SYNTHESIS OF B-NORCORTISOL*

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The synthesis of the 11β,17α,21-trihydroxy-B-norpregn-4-ene-3,20-dione starting from 3β,11β,17α,21-tetrahydroxy-5-pregnen-20-on 3,11,21-triacetate is described.

In our previous papers we dealt with 11-hydroxylated B-norpregnane derivatives[1] and described synthesis of the B-noranalogue of Reichstein's substance S (ref.[2]). In this paper we present the synthesis of the B-noranalogue of cortisol.

Starting from the known[3] triacetate *I* the 17α-hydroxyl was protected by acetylation and the resulting tetraacetate *III* was submited to the B-ring contraction[4]: Chromic acid oxidation gave the keto-acid *V* which on reaction with benzoyl chloride in pyridine afforded the lactone *VII*. Thermal decarboxylation followed by partial hydrolysis yielded the B-norderivative *IX*. Analogous reactions have been carried out with the corresponding 11-oxo compounds starting from the ketone[3] *II*.

The tetrol monoacetate *IX* was transformed to the bismethylenedioxy derivative *XIV*, using the procedure described by Edwards and coworkers[5], the 11β-acetoxy group was hydrolysed with lithiumaluminium hydride and the diol submited to Oppenauer oxidation to yield the ketone *XV*. Removal of the protective group led to the desired B-norcortisol (*XVI*).

EXPERIMENTAL

Melting points were determined on a Kofler block. Analytical samples were dried at 80°C/0·2 Torr, optical measurements were carried out in chloroform unless otherwise stated with an error of ±1°. The infrared spectra were recorded on the Zeiss UR 10 spectrometer in tetrachloromethane unless otherwise stated. UV spectra were recorded on the CF 4 spectrometer in ethanol. The NMR spectra were recorded on the Varian HA-100 instrument in deuteriochloroform with tetramethylsilane as internal reference unless otherwise stated. The chemical shift is given in p.p.m.

3β,11β,17α,21-Tetrahydroxy-5-pregnen-20-one Tetraacetate (*III*)

The tetrol triacetate[3] *I* (5 g) in acetic anhydride (100 ml) was heated to 70°C for 3 hours in the presence of *p*-toluenesulphonic acid (300 mg). After cooling off to the room temperature the reaction mixture was treated with pyridine (50 ml) and decomposed with water. The product

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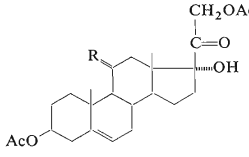
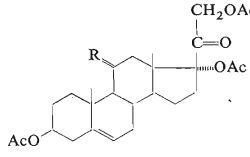
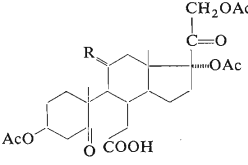


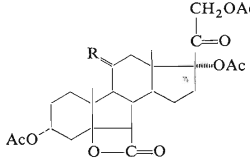
I, R = 17β-OAc, α-H
II, R = O



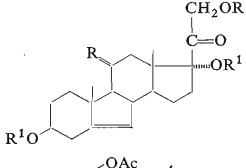
III, R = 17β-OAc, α-H
IV, R = O



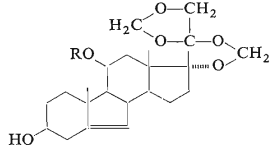
V, R = 17β-OAc, α-H
VI, R = O



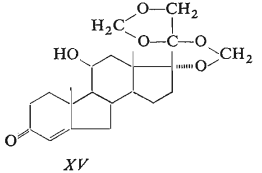
VII, R = 17β-OAc, α-H
VIII, R = O



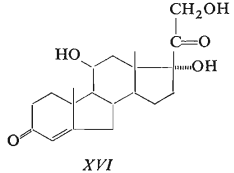
IX, R = 17β-OAc, α-H; R^1 = H
X, R = 17β-OAc, α-H; R^1 = Ac
XI, R = O; R^1 = H
XII, R = O; R^1 = Ac



XIII, R = H
XIV, R = Ac



XV



XVI

was extracted into chloroform. The organic layer was washed with hydrochloric acid (10%), water, sodium hydrogen carbonate, and water, dried, and the solvent was distilled off. The residue was crystallised from acetone–hexane to yield 5 g of the tetraacetate *III*, m.p. 164–165°C, $[\alpha]_D^{20}$ −22° (*c* 1·80). For $C_{29}H_{40}O_9$ (532·6) calculated: 65·39% C, 7·57% H; found: 64·99% C, 7·31% H.

3β,17α,21-Trihydroxy-5-pregnen-11,20-dione Triacetate (*IV*)

The diacetate[3] *II* (850 mg) was acetylated in acetic anhydride (17 ml) in the presence of *p*-toluenesulphonic acid (50 mg) as given in the previous experiment. Similar working up afforded after evaporation of the solvent a residue which was chromatographed over silica gel in benzene–ether (4 : 1). Working up of the corresponding fractions and crystallisation from acetone–hexane yielded 640 mg of the triacetate *IV*, m.p. 160–162°C, $[\alpha]_D^{20}$ −27° (*c* 0·90). For $C_{27}H_{36}O_8$ (488·5) calculated: 66·37% C, 7·43% H; found: 66·15% C, 7·21% H.

3β,11β,17α,12-Tetrahydroxy-B-norpregn-5-en-20-one 11-Acetate (*IX*)

A stirred solution of the tetraacetate *III* (5 g) in acetic acid (50 ml) was treated at 55°C dropwise with a solution of chromic acid (4·2 g) in 50% acetic acid (10 ml). The addition was completed after 2 hours and the reaction mixture was agitated for additional 2 hours at the same temperature. The excess oxidising agent was removed with methanol (5 ml) and organic solvents were removed under reduced pressure. The residue was diluted with a saturated solution of ammonium sulphate and the product taken into ethyl acetate. The extract was washed with a saturated solution of ammonium sulphate, and the oxo acid *V* was extracted with 3% sodium carbonate (200 ml). The alkaline extract was cooled to 0°C, acidified with hydrochloric acid, and the oxo acid *V* taken into ethyl acetate. The extract was washed with a saturated solution of ammonium sulphate, dried, and the solvent distilled off. The residue (3·5 g) was dissolved in pyridine (10 ml) treated at 0°C with benzoyl chloride (3·5 ml) and allowed to stand at room temperature in darkness for 48 hours. The reaction mixture was decomposed with ice, the lactone *VII* was extracted with ethyl acetate, and the extract washed with 5% hydrochloric acid, water, 5% sodium hydrogen carbonate, and water, dried, and the solvent was distilled off to leave the crude lactone *VII*. The residue was heated to 190°C for 10 minutes, and the product was chromatographed on a silica gel column (300 g). Elution with benzene–ether (9 : 1) separated benzoic acid and elution with benzene–ether (4 : 1) afforded fractions with the derivative *X* (1·35 g). It was dissolved in chloroform–methanol (1 : 1; 16 ml), treated with conc. hydrochloric acid (1·2 ml) and allowed to stand at 30°C for 20 hours. The reaction mixture was diluted with water, the product extracted with chloroform, the extract was washed with a sodium hydrogen carbonate solution, water, dried, and chloroform distilled off. The residue (1 g) was chromatographed on a silica gel column (100 g) in chloroform–methanol (9 : 1). Working up of the corresponding fractions afforded a product which on crystallisation from acetone–hexane yielded 460 mg of the tetrol monoacetate *IX*, m.p. 212–214°C, $[\alpha]_D^{20}$ +41° (*c* 0·65 in ethanol). IR (nujol): 3450, 3340, 1700, 1278 cm^{-1}. NMR: 0·64 (s, 18-H), 0·83 (s, 19-H), 1·87 (s, 11β-acetate), 4·07 and 4·50 (dd, J = 18 Hz, 21-H), 5·25 (m, 6-H and 11α-H). For $C_{22}H_{32}O_6$ (392·4) calculated: 67·32% C, 8·22% H; found: 67·08% C, 8·23% H.

3β,17α,21-Trihydroxy-B-norpregn-5-en-11,20-dione (*XI*)

The triacetate *IV* (640 mg) in acetic acid (7 ml) was oxidised with chromic acid (600 mg) in 50% acetic acid (1·5 ml) as described in the foregoing experiment. Similar working up gave the oxo-acid *VI* (250 mg) which was dissolved in pyridine (0·8 ml), treated with benzoyl chloride (0·3 ml),

and allowed to stand at room temperature in darkness for 48 hours. The reaction mixture was worked up as given in the previous experiment to yield after evaporation of the solvent the lactone *VIII*. It was decomposed by heating to 190°C for 10 minutes and the melt was chromatographed over silica gel (25 g) in benzene–ether (4 : 1). Fractions containing the derivative *XII* were combined, evaporated, and the residue (26 mg) was dissolved in chloroform–methanol (1 : 1; 0·5 ml) and treated with one drop of conc. hydrochloric acid. After 20 hours at 30°C the reaction mixture was diluted with water, the product extracted with chloroform, the extract was washed with sodium hydrogen carbonate, water, dried, and the solvent distilled off. The residue (20 mg) was chromatographed over silica gel (2 g) in chloroform–methanol (9 : 1). The corresponding fractions were combined and evaporated, to yield 15 mg of the dione *XI*, m.p. 205–206°C, $[\alpha]_D^{20}$ +170° (*c* 0·90 in ethanol). For $C_{20}H_{28}O_5$ (348·4) calculated: 68·94% C, 8·10% H; found: 68·50% C, 8·15% H.

17,20; 20,21-Bis(methylenedioxy)-B-norpregn-5-en-3β,11β-diol 11-Acetate (*XIV*)

Paraformaldehyde (5·5 g) in water (17 ml) and conc. hydrochloric acid (17 ml) was agitated at room temperature for 15 hours. A solution of the tetrol monoacetate *IX* (550 mg) in ethanol free chloroform (30 ml) was then added and the reaction mixture was agitated at room temperature for another 15 hours. The upper layer was separated, saturated sodium chloride solution (30 ml) was added and the product extracted into ethyl acetate. The extract was washed with 5% sodium hydrogen carbonate, then with a saturated solution of sodium chloride, dried, and evaporated. The residue was chromatographed on a silica gel column (500 g). Elution with benzene–ether (3 : 1) gave fractions with the desired derivative *XIV*, elution with chloroform–methanol (4 : 1) yielded the starting material. Crystallisation from the acetone–hexane afforded 190 mg of the derivative *XIV*, m.p. 240–241°C, $[\alpha]_D^{20}$ – 62° (*c* 0·55). IR (chloroform): 3 600, 1 725, 1 641, 1 258, 1 100, 1 089, 948 cm^{-1}. For $C_{24}H_{34}O_7$ (434·4) calculated: 66·34% C, 7·89% H; found: 66·01% C, 7·82% H.

17,20; 20,21-Bis(methylenedioxy)-B-norpregn-5-en-3β,11β-diol (*XIII*)

A solution of the acetate *XIV* (190 mg) in tetrahydrofuran (20 ml) was treated with lithium-aluminium hydride (190 mg) and stirred at room temperature for 30 minutes. The excess hydride was decomposed with ethyl acetate and water and the product taken into chloroform. The extract was washed with water, dried, and the solvent distilled off. The residue (175 mg) was chromatographed on a silica gel column (20 g) in benzene–ether (1 : 1). The corresponding fractions were combined, evaporated, and the residue was crystallised from ethyl acetate to give 130 mg of the diol *XIII*, m.p. 230–231°C, $[\alpha]_D^{20}$ – 83° (*c* 0·46). IR (chloroform): 3 600, 1 100, 1 090, 947 cm^{-1}. For $C_{22}H_{32}O_6$ (392·4) calculated: 67·32% C, 8·22% H; found: 66·91% C, 8·22% H.

17,20; 20,21-Bis(methylenedioxy)-11β-hydroxy-B-norpregn-4-en-3-one (*XV*)

The diol *XIII* (130 mg) was dissolved in toluene (8 ml) and cyclohexanone ((1·3 ml) and 2 ml of the solvent were distilled off. The reaction mixture was treated with 20% solution of aluminium 2-propoxide (0·7 ml) and 2 ml of distillate were collected within 45 minutes. The reaction mixture was poured on ice, decomposed with hydrochloric acid, and the product extracted with ethyl acetate. The extract was washed with sodium hydrogen carbonate, water, and the volatile components were removed by steam distillation. The product was taken into ethyl acetate, the solution was dried, and the solvent removed. The residue (130 mg) was chromatographed over silica gel (10 g) in benzene–ether (4 : 1). Working up of the corresponding fractions and crystallisation from acetone–hexane yielded 40 mg of the ketone *XV*, m.p. 262–264°C, $[\alpha]_D^{20}$ + 45° (*c* 0·60).

IR (chloroform): 1657, 1100, 946 cm^{-1}. UV: λ_{max} 242 nm, (log ε 4·19). For $C_{22}H_{30}O_6$ (390·4) calculated: 67·67% C, 7·74% H; found: 67·29% C, 7·70% H.

11β,17α,21-Trihydroxy-B-norpregn-4-ene-3,20-dione (*XVI*)

The ketone *XV* (36 mg) in 50% acetic acid (5·5 ml) was stirred at 100°C (boiling water bath) in a nitrogen atmosphere for 3 hours. The reaction mixture was poured into a saturated solution of sodium chloride (10 ml) and the product extracted with ethyl acetate. The solution was washed with sodium hydrogen carbonate, a saturated sodium chloride solution, dried, and the solvent evaporated. The residue (30 mg) was chromatographed over silica gel (10 g) in chloroform–methanol (19 : 1). Working up of the corresponding fractions and crystallisation from acetone–hexane afforded 10 mg of the dione *XVI*, m.p. 215–216°C, $[\alpha]_D^{20} + 179°$ (*c* 0·45 in ethanol). NMR: 0·73 (s, 18-H), 1·17 (s, 19-H), 3·97 (m, 11α-H), 4·15 and 4·46 (dd, $J = 18$ Hz, 21-H), 5·03 (s, 17α-OH), 5·55 (s, 4-H). For $C_{20}H_{28}O_5$ (348·4) calculated: 68·94% C, 8·10% H; found: 68·59% C, 8·02% H.

The analyses were carried out in the Analytical Laboratory of this Institute by Mr V. Štěrba Mrs V. Rusová and Mrs E. Sýkorová under the direction of Dr J. Horáček. The infrared spectra were recorded by Mr P. Formánek and Mrs S. Vaščková under the direction of Dr J. Smolíková. The NMR spectra were recorded and interpreted by Dr M. Buděšinský. Technical assistance was provided by Mrs J. Mašková.

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