488. *Compounds related to the Steroid Hormones. Part II.*[1] *The Action of Hydrogen Bromide on 2-Bromo-3-oxo-Δ¹-5α-Steroids.*

By G. F. H. Green and A. G. Long.

A reaction of the type named in the title, described by Djerassi and Scholz, was believed by them to afford a 4-bromo-Δ¹-3-ketone, from which the corresponding Δ¹,⁴-3-ketone was derived. From 2-bromo-5α-cholest-1-en-3-one (VIII) this reaction has now been traced through the 1,2-dibromides (IV) and (V) to the 1,4-dibromo-ketone (VI); the 1,2-dibromo-compounds can also be derived from 5α-cholest-1-en-3-one (III). Dehydrobromination of the 1,4-dibromo-ketone (VI) gives 4α-bromo-5α-cholest-1-en-3-one (VII) and the 1,4-dien-3-one (IX), which completes a practicable method for making the last-named compound from the Δ¹-3-ketone (III).

Difficulties supervene in the application of these reactions to 4,5α-dihydroprednisone acetate (XII).

Methods of purification, such as differential reactions with the bisulphite ion, are discussed with reference to the preparation of pure specimens of Δ¹- and Δ⁴-3-ketones.

The pharmaceutical value of various steroidal 1,4-dien-3-ones prompted us to study means of making them from 5α-steroids derived commercially from hecogenin. They can be made by dehydrobromination of 2,4-dibromo-3-oxo-5α-steroids, but such bromo-compounds are not always easy to obtain from polyketones, for reasons discussed before.[2] It was accordingly relevant that Djerassi and Scholz [3a] had reported the conversion of an ester of 2-bromo-17β-hydroxyandrost-1-en-3-one into the corresponding 4-bromo-1-en-3-one, by means of hydrogen bromide in acetic acid, and thence by dehydrobromination with collidine into the 1,4-dien-3-one.

We tried their method on 2-bromo-5α-cholest-1-en-3-one (VIII) without success; prolonging the dehydrobromination, however, gave a small yield of cholesta-1,4-dien-3-one (IX). The action of hydrogen bromide in acetic acid on 2-bromo-1-en-3-ones ($\lambda_{max.}$ ~255 mμ) is manifest from the ultraviolet absorption of the products ($\lambda_{max.}$ ~ 234 mμ), but this and the above-mentioned evidence did not rule out the formation also of 1-bromo-Δ¹-3-ones. To test this supposition on a compound unable to rearrange to the 4-bromo-Δ¹-3-ketone, we made 2-bromo-1-dehydroallobetulone (XXII) from allobetulin (XVIII), using a method discussed below with particular reference to 2-bromo-5α-cholest-1-en-3-one (VIII). A solution of the bromoallobetulone (XXII) in acetic acid containing hydrogen bromide suffered little change, which suggests that the formation of 1-bromo-1-en-3-ones is unlikely and that the change in the ultraviolet absorption of compounds that undergo reaction denotes conversion of the 2-bromo-Δ¹-3-oxo- into the 4-bromo-Δ¹-3-oxo-chromophore.

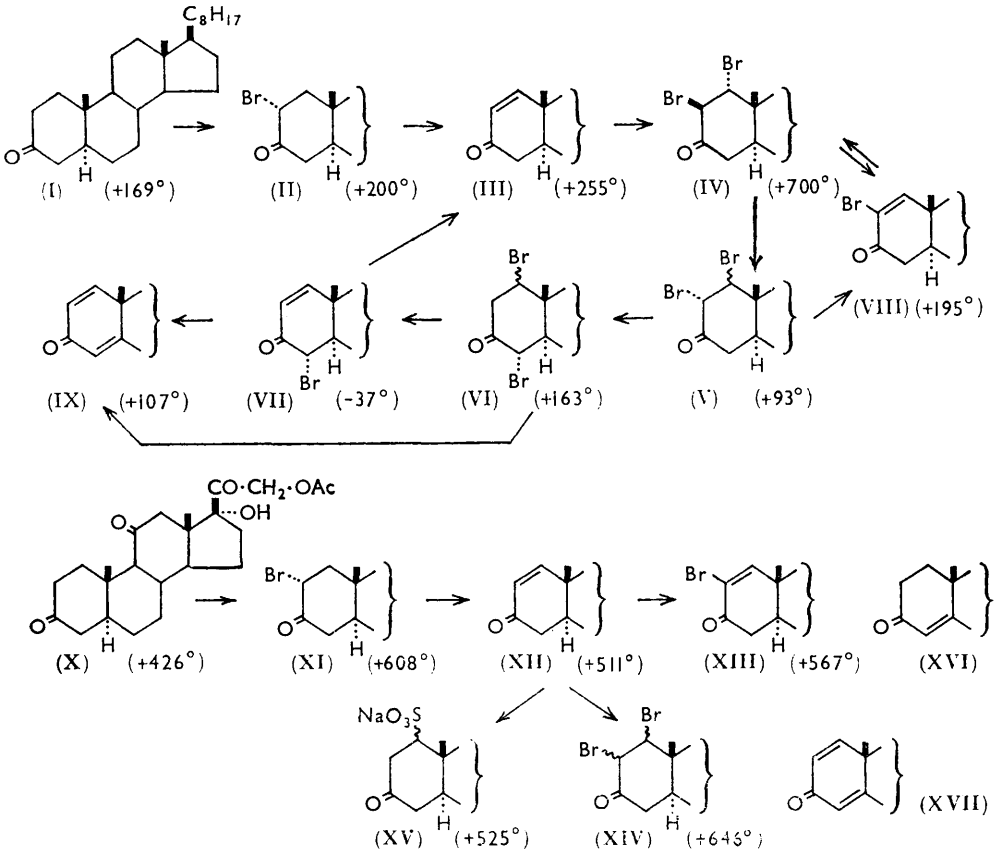
Exploitation of this method needed easier availability of the starting materials: 2-bromo-Δ¹-3-ketones had hitherto been obtained by dehydrobromination of 2,2-dibromo-3-oxo-5α-steroids,[2,4] but this procedure was in some instances tedious and inefficient and was not fully redeemed by improved methods for 2,2-dibromination of 5α-cholestan-3-one (I) and 4,5α-dihydrocortisone acetate (X) in liquid sulphur dioxide (see p. 2537 [5]). A better method for making 2-bromo-Δ¹-3-ketones, described below, is an adaptation of one used by Djerassi and Scholz.[3b]

Acid-catalysed halogenation of simple αβ-unsaturated ketones leads to substitution

[1] Part I, *J.*, 1960, 3333.
[2] Evans, Hamlet, Hunt, Jones, Long, Oughton, Stephenson, Walker, and Wilson, *J.*, 1956, 4356.
[3] Djerassi and Scholz, *J. Amer. Chem. Soc.*, (*a*) 1947, **69**, 2404; (*b*) 1948, **70**, 1911.
[4] Cf. Inhoffen and Zühlsdorff, *Chem. Ber.*, 1943, **76**, 233; Uskoković, Gut, and Dorfman, *J. Amer. Chem. Soc.*, 1960, **82**, 958.
[5] Ross, Percy, Brandt, Gebhart, Mitchell, and Yolles, *Ind. Eng. Chem.*, 1942, **34**, 924.

on the α-carbon atom, but in more complicated examples may occur at the α′- and γ-centres.[6] In halogenation of steroidal Δ^1-3-ketones reaction in the γ-position cannot occur, but halogenation of 5α-cholest-1-en-3-one (III) is nevertheless a complex process. We shall now consider this reaction in detail, and show that it controls the rearrangement that leads to the required 4α-bromo-5α-cholest-1-en-3-one (VII).

For reproducible acid-catalysed bromination of the enone (III), certain precautions were needed: for example, addition of a tertiary base immediately after the uptake of halogen considerably improved the yield of one product, 2α-bromo-5α-cholest-1-en-3-one (VIII). The addition of proton acceptors, such as tertiary bases and epoxides has been



Molecular rotations $[M]_D$ are given in parentheses.

advocated in the halogenation of Δ^4-3-ketones to their 4-halogeno-derivatives, the incidence of allylic substitution being curtailed; and Kirk, Patel, and Petrow[7] showed that such acceptors may favour direct substitution as well as influence the changes that follow addition.

When the halogenation of cholest-1-enone (III) in methylene dichloride was not cut short, a sequence of isomerizations and rearrangements ensued, with changes in rotation. We interpret these as follows. Bromine is taken up on the α-face by the 1,2-double bond, and the resulting bromonium ion is cleaved, yielding the *trans*-diaxial 1α,2β-dibromo-compound (IV), which is highly dextrorotatory.[8] In such a *vic*-dibromo-compound a

[6] *E.g.*, Pauly and Berg, *Chem. Ber.*, 1901, **34**, 2092; Hellthaler, *Annalen*, 1914, **406**, 151; Doeuvre, *Bull. Soc. chim. France*, 1926, **39**, 1594.

[7] Kirk, Patel, and Petrow, *J.*, 1956, 627, 1184.

[8] Cf. Fieser and Fieser, " Steroids," Reinhold Publ. Corp., New York, 1959, p. 38.

subsequent change to the diequatorial 1β,2α-form may be expected, or only the 2-bromo-atom may be epimerized; [9] the direction of rotational change would accord with inversion at the 2-position, but this does not allow us to interpret the stereochemistry at $C_{(1)}$. One bromine atom then migrates from the 2- to the 4-position, so that the final product is the 1,4-dibromo-3-ketone (VI), the last rearrangement being accompanied by an increase in dextrorotation. We can now amplify this evidence by considering bromination in acetic acid, during which the products tended to crystallise out; rotational changes were consequently more difficult to record continuously.

Addition of 1 mole of bromine to an acetic acid solution of the steroid (III) was succeeded immediately by crystallization of the dibromide regarded as 1α,2β-dibromo-5α-cholestan-3-one (IV). This dissolved on addition of hydrogen bromide. In mild conditions the 1ξ,2α-dibromo-isomer (V) was formed thereby and could with a little difficulty be isolated; when the concentration of hydrogen bromide was raised, crystals of yet another dibromo-compound separated, which we regard as 1ξ,4α-dibromocholestanone (VI). We lack evidence of spontaneous dehydrobromination in these conditions, although 4-bromo-Δ^1-3-ketones might arise in the methods of isolation used by Djerassi and Scholz.[3a] Dehydrobromination by means of cold pyridine or collidine gave 2-bromo-5α-cholest-1-en-3-one (VIII) from each of the 1,2-dibromo-isomers and 4α-bromo-5α-cholest-1-en-3-one (VII) from the 1,4-dibromo-compound.

The structures suggested for the above-mentioned compounds are upheld by further evidence. Dehalogenation of the 4-bromo-compound (VII) with chromous chloride gave cholest-1-en-3-one (III), which confirms the position of the double bond; the site occupied by the bromine atom is revealed by dehydrobromination to cholesta-1,4-dien-3-one (IX). The structure of the 1,4-dibromo-compound (VI) is verified by dehydrobromination in suitable conditions, either to the foregoing 4-bromo-enone or to the 1,4-dien-3-one (IX). The magnitude of the rotational change in the conversion of the 1,2-dibromo-ketone (V) into its isomer (VI) did not tally with that expected for a simple migration from the 2- to the 4-position,[2,10] but we cannot assess the effects due to the 1-bromo-atom. Spectroscopic [11] and rotational evidence [12] confirms the 4α-configuration in (VI) and (VII) and the 2β- and 2α-configurations in (IV) and (V).

These results show that the conditions described by Djerassi and Scholz [3] bring about the changes (VIII) ⟶ (IV) ⟶ (V) ⟶ (VI) ⟶ (IX). The 1,2-dibromide (IV) is easily derived from 5α-cholest-1-en-3-one (III), and when the latter is brominated in acetic acid containing hydrogen bromide 1,4-dibromo-5α-cholestan-3-one (VI) crystallizes out after completion of the rearrangements. This compound is then dehydrobrominated with dimethylacetamide and calcium carbonate [13] to the required 1,4-dien-3-one (IX), which is thus obtained in 53% yield from the monounsaturated ketone (III); the best we could achieve by the earlier method was 18% from the 2-bromo-ketone (VIII).

The rearrangements described here can also be used for debrominating 2-bromo-Δ^1-3-ketones, for example, conversion of 2-bromo-5α-cholest-1-en-3-one (VIII) successively into the 1,4-dibromo-compound (VI), and the 4-bromo-compound (VII), and 5α-cholest-1-en-3-one (III). We have found zinc and acetic acid or ethanol unsatisfactory for the direct debromination of 2-bromo-Δ^1-ketones.[14]

Application of the new methods to 4,5α-dihydroprednisone acetate (XII) achieved limited success. An improved preparation of the 2-bromo-1-dehydro-compound (XIII)

[9] Corey, *J. Amer. Chem. Soc.*, 1954, **76**, 175; Corey and Sneen, *ibid.*, 1956, **78**, 6269; cf. Allinger and Allinger, *Tetrahedron*, 1958, **2**, 64; Barton and Cookson, *Quart. Rev.*, 1956, **10**, 70.

[10] Ref. 8, p. 283; Djerassi, *J. Org. Chem.*, 1947, **12**, 823; Djerassi and Sneen, *ibid.*, 1948, **13**, 697; Djerassi, *J. Amer. Chem. Soc.*, 1950, **72**, 4081.

[11] Jones, Ramsay, Herling, and Dobriner, *J. Amer. Chem. Soc.*, 1952, **74**, 2828.

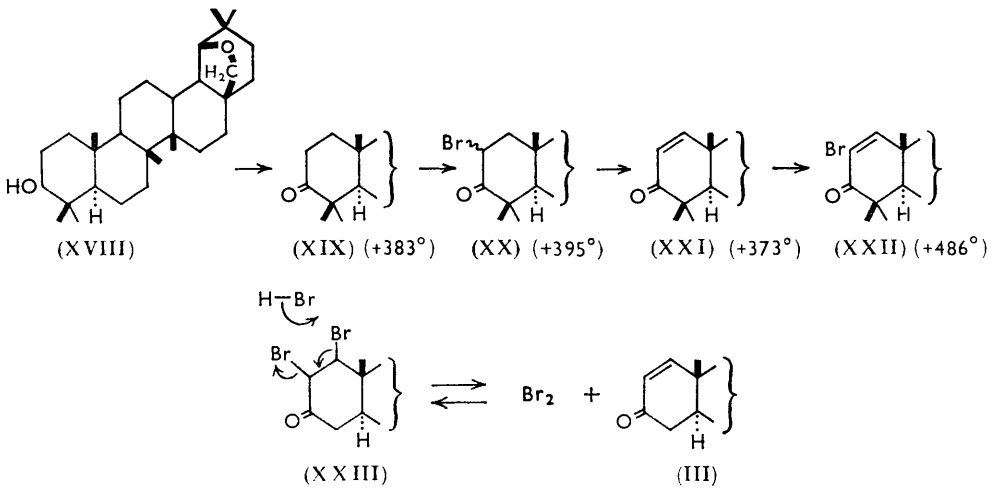
[12] Djerassi, Osiecki, Riniker, and Riniker, *J. Amer. Chem. Soc.*, 1958, **80**, 1216.

[13] Cf. Joly, Warnant, *et al.*, *Bull. Soc. chim. France*, 1958, 366, 367; Hohensee and Langbein, *Z. physiol. Chem.*, 1959, **315**, 83.

[14] Djerassi and Rosenkranz, *Experientia*, 1951, **7**, 93; Shaw and Stevenson, *J.*, 1955, 3549; Yanagita and Tahara, *J. Org. Chem.*, 1955, **20**, 959.

resulted, but with hydrogen bromide this yielded an unstable and probably impure 1,2-dibromo-ketone. Carrying the modified method through with crude products failed to give prednisone acetate (XVII), and further work along these lines was abandoned. This failure can probably be attributed to the nature of the rearrangements, in which a stationary concentration of bromine exists and over which control can be achieved only if the required intermediate products are formed preferentially or are sufficiently insoluble to be easily segregated. We have assumed that the situation in the shift of bromine from the 2-position is represented by (XXIII), so that with a polyketone all the active centres can vie for the substituent; the thermodynamically stable products may therefore contain no bromine in ring A. This uncertainty is less for conversions involving rearrangements in 2,2-dibromo-compounds, which are faster than the transformations described here.[2,15] The addition of β-naphthol or chromous chloride intercepts bromine in the rearrangement of 2-bromo-5α-cholest-1-en-3-one (VIII) in the presence of hydrogen bromide, but neither this evidence nor the changes of rotation explain the detailed mechanism. The isomerization giving 1,2α-dibromo-5α-cholestan-3-one (V) may not be catalysed by hydrogen bromide; we find that it is not promoted by radiation of 365 mμ. Kirk and Petrow[16] mention that the chlorination of a Δ^1-3-ketone gives a 1,2-dichloro-ketone, then a 2-chloro-Δ^1-3-ketone, and finally a 1,1,2α-trichloro-3-ketone. Rearrangements in such chloro-compounds are probably precluded for the reasons put forward[15] to explain the greater stability of 2,2-dichloro- than of 2,2-dibromo-3-keto-5α-steroids.

According to patents, 4,5β-dihydroprednisone acetate with 2 mol. of bromine yields the 1,2,2- and the 1,2,4-tribromo-derivative; the latter is converted by sodium iodide into the 4-bromo-3-oxo-Δ^1-5β-steroid, which is dehydrobrominated by lithium chloride in dimethylformamide to the 1,4-dien-3-one.[17] Yields are not cited.



Dehydrobromination of 4α-bromo-5α-cholest-1-en-3-one (VII) with dimethylacetamide and calcium carbonate is slow, and similar sluggishness with collidine may explain the difficulties in adapting Djerassi and Scholz's method.[3] Dehydrobromination of 4α-bromo-3-oxo-5α-steroids by such methods is also slow, but not that of 1,4- and 2,4-dibromo-3-ketones. It follows that the main reaction of 1,4-dibromocholestanone (VI) with dimethylacetamide and calcium carbonate by-passes the 4-bromo-compound (VII), and that

[15] Crowne, Evans, Green, and Long, *J.*, 1956, 4351.
[16] Kirk and Petrow, *J.*, 1958, 1334.
[17] *E.g.*, Merck and Co. Inc., B.P. 823,940; U.S.P. 2,837,542, 2,846,856, 2,856,416, 2,870.178, 2,904,564.

neighbouring groups influence these transformations. Dehydrobromination of bromo-ketones by semicarbazide or dinitrophenylhydrazine was not feasible in making 1,4-dien-3-oxo-steroids, which were only with difficulty generated from their hydrazones by the methods available at the time of this work.[18]

In establishing the structures of our products we found contaminants in several compounds thought previously to be pure. For instance, 5α-cholest-1-en-3-one (III) made by dehydrobromination of the 2α-bromo-ketone with dimethylacetamide and calcium carbonate differs slightly from specimens made by dehydrobromination with semicarbazide [19] or by dehalogenation of the 4-bromo-derivative (VII). The differences are attributed to traces of the Δ^4-isomer arising by cine-elimination, which is promoted by certain bases.[20] The contaminant is probably not removed by the usual methods of purification. Again, in the preparation of 4,5α-dihydroprednisone acetate (XII), acid-catalysed monobromination of 4,5α-dihydrocortisone acetate (X) gives small amounts of the 4-bromo-derivative as well as 2-bromo-4,5α-dihydrocortisone acetate (XI):[21] crystallization removes most of the former from the latter, or the latter may be selectively converted into its water-soluble bisulphite derivative, from which it can be readily regenerated.[22] Dehydrobromination of the 2-bromo-compound (XI) to the 1,2-dehydro-compound (XII) is accompanied by cine-elimination, giving cortisone acetate (XVI), particularly when bases such as collidine or dimethylacetamide are used and even in conditions stated to lessen such complications.[13] Conversely, dehydrobromination of 2,4-dibromo- or 4-bromo-4,5α-dihydrocortisone acetate may contaminate the desired cortisone acetate with its Δ^1-isomer (XII). (Sodium iodide in acetone and subsequent dehalogenation were used for the former,[2] and the bases [13] for the latter.) In their behaviour towards Girard reagents [2,23] such isomers are well-nigh indistinguishable, but they can be separated by selective addition of the HSO_3^- ion to the enone system in the Δ^1-compound.[24] The product is a water-soluble 3-oxo-1-sulphonate (XV), from which the Δ^1-3-ketone (XII) can be recovered by treatment with semicarbazide or with dimethylacetamide and calcium carbonate. 1,4-Dien-3-ones do not react with the bisulphite ion in these conditions; 4,5α-dihydrocortisone acetate (X) gives a water-soluble 3-hydroxy-3-sulphonate that regenerates the ketone when the concentration of the HSO_3^- ion is reduced (for example, by the addition of potassium carbonate). The detergent-like properties of the sulphonates from cholestanone and its derivatives limit their utility in separations.

Combination of the Girard and the bisulphite method permits complete resolution of the components in a mixture of 4,5α-dihydrocortisone acetate, the Δ^1-compound (XII), cortisone acetate (XVI), and prednisone acetate (XVII).

Experimental

Unless otherwise stated, solvents were: chloroform for optical rotation and dispersion (solutions about 1% for the former and 0·1% for the latter); ethanol for ultraviolet absorption spectra; carbon disulphide (cholestane and allobetulin derivatives) and bromoform (pregnane derivatives) for the infrared spectra (of which some have been described elsewhere [25]). M. p.s were measured on a Kofler apparatus. Specific rotations given for rotational changes have been calculated on the assumption that the molecular weight is unchanged. Paper chromatography

[18] Djerassi, *J. Amer. Chem. Soc.*, 1949, **71**, 1003; Koechlin, Kritchevsky, and Gallagher, *J. Biol. Chem.*, 1950, **184**, 393; cf. Demaecker and Martin, *Bull. Soc. chim. belges*, 1959, **68**, 365; Taub, Hoffsommer, Slates, Kuo, and Wendler, *J. Amer. Chem. Soc.*, 1960, **82**, 4012.

[19] McGuckin and Kendall, *J. Amer. Chem. Soc.*, 1952, **74**, 5811.

[20] See Gates and Hughes, *Chem. and Ind.*, 1956, 1506; Rosenfeld, Hellman, and Gallagher, *J. Biol. Chem.*, 1956, **222**, 321; Djerassi and Marshall, *J. Amer. Chem. Soc.*, 1958, **80**, 3986, and references therein; cf. Bergmann and Yaroslavsky, *ibid.*, 1959, **81**, 2772; Bunnett and Zahler, *Chem. Rev.*, 1951, **49**, 382.

[21] Mattox and Kendall, *J. Biol. Chem.*, 1950, **185**, 593.

[22] Glaxo Laboratories Ltd., B.P. 837,019.

[23] Glaxo Laboratories Ltd., B.P. 788,307; ref. 2.

[24] Glaxo Laboratories Ltd., B.P. 815,832; cf. Knoevenagel, *Chem. Ber.*, 1904, **37**, 4038.

[25] Cummins and Page, *J.*, 1957, 3847.

was carried out with solvent L, and TSTZ as spray reagent.[26] Compounds were identified with authentic specimens by mixed m. p. determinations and infrared spectroscopy.

Commercial 50—60% pyruvic acid was distilled at 16 mm. with a nitrogen leak until yellow material began to come over. A typical product had the assay: ketone (as pyruvic acid), 24%; acid (as pyruvic acid), 60%; water 48% (all w/v); *d ca.* 1·16. Semicarbazide was most conveniently got from the hydrochloride (50 g.) by cooling to 40° a solution in hot water (50 ml.) and adding phenolphthalein; 40% aqueous sodium hydroxide (*ca.* 46 ml.) was run in until the indicator was just coloured, and the solution was evaporated *in vacuo* to dryness; the residue was leached with refluxing dry ethanol (200 ml.) for 30 min., then filtered rapidly; the filtrate yielded, on cooling, the free base (24·2 g., 72%), m. p. 87—92° (capillary). Evaporation of the mother-liquors and re-extraction yielded another 18% of usable material.

Technical collidine (Hopkin and Williams Ltd.) was distilled at 168—170°/760 mm. through a column of glass balls. Infrared spectra indicated that the product consisted of 2,4,6- and 2,3,6-trimethylpyridine in the ratio of 11 : 9. Calcium carbonate for dehydrobrominations was bought in a suitably fine form as Calofort U from J. and E. Sturge Ltd.

The best conditions for preparative dehydrobrominations were established by prior rate-studies, aliquot parts being assessed at various times by spectroscopy, halogen analysis and, when practicable, paper chromatography.

5α-*Cholest*-1-*en*-3-*one* (III).—(i) 2α-Bromo-5α-cholestan-3-one (II) (10·0 g.), finely powdered semicarbazide base (3·0 g., 1·9 mol.), and acetic acid (250 ml.) were heated for 6 min. at the b. p.,[19] becoming orange. Redistilled pyruvic acid (22 ml.) and water (17 ml.) were added, and the solution was refluxed for 20 min., then cooled and poured into water (2 l.). Extraction with methylene dichloride yielded the ketone (III) as a yellow solid (8·2 g.) that crystallized from methanol (charcoal) as yellow plates (5·7 g., 69%), m. p. 97—100°, $[\alpha]_D^{23}$ +67°, $\lambda_{max.}$ 230 mμ (ε 10,200). The yield was raised to 75% by chromatography on alumina of a hexane solution of the residue from the crystallization.

(ii) 2α-Bromo-5α-cholestan-3-one (II) (5·0 g.) was added portionwise to calcium carbonate (4·0 g.) in boiling dimethylacetamide (50 ml.) during 3 min., and refluxing was continued for 14 min. Some of the solvent was distilled off *in vacuo*; the residue was extracted with ether and washed with hydrochloric acid and water. The ether was dried and evaporated, to yield a white solid (4·1 g.) that crystallized from methanol as needles of the ketone (III) (3·4 g., 82%), m. p. 96—99°. An analytical sample had m. p. 98°, $[\alpha]_D^{20}$ +60°, $[\alpha]_{370}$ −400° (min.), $\lambda_{max.}$ 230 mμ (ε 10,200) (Found: C, 84·5; H, 11·5. Calc. for $C_{27}H_{44}O$: C, 84·3; H, 11·5%).

(iii) 3-Acetoxy-5α-cholest-2-ene (0·856 g.) in dry refluxing carbon tetrachloride (30 ml.) was treated with recrystallized *N*-bromosuccinimide (0·40 g., 1·1 mol.), moisture being excluded. After 2 hours' refluxing the mixture was cooled and filtered, and the filtrate (which fumed; presumably it contained acetyl bromide) and washings were washed with water and dried. Evaporation left a gum, which yielded after chromatography on alumina the solid ketone (III) (0·520 g.). Crystallization from ethanol gave material of m. p. 98—99°, $[\alpha]_D^{20}$ +57°, $\lambda_{max.}$ 230 mμ (ε 10,100). This experiment was carried out by Dr. D. Hathway and Mr. L. Stephenson.

A fourth specimen of the ketone (III) was made by dehalogenation of the 4-bromo-Δ^1-3-ketone (VII) (see below). The specimens were examined for their content of the isomeric cholest-4-en-3-one ($\lambda_{max.}$ 241 mμ) by comparison of the ratios of the optical densities at $\lambda_{max.}$ to those at 241 mμ. For the four samples reported above the respective ratios were 1·40, 1·36, 1·38, and 1·42.

2,2-*Dibromo*-5α-*cholestan*-3-*one*.—5α-Cholestan-3-one (I) (1·0 g.), suspended in commercial liquid sulphur dioxide (100 ml.), was treated with 0·96M-bromine in " AnalaR " carbon tetrachloride (6·6 ml., 2·44 mol.) in 4 min. The solution was left for 11 min. more. It still had a bromine colour. Sodium pyrosulphite (5 g.) was added and the steroid extracted into hexane. Evaporation of the washed and dried hexane solution, and trituration of the residue with methanol, yielded a solid (1·34 g.), m. p. 126—134°. Crystallization gave the 2,2-dibromo-ketone (0·778 g., 55%), m. p. 152—156°, $[\alpha]_D^{20}$ +115°, suitable for most purposes. Recrystallization from hexane gave the pure product (0·582 g., 41%), m. p. 155—157°, $[\alpha]_D^{24}$ +118° (Found: C, 59·6; H, 8·3; Br, 29·6. Calc. for $C_{27}H_{44}Br_2O$: C, 59·6; H, 8·15; Br, 29·4%).

Use of the above procedure produced specimens of the *gem*-dibromo-compound devoid

[26] Brooks, Evans, Green, Hunt, Long, Mooney, and Wyman, *J.*, 1958, 4614.

of 2α,4α-dibromo-5α-cholestan-3-one; production of this contaminant was difficult to avoid in other methods of acid-catalysed bromination.[3,10]

When the brominated sulphur dioxide solution above was set aside for 6½ hr., crystalline 2α,4α-dibromo-5α-cholestan-3-one was isolated in 27% yield. Halogenation for 6 min. with 1·3 mol. of bromine gave pure 2α-bromo-5α-cholestan-3-one (II) in 28% yield. Liquid sulphur dioxide dissolves steroids, particularly polyoxopregnane derivatives, quite easily. Experiments with 3β-acetoxy-5α-ergostan-11-one and 3β,21-diacetoxy-17α-hydroxy-5α-pregnane-11,20-dione suggest that bromination in this solvent may affect the 9-position, albeit slowly.[27]

2-*Bromo*-5α-*cholest*-1-*en*-3-*one* (VIII).—A solution of 5α-cholest-1-en-3-one (III) (1·0 g.) in methylene dichloride (25 ml.) and dry ether (2·5 ml.) was stirred during the addition in one lot of 0·99M-bromine in methylene dichloride (2·85 ml., 1·08 mol.). Immediately the bromine colour had disappeared (about 1 min.), pyridine (10 ml.) was added. After 30 min. the solution was extracted with dilute hydrochloric acid, sodium hydrogen carbonate solution, and water, then dried and evaporated. The gum yielded small plates (1·05 g., 87%) (from methanol), m. p. 97—101°, $\lambda_{max.}$ 256 mμ (ε 7890). A further crystallisation from ether–methanol yielded birefringent plates of the bromo-ketone, m. p. 102—104°, $[\alpha]_D^{24}$ +38°, $\lambda_{max.}$ 255·5 mμ (ε 8065) (Found: C, 70·1; H, 9·2; Br, 17·6. Calc. for $C_{27}H_{43}BrO$: C, 69·95; H, 9·35; Br, 17·2%) {lit.,[3a] m. p. 91·5—92·5°, $[\alpha]_D$ +37°, $\lambda_{max.}$ 256 mμ (ε *ca.* 8500)}.

Poorer yields were obtained if the addition of pyridine after the bromination was delayed.

Action of Hydrogen Bromide on 2-*Bromo*-5α-*cholest*-1-*en*-3-*one* (VIII).—The bromo-ketone (VIII) (1·20 g.) was treated in dry acetic acid (53 ml.) with 6N-hydrogen bromide in acetic acid (3·47 ml.; finally 0·36N-hydrogen bromide solution) and set aside for 20 hr. in the dark at room temperature; $[\alpha]_D$ +49° ⟶ +34°. Neutralization with sodium hydrogen carbonate and extraction with ether yielded, after evaporation, a gum (1·19 g.), that was crystallized twice from methanol to give a product (0·27 g.), m. p. 94—114°, $[\alpha]_D^{25}$ +8°, $\lambda_{max.}$ 234 mμ ($E_{1\,cm.}^{1\%}$ 162), $\nu_{max.}$ 1692 cm.$^{-1}$ (Found: Br, 17·0%). A pure specimen of a 4-bromo-Δ^1-3-ketone could not be obtained by crystallization, so the foregoing product (0·100 g.) was heated for 7½ hr. under nitrogen in refluxing collidine (5 ml.). The product isolated in the usual way had to be purified by chromatography on alumina (Grade II); even then the material arose as impure crystals of cholesta-1,4-dien-3-one (IX) (0·016 g., 4%), $\lambda_{max.}$ 244 mμ ($E_{1\,cm.}^{1\%}$ 338), $\nu_{max.}$ 1660, 1628, and 880 cm.$^{-1}$ (Found: Br, 3·65%). Except for the longer period needed for the dehydrobromination these conditions are the same as those described by Djerassi and Scholz [3] for such a reaction. Dehydrobromination with calcium carbonate and dimethylacetamide for 25 min. gave the 1,4-dienone (IX) in 18% yield as prisms (from methanol), m. p. 108—111°, $[\alpha]_D^{22}$ +29°, $\lambda_{max.}$ 245 mμ (ε 15,250); we could not improve on this without resort to modified methods for making the 4-bromo-ketone (VII).

A solution of the 2-bromo-ketone (VIII) (0·100 g.) in dry alcohol-free 0·4N-hydrogen bromide in chloroform (20 ml.) reached a constant $[\alpha]_D$ +42° after 100 min.; the $E_{1\,cm.}^{1\%}$ at 255 mμ had by this time reached a minimum value of 30. From such a solution a gum (0·069 g.), $\lambda_{max.}$ 232 mμ ($E_{1\,cm.}^{1\%}$ 128), was isolated.

1α,2β-*Dibromo*-5α-*cholestan*-3-*one* (IV).—5α-Cholest-1-en-3-one (III) (0·50 g.) was treated in dry " AnalaR " acetic acid (11 ml.) with 0·435M-bromine in acetic acid (2·85 ml., 0·95 mol.) in one lot, with swirling. The bromine was rapidly absorbed and crystals formed. After 1 min. these were filtered off as rapidly as possible on a sintered funnel and were washed at once with sodium hydrogen carbonate solution and water. In this way 1α,2β-*dibromo*-5α-*cholestan*-3-*one* (IV) (0·423 g., 60%), m. p. 80—110°, $[\alpha]_D^{27}$ +120°, $\nu_{max.}$ 1722 cm.$^{-1}$, was obtained (Found: Br, 28·3. $C_{27}H_{44}Br_2O$ requires Br, 29·4%).

Rapid work was essential, as the crystals redissolved in a few minutes. Sunlight appeared to accelerate solution.

Dehydrobromination of 1α,2β-*Dibromo*-5α-*cholestan*-3-*one* (IV).—The dibromo-compound (0·100 g.) was heated in collidine (5 ml.) on the steam-bath for 1 hr., and then set aside at room temperature for 1½ hr. The product was isolated by extraction with ether; washing with dilute hydrochloric acid removed the collidine. The gum crystallized from ether–methanol to yield 2-bromo-5α-cholest-1-en-3-one (VIII) (0·070 g., 82%), m. p. 102—105°, $\lambda_{max.}$ 256 mμ (ε 8160).

1ξ,2α-*Dibromo*-5α-*cholestan*-3-*one* (V).—Polarimetric studies of the rotation ($[\alpha]_D$ +126° ⟶

[27] Henbest, Jones, Wagland, and Wrigley, *J.*, 1955, 2477.

+33°) of the 1α,2β-isomer (IV) in chloroform containing hydrogen bromide led us to expect formation of the 1,2α-dibromo-ketone (V), especially as subsequent dehydrobromination gave a monobromo-enone, $\lambda_{max.}$ 255 mμ. (There was no evidence of a 4-bromo-1-en-3-oxo-chromophore.) The following procedure was adopted to make a specimen of the 1,2α-dibromo-compound (V). 5α-Cholest-1-en-3-one (III) (1·0 g.) in dry methylene dichloride (25 ml.) and ether (2·5 ml.) was treated with 0·90M-bromine in methylene dichloride (3·05 ml., 1·05 mol.) added in one lot. Immediately after the bromine had been taken up (about 1 min.) the solution was stirred vigorously with saturated sodium hydrogen carbonate solution and then with water, dried, and evaporated. The residual gum (1·398 g.) emitted fumes of hydrogen bromide; it was triturated with hexane to yield a white solid (0·310 g., 22%), m. p. 105—106° (decomp.), $[\alpha]_D$ +17°, $\lambda_{max.}$ 256 mμ ($E^{1\%}_{1cm.}$ 23 ⟶ 48 in 15½ hr.), $\nu_{max.}$ 1743 and 738 cm.$^{-1}$ (Found: Br, 27·6. Calc. for $C_{27}H_{44}Br_2O$: Br, 29·4%). This was mainly the 1,2α-dibromo-compound (V). Another attempt at making this compound gave the isomer (IV).

Dehydrobromination of 1ξ,2α-*Dibromo*-5α-*cholestan*-3-*one* (V).—The dibromo-compound (72 mg.) was dissolved in purified pyridine (2 ml.) and set aside for 2 hr. Water was added. 2-Bromo-5α-cholest-1-en-3-one (VIII) (54 mg., 88%) crystallized, having m. p. 100—103°, $[\alpha]_D$ +41°, $\lambda_{max.}$ 255 mμ (ε 7800) (Found: Br, 17·1%).

1ξ,4α-*Dibromo*-5α-*cholestan*-3-*one* (VI).—5α-Cholest-1-en-3-one (III) (2·0 g.) was treated in dry acetic acid (50 ml.) with 0·43M-bromine in acetic acid (12·7 ml., 1·05 mol.) in one lot. The bromine colour dispersed rapidly and a white solid was deposited. Hydrogen bromide in acetic acid (7·4N; 12 ml., 1·2N finally) was added; the solid redissolved and the mixture was set aside for 16 hr. After about 1½ hr. crystallization began. The product was filtered off and washed with sodium hydrogen carbonate solution and with water to yield white crystals (2·0 g., 70%), m. p. 114—119°. Some of this material crystallized from hexane as flat rhombs of the *dibromo-ketone* (VI), m. p. 119—121°, $[\alpha]_D^{25}$ +30°, $\nu_{max.}$ 1735 cm.$^{-1}$ (Found: C, 59·4; H, 7·8; Br, 29·8. $C_{27}H_{44}Br_2O$ requires C, 59·6; H, 8·15; Br, 29·4%).

Alternatively, 2-bromo-5α-cholest-1-en-3-one (VIII) (1·0 g.) in dry acetic acid (35 ml.) was treated with 7·4N-hydrogen bromide in acetic acid (7·0 ml., 1·2N finally) and set aside for 64 hr. The liquor became green and deposited crystals. These were filtered off and washed with sodium hydrogen carbonate solution and with water (767 mg., 65%); they had m. p. 113—116° and were identified with the foregoing dibromo-compound (VI).

Dehydrobromination of 1ξ,4α-*Dibromo*-5α-*cholestan*-3-*one* (VI).—Reaction with calcium carbonate and refluxing dimethylacetamide for 20 min. yielded crystals (from methanol) of cholesta-1,4-dien-3-one (IX), m. p. 106—110°, $[\alpha]_D^{25}$ +29°, $\lambda_{max.}$ 244 mμ (ε 14,900), $\nu_{max.}$ 1664 and 888 cm.$^{-1}$. The yield was 76%. Dehydrobromination with collidine gave the 4-bromo-Δ^1-3-ketone (VII) (see below).

4α-*Bromo*-5α-*cholest*-1-*en*-3-*one* (VII).—1ξ,4α-Dibromo-5α-cholestan-3-one (VI) (0·50 g.) was dissolved in collidine (10 ml.) and set aside for 6½ hr. Collidine hydrobromide began to crystallize after 5 min. The product was isolated by extraction with ether and dilute hydrochloric acid, and crystallized from methanol with a little ether as prisms (343 mg., 81%), m. p. 125—127°. Two further crystallizations yielded birefringent prisms of 4α-*bromo*-5α-*cholest*-1-*en*-3-*one* (VII), m. p. 127·5—128·5°, $[\alpha]_D^{22}$ −8°, $[\alpha]_{370}$ −790° (min.), $\lambda_{max.}$ 232·5 mμ (ε 9360) (Found: C, 69·7; H, 9·2; Br, 16·9. $C_{27}H_{43}BrO$ requires C, 69·95; H, 9·3; Br, 17·2%).

Dehydrobromination of 4α-*Bromo*-5α-*cholest*-1-*en*-3-*one* (VII).—To calcium carbonate (0·50 g.) in refluxing dimethylacetamide (20 ml.) was added with stirring a mixture of the bromo-ketone (VII) (0·50 g.) and calcium carbonate (0·30 g.) in one lot. Refluxing and stirring were continued for 105 min. The cooled mixture was acidified and extracted with ether. The yellow gum (0·392 g.) left on evaporation of the ether yielded cholesta-1,4-dien-3-one (IX) (0·293 g., 71%), m. p. 107—110°, $[\alpha]_D^{24}$ +28°, $\lambda_{max.}$ 245 mμ (ε 14,860).

Debromination of 4α-*Bromo*-5α-*cholest*-1-*en*-3-*one* (VII).—The bromo-ketone (VII) (0·20 g.) was treated in " AnalaR " acetone (25 ml.) with concentrated hydrochloric acid (1 ml.) and 2M-chromous chloride solution (2 ml.) under nitrogen, and set aside for 40 min. The mixture was treated with water and extracted with ether. The gum obtained on evaporation yielded 5α-cholest-1-en-3-one (III) (0·131 g., 79%), m. p. 97—99°, $[\alpha]_D^{25}$ +60°, $\lambda_{max.}$ 228·5 mμ (ε 11,100) (Found: C, 84·0; H, 11·4. Calc. for $C_{27}H_{44}O$: C, 84·3; H, 11·5%). The propertier of specimens of this compound made by different methods, have already been mentioned; the above is probably the purest specimen.

Allobetulone (XIX).—Allobetulin (XVIII) (4·0 g.) was dissolved in purified ethyl methyl

ketone (see below) (300 ml.) at 60° and stirred during the addition [28] in one lot of 0·33M-potassium dichromate in 4N-sulphuric acid (13·5 ml.), and for 4 min. more. A little sodium pyrosulphite was added to remove excess of oxidant, the solution poured into water (2 l.), and the product (3·97 g.) filtered off and washed thoroughly with water. This material, m. p. 228—230°, $[\alpha]_D^{25}$ +85°, was used without further treatment in the bromination stage. A sample of allobetulone (XIX), recrystallized from acetone, had m. p. 234—236°, $[\alpha]_D^{23}$ +87°, $[\alpha]_{310}$ +830° (max) {lit.,[29] m. p. 230—231°, $[\alpha]_D$ +84·4°; m. p. 235—236°}. (Commercial ethyl methyl ketone reacts with the above oxidising solution: it was boiled with chromium trioxide and distilled before use.)

2ξ-*Bromoallobetulone* (XX).—Allobetulone (XIX) (3·0 g.) was dissolved in dry methylene dichloride (120 ml.) and ether (12 ml.), and mechanically stirred. 0·92M-Bromine in methylene dichloride (7·5 ml., 1·0 mol.) was added dropwise in 7 min., and the stirring continued for 5 min. more. There was no significant induction period. The solution was washed with sodium hydrogen carbonate solution and water, then evaporated. Trituration of the residual gum with methanol yielded 2ξ-*bromoallobetulone* * (XX) (3·21 g., 91%), m. p. 212—222° (Found: Br, 16·3%). A similar specimen from another experiment had m. p. 215—220°, $[\alpha]_D^{22}$ +76°, $[\alpha]_{310}$ +720° (max.) (Found: C, 69·0; H, 9·1; Br, 16·3. $C_{30}H_{47}BrO_2$ requires C, 69·3; H, 9·1; Br, 15·4%). It is possible that isomers with ring A in boat and chair forms are produced in this reaction.[30]

1-*Dehydroallobetulone* (XXI).—2ξ-Bromoallobetulone (XX) (1·85 g.) was added portionwise in 4 min. to a boiling suspension of calcium carbonate (1·6 g.) in dimethylacetamide (70 ml.), and boiling continued for 45 min. more. The suspension was cooled and poured into 2N-hydrochloric acid (200 ml.), and the precipitate filtered off and crystallized from aqueous acetone as needles (1·15 g., 74%), m. p. 238—246°, $[\alpha]_D^{24}$ + 84°. After three recrystallizations the material formed needles of 1-*dehydroallobetulone* * (XXI), m. p. 249—251°, $[\alpha]_D^{23}$ +85°, $[\alpha]_{370}$ −730° (min.), $\lambda_{max.}$ 229 mμ (ε 11,060), $\nu_{max.}$ 1672 and 765 cm.$^{-1}$ (Found: C, 82·3; H, 10·9. $C_{30}H_{46}O_2$ requires C, 82·1; H, 10·6%).

2-*Bromo*-1-*dehydroallobetulone* (XXII).—1-Dehydroallobetulone (XXI) (0·822 g.) was dissolved in dry methylene dichloride (33 ml.) and ether (3·3 ml.) and stirred during the addition in 4 min. of 0·57M-bromine in methylene dichloride (3·45 ml., 1·05 mol.). About 90% of the bromine was absorbed rapidly; a yellow colour persisted after this. After 15 min. (total time) pyridine (3 ml.) was added. When a further 15 min. had elapsed the solution (of constant optical rotation) was washed twice with 2N-hydrochloric acid and then with water until neutral. The methylene chloride was evaporated and the gummy residue triturated with methanol to give 2-*bromo*-1-*dehydroallobetulone* (XXII) (0·935 g., 96%), m. p. 249—252°. A sample crystallized twice from methanol formed white needles, m. p. 254—256°, $[\alpha]_D^{23}$ +94°, $\lambda_{max.}$ 257·5 mμ (ε 8020), $\nu_{max.}$ 1690 cm.$^{-1}$ (Found: C, 69·8; H, 9·1; Br, 15·8. $C_{30}H_{45}BrO_2$ requires C, 69·6; H, 8·8; Br, 15·4%).

Treatment of the 2-bromo-ketone (XXII) (0·20 g.) in dry acetic acid (20 ml.) with 7N-hydrobromic acid in acetic acid (1·2 ml.; 0·4N finally) at room temperature did not change the compound; prolongation to 40 hr. still gave 66% of the 2-bromo-ketone, with minor products with $\nu_{max.}$ 1744 and 1232 cm.$^{-1}$ (probably due to acetate groups).

21-*Acetoxy*-2-*bromo*-17α-*hydroxy*-5α-*pregnane*-3,11,20-*trione* (XI).—4,5α-Dihydrocortisone acetate (X) (50 g.) in dry methylene dichloride (500 ml.) and ether (50 ml.) was treated in 5 min. with 2·14M-bromine in methylene dichloride (61 ml., 1·05 mol.). Towards the end of the addition the product began to crystallize. Ether (1 l.) was added, the mixture cooled to −20°, and the product filtered off and washed with ether; it was dried over sodium hydroxide. The crystals (57·1 g., 88%) had m. p. 191—195°, $[\alpha]_D^{24}$ +115°, $\nu_{max.}$ 1742 and 1230, 1725, and 1705 cm.$^{-1}$ [Found: apparent Br, 26·0 (Carius method). Calc. for $C_{23}H_{31}O_6Br,0{\cdot}5CH_2Cl_2$: apparent Br, 26·8%]. The mother-liquors were washed immediately with sodium hydrogen carbonate solution and with water; the organic phase was dried and evaporated and the residue triturated

* Klinot and Vystrčil (*Chem. and Ind.*, 1960, 1360) have recently given further information on these compounds

[28] Cf. Djerassi, Engle, and Bowers, *J. Org. Chem.*, 1956, **21**, 1547; Brooks, Hunt, Long, and Mooney, *J.*, 1957, 1175.

[29] Schulze and Pieroh, *Chem. Ber.*, 1922, **55**, 2332; Ruzicka, Brüngger, and Gustus, *Helv. Chim. Acta*, 1932, **15**, 634.

[30] Cf. Barton, Lewis, and McGhie, *J.*, 1957, 2907.

with ethyl acetate. In this way more material (3·5 g.), m. p. 190—192°, was obtained, giving a total yield of 60·6 g. (93%).

This method is an improvement on those published previously.[2,31]

Crystallization of the 2-bromo-compound from methylene dichloride alone gave needles, m. p. 192—202° (Found: Br, 16·7. Calc. for $C_{23}H_{31}BrO_6$: Br, 16·5%), devoid of solvent of crystallization and of the band at 740 cm.$^{-1}$ due to methylene dichloride. Recrystallization from methylene dichloride containing 10% of ether gave the solvate.

The preparation of the ketone (XII) *via* its semicarbazone [$\lambda_{max.}$ 267 mμ (ε 26,000) in dioxan] has been described.[2] Recrystallization from acetone and then again from ethyl acetate gave a specimen, m. p. 256·5—257·5°, $[\alpha]_D^{20}$ +134°, $\lambda_{max.}$ 226 mμ (ε 11,200). A specimen made from second crops of the 2-bromo-compound (XI), again *via* the semicarbazone ($\lambda_{max.}$ 269 mμ, ε 22,200), had m. p. 225—240°, $[\alpha]_D^{20}$ +150°, $\lambda_{max.}$ 229·5 mμ (ε 10,300); it contained cortisone acetate (XVI) derived from the 4-bromo-isomer present in the sample of 2-bromodihydrocortisone acetate (XI). Dehydrobromination of the pure 2-bromo-compound (XI) with dimethylacetamide and calcium carbonate (10 minutes' refluxing) gave the ketone (XII), m. p. 248—252°, $[\alpha]_D^{24}$ +130°, $\lambda_{max.}$ 227 mμ (ε 10,700). The ratios of the optical densities in these three samples at $\lambda_{max.}$ to those at 237 mμ (cortisone acetate, $\lambda_{max.}$ 237 mμ) were 1·39, 1·23, and 1·25 respectively; this confirms that the first contains the least cortisone acetate (XVI).

21-*Acetoxy*-2-*bromo*-17α-*hydroxy*-5α-*pregn*-1-*ene*-3,11,20-*trione* (XIII).—21-Acetoxy-17α-hydroxy-5α-pregn-1-ene-3,11,20-trione (XII) (3·0 g.) was stirred in solution in dry methylene dichloride (90 ml.) and ether (9 ml.) and brominated in 5 min. with 1·92M-bromine in methylene dichloride (3·95 ml., 1·025 mol.); the bromine uptake was rapid until almost all was added. The solution was stirred for 2 min. more and pyridine (3 ml.) was then added; after a further 20 min. the solution was washed with 2N-hydrochloric acid, saturated sodium hydrogen carbonate solution, and water, then evaporated. The crude solid crystallized from methanol as needles (2·87 g., 80%), m. p. 209—212°. A pure specimen (after two further crystallizations) had m. p. 218—219°, $[\alpha]_D^{29}$ +117°, $\lambda_{max.}$ 255 mμ (ε 7940), $\nu_{max.}$ 1742 and 1230, 1724, 1704, 1688, and 1600 cm.$^{-1}$ (Found: C, 57·5; H, 6·4; Br, 16·5. Calc. for $C_{23}H_{29}BrO_6$: C, 57·4; H, 6·1; Br, 16·6%). A specimen made by dehydrobromination of the 2,2-dibromo-3-ketone [2] had m. p. 200—201° (decomp.), $[\alpha]_D^{20}$ +119°, $\lambda_{max.}$ 255 mμ (ε 7530).

Omission of pyridine in experiments of the above type yielded poor and unreliable results (cf. next paragraph).

21-*Acetoxy*-1ξ,2ξ-*dibromo*-17α-*hydroxy*-5α-*pregnane*-3,11,20-*trione* (XIV).—21-Acetoxy-17α-hydroxy-5α-pregn-1-ene-3,11,20-trione (XII) (1·0 g.) in dry methylene dichloride (40 ml.) and ether (4 ml.), cooled in ice, was stirred and treated with a drop of hydrogen bromide in chloroform, and then with 0·98M-bromine in methylene dichloride (2·55 ml., 1 mol.) during 7 min. Stirring was continued for 3 min. more and hexane (100 ml.) was added to precipitate the white 1,2-*dibromo-compound* (XIV) (1·1 g., 79%), m. p. 109—111° (decomp., capillary), $[\alpha]_D^{21}$ +116° (ethanol-free $CHCl_3$) ⟶ +87° in 140 min., $\nu_{max.}$ 3600—3400, 1740 and 1226, 1716 and 1705 cm.$^{-1}$ (Found: Br, 27·7. $C_{23}H_{30}O_6Br_2$ requires Br, 28·4%). The ultraviolet absorption was observed at intervals on the solution used for polarimetry with the following results, given in the order time (hr.), $\lambda_{max.}$ (mμ), and $E_{1\,cm.}^{1\%}$: 0, *ca.* 250 mμ, 35; 18, 254, 139; 42, 255, 172; 66, 255, 172. At 18 hr. the pH of an aqueous extriact was 4·5.

Action of Zinc and Acetic Acid on 21-*Acetoxy*-2-*bromo*-17α-*hydroxy*-5α-*pregn*-1-*ene*-3,11,20-*trione* (XIII).—The 2-bromo-Δ^1-compound (XIII) (0·50 g.) in chloroform (10 ml.) and acetic acid (10 ml.) was stirred with acid-washed zinc dust (1·5 g.) for 20 hr. at ⩾35°. The product was isolated by means of methylene dichloride. The gum (0·41 g.) obtained yielded crystals (0·10 g.) from acetone of 4,5α-dihydrocortisone acetate [2] (X), m. p. 220—230°, $[\alpha]_D^{25}$ +106°. The gummy residue from the crystallization had no max. from 220 to 290 mμ (Found: Br, 12·0%). Paper chromatography detected four components, of R_F 0·27, 0·50, 0·77, and 0·87.

Action of Hydrogen Bromide on 21-*Acetoxy*-2-*bromo*-17α-*hydroxy*-5α-*pregn*-1-*ene*-3,11,20-*trione* (XIII).—The 2-bromo-ketone (XIII) (0·75 g.) in dry alcohol-free chloroform (7·5 ml.) and acetic acid (20 ml.) was treated with 5·6N-hydrogen bromide in acetic acid (2·5 ml., *i.e.*, finally 0·47N in hydrogen bromide). The $[\alpha]_D$ +71° changed to +29° in 5·5 hr. and to +48° in 22 hr. A product (0·827 g.) (Found: Br, 28·0%) was extracted after 24 hr. with ethyl acetate. Precipitation from aqueous acetic acid gave a buff solid (0·33 g.), R_F 0·95, $\lambda_{max.}$ 230 mμ ($E_{1\,cm.}^{1\%}$

[31] Oliveto, Gerold, and Hershberg, *J. Amer. Chem. Soc.*, 1952, **74**, 2250.

137), $\nu_{max.}$ 1744 and 1230, 1725, 1706, 1690, and 1598 cm.$^{-1}$. This material could not be further purified, and a pure product could not be obtained from it by dehydrobromination with collidine.

Bromination and dehydrobromination of the ketone (XII) as described by Djerassi and Scholz [3] and with the modified methods of dehydrobromination described herein gave impure bromine-containing products, R_F 0·0, 0·46, 0·61, 0·71, 0·81, and 0·87. The spot at R_F 0·61 [prednisone acetate (XVII), R_F 0·61] was weak.

Sodium 21-*Acetoxy*-17α-*hydroxy*-3,11,20-*trioxo*-5α-*pregnane* 1ξ-*sulphonate* (XV).—The ketone (XII) (4·02 g.) in refluxing ethanol (100 ml.) and ethyl acetate (20 ml.) was treated with sodium pyrosulphite (0·95 g., 1 mol.) in hot water (25 ml.) under nitrogen. After 5½ hr. an aliquot part no longer smelt of sulphur dioxide when acidified, so the main bulk was concentrated *in vacuo* to small volume, and the precipitate filtered off for study as described below. The aqueous filtrate gave a violet colour with the TSTZ reagent,[26] but no precipitate with neutral barium chloride. It was extracted thrice with ethyl acetate; the last extract gave no colour with the TSTZ reagent. These extracts were combined with the precipitate above, and are discussed below. The aqueous solution was then evaporated *in vacuo* to dryness, toluene being evaporated off finally to remove the last traces of water. The desiccated residue was extracted into refluxing anhydrous ethanol, which was then filtered through kieselguhr and concentrated to small bulk. Crystallization from the cooled solution was promoted by additions of benzene. Small rhombs separated of the sulphonate (XV) (1·99 g., 38%), m. p. 223—226° (decomp., capillary), 208—214° (slight decomp., Kofler), $[\alpha]_D^{22}$ +100° (*c* 1·75 in H_2O), R_F 0·0, $\lambda_{max.}$ (in H_2O) 290 mμ ($E^{1\%}_{1cm.}$ 1), $\nu_{max.}$ (in Nujol) 1185 and 1038 cm.$^{-1}$, as well as carbonyl absorption, side chain assay (cortisone acetate as standard [32] and allowance for difference in mol. wt.) 103% (Found: C, 52·5; H, 6·4; S, 6·2. Calc. for $C_{23}H_{31}NaO_9S,H_2O$: C, 52·7; H, 6·3; S, 6·1%).[24]

The precipitate and ethyl acetate extracts yielded after combination and evaporation a residue (0·80 g.) that proved to be a nearly 1 : 1 mixture of cortisone acetate (XVI) and its isomer (XII), $\lambda_{max.}$ 233·5 mμ ($E^{1\%}_{1cm.}$ 248), R_F 0·61. This result suggests that the sample of Δ^1-3-ketone (XII) used for this experiment contained about 10% of cortisone acetate, arising by cine-elimination during dehydrobromination of the 2-bromo-ketone (XI) with calcium carbonate in dimethylacetamide.

The sulphonate (as its monohydrate) (0·25 g.) was converted into the ketone (XII) by adding it quickly to refluxing dimethylacetamide (5 ml.) containing calcium carbonate (0·25 g.), under nitrogen; refluxing was continued for 20 min. Separation of the steroid into ethyl acetate, which was washed initially with dilute mineral acid, afforded crystals (0·165 g.). Crystallization from ethyl acetate gave the Δ^1-3-ketone (XII) as fine blades and needles (0·118 g., 62%), m. p. 246—248°, $[\alpha]_D^{21}$ +127°, $\lambda_{max.}$ 227 mμ (ε 11,500), R_F 0·65; there was no evidence of contamination by cortisone acetate (XVI).

The above-described conversion was also achieved as follows. The sulphonate (as the hydrate) (0·139 g.) in water (2 ml.) was heated with M-semicarbazide solution (1 ml.) [from semicarbazide hydrochloride (1·115 g.) and sodium acetate trihydrate (1·361 g.) made up to 10 ml. with water) for 3 hr. on the steam-bath. The precipitated needles were washed with water, and straightway extracted exhaustively with ethyl acetate, chloroform, and 5N-hydrochloric acid; [26] evaporation of the organic phases gave a residue that was treated for 2 hr. at 20° with acetic anhydride (1 ml.) and pyridine (1 ml.). Crystallization of the product from ethyl acetate gave the ketone (XII) (0·031 g., 29%), mainly as needles, m. p. 247—248°, $[\alpha]_D^{20}$ +128°, $\lambda_{max.}$ 227·5 mμ (ε 10,650), R_F 0·64.

Separation of a Mixture by the Use of Pyrosulphite.—The mixture comprised cortisone acetate (XVI) (1·0 g.), its isomer (XII) (0·25 g.), and 4,5α-dihydrocortisone acetate (X) (0·25 g.); it was dissolved in refluxing ethanol (100 ml.) and ethyl acetate (10 ml.), and then treated with sodium pyrosulphite (10 g.) in water (20 ml.). The slurry was refluxed for 15 min.; then a solution of the pyrosulphite (50 g.) in hot water (500 ml.) was added. The mixture was left to cool, finally kept at 0°, and the crystalline precipitate (fraction A) filtered off.

The filtrate was twice extracted with ethyl acetate, evaporation of which gave fraction B. The aqueous phase from the extraction was treated with potassium hydrogen carbonate (60 g.) to adjust the pH to 7; extraction with ethyl acetate until the organic phase was no longer optically active and gave no colour with the TSTZ reagent [26] gave, on evaporation, fraction C.

[32] Mader and Buck, *Analyt. Chem.*, 1952, **24**, 666.

The aqueous phase still gave a violet colour with the TSTZ reagent, and presumably contained the 1-sulphonate from the Δ^1-3-ketone (XII), but it was not further examined. (The TSTZ reagent is not affected by sulphites.)

Fraction A (0·83 g.) recrystallized from ethyl acetate, yielding pure cortisone acetate (XVI) (0·77 g.), $\lambda_{max.}$ 237 mμ (ε 15,300), $[\alpha]_D^{20}$ +181° (in acetone). Fraction B (0·115 g.) consisted of a less pure specimen, $\lambda_{max.}$ 237 mμ (ε 13,600). Fraction C (0·23 g.) crystallized from ethyl acetate, giving almost pure 4,5α-dihydrocortisone acetate (X) (0·21 g.), $[\alpha]_D^{20}$ +113°, $\lambda_{max.}$ 240·5 mμ ($E_{1\,cm.}^{1\%}$ 10).

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