838. *Studies in the Synthesis of Cortisone. Part XVIII.* The Preparation of Cortisone Esters from 4 : 5α-Dihydrocortisone.*

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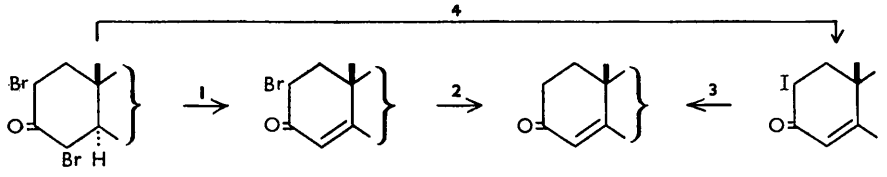
A study of the bromination of 4 : 5α-dihydrocortisone acetate led to isolation of a crystalline 2 : 4-dibromo-derivative, which was converted into cortisone 21-acetate and 17 : 21-diacetate by two different routes. The first proceeds *via* the reaction (first described by Djerassi) of the dibromo-steroid with sodium iodide and bromoacetone in acetone, and a new method using Girard reagents for the separation of cortisone mono- or di-acetate from the by-products of the reaction is described. The alternative route is based on the preferential reduction of 2 : 4-dibromo-3-oxo-5α-steroids to the hitherto unknown 4-bromo-3-oxo-5α-steroids, which are readily converted into the corresponding 3-oxo-Δ^4-steroids.

The difficulty of introducing a 4 : 5-double bond into 3-oxo-5α-steroids has to a great extent precluded the use of sterols and sapogenins of this series as starting materials for preparation of the adrenal hormones. The derivation of the essential 3-oxo-Δ^4-system from 2 : 4-dibromo-3-oxo-5α-steroids was first described by Inhoffen and Zühlsdorff;[1] it is also formed, together with the Δ^1-isomer, during the dehydrohalogenation of 2-bromo-3-oxo-5α-steroids by bases.[2]

Inhoffen and Zühlsdorff's method,[1] which involves partial dehydrobromination of the 2 : 4-dibromo-3-oxo-5α-steroid (I) and reduction of the resulting unsaturated monobromo-ketone (II), was later improved by Rosenkranz *et al.*,[3] who showed that the dibromo-ketone (I) with sodium iodide in acetone under reflux gave a 2-iodo-3-oxo-Δ^4-steroid (IV); this, like the bromo-analogue (II), could be readily reduced to the 3-oxo-Δ^4-steroid (III).



(I) (II) (III) (IV)

Reagents: 1, collidine; 2, Zn,AcOH; 3, HI or $CrCl_2$ or Zn,AcOH; 4, NaI.

The improved method has been widely used for preparation of Δ^4-3-ketones with stable side chains and lacking a substituent at $C_{(11)}$, but was less efficient in the preparation of adrenal hormones (cf. refs. 4 & 5).

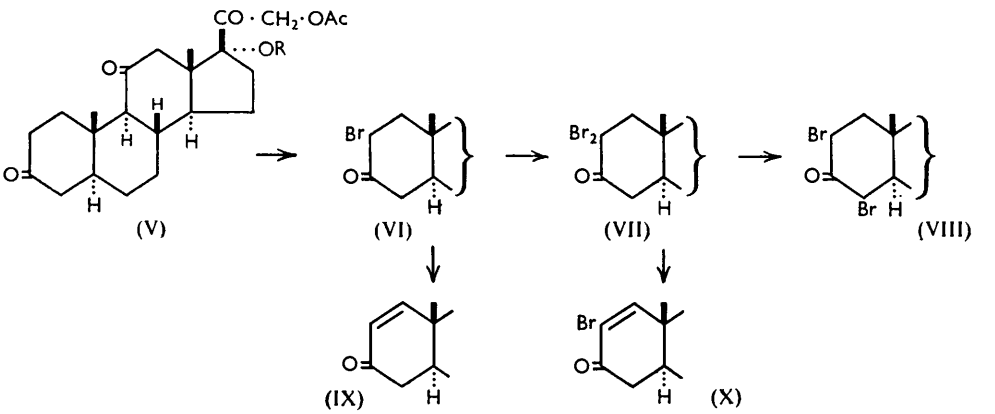
* Part XVII, preceding paper.

[1] Inhoffen and Zühlsdorff, *Ber.*, 1943, **76**, 2351.
[2] Djerassi and Scholz, *J. Amer. Chem. Soc.*, 1947, **69**, 2404; Beereboom and Djerassi, *J. Org. Chem.*, 1954, **19**, 1196.
[3] Rosenkranz, Mancera, Gatica, and Djerassi, *J. Amer. Chem. Soc.*, 1950, **72**, 4077.
[4] Rosenkranz, Pataki, St. Kaufmann, Berlin, and Djerassi, *J. Amer. Chem. Soc.*, 1950, **72**, 4081; Sondheimer, Rosenkranz, Mancera, and Djerassi, *ibid.*, 1953, **75**, 2601.
[5] Rosenkranz, Djerassi, Yashin, and Pataki, *Nature*, 1951, **168**, 28.

By following the method of Sondheimer, Rosenkranz, Mancera, and Djerassi [4] for conversion of 4 : 5α-dihydrocortisone acetate (V; R = H) into cortisone acetate (XII; R = H), we were unable to obtain an overall yield of more than 10% and experienced great difficulty in separating the reaction products, the starting material being the major contaminant. Observation (by ultraviolet absorption and precipitation of sodium bromide) of the rates of formation of the αβ-unsaturated ketone system during the reaction of the crude dibromo-ketone (VIII; R = H) with sodium iodide in acetone, revealed wide variations and led us to suspect the purity of the bromo-steroid. Attempts to purify this intermediate by chromatography on alumina led to a marked loss of halogen and on several occasions a small quantity of a diacetate, later identified as (VI; R = Ac), was isolated. Since the dibromo-ketone (VIII; R = H) was common to other projected routes for the conversion of the dihydro-acetate (V; R = H) into cortisone acetate (XII; R = H), we made a detailed study of its preparation.

Monobromination of the triketone (V; R = H) in acetic acid [6,7] gave the compound (VI; R = H) but, contrary to the observations of Oliveto *et al.*,[7] we found that dehydrobromination *via* the semicarbazone proceeded smoothly to the Δ^1-ketone (IX; R = H) (there are notable differences in the records of physical properties for this compound [6,8] and our observations do not completely confirm any of the records). Dehydrobromination of the bromo-ketone (VI; R = H) by collidine may lead to contamination of the product with the corresponding Δ^4-3-ketone (cf. Djerassi *et al.*[2]).

Attempted free-radical bromination of the monobromo-ketone (VI; R = H), by means of *N*-bromosuccinimide in allyl bromide with the addition of benzoyl peroxide or on irradiation,[9] failed to yield the 2 : 2-dibromo-ketone (VII; R = H), and acid-catalysed bromination was unsuccessful. However, as with 2-bromocholestan-3-one (see preceding paper), base-catalysed bromination gave the 2 : 2-dibromo-compound (VII) smoothly and its structure was confirmed by carefully controlled dehydrobromination in collidine to the bromo-Δ^1-3-ketone (X; R = H).



Polarimetric studies showed that the rearrangement (VII; R = H) ⟶ (VIII; R = H) catalysed by hydrogen bromide was complete within 15—30 minutes, in contrast to the 16 hours allowed by Rosenkranz, Djerassi, Yashin, and Pataki,[5] also that in a number of media the rearrangement was a first-order reaction with reference to the ketone (VII; R = H) (see p. 4362). Experiments on a larger-scale gave the crystalline 2 : 4-dibromo-ketone (VIII; R = H), which, unlike the product obtained in our earlier experiments, was stable and homogeneous when chromatographed on alumina. However, a slow change occurred in acetic acid containing hydrogen bromide, the α_D of the solution decreasing steadily. This might be accounted for in part by acetylation of the

[6] Wilson and Tishler, *J. Amer. Chem. Soc.*, 1952, **74**, 1609.
[7] Oliveto, Gerold, and Hershberg, *ibid.*, p. 2248.
[8] Kendall and Mattox, U.S.P. 2,590,978; Kaufmann and Pataki, *Experientia*, 1951, **7**, 260.
[9] Djerassi and Scholz, *ibid.*, 1947, **3**, 107; Hare and Wettstein, *Helv. Chim. Acta*, 1953, **36**, 891.

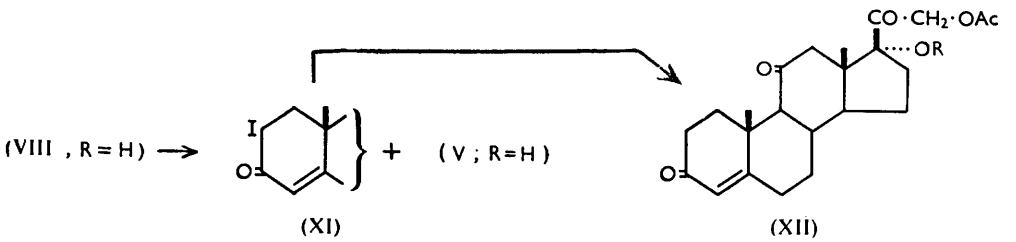
17α-hydroxy-group, since the acetate (VI; R = Ac) had already been isolated from the crude dibromo-ketone.

Our new evidence on the rearrangement and probable side reactions proved that the time taken in the direct preparation of the 2 : 4-dibromo-ketone (VIII; R = H) from dihydrocortisone acetate (V; R = H) had been excessive. In acetic acid containing hydrogen bromide (1·0N), the first mol. of bromine was absorbed instantaneously and the second in 3—5 minutes. The optical rotation of the solution became steady after a further 15 minutes and isolation of the products at this point gave crystalline 2 : 4-dibromo-ketone (VIII; R = H).

The reaction of this crystalline 2 : 4-dibromo-ketone (VIII; R = H) with sodium iodide in boiling acetone seemed to be complete within three hours. At high dilutions an induction period of 30—60 minutes occurred, but was avoided by adding a trace of mineral acid. Lithium iodide in place of sodium iodide gave similar results and no solvent was found to be superior to acetone.

The appearance of iodine during the reaction and the presence of saturated keto-steroids amongst the reaction products indicated reduction of the intermediate halogeno-steroids by hydrogen iodide. Separate experiments showed that hydrogen iodide in acetone readily reduced the dibromo-ketone (VIII; R = H) and that the reduction of the Δ^4-bond in the αβ-unsaturated ketones could not be held responsible for the low ultraviolet absorption of the products (cf. Fried and Sabo [10]). Attempts to remove the hydrogen iodide by the addition of inorganic or organic bases or epoxides served only to retard or inhibit the reaction, but favourable results were obtained by the inclusion of a second α-iodo-ketone, *e.g.*, iodoacetone, to react competitively with the hydrogen iodide, but the addition of large amounts of it did not completely prevent the formation of saturated keto-steroids.

The 2-iodo-steroid (XI; R = H), being too unstable for isolation in the pure state, was converted by controlled dehalogenation into crude cortisone acetate by hydrogen iodide generated *in situ*. Chromous chloride, or zinc and acetic acid, could also be used in the presence of sodium iodide though they reduced the Δ^4-bond. The halogen-free product isolated at this stage consisted predominantly of cortisone 21-acetate, but, in spite of the



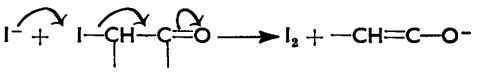
(XI) (XII)

use of iodoacetone in the foregoing reaction, 4 : 5α-dihydrocortisone 21-acetate (V; R = H) still appeared in appreciable amounts. This mixture could not be readily separated by crystallisation or chromatography, but Anchel and Schoenheimer's method [11] with the carboxyphenylhydrazones was successful, although some destruction of the steroids occurred during formation of the derivatives. A greatly improved method was found, however, by use of formaldehyde for the selective decomposition of the Girard P and T [12] derivatives: at pH 7 the saturated ketone (V; R = H) was liberated, whereas cortisone acetate (XII; R = H) was regenerated only at pH 1. The fraction obtained at pH 7 (formaldehyde–acetic acid–alcohol) was contaminated with αβ-unsaturated ketones, probably cortisone acetate and compounds with Δ^1-3-oxo-, $\Delta^{1:4}$-3-oxo-, and $\Delta^{8(9)}$-11-oxo-chromophores. Compounds of the last-mentioned type presumably arose from the corresponding 9α-bromo-steroids.[13] Further separation of this mixture was not practicable, but it was reduced catalytically to give some 4 : 5α-dihydrocortisone

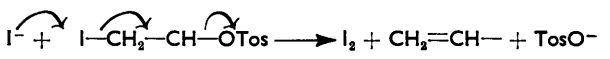
[10] Fried and Sabo, *J. Amer. Chem. Soc.*, 1953, **75**, 2273.
[11] Anchel and Schoenheimer, *J. Biol. Chem.*, 1936, **114**, 539.
[12] Reichstein, *Helv. Chim. Acta*, 1935, **19**, 1107.
[13] Crawshaw, Henbest, Jones, and Wagland, *J.*, 1955, 3420.

21-acetate (V; R = H). Crystallisation of the fraction from the Girard derivatives that decomposed at pH 1 yielded pure cortisone 21-acetate.

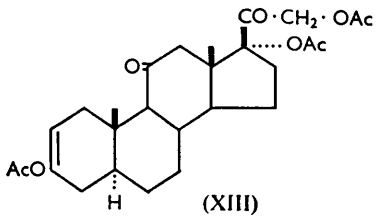
The fact that iodoacetone did not completely prevent the formation of 4 : 5α-dihydrocortisone acetate (V; R = H) may, perhaps, be explained by assuming that the iodide ion itself may act as a reducing agent in the following way :



A precedent for this mechanism is set by the action of sodium iodide on the toluene-*p*-sulphonyl esters of certain α-glycols : [14]



In the earlier phases of these investigations we had thought that the low yields of cortisone acetate (XII; R = H) might be accounted for by the destruction of the cortical side chain during the reactions necessary for introducing the double bond and that such difficulties might be overcome by esterification of the 17α-hydroxyl group. We therefore investigated the reactions with the corresponding 17α : 21-diacetates. The preparation of 17α-acetates with acetic anhydride alone or with acid catalysts has been described by Turner and others,[15] and we found that in a like manner the reaction between acetic anhydride and dihydrocortisone acetate (V; R = H) in benzene [16] catalysed by perchloric acid gave 3β : 17α : 21-triacetoxy-5α-pregn-2-ene-11 : 20-dione (XIII) in high yield. The position of the double bond was in accord with earlier observations,[17] as shown by bromination in acetic acid to the 2-bromo-ketone (VI; R = Ac), and was confirmed by alkaline hydrolysis, with subsequent acetylation, to dihydrocortisone monoacetate (V; R = H), whereas acid hydrolysis with subsequent acetylation gave the diacetate (V; R = Ac). [The physical properties recorded by Huang-Minlon, Wilson, Wendler, and Tishler[15b] for the diacetate, which they obtained by acetylation of the monoacetate catalysed by toluene-*p*-sulphonic acid, did not agree with those of our material, but were identical with those we obtained for the unsaturated triacetate (XIII) : repetition of their experiment gave in fact the latter product.]



(XIII)

Further bromination of the 2-bromo-ketone (VI; R = Ac) in acetic acid containing sodium acetate at 70° gave the 2 : 2-dibromo-ketone (VII; R = Ac), which rearranged under the influence of hydrogen bromide in chloroform to the 2 : 4-dibromo-ketone (VIII; R = Ac). This compound, however, was prepared more conveniently from the Δ^2-triacetate (XIII) by 2 mols. of bromine in chloroform, as described for the corresponding 17α-hydroxy-compound. Treatment of the dibromo-ketone (VIII; R = Ac) with sodium iodide in the presence of iodoacetone in refluxing acetone, de-iodination, and separation of the products gave cortisone diacetate (XII; R = Ac).

Acid hydrolysis of the esters (V and XII; R = Ac) removed only the 21-acetoxy-groups, but methanolic sodium hydroxide or methoxide gave the corresponding 17α : 21-diols. The amount of alkali was found to be critical : more than 2 equivalents caused destruction of the side chain, and only 1 equivalent was necessary for complete hydrolysis.*

* Similar observations have recently been made on Reichstein's substance S by Reingold, Rosenkranz, and Sondheimer, *J. Amer. Chem. Soc.*, 1956, **78**, 820.

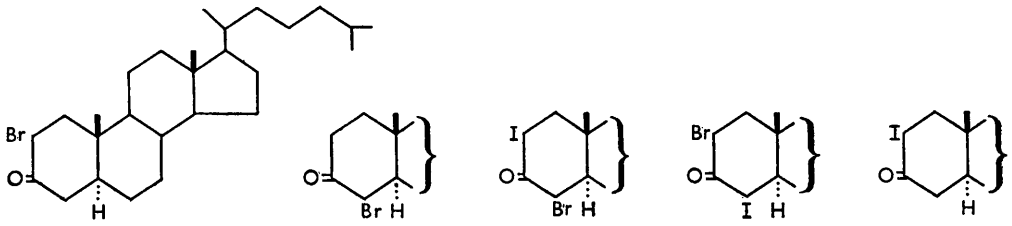
[14] Foster and Overend, *J.*, 1951, 3452; Newth, *J.*, 1956, 471.

[15] (*a*) Turner, *J. Amer. Chem. Soc.*, 1952, **74**, 4220; 1953, **75**, 3489; Moffett and Anderson, *ibid.*, 1954, **76**, 5394; Oliveto, Gerold, Weber, Jorgensen, Rausser, and Hershberg, *ibid.*, 1953, **75**, 5486; (*b*) Huang-Minlon, Wilson, Wendler, and Tishler, *J. Amer. Chem. Soc.*, 1952, **74**, 5394.

[16] Barton, Evans, Hamlet, Jones, and Walker, *J.*, 1954, 747.

[17] Inhoffen, Becker, and Kölling, *Annalen*, 1950, **576**, 181; Rubin and Armbrecht, *J. Amer. Chem. Soc.*, 1953, **75**, 3513.

The efficient formation of 3-oxo-Δ^4-steroids from the corresponding 4-bromo-3-oxo-5β-steroids [18,19] led us to investigate the preparation of the hitherto unknown 4-bromo-3-oxo-5α-steroids, with a view to finding an alternative route to cortisone acetate from the 2 : 4-dibromo-ketone (VIII; R = H). Preliminary attempts to hydrogenolise preferentially the 2-bromine atom in 2 : 4-dibromocholestan-3-one with a palladium catalyst failed. With the theoretical amount of chromous acetate in acetic acid a monobromo-ketone (XV*a*) was obtained, which differed from the known 2-bromo-compound (XIV). The

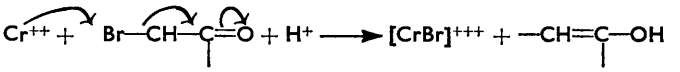


(XIV) (XV) (XVI) (XVII) (XVIII)

Series (*a*) : cholestanone type.
,, (*b*) : 4 : 5α-dihydrocortisone 21-acetate type.

4-position of the bromine atom was established by conversion of the product into cholest-4-en-3-one on treatment with semicarbazide [19] and subsequent hydrolysis [20] of the 3-semicarbazonocholest-4-ene.

Carefully controlled reductions of 21-acetoxy-2 : 4-dibromo-17α-hydroxy-5α-pregnane-3 : 11 : 20-trione (VIII; R = H) with chromous salts gave mainly the 4-bromo-ketone (XV*b*), which was converted into cortisone 21-acetate (XII; R = H) by the semicarbazide procedure.[18] The by-products of these reductions contained the 2-bromo-isomer from which 4 : 5α-dihydrocortisone acetate could be recovered by dehalogenation. Titanous sulphate was slightly less effective in producing the 4-bromo-ketone (XV*b*), and the use of halogen acceptors such as phenol and β-naphthol (cf. preceding paper) gave mixtures of bromo-ketones. We suggest that the reducing cation may act thus :



Acid-catalysed halogenation of 4-bromocholestanone (XV*a*) and 4-bromo-4 : 5α-dihydrocortisone 21-acetate (XV*b*) proceeded smoothly with bromine or iodine monochloride, giving the corresponding 2 : 4-dihalogeno-steroids. The 2 : 4-dibromocholestan-3-one so obtained was identical with that prepared by acid-catalysed bromination of cholestan-3-one, but the dibromo-ketone obtained from the Δ^4-ketone (III*b*) had a specific rotation lower than that of the product resulting from the direct bromination of the saturated ketone (V; R = H).

In contrast to the behaviour of 2-bromo-3-oxo-5α-steroids, replacement of the bromine atom in the 4-bromo-3-oxo-5α-steroids by means of sodium iodide does not occur in acetone at room temperature or on boiling, and was very slow in boiling ethyl methyl ketone. This behaviour resembles that of 4-bromo-3-oxo-5β-steroids [21] and emphasises the great reactivity of both bromine atoms in 2 : 4-dibromo-3-oxo-5α-steroids. Attempts to prepare the 4-bromo-2-iodosteroids (XVI*a* and *b*) by reaction of the 2 : 4-dibromo-5α-steroids with sodium iodide in acetone [3] at 20° were unsuccessful, and de-iodination of the crude products by sodium metabisulphite gave mixtures of 2- and 4-bromo-ketones. The bromoiodo-ketone so prepared differed from that prepared from (XV*a*) by reaction with iodine monochloride.

The difference in reactivities of 2- and 4-bromine atoms in 5α-steroids was used as the basis

[18] McGuckin and Kendall, *J. Amer. Chem. Soc.*, 1952, **74**, 5811.
[19] Holysz, *ibid.*, 1953, **75**, 4432.
[20] Hershberg, *J. Org. Chem.*, 1948, **13**, 542.
[21] Julian and Karpel, *J. Amer. Chem. Soc.*, 1950, **72**, 362.

of a modified preparation of cortisone acetate. The crude product obtained as above by chromous chloride reduction of the 2 : 4-dibromo-compound (VIII; R = H) was refluxed with sodium iodide in acetone, and the resulting mixture of 2-iodo- (XVIII*b*) and 4-bromo-3-oxo-5α-steroids (XV*b*) was reduced by sodium hydrogen sulphite or titanous chloride (both of which preferentially reduce the 2-iodine atom), or with the calculated quantity of chromous chloride solution. The product, which then consisted of 4 : 5α-dihydrocortisone 21-acetate and the 4-bromo-ketone (XV*b*), was treated with semicarbazide, the semicarbazones were hydrolysed, and the resulting mixture was separated by Girard P reagent, as described earlier.

	ΔM_D
2-Bromination.	
Cholestan-3-one ⟶ 2-bromocholestan-3-one (XIV)	+ 28°
4 : 5α-Dihydrocortisone acetate (V) ⟶ (VI)	+214
2 : 4-Dibromination.	
Cholestan-3-one ⟶ 2 : 4-dibromocholestan-3-one	−142
4 : 5α-Dihydrocortisone acetate (V) ⟶ (VIII)	+ 63
4-Bromination.	
Cholestan-3-one ⟶ 4-bromocholestan-3-one (XVI*a*)	−159
4 : 5α-Dihydrocortisone acetate (V) ⟶ (XV*b*)	−156

The equatorially disposed C–Br bonds of 2- and 4-bromocholestanone cause characteristic shifts of the ketone absorption,[22] whereas it is not possible to observe changes in the ultraviolet and infrared absorption of the polyketones under discussion which might be due to the differing orientation of 2- and 4-bromine atoms. We have not attributed configurations to the bromine atoms in the derivatives of 4 : 5α-dihydrocortisone acetate because the compounds, although made by the usual methods, show irregularities in the molecular-rotation differences accompanying their formation. From 2-bromination there is a greater rotational increase in 4 : 5α-dihydrocortisone acetate than in cholestan-3-one, and the difference is still present in the 2 : 4-dibromo-compounds, the effect of 4-bromination being nearly the same in both instances (see Table). The large rotational increment on 2-bromination of 4 : 5α-dihydrocortisone acetate may indicate a different 2-bromo-configuration in 11-oxo-steroids. Bromination of 4-bromo-4 : 5α-dihydrocortisone acetate gave a product with a specific rotation 10° lower than that of the 2 : 4-dibromo-ketone obtained from the 2-bromo-compound. The $[\alpha]_D$ rose 7° on equilibration in acetone with lithium bromide and therefore the 2 : 4-dibromo-compound could contain variable proportions of 2α- and 2β-epimers.

Experimental

Solvents (except when otherwise stated) were $CHCl_3$ for optical rotations (concn. limits 0·5—1·5%), EtOH for ultraviolet absorption spectra, and bromoform for infrared spectra.* The infrared spectra were recorded on a Perkin–Elmer Model 21 double-beam spectrophotometer fitted with sodium chloride optics, and the assignments are based on those summarised by Jones and Herling.[23]

4 : 5α-*Dihydrocortisone* 21-*Acetate* (V; R = H).—This was prepared from 3β-acetoxy-17α-hydroxy-5α-pregnane-11 : 20-dione [25] by the method described by Pataki, Rosenkranz, and Djerassi,[26] except that *tert.*-butyl alcohol and pyridine were used as solvent for the oxidation. Chromatography and crystallisation from acetone and benzene gave prisms, m. p. 231—236° (sintering at temperatures above 200°), $[\alpha]_D^{25}$ +103° (*c* 0·6), +89° (*c* 0·2 in acetone), $\lambda_{max.}$ 295 mμ

* Bromoform [24] has a great advantage over chloroform as a solvent for the infrared study of compounds that are insoluble in carbon disulphide and carbon tetrachloride, since in addition to transmitting in the C=O stretching region (1800—1600 cm.$^{-1}$), it transmits in the C–O stretching region (1270—1200 cm.$^{-1}$), and permits the acetate C–O band to be identified. However, Nujol transmits over a wider spectral region than bromoform.

[22] Jones, Ramsey, Herling, and Dobriner, *ibid.*, 1952, **74**, 2828; Jones, *ibid.*, 1953, **75**, 4839; Corey, *ibid.*, p. 4832; Fieser and Huang, *ibid.*, p. 4837.
[23] Jones and Herling, *J. Org. Chem.*, 1954, **19**, 1252.
[24] Tarpley and Vitiello, *Analyt. Chem.*, 1952, **24**, 315.
[25] Cf. ref. 16.
[26] Pataki, Rosenkranz, and Djerassi, *J. Amer. Chem. Soc.*, 1952, **74**, 5615.

(ε 249; *c* 0·004), $\nu_{max.}$ 1743 and 1231 (21-OAc), 1725 (20-CO), and 1704 cm.$^{-1}$ (3- and 11-CO) (Found: C, 68·4; H, 7·9. Calc. for $C_{23}H_{32}O_6$: C, 68·3; H, 8·0%). These properties differ from those given in the literature.[6,7,26,27]

21-*Acetoxy*-2-*bromo*-17α-*hydroxy*-5α-*pregnane*-3 : 11 : 20-*trione* (VI; R = H).—Bromine (8·3 g., 1·05 mol.) in acetic acid (100 ml.) was added to a stirred solution of 4 : 5α-dihydrocortisone acetate (V; R = H) (20 g.) in acetic acid (2·5 l.) containing a trace of hydrogen bromide. After the bromine was taken up, water was added and the steroid extracted into chloroform. The residue, evaporated under reduced pressure, crystallised from ethyl acetate as needles of the solvated 2-bromo-ketone (VI; R = H) (18 g., 64%), m. p. 185—192° (decomp.), $[\alpha]_D^{20}$ +110°, $\lambda_{max.}$ 207 and 292 mμ (ε 2320 and 131 respectively), $\nu_{max.}$ 1745 and 1232 (21-OAc), 1727 (20-CO) and 1708 cm.$^{-1}$ (CO) (Found: Br, 14·7. Calc. for $C_{23}H_{31}O_6Br,CH_3{\cdot}CO_2C_2H_5$: Br, 14·0%). Wilson and Tishler[6] give m. p. 179—185° (decomp.), $[\alpha]_D^{24}$ +102°. The product was eluted quantitatively by benzene from an alumina column. It formed also a benzene solvate, m. p. 182—192° (decomp.), $[\alpha]_D^{20}$ +112° (Found: C, 59·6; H, 6·45; Br, 14·8. Calc. for $C_{23}H_{31}O_6Br,\frac{1}{2}C_6H_6$: C, 59·8; H, 6·5; Br, 15·3%), and an acetone solvate, m. p. 187—189° (decomp.), $[\alpha]_D^{22}$ +116° (Found: C, 57·9; H, 6·5; Br, 14·6. Calc. for $C_{23}H_{31}O_6Br,C_3H_6O$: C, 57·7; H, 6·9; Br, 14·8%).

21-*Acetoxy*-17α-*hydroxy*-5α-*pregn*-1-*ene*-3 : 11 : 20-*trione* (IX; R = H).—2-Bromo-4 : 5α-dihydrocortisone acetate (VI; R = H) (14 g.; ethyl acetate solvate) in dry alcohol-free chloroform (240 ml.) and *tert.*-butyl alcohol (320 ml.) was shaken under carbon dioxide with finely powdered semicarbazide (3·2 g.) for 30 min. The residue, after removal of the solvents under reduced pressure, was triturated with ethanol (152 ml.) and then water (104 ml.), and filtered. The washed, wet solid was suspended in acetic acid (265 ml.), water (95 ml.), and 1·13N-aqueous pyruvic acid (34 ml.) and heated at 75° for 30 min. The solution was diluted with hot water and kept at room temperature overnight; the Δ^1-3-ketone (IX; R = H) crystallised as needles (6·5 g., 67%), m. p. 250—252° (decomp.), $[\alpha]_D^{25}$ +129°, +118° (in acetone), $\lambda_{max.}$ 227 mμ (ε 11,700), $\nu_{max.}$ 1745 and 1228 (21-OAc), 1725 (20-CO), 1704 (CO), 1668, 1600, and 780 cm.$^{-1}$ (α : β-unsaturated ketone) (Found: C, 68·5; H, 7·6. Calc. for $C_{23}H_{30}O_6$: C, 68·6; H, 7·5%). Recorded data[6,7,8] are divergent. The 3-(2 : 4-dinitrophenylhydrazone) had m. p. 240—242°, $\lambda_{max.}$ 385 mμ (ε 34,700 in $CHCl_3$) (Found: N, 9·6. Calc. for $C_{29}H_{34}O_9N_4$: N, 9·6%); Wilson and Tishler[6] give $\lambda_{max.}$ 375 mμ (log ε 4·45 in MeOH) for the unpurified hydrazone.

21-*Acetoxy*-2 : 2-*dibromo*-17α-*hydroxy*-5α-*pregnane*-3 : 11 : 20-*trione* (VII; R = H).—Bromine (3·22 g., 1·15 mol.) in 0·5N-potassium acetate solution in acetic acid (100 ml.) was added to 21-acetoxy-2-bromo-17α-hydroxy-5α-pregnane-3 : 11 : 20-trione (VI; R = H) (10 g.; ethyl acetate solvate) in 0·5N-potassium acetate solution in acetic acid (500 ml.). The solution was heated on a steam-bath until the colour had disappeared (15 min.) and then poured into brine (*ca.* 10 l.). The precipitated white solid was collected, washed, and dried (10 g.; $[\alpha]_D^{20}$ +138°). Crystallisation from ethyl acetate–*n*-hexane yielded rhombs of the 2 : 2-*dibromo-ketone* (VII; R = H) (4·25 g., 44%), m. p. 160—164° (decomp.), $[\alpha]_D^{20}$ +152°. Recrystallisation from ethyl acetate–*n*-hexane gave rhombs, m. p. 160—166° (decomp.), $[\alpha]_D^{19}$ +151°, $\lambda_{max.}$ 206 mμ (ε 3710) (at 292 mμ ε was 422), $\nu_{max.}$ 1748 and 1230 (21-OAc), 1725 (20-CO), and 1707 cm.$^{-1}$ (CO) (Found: C, 49·4; H, 5·5; Br, 28·1. $C_{23}H_{30}O_6Br_2$ requires C, 49·1; H, 5·3; Br, 28·4%).

21-*Acetoxy*-2-*bromo*-17α-*hydroxy*-5α-*pregn*-1-*ene*-3 : 11 : 20-*trione* (X; R = H).—2 : 2-Dibromo-4 : 5α-dihydrocortisone acetate (4 g.) was added to boiling *sym.*-collidine (20 ml.; redistilled), and the mixture refluxed for 2 min., rapidly cooled to room temperature, and diluted with benzene (50 ml.). Extraction of the collidine with 2N-hydrochloric acid (4 × 50 ml.), washing of the benzene solution with aqueous sodium hydrogen carbonate and water, and evaporation yielded a residue (3·1 g.) which was chromatographed on alumina. Benzene eluted a solid (1·66 g.), crystallising from methanol as rods of the 2-*bromo*-Δ^1-*ketone* (X; R = H) (1·28 g., 39%), m. p. 200—201° (decomp.), $[\alpha]_D^{20}$ +119°, +102° (in acetone), $\lambda_{max.}$ 255 mμ (ε 7500), $\nu_{max.}$ 1745 and 1230 (21-OAc), 1725 (20-CO), 1704 (CO), 1688 and 1595 cm.$^{-1}$ (αβ-unsaturated α-bromo-ketone) (Found: C, 57·2; H, 6·1; Br, 16·5. $C_{23}H_{29}O_6Br$ requires C, 57·4; H, 6·1; Br, 16·6%).

Polarimetric Study of the Rearrangement of the 2 : 2- (VII; R = H) *to the* 2 : 4-*Dibromo-compound* (VIII; R = H).—The 2 : 2-dibromo-compound (VII; R = H) (100 mg.) was dissolved in anhydrous solvents (25 ml.) made 0·8N with respect to hydrogen bromide, and the rotations of the solutions were taken at suitable intervals. The temperature variations were

[27] Djerassi, Rosenkranz, Pataki, and Kaufmann, *J. Biol. Chem.*, 1952, **194**, 115.

$\gtrsim$1°, and all the experiments were undertaken within the range 20° ± 2°. The results are as follows, each set being in the order $t_{0.5}$ (min.), k (min.$^{-1}$), and σ: acetic acid, 1·5, 0·396, ± 0·069; benzene, 11, 0·033, ± 0·004; chloroform, 29, 0·021, ± 0·001; dioxan, 8, 0·09, ± 0·001; ethyl acetate, 3, 0·233, ± 0·018; ethyl bromide, 3, 0·125, ± 0·018; methylene dichloride, 7, 0·091, ± 0·004; nitromethane, 8, 0·090, ± 0·008.

21-*Acetoxy*-2 : 4-*dibromo*-17α-*hydroxy*-5α-*pregnane*-3 : 11 : 20-*trione* (VIII; R = H) *from the* 2 : 2-*Dibromo-ketone* (VII; R = H).—The 2 : 2-dibromo-ketone (VII; R = H) (1·2 g.) in acetic acid (250 ml.) was treated with 3·4N-hydrogen bromide in acetic acid (6 ml.). After 2 min. the optical rotation $[\alpha]_D$ had decreased from +157° (in acetic acid) to +137° and after 16 min. had reached +88°, then remaining constant. An excess of water was then added and the solid (0·87 g.) collected, washed with water, and dried. Crystallisation from benzene–*n*-hexane and finally ethyl acetate–*n*-hexane gave colourless rods of the 2 : 4-dibromo-ketone (VIII; R = H), m. p. 172—173° (decomp.), $[\alpha]_D^{22}$ +87°. Recrystallisation from the same solvent mixture gave a product, m. p. 174—176° (decomp.), $[\alpha]_D^{23}$ +85°, $[\alpha]_D^{21}$ +69° (acetone), $\lambda_{max.}$ 210 and 292 mμ (ε 2580 and 141 respectively), $\nu_{max.}$ 1746 and 1230 (21-OAc), 1725 (20-CO), and 1708 cm.$^{-1}$ (CO) (Found: C, 49·2; H, 5·3; Br, 27·9. Calc. for $C_{23}H_{30}O_6Br_2$: C, 49·1; H, 5·4; Br, 28·4%). [Rosenkranz *et al.*[5] give m. p. 150—153° (decomp.).] A 49% yield of the 2 : 4-dibromo-ketone was obtained by starting with a suspension of the 2 : 2-dibromo-compound (3·4 g.) in acetic acid (100 ml.) containing hydrogen bromide.

21-*Acetoxy*-2 : 4-*dibromo*-17α-*hydroxy*-5α-*pregnane*-3 : 11 : 20-*trione* (VIII; R = H) *from* 4 : 5α-*Dihydrocortisone Acetate* (V; R = H).—Bromine (24·9 g., 2·1 mol.) in acetic acid (100 ml.) was added during 4 min. to a rapidly stirred fine suspension (60-mesh sieve) of 4 : 5-dihydrocortisone acetate (V; R = H) (30 g.) in acetic acid (350 ml.) at 16°, containing hydrogen bromide (22 ml.; 6·8N-solution in acetic acid; 2 mol.). The cooling-bath was removed and the solution stirred for a further 10 min., poured into water, and extracted with methylene chloride. The extract was washed with water, aqueous sodium hydrogen carbonate, and water, dried ($MgSO_4$), and concentrated under reduced pressure to small bulk. Ethyl acetate (100 ml.) was added and the solution evaporated *in vacuo*. The solid residue (41 g.) containing solvent (9 g.) was added with stirring to a boiling mixture of pure ethyl acetate (17·5 ml.) and *cyclo*hexane (22·5 ml.), whereupon the 2 : 4-dibromo-ketone (VIII; R = H) separated. The slurry was cooled to room temperature and diluted with benzene (50 ml.) and the solid collected, washed with benzene, then *n*-hexane, and air-dried {28·1 g., 68%; m. p. 173—175° (decomp.); $[\alpha]_D^{20}$ +85° (Found: Br, 27·3%)}.

Dehalogenation of the residue from the evaporated filtrate (12·5 g.) with sodium iodide and oxalic acid as described for the reduction of (XI), and crystallisation of the product twice from acetone furnished 4 : 5α-dihydrocortisone acetate (V; R = H) (2·9 g.), m. p. 230—233°, $[\alpha]_D^{20}$ +102°, identical with an authentic specimen.

When the acetate (V; R = H) was dibrominated in solution in acetic acid, the product was isolated after 15 hr. at room temperature. Chromatography on alumina gave, on elution with benzene–light petroleum, 17α : 21-diacetoxy-2-bromo-5α-pregnane-3 : 11 : 20-trione (VI; R = Ac), as prisms (from methanol) (12%), m. p. 220—223°, $[\alpha]_D^{20}$ +42°, identified with an authentic specimen by its infrared spectrum (see below). Benzene eluted the 2 : 4-dibromo-ketone (VIII; R = H; 20%), m. p. 170—172° (decomp.), $[\alpha]_D^{20}$ +86°.

Reaction of 21-*Acetoxy*-2 : 4-*dibromo*-17α-*hydroxy*-5α-*pregnane*-3 : 11 : 20-*trione* (VIII; R = H) *with Sodium Iodide.*—(a) *Preliminary investigations.* Crystalline trione (1 g.) in acetone (200 ml.) containing sodium iodide (2·12 g., 4 mol.) was refluxed under nitrogen. Samples (10 ml.) of the mixture were removed at intervals, the free iodine being estimated by titration with 0·1N-sodium thiosulphate and the intensity of absorption at 239 mμ recorded. Both values reached a steadily but slowly increasing value after 4 hr. (*ca.* 1·25 mol. of iodine; $E_{1\,cm.}^{1\%}$ 135). In more concentrated solution, *e.g.*, steroid (1 g.) in acetone (50 ml.) containing sodium iodide (4 g.), similar figures were reached in 1—1½ hr. The iodine content of the steroid was 18—20% (Calc. for $C_{23}H_{29}O_6I$: I, 24·0%) at this stage but fell steadily, with subsequent increase in intensity of light absorption and amount of free iodine as the time of reflux was prolonged. After 24 hr. the iodine content of the steroid had fallen to 15% in the dilute, and 8% in the more concentrated, conditions. The precipitation of sodium bromide (0·365 g.) from mixtures containing the 2 : 4-dibromo-ketone (1 g.) was in accordance with complete replacement or elimination by iodine (2 mol., 0·366 g.), coinciding approximately with the termination of the initial rapid increase in light absorption.

(b) *Crude* 2-*iodocortisone acetate* (XI; R = H) *and crude cortisone* 21-*acetate* (XII; R = H). The 2 : 4-dibromo-compound (20 g.) was treated as described for the concentrated conditions

in (a). After 2½ hours' refluxing the iodine was removed with 0·1N-sodium thiosulphate. Water was then added and the product extracted with methylene chloride, yielding 2-iodocortisone acetate (18·2 g.), $\lambda_{max.}$ 240 ($E^{1\%}_{1\,cm.}$ 205) (Found : I, 21·5. Calc. for $C_{23}H_{29}O_6I$: I, 24·0%). A sample reprecipitated from water–methanol showed $\lambda_{max.}$ 241 mμ ($E^{1\%}_{1\,cm.}$ 235) (Found : I, 21·0%), m. p. 139—140°, $[\alpha]_D^{20}$ +199°, +170° (in acetone). The substance readily decomposed in chloroform solution, the colour of free iodine appearing. The crude iodo-compound was treated in acetone (300 ml.) with 1·2N-chromous chloride (200 ml.) under carbon dioxide. After 30 min., the solution was diluted with water and extracted with ethyl acetate. The extract was washed and evaporated, to yield crude cortisone acetate (XII; R = H) (14·2 g.), m. p. 215—218°, $[\alpha]_D^{20}$ +188°, $\lambda_{max.}$ 238 mμ ($E^{1\%}_{1\,cm.}$ 268).

(c) *Crude cortisone* 21-*acetate* (XII; R = H) : *general methods*. Bromine (26·78 ml.) was added to acetone (750 ml.) with cooling and, when this solution became colourless, sodium carbonate (70 g.) was added with stirring and continued cooling. When free from hydrogen bromide (20—30 min.), the solution was filtered and the filtrate added to hot acetone (2·7 l.) containing sodium iodide (700 g.). This solution was refluxed for 15 min., whereafter the crude 2 : 4-dibromo-ketone (VIII; R = H) (139 g.) from 4 : 5α-dihydrocortisone acetate (160 g.) was added. Refluxing was continued for 2½ hr. during which much free iodine appeared. Oxalic acid (139 g.; commercial) was then added and the mixture refluxed for a further hour; then it was cooled, ethyl acetate (3 l.) added, and the solid filtered off. The filtrate was washed with water, sodium hydrogen carbonate solution, and water, and the remaining free iodine removed with zinc dust (350 g.) and acetic acid (30 ml.). The mixture was filtered, and the filtrate washed with water, then sodium hydrogen carbonate solution, and evaporated to dryness, giving crude cortisone acetate (XII; R = H) (97 g.), $\lambda_{max.}$ 237 mμ ($E^{1\%}_{1\,cm.}$ 265), m. p. 209—215°, $[\alpha]_D^{20}$ +188°.

Isolation of Cortisone 21-*Acetate* (XII; R = H) *from a Crude Mixture by Means of Girard* P *Reagent.*—A crude mixture containing cortisone acetate ($\lambda_{max.}$ 238 mμ, $E^{1\%}_{1\,cm.}$ 271), $[\alpha]_D$ +182° (13·4 g.), Girard P reagent (6·7 g.), anhydrous ethanol (200 ml.), and glacial acetic acid (10 ml.) was refluxed for 30 min. The solution was cooled to 20°, 40% aqueous formaldehyde solution (27 ml.) added, and the whole kept at room temperature for 25 min., then poured into 4% aqueous sodium hydrogen carbonate (500 ml.) and extracted with ethyl acetate (3 × 150 ml.). The extracts were combined, washed with water, dried, and evaporated under reduced pressure to give crude dihydrocortisone acetate (V; R = H) (4·53 g.), $\lambda_{max.}$ 238 mμ ($E^{1\%}_{1\,cm.}$ 90), $\nu_{max.}$ 1742 and 1232 (OAc), 1728 (20-CO), 1705 (CO), weak 1658, 1616, and 1600 cm.$^{-1}$ (αβ-unsaturated ketone) (fraction *A*, see below). The aqueous layer after extraction was acidified to pH 1 with hydrochloric acid and set aside for 2 hr. The resulting precipitate was filtered off, washed and dried [7·22 g.; $\lambda_{max.}$ 237·5 mμ (ε 14,800)]. After treatment with charcoal, recrystallisation from ethyl acetate gave cortisone acetate (XII; R = H) as plates, m. p. 243—244°, $[\alpha]_D^{20}$+220°, $\lambda_{max.}$ 237·5 mμ (ε 15,500), $\nu_{max.}$ 1745 and 1230 (21-OAc), 1726 (20-CO), 1705 (CO), 1662, 1618, and 864 cm.$^{-1}$ (αβ-unsaturated ketone) (Found : C, 68·8; H, 7·6 Calc. for $C_{23}H_{30}O_6$: C, 68·6; H, 7·5%).

The filtrate from the cortisone acetate precipitation was extracted with ethyl acetate. The extract was washed with aqueous sodium hydrogen carbonate and water, dried, and evaporated under reduced pressure, to give a pale yellow solid (1·483 g.), $\lambda_{max.}$ 237 mμ ($E^{1\%}_{1\,cm.}$ 332), $\nu_{max.}$ weak 1742 and 1232 (21-OAc), 1728 (20-CO), 1708 (CO), 1662, 1616, and 1600 cm.$^{-1}$ (αβ-unsaturated ketone), $[\alpha]_D$ +183°. Reacetylation in pyridine–acetic anhydride, Girard P separation, and crystallisation yielded cortisone 21-acetate (1 g.), $\lambda_{max.}$ 238 mμ (ε 15,000), identified as above. The material from the mother-liquors from this crystallisation, on chromatography on acid-washed alumina in ether–chloroform, gave a large fraction (40%) showing $\lambda_{max.}$ 237 mμ ($E^{1\%}_{1\,cm.}$ 364—398) and a greatly enhanced conjugated ketone band at 1662 cm.$^{-1}$, considerably more intense than that of cortisone acetate itself. This compound is tentatively formulated as 21-acetoxy-17α-hydroxypregna-4 : 8(9)-diene-3 : 11 : 20-trione originating from a 9-bromo-ketone.[13]

Fraction *A* (see above), on crystallisation, hydrogenation over palladium–charcoal, and recrystallisation from ethyl acetate, gave 4 : 5α-dihydrocortisone 21-acetate in 50% yield from the crude material. A filtrate from the crystallisation before hydrogenation was evaporated to dryness and triturated with ether–benzene, and the insoluble crystalline residue was filtered off and identified as 21-acetoxy-3β : 17α-dihydroxy-5α-pregnane-11 : 20-dione (Reichstein's D monoacetate), m. p. 237—238°, $[\alpha]_D^{20}$ +89°, +66° (in acetone), $\nu_{max.}$ (in Nujol) 3530 and 3450 (OH), 1752 and 1231 (21-OAc), 1730 (20-CO) and 1695 cm.$^{-1}$ (CO). Pataki *et al.*[26] give m. p. 235—237°, $[\alpha]_D^{20}$ +66° (in acetone).

3β : 17α : 21-*Triacetoxy*-5α-*pregn*-2-*ene*-11 : 20-*dione* (XIII).—(*a*) 60% Aqueous perchloric acid (0·125 ml.) was added to acetic anhydride (100 ml.) at 0°. The resulting solution was shaken with a suspension of 21-acetoxy-17α-hydroxy-5α-pregnane-3 : 11 : 20-trione (50 g.) in benzene (800 ml.) at room temperature for 20 min. The whole was washed with water, aqueous sodium hydrogen carbonate, and water, dried ($MgSO_4$), and evaporated, to yield a solid that was washed with a little ether and crystallised from methanol. The *triacetate* (XIII) (45 g.) separated as needles, m. p. 175—181°, $[\alpha]_D$ +46°, $\nu_{max.}$ (in CS_2) 1752 and 1218 (enol OAc), 1740 and 1236 (OAc), and 1710 cm.$^{-1}$ (CO) (Found: C, 66·4; H, 7·5. $C_{27}H_{36}O_8$ requires C, 66·4; H, 7·4%).

(*b*) (Cf. Huang-Minlon *et al.*[15b]) 21-Acetoxy-17α-hydroxy-5α-pregnane-3 : 11 : 20-trione (3 g.) was stirred with toluene-*p*-sulphonic acid (1·75 g.) and acetic anhydride (38 ml.) for 17 hr. The product was cooled to 0° and water (150 ml.) added. After the mixture had been stirred at 0° for 1 hr. and room temperature for 2½ hr., the solid was collected and twice crystallised from methanol, to yield the triacetate (1·77 g.), m. p. 175—181°, $[\alpha]_D$ +46°, identical with the specimen described above.

17α : 21-*Diacetoxy*-2-*bromo*-5α-*pregnane*-3 : 11 : 20-*trione* (VI; R = Ac).—(*a*) A 1·32N-solution of bromine in acetic acid (76 ml., 1·0 mol.) was added in one portion to a solution of the triacetate (XIII) (24 g.) in acetic acid (100 ml.) at room temperature. The colour disappeared almost immediately and the product crystallised. After a further 15 min., the solid (18 g.) was collected, washed with ether, dried, and recrystallised from acetone, to give the 2-*bromo-ketone* (VI; R = Ac) as colourless rhombs, m. p. 230—232° (decomp.), $[\alpha]_D$ +45°, $\nu_{max.}$ 1735 and 1232 (OAc), and 1710 cm.$^{-1}$ (CO) (Found: C, 57·3; H, 6·3; Br, 15·5. $C_{25}H_{33}O_7Br$ requires C, 57·2; H, 6·3; Br, 15·2%).

(*b*) *Bromination of* 17α : 21-*diacetoxy*-5α-*pregnane*-3 : 11 : 20-*trione* (V; R = Ac). The diacetate (V; R = Ac) (described below) was brominated in the same way as the triacetate (XIII), yielding 80% of the same 2-bromo-ketone (VI; R = Ac), m. p. 230—232° (decomp.), $[\alpha]_D$ +45°.

17α : 21-*Diacetoxy*-5α-*pregnane*-3 : 11 : 20-*trione* (VI; R = Ac).—(*a*) The 2-bromo-ketone (VI; R = Ac) (4 g.) was dehalogenated in acetone by excess of chromous chloride solution. Crystallisation of the product from acetone gave needles of the *diacetate* (V; R = Ac) (2·8 g.), m. p. 228—230°, $[\alpha]_D$ +32°, $\nu_{max.}$ 1732 and 1232 (OAc), and 1700 cm.$^{-1}$ (CO) (Found: C, 67·3; H, 7·7. $C_{25}H_{34}O_7$ requires C, 67·2; H, 7·7%).

(*b*) Concentrated hydrochloric acid (24 ml.) was added to a solution of the triacetate (XIII) (10 g.) in a mixture of chloroform (100 ml.), methanol (350 ml.), and water (35 ml.). After 20 hr. at room temperature, water was added, and the chloroform layer separated, washed with aqueous sodium hydrogen carbonate, then with water, and dried ($MgSO_4$). Evaporation gave a gum which was acetylated with acetic anhydride (60 ml.) and pyridine (100 ml.) at room temperature, and the diacetate (V; R = Ac) was crystallised from acetone. It (7 g.), had m. p. 228—230°, $[\alpha]_D$ +32°.

Alkaline Hydrolysis of the Triacetate (XIII) *and the Diacetate* (V; R = Ac).—The triacetate (1 g.) in methanol (100 ml.) was treated with aqueous 0·1N-sodium hydroxide (41 ml., 2 mol.) under nitrogen for 5 min. Water was added and the mixture extracted with methylene chloride. Evaporation of the solvent gave a product which, after acetylation with acetic anhydride (6 ml.) and pyridine (10 ml.) at room temperature, crystallised from ethyl acetate to give 21-acetoxy-17α-hydroxy-5α-pregnane-3 : 11 : 20-trione (V; R = H) (0·5 g.), m. p. 230°, $[\alpha]_D$ +100°. A similar product was obtained by use of 3 equivs. of alkali. The diacetate treated with one or two equivs. of alkali yielded the same product (V; R = H).

17α : 21-*Diacetoxy*-2 : 2-*dibromo*-5α-*pregnane*-3 : 11 : 20-*trione* (VII; R = Ac).—Bromine in acetic acid (1·15N; 24 ml., 1·3 mol.) was added in one portion to a solution of 17α : 21-diacetoxy-2-bromo-5α-pregnane-3 : 11 : 20-trione (VI; R = Ac) (5 g.) in acetic acid (750 ml.) containing potassium acetate (7·5 g.) and acetic anhydride (0·75 ml.). The solution was maintained at 85° for 1½ hr., by which time all the bromine had reacted. Water (4 l.) was added to the cooled solution; the precipitated solid, when dried and crystallised from methylene chloride–ether, yielded the 2 : 2-*dibromo-ketone* (VII; R = Ac) (3·79 g.), m. p. 153—155°, resolidified and melted 195—215° (decomp.), $[\alpha]_D$ +77° (Found: C, 49·7; H, 5·2; Br, 25·6. $C_{25}H_{32}O_7Br_2$ requires C, 49·7; H, 5·3; Br, 26·45%).

17α : 21-*Diacetoxy*-2 : 4-*dibromo*-5α-*pregnane*-3 : 11 : 20-*trione* (VIII; R = Ac).—(*a*) A solution of the 2 : 2-dibromo-ketone (VII; R = Ac) (2 g.) in dry alcohol-free chloroform (101 ml.) containing hydrogen bromide (1·37 g.) was set aside for 3 hours. The mixture was then washed with sodium hydrogen carbonate solution, and water, and the solvent removed under

reduced pressure to give the 2 : 4-*dibromo-ketone* (VIII; R = Ac) (1·99 g.), m. p. 185° (decomp.), $[\alpha]_D^{20}$ +26°, $\nu_{max.}$ 1732 and 1236 (OAc), and 1710 cm.$^{-1}$ (CO) (Found: C, 49·4; H, 5·1; Br, 25·8%).

(*b*) Bromine in dry alcohol-free chloroform (0·504N; 161 ml.) was added rapidly to a solution of the above triacetate (XIII) (20 g.) in chloroform containing hydrogen bromide (13·6 g.). Then more bromine in chloroform (0·504N; 161 ml.) was added during 0·5 hr. The solution was washed with water, aqueous sodium hydrogen carbonate, and water, dried ($MgSO_4$), and evaporated *in vacuo* at room temperature. Trituration of the residue with ether and the removal of the solvent *in vacuo* gave the 2 : 4-dibromo-compound (VIII; R = Ac), m. p. 180° (decomp.), $[\alpha]_D$ +27°, quantitatively.

17α : 21-*Diacetoxypregn*-4-*ene*-3 : 11 : 20-*trione* (*Cortisone Diacetate*) (XII; R = Ac).—Bromine (3·4 ml.) was added to acetone (250 ml.), and when the solution became colourless, sodium carbonate (10 g.) was added. The mixture was occasionally shaken for 30 min. and then filtered into sodium iodide (100 g.) in acetone (300 ml.). After the solution had been refluxed for 0·5 hr., the 2 : 4-dibromo-compound (VIII; R = Ac) (20 g.; crude from the previous experiment) was added and the mixture refluxed for 4½ hr. Oxalic acid (20 g.) was added and the mixture refluxed for a further ½ hr., diluted with ethyl acetate (1 l.), and filtered, and the organic layer in the filtrate was washed with water, saturated aqueous sodium hydrogen carbonate, and water. Acetic acid (5 ml.) and zinc dust (25 g.) were added and the solution was shaken until colourless. The zinc was filtered off and the filtrate washed with water, saturated aqueous sodium hydrogen carbonate and water, and dried. Evaporation gave a yellow solid (13·1 g.), $\lambda_{max.}$ 237·5 mμ ($E_{1\,cm.}^{1\%}$ 250). This product was refluxed with Girard reagent P (13·1 g.) and ethanol (300 ml.) containing acetic acid (30 ml.) for 0·5 hr., the solution cooled to room temperature, and 40% aqueous formaldehyde (50 ml.) added. After 0·5 hr. the mixture was poured into saturated aqueous sodium hydrogen carbonate (1560 ml.) and extracted with ethyl acetate (3 × 300 ml.). The solvent was evaporated from the combined ethyl acetate layers to yield a solid (5·2 g.), $\lambda_{max.}$ 246 mμ ($E_{1\,cm.}^{1\%}$ 70). The aqueous layer was acidified to pH 1 with concentrated hydrochloric acid, and after 3 hr. was extracted with ethyl acetate (2 × 250 ml.). The extract was washed as previously and evaporated, to yield a solid (7 g.), m. p. 207—214°, $\lambda_{max.}$ 238 mμ ($E_{1\,cm.}^{1\%}$ 345). Crystallisation from methanol gave cortisone diacetate (XII; R = Ac) (5·3 g.) as colourless thick needles, m. p. 218—220°, $[\alpha]_D$ +128°, $\lambda_{max.}$ 238 mμ (ε 15,300), $\nu_{max.}$ 1735 and 1230 (OAc), 1707 (CO), 1664, 1616, and 864 cm.$^{-1}$ (αβ-unsaturated ketone) (Found: C, 67·7; H, 7·2. Calc. for $C_{25}H_{32}O_7$: C, 67·55; H, 7·3%). Huang-Minlon *et al.*[15b] give m. p. 221—222°, $[\alpha]_D^{23}$ +133°, $\lambda_{max.}$ 238 mμ (log ε 4·2 in MeOH). Moffett and Anderson [28] give m. p. 216·5—218°.

Conversion of Cortisone Diacetate (XII; R = Ac) *into Cortisone Acetate* (XII; R = H).—A N-solution of sodium ethoxide in methanol (14 ml.) was added to cortisone diacetate (XII; R = Ac) (9·47 g.) in methanol (500 ml.). After 5 min. at room temperature, a few ml. of water were added and the alkali was neutralised with acetic acid. The mixture was concentrated *in vacuo*, diluted with water, and extracted with methylene chloride. The extract was washed with sodium hydrogen carbonate solution and water, and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue acetylated with pyridine (50 ml.) and acetic anhydride (30 ml.) at room temperature for 1 hr. Working up in the usual way gave crude cortisone acetate (XII; R = H) (7·5 g.), $[\alpha]_D$ +224°, m. p. 210—230°, $\lambda_{max.}$ 238 mμ ($E_{1\,cm.}^{1\%}$ 365). Crystallisation from methanol gave the pure compound, m. p. 236—240°, $[\alpha]_D$ +220°, $\lambda_{max.}$ 238 mμ (ε 14,900), identified with authentic material by its infrared spectrum.

4α-*Bromocholestan*-3-*one* (XV*a*).—A solution of 2 : 4-dibromocholestan-3-one (20 g.) in anhydrous alcohol-free chloroform (175 ml.) and acetic acid (370 ml.) was treated with 93% chromous acetate (20 g., 2·3 mol.). Vigorous stirring and an atmosphere of nitrogen were maintained throughout the experiment. After 30 min. water was added and the product (16·7 g.), $[\alpha]_D^{24}$ +13°, isolated by chloroform. Several crystallisations from methyl acetate gave 4α-*bromocholestan*-3-*one* (XV*a*) as rods (3·63 g.), m. p. 144—146°, $[\alpha]_D^{24}$ ±0°, $\lambda_{max.}$ 283 mμ (ε 25), $\nu_{max.}$ (in CS_2) 1730 cm.$^{-1}$ [minor peaks at 1168, 828, and 730 cm.$^{-1}$ distinguish the spectrum from that of the 2-bromo-isomer (XIV)] (Found: C, 69·3; H, 9·75; Br, 16·45. $C_{27}H_{45}OBr$ requires C, 69·6; H, 9·7; Br, 17·2%).

Cholest-4-*en*-3-*one*.—Powdered semicarbazide (322 mg., 2 mol.) was added to 4-bromocholestan-3-one (XV*a*) (1·0 g.) in alcohol-free chloroform (17 ml.) and *tert.*-butanol (30 ml.), and the mixture shaken under nitrogen for 30 min. The orange-yellow colour reached maximum intensity in 13 min., and then faded. The solvents were evaporated under reduced pressure

[28] Moffett and Anderson, *J. Amer. Chem. Soc.*, 1954, **76**, 747.

and the residue was triturated with ethanol (15 ml.) and water (10 ml.), and the solid filtered off and dried (0·9 g.). Crystallisation from ethanol–ethyl acetate gave 3-semicarbazonocholest-4-ene (0·63 g., 66%), m. p. 235—237° (decomp.), $[\alpha]_D^{25}$ +133°, $\lambda_{max.}$ 270 mμ (ε 26,400 in EtOH). The semicarbazone (0·59 g.) was decomposed according to Hershberg's method, giving cholest-4-en-3-one (0·27 g., 55%), m. p. 77—79°, $[\alpha]_D^{23}$ +87°, $\lambda_{max.}$ 242·5 mμ (ε 15,000), identity being confirmed by the infrared spectrum.

2α : 4α-*Dibromocholestan*-3-*one from* 4-*Bromocholestan*-3-*one* (XV*a*).—The 4-bromo-ketone (0·8 g.) in acetic acid (50 ml.) containing hydrogen bromide (6·8N in acetic acid; 0·25 ml., 1 mol.) was treated with a solution of bromine (0·325 g., 1·1 mol.) in acetic acid (3 ml.). After 10 min. the solution was diluted with water (400 ml.), and the solid collected, washed, and dried (0·95 g.). Recrystallisation from light petroleum (b. p. 60—80°) gave needles of 2α : 4α-dibromocholestan-3-one (0·48 g., 51%), m. p. 192—194°, $[\alpha]_D^{23}$ ±0°, identified by its infrared spectrum (Found: Br, 29·6. Calc. for $C_{27}H_{44}OBr_2$: Br, 29·3%).[29]

21-*Acetoxy*-4-*bromo*-17α-*hydroxy*-5α-*pregnane*-3 : 11 : 20-*trione* (XV*b*).—(*a*) 21-Acetoxy-2 : 4-dibromo-17α-hydroxy-5α-pregnane-3 : 11 : 20-trione (VIII; R = H) (10 g.) in acetone (50 ml.) and methanol (150 ml.) containing concentrated hydrochloric acid (5 ml.) was treated at −45°, under nitrogen, with 1·4N-chromous chloride (22·25 ml., 1·75 mol.) in 8 min. The mixture was allowed to warm to room temperature, and the product was precipitated with water and filtered off (8·75 g.). Several crystallisations from ethyl acetate gave rods of 21-*acetoxy*-4-*bromo*-17α-*hydroxy*-5α-*pregnane*-3 : 11 : 20-*trione* (XV*b*) as the *solvate* (2·21 g., 21%), m. p. 206—208° (decomp.), $[\alpha]_D^{22}$ +47° (*c* 1·26) (Found: C, 57·0; H, 6·9; Br, 14·0. $C_{23}H_{31}O_6Br,C_4H_8O_2$ requires C, 56·7; H, 6·9; Br, 14·0%). The solvent-free compound, obtained from benzene, had m. p. 204—206° (decomp.), $[\alpha]_D^{26}$ +56°, +42° (in acetone), $\lambda_{max.}$ 292 mμ (ε 122), $\nu_{max.}$ 1745 and 1234 (OAc), 1726 (20-CO) and 1708 cm.$^{-1}$ (CO) (Found: C, 57·35; H, 6·5; Br, 16·3. $C_{23}H_{31}O_6Br$ requires C, 57·15; H, 6·5; Br, 16·5%).

(*b*) The 2 : 4-dibromo-compound was prepared in solution in acetic acid from 4 : 5α-dihydrocortisone 21-acetate (40 g.) as described above. The solution from the bromination was used without further treatment. A stream of carbon dioxide was passed through it with stirring for 5 min., then 2·28N-chromous chloride (104·4 ml.) was added during 70 min. through a jet immersed in the liquid. The 4-bromo-compound (XV*b*) was precipitated by water, filtered off, and dried (43 g., 92%; $[\alpha]_D$ +74°) (Found: Br, 15·5%). The best yields of pure product were obtained when the bromine values lay between 15 and 16%. Crystallisation from aqueous acetic acid followed by ethyl acetate gave the 4-bromo-ketone (XV*b*) as the solvate (24·05 g.), $[\alpha]_D$ +51°. Identity with the pure material described above was established by the infrared spectrum.

Cortisone 21-*Acetate* (XII; R = H) *from the* 4-*Bromo-compound* (XV*b*).—The 4-bromo-compound (XV*b*) (23·5 g.; ethyl acetate solvate; prepared as in the last experiment) in *tert.*-butanol (395 ml.) and alcohol-free chloroform (198 ml.) was added to a suspension of finely powdered semicarbazide (7·5 g.) in similar quantities of the two solvents. An atmosphere of carbon dioxide was maintained and the mixture set aside for 1½ hr., being shaken occasionally. The solvents were removed under reduced pressure and the residue was triturated with hot ethanol (535 ml.) to which water (1·5 l.) was then added. The solid was filtered off, washed, and taken up in hot acetic acid (640 ml.). 50—60% Aqueous pyruvic acid (10·6 ml.) in water (200 ml.) was added and the solution kept overnight at room temperature, then warmed to 60° for 30 min. The product, isolated by chloroform, was cortisone 21-acetate (16·15 g., 98%), m. p. 225—227°, $[\alpha]_D$ +213°, $\lambda_{max.}$ 237 mμ (ε 14,400). Crystallisation from acetone gave needles (desolvated at 100—120°/0·2 mm.) (13·64 g., 84·3%), m. p. 238—240°, $[\alpha]_D$ +219°, $\lambda_{max.}$ 237 mμ (ε 14,700).

Cortisone 21-*Acetate from the Crude Mixture of* 2- *and* 4-*Bromo-compounds.*—(a) *Replacement of the* 2-*bromine atom by iodine.* 21-Acetoxy-2-bromo-17α-hydroxypregnane-3 : 11 : 20-trione (1 g.) in acetone (30 ml.) containing sodium iodide (1·3 g.) was refluxed for 7 hr. under nitrogen. Isolation, treatment with dilute sodium thiosulphate solution, and crystallisation from methanol gave the iodo-trione (XVIII*b*) (0·62 g.), m. p. 191° (decomp.), $[\alpha]_D^{20}$ +107°, $\lambda_{max.}$ 252 mμ (ε 1010), giving all the usual infrared bands for the functional groups (Found: I, 20·5. Calc. for $C_{23}H_{31}O_6I,CH_3{\cdot}OH$: I, 22·6%).

(b) *Stability of the* 4-*bromine atom to the above conditions.* The 4-bromo-compound (XV*b*), m. p. 181° (decomp.), $[\alpha]_D$ +61° (Found: Br, 16·3%) (0·3 g.), in acetone (7 ml.) containing

[29] Ruzicka, Bossard, Fischer, and Wirz, *Helv. Chim. Acta*, 1936, **19**, 1151; Butenandt, Schramm, Wolff, and Kudszus, *Ber.*, 1936, **69**, 2779; Inhoffen, *Ber.*, 1937, **70**, 1695; Wilds and Djerassi, *J. Amer. Chem. Soc.*, 1946, **68**, 1712; Djerassi and Scholz, *ibid.*, 1948, **70**, 417.

sodium iodide (0·3 g.) was refluxed for 1 hr. No sodium bromide separated when the solution was cooled, and the product was precipitated, by the addition of dilute sodium thiosulphate solution, as a white powder (0·30 g.), m. p. 180—181° (decomp.), $[\alpha]_D$ +61°; no appreciable ultraviolet absorption (Found : Br, 14·7%).

(c) *Application of the above conditions to the mixture.* The mixture of the 2- and 4-bromosteroids (3 g.; $[\alpha]_D$ +76°; Br, 17·5%) from the chromous chloride reduction of the 2 : 4-dibromo-compound (VII; R = H), was refluxed with sodium iodide (3 g.) in acetone (60 ml.) for 1 hr. and then the whole was poured into 1% sodium thiosulphate solution. The precipitate was filtered off and treated in acetone (160 ml.) with 0·7N-titanous chloride (30 ml.) for 15 min. Dilution and extraction with chloroform gave an iodine-free product (2·71 g.) (Found : Br, 9·0%). This material (2·61 g.) in chloroform (50 ml.) and *tert.*-butanol (65 ml.) was treated with semicarbazide base (0·7 g.) under carbon dioxide for 15 min. at room temperature. The solvent was removed under reduced pressure and the residue triturated with ethyl alcohol (35 ml.) and water (25 ml.). The solid was filtered off and treated with 1·0N-pyruvic acid (9 ml.) in acetic acid (55 ml.) and water (18 ml.) at 60°. The solution was then kept at room temperature for 18 hr. Dilution with water and extraction gave crude cortisone acetate (1·92 g.), $\lambda_{max.}$ 238 mμ ($E^{1\%}_{1cm.}$ 220), which was subjected to the separation by Girard P reagent as already described. The 4 : 5α-dihydrocortisone acetate fraction gave 0·8 g., $\lambda_{max.}$ 239 mμ (ε 920). The cortisone acetate fraction gave 1·0 g., $\lambda_{max.}$ 238 mμ (ε 14,100), which yielded on crystallisation from ethyl acetate 0·835 g., m. p. 240—242°, $[\alpha]_D$ +216°, $\lambda_{max.}$ 237 mμ (ε 14,200), identified by its infrared spectrum.

21-*Acetoxy*-2 : 4-*dibromo*-17α-*hydroxy*-5α-*pregnane*-3 : 11 : 20-*trione* (VIII; R = H) *from the* 4-*Bromo-ketone* (XV*b*).—The 4-bromo-compound (XV*b*) (7 g.) in acetic acid (205 ml.) containing hydrogen bromide (6·8N in acetic acid; 21·1 ml., 1 mol.) was treated with bromine (2·435 g., 1·05 mol.) in acetic acid (21 ml.). The product (8·98 g.) was isolated by methylene chloride and after crystallisation from ethyl acetate–*cyclo*hexane (3·5 + 3·5 ml.) yielded the 2 : 4-dibromo-compound (VIII; R = H) (6·48 g., 80%), m. p. 172—176° (decomp.), $[\alpha]_D^{22}$ +76° (Found : C, 48·8; H, 5·5; Br, 28·6%). After being kept in acetone containing lithium bromide for 18 hr. at room temperature this product gave a 2 : 4-dibromo-ketone (VIII; R = H), m. p. 165—173° (decomp.), $[\alpha]_D^{22}$ +83° (Found : C, 49·3; H, 5·5; Br, 28·3%). We attribute the differences between these two bromo-ketones to epimerism about the C–Br bonds.

4-*Bromo*-2-*iodocholestan*-3-*one* (XVI*a*).—4-Bromocholestan-3-one (XV*a*) (0·5 g.) in acetic acid (25 ml.) was treated at 75° with iodine monochloride (0·35 g., 2 mol.) in acetic acid (8 ml.). After 8 min. the product was precipitated with water at 0° and filtered off (0·55 g.). Crystallisation from aqueous acetone gave needles of 4-*bromo*-2-*iodocholestan*-3-*one* (XVI*a*) (0·32 g., 47%), m. p. 154—158° (decomp.), $[\alpha]_D^{23}$ −8°, $\lambda_{max.}$ 254 mμ (ε 810) (Found : 14·92 mg. gave 9·8 mg. of Ag halide. $C_{27}H_{44}OBrI$ requires 10·3 mg.).

Deiodination. 4-Bromo-2-iodocholestan-3-one (0·3 g.) in ether (10 ml.) and benzene (10 ml.) was shaken for 3 hr. with 10% aqueous sodium hydrogen sulphite solution (25 ml.). Separation and evaporation of the solvents gave a residue which on crystallisation from *n*-hexane gave rods of 4-bromocholestan-3-one (XV*a*) (0·11 g., 47%), m. p. 144—145°, $[\alpha]_D$ +1° (Found : Br, 16·95%). Identification was confirmed by the infrared spectrum.

Sodium iodide (2 g.) in ethyl methyl ketone (25 ml.) was added to 2 : 4-dibromocholestan-3-one (2 g.) in ethyl methyl ketone, and the solution kept at 20° for 30 min. Sodium bromide was precipitated and filtered off (Found : 370 mg. Calc. for 1 mol. : 380 mg.). Sodium thiosulphate solution was added until the free iodine was just removed and the product precipitated with water, yielding a solid (1·85 g.), $[\alpha]_D$ −5°, which crystallised from acetone as plates of bromoiodocholestan-3-ones (XVI*a* and XVII*a*), m. p. 174—176° (decomp.), $[\alpha]_D$ −16° (Found : Ag halide, 4·715 mg. from 6·553 mg. of steroid. Calc. for $C_{27}H_{44}OBrI$: Ag halide, 4·690 mg.).

This bromoiodo-ketone (0·561 g.) was shaken for 3 hr. in ether (10 ml.) and benzene (10 ml.) with 10% aqueous sodium hydrogen sulphite (25 ml.). The product, isolated in the usual manner, crystallised from *n*-hexane as rods (0·111 g.), m. p. 140—142° (decomp.), $[\alpha]_D^{23}$ +26° (Found : Br, 16·7%). The infrared spectrum showed bands due to both 2- and 4-bromocholestan-3-one.

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