5,7-CYCLO-B-HOMOPREGNANE DERIVATIVES WITH THE CORTICOID KETOL SIDE CHAIN*

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Syntheses of the epimeric 5,7-cyclo-B-homopregnane derivatives carrying an oxygen function in positions 17α and 21 are described and the structures of the products are established by spectral means.

In our previous papers we described syntheses of the isomeric 5,7-cyclo-B-homopregnane derivatives hydroxylated either in the 17α-position[1] or in the 21-position[2]. The goal of these studies were syntheses of corticoid type compounds with a cyclopropane ring attached to the steroid molecule. In this paper we describe syntheses of such analogues of Reichstein's Substance S.

We set out from the 17α-hydroxy derivatives *I* and *VI* respectively. The first step, bromination at $C_{(21)}$ was carried out with dioxane–dibromide[3] in methanol. This reagent proved to be superior in this case to some other brominating agent we studied. We thus obtained the bromo ketones *II* and *VII* in about 65% yield. The next step, the acetoxylation, was carried out with potassium acetate in dimethylformamide to afford the 21-acetoxy derivatives *III* and *VIII* in good yields. These alcohols were oxidised with Jones' reagent to the ketones *V* and *X* which on hydrolysis with potassium carbonate in methanol yielded the isomeric cyclopropano analogues of Reichstein's Substance S *IV* and *IX*.

EXPERIMENTAL

Melting points were determined on a Kofler block. Optical measurements were carried out in chloroform–methanol (1 : 1). The infra-red spectra were recorded on a Zeiss UR 20 spectrometer in tetrachloromethane unless otherwise stated. The ^{1}H-NMR spectra were recorded on a Tesla 60 MHz instrument in deuteriochloroform–hexadeuteriodimethyl sulphoxide solution and corrected to tetramethylsilane (7·25 ppm) unless otherwise stated. Chemical shifts are given in ppm. The mass spectra were recorded on a AEI MS 902 mass spectrometer.

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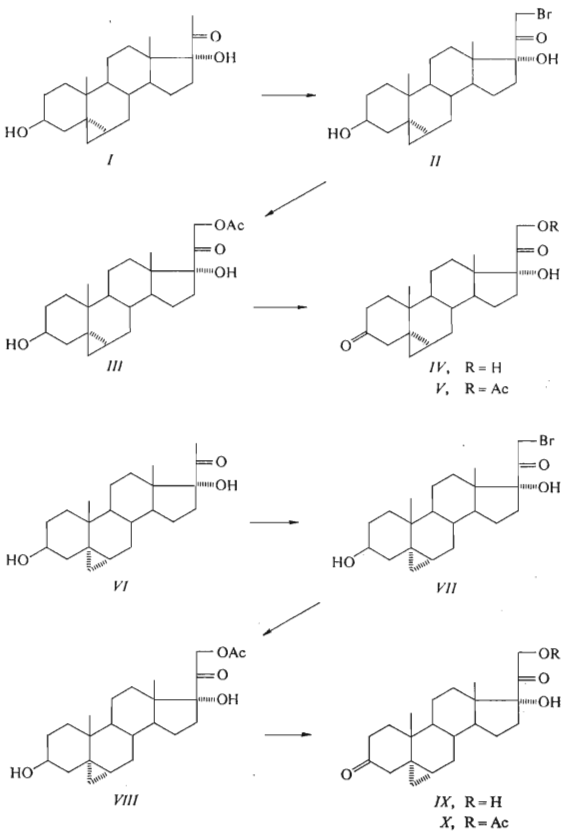

20-Oxo-21-bromo-5,7α-cyclo-B-homo-5α-pregnane-3β,17α-diol (*II*)

The ketone *I* (200 mg) in methanol (25 ml) was treated dropwise under stirring with a solution of dioxane-dibromide[3] (350 mg) in methanol (3 ml). After 5 h of stirring the mixture was diluted with chloroform, the solution was washed with 0·2% sodium hydroxide solution, 2% sodium thiosulphate solution, water, dried and the solvent was removed. The crude bromo ketone (250 mg)

was purified by preparative TLC on silica gel in chloroform–methanol (19 : 1). The corresponding zones were extracted with chloroform, solvent was distilled off, and the residue was crystallised from ethyl acetate–hexane to yield 120 mg of the bromoketone *II*, m.p. 226—227°C, $[\alpha]_D^{20}$ +35° (*c* 2·30). Mass spectrum: M^+ 425. ^{1}H-NMR spectrum: —0·26 to +0·03 and 0·16—0·43 (two m, cyclopropane protons), 0·51 (s, 18-H), 0·81 (s, 19-H), 3·66 (m, 3α-H), 4·08 and 4·48 (2 d, J = = 15 Hz, AB system, 21-H). For $C_{22}H_{33}BrO_3$ (425·5) calculated: 62·10% C, 7·82% H, 18·78% Br; found: 62·07% C, 7·72% H, 19·10% Br.

20-Oxo-5,7α-cyclo-B-homo-5α-pregnane-3β,17α,21-triol 21-Monoacetate (*III*)

The bromo ketone *II* (250 mg) in dimethylformamide (25 ml) was heated to 65°C under stirring with anhydrous potassium acetate (250 mg) for 1 h. After cooling off the mixture was diluted with water and the product taken into ether. The ethereal solution was washed with 5% hydrochloric acid, water, 5% sodium hydrogen carbonate solution, dried, and solvent removed under reduced pressure. The residue (230 mg) was crystallised from ethyl acetate to yield 125 mg of a pure product. The mother liquors were purified by preparative TLC on silica gel in chloroform–methanol (19 : 1) and the product was crystallised from ethyl acetate. Total yield 200 mg of the monoacetate *III*, m.p. 262—263°C, $[\alpha]_D^{20}$ +28° (*c* 2·30). Mass spectrum: M^+ 404. IR spectrum (KBr): 1755 (acetate), 1735 cm^{-1} (carbonyl). ^{1}H-NMR spectrum (pentadeuteriopyridine–deuteriochloroform 1 : 1): 0·73 (s, 18-H), 0·86 (s, 19-H), 2·10 (s, acetate), 4·00 (m, $W_{1/2}$ = = 17·5 Hz, 4α-H), 5·04 and 5·40 (2 d, J = 18 Hz, AB system, 21-H). For $C_{24}H_{36}O_5$ (404·5) calculated: 71·25% C, 8·97% H; found: 70·95% C, 8·62% H.

3,20-Dioxo-5,7α-cyclo-B-homo-5α-pregnane-17α,21-diol (*IV*)

A solution of the acetate *V* (100 mg) in methanol (17 ml) was heated to 65°C in a nitrogen atmosphere with a solution of potassium carbonate (100 mg) in water (3 ml) for 20 min. Methanol was removed *in vacuo*, the residue was treated with water, and the product taken into chloroform. The extract was washed with water, dried, and solvent distilled off. The residue was purified by preparative TLC on silica gel in chloroform–methanol (19 : 1). The corresponding zones were extracted with chloroform, solvent was removed, and the product was crystallised from ethyl acetate to yield 50 mg of the diol *IV*, m.p. 253—255°C, $[\alpha]_D^{20}$ +91° (*c* 2·30). Mass spectrum: M^+ 360. IR spectrum (KBr): 3525, 3480 (hydroxyl), 3070 (cyclopropane), 1707 cm^{-1} (carbonyls). ^{1}H-NMR spectrum: 0·00—0·48 (m, cyclopropane protons), 0·59 (s, 18-H), 0·95 (s, 19-H), 4·20 and 4·74 (two d, J = 20 Hz, AB system, 21-H). For $C_{22}H_{32}O_4$ (360·5) calculated: 73·30% C, 8·95% H; found: 73·21% C, 8·58% H.

3,20-Dioxo-5,7α-cyclo-B-homo-5α-pregnane-17α,21-diol 21-Monoacetate (*V*)

A solution of the acetate *III* (350 mg) in acetone (75 ml) was treated with excess Jones' reagent and allowed to stand at room temperature for 10 min. The excess oxidising agent was removed with methanol, part of the solvents was removed *in vacuo*, and the mixture was diluted with water. The product was extracted into ether, the ethereal solution was washed with water and sodium hydrogen carbonate solution, dried, and solvent removed. The residue was crystallised from methanol to yield 200 mg of the first crop. The mother liquors were purified by preparative TLC on silica gel in a mixture of ligroin (b.p. 40—60°C) and ethyl acetate (1 : 1). The product from the corresponding zones was extracted with chloroform, solvent was distilled off, and the residue was crystallised from methanol to yield additional 50 mg of the dione *V*, m.p. 227—228°C,

$[\alpha]_D^{20}$ +95° (*c* 2·30). Mass spectrum: M^+ 402. IR spectrum (chloroform): 3615 (hydroxyl), 3075 (cyclopropane), 1745, 1722 ($C_{(20)}$-carbonyl and acetate), 1711 cm^{-1} ($C_{(3)}$-carbonyl). ^{1}H-NMR spectrum: 0·14—0·50 (m, cyclopropane protons), 0·66 (s, 18-H), 0·98 (s, 19-H), 2·16 (s, acetate), 4·78 and 5·15 (two d, J = 17·5 Hz, AB system, 21-H). For $C_{24}H_{34}O_5$ (402·5) calculated: 71·61% C, 8·51% H; found: 71·93% C, 8·44% H.

20-Oxo-21-bromo-5,7β-cyclo-B-homo-5β-pregnane-3β,17α-diol (*VII*)

The ketone *VI* (200 mg) was brominated with dioxane–dibromide[3] in methanol as described for the 5α,7α-isomer *II*. Similar working up and crystallisation from ethyl acetate afforded 150 mg of the bromo ketone *VII*, m.p. 236—237°C, $[\alpha]_D^{20}$ —14° (*c* 1·64). Mass spectrum: M^+ 425. ^{1}H-NMR spectrum: —0·05 to +0·38 and 0·60—0·88 (two m, cyclopropane protons), 0·50 (s, 18-H), 1·05 (s, 19-H), 3·56 (m, $W_{1/2}$ = 27 Hz, 3α-H), 4·13 and 4·52 (two d, J = 15 Hz, AB system, 21-H). For $C_{22}H_{33}BrO_3$ (425·5) calculated: 62·10% C, 7·82% H, 18·78% Br; found: 62·07% C, 7·90% H, 19·16% Br.

20-Oxo-5,7β-cyclo-B-homo-5β-pregnane-3β,17α,21-triol 21-Monoacetate (*VIII*)

The bromo ketone *VII* (300 mg) in dimethylformamide (30 ml) was treated with potassium acetate (300 mg) as described above for the 5α,7α-isomer *III*. Similar working up and crystallisation from ethyl acetate yielded 200 mg of the acetate *VIII*, m.p. 218—219°C, $[\alpha]_D^{20}$ —19° (*c* 3·06). Mass spectrum: M^+ 404, IR spectrum: 1752 (acetate), 1732 cm^{-1} (carbonyl). ^{1}H-NMR spectrum: 0·09—0·40 (m, cyclopropane protons), 0·59 (s, 18-H), 1·09 (s, 19-H), 2·15 (s, acetate), 3·72 (m, 3α-H), 4·80 and 5·20 (two d, J = 18 Hz, AB system, 21-H). For $C_{24}H_{36}O_5$ (404·5) calculated: 71·25% C, 8·97% H; found: 71·22% C, 9·01% H.

3,20-Dioxo-5,7β-cyclo-B-homo-5β-pregnane-17α,21-diol (*IX*)

The acetate *X* (100 mg) was hydrolysed with potassium carbonate (100 mg) in methanol (17 ml) as described above for the isomer *IV*. Similar working up and crystallisation from methanol–water yielded 52 mg of the alcohol *IX*, m.p. 215—216°C, $[\alpha]_D^{20}$ +18° (*c* 1·46). Mass spectrum: M^+ 360. IR spectrum (KBr): 3525, 1106, 1045 (hydroxyl), 3080 (cyclopropane), 1711 cm^{-1} (carbonyls). ^{1}H-NMR spectrum: 0·06—0·48 (cyclopropane protons), 0·59 (s, 18-H), 1·29 (s, 19-H), 4·42—4·51 (two d, J = 12-Hz, AB system, 21-H). For $C_{22}H_{32}O_4$ (360·5) calculated: 73·30% C, 8·95% H; found: 72·94% C, 9·09% H.

3,20-Dioxo-5,7β-cyclo-B-homo-5β-pregnane-17α,21-diol 21-Monoacetate (*X*)

The alcohol *VIII* (250 mg) in acetone (50 ml) was oxidised with Jones' reagent as described above for the epimer *V*. Similar working up and crystallisation from ethyl acetate afforded 200 mg of the dione *X*, m.p. 240—241°C, $[\alpha]_D^{20}$ +20° (*c* 1·73). Mass spectrum: M^+ 402. IR spectrum (chloroform): 3618 (hydroxyl), 3070 (cyclopropane), 1745 (acetate), 1728 ($C_{(20)}$-carbonyl), 1710 cm^{-1} ($C_{(3)}$-carbonyl). ^{1}H-NMR spectrum: 0·12—0·43 (m, cyclopropane protons), 0·66 (s, 18-H), 1·21 (s, 19-H), 2·17 (s, acetate), 4·77 and 5·15 (two d, J = 17 Hz, AB system, 21-H). For $C_{24}H_{34}O_5$ (402·5) calculated: 71·61% C, 8·51% H; found: 71·63% C, 8·67% H.

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REFERENCES

1. Mironowicz A., Kohout L., Fajkoš J.: This Journal *39*, 1780 (1974).
2. Kočovský P., Kohout L., Fajkoš J.: This Journal *40*, 468 (1975).
3. Suvorov M., Sokolova L., Jaroslavtseva Z., Ovchinnikov V., Leibelmann F.: J. Gen. Chem. USSR *31*, 3469 (1962).

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