and responsible for many related positional rearrangements, has proved difficult to realise in this system; surprisingly so, since debromination accompanies deprotonation to




(15)

the extent of *ca.* 10% in the rearrangement of 2,6-di-t-butylcyclohexa-2,5-dienone catalysed by hydrogen bromide,[22] and since the 6β-bromine atom is relatively favourably disposed axially for nucleophilic attack. It may however, be responsible for the formation of the dibrominated products noted above.

*Bromination of* 6β-*Bromocholest*-4-*en*-3-*one*.—Other workers [25] have found that the further bromination of 6β-bromocholest-4-en-3-one occurs in the 2α-position. We have confirmed this; the further acid-catalysed bromination of the equilibrating mixture of geometrical isomers, obtained from either cholesta-3,5-dienyl acetate or cholest-4-en-3-one in acetic acid, gave 2α,6β-dibromocholest-4-en-3-one and its 2α,6α-isomer. Both these have equatorial 2-Br, and neither of the isomeric 2β-derivatives was detected in the product of reaction. Further HBr-catalysed bromination in a mixture of diethyl ether and acetic acid gave 2,2,6β-tribromocholest-4-en-3-one.

We thank Dr. J. W. Barnett for assistance with the experiments involving cholest-5-en-3-one.

[3/628 *Received*, 26*th March*, 1973]

[23] S. K. Malhotra and H. J. Ringold, *J. Amer. Chem. Soc.*, 1965, **87**, 3228.

[24] J. Fishman, *J. Org. Chem.*, 1962, **27**, 1745.

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