SYNTHESIS OF 11-HYDROXYLATED ANDROSTANE DERIVATIVES*

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Reaction conditions for selective reduction of 3- and 17-oxo groups are described and applied to syntheses of 11-hydroxylated derivatives.

The sodium bismuthate degradation of the corticoid side chain represents a frequently used reaction for preparation of the 11-oxygenated androstane derivatives. The reaction proceeds smoothly and has been applied to analytical determination[1,2] of 17-hydroxycorticoids. Thus the unsaturated ketone *I* may be prepared from cortisol in about 80% yield. However, the syntheses of the saturated and 3-hydroxylated androstane derivatives of this type require preparation of the corresponding corticoids for the subsequent bismuthate degradation. Such corticoid derivatives with the proper configurations at $C_{(3)}$ and $C_{(5)}$ are not easily accessible in pure state, especially in large quantities.

We therefore turned our attention to the unsaturated ketone *I* and worked out methods for selective gradual reduction of the oxo groups as well as of the double bond. The degradation of cortisol was carried out essentially as described in the literature[2]. The resulting dione *I* was transformed to the formate[3] *II*. This protection proved advantageous for further steps and chromatographic separations. Catalytic hydrogenation of the olefin *II* over $Pd/CaCO_3$ catalyst in ethyl acetate–ethanol followed by chromatographic separation afforded the isomers *VI* and *VIII*. The next step, reduction of the 3-oxo group, was achieved with high selectivity using calculated amount of lithium tri-tert-butoxyaluminium hydride. The reduction was started at −65°C and the reaction mixture was allowed to reach the room temperature within 4 h. Under these conditions the 17-oxo group remained unchanged and after chromatographic purification the desired 3-hydroxy derivatives *X* and *XII*, respectively, were obtained in about 80% yield. Similarly, in the unsaturated dione *II* the more reactive 17-oxo group may be reduced selectively to the 17β-hydroxy derivative *IV* in good yield. Compounds *IV*, *X* and *XII* may then be converted by known procedures

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(inversion at $C_{(3)}$ or hydrogenation of the 4,5-double bond) to the desired isomers of the 11-hydroxylated androstane derivatives. The formates *IV*, *VI*, *VIII*, *X* and *XII* synthetized by the described procedure afforded on hydrolysis with methanolic potassium hydroxide the known 11β-hydroxyandrostane derivatives *III*, *V*, *VII*, *IX*, and *XI*.

EXPERIMENTAL

Melting points were determined on a Kofler block. Optical measurements were carried out in chloroform with an error of ±2°. The infrared spectra were recorded on the Zeiss UR 20 spectrometer in tetrachloromethane. The identity of samples was checked by mixture melting point determination, by thin-layer chromatography (TLC) and by spectral evidence. Usual working up of a solution implies washing the solution with 5% aqueous hydrochloric acid, water, drying over sodium sulphate, and evaporation of the solvent under reduced pressure. Ligroin refers to the fraction of b.p. 40–60°C. The reductions were carried out with lithium tri-tert-butoxyaluminium hydride containing 0·28% of active hydrogen (calculated: 0·39%). The hydrolyses of the 11β--formates were carried out with 5% methanolic potassium hydroxide at 50°C for 1 h.

11β-Hydroxyandrost-4-ene-3,17-dione (*I*)

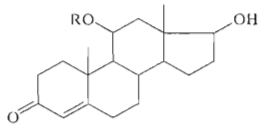
A solution of cortisol (4 g) in acetic acid (60 ml) and water (60 ml) was agitated with sodium bismuthate (25 g) under exclusion of light for 3 h. The mixture was diluted with water and extracted with six portions (70 ml each) of ethyl acetate. The organic solution was washed with 5% hydrochloric acid, a sodium hydrogen carbonate solution, water, dried, and the solvent was removed under reduced pressure. The residue (3·8 g) was crystallized from ethyl acetate to yield 3·2 g of the dione *I*, m.p. 198–201°C, $[\alpha]_D^{20}$ +222° (*c* 1·45), in accordance with the lit.[4].

11β-Formyloxyandrost-4-ene-3,17-dione (*II*)

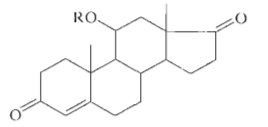
The alcohol *I* (3·2 g) was dissolved in formic acid (40 ml; 98–100%), treated with *p*-toluenesulphonic acid (400 mg) and heated to 30°C for 20 h. The mixture was poured on ice, neutralized with sodium hydroxide solution, and the product was extracted with ether. The ethereal solution was worked up, ether was distilled off, and the residue was crystallized from chloroform–ether to yield 3·05 g of the formate *II*, m.p. 136–138°C, $[\alpha]_D^{20}$ +207° (*c* 1·64). For $C_{20}H_{26}O_4$ (330·4) calculated: 72·70% C, 7·93% H; found: 72·64% C, 7·85% H.

11β-Formyloxy-5α-androstane-3,17-dione (*VI*)

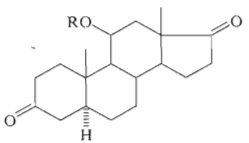
A solution of the unsaturated dione *II* (5 g) in ethyl acetate (300 ml) and ethanol (40 ml) was hydrogenated over 5% $Pd/CaCO_3$ catalyst (5 g) for two h. The catalyst was filtered off, washed with ether, and solvents were removed under reduced pressure. The residue was chromatographed on a silica gel column (800 g) in ether. Fractions with the lipophilic component were combined, solvent was distilled off, and the residue was crystallized from chloroform–ether to yield 2·8 g of the formate, *VI*, m.p. 179–180°C, $[\alpha]_D^{20}$ +92° (*c* 1·23). CD spectrum: $\Delta\varepsilon_{294}$ +3·62 (methanol). For $C_{20}H_{28}O_4$ (332·4) calculated: 72·26% C, 8·49% H; found: 72·18% C, 8·39% H. Hydrolysis afforded the alcohol *V*, m.p. 227–228°C, $[\alpha]_D^{20}$ +95° (*c* 1·34) in accordance with the lit.[5], and identical with the authentic sample.



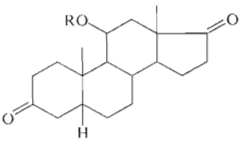
III, R = H
IV, R = HCO



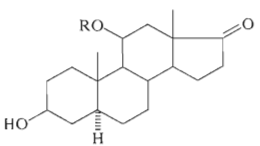
I, R = H
II, R = HCO



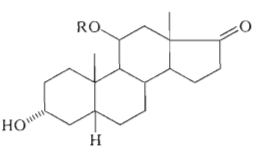
V, R = H
VI, R = HCO



VII, R = H
VIII, R = HCO



IX, R = H
X, R = HCO



XI, R = H
XII, R = HCO

11β-Formyloxy-5β-androstane-3,17-dione (*VIII*)

Elution of the chromatography from the foregoing experiment with the same solvent afforded fractions with the polar component. Working up and crystallization from ether–ligroin yielded 1·3 g of the formate *VIII*, m.p. 147–148°C, $[\alpha]_D^{20}$ +96° (*c* 1·07). CD spectrum: $\Delta\varepsilon_{297}$ +2·21 (methanol). For $C_{20}H_{28}O_4$ (332·4) calculated: 72·26% C, 8·49% H; found: 72·14% C, 8·45% H. Hydrolysis afforded the alcohol *VII*, m.p. 212–213°C, $[\alpha]_D^{20}$ +114° (*c* 1·28) in accordance with the literature[6], and identical with the authentic sample.

11β-Formyloxy-3β-hydroxy-5α-androstan-17-one (*X*)

A solution of the dione *VI* (2 g) in 1,2-dimethoxyethane (50 ml) was cooled to −65°C and treated with a solution of lithium tri-tert-butoxyaluminium hydride (1·75 g) in the same solvent (50 ml). The mixture was allowed to reach the room temperature in the course of 4 h. TLC showed absence of the starting material and essentially one single product was detected. Ether (700 ml) was added, the solution was washed with 2% hydrochloric acid, a sodium hydrogen carbonate solution, water, dried, and the solvents removed. The residue was purified by column chromatography on silica gel (50 g) in ether. The corresponding fractions were worked up, and the residue (1·75 g) was crystallized from methanol–water to yield 1·52 g of the alcohol *X*, m.p. 179–180°C, $[\alpha]_D^{20}$ +71° (*c* 1·48). For $C_{20}H_{30}O_4$ (334·4) calculated: 71·82% C, 9·04% H; found: 71·74% C, 8·86% H. Hydrolysis afforded the diol *IX*, m.p. 236–238°C, $[\alpha]_D^{20}$ + 86° (ethanol, *c* 1·52) in accordance with the lit.[7], and identical with the authentic sample.

11β-Formyloxy-3α-hydroxy-5β-androstan-17-one (*XII*)

The dione *VIII* (2·5 g) in 1,2-dimethoxyethane (60 ml) was reduced with lithium tri-tert-butoxyaluminium hydride (2·19 g) under analogous conditions as described in the foregoing experiment. Similar working up afforded a product essentially pure on TLC. Chromatographic purification over silica gel (60 g) in ether afforded after working up 2·15 g of a product which on crystallization from chloroform–ligroin gave 1·85 g of the alcohol *XII*, m.p. 88–92°C, $[\alpha]_D^{20}$ +82° (*c* 1·07). For $C_{20}H_{30}O_4$ (334·4) calculated: 71·82% C, 9·04% H; found: 71·71% C, 8·90% H. Hydrolysis afforded the diol *XI*, m.p. 241–242°C $[\alpha]_D^{20}$ +108° (dioxan, *c* 1·63) in accordance with the lit.[8].

11β-Formyloxy-17β-hydroxyandrost-4-en-3-one (*IV*)

The unsaturated dione *II* (3 g) in 1,2-dimethoxyethane (60 ml) was reduced with lithium tri-tert-butoxyaluminium hydride (2·63 g) as described above. Similar working up and purification over silica gel (100 g) in ether afforded 2·1 g of the alcohol *IV*, which resisted all attempts at crystallization; $[\alpha]_D^{20}$ +135° (*c* 1·08). IR spectrum: 1 667, 1 620 (carbonyl), 1 719, 1 713, 1 180 (formate), 3 615 cm^{-1} (hydroxyl). For $C_{20}H_{28}O_4$ (332·4) calculated: 72·26% C, 8·49% H; found: 72·21% C, 8·36% H. Hydrolysis afforded the diol *III*, m.p. 240–241°C, $[\alpha]_D^{20}$ +163° (*c* 1·74) in accordance with the lit.[9] and identical with the authentic sample.

The analyses were carried out in the Analytical Laboratory of this Institute by Mrs E. Sýkorová and Mrs E. Šípová under the direction of Dr J. Horáček. The IR spectra were recorded by Mr P. Formánek under the direction of Dr J. Smolíková. The CD *spectra were recorded by Dr S. Vašíčková.*

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