232. *The Stereochemistry of Steroids. Part IV. The Concept of Equatorial and Polar Bonds.**

By D. H. R. Barton and W. J. Rosenfelder.

The application of the concept of equatorial and polar bonds in steroid chemistry is outlined. The configurations assigned previously (Barton, *Experientia*, 1950, **6**, 316) to the cholestan-4-ols are confirmed. The importance of coplanarity of participating atomic centres in the elimination reactions of *cyclo*hexane derivatives is further emphasized and illustrated, *inter alia* by a study of the stereochemical aspects of the debromination of 1 : 2-dibromides. A *trans*-1 : 2-dibromide with the two C–Br bonds polar is debrominated more easily than the stereoisomeric *trans*-1 : 2-dibromide with the two C–Br bonds equatorial.

In recent years it has become generally accepted that the chair conformation of *cyclo*hexane is more stable than the boat. In the chair conformation it is possible (Hassel and Viervoll, *Acta Chem. Scand.*, 1947, **1**, 149; and earlier papers by Hassel) to distinguish two types of carbon–hydrogen bond : those which lie parallel to the three-fold axis of symmetry of the ring and those which are not so oriented. The former type have been called " polar " and the latter " equatorial " (Beckett, Pitzer, and Spitzer, *J. Amer. Chem. Soc.*, 1947, **69**, 2488).

There can be little doubt that this distinction between carbon–hydrogen bonds is of importance in considering the more subtle aspects of the stereochemistry of *cyclo*hexane and its congeners. In Part III of this series * we have shown that it is possible to correlate the reactivity or stability of a substituent at a given position in the steroid nucleus with its existence as a polar or equatorial bond. A similar correlation has recently been made by Reeves (*J. Amer. Chem. Soc.*, 1950, **72**, 1499) for a number of monosaccharides. Such correlations demand a prior knowledge of the most stable conformation of the molecule under consideration. In the case of the steroid ring system we have adopted (Barton, *loc. cit.*) the conformations shown in Figs. 1 or 2 (α-bonds broken, β-bonds full lines) depending on whether the A–B ring fusion is *trans* or *cis*. These conformations have the maximum number of *cyclo*hexane chairs; their justification is discussed in more detail elsewhere (Barton, *loc. cit.*; W. S. Johnson, *Experientia*, 1951, **7**, in the press).

Three of the more important aspects of equatorial and polar bonds are the following. (i) At a given position in (say) the steroid nucleus a substituent linked by an equatorial bond is, in general, thermodynamically more stable than the same substituent at the same carbon atom linked by a polar bond. Thus cholestan-3β-ol is more stable than cholestan-3α-ol,

* Parts I and II : Barton and Miller, *J. Amer. Chem. Soc.*, 1950, **72**, 370, 1066. Part III : Barton, *Experientia*, 1950, **6**, 316.

coprostan-3α-ol is more stable than coprostan-3β-ol, and so on. (ii) For ionic elimination reactions involving substituents on adjacent carbon atoms, the elimination proceeds most readily when the two substituents form polar bonds. This generalisation has been illustrated by Barton and Miller (*J. Amer. Chem. Soc.*, 1950, **72**, 1066) and is discussed further below. (iii) At a given position in (say) the steroid nucleus a substituent forming an equatorial bond is, in general, less hindered sterically than the same substituent at the same carbon atom forming a polar bond.

The justification for these three statements has been given in detail in Part III. In that paper we assigned configurations to the two cholestan-4-ols on the basis that the isomer, m. p. 188—189°, $[\alpha]_D$ +5°, prepared by sodium and alcohol reduction of cholestan-4-one (Windaus, *Ber.*, 1920, **53**, 488; Tschesche and Hagedorn, *ibid.*, 1935, **68**, 2251) must be cholestan-4α-ol.

FIG. 1.

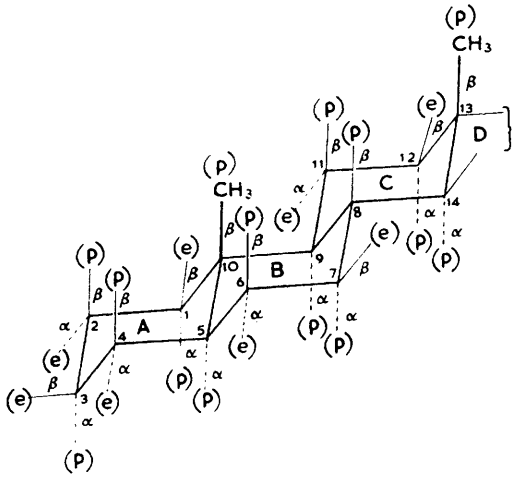
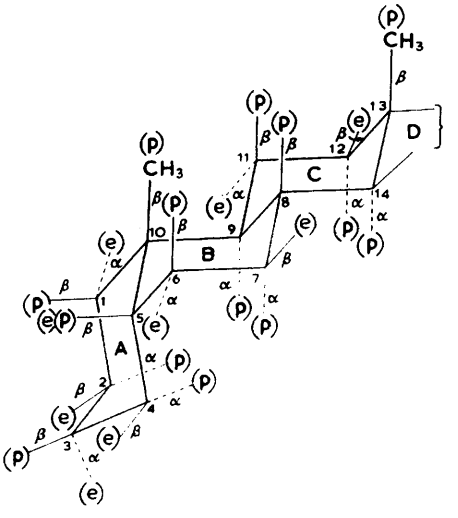
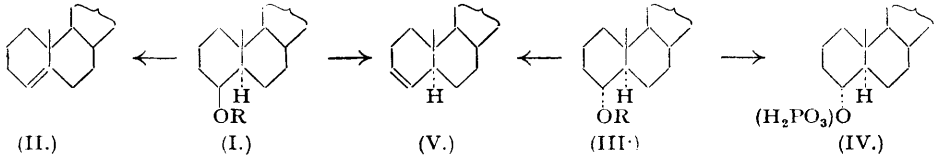


FIG. 2.



Our reasoning was that this method of reduction of ketones is known to give the thermodynamically more stable epimer (Vavon, *Bull. Soc. chim.*, 1931, [iv], **49**, 937; Hückel, *Annalen*, 1937, **533**, 1) which, at the 4-position, should be the 4α-compound for this is the epimer with the hydroxyl equatorial (see Fig. 1). The second cholestan-4-ol, m. p. 131—132°, $[\alpha]_D$ +29°, prepared by catalytic hydrogenation of cholestan-4-one, was assigned the 4β-configuration. Experiments that we now report confirm our conclusions.

(a) *Elimination Evidence.*—Treatment of cholestan-4β-ol (I; R = H) with phosphorus oxychloride and pyridine at room temperature afforded pure cholest-4-ene (II), m. p. 81°, $[\alpha]_D$ +75°. The rotation was appreciably higher than is usually accepted for cholest-4-ene (about +65°), but the purity of the product was checked carefully and it was shown that cholest-4-ene of the same rotation could be obtained by regeneration from the purified dibromide. In contrast, under the same reaction conditions, cholestan-4α-ol (III; R = H) afforded no hydrocarbon. The reaction product analysed as cholestan-4α-yl dihydrogen phosphate (IV). In cholestan-4β-ol the $C_{(4)}$–OH and $C_{(5)}$–H bonds are both polar and thus the ease of elimination



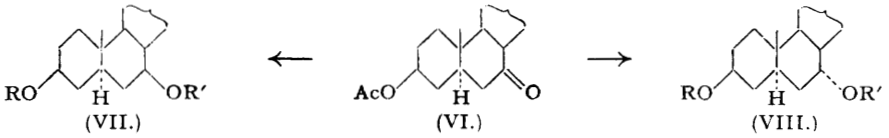
(II.) (I.) (V.) (III.) (IV.)

is explained. In cholestan-4α-ol the $C_{(4)}$–OH bond is equatorial and thus elimination is relatively difficult.

In previous papers (Barton, *J.*, 1949, 2174; Barton and Rosenfelder, *ibid.*, p. 2459) it has been demonstrated that pyrolytic elimination reactions which proceed by a molecular mechanism

are stereochemically specific in requiring a *cis*-relation of the eliminated groups. This generalisation has now been applied to the cholestan-4-yl benzoates. Pyrolysis of cholestan-4β-yl benzoate (I; R = C_6H_5·CO) afforded pure cholest-3-ene (V), with physical constants in good agreement with those reported recently by Lardelli and Jeger (*Helv. Chim. Acta*, 1949, **32**, 1817). Pyrolysis of cholestan-4α-yl benzoate gave a mixture, the rotation of which indicated that it consisted of cholest-3- (approx. 40%) and -4-ene (approx. 60%). These results are again in agreement with the assigned configurations.

(b) *Steric Hindrance Evidence.*—A comparison of the rates of alkaline hydrolysis of the cholestan-4-yl benzoates provided further confirmation for the assigned configurations.



(VII.) (VI.) (VIII.)

Cholestan-4α-yl benzoate (equatorial bond) was hydrolysed at a greater rate than cholestan-4β-yl benzoate (polar bond) (see Experimental).

Although there can no longer be any doubt as to the correctness of the configurations assigned at the 7-position in steroids (*inter al.*, Fieser, Fieser, and Chakravarti, *J. Amer. Chem.*

FIG. 3.

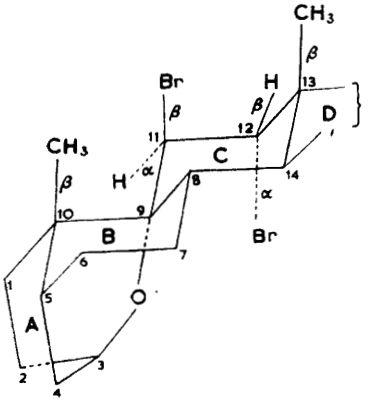


FIG. 4.

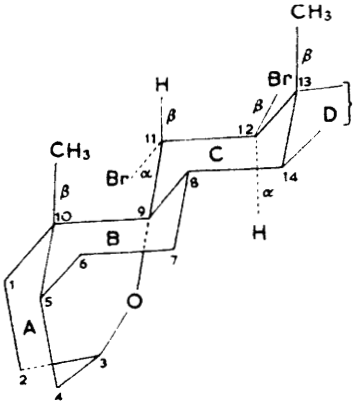


FIG. 5

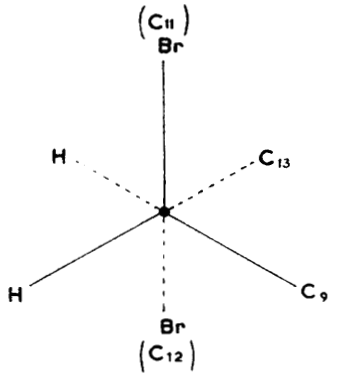
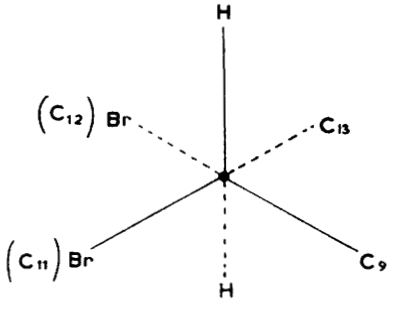


FIG. 6.



Soc., 1949, **71**, 2226; Barton, *J.*, 1949, 2174) a comprehensive correlation with the concept of polar and equatorial bonds is not possible on the basis of published evidence. We have made a number of experiments on the subject. Reduction of 7-ketocholestan-3β-yl acetate (VI) by sodium and alcohol furnished a mixture the rotation and other properties of which indicated that it consisted of 78% of cholestane-3β : 7β-diol (VII; R = R′ = H) and 22% of

cholestane-3β : 7α-diol (VIII; R = R′ = H). The predominance of the former compound with the equatorial bond at $C_{(7)}$ is in agreement with our general thesis.

Comparative experiments on the rates of alkaline hydrolysis of 3β-acetoxycholestan-7α-yl and -7β-yl benzoates (VIII and VII; R = CH_3·CO, R′ = C_6H_5·CO) (see Experimental) showed that the 7β-compound, with the equatorial bond, was hydrolysed at a faster rate than the 7α-compound with the polar bond. This is an interesting result because a consideration of Stuart models could easily lead to a prediction of the opposite order.

In Part II of this series (Barton and Miller, *loc. cit.*) a study was made of the relative rates of debromination (see Table) of the two cholesteryl benzoate dibromides. It was emphasized that the results could be simply explained if elimination reactions of this type required that the four centres participating in the reaction (the two carbon atoms and the two bromine atoms) should lie, suitably disposed with respect to each other, in one plane for maximal ease of reaction. In *cyclo*hexane compounds this is equivalent to the requirement that the two groupings eliminated should be polar in the stereochemical sense. This is only possible for a dibromide which is configurationally *trans*. There is, however, an alternative conformation for a *trans*-1 : 2-dibromo*cyclo*hexane with both C–Br bonds equatorial (compare the discussion by Barton and Schmeidler, *J.*, 1948, 1197). An opportunity to test this theory further was provided by the two methyl 3α : 9α-epoxychol-11-enate dibromides, specimens of which were kindly provided by Dr. Max Tishler of Merck and Co. Inc., Rahway, New Jersey. These have been assigned the configurations 11β : 12α and 11α : 12β (Fieser and Fieser, " Natural Products Related to Phenanthrene," 3rd Edn., Reinhold Publ. Corp., 1949, p. 661) for reasons that we regard as adequate. Because of the nature of the oxide ring and of the locking of rings B, C, and D, the relative spatial positions of the atoms in the molecule are rigidly defined as shown in the conformations illustrated in Figs. 3 and 4 for the 11β : 12α- and 11α : 12β-dibromides respectively. Figs. 5 and 6 show the respective views observed on looking down the $C_{(11)}$–$C_{(12)}$ axis. In the 11β : 12α-dibromide the four centres are in one plane (two polar C–Br bonds); in the 11α : 12β-dibromide (two equatorial C–Br bonds) this is not the case. The experimental results summarised in the Table support the theory; they show that the 11β : 12α-dibromide was debrominated by iodide ion in the course of a few days, whereas the 11α : 12β-dibromide showed no indication of reaction even after six months. This is a remarkable demonstration of the influence of geometry on chemical reactivity.

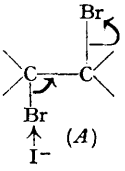
		Percentage reacted.*					
	Molarity.	15 mins.	225 mins.	15 hrs.	53 hrs.	12 days	
Cholest-2-ene dibromide	0·00758	—	—	3·4	—	22·5	46·6 (22 days)
Cholest-3-ene dibromide	0·00319	0·0	0·0	0·0	0·0	0·0	0·1 (22 days)
Cholest-4-ene dibromide	0·006475	79·7	—	100·0	—	—	—
5α : 6β-Dibromocholestan-3β-yl benzoate †	0·00611	30·1	69·8	—	—	—	—
5β : 6α-Dibromocoprostan-3β-yl benzoate †	0·00662	0·0	0·0	6·3	—	—	—
Methyl 11α : 12β-dibromo-3α : 9α-epoxycholanate	0·00677	0·0	0·0	0·0	0·0	0·0	0·1 (6 months)
Methyl 11β : 12α-dibromo-3α : 9α-epoxycholanate	0·00649	—	12·6	—	53·1	93·7	—

* For details of procedure see Exptl. All experiments at room temperature (20—25°) unless specified to the contrary.

† Data from Barton and Miller (*J. Amer. Chem. Soc.*, 1950, **72**, 1066). The figures for the 5α : 6β-compound are for 5°.

The relative rates of debromination of a number of other steroidal dibromides have also been studied (see table). From the results cholest-2-ene dibromide can be tentatively assigned the (dipolar) 2β : 3α-configuration, and cholest-3-ene dibromide the (diequatorial) 3β : 4α-configuration, in agreement with its complete resistance to debromination by iodide ion. In cholest-4-ene dibromide the two C–Br bonds are clearly polar but, since both the 4β : 5α- and the 4α : 5β-configurations satisfy this requirement a distinction between the two cannot be made.

It has been suggested (Young, Pressman, and Coryell, *J. Amer. Chem. Soc.*, 1939, **61**, 1640; Winstein, Pressman, and Young, *ibid.*, p. 1645) that the debromination of 1 : 2-dibromides by iodide ion is an *E*2 type elimination reaction, as illustrated in transition state (*A*).* Such a view is in agreement with our investigations of the stereochemistry of such reactions. It is of interest, however that other elimination reactions which are generally regarded (Hughes, Ingold, *et al.*, *J.*, 1948, 2117) as kinetically of the *E*1 type also show a similar geometric specificity. Examples are the solvolysis of toluene-*p*-sulphonates (Hückel, *Ber.*, 1944, **77**, 805, and papers there cited), the acid-catalysed dehydration of alcohols (Hughes, Ingold, *et al.*, *loc. cit.*), and olefin formation resulting from the action of nitrous acid on primary amines (for references to illustrative work on the menthylamines and related compounds see Simonsen and Owen, " The Terpenes," 2nd edn., Vol. 1, p. 245).



(*A*)

Experimental.

M.p.s are uncorrected. Unless specified to the contrary rotations were determined for the sodium D line in chloroform solution at room temperature, which varied from 15° to 25°. For rotation measurements all specimens were dried *in vacuo* at 20° below their m.p.s or at 110°, whichever was the lower temperature. Values of $[\alpha]_D$ have been approximated to the nearest degree.

Savory and Moore's alumina for chromatography was used in all cases unless specified to the contrary.

In the text below the phrase " in the usual way " refers to dilution with water, extraction with ether, washing successively with aqueous potassium hydroxide, aqueous hydrochloric acid, and then water, followed by evaporation of the ethereal solution *in vacuo*. Where necessary, water was removed from the residue by azeotropic distillation *in vacuo* with benzene as entrainer.

Alkaline hydrolyses were effected by using several equivalents of potassium hydroxide and refluxing the reactants for 30—60 minutes in methanolic or dioxan–methanolic solution depending on the solubility requirements of the ester.

Cholest-2-ene Dibromide.—Crude cholest-2-ene (640 mg.), prepared by the pyrolysis of cholestanyl benzoate (Barton and Rosenfelder, *J.*, 1949, 2359), in 100 ml. of 1 : 1 ether–acetic acid was brominated by addition of a slight excess of bromine in acetic acid and set aside overnight. Working up in the usual way and repeated recrystallisation from ethyl acetate–methanol gave 190 mg. of cholest-2-ene dibromide, plates, m. p. 124—124·5°, $[\alpha]_D$ +76° (*c*, 4·60). On treatment with zinc dust in acetic acid solution at water-bath temp. the dibromide was smoothly debrominated to furnish pure cholest-2-ene, m. p. 74·5—75°, $[\alpha]_D$ +69° (*c*, 1·58) (cf. Fürst and Plattner, *Helv. Chim. Acta*, 1949, **32**, 279).

The following technique was used in studying the rate of debromination of cholest-2-ene dibromide and of the other dibromides mentioned below. Approx. 0·006M-solutions of the dibromides in dry acetone (" AnalaR ") were mixed in equal volume with 0·134N-sodium iodide in the same solvent. The course of the reaction was followed from time to time by thiosulphate titration of the iodine liberated. Between titrations the solutions were kept in a dark cupboard.

Cholest-4-ene.—For the large-scale preparation of this hydrocarbon a slight modification of Hauptmann's process (*J. Amer. Chem. Soc.*, 1947, **69**, 562) was found to be suitable. Cholest-4-en-3-one (5 g.) in toluene-ω-thiol (5 ml.) was cooled to 0° and a suspension of 60% aqueous perchloric (0·5 ml.) acid in toluene-ω-thiol (4 ml.) added. The mixture was well shaken until it set solid (3 minutes). After a further 10 minutes water was added and the reaction product worked up in the usual way. Recrystallisation from benzene–methanol gave the dibenzyl mercaptal, m. p. 123—124°, in almost quantitative yield. For desulphurisation the following procedure was adopted. The benzyl mercaptal (1 g.) in dioxan (30 ml.) was refluxed for 7 hours with Raney nickel (2 g.). Benzene was then added, the nickel removed by filtration, and the reaction product worked up in the usual way. Filtration through alumina and recrystallisation from ethyl acetate–methanol furnished cholest-4-ene, m. p. 74—75°.

For the preparation of cholest-4-ene dibromide, cholest-4-ene (500 mg.) in dry ether (50 ml.) was treated with a slight excess of bromine in acetic acid (4 ml.). After 15 minutes at room temperature the ether was removed *in vacuo* at room temperature. Recrystallisation from chloroform–methanol of the crystals thus deposited gave cholest-4-ene dibromide, m. p. 116—117°, $[\alpha]_D$ +39° (*c*, 4·48), unchanged on further recrystallisation.

Treatment of this dibromide with excess of sodium iodide in acetone, working up in the usual way, and recrystallisation from ethyl acetate–methanol afforded pure cholest-4-ene, m. p. 82·5°, $[\alpha]_D$ +77° (*c*, 4·87), unchanged on further recrystallisation.

Cholestan-4α-ol.—Cholestan-4-one was prepared by a slight modification of Windaus's method (*Ber.*, 1920, **53**, 488). Cholest-4-ene (1·5 g.), suspended in glacial acetic acid (10 ml.), was treated with a mixture of fuming nitric acid (5 ml.) and glacial acetic acid (8 ml.), the addition being made with good mechanical stirring. On warming to 75° the solution cleared. It was held at this temperature for 2 hours, before being poured into water and worked up in the usual way. The reaction product (4-nitrocholest-4-ene) was not isolated in a state of purity, but was at once reduced by the Windaus (*loc. cit.*) procedure. The product of the reduction, isolated in the usual way, was chromatographed to give cholestan-4-one, eluted with benzene, and recrystallised from light petroleum (b. p. 40—60°) at −80°; it had m. p. 95—96°.

* In this transition state we regard the two carbon atoms and the two bromine atoms as lying in one plane, though this was not stated specifically in the original paper.

Reduction of cholestan-4-one by sodium and ethanol (Tschesche and Hagedorn, *Ber.*, 1935, **68**, 2251) furnished cholestan-4α-ol (from chloroform–methanol), m. p. 188—189°, $[\alpha]_D$ +5° (*c*, 1·28).

Redistilled phosphorus oxychloride (0·4 ml.) was added with cooling, to cholestan-4α-ol (90 mg.) dissolved in dry pyridine (5 ml.) and left at room temperature overnight. Dilution with water and extraction with ether revealed the absence of any neutral material. Acidification of the aqueous pyridine solution gave a precipitate of *cholestan-4α-yl dihydrogen phosphate* which, recrystallised from chloroform, decomposed at 270—290° (Found : P, 6·1. $C_{27}H_{49}O_4P$ requires P, 6·6%).

Benzoylation of cholestan-4α-ol with benzoyl chloride in pyridine at room temperature for 24 hours and working up in the usual way furnished cholestan-4α-yl benzoate (from ethyl acetate–methanol), m. p. 115—116°, $[\alpha]_D$ −20° (*c*, 3·50). Ruzicka *et al.* (*Helv. Chim. Acta*, 1944, **27**, 727) reported m. p. 117·5—118° (corr.) for this compound.

Cholestan-4β-ol.—Cholestan-4-one was hydrogenated in acetic acid according to the directions of Tschesche and Hagedorn (*loc. cit.*). Working up in the usual way afforded cholestan-4β-ol (from methanol), m. p. 131—132°, $[\alpha]_D$ +29° (*c*, 1·94), unchanged by further recrystallisation.

Cholestan-4β-ol (40 mg.) was treated with phosphorus oxychloride at room temperature overnight in the same way as the 4α-isomer (see above). The neutral product had m. p. 79—80° and, after one recrystallisation from chloroform–methanol, gave pure cholest-4-ene (20 mg.), m. p. 81°, $[\alpha]_D$ +75° (*c*, 1·21), undepressed in m. p. on admixture with cholest-4-ene regenerated from the dibromide (see above).

Benzoylation of cholestan-4β-ol with benzoyl chloride in pyridine at room temperature for 24 hours and working up in the usual way furnished *cholestan-4β-yl benzoate* (from ethyl acetate–methanol), m. p. 114·5—115·5°, $[\alpha]_D$ +57° (*c*, 2·62) (Found : C, 82·8; H, 10·4. $C_{34}H_{52}O_2$ requires C, 82·9; H, 10·5%).

Pyrolysis of Cholestan-4α-yl Benzoate.—Cholestan-4α-yl benzoate (95 mg., see above) was slowly distilled at 1 mm. pressure in a stream of dry oxygen-free nitrogen through a small electric furnace heated to 400° (time of distillation 40 minutes). The benzoic acid liberated corresponded to 99% of theory. The distillate was chromatographed when the first fraction, eluted by 30 ml. of light petroleum (b. p. 40—60°), had m. p. 71—72° unchanged on recrystallisation from ethyl acetate–methanol, $[\alpha]_D$ +69° (*c*, 1·56). The m. p. was not depressed by pure cholest-3- or -4-ene. The optical rotation indicates that the hydrocarbon mixture consisted of about 40% of cholest-3-ene and 60% of cholest-4-ene.

Pyrolysis of Cholestan-4β-yl Benzoate.—Cholestan-4β-yl benzoate (100 mg.) (see above) was pyrolysed as was the 4α-isomer (see above). The benzoic acid liberated corresponded to 98% of theory. The distillate was chromatographed, the first fraction, eluted by 30 ml. of light petroleum (b. p. 40—60°), having m. p. 71—72°. A second fraction contained no hydrocarbon. Recrystallisation from ethyl acetate–methanol gave pure cholest-3-ene, m. p. 72—72·5°, $[\alpha]_D$ +57° (*c*, 1·88), +57° (*c*, 1·37), depressed in m. p. to 69° by admixture with pure cholest-4-ene (see above).

Alkaline Hydrolysis of the Cholestan-4-yl Benzoates.—Cholestan-4α-yl benzoate (64 mg.) in dioxan (10 ml.) and ethanol (10 ml.) was treated with 10 ml. of 0·0855N-ethanolic potassium hydroxide and the mixture left at room temperature for 7 days. The total steroidal product, worked up in the usual way, had $[\alpha]_D$ −5·1° (*c*, 2·03), from which figure it can be calculated that 56% of the ester had been hydrolysed.

Cholestan-4β-yl benzoate (62·9 mg.) was simultaneously treated in the same way. The rotation of the reaction product was $[\alpha]_D$ +46·9° (*c*, 2·38), from which it can be calculated that 36% of the ester had been hydrolysed.

Cholest-3-ene Dibromide.—Pure cholest-3-ene (23·5 mg.), prepared as described above, was dissolved in dry ether (5 ml.) and treated with a 2% solution (0·5 ml.) of bromine in acetic acid at room temperature for 15 minutes. Removal of the ether *in vacuo* and addition of methanol afforded the crude dibromide, m. p. 121—122° {$[\alpha]_D$ −3° (*c*, 0·60) unchanged after 6 days at room temperature}. Recrystallisation from ethyl acetate–methanol furnished pure *cholest-3-ene dibromide*, m. p. 124—124·5°, in long needles (Found : Br, 30·15. $C_{27}H_{56}Br_2$ requires Br, 30·2%).

Reference has already been made to the preparation of cholest-2-ene dibromide (see above) from the cholestene prepared by the pyrolysis of cholestanyl benzoate. The mother-liquors from the crystallisation of this dibromide were evaporated to dryness *in vacuo* and the residue was refluxed with potassium iodide (3 g.) in dry " AnalaR " acetone (250 ml.) for 6 hours. After being worked up in the usual way ($Na_2S_2O_3$ wash) the product was dissolved in 100 ml. of 1 : 1 ether–acetic acid and treated with 100 mg. of CrO_3 at 37° for 30 minutes. The excess of chromic acid was destroyed by methanol, and the product isolated in the usual way. It was dissolved in light petroleum (b. p. 40—60°) and chromatographed over alumina. The easily eluted fractions, recrystallised from ethyl acetate–methanol, gave long needles, m. p. 121—122°, $[\alpha]_D$ +6° (*c*, 4·45), showing a marked depression in m. p. with cholest-2-ene dibromide but no depression with cholest-3-ene dibromide. Further treatment with sodium iodide in acetone and recrystallisation from ethyl acetate–methanol afforded pure cholest-3-ene dibromide, m. p. 123—124°, $[\alpha]_D$ +6° (*c*, 1·53), +6° (*c*, 1·85). The identity of the dibromide was checked by debromination with zinc dust in acetic acid solution on the water-bath, which afforded pure cholest-3-ene, m. p. 74·5—75°, depressed to 64—65° on admixture with cholest-2-ene, but undepressed on admixture with cholest-3-ene of established constitution (see above).

Reduction of 3β-Hydroxycholestan-7-one.—7-Ketocholestanyl acetate (600 mg.), m. p. 149—150°, prepared and purified as described by Barton and Cox (*J.*, 1948, 783), was dissolved in *n*-propanol (25 ml.) and reduced under reflux by the addition of sodium (2·5 g.) during 1·5 hours. The solution was refluxed for a further 1·5 hours to ensure complete dissolution of the sodium and then poured into water. Working up in the usual way, and drying the residue azeotropically, gave a mixture, m. p. 148—152°, $[\alpha]_D$ +43° (*c*, 2·48), of cholestan-3β : 7α- and -3β : 7β-diol. That the reduction was complete was shown by tests (negative) with 2 : 4-dinitrophenylhydrazine. On trituration with light petroleum (b. p. 40—60°), the mixture had unchanged m. p., and $[\alpha]_D$ +40° (*c*, 6·55). Authentic cholestan-3β : 7α-

and -3β : 7β-diol, prepared according to Wintersteiner and Moore (*J. Amer. Chem. Soc.*, 1943, **65**, 1503), had m. p. 149—150°, $[\alpha]_D$ +12° (*c*, 4·53), +12° (*c*, 2·44), and m. p. 167—168°, $[\alpha]_D$ +52° (*c*, 5·02), respectively. From these rotations the mixture of diols, $[\alpha]_D$ +43°, obtained by reduction contained 78% of the 3β : 7β-diol. This was confirmed by dissolving the correct proportions of the two authentic diols in a little dioxan and precipitation with excess of water. The m. p. of the mixture was 148—151°, undepressed on admixture with the reduction product, m. p. 148—152°, $[\alpha]_D$ +43°.

The reduction product, m. p. 148—152°, $[\alpha]_D$ +43°, was acetylated with pyridine and acetic anhydride at room temperature for 24 hours. Working up in the usual way gave a colourless oil, $[\alpha]_D$ +35° (*c*, 8·63). If the rotations of +55° (m. p. 81—87°) and −17° (m. p. 64—69°) recorded by Wintersteiner and Moore (*loc. cit.*) are accepted for the respective diacetates of the 3β : 7β- and 3β : 7α-diols, this rotation corresponds to 72% of the diacetate of cholestan-3β : 7β-diol.

Alkaline Hydrolysis of the Cholestan-3β : 7-diol 3-Acetate 7-Benzoates.—3β-Acetoxycholestan-7α-yl and -7β-yl benzoates were prepared as described previously (Barton and Rosenfelder, *loc. cit.*) and 0·0122M-solutions of the two benzoates were made up in absolute ethanol. 100-Ml. portions of the two solutions were mixed with the same volume of 0·0968N-ethanolic potassium hydroxide and heated under reflux. From time to time approx. 25-ml. portions were withdrawn and diluted with water, excess of dilute hydrochloric acid was added, the whole was extracted with benzene, and the extracts were washed further with aqueous sodium hydrogen carbonate and then water. Evaporation of the benzene extracts *in vacuo* gave in each case a solid product. This was dried *in vacuo* and a part weighed for the determination of the rotation. The following results were obtained.

Time of reflux, hours :		0·5	3·0	6·0	11·0	23·0	35·0	72·0
3β-Acetoxy-7α-yl benzoate ...	$[\alpha]_D$	−10·5°	−9·0°	−8·2°	−7·6°	−4·3°	+0·6°	+6·9°
	c	3·71	4·35	4·06	3·68	3·94	3·40	2·92
Hydrolysed, %	—	—	8	12	14	29	51	78
3β-Acetoxy-7β-yl benzoate ...	$[\alpha]_D$	+82·3°	+80·1°	+76·8°	+70·7°	+61·6°	+52·5°	—
	c	3·94	3·84	3·68	3·68	3·08	3·12	—
Hydrolysed, %	—	—	9	20	40	70	100	—

The 3β-acetate residue is rapidly hydrolysed during the first ½ hour's refluxing. Therefore the rotations of the two alcohols, 3β-hydroxycholestan-7α- and -7β-yl benzoates, can be estimated by extrapolation of the above recorded rotations to zero time to be −10·8° and +82·8° respectively. The first of these figures can be checked, for Wintersteiner and Moore (*J. Amer. Chem. Soc.*, 1950, **72**, 1923) have found the rotation of the pure compound to be −11° with which our extrapolated value is in excellent agreement. When the rotations of the cholestan-3β : 7α- and -3β : 7β-diols are taken as +11·5° and +52·3° respectively (see above), the % hydrolysis of the 7-benzoate grouping can readily be calculated from the observed rotations. This procedure is justified because the hydrolysis of the 7-benzoate residue is so slow relative to that of the 3-acetate grouping.

Debromination of the Stereoisomeric 11 : 12-Dibromides.—For the rates of debromination see Table. Methyl 11α : 12β-dibromo-3α : 9α-epoxycholanate, recrystallised from chloroform–methanol, had m. p. 122—122·5°, $[\alpha]_D$ +18° (*c*, 2·97). Kendall *et al.* (*J. Biol. Chem.*, 1946, **164**, 583) reported m. p. 123—124·6°, $[\alpha]_D$ +21°, for this compound. The dibromide showed no mutarotation in chloroform during 7 days at room temperature.

Methyl 11β : 12α-dibromo-3α : 9α-epoxycholanate, recrystallised from chloroform–methanol, had m. p. 140·5—141°, $[\alpha]_D$ +45° (*c*, 3·56). Kendall *et al.* (*loc. cit.*) reported m. p. 142·5—143°, $[\alpha]_D$ +45°. The dibromide showed no mutarotation in chloroform during 7 days at room temperature.

After being kept at room temperature in acetone with excess of sodium iodide for 13 days the 11β : 12α-dibromide (over 90% debrominated, see table) was worked up by pouring the mixture into water, extraction with ether, and washing with sodium thiosulphate. Evaporation of the ether gave a partly crystalline residue which was characterised by bromination according to the directions of Kendall *et al.* (*J. Biol. Chem.*, 1946, **164**, 583) for methyl 3α : 9α-epoxychol-11-enate. In this way a 55% yield of the 11β : 12α-dibromide, recrystallised from chloroform–methanol, m. p. 139—140°, $[\alpha]_D$ +43° (*c*, 3·01), and undepressed in m. p. on admixture with starting material, was obtained. Kendall *et al.* (*loc. cit.*) reported a 57% yield for reaction under the same conditions.

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