896. *Compounds Related to the Steroid Hormones. Part VII.*[1] *Preparation of* $\Delta^{9(11)}$*-Steroids from* 11β*-Trifluoroacetates.*

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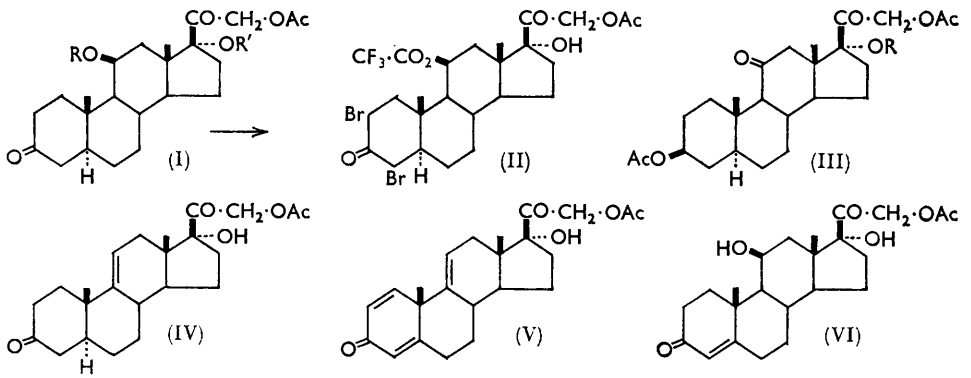
Trifluoroacetylation of 21-acetoxy-11β,17-dihydroxy-5α-pregnane-3,20-dione gave the 21-acetate 11,17-bistrifluoroacetate, which could be hydrolysed selectively to the 21-acetate 11-trifluoroacetate. 2,4-Dibromination of this diester proceeded without loss of the trifluoroacetoxy-group, but treatment of the product with calcium carbonate in boiling dimethylacetamide gave 21-acetoxy-17-hydroxypregna-1,4,9-triene-3,20-dione. A similar elimination of the 11β-trifluoroacetoxy-group occurred when the unbrominated 11β-trifluoroacetate was treated with the same reagent.

An earlier publication [2] from these Laboratories described the preparation of some 11β-acyloxy-steroids; for the most part they proved disappointingly prone to undergo elimination under the acid conditions employed in the conversion of a 3-oxo-5α-steroid into its 2,4-dibromo-derivative. In extension of this work, we have examined the bromination and dehydrobromination of 21-acetoxy-17-hydroxy-11β-trifluoroacetoxy-5α-pregnane-3,20-dione (I; R = CF_3·CO, R′ = H), in the hope of avoiding some of the difficulties associated with bromination of 3-oxo-steroids containing free 11β-hydroxy-groups and, at the same time, of being able ultimately to hydrolyse the 11β-ester grouping without damaging the cortical side chain.[3]



Treatment of 21-acetoxy-11β,17-dihydroxy-5α-pregnane-3,20-dione (I; R = R′ = H) with trifluoroacetic anhydride in pyridine and isolation of the product by dilution of the reaction mixture with ether before addition of water gave the 21-acetate 11,17-bistrifluoroacetate (I; R = R′ = CF_3·CO). As the 17-trifluoroacetoxy-group in the bistrifluoroacetate is readily hydrolysed in aqueous solution, dilution of the acylation mixture with water before extraction of the product gave the 21-acetate 11-trifluoroacetate (I; R = CF_3·CO, R′ = H) in good yield. Further hydrolysis of this diester with alkali was non-stoicheiometric, 1·3 equiv. of sodium hydroxide in methanol–methylene chloride proving sufficient to remove both the ester groups. However, a better product was obtained by use of two equiv. of alkali, as assessed by reacetylation of the hydrolysis product to the 21-acetate (I; R = R′ = H) in 74% rather than 57% yield.

Dibromination of the 21-acetate 11-trifluoroacetate (I; R = CF_3·CO, R′ = H) in acetic acid gave a crude 2,4-dibromo-compound (II),[3a] which, judged by its infrared

[1] Part VI, preceding paper.
[2] Evans, Green, Hunt, Long, Mooney, and Phillipps, *J.*, 1958, 1529.
[3] (*a*) B.P. 824,109; (*b*) U.S.P. 2,800,489.

absorption,[4] was essentially the 2α,4α-dibromo-isomer. Dehydrobromination of either the crude or the partially purified dibromo-compound (II) by boiling it in dimethylacetamide in the presence of calcium carbonate [5] gave similar products, in which the trifluoroacetoxy-group was no longer present. Purification of the product from the crude dibromo-compound yielded 36·5% of 21-acetoxy-17-hydroxypregna-1,4,9-triene-3,20-dione (V), identical with a sample obtained by dehydration of 21-acetoxy-11β,17-dihydroxypregna-1,4-diene-3,20-dione.[1] The trienedione (V) is a useful source of biologically active 9α-halogeno-compounds.

A somewhat similar reaction involving simultaneous dehydrobromination and elimination of an 11α-methanesulphonyloxy-group has been reported [6] to give a good yield in the preparation of 21-acetoxy-17-hydroxy-16α-methylpregna-1,4,9-triene-3,20-dione.

Elimination of the 11β-trifluoroacetoxy-group by boiling dimethylacetamide containing calcium carbonate also occurred with the unbrominated diester (I; R = CF_3·CO, R′ = H), the Δ^9-steroid (IV) being obtained in high yield. Under similar conditions, the 17-trifluoroacetoxy-group in 3β,21-diacetoxy-17-trifluoroacetoxy-5α-pregnane-11,20-dione (III; R = CF_3·CO) [prepared from the 17-hydroxy-compound (III; R = H) with trifluoroacetic anhydride in pyridine] was not eliminated, but it was apparently hydrolysed during working up with water, the product being simply the 17-hydroxy-compound (III; R = H).

The use of collidine for the dehydrobromination was also examined. The 11-trifluoroacetate (I; R = CF_3·CO, R′ = H) could be recovered after being boiled with collidine, but if the dibromo-compound (II) was treated similarly the sole isolated product, obtained in only 7·5% yield, was the 1,4,9-triene (V). This contrasts with the Patent claim to have obtained 11β,17,21-trihydroxypregna-1,4-diene-3,20-dione from 2,4-dibromo-11β,17,21-tristrifluoroacetoxy-5α-pregnane-3,20-dione by dehydrobromination with collidine and subsequent hydrolysis of the ester groups.[3a]

Treatment of the crude 2,4-dibromo-compound (II) with sodium iodide in acetone containing bromoacetone [7] and subsequent reduction with chromous chloride gave a mixture of saturated and αβ-unsaturated ketones, which still contained trifluoroacetoxy-groups. Alkaline hydrolysis of the ester groups and reacetylation gave a product from which cortisol acetate (VI) was isolated in 13% yield. This yield is little better than the 10% obtained previously without protection of the 11β-hydroxyl group.[2]

Experimental

M. p.s were measured with a Kofler block; optical rotations and ultraviolet and infrared absorptions are for solutions in $CHCl_3$, EtOH, and $CHBr_3$, respectively, unless otherwise stated.

21-Acetoxy-11β,17-bistrifluoroacetoxy-5α-pregnane-3,20-dione (I; R = R′ = CF_3·CO).—21-Acetoxy-11β,17-dihydroxy-5α-pregnane-3,20-dione (1·0 g.) was added to a mixture of pyridine (11 ml.) and trifluoroacetic anhydride (2 ml.) at room temperature, and after 30 min. the mixture was diluted with ether and washed with 2N-hydrochloric acid, aqueous sodium hydrogen carbonate, and water. Removal of the solvent from the dried ethereal solution left a froth (0·6 g.), which showed no absorption for hydroxyl in its infrared spectrum. Addition of water to a cold solution of the froth in methanol gave the *bistrifluoroacetate* as a methanol solvate, m. p. 85—90°, $[\alpha]_D$ +20°, $\nu_{max.}$ 1778 (CF_3·CO_2), 1750 and 1224 (21-OAc), 1734 (20-C=O), 1706 (C=O), and 3620 and 1012 cm.$^{-1}$ (MeOH). The analytical sample was desolvated at 90°/0·1 mm. (Found: C, 54·6; H, 5·7; F, 17·8. $C_{27}H_{32}F_6O_8$ requires C, 54·2; H, 5·4; F, 19·0%).

A solution of the bistrifluoroacetate (50 mg.) in alcohol (4 ml.) and water (1 ml.) became acidic on being heated on a steam-bath for 20 min., and dilution with water then gave the

[4] Jones, Ramsay, Herling, and Dobriner, *J. Amer. Chem. Soc.*, 1952, **74**, 2828.
[5] Green and Long, *J.*, 1961, 2532.
[6] Wieland, Heusler, and Wettstein, *Helv. Chim. Acta*, 1960, **43**, 523.
[7] Evans, Hamlet, Hunt, Jones, Long, Oughton, Stephenson, Walker, and Wilson, *J.*, 1956, 4356.

11-monotrifluoroacetate (30 mg.), m. p. 165—170°, with an infrared spectrum identical with that of the material prepared as in the following experiment.

21-Acetoxy-17-hydroxy-11β-trifluoroacetoxy-5α-pregnane-3,20-dione (I; R = CF_3·CO, R′ = H).—21-Acetoxy-11β,17-dihydroxy-5α-pregnane-3,20-dione (4·0 g.) was treated as in the foregoing experiment, but the reaction mixture was poured into water before extraction of the product into ether. The extracted product crystallised from aqueous alcohol, to give the *11-trifluoroacetate* (3·87 g., 78%), m. p. 177—179°, $[\alpha]_D$ +83°, which on further crystallisation from ethyl acetate–hexane gave the analytical sample, m. p. 181—182°, $[\alpha]_D$ +84° (Found: C, 59·6; H, 6·5; F, 10·3. $C_{25}H_{33}F_3O_7$ requires C, 59·7; H, 6·6; F, 11·3%), $\nu_{max.}$ 1774 (CF_3·CO_2), 1744 and 1222 (21-OAc), 1722 (20-C=O), and 1708 cm.$^{-1}$ (C=O).

Hydrolysis of 21-Acetoxy-17-hydroxy-11β-trifluoroacetoxy-5α-pregnane-3,20-dione.—The diester (2·0 g.) in methylene chloride (80 ml.) was treated under nitrogen with 0·104N-sodium hydroxide in methanol (84 ml., 2 equiv.), and after 20 min. the solution was acidified with 1% acetic acid (25 ml.), concentrated to small bulk *in vacuo*, and diluted with water. The solid precipitate (1·37 g., 95%), m. p. 215—225°, showed no bands for acetate or trifluoroacetate in its infrared spectrum, and on acetylation with acetic anhydride and crystallisation gave the 21-acetate (I; R = R′ = H) (74%), m. p. 220—223°, $[\alpha]_D$ +79·5°.

In another experiment with 1·3 equiv. of alkali both the ester groups were removed but after reacetylation the 21-acetate (I; R = R′ = H) was obtained in only 57% yield.

21-Acetoxy-2,4-dibromo-17-hydroxy-11β-trifluoroacetoxy-5α-pregnane-3,20-dione (II).—Bromine (0·42 ml.) was added during 1 min. to a stirred solution of the 11-trifluoroacetate (I; R = CF_3·CO, R′ = H) (6·0 g.) in acetic acid (90 ml.) at room temperature, and after 30 min. the solution was poured into water to precipitate the crude dibromo-compound (7·83 g., 99%), m. p. 120—135°, $[\alpha]_D$ +57°. Crystallisation from ether–hexane, then benzene–hexane, gave dense prisms of the *2,4-dibromo-compound*, m. p. 165° (decomp.), $[\alpha]_D$ +65° (Found: C, 46·2; H, 5·1; Br, 23·5; F, 8·3. $C_{25}H_{31}Br_2F_3O_7$ requires C, 45·5; H, 4·7; Br, 24·2; F, 8·6%), $\nu_{max.}$ 1778 (CF_3·CO_2), 1748 (21-OAc and 2,4-dibromo-3-ketone), 1225 (21-OAc), and 1726 cm.$^{-1}$ (20-C=O) (lit.,[3a] m. p. 175—182°).

Dehydrobromination of the Dibromo-compound (II).—(a) *With calcium carbonate in dimethylacetamide.* The foregoing crude dibromo-compound (II) (2·5 g.) in cold dimethylacetamide (5 ml.) was added during 1·5 min. to a refluxing suspension of finely divided calcium carbonate (2·0 g.) in dimethylacetamide (20 ml.). After 12 min. the suspension was concentrated *in vacuo*, cooled, and poured into water (200 ml.). The aqueous suspension was acidified with 2N-hydrochloric acid, the product was extracted with methylene chloride, and the extract was washed with 2N-hydrochloric acid, aqueous sodium hydrogen carbonate, and water. Removal of solvent from the dried extract *in vacuo* left a brown solid (1·35 g.), m. p. 195—210°, $\lambda_{max.}$ 239 mμ ($E^{1\%}_{1cm.}$ 354). A solution of the solid (1·25 g.) in ethyl acetate (25 ml.) and benzene (75 ml.) was decolorised by passage through a column of Florisil (50 g.) and elution with the same solvent mixture (600 ml.). The eluted steroid crystallised from ethyl acetate–hexane to give 21-acetoxy-17-hydroxypregna-1,4,9-triene-3,20-dione (V) (0·524 g., 36·5%), m. p. 225—228°, $[\alpha]_D$ +51°, $\lambda_{max.}$ 239 mμ (ε 14,000), with an infrared spectrum identical with that of material prepared by dehydration of 21-acetoxy-11β,17-dihydroxypregna-1,4-diene-3,20-dione.[1]

A similar experiment starting with crystallised dibromo-compound (II) (500 mg.) gave a crude product (260 mg.), m. p. 190—205°, $\lambda_{max.}$ 239 mμ ($E^{1\%}_{1cm.}$ 370), with an infrared spectrum similar to that of the above crude product.

(b) *With collidine.* The crude dibromo-compound (II) (3·85 g.) was added to boiling collidine (30 ml.) containing water (0·1 ml.) and after 1 hr. the solvent was removed at 100° *in vacuo*. A solution of the residue in methylene chloride was washed with 2N-hydrochloric acid, aqueous sodium hydrogen carbonate, and water. Removal of solvent from the dried solution left a gum (1·8 g.), $\lambda_{max.}$ 240 mμ ($E^{1\%}_{1cm.}$ 334) (Found: Br, 11·2%), which from its infrared spectrum contained <50% of $\Delta^{1,4}$-3-oxo-compounds.

The crude product (1·7 g.) and Girard reagent P (1·0 g.) were boiled under reflux for 30 min. in ethanol (30 ml.) and acetic acid (3 ml.), and the cooled solution was poured into an excess of aqueous sodium hydrogen carbonate. The unreactive $\Delta^{1,4}$-3-ketones (0·8 g.) were extracted into ethyl acetate and after treatment with Florisil as in (a) crystallised to give the $\Delta^{1,4,9}$-triene (V) (180 mg., 7·5%), m. p. 217—221°, $[\alpha]_D$ +50°.

21-Acetoxy-17-hydroxy-5α-pregn-9-ene-3,20-dione (IV).—21-Acetoxy-17-hydroxy-11β-trifluoroacetoxy-5α-pregnane-3,20-dione (0·5 g.) was added to a boiling suspension of finely

divided calcium carbonate (0·35 g.) in dimethylacetamide (5 ml.) and after 13 min. the cooled suspension was poured into water and acidified with 2N-hydrochloric acid. The precipitated product (0·37 g.), m. p. 230—240°, crystallised from ethyl acetate to give the Δ^9-compound (IV) as plates (0·18 g., 47%), m. p. 247—253°, with an infrared spectrum identical with that of a sample prepared from the 11β-alcohol (I; R = R′ = H).[2]

When the 11-trifluoroacetate (2·0 g.) was treated with collidine as in the foregoing experiment (b), starting material (1·65 g.), m. p. 177—181°, was recovered.

3β,21-*Diacetoxy*-17-*trifluoroacetoxy*-5α-*pregnane*-11,20-*dione* (III; R = CF_3·CO).—3β,21-Diacetoxy-17-hydroxy-5α-pregnane-11,20-dione (III; R = H) (1·0 g.) in pyridine (11 ml.) was treated with trifluoroacetic anhydride (2 ml.) and after 10 min. the mixture was diluted with ether. The solvent was removed from the washed and dried solution to leave crystals (1·1 g.), m. p. 163—168°, which, on recrystallisation from ethyl acetate–hexane, gave the 17-*trifluoroacetate* (670 mg.), m. p. 166—168°, $[\alpha]_D$ +2° (Found: C, 59·8; H, 6·4. $C_{27}H_{35}F_3O_8$ requires C, 59·55; H, 6·5%), $\nu_{max.}$ 1784 (CF_3·CO_2), 1748 and 1230 (21-OAc), 1725 (20-C=O), and 1712 $cm.^{-1}$ (11-C=O).

When the 17-trifluoroacetate was treated with boiling dimethylacetamide containing calcium carbonate for 10 min., the product, isolated as in above experiments, showed only low general absorption in the ultraviolet region and was identified from its infrared spectrum as the 17-hydroxy-compound (III; R = H).

Cortisol 21-*Acetate* (VI).—The crude 21-acetoxy-2,4-dibromo-17-hydroxy-11β-trifluoroacetoxy-5α-pregnane-3,20-dione (II) (3·85 g.) was treated with sodium iodide (19 g.) in acetone (90 ml.) containing bromoacetone, as described previously.[7] Part (2·5 g.) of the crude product (2·6 g.), $\lambda_{max.}$ 237·5 mμ ($E^{1\%}_{1\,cm.}$ 199), was hydrolysed with 0·1N-sodium hydroxide in methanol (100 ml.) under nitrogen for 15 min. The solution was neutralised with acetic acid, concentrated, and diluted with water. The precipitate was reacetylated with acetic anhydride in pyridine, giving a mixture of saturated and unsaturated ketones (1·5 g.), $\lambda_{max.}$ 242 mμ ($E^{1\%}_{1\,cm.}$ 194). Segration of the αβ-unsaturated ketone in the product by means of its Girard derivative and crystallisation from ethyl acetate gave cortisol 21-acetate (297 mg., 13%), m. p. 216—220°, $\lambda_{max.}$ 240 mμ (ε 15,000), with an infrared spectrum (in Nujol) resembling that of an authentic sample.

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