926. *By-ways of Synthesis of Cortisone from Hecogenin. Part I.* 9 : 11-*Dehydrohecogenin as Intermediate in Preparation of* 11-*Oxygenated Compounds* (11-*Oxotigogenin and* 3β-*Acetoxy*-17α-*hydroxy*allo-*pregnane*-11 : 20-*dione*).

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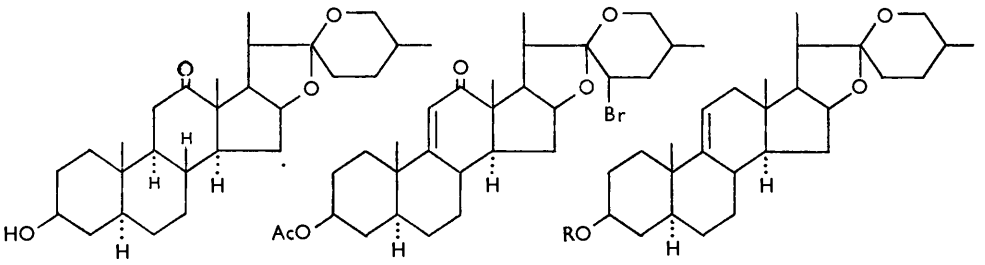
9 : 11-Dehydrohecogenin can be reduced to 9 : 11-dehydrotigogenin, which, by way of the 9 : 11-bromohydrin, yields 11-oxotigogenin. By another route, degradation of 9 : 11-dehydrotigogenin to 3β-acetoxy*allo*-pregna-9(11) : 16-dien-20-one was carried out, and by a series of reactions, again through a 9 : 11-bromohydrin, 3β-acetoxy-17α-hydroxy*allo*pregnane-11 : 20-dione was prepared. 11β-Acetoxy-compounds in this series have been prepared, but are not possible intermediates in the synthesis of cortisol.

THE many stages of the known routes for the partial synthesis of cortisone from hecogenin [1] can be accomplished in different orders and by different means; some of these other routes have now been explored. In this paper we describe a method of introducing an oxygen atom at $C_{(11)}$ which can be applied at either the sapogenin stage or the pregnane stage and

[1] For references see Cameron, Evans, Hamlet, Hunt, Jones, and Long, *J.*, 1955, 2807.

provides another practical method for bringing about the change from 12-oxo- to 11-oxo-compounds.[2-5] This is essentially the series of reactions applied by Hicks and Wallis [6] who obtained methyl 3α-acetoxy-11-oxocholanate from methyl 3α-acetoxy-9(11)-cholenate in very poor yield.

Methods for obtaining 9 : 11-dehydrotigogenin (III; R = H) from hecogenin (I) have been described by Djerassi, Martinez, and Rosenkranz [7] and by Hirschmann, Snoddy, and Wendler.[8] The latter method, in our hands, gave a rather poor yield, and we devoted our



(I) (II) (III)

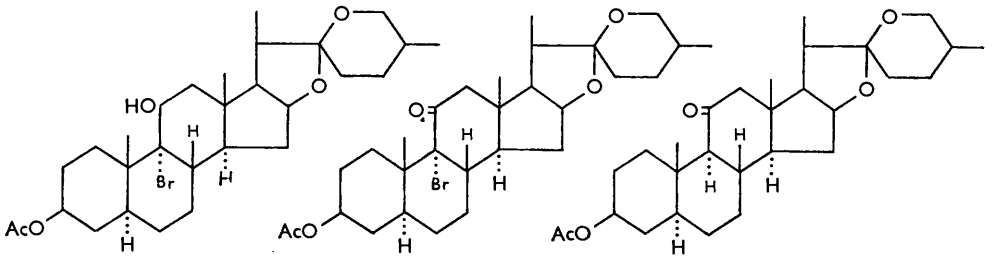
attention to improving the yields of the four stages of the former method. Hecogenin acetate is conveniently brominated in benzene, and the product treated directly with boiling collidine gave 23-bromo-9 : 11-dehydrohecogenin acetate (II) in an over-all yield of 71%. The described [2] method of debromination with zinc in acetic acid went rather slowly, and loss of αβ-unsaturated ketone occurred, but reduction with a zinc–copper couple gave 81% of 9 : 11-dehydrohecogenin acetate. Removal of the 12-oxo-group by preparing a thioketal with ethanedithiol or 3-hydroxypropane-1 : 2-dithiol followed by treatment with Raney nickel gave yields of 40 and 37%, respectively, but reduction by the Huang-Minlon modification of the Wolff–Kishner reaction and reacetylation of the crude product gave 9 : 11-dehydrotigogenin acetate (III; R = Ac) in 75% yield. Two routes in continuance of the synthesis were then followed. In the first, 9 : 11-dehydrotigogenin acetate was converted by *N*-bromoacetamide into the 9 : 11-bromohydrin (IV) which, by oxidation to the 9α-bromo-11-oxo-compound (V) and removal of bromine yielded 11-oxotigogenin acetate (VI).

The second route was the degradation of 9 : 11-dehydrotigogenin by way of the ψ-compound and oxidation to 3β-acetoxy*allo*pregna-9(11) : 16-dien-20-one, which was obtained in a yield of 77%. The 9(11)-ethylenic linkage was inert to oxidation by chromium trioxide under the conditions used. As both ethylenic linkages were attacked by per-acids, the preferred path was by preparation of the 16 : 17-epoxide by the action of alkaline hydrogen peroxide, conversion into the 16-bromo-17α-hydroxy-compound, and debromination with Raney nickel to give 3β-acetoxy-17α-hydroxy*allo*pregn-9(11)-en-20-one (cf. ref. 9). Hypobromous acid was then added to the 9(11)-ethylenic linkage, and oxidation and debromination yielded the known 3β-acetoxy-17α-hydroxy*allo*pregnane-11 : 20-dione. Both this compound and 11-oxotigogenin have already been used as intermediates in the synthesis of cortisone : a route to the biologically active 9α-halogeno-compounds is also opened by way of the 9 : 11-bromohydrin of the pregnene.

Concurrently with this work, an investigation was made of a synthesis of cortisol with a protected 11β-hydroxyl group introduced at an earlier stage, rather than obtained at the

[2] Djerassi, Martinez, and Rosenkranz, *J. Org. Chem.*, 1951, **16**, 303.
[3] Cornforth, Osbond, and Phillipps, *J.*, 1954, 907.
[4] Schmidlin and Wettstein, *Helv. Chim. Acta*, 1953, **36**, 1241.
[5] Chapman, Elks, and Wyman, *Chem. and Ind.*, 1955, 603.
[6] Hicks and Wallis, *J. Biol. Chem.*, 1946, **162**, 641.
[7] Djerassi, Martinez, and Rosenkranz, *J. Org. Chem.*, 1951, **16**, 1278.
[8] Hirschmann, Snoddy, and Wendler, *J. Amer. Chem. Soc.*, 1953, **75**, 3252.
[9] Julian, Meyer, Karpel, and Waller, *ibid.*, 1950, **72**, 5145.

end by reduction of the 11-oxo-group of cortisone. Normal acetylation of 11β-hydroxytigogenin yielded only a monoacetate,[3] but under forcing conditions (cf. Turner [10] and Huang-Minlon *et al.*[11]) a 3β : 11β-diacetate was obtained. However, hydrolysis of the 11β-acetoxyl group required such vigorous treatment with methanolic alkali that no



compound in the later stages of the synthesis would be likely to survive. In fact, 11β-hydroxytigogenin could be recovered from its diacetate, but 3β : 11β-diacetoxy-16 : 17-epoxy*allo*pregnan-20-one was broken down to unidentifiable products when an attempt was made to remove both acetyl groups. In the meantime, it has been shown [12,13] that 11β-formylation or 11β-trifluoroacetylation can be usefully employed in analogous series of reactions.

Experimental

M. p.s were determined in a Kofler apparatus with polarised light, and are corrected. Optical rotations were determined in chloroform solutions of concentrations within the limits 0·5—1·0%. Infrared absorption was measured with a double-beam instrument with a rock-salt prism (Perkin–Elmer Model 21), KBr or KCl discs being used unless otherwise stated.

23-*Bromo*-9 : 11-*dehydrohecogenin Acetate*.—Hecogenin acetate (25 g.) was brominated as described by Elks *et al.*[14] and the crude product boiled with collidine for 2 hr. The mixture was diluted with chloroform (250 ml.), and washed with dilute hydrochloric acid, sodium hydrogen carbonate solution, and water. Evaporation and treatment of the residue with methanol (150 ml.) yielded crude 23-bromo-9 : 11-dehydrohecogenin acetate (20·4 g.), m. p. 219—221° (decomp.), $\lambda_{max.}$ 238 mμ (log ε 4·12, in EtOH).

9 : 11-*Dehydrohecogenin Acetate*.—The bromo-derivative (6·2 g.) was dissolved in a mixture of dioxan (25 ml.) and industrial spirit (95% ethanol + 5% methanol) (225 ml.). To this was added a zinc–copper couple prepared from 30 g. of zinc, and the mixture was boiled under reflux for 8 hr. The solution was filtered, evaporated to half bulk, and then poured into water. The precipitate was taken up in chloroform; drying and evaporation left a residue which, after being boiled with methanol, yielded 9 : 11-dehydrohecogenin acetate (4·27 g.), m. p. 215—218°, $[\alpha]_D$ −10°, $\lambda_{max.}$ 238 mμ (log ε 4·18, in MeOH).

9 : 11-*Dehydrotigogenin Acetate*.—9 : 11-Dehydrohecogenin acetate (4·5 g.), ethylene glycol (105 ml.), and hydrazine hydrate (90%; 3 ml.) were boiled for 1 hr. To the cooled mixture potassium hydroxide (9·2 g.) in water (10 ml.) was added and the mixture was boiled for 20 min.; the condenser was then removed and water boiled off until the temperature of the mixture reached 197°. The condenser was then replaced and refluxing continued for 2½ hr. The mixture was cooled, acidified, and extracted with chloroform. The extract, washed and evaporated, gave a residue which was treated with acetic anhydride (10 ml.) and pyridine (10 ml.) for ½ hr. at 100°. The residue after evaporation was purified by chromatography on alumina. Benzene–light petroleum (b. p. 80—100°) (1 : 9) eluted 9 : 11-dehydrotigogenin acetate, m. p. 199—202·5° (from ethanol), $[\alpha]_D^{21}$ −57°; the yield was 2·75 g. (65% of theory), and 0·4 g. was obtained as a second crop.

[10] Turner, *J. Amer. Chem. Soc.*, 1952, **74**, 4220.
[11] Huang-Minlon, Wilson, Wendler, and Tischler, *ibid.*, p. 5394.
[12] Oliveto, Gerold, and Hershberg, *Arch. Biochem. Biophys.*, 1954, **49**, 244.
[13] Lardon and Reichstein, *Helv. Chim. Acta*, 1954, **37**, 443.
[14] Elks, Phillipps, Walker, and Wyman, *J.*, 1956, 4330.

11-*Oxotigogenin Acetate*.—9 : 11-Dehydrotigogenin acetate (0·5 g.) was dissolved in dioxan (70 ml.), water (15 ml.) added, and the solution filtered. *N*-Bromoacetamide (0·2 g.) was added, the flask was covered to exclude light, and 10% aqueous perchloric acid (4 ml.) was added. The mixture was shaken for 5 min., diluted with water to a volume of 250 ml., and kept at 5° for 30 min.; the precipitate was washed with water and dried *in vacuo*. This bromohydrin, acetic acid (30 ml.), and chromic acid (0·4 g.) in water (10 ml.) were shaken for 1 hr. and then filtered, and the product recovered by addition of water and extraction with ether. The washed, dried extract yielded a gum (0·44 g.) which gave from methanol 9α-*bromo*-11-*oxotigogenin acetate*, m. p. 201—206° (decomp.), $[\alpha]_D$ +60°, $\nu_{max.}$ 1730 (acetate), 1708 (ketone), 1248 cm.$^{-1}$ (acetate) and bands in the fingerprint region generally resembling those of the unbrominated compound (no band assignable to C–Br was visible) (Found: C, 63·4; H, 7·9; Br, 14·2. $C_{29}H_{43}O_5Br$ requires C, 63·2; H, 7·9; Br, 14·3%). This material was debrominated by boiling a solution in acetic acid (60 mg. in 2 ml.) with zinc dust (0·5 g.) for 1 hr. The mixture was taken to dryness under reduced pressure, the residue extracted with chloroform, and the extract evaporated. The residual gum crystallised from methanol in prisms, m. p. 217—228°, $[\alpha]_D^{22}$ −38·5°. Recrystallised from acetone, the m. p. rose to 222—230° (Found: C, 73·6; H, 8·9. Calc. for $C_{29}H_{44}O_5$: C, 73·7; H, 9·4%); the infrared absorption was identical with that of an authentic specimen of 11-oxotigogenin acetate.

3β-*Acetoxy*allo*pregna*-9(11) : 16-*dien*-20-*one*.—ψ-9 : 11-Dehydrotigogenin acetate was prepared by boiling 9 : 11-dehydrotigogenin acetate with octanoic acid [15] and acetylating the product (3·6 g.). The acetate, without purification, was oxidised directly by adding to its acetic acid solution (35 ml.) a solution (35 ml. of 4·5%) of chromic acid in 90% acetic acid. After ¾ hr. water was added and the solution extracted with ether. The extract was evaporated and the residue dissolved in benzene (40 ml.) and light petroleum (b. p. 40—60°) (50 ml.) and treated with alumina (50 g.). After 2 hr. the alumina was removed and the filtrate evaporated. The product yielded 3β-acetoxy*allo*pregna-9(11) : 16-dien-20-one, m. p. 171—173° (from methanol), $[\alpha]_D$ +101°, $[\alpha]_{5461}$ +124°, $\lambda_{max.}$ 238 mμ (log ε 3·95, in MeOH), $\nu_{max.}$ 1730 (acetate), 1660 (ketone), 1592 (double bond), 1250 (acetate), 823 (double bond) cm.$^{-1}$ (Found: C, 77·1; H, 9·6. Calc. for $C_{23}H_{32}O_3$: C, 77·5; H, 9·1%). Djerassi *et al.*[7] give m. p. 164—166°, $[\alpha]_D^{20}$ +67°, $\lambda_{max.}$ 238 mμ (log ε 4·07), $\nu_{max.}$ 1739, 1672, and 1239 cm.$^{-1}$.

3β-*Acetoxy*-16 : 17-*epoxy*allo*pregn*-9(11)-*en*-20-*one*.—To 3β-acetoxy*allo*pregna-9(11) : 16-dien-20-one (0·27 g.) in ethanol (60 ml.) was added hydrogen peroxide (30%; 2 ml.) and 2N-sodium hydroxide (2 ml.). After 48 hr. at 3° water was added and the precipitate (0·18 g.; m. p. 180—205°) was acetylated. 3β-*Acetoxy*-16 : 17-*epoxy*allo*pregn*-9(11)-*en*-20-*one* had m. p. 208—212° (from methanol), $[\alpha]_D$ +88° (Found: C, 73·9; H, 8·8. $C_{23}H_{32}O_4$ requires C, 74·2; H, 8·7%), $\nu_{max.}$ 3400 (hydroxyl), 1735 (acetate), 1705 (ketone), 1248 (acetate), 860 (epoxide), 815 cm.$^{-1}$ (double bond). A band at 1300 cm.$^{-1}$ seems to be peculiar to this and the unesterified compound (obtained in impure form).

3β-*Acetoxy*-16-*bromo*-17α-*hydroxy*allo*pregn*-9(11)-*en*-20-*one*.—The epoxy-acetate (0·1 g.) in acetic acid (5 ml.) was treated with 48% hydrobromic acid (2 drops). After 12 hr. the solution was poured into water. The precipitate, when crystallised from aqueous methanol, yielded 3β-*acetoxy*-16-*bromo*-17α-*hydroxy*allo*pregn*-9(11)-*en*-20-*one* as silvery plates (60 mg.), m. p. 180—184°, $[\alpha]_D$ +8° (Found: C, 60·8; H, 7·5; Br, 17·9. $C_{23}H_{33}O_4Br$ requires C, 60·9; H, 7·35; Br, 17·7%).

3β-*Acetoxy*-17α-*hydroxy*allo*pregn*-9(11)-*en*-20-*one*, obtained by boiling the bromohydrin (550 mg.) for 3 hr. in ethanol (25 ml.) with Raney nickel (3 g.), formed silvery plates (from ethanol), m. p. 198·5—200·5°, $[\alpha]_D^{23}$ −15° (Found: C, 73·4; H, 8·9. $C_{23}H_{34}O_4$ requires C, 73·7; H, 9·13%), $\nu_{max.}$ 1710, with shoulder at 1720 (ketone and acetate), 1260 (acetate), 816 cm.$^{-1}$ (double bond).

3β-*Acetoxy*-9α-*bromo*-17α-*hydroxy*allo*pregnane*-11 : 20-*dione*.—The pregnenone (0·43 g.) was dissolved in dioxan (60 ml.) and water (16 ml.), and *N*-bromoacetamide (0·215 g.) and 1% aqueous perchloric acid (4 ml.) were added successively. The flask was protected from light and shaken for 5 min., and water added to a volume of 250 ml. After ½ hr. at 5° the precipitate was dried [0·1 g., m. p. 155—162° (decomp.), $\nu_{max.}$ 3460 (s) (hydroxyl), 1705 (vs) with shoulder at 1725, 1265, 1240 (acetate), 743 cm.$^{-1}$ (C–Br)].

The bromohydrin was not purified because of its instability, but was oxidised directly. To a suspension in acetic acid (0·1 g. in 8 ml.) a solution of chromic oxide (0·1 g.) in water (2 ml.) was added. After 30 min. water was added and the mixture extracted with ether. The washed

[15] Cameron, Evans, Hamlet, Hunt, Jones, and Long, *J.*, 1955, 2807.

and dried extract was evaporated and the residue (85 mg.) crystallised from acetone–hexane to give the desired 9α-*bromo-compound* (59 mg.), m. p. 195—200° (decomp.), $[\alpha]_D^{22}$ +132° (Found : C, 58·4; H, 7·0. $C_{23}H_{33}O_5Br$ requires C, 58·8; H, 7·1%), $\nu_{max.}$ 3420 (hydroxyl), 1728 (acetate), 1697 (ketone), 1250 (acetate), 743 cm.$^{-1}$ (C–Br).

3β-*Acetoxy*-17α-*hydroxy*allo*pregnane*-11 : 20-*dione*.—The 9α-bromo-ketone (52 mg.) in ethyl acetate (25 ml.) was hydrogenated for 4 hr. in presence of 2% palladium–strontium carbonate (130 mg.). Removal of catalyst, evaporation of solvent, and crystallisation of the residue twice from hexane yielded 3β-acetoxy-17α-hydroxy*allo*pregnane-11 : 20-dione, m. p. 171—174° (Found : C, 70·6; H, 8·6. Calc. for $C_{23}H_{34}O_5$: C, 70·7; H, 8·8%), $\nu_{max.}$ 3440 (hydroxyl), 1730 (acetate), 1705 (ketone), 1250 cm.$^{-1}$ (acetate) {Pataki *et al.*[16] give m. p. 171—173°, $[\alpha]_D^{20}$ +8°, $\nu_{max.}$ (in $CHCl_3$) 1720 and 1700 cm.$^{-1}$ and free hydroxyl band}.

Authentic 3β : 17α-dihydroxy*allo*pregnane-11 : 20-dione, kindly made available to us by Dr. J. Elks of Glaxo Laboratories, yielded a 3-acetate, m. p. 175—176·5°, $[\alpha]_D^{22}$ +10° (Found : C, 70·8; H, 8·85%), having an infrared absorption identical with that of the material prepared as above.

11β-*Hydroxytigogenin Diacetate*.—(*a*) 11β-Hydroxytigogenin (0·3 g.) was kept overnight in a mixture of acetic anhydride (1 ml.), acetic acid (1 ml.), and toluene-*p*-sulphonic acid (50 mg.). The solution was poured into sodium hydrogen carbonate solution and extracted with ether. The washed and dried extract yielded a residue (0·25 g., 77%), m. p. 106—110°, on crystallisation from acetone. Recrystallisation gave the 3β : 11β-*diacetate*, m. p. 141—142·5°, $[\alpha]_D^{21}$ −35° (Found : C, 71·8; H, 9·5. $C_{31}H_{48}O_5$ requires C, 72·0; H, 9·4%). The infrared absorption (in Nujol) showed no hydroxyl band, but 1730 (acetate) and 1250—1240 cm.$^{-1}$ (acetate) bands were strong and the spiroketal bands were present. The same compound was obtained in lower yield by using the same reaction mixture as above, but with one drop of 60% perchloric acid instead of the toluene-*p*-sulphonic acid, or by treatment of 11β-hydroxytigogenin (300 mg.) with *iso*propenyl acetate (2 ml.) and toluene-*p*-sulphonic acid(100 mg.).

A partial hydrolysis of the diacetate (0·9 g.) was achieved by dissolving it in a mixture of chloroform (10 ml.) and methanol (3·5 ml.) and adding water (3·5 ml.) followed by concentrated hydrochloric acid (2·1 ml.), keeping the temperature $\not>$23°. After 48 hr. at 5° the product was recovered by evaporation. Purification was extremely difficult : a material which separated from light petroleum (b. p. 60—80°) was amorphous and had m. p. 202·5—205°, $[\alpha]_D^{22}$ −39°. The infrared absorption distinguished it from the diacetate or the 3-monoacetate. The (?)11β-monoacetate in Nujol showed $\nu_{max.}$ 3240 (bonded hydroxyl), with a shoulder at 3160 and acetate bands at 1732 and at 1270—1240 cm.$^{-1}$ (complex). The 3-monoacetate in Nujol has $\nu_{max.}$ 3480, 1715, and 1270 cm.$^{-1}$.

Attempts were made to hydrolyse the 11-monoacetate by 0·5N-ethanolic potassium hydroxide at room temperature or by 0·3N-sodium methoxide in boiling methanol, but without success, for the infrared absorption was unchanged. Complete hydrolysis resulted from boiling it for 1 hr. with 4% potassium hydroxide in ethanol. With 2% potassium hydroxide the starting material was recovered.

3β : 11β-*Diacetoxy*allo*pregn*-16-*en*-20-*one*.—This was obtained by oxidation of 11β-hydroxy-ψ-tigogenin triacetate, prepared by the usual method,[16] but not purified or characterised. It formed crystals from light petroleum (b. p. 60—80°), having m. p. 111° and 148—156°, $\lambda_{max.}$ 238 mμ (log ε 3·8, in EtOH) (Found : C, 73·9; H, 8·8. $C_{25}H_{36}O_5$ requires C, 72·1; H, 8·7%). Infrared absorption (in Nujol) showed no hydroxyl, but bands at 1730 (acetate), 1665 (ketone), 1590 (double bond), and 1250 cm.$^{-1}$ (broad; acetate).

11β-*Acetoxy*-16 : 17-*epoxy*-3β-*hydroxy*allo*pregnan*-20-*one* was prepared by treatment of the last-named compound with alkaline hydrogen peroxide and formed crystals [from benzene–light petroleum (b. p. 60—80°)], m. p. 176—177° (Found : C, 70·7; H, 8·5. $C_{23}H_{34}O_5$ requires C, 70·7; H, 8·8%), $\nu_{max.}$ (in Nujol) 3300 and shoulder at 2920 (hydroxyl), 1730 (acetate), 1700 (ketone), 1240 (acetate), and 856 cm.$^{-1}$ (epoxide).

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[16] Pataki, Rosenkranz, and Djerassi, *J. Amer. Chem. Soc.*, 1952, **74**, 5615.