25. *Compounds Related to the Steroid Hormones. Part XIV.*[1] $\Delta^{8(9)}$-11-*Oxo-steroids in the* 14α- *and* 14β-*Series.*

By S. Eardley, A. G. Long, and C. H. Robinson.

9α-Bromo-11-ketones have been made by acid-catalysed bromination of 11-keto-steroids and by oxidation of a 9α-bromo-11β-hydroxy-compound (V; R = Br). *N*-Bromosuccinimide brominates 11-ketones at the 9-position. Dehydrobromination of 9α-bromo-11-oxo-14α-steroids occurs with inversion at the 14-position, unless accumulation of hydrogen bromide is prevented. Correction of some discrepancies shows that $\Delta^{8(9)}$-11-oxo-compounds isomeric at the 14-position can be distinguished by their spectra and so related to steroids of proven stereochemistry. The ultraviolet absorption of the $\Delta^{8(9)}$-11-oxo-14β-steroids, $\lambda_{max.}$ ~247 mμ, agrees with prediction for this chromophore. Comment is made on interannular effects in ultraviolet absorption and optical rotation.

Yellow by-products accompany Δ^4- and $\Delta^{1,4}$-3-ketones manufactured by bromination and dehydrobromination of 3,11-dioxo-5α-steroids.[2] Their infrared absorption and high dextrorotation hint at the presence of the $\Delta^{8(9)}$-11-oxo-chromophore, which could originate in bromination at the 9-position, with subsequent dehydrobromination;[3] moreover, 8,9-dehydrocortisone acetate (VIIIa) has been described as a yellow compound, although the colour is hard to explain.[4]

We have studied the preparation and dehydrobromination of certain 9-bromo-11-ketones. Acid-catalysed bromination of 11-oxo-5α-steroids is satisfactory in acetic acid (in which, however, esterification of 3β-hydroxy-groups may occur)[3] or dioxan;[5] also, *N*-bromosuccinimide (in solvents such as benzene or carbon tetrachloride) halogenates such compounds at the 9-position. By these methods we have made the following monobromo-compounds from the corresponding 11-ketones: 3β-acetoxy-9α-bromo-5α-ergostan-11-one (I; R = Ac, R^1 = Br, $R^2 = C_9H_{19}$); 3β,21-diacetoxy-9α-bromo-17α-hydroxy-5α-pregnane-11,20-dione (XII; R = R^2 = Ac, R^1 = Br); and 21-acetoxy-3β,17-dihydroxy-5α-pregnane-11,20-dione (XII; R = H, R^1 = Br, R^2 = OAc). Bromination at the 9-position is accompanied, in agreement with precedent,[3] by an increase in dextrorotation (ΔM_D ~ +550°).

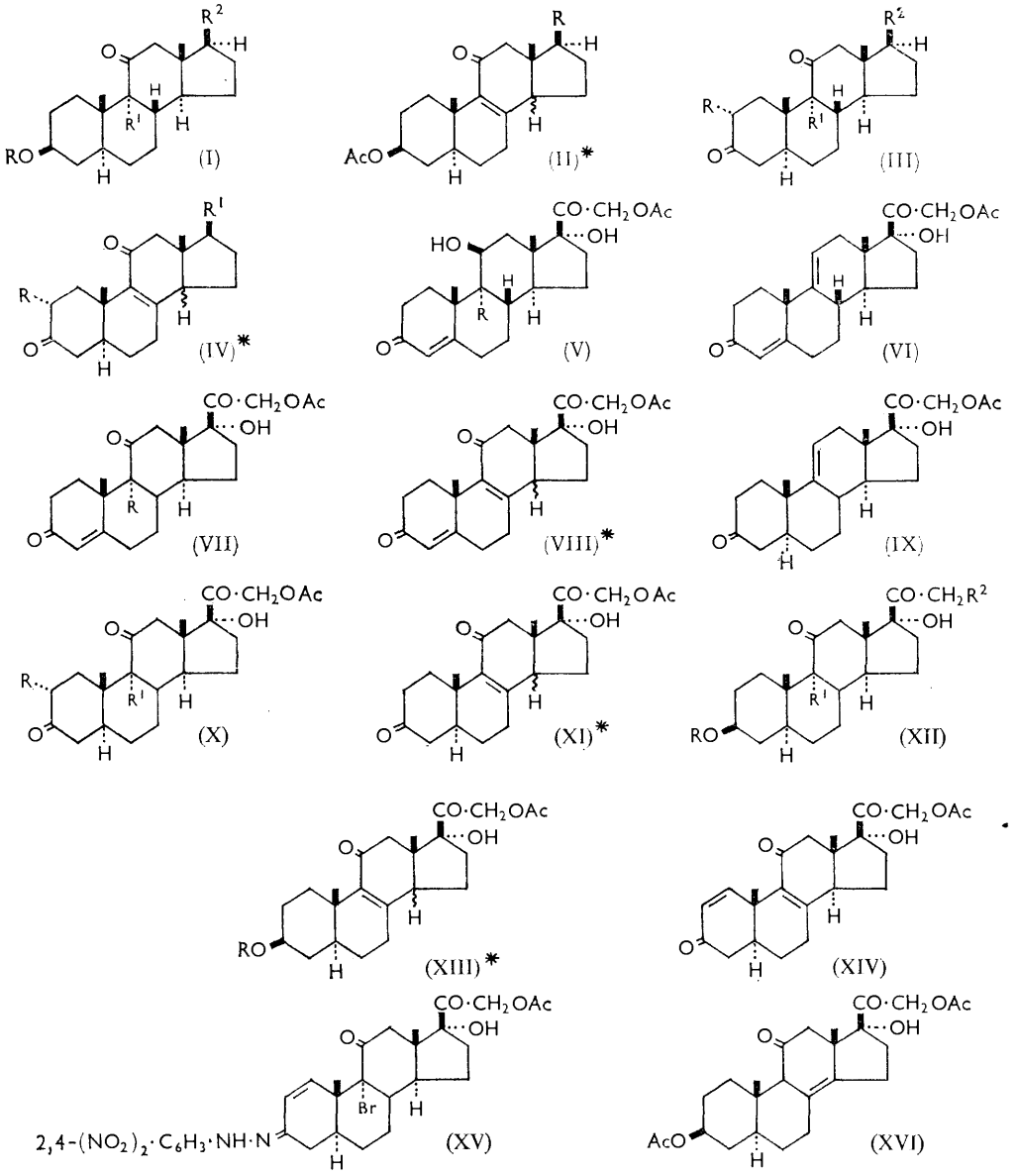
Acid-catalysed dibromination of 3β-formyloxy-17-hydroxy-5α-pregnane-11,20-dione (XII; R = CHO, R^1 = R^2 = H) gave a product which could not be purified. Treatment with potassium acetate and then with aqueous acetic acid converted it into 21-acetoxy-9α-bromo-3β,17-dihydroxy-5α-pregnane-11,20-dione (XII; R = H, R^1 = Br, R^2 = OAc), identical with the compound mentioned in the preceding paragraph. Oxidation of this product yielded the 3,11,20-trione (X; R = H, R^1 = Br). The rotations of solutions of this bromo-trione in acetic acid containing hydrogen bromide decreased with time, probably because of a process of debromination and promiscuous rebromination;[6] nonetheless, bromine (1 equivalent), in this solvent or in dioxan, halogenated the compound to the 2α,9α-dibromo-3,11,20-trione (X; R = R^1 = Br), whose structure is upheld by interpretation of the physical properites and by dehydrohalogenation (see below). Solutions of this 2,9-dibromo-ketone mutarotated when hydrogen bromide was present.

Acid-catalysed halogenation of 3,11-dioxo-5α-steroids results, in most examples,[2,5] in products in which disubstitution in ring A has taken precedence over halogenation in ring C. Bromination of 3,11-dioxobisnor-5α-cholanic acid (III; R = R^1 = H, R^2 = CH(Me)·CO_2H)

[1] Part XIII, preceding Paper.
[2] Evans, Hamlet, Jones, Long, Oughton, Stephenson, Walker, and Wilson, *J.*, 1956, 4356.
[3] Henbest, Jones, Wagland, and Wrigley, *J.*, 1955, 2477; Glaxo Laboratories Ltd., B.P. 794,335.
[4] Wendler, Graber, Snoddy, and Bollinger, *J. Amer. Chem. Soc.*, 1957, **79**, 4476.
[5] Cf. Evans, Green, Hunt, Long, Mooney, and Phillipps, *J.*, 1958, 1529.
[6] Crowne, Evans, Green, and Long, *J.*, 1956, 4351.

was exceptional, for it yielded a 2α,9α-dibromo-acid (III; R = R^1 = Br, R^2 = $CH(Me)\cdot CO_2H$).

The infrared spectra of the 2,9-dibromo-3,11-diones indicate the presence of one



* The suffixes a and b in the text denote 14α- and 14β-configurations, respectively.

equatorial bromine atom next to a carbonyl group,[7] and the compounds have high dextrorotation. These facts agree with the dextrorotatory increments associated [8] with the 2α-bromo-(equatorial) and 9α-bromo-substituents (axial), the former slight, the latter large; the effects of other configurations—the 2β-bromo (axial) is strongly dextrorotatory

[7] Jones, Ramsay, Herling, and Dobriner, *J. Amer. Chem. Soc.*, 1952, **74**, 2828.
[8] Carrington, Eardley, Elks, Green, Gregory, Long, and Sly, *J.*, 1961, 4560; see also refs. 2 and 3.

and the 4α- (equatorial) and 4β-bromo (axial) are lævorotatory—make other combinations unlikely, especially as the results of dehydrobromination limit the sites of substitution to the 2- and 9-positions (see below).

In spite of indications [9] of the ease of attack at the 2-position in 5α-cholestan-3-one, *N*-bromosuccinimide halogenated 4,5-dihydrocortisone acetate mainly at the 9-position, giving a product rich in the 9-bromo-3,11,20-trione (X; R = H, R^1 = Br) described above.

9-Bromo-3,11,20-trioxo-Δ^4-steroids must be prepared from the corresponding 9,11-bromohydrins. 21-Acetoxy-17-hydroxypregna-4,9(11)-diene-3,20-dione (VI) was made from cortisol acetate (V; R = H), best by treatment [1,10-12] with thionyl chloride and pyridine at −10°. A by-product was converted by sodium pyrosulphite into a water-soluble derivative,[13] and so removed. 4,5-Dihydrocortisol acetate is converted efficiently by hydrogen bromide or lithium bromide in acetic acid [14] into the corresponding $\Delta^{9(11)}$-compound (IX), but this facility does not extend to the transformation of cortisol acetate. We treated the 3,20-dione (VI) with *N*-bromoacetamide and perchloric acid [15] to get the bromohydrin (V; R = Br), whose oxidation with chromic oxide in pyridine [16] was slow and inefficient. Acidified potassium dichromate in acetone [17] offered a better means for obtaining the 9-bromo-3,11-diketone (VII; R = Br), although the reaction was still sluggish.

Dehydrobromination of this compound has been reported by two groups,[3,4,15] with minor discrepancies. With basic agents (such as pyridine, collidine, and dimethylacetamide with calcium carbonate [13]) we expected to get the 4,9-diene (VIIIa) with the 14α-configuration: our products had the properties quoted for this compound, and they were yellow, a property mentioned before,[4] but paper chromatography showed such specimens to be impure, and we were able to extract the yellow contaminants with aqueous sodium hydroxide, in which they gave red solutions. These contaminants were optically active, and their infrared spectra bore witness to their steroidal nature, but we did not examine them further. Chromatography of the neutral material on charcoal yielded a white specimen of the pure 3,11-dione (VIIIa), $\lambda_{max.}$ 234—236 mμ.

Dehydrobromination of the bromo-trione (VII; R = Br) with lithium chloride in *N*,*N*-dimethylformamide gave the pure 14β-diene-dione (VIIIb), $\lambda_{max.}$ 235—237 mμ, similar to that described by Wendler's group.[4] The ultraviolet spectra of these isomers betrayed interaction between the Δ^4-3-oxo- ($\lambda_{max.}$ ~238 mμ) and $\Delta^{8(9)}$-11-oxo-chromophores ($\lambda_{max.}$ ~254 mμ).[18]

Calcium carbonate in dimethylacetamide converted 3β-acetoxy-9α-bromo-5α-ergostan-11-one (I; R = Ac, R^1 = Br, R^2 = C_9H_{19}) into the 14α-$\Delta^{8(9)}$-11-ketone (IIa; R = C_9H_{19}), $\lambda_{max.}$ 253·5 mμ; with pyridine or collidine as dehydrobrominating agent we obtained mixtures, $\lambda_{max.}$ 253 mμ. Sodium iodide in acetone [19] caused some dehalogenation, but also gave unsaturated ketones, $\lambda_{max.}$ 253 mμ. On the other hand, treatment with dimethylformamide (with or without lithium chloride) gave the 14β-isomer (IIb; R = C_9H_{19}), $\lambda_{max.}$ 248 mμ, which was also obtained by treating the compound (IIa; R = C_9H_{19}), $\lambda_{max.}$ 253·5 mμ, with hydrogen chloride in chloroform.[4]

[9] Djerassi and Scholz, *Experientia*, 1947, **3**, 107.
[10] (*a*) Graber, Haven, and Wendler, *J. Amer. Chem. Soc.*, 1953, **75**, 4722; (*b*) Bernstein *et al.*, *ibid.*, p. 4860, 1955, **77**, 1028; (*c*) Rosenkranz, Mancera, and Sondheimer, *ibid.*, 1954, **76**, 2227; (*d*) Chamberlin, Tristram, Utne, and Chemerda, *J. Org. Chem.*, 1960, **25**, 295; (*e*) Upjohn Co., B.P. 790,452.
[11] Bladon, Henbest, Jones, Lovell, Wood, Woods, Elks, Evans, Hathway, Oughton, and Thomas, *J.*, 1953, 2921.
[12] Eardley and Long, *J.*, 1965, 130; Eardley, Green, and Long, preceding Paper.
[13] Green and Long, *J.*, 1961, 2532.
[14] Olin Mathieson Chem. Corp., U.S.P. 2,842,568.
[15] Fried and Sabo, *J. Amer. Chem. Soc.*, 1957, **79**, 1130.
[16] Poos, Arth, Beyler, and Sarett, *J. Amer. Chem. Soc.*, 1953, **75**, 422.
[17] Brooks, Hunt, Long, and Mooney, *J.*, 1957, 1175.
[18] Cf. Dorfman, *Chem. Rev.*, 1953, **53**, 47.
[19] Rosenkranz, Mancera, Gatica, and Djerassi, *J. Amer. Chem. Soc.*, 1950, **72**, 4077

Similar experiments on 9α-bromo-4,5α-dihydrocortisone acetate (X; R = H, R^1 = Br) had a similar outcome: dehydrobromination in the presence of calcium carbonate resulted in the unepimerised enone (XIa), $\lambda_{max.}$ 255 mμ, whereas dimethylformamide with lithium chloride gave the 14β-isomer (XIb), $\lambda_{max.}$ 246 mμ. Treatment of the 14α-compound with hydrogen chloride in chloroform, or with dimethylformamide containing hydrogen bromide and lithium chloride, gave the 14β-epimer. Dimethylacetamide containing calcium carbonate converted 3β,21-diacetoxy-9α-bromo-17-hydroxy-5α-pregnane-11,20-dione (XII; R = R^2 = Ac, R^1 = Br) into the unepimerised $\Delta^{8(9)}$-11-ketone (XIIIa; R = Ac), treatment of which with hydrogen chloride in chloroform caused disappearance of its ultraviolet absorption.

The inversion 14α ⟶ 14β in the $\Delta^{8(9)}$-11-ketones is also catalysed by hydroxide ion;[20] it does not occur in dimethylformamide containing lithium chloride. Calcium carbonate is an apt inorganic base for dehydrobromination, since it removes hydrogen bromide without prompting base-catalysed inversion or rearrangement.[21] During epimerisation with hydrogen chloride in chloroform the ultraviolet absorption at ~255 mμ dwindles and a maximum subsequently develops at ~245 mμ; intermediate formation of the unconjugated $\Delta^{8(14)}$-11-ketone probably occurs.[4]

Action of calcium carbonate in dimethylacetamide on 2α,9α-dibromo-4,5α-dihydrocortisone acetate (X; R = R^1 = Br) yielded the $\Delta^{1,8(9)}$-3,11,20-trione (XIV), $\lambda_{max.}$ 226·5 mμ, in which the chromophore in ring A (normally $\lambda_{max.}$ ~228 mμ) dominates the ultraviolet absorption. In this instance as in the $\Delta^{4,8(9)}$-3,11-diones,[4] the absorption of the $\Delta^{8(9)}$-11-ketone is not merely submerged, for the optical density in the range 245—255 mμ is too weak to be an aggregate of the contributions due to the isolated chromophores.*

Interaction of groups in rings A and C is not uncommon:[22] for example, halogen substituents at the 9-position affect the ultraviolet absorption due to the Δ^4-3-oxo-system,[15] and the absorption of lanosta-1,8(9)-dien-3-one, $\lambda_{max.}$ 225 mμ, reveals a hypsochromic effect attributable to the 8,9-double bond.[23] Several crystallisations of the 1,8(9)-dien-3,11,20-trione (XIV) failed to free it from its yellowness.

Cine-elimination [8,13] in ring A during dehydrobromination of the 2,9-dibromide (X; R = R^1 = Br) may confuse deductions of structure. This objection may be set aside by consideration of the 2,4-dinitrophenylhydrazone, $\lambda_{max.}$ (chloroform) 381 mμ. Its ultraviolet absorption [24] befits a derivative of a Δ^1-3-ketone, and the absence of reaction at the 11-position and the retention of one bromine atom are in keeping with the suggested structure (XV).

The action of sodium iodide in acetone on 2α,9α-dibromo-3,11-dioxobisnor-5α-cholanic acid (III; R = R^1 = Br, R^2 = CH(Me)·CO_2H) generated iodine and 1·4 equivalents of sodium bromide. Dehalogenation of the product gave an acid, $\lambda_{max.}$ 253 mμ, which yielded a yellow 2,4-dinitrophenylhydrazone regarded, on the basis of its ultraviolet absorption, $\lambda_{max.}$ (chloroform) 363 mμ, as the derivative of a 3-oxo-group not conjugated with a double bond. These clues verify the following explanation of the reaction: the 2α-bromo-atom is replaced by iodine, with the precipitation of an equivalent amount of sodium bromide; dehydrobromination in ring C is complicated by the action of the liberated hydrogen bromide, which causes dehalogenation, with consequent production of iodine and sodium bromide. Evidence from other reactions suggests that hardly enough hydrogen halide

* Intramolecular effects in enolic forms may account for the anomalies.

[20] Cf. Djerassi and Thomas, *J. Amer. Chem. Soc.*, 1957, **79**, 3835; see also ref. 4.

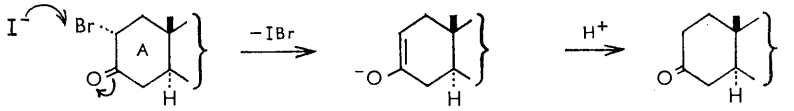
[21] (*a*) Cox, *J.*, 1960, 4508; (*b*) Tchoubar, *Bull. Soc. chim. France*, 1955, 1363; Fort, *J. Amer. Chem. Soc.*, 1962, **84**, 4979; House and Thompson, *J. Org. Chem.*, 1963, **28**, 164; Cookson and Nye, *Proc. Chem. Soc.*, 1963, 129; (*c*) Kane and Stevenson, *Tetrahedron*, 1961, **15**, 223; Shoppee and Johnson, *J.*, 1962, 1246; Chinoporos, *Chem. Rev.*, 1963, 235; (*d*) Arens, *Rec. Trav. chim.*, 1963, **82**, 183.

[22] Cf. Cookson and Wariyar, *J.*, 1956, 2302; Meinwald and Wiley, *J. Amer. Chem. Soc.*, 1957, **79**, 2569; Georgian, *Chem. and Ind.*, 1957, 1480.

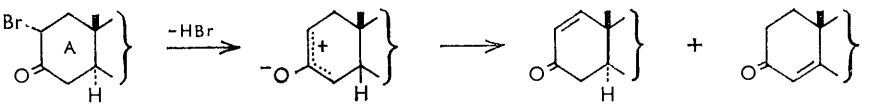
[23] Barton, Lewis, and McGhie, *J.*, 1957, 2907.

[24] Djerassi and Ryan, *J. Amer. Chem. Soc.*, 1947, **71**, 1000; see also ref. 18.

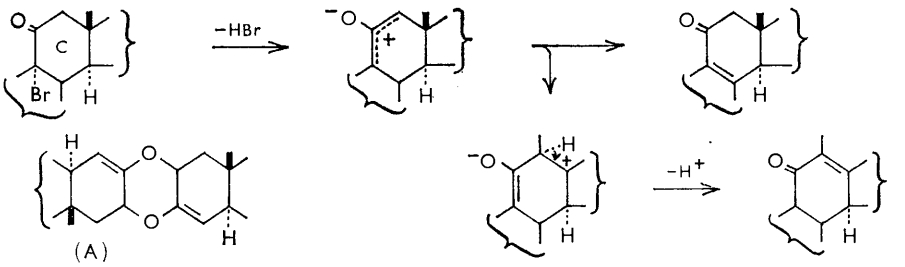
is free in such reactions to initiate epimerisation at the 14-position in the $\Delta^{8(9)}$-11-oxo-products. The occurrence of debromination, even when steps [2] are taken to remove hydrogen halides, suggests that nucleophilic attack on halogen may accompany dehydrobromination: [21d]



Dehydrohalogenation of α-halogeno-ketones may involve cyclopropanones or the equivalent betaines.[21b] Cine-eliminations in ring A can then be attributed to discharge of such intermediates in the two senses shown in the accompanying diagrams:



In the dehydrohalogenation of 9-halogeno-11-ketones opportunity arises for rearrangements of the type shown:



Presence of the consequent products would account for difficulty in freeing the $\Delta^{4,8(9)}$-11-ketones of impurities with strong ultraviolet absorption; acidic by-products may derive from intermediates common to these and to Faworsky reactions and, as diosphenols, from products such as (A) arising from α-oxo-carbenes.[21c] Further possibilities resemble those in the photolysis of αβ-unsaturated ketones.

Although $\Delta^{8(9)}$-11-oxo-steroids have already been exemplified in their 14α- and 14β-pairs, the effects of inversion at the 14-position still include anomalies. The ultraviolet absorption of 8(9)-dehydro-11-oxotigogenin [20,25] is reported to have the same maximum (252 mμ) for the 14α- (as the 3-propionate) and 14β-forms, and no difference was noted between the maxima of ethanolic solutions of the 14α- and 14β-epimers of 3β-acetoxy-ergosta-8(9),22-dien-7-one (II; R = C_9H_{17}), although the maxima of ethereal solutions were reported as 244 and 248 mμ, respectively.[26,27] Thanks to the good offices of Professors Djerassi and Henbest, we have been able to measure on our machine the absorption of their compounds: the properties of ethanolic solutions accorded with those of our other examples, inasmuch as the 14α- and 14β-epimers had $\lambda_{max.}$ 255 and 249 mμ, respectively.

In the infrared region, the band due to the $\Delta^{8(9)}$-11-oxo-chromophore falls about 10 cm.$^{-1}$ higher in the 14β-isomer, and we have confirmed that a band at 1050 cm.$^{-1}$ is peculiar to compounds in the 14α-series.[25] The nature of the C–D-ring fusion affects the

[25] Djerassi, Frick, Rosenkranz, and Sondheimer, *J. Amer. Chem. Soc.*, 1953, **75**, 3496.
[26] Laubach, Schreiber, Agnello, and Brunnings, *J. Amer. Chem. Soc.*, 1956, **78**, 4746.
[27] Bream, Eaton, and Henbest, *J.*, 1957, 1974.

infrared absorption due to 7- and 15-oxo-groups, and similar changes are associated with inversion at the 9-position in saturated 11-ketones and in $\Delta^{7(8)}$-11-ketones.[28]

Comparison of molecular rotations suffers from extra effects in pairs of epimers containing any but the simplest substituents, though certain compounds behave consistently: the change 14α ⟶ 14β had ΔM_D +41° in the ergostanones (II; R = C_9H_{19}) and +54° in the ergostenones (II; R = C_9H_{17}), and the comparison reveals a contribution ΔM_D −44° due to the 22,23-double bond, which agrees with analogous instances.[29] [There is a discrepancy in the rotations cited [26,27] for the 14β-enone (IIb; R = C_9H_{17}). We have chosen the value that suits our purpose the better.]

The relative stabilities of *cis*- and *trans*-fusions of rings C and D are sensitive to substituents in the steroid skeleton,[30] but infrared and ultraviolet spectra and optical rotations can now combine to relate the structures of new $\Delta^{8(9)}$-11-ketones to those of proven stereochemistry at the 14-position.[31] The maximum, ~247 mμ, of ethanolic solutions of the $\Delta^{8(9)}$-11-oxo-14β-steroids agrees with the calculated position of the maximum for this chromophore.[18] Earlier failures to differentiate the ultraviolet spectra of the epimers may indicate a photochemical equilibration, for we took care to make expeditious readings of the absorption.

Experimental

Unless other information is given, m. p.s were measured on a Kofler hot-stage apparatus; optical rotations are given for solutions in chloroform (*c* 0·5—1·5%), and infrared and ultraviolet spectra for solutions in bromoform and ethanol, respectively, all at 15—25°. Identity of specimens was confirmed by mixed m. p.s and infrared spectroscopy and, when possible, by paper chromatography. Paper chromatograms were run with solvent mixture L and fractions were traced by means of the TSTZ spray, as described before.[12] The alumina and Florisil used in this work have been described before.[12] Solvents for reactions involving *N*-bromosuccinimide were purified by refluxing them for 24 hr. in the presence of an excess of the reagent, filtration, washing with sodium hydrogen carbonate, drying, and distillation.

3β-Acetoxy-9α-bromo-5α-ergostan-11-one (I; R = Ac, R^1 = Br, R^2 = C_9H_{19}).—(*a*) 3β-Acetoxy-5α-ergostan-11-one (I; R = Ac, R^1 = H, R^2 = C_9H_{19}),[11] in carbon tetrachloride (100 ml.) containing *N*-bromosuccinimide (1·60 g.) and benzoyl peroxide (52 mg.), was heated at reflux for 0·5 hr. over a 300 w lamp. The cooled and filtered solution was washed successively with acidified potassium iodide, sodium pyrosulphite, sodium hydrogen carbonate, and water. Evaporation left a residue which was chromatographed on alumina; elution with hexane–benzene (1 : 1) yielded a solid (0·706 g., 48%) which crystallised from methanol as plates, m. p. 153—155°, identified with an authentic specimen [3] of the bromo-ketone, m. p. 155—157°.

Benzene could be used, less efficiently, as solvent for this bromination.

(*b*) A solution of the 11-ketone (I; R = Ac, R^1 = H, R^2 = C_9H_{19}) (2·29 g.) in dioxan (50 ml.) was treated with 6N-hydrogen bromide in acetic acid (0·3 ml.) and then with bromine (0·840 g.) in alcohol-free chloroform (6·67 ml.), added quickly with shaking. After 1·5 hr. at room temperature the bromine colour had disappeared. Water was added to precipitate the steroid, which was extracted into chloroform and washed therein. Evaporation, and two crystallisations of the residue from chloroform–methanol, gave the 9-bromo-11-ketone (1·69 g., 63%) as plates, m. p. 157—160°, $[\alpha]_D$ +130° identified with other specimens of this compound.[3]

3β-Acetoxy-5α-ergost-8(9)-en-11-one (IIa; R = C_9H_{19}).—The 9α-bromo-11-ketone (I; R = Ac, R^1 = Br, R^2 = C_9H_{19}) (0·50 g.) was dehydrobrominated for 20 min. with calcium carbonate (0·25 g.) in refluxing *NN*-dimethylacetamide (16 ml.).[13] Segregation with ethyl acetate gave, after evaporation of the solvent, a solid, $\lambda_{max.}$ 254 mμ (ε 6800). Crystallisation from methanol gave the $\Delta^{8(9)}$-11-ketone as needles (0·278 g.), m. p. 130—134°, $[\alpha]_D$ +109° (*c* 1·54%). Recrystallisations twice from methanol gave needles (90 mg.), m. p. 137—139°, $[\alpha]_D$ +117°, $\lambda_{max.}$ 253 mμ (ε 7000), $\nu_{max.}$ (CS_2) 1735 and 1240 (OAc), and 1662 and 902 cm.$^{-1}$ ($\Delta^{8(9)}$-11-ketone) {lit.,[11] m. p. 140°, $[\alpha]_D$ +119°, $\lambda_{max.}$ 254 mμ (ε 9000)}.

[28] Elks, Evans, Robinson, Thomas, and Wyman, *J.*, 1953, 2933; Barton and Laws, *J.*, 1954, 52.
[29] Examples taken from Mathieu and Petit, " Pouvoir Rotatoire Naturel, I. Stéroïdes," Masson et Cie., Paris, 1956.
[30] See Dreiding, *Chem. and Ind.*, 1954, 992.
[31] Djerassi *et al.*, *J. Amer. Chem. Soc.*, 1956, **78**, 4401, 4746.

Dehydrohalogenations in refluxing collidine or pyridine [3] (2 hr. each) yielded the same product, but less efficiently.

This ketone was recovered after heating it at 94° for 2 hr. under nitrogen in *NN*-dimethylformamide containing lithium chloride.[32]

Action of Sodium Iodide in Acetone on the 9α-*Bromo-ketone* (I; R = Ac, R^1 = Br, R^2 = C_9H_{19}).—A solution of the bromo-ketone (0·107 g.) and sodium iodide (0·560 g.) in acetone (10 ml.) was refluxed for 56 hr., samples being removed from time to time for measurements of ultraviolet absorption, with these results [time (hr.), $\lambda_{max.}$ (mμ), $E^{1\%}_{1\,cm.}$]: 24, 251, 80; 31, 252·5, 124; 56, 253, 98. Crystallisation from methanol of material extracted into ether gave needles (30 mg.), m. p. 134—136°, $[\alpha]_D$ +68° $\lambda_{max.}$ 252 mμ ($E^{1\%}_{1\,cm.}$ 38). In a similar experiment, except that bromoacetone was added,[2] the spectroscopic results were: 5·5, 248, 89; 22, 249—252, 112; 24, 252, 117. The product was isolated in ethyl acetate and treated therein for 10 min. with zinc and acetic acid. Filtration, evaporation, and crystallisation of the residue from methanol gave needles, m. p. 125—137°, $[\alpha]_D$ +120°, $\lambda_{max.}$ 253 mμ ($E^{1\%}_{1\,cm.}$ 146) of the nearly pure 14α-isomer (IIa; R = C_9H_{19}).

3β-*Acetoxy*-5α,14β-*ergost*-8(9)-*en*-11-*one* (IIb; R = C_9H_{19}).—(*a*) The 9α-bromo-ketone (I; R = Ac, R^1 = Br, R^2 = C_9H_{19}) (0·537 g.) was dehydrobrominated for 2 hr. at 94° under nitrogen with *NN*-dimethylformamide (7 ml.) containing lithium chloride (0·127 g.).[32] The product (0·45 g.) was segregated in ether. Rubbing with ethanol and chilling yielded a solid (0·14 g.), m. p. 77—82°, which gave the $\Delta^{8(9)}$-11-*oxo*-14β-*steroid*, plates (81 mg.), m. p. 82—85° (from aqueous ethanol), $[\alpha]_D$ +126°, $\lambda_{max.}$ 249 mμ (ε 8400), $\nu_{max.}$ (CS_2) 1735 and 1240 (OAc), and 1672 and 900 cm.$^{-1}$ ($\Delta^{8(9)}$-11-ketone) (Found: C, 78·5; H, 10·7. $C_{30}H_{48}O_3$ requires C, 78·9; H, 10·6%).

Material heated with refluxing aqueous ethanolic alkali, with subsequent acetylation, was identified with the starting material (IIb; R = C_9H_{19}), $\lambda_{max.}$ 248 mμ.

(*b*) The bromo-ketone (I; R = Ac, R^1 = Br, R^2 = C_9H_{19}) (90 mg.) was heated for 2 hr. under nitrogen in refluxing *NN*-dimethylformamide (7 ml.). Extraction with ether, washing with 2N-hydrochloric acid, and evaporation of the ether gave an oil (74 mg.). By chromatography on Florisil a fraction (59 mg.) was eluted with hexane–benzene (2 : 3), part (34 mg.) of which gave, from aqueous methanol, crystals (18 mg., 23%), m. p. 72—77°, $\lambda_{max.}$ 249 mμ (ε 6400), identified with an authentic specimen of 3β-acetoxy-5α,14β-ergost-8(9)-en-11-one (IIb; R = C_9H_{19}).

(*c*) Hydrogen chloride was passed (2 bubbles per sec.) for 10 hr. through a solution of the $\Delta^{8(9)}$-11-ketone (IIa; R = C_9H_{19}) (0·20 g.) in alcohol-free chloroform (30 ml.) at 0°. The product was diluted with chloroform and washed with water; evaporation yielded an oil that gave, by elution from Florisil with hexane–benzene (2 : 3), an oil (84 mg.) that solidified when triturated with methanol. Crystallisation from aqueous methanol furnished the $\Delta^{8(9)}$-11-oxo-14β-steroid (IIb; R = C_9H_{19}) as plates, m. p. 80—83°, $[\alpha]_D$ +124°, identified with authentic material.

(*d*) A solution of the $\Delta^{8(9)}$-11-ketone (IIa; R = C_9H_{19}) (0·172 g.) in 5% methanolic potassium hydroxide (15 ml.) was refluxed for 2 hr. The cooled solution was poured into water and the product was extracted into ether, in which it was washed with water. Evaporation of the ether, acetylation (with pyridine and acetic anhydride, overnight at room temperature), and chromatography on Florisil (8 g.) yielded a fraction (0·108 g., 63%), eluted with hexane–benzene (3 : 7), which gave the pure $\Delta^{8(9)}$-11-oxo-14β-steroid, m. p. 80—83° (from aqueous methanol), $[\alpha]_D$ +122° (*c* 0·4%), $\lambda_{max.}$ 248·5 mμ (ε 7800), identified with authentic material.

3β-*Formyloxy*-17-*hydroxy*-5α-*pregnane*-11,20-*dione* (XII; R = CHO, R^1 = R^2 = H).—A suspension of the dihydroxy-diketone (XII; R = R^1 = R^2 = H) (5·0 g.) in benzene (250 ml.) and 98% formic acid (50 ml.) was heated so that a distillate (150 ml.) collected in 2 hr. Benzene (200 ml.) was added and the distillation continued to remove all the formic acid. The mixture was evaporated *in vacuo* to dryness, and the product crystallised from benzene, giving the *formate* (XII; R = CHO, R^1 = R^2 = H) as heavy plates (4·3 g.) (two crops), m. p. 207—211°, $[\alpha]_D$ +15° (*c* 2·5%), $\nu_{max.}$ (Nujol) 3450 (OH), 1710 and 1174 (formate), and 1695 cm.$^{-1}$ (ketone) (Found: C, 70·55; H, 8·4. $C_{22}H_{32}O_5$ requires C, 70·2; H, 8·5%). We owe our thanks to Dr. J. Elks and Mr. B. Mooney for allowing us to publish the results of this and the next experiment.

[32] Holysz, *J. Amer. Chem. Soc.*, 1953, **75**, 4432.

9α,21-*Dibromo*-3β-*formyloxy*-17-*hydroxy*-5α-*pregnane*-11,20-*dione* (XII; R = CHO, R^1 = R^2 = Br).—The formate (XII; R = CHO, R^1 = R^2 = H) (15 g.) was brominated in acetic acid (800 ml.) with bromine (12·8 g.) in acetic acid (50 ml.). The colour disappeared in 1·5 hr. Addition of water precipitated the *bromo-ketone* (XII; R = CHO, R^1 = R^2 = Br) (21 g.), m. p. 193—194° (from hexane–chloroform), $[\alpha]_D$ +154°, $\nu_{max.}$ (Nujol) 3440 (OH), 1704 and 1212 (formate), and 1725 and 1690 cm.$^{-1}$ (ketones) (Found: Br, 30·4. $C_{22}H_{30}Br_2O_5$ requires Br, 30·0%).

21-*Acetoxy*-9α-*bromo*-3β,17-*dihydroxy*-5α-*pregnane*-11,20-*dione* (XII; R = H, R^1 = Br, R^2 = OAc).—(*a*) The 21-acetoxy-3,17-diol (XII; R = R^1 = Br, R^2 = OAc) (4·87 g.), R_F 0·30, in dioxan (140 ml.) and ethanol-free chloroform (45 ml.) was treated at room temperature with 6N-hydrogen bromide in acetic acid (3 drops) and then with bromine (2·02 g.) in ethanol-free chloroform (14·9 ml.), added quickly; the solution was left to stand for 45 min. Addition of water and extraction of the precipitated steroid with chloroform, with subsequent evaporation, gave a solid which yielded the 9-*bromo-diketone* as needles (2·60 g., 45%), m. p. 178—186° (decomp., with sintering above 140°) (from acetone–methanol), $[\alpha]_D$ +195° R_F 0·45, $\nu_{max.}$ 3620 (OH), 1744 and 1230 (21-OAc), 1726 (20-ketone), and 1706 cm.$^{-1}$ (11-ketone) (Found: C, 56·7; H, 6·8; Br, 16·3. $C_{23}H_{33}BrO_6$ requires C, 56·9; H, 6·85; Br, 16·5%). Prolonged drying was necessary to free the crystals from solvent.

Bromination of the dihydroxy-dione (XII; R = R^1 = H, R^2 = OAc) (0·408 g.) with *N*-bromosuccinimide (0·356 g.) and benzoyl peroxide (50 mg.) in benzene (100 ml.) gave, after chromatography on Florisil (40 g.), a solid (0·205 g.) that separated from methanol as felted needles,[3] m. p. 190—193° (decomp.), $[\alpha]_D$ +155° (*c* 0·42%) (Found: Br, 16·6%). Later preparations (see above) showed that this was not a pure compound.

(*b*) The crude dibromo-dione (XII; R = CHO, R^1 = R^2 = Br) was refluxed for 1 hr. in acetone (270 ml.) containing freshly dried potassium acetate (16 g.). Filtration, evaporation of the filtrate, and dilution of the concentrate with water gave a precipitate that was dissolved, without drying, in hot acetic acid (200 ml.). Water (100 ml.) was added and the mixture heated for 1 hr. on a steam-bath. The solution was poured into brine and the precipitate washed with sodium hydrogen carbonate and water. A solution of this material and Girard's reagent P (1·5 g.) in methanol (106 ml.) and acetic acid (2 ml.) was refluxed for 45 min. The solution was stored overnight in the refrigerator; solvated crystals of the 9-bromo-ketone separated (3·55 g.), m. p. 158—161° (decomp., after softening), $[\alpha]_D$ +170° (Found: Br, 15·3. $C_{23}H_{33}BrO_6$ requires Br, 15·4%).

3β,21-*Diacetoxy*-9α-*bromo*-17-*hydroxy*-5α-*pregnane*-11,20-*dione* (XII; R = Ac, R^1 = Br, R^2 = OAc).—(*a*) The 3,21-diacetate (XII; R = Ac, R^1 = H, R^2 = OAc) (0·448 g.),[12] R_F 0·85, in benzene (50 ml.) containing *N*-bromosuccinimide (0·534 g.) and benzoyl peroxide (50 mg.) was heated at reflux for 0·5 hr. over a 300W lamp. The filtered solution was evaporated to dryness and the residue crystallised from ethyl acetate to give needles, m. p. 194—200° (Found: Br, 6·6%). As bromination was incomplete, crystals and mother-liquors were combined, the mixture evaporated to dryness, and rebrominated for 2 hr. in the manner described above. The resultant yellow oil was chromatographed on Florisil (15 g.). Hexane–benzene (4 : 1) eluted a solid that was crystallised twice from ethyl acetate to furnish the 9α-*bromo-ketone* (60 mg.), m. p. 204—208° (decomp.), $[\alpha]_D$ +159°, R_F 0·90, $\nu_{max.}$ 3620 (OH), 1740 and 1230 (21-OAc), 1720 (20-ketone), and 1705 cm.$^{-1}$ (11-ketone) (Found: C, 57·2; H, 6·7; Br, 15·2. $C_{25}H_{35}BrO_7$ requires C, 56·85; H, 6·7; Br, 15·15%). This compound was identified with a specimen, m. p. 194—196°, $[\alpha]_D$ +160°, provided by Professor Henbest.

(*b*) A solution of the 21-acetoxy-3,17-diol (XII; R = R^1 = H, R^2 = OAc) (1·224 g.) in acetic acid (100 ml.) was treated with 6N-hydrogen bromide in acetic acid (1 ml.) and then with bromine (0·48 g.) in acetic acid (5·4 ml.). The solution was swirled for 5 min. at room temperature; the colour disappeared in this time. After a further hour the steroid was precipitated by the addition of water, and isolated and washed in ether. Evaporation left a solid (1·46 g.), $[\alpha]_D$ +167°. Four crystallisations from methanol–ethyl acetate gave the bromo-compound as needles (0·30 g.), m. p. 201—204°, $[\alpha]_D$ +166° (Found: C, 56·9; H, 6·6; Br, 15·0%), identical with material made by method (*a*).

9α-*Bromo*-4,5α-*dihydrocortisone Acetate* (X; R = H, R^1 = Br).—A solution of the 3,17-dihydroxy-11,20-dione (XII; R = R^1 = H, R^2 = OAc) (9·74 g.), R_F 0·30, in dioxan (370 ml.) containing 6N-hydrogen bromide in acetic acid (6 drops), was treated at room temperature with bromine (4·03 g.) in ethanol-free chloroform (28·7 ml.), added quickly, with shaking.[33] The

[33] Glaxo Laboratories Ltd., B.P. 762,716; see also ref. 12.

solution was left to stand for 1 hr., and the steroid was isolated by precipitation with water, extraction into chloroform, and evaporation. The residue was oxidised in AnalaR acetone (200 ml.) at 5° with chromic acid in sulphuric acid (6·52 ml.) [made by dissolving chromic oxide (266·7 g.) in sulphuric acid (1 l.)].[34] The orange-brown mixture was left for 0·5 hr. at room temperature. Methanol (1 ml.) was added to reduce the excess of oxidant, and the steroid was isolated by precipitation with water. Crystallisation from acetone–methanol afforded the acetate (4·8 g.), m. p. 201—204° (decomp.), $[\alpha]_D$ +202°, with a second crop (3·2 g.), m. p. 198—201° (decomp.), $[\alpha]_D$ +201°; these materials were identified with a specimen made by method (*b*).

Bromination was also accomplished with *N*-bromosuccinimide. A solution of 4,5α-dihydrocortisone acetate (X; R = R^1 = H), *N*-bromosuccinimide (1·0 g.), benzoyl peroxide (50 mg.), and benzene (100 ml.) was refluxed under nitrogen for 0·5 hr. The solution became yellow and did not liberate iodine from acidified potassium iodide. After washing (as described in previous examples) and evaporation, a solid (1·099 g.), R_F 0·77 (weak) and 0·85, remained. Crystallisation twice from benzene gave material (0·28 g.), m. p. 181—182° (cap.), $[\alpha]_D$ +162°, R_F 0·90 (Found: Br, 17·6%). Recrystallisation from methanol afforded solvated needles, m. p. 187—187·5°, $[\alpha]_D$ +172° (*c* 0·34%), similar to other specimens of the 9-bromo-compound (X; R = H, R^1 = Br).

(*b*) A solution of 21-acetoxy-9α-bromo-3β,17-dihydroxy-5α-pregnane-11,20-dione (XII; R = H, R^1 = Br, R^2 = OAc) (3·25 g.) in boiling acetone (100 ml.) was cooled to 45°, and oxidised with potassium dichromate (0·95 g.) in water (10 ml.) containing sulphuric acid (1·1 ml.).[17] Five minutes later an excess of sodium pyrosulphite was added and the solution diluted with brine. The precipitate was extracted with methylene dichloride, washed therein with water and sodium hydrogen carbonate, and the product (3·23 g.), m. p. 183° (decomp.), obtained by evaporation of the solution. Crystallisation from ethyl acetate gave the 9-bromo-ketone as a *solvate* (2·04 g., 57%), m. p. between 195 and 212° (according to the rate of heating), $[\alpha]_D$ +191° (Found: Br, 14·0. $C_{23}H_{31}BrO_6,C_4H_8O_2$ requires Br, 14·0%). Crystallisation from benzene gave another solvate, $[\alpha]_D$ +195°; desiccation of this material at 70°/0·5 mm. gave the solvent-free *9-bromo-11-ketone* (X; R = H, R^1 = Br), m. p. 198—204° (decomp.), $[\alpha]_D$ +202°, R_F 0·90, $\nu_{max.}$ (Nujol) 3500 (OH), 1742 and 1228 (21-acetate), 1724 (20-ketone), and 1704 cm.$^{-1}$ (11-ketone) (Found: C, 57·2; H, 6·5; Br, 16·4. $C_{23}H_{31}BrO_6$ requires C, 57·25; H, 6·4; Br, 16·5%).

The rotation of a solution in acetic acid containing hydrogen bromide diminished.

2α,9α-Dibromo-4,5α-dihydrocortisone Acetate (X; R = R^1 = Br).—A solution of the 9-bromo-ketone (X; R = H, R^1 = Br) (0·970 g.) in dioxan (20 ml.) containing 6N-hydrogen bromide in acetic acid (3 drops) was treated with bromine (0·336 g.) in alcohol-free chloroform (2·6 ml.), added at the rate of decolorisation. Within a few minutes a product began to crystallise out. After 10 min. the mixture was filtered, giving the *2,9-dibromo-ketone* (0·736 g.) (65%), which crystallised from acetone as needles, m. p. 205—207° (decomp.), $[\alpha]_D$ +174° (dioxan), $\nu_{max.}$ (Nujol) 3620 and 3350 (OH), 1726 and 1235 (21-acetate), 1726 (20-ketone), and 1702 cm.$^{-1}$ (11-ketone) (Found: C, 48·2; H, 5·6; Br, 27·1. $C_{23}H_{30}Br_2O_6,\frac{1}{2}H_2O$ requires C, 48·35; H, 5·5; Br, 28·0%). A specimen dried at 80° *in vacuo* for 8 hr. still analysed as a hemihydrate.

The $[\alpha]_D$ of a solution of the 2,9-dibromo-ketone (40 mg.) in acetic acid (8·5 ml.) containing 6N-hydrogen bromide in acetic acid (1·5 ml.) diminished, at room temperature, to +90° in 460 min. A pure product could not then be isolated.

3β,21-Diacetoxy-17-hydroxy-5α-pregn-8(9)-ene-11,20-dione (XIIIa; R = Ac).—The 9-bromo-ketone (X; R = H, R^1 = Br) (0·70 g.) was added, in one lot, to refluxing *NN*-dimethylacetamide (20 ml.) containing calcium carbonate;[13] refluxing was continued for 10 min., most of the solvent was evaporated off, and the concentrate diluted with 2N-hydrochloric acid. Chloroform extracted the $\Delta^{8(9)}$-dione (0·365 g., 62%), m. p. 191—193° (from methanol) $[\alpha]_D$ +191°, $\lambda_{max.}$ 256 mμ (ε 7800) {lit.,[27] m. p. 191—193·5°, $[\alpha]_D$ +180°, $\lambda_{max.}$ 256 mμ (ε 7300)}.

3β,21-Diacetoxy-17-hydroxy-5α-pregn-8(14)-ene-11,20-dione (XVI).—A solution of the $\Delta^{8(9)}$-ketone (XIIIa; R = Ac) in alcohol-free chloroform at 0° was treated with hydrogen chloride (2 bubbles per sec.). The ultraviolet absorption varied as follows [time (hr.), $\lambda_{max.}$ (mμ), $E^{1\%}_{1\,cm.}$]: 0·5, 254·5, 104; 1·2, 211·5, 138; 5·0, 248, 135. On a preparative scale the steroid (XIIIa; R = Ac) (0·25 g.) in chloroform at 0° was subjected for 1 hr. to a stream of hydrogen

[34] Curtis, Heilbron, Jones, and Woods, *J.*, 1953, 461.

chloride. The product was chromatographed on Florisil. Elution with benzene–ether (7 : 3) gave a crystalline fraction (95 mg.); crystallisation from ethanol gave the $\Delta^{8(14)}$-*dione* as prisms, m. p. 215—221°, $[\alpha]_D$ +105° (*c* 0·47%), $\lambda_{infl.}$ 205—210 mμ (ε 7000) (Found: C, 67·7; H, 7·9. $C_{25}H_{34}O_7$ requires C, 67·2; H, 7·7%).

21-*Acetoxy*-17-*hydroxy*-5α-*pregn*-8(9)-*ene*-3,11,20-*trione* (XIa).—A solution of the 9α-bromo-ketone (X; R = H, R^1 = Br) (0·50 g.) was heated under nitrogen for 2 hr. in refluxing pyridine (10 ml.). Concentration by evaporation, dilution with 2N-hydrochloric acid, extraction into ethyl acetate (in which it was washed) and evaporation left a solid (0·448 g.) that separated (0·339 g.) from acetone. Recrystallisation gave the pure $\Delta^{8(9)}$-*trione* (0·245 g.) as blades, m. p. 228—234°, $[\alpha]_D$ +242°, $\lambda_{max.}$ 254·5 mμ (ε 8300), R_F 0·60, $\nu_{max.}$ 1745 and 1230 (21-acetate), 1726 (20-ketone), 1706 (ketone), and 1656 and 900 cm.$^{-1}$ ($\Delta^{8(9)}$-11-ketone) (Found: C, 68·3; H, 7·4. $C_{23}H_{30}O_6$ requires C, 68·6; H, 7·5%).

Dehydrobromination of the bromo-ketone (X; R = H, R^1 = Br) (0·30 g.) with calcium carbonate (0·15 g.) in *NN*-dimethylacetamide (10 ml.),[13] at reflux for 10 min., gave the same product (0·240 g.).

21-*Acetoxy*-17α-*hydroxy*-5α,14β-*pregn*-8(9)-*ene*-3,11,20-*trione* (XIb).—(*a*) A solution of the bromo-ketone (X; R = H, R^1 = Br) (0·483 g.) in *NN*-dimethylformamide (5 ml.) containing lithium chloride (0·127 g.) [13] was kept at 94° for 2 hr. under nitrogen. The product was isolated by precipitation with water and extraction with ether; it crystallised from chloroform–ethyl acetate as plates (0·200 g.) that gave the pure 14β-*trione* as needles, m. p. 212—216° (from chloroform–ethanol) (not reproducible), $[\alpha]_D$ +227°, R_F 0·68, $\lambda_{max.}$ 246 mμ (ε 8800), $\nu_{max.}$ 1744 and 1236 (21-acetate), 1726 (20-ketone), 1704 (ketone), and 1660 and 1610 cm.$^{-1}$ (αβ-unsaturated ketone) (Found: C, 68·5; H, 7·65%).

(*b*) Hydrogen chloride was bubbled (2 bubbles per sec.) for 4·5 hr. through a solution of the $\Delta^{8(9)}$-trione (XIa) (0·45 g.) in chloroform (40 ml.), cooled to 0°. [A prior experiment had shown that the $\lambda_{max.}$ at ~255 mμ disappeared within 1 hr., so that the solution was almost transparent between 220 and 300 mμ; after 2 hr., the $\lambda_{max.}$ 246 mμ (ε 5200) had appeared, and in 4 hr. it had developed fully (ε 7000)]. The solution was washed with water and evaporated to dryness. Chromatography on Florisil yielded, in the benzene–ethyl acetate (9 : 1) eluates, a solid (56 mg., 12%); repeated crystallisation from aqueous methanol gave needles, m. p. 209—216°, identified with an authenetic specimen of the $\Delta^{8(9)}$-3,11,20-trioxo-14β-steroid.

(*c*) A solution of the $\Delta^{8(9)}$-trione (XIa) (0·152 g.), lithium chloride (45 mg.) and *NN*-dimethylformamidinium bromide (0·2 g.) was heated under nitrogen for 2 hr. on a steam-bath. The product was isolated with ethyl acetate and washed therein successively with dilute hydrochloric acid, sodium hydrogen carbonate, and water; evaporation afforded a residue (0·145 g.), $\lambda_{max.}$ 247 mμ ($E^{1\%}_{1cm.}$ 217). Crystallisation from chloroform–ethyl acetate yielded prisms (83 mg.) of the 14β-triketone, m. p. 223—225°, $\lambda_{max.}$ 247·5 mμ (ε 8510), $[\alpha]_D^{21}$ +226°, identified with an authentic specimen.

21-*Acetoxy*-17-*hydroxy*-5α-*pregna*-1,8(9)-*diene*-3,11,20-*trione* (XIV).—The 2,9-dibromotrione (X; R = R^1 = Br) (0·40 g.) was dehydrobrominated in 10 min. in refluxing *NN*-dimethylacetamide (13 ml.) containing calcium carbonate (0·20 g.).[13] The product was segregated into ether, evaporation of which yielded, after crystallisation from methanol, yellow needles (0·135 g., 48%) of the *dienetrione* (XIV). Two more crystallisations gave yellow needles, m. p. 252—255°, $[\alpha]_D$ +328°, $\lambda_{max.}$ 226·5 mμ (ε 13,000), $\nu_{max.}$ 1744 and 1232 (21-acetate), 1726 (20-ketone), 1660 and 902 ($\Delta^{8(9)}$-11-ketone), and 1660 and 782 cm.$^{-1}$ (Δ^1-3-ketone) (Found: C, 69·6; H, 7·2. $C_{23}H_{28}O_6$ requires C, 69·0; H, 7·05%).

Partial dehydrobromination, under nitrogen, of the 2,9-dibromo-triketone (X; R = R^1 = Br) (0·43 g.) in acetic acid (25 ml.) with 2,4-dinitrophenylhydrazine hydrochloride (0·20 g.) in acetic acid (15 ml.) gave, after 30 min. on a steam-bath and dilution with water, a precipitate (0·45 g.) that was chromatographed on alumina. Elution with benzene–ethyl acetate (9 : 1) yielded a fraction that was crystallised thrice from chloroform–methanol to give 21-*acetoxy*-9α-*bromo*-17-*hydroxy*-5α-*pregn*-1-*ene*-3,11,20-*trione* 3-(2,4-*dinitrophenylhydrazone*) (XV) as orange needles, m. p. 247—250° (decomp.), $\lambda_{max.}$ ($CHCl_3$) 381 mμ (ε 29,500) (Found: Br, 12·2. $C_{29}H_{33}BrN_4O_9$ requires Br, 12·1%).

3,11-*Dioxobisnor*-5α-*cholanic Acid* (III; R = R^1 = H, R^2 = CH(Me)·CO_2H).—A warm solution of the oxo-acid (I; R = R^1 = H, R^2 = CH(Me)·CO_2H) (10·0 g.) [36] in t-butyl alcohol

[35] Djerassi, *J. Amer. Chem. Soc.*, 1949, **71** 1003; Gates and Shepard, *ibid.*, 1962, **84**, 4125.
[36] Cameron, Hunt, Oughton, Wilkinson, and Wilson, *J.*, 1953, 3864.

(1 l.) was cooled, and treated immediately with pyridine (28 ml.) and *N*-bromoacetamide (98% pure; 7·8 g.). The mixture was stored at 25° under nitrogen for 21 hr., and filtered into ice-cold water (1 l.) containing concentrated hydrochloric acid (15 ml.). Ether extracted the steroidal material, which was washed with sodium thiosulphate and water. Evaporation left a residue which gave irregular white crystals (6·54 g., 66%) from ethyl acetate. Recrystallisation gave birefringent prisms of the *dioxo-acid* (III; R = R^1 = H, R^2 = CH(Me)·CO_2H), m. p. 256—260°, $[\alpha]_D$ +51° (acetone), $\nu_{max.}$ (Nujol) 2600, 1722, and 1266 (CO_2H), and 1700 cm.$^{-1}$ (ketones) (Found: C, 73·6; H, 8·9. $C_{22}H_{32}O_4$ requires C, 73·3; H, 8·95%).

Saponification of the ester (III; R = R^1 = H, R^2 = CH(Me)·CO_2Me) (0·30 g.) (see below) in refluxing methanol (20 ml.) with 20% potassium hydroxide (15 ml.), under nitrogen, gave similar material. The yellow 2,4-*dinitrophenylhydrazone* had m. p. 289—290° (from chloroform–ethyl acetate), $[\alpha]_D$ +36° (*c* 0·2% in dioxan), $\lambda_{max.}$ ($CHCl_3$) 367·5 mμ (ε 23,400), $\nu_{max.}$ (Nujol) 1720 and 1285 (CO_2H), 1710 (ketone), and 1520 and 1330 cm.$^{-1}$ (NO_2) (Found: N, 10·4. $C_{28}H_{36}N_4O_7$ requires N, 10·4%).

Methyl 3,11-*Dioxobisnor*-5α-*cholanate* (III; R = R^1 = H, R^2 = CH(Me)·CO_2Me).—The ketol ester (I; R = R^1 = H, R^2 = CH(Me)·CO_2Me (0·50 g.) [36] in acetone (50 ml.) was oxidised [37] with 8N-chromium trioxide at about 35°. Crystallisation from methanol of the crude product (0·44 g.) gave the dioxo-ester as prisms (0·37 g., 74%), m. p. 201—202°, $[\alpha]_D$ +60°, $\nu_{max.}$ (CS_2) 1738 and 1162 (CO_2Me), and 1710 cm.$^{-1}$ (ketones) (lit.,[38] m. p. 201—204°, $[\alpha]_D$ +63°).

2α,9α-*Dibromo*-3,11-*dioxobisnor*-5α-*cholanic Acid* (III; R = R^1 = Br, R^2 = CH(Me)·CO_2H).—The diketo-acid (III; R = R^1 = H) (1·952 g.) in AnalaR acetic acid (50 ml.) was treated with bromine (1·8 g., 2 mol.) in acetic acid (25 ml.), added gradually over 15 min. The halogen was absorbed instantly. 4N-Hydrogen bromide in acetic acid (1 ml.) was added. Mutarotation ceased within 2 hr.; the solution was kept overnight at room temperature, poured into ice-water (300 ml.), and the precipitate spun off and washed. This material (2·53 g., 90%), m. p. 186—187° (decomp.), $[\alpha]_D$ +48° (Found: Br, 31·2%), yielded from ethyl acetate–hexane crystals of the 2,9-*dibromo-dioxo-acid*, m. p. 202—204° (decomp. >199°), $[\alpha]_D$ +58°, $\nu_{max.}$ (Nujol) 1735 (2α-bromo-3-ketone), 1715 and 1270 (CO_2H), and 1695 cm.$^{-1}$ (11-ketone) (Found: C, 51·05; H, 6·05; Br, 31·0. $C_{22}H_{30}Br_2O_4$ requires C, 51·0; H, 5·8; Br, 30·9%).

Action of Sodium Iodide in Acetone on the Dibromo-dioxo-acid (III; R = R^1 = Br).—The crystalline acid (1·70 g.) was heated for 20 hr. at reflux under nitrogen in AnalaR acetone (100 ml.) containing sodium iodide dihydrate (2·4 g.). Sodium bromide (0·504 g., 1·43 mol.) separated out, and the mixture turned brown. The mixture was filtered, concentrated to 30 ml., and water was added to precipitate a solid. Colour was discharged by addition of sodium thiosulphate, so that a nearly white product, $[\alpha]_D$ +110° (Found: I, 23·0%), was obtained. This was dehalogenated in solution in acetone (40 ml.) with chromous chloride [39] [from chomic chloride (4·0 g.)]. 8,9-Dehydro-3,11-dioxobisnor-5α-cholanic acid (0·185 g.) was then isolated, m. p. 201—222° (from ethyl acetate–hexane), $[\alpha]_D$ +129°, $\lambda_{max.}$ 251 mμ (ε 3620), $\nu_{max.}$ 1730 and 1263 (CO_2H), 1705 (ketone), and 1655 and 1595 cm.$^{-1}$ (αβ-unsaturated ketone), giving an orange 2,4-*dinitrophenylhydrazone*, m. p. 192—195°, $\lambda_{max.}$ ($CHCl_3$) 363 mμ (ε 24,200) (Found: N, 10·6. $C_{28}H_{34}N_4O_7$ requires N, 10·4%).

21-*Acetoxy*-17-*hydroxypregna*-4,9-*diene*-3,20-*dione* (VI).—(*a*) Thionyl chloride (0·8 ml.) and pyridine (20 ml.) were mixed at −10°, and cortisol acetate (V; R = H) (2 g.) in pyridine (20 ml.) at −10° was added. The solutions were kept under nitrogen. The mixture was shaken; after 5 min. solid began to separate, and shaking was continued for 4 min. more. The mixture was poured into saturated sodium hydrogen carbonate (100 ml.), left to stand for 0·5 hr. in the refrigerator, and filtered. The washed and dried precipitate was crystallised from acetone (plus a little methylene dichloride) to give the solvated dione (VI). Drying at 110°/0·2 mm. removed acetone and left the solvent-free compound (1·44 g.), m. p. 227—229°, $[\alpha]_D$ +128°, R_F 0·77 and 0·90 (weak), $\lambda_{max.}$ 239 mμ (ε 16,800). The contaminant, R_F 0·90, could be removed as follows.[13] Material (5 g.) made in the manner just described was heated in a refluxing mixture of ethanol (340 ml.) and ethyl acetate (40 ml.), to which sodium pyrosulphite (33 g.) in water (70 ml.) was added. Refluxing was continued for 8 hr. under nitrogen and the mixture was poured into water (1·67 l.) containing sodium pyrosulphite (167 g.), and left

[37] Bladon, Fabian, Henbest, Koch, and Wood, *J.*, 1951, 2402.
[38] Merck Inc., U.S.P. 2,854,451.
[39] Rosenkranz, Djerassi *et al.*, *J. Amer. Chem. Soc.*, 1950, **72**, 4077, 4081; *J. Org. Chem.*, 1952, **17**, 1066.

overnight. The precipitate (4·85 g.) crystallised from acetone–methylene chloride to give, after desiccation at 110°/0·2 mm., the pure diene-dione (4·62 g.), m. p. 238—241°, $[\alpha]_D$ +125°, R_F 0·77, $\lambda_{max.}$ 239 mμ (ε 16,400), $\nu_{max.}$ 1742 and 1232 (21-acetate), 1724 (20-ketone), and 1660 and 868 cm.$^{-1}$ (Δ^4-3-ketone) {lit.,[10a,15] m. p. 236—237°, $[\alpha]_D$ +120°, $\lambda_{max.}$ 238 mμ (ε 16,500); m. p. 231·5—234·5°, $[\alpha]_D$ +124°, $\lambda_{max.}$ (MeOH) 240 mμ (ε 15,800); see also ref. 5}.

9α-*Bromocortisol Acetate* (V; R = Br).—A stirred suspension of the Δ^9-steroid (VI) (1·0 g.) in dioxan (10 ml.) containing 0·46N-perchloric acid (1·5 ml.) was treated,[40] in the dark at room temperature, with *N*-bromoacetamide (0·47 g.), added in 1 hr. Solution was achieved in this time. The reaction was given 170 min. in all. Addition of 10% sodium sulphate and isolation with chloroform yielded, on evaporation, a syrup that dissolved in acetone at room temperature. Storage of this solution in the refrigerator yielded the crystalline bromohydrin (V; R = Br) (1·03 g., 82%), m. p. 128—132°, R_F 0·51, $\lambda_{max.}$ 243 mμ (ε 14,600) [lit.,[15] m. p. 130—131° (decomp.), $\lambda_{max.}$ 243 mμ (ε 14,500)].

9α-*Bromocortisone Acetate* (VII; R = Br).—0·33M-Potassium dichromate in 4N-sulphuric acid (4 ml.) was added to a gently refluxing solution of the bromohydrin (V; R = Br) (0·523 g.) in acetone (52 ml.) which had been previously refluxed with the oxidant and distilled.[17] Refluxing was continued for 5 min. Sodium pyrosulphite was added to end reaction. Extraction with methylene dichloride and evaporation left a residue (0·51 g.) which crystallised from ethanol as needles (3 crops; 0·42 g., 80%). Recrystallisation yielded the pure ketone m. p. 220—221°, $[\alpha]_D^{21}$ +256°, R_F 0·73, $\lambda_{max.}$ 237 mμ (ε 15,900), $\nu_{max.}$ 1744 and 1230 (21-acetate), 1726 (20-ketone), 1710 (11-ketone), 1668 and 866 cm.$^{-1}$ (Δ^4-3-ketone) (Found: C, 57·6; H, 6·2; Br, 16·75. Calc. for $C_{23}H_{29}BrO_6$: C, 57·4; H, 6·1; Br, 16·6%) {lit.,[15] m. p. 219°, $[\alpha]_D$ +242°, $\lambda_{max.}$ 237 mμ (ε 16,100)}.

Oxidation of the bromohydrin (V; R = Br) with chromic oxide in pyridine [16] was sluggish and produced poor yields of the ketone (VII; R = Br), shown by paper chromatography to be impure.

8(9)-*Dehydrocortisone Acetate* (VIIIa).—9α-Bromocortisone acetate (VII; R = Br) (0·50 g.) was added to pyridine, kept at room temperature under nitrogen. The mixture was heated, and the resulting solution refluxed for 1 hr. The solvent was distilled off and the steroid was extracted into ethyl acetate, and washed therein with 2N-hydrochloric acid and with saturated sodium carbonate. The latter extracted yellow material which turned red in the alkali. Evaporation of the ethyl acetate left a yellow residue (0·397 g.) which was chromatographed on charcoal (Nuchar G-190; unground) (12 g.). Chloroform–benzene (15 : 85) eluted material that crystallised from ethanol as prisms (0·255 g., 61%). Further chromatography and crystallisation yielded colourless prisms of the unsaturated ketone (VIIIa), m. p. 253—255° (decomp.), $[\alpha]_D$ +401°, R_F 0·52, $\lambda_{max.}$ 234—236 mμ (ε 18,700), $\nu_{max.}$ 1742 and 1238 (21-OAc), 1728 (20-ketone), 1660, 1625, and 866 (Δ^4-3-ketone), and 1660 and 1596 cm.$^{-1}$ ($\Delta^{8(9)}$-11-ketone) (Found: C, 69·2; H, 7·1. Calc. for $C_{23}H_{28}O_6$: C, 69·0; H, 7·05%) {lit.,[3,15] m. p. 241—248° (decomp.), $[\alpha]_D$ +422°, $\lambda_{max.}$ 236·5 mμ (ε 17,700); m. p. 248—249° (decomp.), $[\alpha]_D$ +424°, $\lambda_{max.}$ 235 mμ (broad) (ε 17,200)}.

Similar results were obtained when dehydrobromination was carried out (i) with calcium carbonate (1·85 g.) and the bromo-ketone (VII; R = Br) (0·926 g.) in *NN*-dimethylacetamide (50 ml.), refluxed under nitrogen for 10 min.,[13] or (ii) with calcium carbonate (0·67 g.) and the bromo-ketone (VII; R = Br) (0·33 g.) in collidine, refluxed under nitrogen for 10 min.

8(9)-*Dehydro*-14β-*cortisone Acetate* (VIIIb).—9α-Bromocortisone acetate (VII; R = Br) (0·375 g.) and lithium chloride (0·38 g.) were added to *NN*-dimethylformamide (3·75 ml.), kept under nitrogen. The mixture was kept at 100° for 2 hr.; it changed from bright red to yellow. Dilution with water and extraction with ethyl acetate, washing of the extracts with saturated sodium carbonate (which removed yellow material that turned red in alkali), and evaporation furnished a yellow residue. Chromatography (twice) on charcoal, with chloroform–benzene (15 : 85) as eluant, gave a fraction (0·10 g.) which yielded the 14β-ketone (2 crops; 51 mg., 21%) m. p. 191—196° (from acetone–ether), $[\alpha]_D$ +358°, R_F 0·59, $\lambda_{max.}$ 235—236·5 mμ (ε 20,300), $\nu_{max.}$ 3600 (OH), 1744 and 1232 (21-acetate), 1726 (20-ketone), 1664 and 864 (Δ^4-3-ketone), and 1664 and 900 cm.$^{-1}$ ($\Delta^{8(9)}$-11-ketone) (Found: C, 69·0; H, 6·9. Calc. for $C_{23}H_{28}O_6$: C, 69·0; H, 7·05%) {lit.,[4] m. p. 195—198°, $[\alpha]_D$ +348°, $\lambda_{max.}$ (MeOH) 237·5 mμ (ε 19,700)}.

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[40] Evans, Green, Hunt, Long, Mooney, and Phillipps, *J.*, 1958, 1529.