895. *Compounds Related to the Steroid Hormones. Part VI.*[1] *The Synthesis of the 9α-Fluoro-16β-methyl Derivatives of Hydrocortisone and Prednisolone.*

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Dehydrogenation of 21-acetoxy-17-hydroxy-5α-pregn-9-ene-3,20-dione and its 16β-methyl analogue to the 1,4,9-trienes has been accomplished by a bromination–dehydrobromination sequence. When the double bond of ring c was protected as a 9α,11β-dichloro- or a 9α-bromo-11β-acyloxy-derivative, subsequent dehydrogenation by bromination and dehydrobromination failed owing to rapid elimination of the protecting groups which led to the formation of 7,9-dienes.

21-Acetoxy-9α-fluoro-11β,17-dihydroxypregn-4-ene-3,20-dione and its 16β-methyl analogue were prepared from the corresponding ring-A saturated 9α,11β-fluorohydrins by dibromination, selective dehydrobromination, and subsequent debromination of the 2-bromo-Δ^4-3-ketones. Complete dehydrobromination of the 16-unsubstituted dibromide gave a mixture of 9α-fluoroprednisolone acetate and its $\Delta^{4,6}$-isomer.

Conversion of 5α-pregn-9-en-3-ones such as (VII) (see preceding paper) into the corresponding 1,4,9-trien-3-ones (XVII) by a bromination–dehydrobromination sequence is an important stage in synthesising analogues of steroid hormones from hecogenin *via* intermediates unsaturated at position 9(11). Some initial difficulties were encountered in preparing 2,4-dibromo-5α-pregn-9-en-3-ones (*e.g.*, XV) by brominating the corresponding 3-ketones (VII), and we simultaneously investigated methods of protecting the double bond during dehydrogenation of ring A.

21-Acetoxy-11β,17-dihydroxy-5α-pregnane-3,20-dione was converted[2,3] into the Δ^9-compound (I), which was treated with chlorine (cf. similar reactions with 4,9-dien- and 1,4,9-trien-3-ones[4]) to give 21-acetoxy-9α,11β-dichloro-17-hydroxy-5α-pregnane-3,20-dione (II; X = Y = Cl) in *ca.* 60% yield. Treatment of this dichloride under conditions (see below) used for dehydrohalogenation of 2,4-dibromo-3-oxo-steroids led to ready elimination of two molecules of hydrogen chloride, with formation of a product that appeared from its ultraviolet spectrum (cf. refs. 5, 6, 7) to be a mixture of the 7,9-diene (III) and, probably, the isomeric 8(14),9-diene (IV). On conducting the dehydrochlorination with lithium carbonate and lithium chloride in dimethylacetamide (cf. ref. 8) at 95° and purifying the product by treatment with maleic anhydride to remove the homoannular diene (IV), we were able to isolate 21-acetoxy-17-hydroxy-5α-pregna-7,9-diene-3,20-dione (III). Further experiments showed that 21-acetoxy-9α,11β-dichloro-17-hydroxypregna-1,4-diene-3,20-dione[4] was more stable to dehydrochlorination than was the ring-A saturated compound (II; X = Y = Cl).

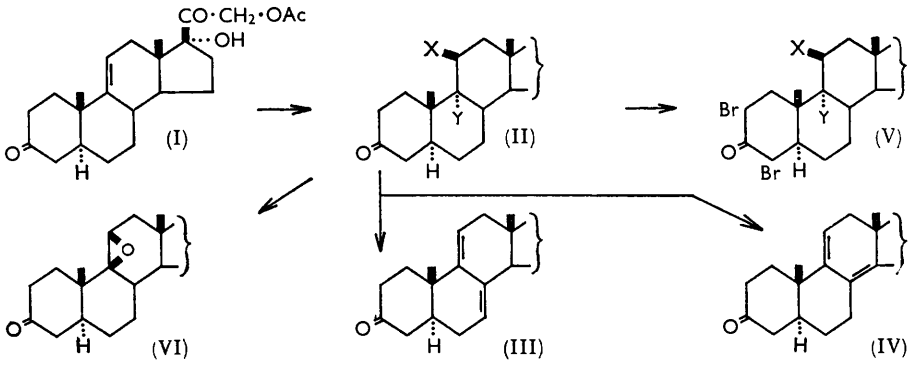
Bromination of the dichloro-compound (II; X = Y = Cl) in acetic acid gave crude 21-acetoxy-2,4-dibromo-9α,11β-dichloro-17-hydroxy-5α-pregnane-3,20-dione (V; X = Y = Cl). Dehydrohalogenation of this material at 55° with dimethylacetamide containing

[1] Part V, preceding paper.
[2] Evans, Green, Hunt, Long, Mooney, and Phillipps, *J.*, 1958, 1529.
[3] Elks, Phillipps, and Wall, *J.*, 1958, 4001.
[4] Robinson, Finckenor, Oliveto, and Gould, *J. Amer. Chem. Soc.*, 1959, **81**, 2191; Reimann, Oliveto, Neri, Eisler, and Perlman, *ibid.*, 1960, **82**, 2308; Robinson, Finckenor, Tiberi, Eisler, Neri, Watnick, Perlman, Holroyd, Charney, and Oliveto, *ibid.*, p. 4611.
[5] Dorfman, *Chem. Rev.*, 1953, **53**, 47; Antonucci, Bernstein, Giancola, and Sax, *J. Org. Chem.*, 1951, **16**, 1891; Heusler and Wettstein, *Helv. Chim. Acta*, 1952, **35**, 284.
[6] Wendler, Graber, Snoddy, and Bollinger, *J. Amer. Chem. Soc.*, 1957, **79**, 4476.
[7] Fried and Sabo, *J. Amer. Chem. Soc.*, 1954, **76**, 1455; 1957, **79**, 1130.
[8] Holysz, *J. Amer. Chem. Soc.*, 1953, **75**, 4432.

calcium carbonate [9] gave bromine-containing products with the characteristic ultraviolet absorption of the 7,9-diene chromophore, but without the infrared absorption attributable to conjugated chromophores in ring A. Similar results were obtained with collidine at 95°.

Dechlorination of the 9α,11β-dichloro-compound (II; X = Y = Cl) to the Δ^9-steroid (I) was effected in high yield by either 2 mol. of chromous chloride [1,4] or hydrogen and palladised charcoal, preferably in the presence of triethylamine.[1] We attempted to prepare 21-acetoxy-2,4-dibromo-17-hydroxy-5α-pregn-9-ene-3,20-dione (*e.g.*, XV; R = H) by selective dechlorination of the 2,4-dibromo-9α,11β-dichloro-compound (V; X = Y = Cl) with 2 mol. of chromous chloride, but obtained only an impure product with infrared absorption attributable to mono-α-bromo-ketones. Hydrogenolysis of the tetrahalide (V; X = Y = Cl) over palladium–charcoal in tetrahydrofuran containing triethylamine gave a mixture of the 9-ene (I) (81%) and the 9α,11β-dichloro-compound (II; X = Y = Cl) (13%). The latter was obtained in 74% yield when hydrogenolysis was carried out in acetic acid.

In another attempt to protect the 9,11-double bond, compound (I) was treated with *N*-bromoacetamide in formic or acetic acid containing, respectively, sodium formate or lithium acetate, to give the corresponding 9α-bromo-11β-acyloxy-derivatives [10,11] (II; Y = Br, X = H·CO_2 and AcO, respectively) in moderate yields. Preliminary experiments in which these derivatives were treated with calcium carbonate in dimethylacetamide at the b. p. or 95—100° afforded the 7,9-diene (III), possibly contaminated with the 8(14),9-diene (IV). In view of the similarity between these products and those obtained by



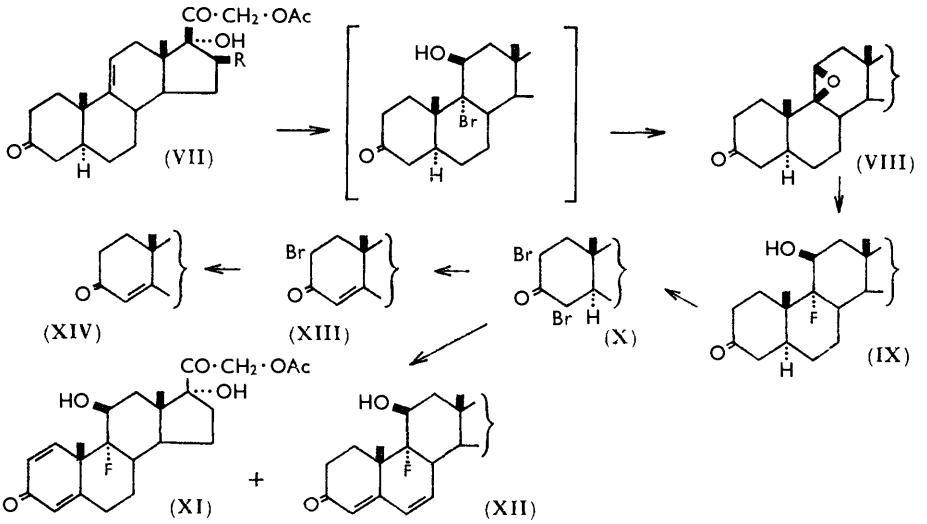
dehydrochlorination of the 9α,11β-dichloro-compound (II; X = Y = Cl), we did not pursue attempts at dehydrobrominating the 11β-acyloxy-2,4,9α-tribromides (V; X = R·CO_2, Y = Br) in ring A.

Treating 21-acetoxy-9α-bromo-11β-formyloxy-17-hydroxy-5α-pregnane-3,20-dione (II; X = H·CO_2, Y = Br) in aqueous dioxan with a solution of sodium hydroxide [10] and reacetylating the product gave a 79% yield of the 9β,11β-epoxide (VI). When, however, we attempted this conversion by refluxing the formate in ethanol containing potassium acetate,[3,7,12] we obtained a mixture of the 7,9-diene (III), the 9β,11β-epoxide (VI), and 21-acetoxy-17-hydroxy-5α-pregnane-3,11,20-trione. The formation of an 11-ketone from 9α-bromo-11β-hydroxyergostan-3-one in similar circumstances has been reported.[3]

Acid-catalysed bromination of the epoxide (VI) led to simultaneous cleavage of the oxiran [13] and bromination of ring A to give the crude tribromide (V; X = OH, Y = Br). Attempts to reform the 9β,11β-epoxide ring, with or without dehydrobromination in ring A, were unsuccessful.

[9] Part II, Green and Long, *J.*, 1961, 2532.
[10] Robinson, Finckenor, Kirtley, Gould, and Oliveto, *J. Amer. Chem. Soc.*, 1959, **81**, 2195.
[11] Levine and Wall, *J. Amer. Chem. Soc.*, 1959, **81**, 2826.
[12] Hirschmann, Miller, Wood, and Jones, *J. Amer. Chem. Soc.*, 1956, **78**, 4956.
[13] Fried and Sabo, *J. Amer. Chem. Soc.*, 1955, **77**, 4181; B.P. 829,632, 829,633.

A route [3,13,14,15] to 9α-fluoroprednisolone acetate (XI) that avoids the necessity for brominating a Δ^9-5α-3-ketone involves conversion of such a compound (VII; R = H) into the corresponding 9α-fluoro-11β-hydroxy-5α-3-ketone (IX; R = H), which is then dehydrogenated *via* the 2,4-dibromo-compound (X; R = H) into the required $\Delta^{1,4}$-3-ketone (XI). This route has previously given poor results, but it seemed to merit reinvestigation, and we therefore studied the complete dehydrobromination of the crude 2,4-dibromide [3] (X; R = H) with calcium carbonate in boiling dimethylacetamide,[9] with the same reagents and lithium bromide, or with collidine and dimethylformamide.[15] We had hoped that the inclusion of a metal carbonate [16] would prevent formation of the 4,6-dienone isolated by previous workers [13,14,15] when the dehydrobromination was carried out in a mixture of collidine and dimethylformamide. However, in each instance the product was a mixture (cf. refs. 13, 14, 15, 17) of 9α-fluoroprednisolone acetate (XI) and the isomeric 4,6-dien-3-one (XII); after separation with Girard's reagent P the best yield



of the former was 17%, with 15% of the latter. The ratio of these isomers was dependent on the dehydrobrominating conditions; a low concentration of the steroid and a large excess of suspended calcium carbonate favoured the formation of the cross-conjugated isomer (XI). Addition of lithium bromide resulted in faster reaction [8] and favoured formation of the 4,6-dien-3-one (XII). At lower temperatures (*e.g.*, 100°) complete dehydrobromination was difficult to achieve.

Further investigation of this dehydrobromination confirmed Fried's report [15] that the second molecule of hydrogen bromide is eliminated much more slowly than the first. Several other instances of selective monodehydrobromination of diequatorial 2,4-dibromo-3-ketones in both the 5α- and the 5β-series have been reported.[16,18,19] By conducting the reaction at 100° with calcium carbonate and lithium bromide in dimethylacetamide, we isolated 21-acetoxy-2-bromo-9α-fluoro-11β,17-dihydroxypregn-4-ene-3,20-dione [15] (XIII; R = H). Debromination with chromous chloride then gave 9α-fluorocortisol acetate [3,7,12]

[14] Hirschmann, Miller, Beyler, Sarett, and Tishler, *J. Amer. Chem. Soc.*, 1955, **77**, 3166; U.S.P. 2,837,541.
[15] Fried, U.S.P. 2,848,464—5.
[16] Joly, Warnant, Nominé, and Bertin, *Bull. Soc. chim. France*, 1958, 366, 367; Joly and Warnant, U.S.P. 2,957,890.
[17] Bernstein, Brown, Feldman, and Rigler, *J. Amer. Chem. Soc.*, 1959, **81**, 4956.
[18] Inhoffen and Zühlsdorff, *Ber.*, 1943, **76**, 233; Djerassi and Scholz, *J. Amer. Chem. Soc.*, 1947, **69**, 2404; *J. Org. Chem.*, 1948, **13**, 697.
[19] Wieland, Heusler, and Wettstein, *Helv. Chim. Acta*, 1960, **43**, 523.

(XIV; R = H) in 43% yield from the dibromide (X; R = H). In the same way the 16β-methyl-fluorohydrin (IX; R = Me), prepared by the usual method from the Δ^9-compound (VII; R = Me), was converted into the corresponding dibromide (X; R = Me); subsequent monodehydrobromination and debromination gave 21-acetoxy-9α-fluoro-11β,17-dihydroxy-16β-methylpregn-4-ene-3,20-dione [20] (XIV; R = Me) in 22% yield. The low yield obtained in the 16β-methyl series compared with that in the unsubstituted series is attributed, at least in part, to a less polar impurity arising during the bromination of the fluorohydrin (IX; R = Me) in glacial acetic acid. A corresponding fraction occurring (paper chromatography) in the subsequent stages was easily removed during crystallisation of the final product and is tentatively considered to be due to loss of the 17-hydroxy-group and formation of a 16-methyl-Δ^{16}-20-ketone. The easy elimination of a 17α-hydroxy-group in the 16β-methyl series compared with elimination in the 16α-methyl or unmethylated series has been commented upon previously.[20]

Meanwhile we had found suitable conditions for bromination of 3-oxo-5α-pregn-9-enes (VII) in ring A. A few such examples have been recorded elsewhere for both 5α- [2,3] and 5β-steroids.[21] We studied the bromination of 21-acetoxy-17-hydroxy-5α-pregn-9-ene-3,20-dione (VII; R = H) in several solvents. The crude 2,4-dibromides [2] were assayed by determining the yield of triene (XVII; R = H) [4,13,14,22] obtained on dehydrobromination under standard conditions. Best yields (*ca.* 40%) were obtained when the bromination was conducted in dioxan–acetic acid (cf. ref. 19). More reliable brominations were achieved by initiating the reaction with hydrogen bromide, presumably because bromination of the 3-ketone is acid-catalysed and therefore favoured over addition of bromine to the ring-C double bond.

Dibromination of the 16β-methyl analogue [1] (VII; R = Me) was best conducted in dioxan, either alone or containing up to an equal volume of acetic acid.[19] Under these conditions two crystalline 2,4-dibromides were isolated, whose debromination regenerated the starting material (VII; R = Me). The more plentiful, dextrorotatory, isomer was assigned the 2α,4α(*eq,eq*)-dibromo-ketone structure (XV; R = Me), and the minor, lævorotatory, component was assigned the 2α,4β(*eq,ax*)-dibromo-structure (XVI; R = Me) on the evidence presented below. French workers [23] have found that bromination of 21-acetoxy-4β-bromo-17-hydroxy-5β-pregnane-3,11,20-trione and related compounds in dioxan leads to the 2α,4β(*ax,eq*)-dibromo-5β-pregnane whereas bromination with *N*-bromosuccinimide in benzyl alcohol gives the 2β,4β(*eq,eq*)-isomer. Acid-catalysed bromination in solvents other than dioxan gave inseparable isomeric mixtures. It is significant that the energies of axial and equatorial forms of some α-bromo-ketones are nearly the same in dioxan solution, whereas they differ much more in other solvents.[24]

The main features distinguishing the infrared spectra [23,25] of dibromides (XV and XVI; R = Me) in bromoform solution are bands, in the former, at 948 (unassigned) and 1745 cm.$^{-1}$, which are absent from the spectrum of the latter. The low-frequency spectrum (potassium bromide prism) in carbon disulphide of the 2α,4α-dibromide (XV; R = Me) showed expected [25] bands at 687 and 614 cm.$^{-1}$, absent from the spectrum of its isomer. Crude bromination products showed absorption at 1745 cm.$^{-1}$, less intense than that of the pure 2α,4α-isomer (XV; R = Me).

Differences in molecular rotation provide some support for the assignment of these structures. Of the four possible types of 2,4-dibromo-3-oxo-5α-steroids, only

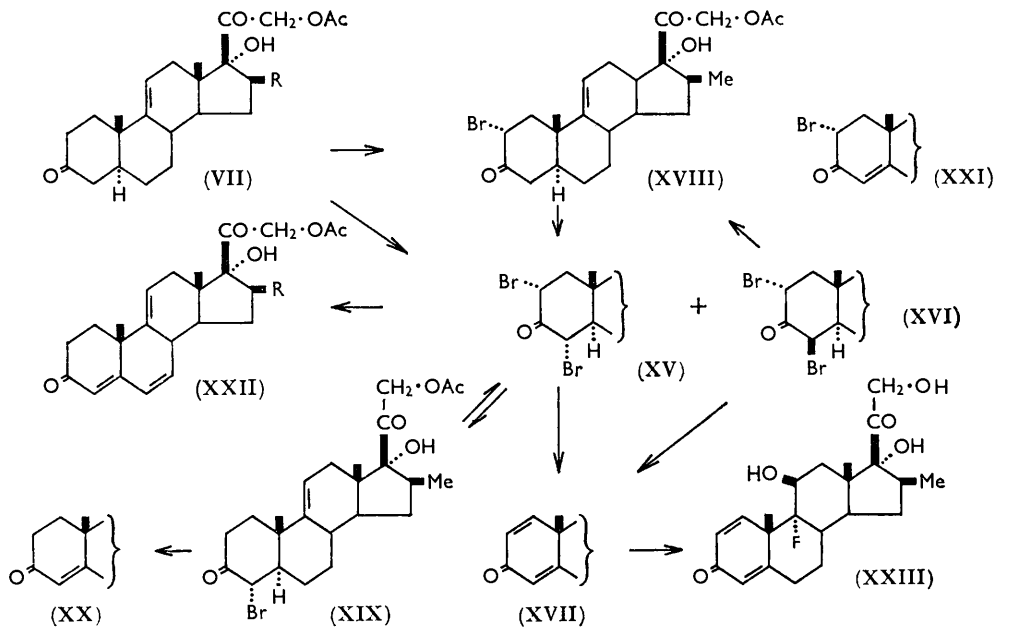
[20] Taub, Hoffsommer, Slates, Kuo, and Wendler, *J. Amer. Chem. Soc.*, 1960, **82**, 4012.
[21] Graber, Haven, and Wendler, *J. Amer. Chem. Soc.*, 1953, **75**, 4722; Casanova, Shoppee, and Summers, *J.*, 1953, 2983.
[22] Hogg, Lincoln, Nathan, Hanze, Schneider, Beal, and Korman, *J. Amer. Chem. Soc.*, 1955, **77**, 4438.
[23] Muller, Joly, Nominé, and Bertin, *Bull. Soc. chim. France*, 1956, 1457; Joly, Nominé, and Bertin, *ibid.*, p. 1459.
[24] Alinger and Alinger, *Tetrahedron*, 1958, **2**, 64; Kumler and Huitric, *J. Amer. Chem. Soc.*, 1956, **78**, 3369.
[25] Cummins and Page, *J.*, 1957, 3847, and refs. therein cited.

the 2α,4α-compounds have been described in the literature. However, the effect of 2,4-dibromination on the molecular rotation of a 3-oxo-5α-steroid can be calculated from the individual effects of 2- and 4-monobromination,[26] if vicinal action is assumed to be absent; rotation differences calculated in this way are presented in the Table.

Br	2α, 4α	2α, 4β	2β, 4α	2β, 4β
$\Delta[M]_D$	−65° to −157°	−338° to −486°	+333° to +477°	+4° to +211°

Some justification for this method is found in the fact that the observed values of $\Delta[M]_D$ for 2α,4α-dibromination of a number of 3-oxo-5α-steroids lie within the range quoted; an 11-oxo-group may introduce anomalies,[27] but, significantly for our present purpose, a 9,11-double bond does not.[2] The observed values of $\Delta[M]_D$ for our 2α,4α- (XV; R = Me) and 2α,4β-dibromo-compounds (XVI; R = Me) in comparison with the parent ketone (VII; R = Me) were −67° and −476°, respectively, both lying within the calculated ranges.

Optical rotatory dispersion measurements show that the 2α,4α-dibromo-ketone (XV; R = Me) gives a positive Cotton effect, whereas with the 2α,4β-isomer (XVI; R = Me) the effect is negative. The shift of the extremum (315 ⟶ 330 mμ) and application of the halogeno-ketone rule [28,29] accord with the proposed structures (XV and XVI; R = Me) provided that ring A is in the chair conformation.



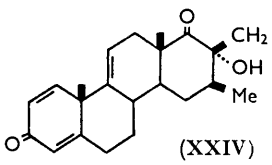
Partial reduction of the 2α,4α- (XV; R = Me) and the 2α,4β-dibromo-ketones (XVI; R = Me) with chromous chloride gave the 4α- [26,27] (XIX) and the 2α-bromo-ketones (XVIII), respectively, the latter also arising on monobromination of the unsubstituted ketone (VII; R = Me). Attention is called to the fact that the axial bromine in the

[26] Malunowicz, Fajkoš, and Šorm, *Coll. Czech. Chem. Comm.*, 1960, **25**, 1359; Fajkoš and Šorm, *ibid.*, 1959, **24**, 3115; Klinot and Vystrčil, *Chem. and Ind.*, 1960, 1360.
[27] Evans, Hamlet, Hunt, Jones, Long, Oughton, Stephenson, Walker, and Wilson, *J.*, 1956, 4356.
[28] Djerassi, "Optical Rotatory Dispersion: Applications to Organic Chemistry," McGraw-Hill, New York, 1960.
[29] Klyne in "Advances in Organic Chemistry, Methods and Results." Interscience Publ., Inc., New York, 1960, Vol. I, pp. 239 *et seq.*

2α,4β-dibromide (XVI; R = Me) was preferentially reduced. Bromination of the 4α-bromo-compound (XIX; R = Me) gave the 2α,4α-dibromide (XV; R = Me), whereas dehydrobromination with semicarbazide base and subsequent treatment with pyruvic acid [27] gave 21-acetoxy-17-hydroxy-16β-methylpregna-4,9-diene-3,20-dione [20] (XX). Partial dehydrobromination of the 2α,4β-dibromide (XVI; R = Me) gave the corresponding 2-bromo-3-oxo-4-ene (XXI; R = Me) (cf. refs. 16, 18, 19) which was not fully purified.

Each of the 2,4-dibromo-3-ketones (XV, XVI; R = Me) gave the triene (XVII; R = Me) [20] on complete dehydrobromination, but rather better overall yields were obtained by using the total crude bromination product. Dehydrobromination could be effected with calcium carbonate in boiling dimethylacetamide,[9] but more reliable results attended the use of these reagents, together with lithium bromide at about 100°. Surprisingly,[16,19] the replacement of calcium carbonate with lithium carbonate was conducive to the formation of the 4,6-dien-3-one (XXII; R = Me). After removal of by-products with Girard's reagent P,[27] 21-acetoxy-17-hydroxy-16β-methylpregna-1,4,9-triene-3,20-dione [20,30] (XVII; R = Me) was obtained in about 50% overall yield from the Δ^9-compound (VII; R = Me).

The crude dehydrobromination products contained, besides the isomeric trienes (XVII and XXII; R = Me), at least one D-homo-compound (*e.g.*, XXIV); an isolated specimen had infrared absorption, optical rotation, and paper-chromatographic characteristics consistent with such a structure (cf. ref. 20). A band at 1810 cm.$^{-1}$ in the infrared spectra of some crude specimens of the triene (XVII; R = Me) was attributed to the carbonyl group in a 17α,21-oxide but we did not isolate a pure compound.



(XXIV)

The 16β-methyl-triene (XVII; R = Me) was converted into 9α-fluoro-11β,17,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione (XXIII) through the 9α,11β-bromohydrin and the 9β,11β-epoxide by methods similar to those reported elsewhere.[20,30]

Experimental

M. p.s were taken on the Kofler block and are uncorrected; " cap." refers to m. p.s (corrected) taken in a capilliary tube. Unless otherwise stated, ultraviolet and infrared spectra were measured for solutions in ethanol and bromoform, respectively. Optical rotations refer to 1·0 ± 0·3% solutions in chloroform at 22° ± 4°; optical rotatory dispersion [31] values are for 0·1% solutions in chloroform. Paper chromatograms were run at 35° on Whatman No. 2 papers with solvent F [32] or propylene glycol and toluene [33] (indicated by the letters F and Z respectively); the components were located with TSTZ spray [32] or reflex photography with an ultraviolet light source. The pure 20-oxo-17α,21-diols and their esters were assayed by the tetrazolium method [34] (with cortisone acetate as standard), the results being within ±5% of the theoretical values. Extracts in organic solvents were dried over magnesium sulphate before evaporation. Chromous chloride was made either by the reduction of the chromic salt [35] or, better, by dissolving 99·999% pure chromium (New Metals and Chemicals Ltd., Chancery Lane, London, W.C.2) in warm, dilute hydrochloric acid (3 mol.) under nitrogen.[36] Calcium carbonate in a suitably fine form was bought as " Calofort U " from J. and E. Sturge Ltd., 1, Whealeys Road, Birmingham. Charcoal (Nuchar G-190, unground) was obtained from the Pulp and Paper Co., 230, Park Avenue, New York 17, U.S.A. Dioxan, purified as described by Vogel,[37] was stored in the frozen state under nitrogen.

[30] Oliveto, Rausser, Herzog, Hershberg, Tolksdorf, Eisler, Perlman, and Pechet, *J. Amer. Chem. Soc.*, 1958, **80**, 6687.
[31] Klyne and Parker in " Technique of Organic Chemistry, Vol. I; Physical Methods of Organic Chemistry, Part III," Interscience Publ., Inc., New York, 1960, pp. 2335 *et seq.*
[32] Brooks, Hunt, Long, and Mooney, *J.*, 1957, 1175.
[33] Neher in " Chromatographic Reviews," Elsevier, Amsterdam, 1959, pp. 141 *et seq.*
[34] Mader and Buck, *Analyt. Chem.*, 1952, **24**, 666.
[35] Rosenkranz, Mancera, Gatica, and Djerassi, *J. Amer. Chem. Soc.*, 1950, **72**, 4077.
[36] Lux and Illmann, *Chem. Ber.*, 1958, **91**, 2143.
[37] Vogel, " Text-Book of Practical Organic Chemistry," Longman, Green and Co., London, 1948, p. 175.

21-*Acetoxy*-17-*hydroxy*-5α-*pregn*-9-*ene*-3,20-*dione* (I).—21-Acetoxy-11β,17-dihydroxy-5α-pregnane-3,20-dione was dehydrated as previously described;[2] the product was crystallised from chloroform and dried by refluxing it with toluene in a Dean–Stark apparatus to give the steroid (I), m. p. 243—254° (decomp.), $[\alpha]_D$ +69°. Complete removal of solvent was difficult; a sample sublimed at 180—200° *in vacuo* had m. p. 256—257°, $[\alpha]_D$ +71°. This compound was also prepared in good yield by refluxing the 11β-alcohol in glacial acetic acid containing lithium bromide [38] for 30 minutes.

21-*Acetoxy*-9α,11β-*dichloro*-17-*hydroxy*-5α-*pregnane*-3,20-*dione* (II; X = Y = Cl).—(*a*) The Δ^9-compound (I) (0·5 g.) in chloroform (75 ml.) containing pyridine (0·31 ml., 3 mol.) was treated with a solution of chlorine (106 mg., 1·1 mol.) in carbon tetrachloride (3·4 ml.). After 8 min. the mixture was washed successively with dilute sodium thiosulphate, dilute hydrochloric acid, aqueous sodium hydrogen carbonate, and water. The chloroform layer yielded a solid which crystallised from acetone to give the 9α,11β-*dichloride* (II; X = Y = Cl) (0·38 g., 64%), m. p. 205—209° (decomp.), $[\alpha]_D$ +84°, $\nu_{max.}$ 1744 and 1230 (21-OAc), 1725 (20-C=O) and 1705 cm.$^{-1}$ (3-C=O) (Found: C, 60·0; H, 6·9; Cl, 15·3. $C_{23}H_{32}Cl_2O_5$ requires C, 60·1; H, 7·0; Cl, 15·4%). Attempts to crystallise this material from methanol resulted in degradation to products containing the 7,9-diene chromophore.

(*b*) To a stirred suspension of the Δ^9-compound (I) (10·0 g.) in acetic acid (600 ml.) containing anhydrous lithium chloride (60 g.) was added *N*-chlorosuccinimide (4·0 g.; 94% active halogen) and anhydrous hydrogen chloride (1·2 g.) in tetrahydrofuran (12 ml.). Complete solution was achieved in 10 min.; after a total of 1 hr. the solution was poured into water, and the product was crystallised from acetone, giving the dichloride (II; X = Y = Cl) (6·0 g., 51%), m. p. 207—210° (decomp.), $[\alpha]_D$ +84°. The mother-liquors, treated under nitrogen with chromous chloride, gave the Δ^9-compound (I) (1·5 g.), m. p. 238—240°.

Dehydrochlorination of 21-*Acetoxy*-9α,11β-*dichloro*-17-*hydroxy*-5α-*pregnane*-3,20-*dione* (II; X = Y = Cl).—The dichloride (4·0 g.) was added to a stirred suspension of lithium chloride (1·5 g.) and lithium carbonate (4·8 g.) in dimethylacetamide (60 ml.) at 95°. After 20 min. the mixture was poured into an excess of dilute hydrochloric acid and the steroid (3·9 g.), $\lambda_{max.}$ ($E^{1\%}_{1\,cm.}$) at 235 (244), 242 (269), 250 (186), and 271 mμ (26), was isolated with methylene chloride. This material was refluxed for 5 hr. in toluene (150 ml.) containing maleic anhydride (1·5 g.). The resulting crystals were recrystallised twice from ethanol and dried azeotropically with xylene, giving the 7,9-*diene* (III), m. p. 228—230°, $[\alpha]_D$ +87°, $\lambda_{max.}$ 234·5 (ε 14,900), 241·5 (ε 16,200), and 250 mμ (ε 10,900), $\nu_{max.}$ 1745 and 1240 (21-OAc), 1728 (20-C=O) and 1708 cm.$^{-1}$ (3-C=O). Despite extensive drying the analysis was not very satisfactory and infrared spectra showed traces of moisture (Found: C, 70·9; H, 7·8. $C_{23}H_{30}O_5$ requires C, 71·5; H, 7·8%).

Similar crude dehydrochlorination products were obtained when the dichloride (II; X = Y = Cl) was treated with calcium carbonate in dimethylacetamide at the b. p., 95°, and 55°, whereas no reaction was apparent at room temperature over a period of 18 hr. Rapid dehydrochlorination also occurred in boiling collidine. In comparison with these results the cross-conjugated ketone 21-acetoxy-9α,11β-dichloro-17-hydroxypregna-1,4-diene-3,20-dione was unchanged by being heated at 55° or at 95° for 6 hr. in dimethylacetamide containing calcium carbonate.

21-*Acetoxy*-2,4-*dibromo*-9α,11β-*dichloro*-17-*hydroxy*-5α-*pregnane*-3,20-*dione* (V; X = Y = Cl).—The dichloride (II; X = Y = Cl) (1·0 g.) in acetic acid (90 ml.) was treated with a solution of bromine (770 mg., 2·1 mol.) in acetic acid (11 ml.). The optical rotation of the mixture reached a steady value in 16 hr. Dilution with water gave crude 2,4-dibromo-9α,11β-dichloride (V; X = Y = Cl), m. p. 141—143°, $[\alpha]_D$ +56° (Found: halogen, 38·4. Calc. for $C_{23}H_{30}Br_2Cl_2O_5$: halogen, 37·4%), which was not purified.

Dehydrohalogenation of this material resulted in preferential elimination of hydrogen chloride.

Dehalogenation of 21-*Acetoxy*-9α,11β-*dichloro*-17-*hydroxy*-5α-*pregnane*-3,20-*dione* (II; X = Y = Cl).—(a) *With chromous chloride.* The dichloride (0·17 g.) in acetone (40 ml.) consumed 1·97 equiv. of M-chromous chloride (5 ml.) in 30 min. at room temperature, to give the Δ^9-compound (I), m. p. 235—247°.

(b) *By hydrogenation.* The dichloride (II; X = Y = Cl) (0·46 g., 1 mmole) in tetrahydrofuran (40 ml.) containing triethylamine (0·42 ml., 3 mmoles) was hydrogenated in the presence

[38] Herz and Fried, U.S.P. 2,842,568.

of pre-reduced 10% palladium–charcoal (0·10 g.). After 18 min. hydrogen uptake was complete and the Δ^9-compound (I) (0·38 g.), m. p. 241—244°, was isolated; crystallisation from chloroform raised the m. p. to 253—257°.

Dehalogenation of the Tetrahalide (V; X = Y = Cl).—(a) *With chromous chloride.* Reduction of the tetrahalide with chromous chloride in acetone or acetic acid was conducted at −30°, 0°, or room temperature. The products contained bromine and chlorine and showed infrared absorption at 1725 cm.$^{-1}$ attributed to α-monobromo-ketones. No pure compound was isolated.

(b) *By hydrogenation.* The tetrahalide (V; X = Y = Cl) (0·5 g.) in acetic acid (50 ml.) was hydrogenated in the presence of pre-reduced 10% palladium–charcoal (50 mg.). The product, isolated after the uptake of 2 mol. of hydrogen, was proved by mixed m. p. and infrared spectra to be the dichloride (II; X = Y = Cl) (0·28 g., 74%). Hydrogenation in tetrahydrofuran containing triethylamine (4 equiv.) gave the 9-ene (I) (81%) and the dichloride (II; X = Y = Cl) (13%).

21-*Acetoxy*-9α-*bromo*-11β-*formoxy*-17-*hydroxy*-5α-*pregnane*-3,20-*dione* (II; X = H·CO_2, Y = Br).—A stirred suspension of 21-acetoxy-17-hydroxy-5α-pregn-9-ene-3,20-dione (I) (5·0 g.) and sodium formate (20 g.) in 98% formic acid (50 ml.) was treated under nitrogen with *N*-bromosuccinimide (2·0 g.) during 1 hr. Then the clear solution was stirred for 2 hr. The product (5·35 g.), isolated by dilution with water (1 l.), crystallised from ether–acetone to give the 9α-*bromo*-11β-*formate* (4·6 g., 70%), m. p. 152—157°. A specimen dried at 80° *in vacuo* had m. p. 159—161°, $[\alpha]_D$ +99°, $\nu_{max.}$ 1745 and 1236 (21-OAc), 1722 (20-C=O), and 1714 cm.$^{-1}$ (11β-formate) (Found: C, 55·6; H, 6·7; Br, 15·6. $C_{24}H_{33}BrO_7$ requires C, 56·1; H, 6·5; Br, 15·6%).

11β,21-*Diacetoxy*-9α-*bromo*-17-*hydroxy*-5α-*pregnane*-3,20-*dione* (II; X = OAc, Y = Br).—When a similar preparation to the last was carried out with lithium acetate (20 g.) in acetic acid (250 ml.) the diacetate (4·1 g., 61%) was obtained with m. p. 135—137°, $[\alpha]_D$ +102°, $\nu_{max.}$ 1740 and 1235 (21-OAc), 1725 and 1250 (11β-OAc), 1725 (20-C=O), and 1705 cm.$^{-1}$ (3-C=O). This compound could not be freed from traces of solvent and water and a satisfactory analysis was not obtained. These products gradually darkened to a deep purple when left at room temperature for several weeks.

Stability of the 9α-*Bromo*-11β-*acylates to Dehydrobrominating Conditions.*—The formate (II; X = H·CO_2, Y = Br) (0·25 g.) was added to a stirred suspension of calcium carbonate (0·25 g.) in dimethylacetamide (10 ml.) at *ca.* 95°. Aliquot parts taken after 5, 10, and 20 min. showed ultraviolet, infrared, and paper-chromatographic characteristics (Z) consistent with those of the 7,9-diene (III). A similar result was obtained by treating the diacetate (II; X = OAc, Y = Br) with calcium carbonate in refluxing dimethylacetamide for 5 min.

21-*Acetoxy*-9β,11β-*epoxy*-17-*hydroxy*-5α-*pregnane*-3,20-*dione* (VI) *from the* 9α-*Bromo*-11β-*formate* (II; X = H·CO_2, Y = Br).—The bromo-formate (5 g.) in dioxan (200 ml.) and water (50 ml.) was stirred under nitrogen and treated with 2N-sodium hydroxide (15 ml.) during 20 min. at such a rate that the pH did not rise above 10. Water (100 ml.) was added during the reaction to maintain a one-phase mixture. After adjustment of the pH to *ca.* 6 the solution was evaporated to a slurry (50 ml.) and diluted with water, to give a white solid (3·2 g.). Acetylation with acetic anhydride in pyridine on the steam-bath for 30 min. and crystallisation of the product from ethyl acetate gave the 9β,11β-epoxide (VI) (2·8 g., 71%), m. p. 214—217°, $[\alpha]_D$ +71°, further identified by comparison of its infrared spectrum with that of authentic material.[3] The mother-liquors yielded a second crop (0·3 g., 8%), m. p. 210—215°.

Treatment of 21-*Acetoxy*-9α-*bromo*-11β-*formoxy*-17-*hydroxy*-5α-*pregnane*-3,20-*dione* (II; X = H·CO_2, Y = Br) *with Potassium Acetate in Ethanol.*—The formate (5 g.) was added to anhydrous potassium acetate (20 g.) in boiling absolute ethanol (500 ml.). After 2 hr. the mixture was concentrated to *ca.* 60 ml. and poured into water (1 l.). The oily product, isolated with methylene chloride, was treated with acetic anhydride in pyridine for 30 min. on a steam-bath. A part (2·0 g.) of the isolated material (3·2 g.) in benzene (40 ml.) was separated into its components by chromatography on Florisil (60 g.). Individual fractions were submitted to paper chromatography (Z); combination of appropriate fractions and crystallisation gave three compounds (characterised by their ultraviolet, infrared, and paper-chromatographic behaviour): (*a*) the 7,9-diene (III) (0·31 g.), m. p. 223—226°, $[\alpha]_D$ +79° (*c* 0·31), (*b*) the 9β,11β-epoxide (VI) (0·22 g.), m. p. 208—211°, $[\alpha]_D$ +72° (*c* 0·61), and (*c*) 21-acetoxy-17-hydroxy-5α-pregnane-3,11,20-trione [28] (0·12 g.), m. p. 225—232°, $[\alpha]_D$ +105° (*c* 0·67).

21-*Acetoxy*-9β,11β-*epoxy*-17-*hydroxy*-16β-*methyl*-5α-*pregnane*-3,20-*dione* (VIII; R = Me).—A stirred suspension of 21-acetoxy-17-hydroxy-16β-methyl-5α-pregn-9-ene-3,20-dione [1] (VII; R = Me) (25 g.) in dioxan (1 l.) containing 0·46N-perchloric acid (100 ml.) was treated in the dark and in a nitrogen atmosphere with *N*-bromoacetamide (11·2 g., 1·3 mol.) at room temperature during 15 min. Thereafter the mixture was stirred for 20 min. The solution was treated with aqueous sodium pyrosulphite until a negative starch–iodide test was obtained. 2N-Sodium hydroxide (95 ml.) was added in 10 min. to bring the pH of the solution to *ca.* 10; during this period it was necessary to add water (600 ml.) to maintain a one-phase solution. After a further 20 min. the pH was adjusted to *ca.* 6 with acetic acid and the solution was concentrated *in vacuo* to 800 ml. Extraction with chloroform and ethyl acetate led to isolation of crude 9β,11β-epoxy-17,21-dihydroxy-16β-methyl-5α-pregnane-3,20-dione as a yellow solid (26 g.). Acetylation with acetic anhydride in pyridine for 30 min. on the steam-bath and crystallisation of the ester from ethanol gave the *acetoxy*-9β,11β-*epoxide* (VIII; R = Me) (20·8 g., 80%), m. p. 209—214° raised by further crystallisation to 213—217°, $[\alpha]_D$ +97°, $\nu_{max.}$ 1742 and 1235 (21-OAc), 1728 (20-C=O), and 1708 cm.$^{-1}$ (3-C=O) (Found: C, 69·2; H, 8·1. $C_{24}H_{34}O_6$ requires C, 68·9; H, 8·2%).

21-*Acetoxy*-9α-*fluoro*-11β,17-*dihydroxy*-16β-*methyl*-5α-*pregnane*-3,20-*dione* (IX; R = Me).—The epoxide (VIII; R = Me) (10·0 g.) in chloroform (150 ml.) was cooled to −30° and added to a similarly cooled solution (60 ml.; 32·2% w/v) of hydrogen fluoride in tetrahydrofuran in a Polythene bottle. The mixture was stirred with a Polythene-coated magnetic stirrer and allowed to warm to 0° in 45 min. Thereafter the temperature was maintained at 0—5° for 5 hr. The mixture was poured into a solution of potassium carbonate (70 g.) in ice-water. Extraction with chloroform led to a crude product (10·6 g.), and three crystallisations from benzene gave the 16β-*methyl-fluorohydrin* (IX; R = Me) (4·7 g., 45%), m. p. 215—219°, $[\alpha]_D$ +75°, $\nu_{max.}$ 1744 and 1236 (21-OAc), 1728 (20-C=O) and 1708 cm.$^{-1}$ (3-C=O) (Found: C, 66·0; H, 8·0. $C_{24}H_{35}FO_6$ requires C, 65·7; H, 8·0%).

21-*Acetoxy*-2,4-*dibromo*-9α-*fluoro*-11β,17-*dihydroxy*-16β-*methyl*-5α-*pregnane*-3,20-*dione* (X; R = Me).—(a) *In acetic acid.* The fluorohydrin (IX; R = Me) (1·6 g.) in acetic acid (40 ml.) was treated successively with 6·6N-hydrogen bromide in acetic acid (1·6 ml.) and a solution of bromine (1·23 g., 2·1 mol.) in acetic acid (4·5 ml.). Mutarotation ceased within 40 min. Dilution with water gave the crude 2,4-dibromide (X; R = Me) (1·8 g., 83%), $[\alpha]_D$ +38°, $\lambda_{max.}$ 250 mμ ($E^{1\%}_{1cm.}$ 19·2), R_F 0·30 (strong) and 0·70 (weak) (Z). (b) *In dioxan.* In a similar manner the fluorohydrin (IX; R = Me) (2·0 g.) in dioxan (50 ml.) containing 0·6N-hydrogen bromide in acetic acid (2 ml.) was treated with bromine (1·47 g.). After 30 min. the crude dibromide (2·5 g., 92%), $[\alpha]_D$ +44°, was isolated. This product showed no excessive ultraviolet absorption at 250 mμ.

Selective Dehydrobromination of the Dibromide (X; R = Me).—The dibromide (X; R = Me) (1·7 g.; from a bromination in acetic acid) was added to a vigorously stirred suspension of calcium carbonate (1·1 g.) and anhydrous lithium bromide (0·8 g.) in dimethylacetamide (17 ml.) kept at 100° under nitrogen. After 1 hr. the cooled mixture was poured into an excess of dilute hydrochloric acid, to give a solid (1·2 g.). Chromatography on Florisil (30 g.) gave the crude monobromide as a foam (XIII; R = Me) (0·55 g.), $[\alpha]_D$ +128°, $\lambda_{max.}$ 241 mμ ($E^{1\%}_{1cm.}$ 268), $\nu_{max.}$ 1742 and 1238 (21-OAc), 1728 (20-C=O) and 1680 cm.$^{-1}$ (2-bromo-Δ^4-3-ketone), R_F 0·24 (strong) and 0·65 (weak) (Z) (Found: Br, 14·9. Calc. for $C_{24}H_{32}BrFO_6$: Br, 15·5%), which was not purified. A similar material, but showing only one spot (R_F 0·25) on paper chromatography was isolated from the crude dibromide (X; R = Me) obtained by bromination in dioxan.

21-*Acetoxy*-9α-*fluoro*-11β,17-*dihydroxy*-16β-*methylpregn*-4-*ene*-3,20-*dione* (XIV; R = Me).—A stirred solution of the 2-bromo-Δ^4-3-ketone (XIII; R = Me) (0·52 g.) in acetone (35 ml.) was debrominated, under nitrogen, with 2·3M-chromous chloride (3 ml.), during 30 min. Isolation with chloroform gave an off-white solid (0·42 g.), $[\alpha]_D$ +135°, $\lambda_{max.}$ 238·5 mμ (ε 15,000), R_F 0·1 (strong), 0·46 (weak) (Z). Two crystallisations from ethyl acetate gave pure 21-*acetoxy*-9α-*fluoro*-11β-17-*dihydroxy*-16β-*methylpregn*-4-*ene*-3,20-*dione* (XIV; R = Me) [0·25 g., 22% based on the dibromide (X; R = Me)], m. p. 223—226° with sintering from 212°, $[\alpha]_D$ +154°, (Found: C, 66·3; H, 7·6. $C_{24}H_{33}FO_6$ requires C, 66·0; H, 7·6%), $\lambda_{max.}$ 238 mμ (ε 16,600), $\nu_{max.}$ 3620 (OH), 1742, and 1238 (21-OAc), 1728 (20-C=O), and 1662 cm.$^{-1}$ (Δ^4-3-C=O), $\nu_{max.}$ (in Nujol) 1740 and 1248 (21-OAc), 1726 (20-C=O), 1664 and 860 cm.$^{-1}$ (Δ^4-3-C=O), R_F 0·10 (Z). Further crystallisation from acetone–hexane gave a polymorphic form [cf. the fluorohydrin (XIV;

R = H)], m. p. 202—206°, $[\alpha]_D$ +153°, $\lambda_{max.}$ 238 mμ (ε 16,800). Taub *et al.*[20] give m. p. 215—225°, $[\alpha]_D$ +170°, $\lambda_{max.}$ 238 mμ (ε 16,800) in MeOH.

Conversion of 21-*Acetoxy*-17-*hydroxy*-5α-*pregn*-9-*ene*-3,20-*dione* (VII; R = H) *into the Fluorohydrin* (XIV; R = H).—The route used for this conversion was that described above for the 16β-methyl series. The Δ^9-steroid (VII; R = H) was converted into the saturated fluorohydrin (IX; R = H), m. p. 227—233°, $[\alpha]_D$ +65°, as previously described.[3] Bromination in acetic acid for 15 min. as described above for the 16β-methyl analogue gave a crude dibromide (X; R = H) (93%) that showed no ultraviolet absorption at *ca.* 250 mμ and only showed one spot on a paper chromatogram (Z). Selective dehydrobromination gave the 2-bromo-Δ^4-compound (XIII; R = H) which crystallised from acetone–hexane as prisms, m. p. 155—168° (decomp.), $[\alpha]_D$ +155°, $\lambda_{max.}$ 240 mμ (ε 15,600), $\nu_{max.}$ 1742 and 1240 (21-OAc), 1730 (20-C=O) 1680, 1630 and 865 cm.$^{-1}$ (2-bromo-Δ^4-3-ketone) (Found: C, 54·8; H, 6·1. Calc. for $C_{23}H_{30}BrFO_6$: C, 55·1; H, 6·0%). Fried [15] reports m. p. 174—175°, $[\alpha]_D$ +136°, $\lambda_{max.}$ 242 mμ (ε 12,200). Debromination of this material with chromous chloride gave 21-acetoxy-9α-fluoro-11β,17-dihydroxypregn-4-ene-3,20-dione [3,7,12] (XIV; R = H), m. p. 208—212° and 231—233° (polymorphic change), $[\alpha]_D$ +149°, $\lambda_{max.}$ 237·5 mμ (ε 16,300), in 43% yield based on the dibromide (X; R = H).

Complete Dehydrobromination of the Dibromide (X; R = H).—The crude dibromide (X; R = H) (1·37 g.) was added to a stirred suspension of calcium carbonate (0·7 g.) in boiling dimethylacetamide (48 ml.). After 80 min. the mixture was cooled and the crude product was isolated by pouring the whole into dilute hydrochloric acid; it (0·98 g.) had $\lambda_{max.}$ ($E^{1\%}_{1\,cm.}$) 241·5 (230) and 276 mμ (250). This material (0·96 g.) in ethanol (15 ml.) containing acetic acid (1·5 ml.) was boiled for 30 min. with Girard's reagent P (0·5 g.). The cooled mixture was poured into sodium hydrogen carbonate solution (150 ml.) and the unchanged material was isolated with ethyl acetate, purified by chromatography on Florisil (5 g.), and crystallised from ethyl acetate, to give the $\Delta^{1,4}$-3-ketone (XI) (0·17 g., 17%), m. p. 230—244° raised by a further crystallisation to 242—247°, $[\alpha]_D$ +103·5° (in acetone), $\lambda_{max.}$ 237·5 mμ (ε 15,600), further identified by comparison of its infrared spectrum with that of authentic material.[3,13,15]

The material forming a Girard's P derivative was regenerated by acidifying the aqueous layer to pH ~ 1 with hydrochloric acid. Isolation and purification as described above gave the $\Delta^{4,6}$-3-ketone (XII) (0·15 g., 15%), m. p. 212—216°, $[\alpha]_D$ +135°, $\lambda_{max.}$ 280 mμ (ε 23,900), $\nu_{max.}$ 1745 and 1235 (21-OAc), 1728 (20-C=O), 1655 and 880 cm.$^{-1}$ ($\Delta^{4,6}$-3-C=O) (Found: C, 65·3; H, 7·0. Calc. for $C_{23}H_{29}FO_6$: C, 65·7; H, 7·0%). For this compound Fried *et al.*[13,15] report m. p. 216—217°, $[\alpha]_D$ +135°, $\lambda_{max.}$ 281 mμ (ε 23,000); Hirschmann *et al.*[14] give m. p. 208°, $[\alpha]_D$ −106° (in acetone), $\lambda_{max.}$ 281 mμ (ε 25,100).

A similar dehydrobromination in which the steroid concentration was 3·2 times as great gave a crude product containing ~70% (ultraviolet and infrared spectra) of the $\Delta^{4,6}$-diene (XII). The addition of anhydrous lithium bromide to the dehydrobromination reaction increased the rate of reaction and also gave mixtures containing a high proportion of the $\Delta^{4,6}$-isomer (XII).

21-*Acetoxy*-17-*hydroxypregna*-1,4,9-*triene*-3,20-*dione* (XVII; R = H).—(a) *From the* Δ^9-*compound* (VII; R = H). A stirred suspension of the Δ^9-steroid (1·0 g.; rubbed through a 100-mesh sieve) in pure dioxan (100 ml.) containing 6·6N-hydrogen bromide in acetic acid (1·66 ml.) was treated (2 min.) with a 1·26N-solution of bromine in acetic acid (8·17 ml., 2·0 mol.). The steroid dissolved during the next 6 min. and after a total of 20 min. the mixture was poured into 15% sodium acetate solution (750 ml.). The crude dibromo-steroid was isolated as a white powder by extraction into ether and removal of solvent *in vacuo* at <25°; last traces of dioxan were eliminated by freeze-drying.

An intimate mixture of this material with calcium carbonate (0·75 g.) was added to a stirred suspension of calcium carbonate (0·75 g.) in refluxing dimethylacetamide (15 ml.) under nitrogen. After 15 min. the mixture was cooled and poured into ice-cold 2N-hydrochloric acid (200 ml.). Extraction with ethyl acetate led to a brown solid (0·93 g.) that was boiled for 15 min. in ethanol (30 ml.) containing acetic acid (0·9 ml.) and Girard's reagent P (0·6 g.). The portion that failed to form a water-soluble derivative was isolated with chloroform, dissolved in benzene, and purified on a column of charcoal, the fractions being tested by paper chromatography. Combination of appropriate fractions (0·56 g.) and crystallisation from acetone–light petroleum (b. p. 60—80°) (1 : 5) gave the triene (XVII; R = H) (0·41 g., 42%), m. p. 221—226°, $[\alpha]_D$ +54° (*c* 0·38), $\lambda_{max.}$ 237·5 mμ (ε 14,700).

Use of chloroform, acetic acid, or tetrahydrofuran as solvents for the bromination resulted in isolation of the triene (XVII; R = H) in 33, 28, and 26% yield respectively. In the case of chloroform there was evidence of uptake of bromine from hydrogen bromide alone.

(b) *By dehydration of* 21-*acetoxy*-11β,17-*dihydroxypregna*-1,4-*diene*-3,20-*dione*. A solution of prednisolone acetate [39] (40 g.) in dry pyridine (600 ml.) at *ca.* −25° was added, with stirring and under nitrogen, to a mixture of freshly distilled thionyl chloride (16 ml.) in dry pyridine (600 ml.) prepared and maintained at *ca.* −25°. After 45 min. at this temperature the reaction mixture was poured with stirring into ice and dilute hydrochloric acid. After 1 hr. the solid was collected, washed with water, and dried *in vacuo* [37·5 g., 98%; R_F 0·73, and 0·92 (weak) (F)]. The fast-running impurity remains unidentified.

The product was purified by dissolving it in boiling ethanol (2·5 l.) and ethyl acetate (300 ml.) and adding a solution of sodium pyrosulphite (250 g.) in water (500 ml.). The resulting suspension was boiled for 4 hr., cooled, and poured into 10% sodium pyrosulphite (10 l.). The solid was collected, dried, and crystallised from ethyl acetate, to give the triene (XVII; R = H) (27·8 g., 73%), m. p. 224—227°, $[\alpha]_D$ +54°, R_F 0·73 (F), $\lambda_{max.}$ 237·5 mμ (ε 15,700), $\nu_{max.}$ 1743, and 1235 (21-OAc), 1725 (20-C=O), 1658, and 888 cm.$^{-1}$ ($\Delta^{1,4}$-3-C=O). Hogg *et al.*[22] give m. p. 223—226°, $[\alpha]_D$ +75°; however, constants quoted elsewhere [4,7] are in good agreement with ours.

21-*Acetoxy*-2α,4α-*dibromo*-17-*hydroxy*-16β-*methyl*-5α-*pregn*-9-*ene*-3,20-*dione* (XV; R = Me).—(*a*) The Δ^9-compound (VII; R = Me) (10 g.) was suspended in dioxan (125 ml.) and acetic acid (125 ml.) and stirred under nitrogen. Successive additions of 0·6N-hydrogen bromide in acetic acid (9·0 ml.) and 0·94M-bromine in acetic acid (56·0 ml., 2·0 mol.) were completed in 4 min. The pale yellow solution was stirred for a total of 22 min. to allow for completion of mutarotation. The solid, obtained by pouring the mixture into sodium acetate in ice-water, was extracted with ether, washed with aqueous sodium hydrogen carbonate, dried, and recovered at <30°. Crystallisation of the product from a mixture of ethyl acetate (120 ml.) and hexane (500 ml.) gave the 2α,4α-*dibromide* (XV; R = Me) as needles (6·45 g., 47%), m. p. 201—203° (cap.; corr.) with decomposition, $[\alpha]_D$ +45°, R.D. [α] (*318* mμ) +1430°, $\nu_{max.}$ 1745 (2α,4α-dibromo-3-ketone), 1745 and 1236 (21-OAc), and 1728 cm.$^{-1}$ (20-C=O) (Found: C, 51·2; H, 5·8; Br, 29·0. $C_{24}H_{32}Br_2O_5$ requires C, 51·5; H, 5·8; Br, 28·5%).

During one experiment the crude dibromide, isolated by extraction with methylene chloride, darkened and partly decomposed when left at *ca.* 5° overnight. During recovery of starting material (VII; R = Me) by hydrogenolytic debromination we also isolated a small amount of 21-*acetoxy*-16β-*methyl*-5α-*pregna*-9,16-*diene*-3,20-*dione* as birefringent plates, m. p. 174—181°, $[\alpha]_D$ +77° (*c* 0·52), $\lambda_{max.}$ 251 mμ (ε 8200), $\nu_{max.}$ 1744 and 1230 (21-OAc), 1706 (3-C=O), 1668, and 1600 (16-methyl-Δ^{16}-20-ketone) (Found: C, 75·2; H, 8·4. $C_{24}H_{32}O_4$ requires C, 75·0; H, 8·4%).

(*b*) *From* 21-*acetoxy*-4α-*bromo*-17-*hydroxy*-16β-*methyl*-5α-*pregn*-9-*ene*-3,20-*dione* (XIX).—The 4α-bromide (XIX) (2·0 g.) in dioxan–acetic acid was treated with hydrogen bromide and bromine (1·05 mol.) for 6 min. as described above; it gave the 2α,4α-dibromide (XV; R = Me) (1·66 g., 71%), m. p. 192—200° (decomp.), $[\alpha]_D$ +49° (Found: Br, 28·9%).

21-*Acetoxy*-2α,4β-*dibromo*-17-*hydroxy*-16β-*methyl*-5α-*pregn*-9-*ene*-3,20-*dione* (XVI; R = Me).—The mother-liquors from the crystallisation of the 2α,4α-dibromide described in (*a*) above were evaporated and the resulting solid was thrice crystallised from ether, giving white needles, m. p. 120—126°, $[\alpha]_D$ −22°. Two crystallisations from acetone gave the 2α,4β-*dibromide* (XVI; R = Me), m. p. 188° (decomp., softening from 170°), $[\alpha]_D^{23}$ −26°, R.D. [α] (*330* mμ), −705°, (*295*), +645°, $\nu_{max.}$ 1740, 1236 (21-OAc), 1740 (2α,4β-dibromo-3-ketone), 1728 cm.$^{-1}$ (20-C=O) (Found: C, 51·3; H, 5·7; Br, 29·0. $C_{24}H_{32}Br_2O_5$ requires C, 51·5; H, 5·8; Br, 28·5%).

Debromination of the Dibromides (XV and XVI; R = Me).—Hydrogenation of the 2α,4α-dibromide (0·50 g.) in 1 : 1 acetic acid–ethyl acetate (50 ml.) containing N-potassium acetate in acetic acid (2·75 ml.) over pre-reduced 5% palladium–carbon, gave the Δ^9-compound (VII; R = Me) (identified by mixed m. p. and infrared spectra) in 78% yield. Similarly, debromination of the 2α,4β-dibromide was accomplished in 79% yield.

21-*Acetoxy*-4α-*bromo*-17-*hydroxy*-16β-*methyl*-5α-*pregn*-9-*ene*-3,20-*dione* (XIX).—The 2α,4α-dibromide (XV; R = Me) (2·0 g.) in acetone (100 ml.) was stirred at −45° under nitrogen while 0·99M-chromous chloride (7·2 ml., 2·0 mol.) was added dropwise. The mixture was allowed to warm to 10° in 35 min., then most of the acetone was removed *in vacuo*. Addition of water and crystallisation of the resulting white solid (1·71 g.) from ethyl acetate gave the

[39] Herzog, Payne, Jevnik, Gould, Shapiro, Oliveto, and Hershberg, *J. Amer. Chem. Soc.*, 1955, **77**, 4781.

4α-*bromide* (XIX) (0·77 g., 45%) as prisms, m. p. 186—191° (decomp.), $[\alpha]_D$ +34°, R.D. [α] (*313* mμ), +1240°, (*270*), −1500°, $\nu_{max.}$ 1742, and 1235 (21-OAc) and 1725 cm.$^{-1}$ (20-C=O and 4α-bromo-3-ketone) (Found: C, 60·2; H, 7·0; Br, 16·3. $C_{24}H_{33}BrO_5$ requires C, 59·9; H, 6·9; Br, 16·6%).

21-*Acetoxy*-2α-*bromo*-17-*hydroxy*-16β-*methyl*-5α-*pregn*-9-*ene*-3,20-*dione* (XVIII).—(a) *By bromination of the* 9-*ene* (VII; R = Me). The ketone (VII; R = Me) (2·0 g.) was dissolved in acetic acid (120 ml.) with warming; the cooled (26°) solution was treated under nitrogen with 0·24M-bromine in acetic acid (24·7 ml., 1·2 mol.) during 5 min. After a total of 15 min. an excess of sodium acetate solution (300 ml.) was added, and the resulting white solid (2·1 g.), $[\alpha]_D$ +89°, was crystallised three times from aqueous acetone, giving prisms of the 2α-*bromide* (XVIII), m. p. 211—212° (decomp.), $[\alpha]_D$ +93°, R.D. [α] (*313* mμ), +1740°, $\nu_{max.}$ 1745, 1236 (21-OAc), 1730 (20-C=O and 2α-bromo-3-ketone) (Found: C, 59·6; H, 6·9; Br, 16·8%).

(b) *By debromination of the* 2α,4β-*dibromide* (XVI; R = Me). A stirred solution of the 2α,4β-dibromide (1·0 g.) in acetone (50 ml.) at −45° under carbon dioxide was treated with 1·06M-chromous chloride (3·4 ml., 2·0 mol.). The mixture warmed to 10° in 26 min.; the acetone was removed *in vacuo* and water was added to precipitate a white solid (0·83 g.), $[\alpha]_D$ +74°. Two crystallisations from aqueous acetone gave the 2α-bromo-ketone (XVIII) (0·58 g., 68%), m. p. 208—211°, $[\alpha]_D$ +92°, identified by infrared spectra with the specimen described above.

21-*Acetoxy*-17-*hydroxy*-16β-*methylpregna*-4,9-*diene*-3,20-*dione* (XX).—The 4α-bromide (XIX) (1·0 g.) and finely powdered semicarbazide (0·4 g.) were stirred in a mixture of t-butyl alcohol (80 ml.) and methylene chloride (40 ml.) under carbon dioxide until the solution was colourless (3 hr.).[27] Isolation by standard means gave a halogen-free (Beilstein test) white solid (0·95 g.), $\lambda_{max.}$ 270·5 mμ ($E^{1\%}_{1\,cm.}$ 601). This material in acetic acid (30 ml.) was heated with redistilled pyruvic acid (0·58 ml., 4 mol.) and water (10 ml.) on a steam-bath for 30 min. The crystalline product, dissolved in methylene chloride, was washed with sodium hydrogen carbonate solution and dried. Three crystallisations of the product from ethanol gave plates of the 4,9-diene (XX), m. p. 213—215°, $[\alpha]_D$ +130°, $\lambda_{max.}$ 238·5 mμ (ε 16,030), $\nu_{max.}$ 1742 and 1230 (21-OAc), 1730 (20-C=O), 1662, 1618, and 866 cm.$^{-1}$ (Δ^4-3-C=O) (Found: C, 71·9; H, 8·2. Calc. for $C_{24}H_{32}O_5$: C, 72·0; H, 8·1%). Taub *et al.*[20] give m. p. 210—215°, $[\alpha]_D$ +145°, $\lambda_{max.}$ 238 mμ (ε 17,000 in MeOH), and describe the isolation of a D-homo-isomer, m. p. 154—157°, $[\alpha]_D$ +95°, of the Δ^4-3-ketone (XX). In the infrared spectrum of our specimen reduced intensity of the band at 1410 cm.$^{-1}$ indicated the presence of some (*ca.* 15%) D-homo-compound.

21-*Acetoxy*-17-*hydroxy*-16β-*methylpregna*-1,4,9-*triene*-3,20-*dione* (XVII; R = Me).—(a) *From the* 2α,4α-*dibromide* (XV; R = Me). To a stirred suspension of calcium carbonate (0·96 g.) and lithium bromide (1·1 g.) in dimethylacetamide (30 ml.) at 96·5° under nitrogen was added a mixture of the 2α,4α-dibromide (2·4 g.) and calcium carbonate (2·4 g.). After 22 hr. the product was isolated as a pale brown solid (1·65 g.; $\lambda_{max.}$ 238 mμ, $E^{1\%}_{1\,cm.}$ 371) by pouring the cooled reaction mixture into 2N-hydrochloric acid (500 ml.). This material (1·6 g.) and Girard's P reagent (0·4 g.) were refluxed for 1 hr., under nitrogen, in methanol (26 ml.) containing acetic acid (1·3 ml.). The fraction not forming a water-soluble derivative was isolated with ethyl acetate and treated with charcoal; concentration of the solution to 15 ml. yielded birefringent prisms (0·89 g., 52%) of the triene (XVII; R = Me), m. p. 219—223°, $[\alpha]_D$ +70°, $[\alpha]_D$ +73° (in dioxan), R.D. in dioxan (*c* 0·067) [α] (*320* mμ) +1810°, $\lambda_{max.}$ 238·5 mμ (ε 15,750), $\nu_{max.}$ 1742 and 1236 (21-OAc), 1728 (20-C=O), 1660 and 888 cm.$^{-1}$ ($\Delta^{1,4}$-3-C=O) (Found: C, 72·1; H, 7·6. Calc. for $C_{24}H_{30}O_5$: C, 72·3; H, 7·6%). Two further crops (0·16 g. and 40 mg.) brought the total yield to 64%. Taub *et al.*[20] give m. p. 208—212°, $[\alpha]_D$ +75°, $\lambda_{max.}$ 238 mμ (ε 15,200) in MeOH. The physical constants for this material recorded [30] by Oliveto *et al.* differ considerably from those given above. A personal communication from the Schering Corporation has confirmed that the constants obtained during the present work are correct.

Hydrolysis of the 21-acetate (XVII; R = Me) (1·5 g.) under nitrogen with potassium hydrogen carbonate in aqueous methanol [7] for 4 hr. at room temperature, and crystallisation of the product from ethyl acetate, gave 17,21-*dihydroxy*-16β-*methylpregna*-1,4,9-*triene*-3,20-*dione* (0·65 g.), m. p. 219—225° (cap.), $[\alpha]_D$ +43° (*c* 0·44 in dioxan), $\lambda_{max.}$ 237 mμ (ε 15,800), $\nu_{max.}$ (in Nujol) 1720 (20-C=O), 1660 and 880 cm.$^{-1}$ ($\Delta^{1,4}$-3-C=O) (Found: C, 73·9; H, 8·0. $C_{22}H_{28}O_4$ requires C, 74·1; H, 7·9%).

(b) *From the* 2α,4β-*dibromide* (XVI; R = Me). Dehydrobromination of the 2α,4β-dibromide as in (a) gave the triene (62%), m. p. 225—228°, $[\alpha]_D$ +71° (*c* 0·4 in dioxan), $\lambda_{max.}$ 238

mμ (ε 15,800). A second crop (10%), m. p. 213—219°, was obtained from the mother-liquors.

(c) *From* 21-*acetoxy*-17-*hydroxy*-16β-*methyl*-5α-*pregn*-9-*ene*-3,20-*dione* (VII; R = Me) *without isolation of the dibromide.* The crude dibromide, prepared from the 16β-methyl-Δ^9-steroid (VII; R = Me) (50 g.) as described above, was obtained as a solution in ethyl acetate. Concentration *in vacuo* at room temperature (nitrogen bubbler) gave a gel, which was dissolved in dimethylacetamide (75 ml.); residual ethyl acetate was removed by evaporation *in vacuo*. This solution was added during 10 min. to a stirred suspension of calcium carbonate (98 g.) and lithium bromide (32 g.) in dimethylacetamide (800 ml.) at 98° under nitrogen. After 40 hr. the mixture was concentrated *in vacuo* to *ca.* 500 ml., cooled, and poured with stirring into 2N-hydrochloric acid (5 l.). The resulting buff solid was washed with sodium hydrogen carbonate solution and then with water until the washings were neutral The crude dry product (43·6 g., 88%), after being purified by treatment with Girard's reagent P and with charcoal, yielded the triene (XVII; R = Me) (19·2 g., 39%), m. p. 221—225°, 214—218° (cap.), $[\alpha]_D$ +71° (*c* 1·45 in dioxan), $\lambda_{max.}$ 238 mμ (ε 15,300). Two further crops brought the total yield to 50%.

An increase in the concentration of the dibromide in the dehydrobromination mixture, other factors being the same, led to increased contamination of the product with the isomeric $\Delta^{4,6,9}$-triene (XXII). This effect was only partially redressed by increasing the proportion of calcium carbonate.

Dehydrobromination at temperatures in the range 90° to 150° provided comparable yields of the triene (XVII; R = Me), the optimum time of reaction decreasing with increasing temperature (*e.g.*, 4 hr. and 130°). Reactions in boiling dimethylacetamide with calcium carbonate were less successful; in one case dehydrobromination of a crude dibromide (1·5 g.; prepared by bromination in acetic acid) led to the isolation of a D-*homo-compound* (*e.g.*, XXIV), (0·27 g.), m. p. 242—245° (cap.), $[\alpha]_D$ −7° (*c* 0·5 in dioxan), R_F 0·78 (Z), $\lambda_{max.}$ 237 mμ (ε 16,000), $\nu_{max.}$ 1734 and 1240 (21-OAc), 1702 (20-C=O), 1662 and 888 cm.$^{-1}$ ($\Delta^{1,4}$-3-C=O) (Found: C, 72·9; H, 7·6. $C_{24}H_{30}O_5$ requires C, 72·3; H, 7·6%). The factors leading to dehydrobromination products containing relatively high proportions of D-homo-isomers remain obscure.

21-*Acetoxy*-17-*hydroxy*-16β-*methylpregna*-4,6,9-*triene*-3,20-*dione* (XXII; R = Me).—The crystalline 2α,4α-dibromide (XV; R = Me) (5·0 g.) was dehydrobrominated with lithium carbonate (4·0 g.) and lithium bromide (2·3 g.) in dimethylacetamide (31 ml.) at 98° for 15 hr. under nitrogen. The crude product (3·3 g.), isolated in the usual manner, had $\lambda_{max.}$ 239 mμ ($E^{1\%}_{1cm.}$ 296) and 275 mμ ($E^{1\%}_{1cm.}$ 263). This product (3·27 g.) and Girard's reagent P (1·65 g.) were heated at reflux for 45 min. in methanol (50 ml.) containing acetic acid (2·5 ml.). The mixture was poured into 4% sodium hydrogen carbonate solution (500 ml.) and extracted with ethyl acetate, to give the crude 1,4,9-triene (XVII; R = Me) (2·1 g.), $\lambda_{max.}$ 237·5 mμ (ε 14,000). The Girard-forming material (0·6 g.) was isolated with ethyl acetate from the acidified (pH ~1) layer. Purification of this product on Florisil (20 g.) gave the 4,6,9-*triene* (0·26 g.), as birefringent plates (from ethyl acetate), m. p. 227—228° (crystal change to needles at >204°), $[\alpha]_D$ −15° (in dioxan), $\lambda_{max.}$ 282 mμ (ε 26,650), $\nu_{max.}$ 1742 and 1232 (21-OAc), 1725 (20-C=O), 1657 and 875 cm.$^{-1}$ ($\Delta^{4,6}$-3-C=O) (Found: C, 72·2; H, 7·6. $C_{24}H_{30}O_5$ requires C, 72·3; H, 7·6%).

We have not investigated the effect of varying the rate of stirring or the particle size of the lithium carbonate on the ratio of isomeric trienes (XVII and XXII; R = Me) formed.

21-*Acetoxy*-2α-*bromo*-17-*hydroxy*-16β-*methylpregn*-4,9-*diene*-3,20-*dione* (XXI).—The 2α,4β-dibromide (XVI; R = Me) (0·25 g.) in collidine (2·5 ml.) was heated under nitrogen on the steam-bath for 3 hr. The product was isolated with ethyl acetate, triturated with ether, and crystallised from aqueous acetone to give a specimen of the 2-bromo-Δ^4-3-ketone (XXI; R = Me), as plates, m. p. 181—182° (cap.), $\lambda_{max.}$ 242 mμ (ε 12,900).

A similar product, obtained by treating the 2α,4α-dibromide (XV; R = Me) with calcium carbonate and lithium bromide in dimethylacetamide at room temperature (~20°) for 25 days, crystallised from methanol to give the 2α-*bromo*-Δ^4-3-*ketone* (XXI; R = Me), m. p. 171—172° (cap., decomp.), $[\alpha]_D$ +126° (in dioxan), $\lambda_{max.}$ 242 mμ (ε 14,800), $\nu_{max.}$ 1742 and 1236 (21-OAc), 1728 (20-C=O), and 1680 cm.$^{-1}$ (2α-bromo-Δ^4-3-ketone) (Found: C, 59·5; H, 6·6; Br, 16·0. $C_{24}H_{31}BrO_5$ requires C, 60·1; H, 6·6; Br, 16·7%).

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