SYNTHESIS OF 19-NORDEOXYCORTICOSTERONE 3-(O-CARBOXYMETHYL)-OXIME*

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Starting from the epoxide *I* a convenient synthesis of 19-nordeoxycorticosterone and its 3-(O-carboxymethyl)-oxime is described.

The potent mineralocorticoid hormone – 19-nordeoxycorticosterone – has recently been found of considerable biological interest and a study of its biological properties was desirable. Several syntheses of this compound have been described[1–4] in past, however, none of them promised satisfactory yields. Since we required relatively large amounts of this substance and its 3-(O-carboxymethyl)-oxime as well we have devised a reaction sequence represented by formulae *I* to *X* that permits the preparation of these derivatives in about 28% overall yield starting from the accessible epoxide *I*.

The epoxide *I* was prepared from the corresponding bromohydrin by lead tetraacetate oxidation as described by Bowers and coworkers[5]. The first step, introduction of the acetoxy groups in position 21 was carried out by the lead tetraacetate method modified by Henbest[6], *i.e.* in the presence of boron trifluoride etherate and methanol in benzene solution. The alcohol *II* was then oxidised with Jones' reagent to the bromo ketone *III* which on steam distillation in the presence of pyridine gave the unsaturated ketone *IV* in excellent yields. Reductive cleavage of the epoxide ring was carried out with zinc dust in acetic acid in the usual way[7,8] to yield the 19-hydroxy derivative *V*. Following oxidation with Jones' reagent at 35°C afforded smoothly the acid *VI* which on decarboxylation with methanolic hydrochloric acid[9] gave the 19-nordeoxycorticosterone (*VII*) as the sole product. Direct oximation of *VII* under various conditions led to a complex mixture of oximes. However, in the acetate *VIII* the 3-oxo group was preferentially attacked by the oximating reagent to yield the corresponding 3-(O-carboxymethyl)-oxime *X* as the sole product, contaminated slightly with the 3,20-dioxime. Alkaline hydrolysis of *X* yielded the desired 19-nordeoxycorticosterone 3-(O-carboxymethyl)-oxime (*IX*).

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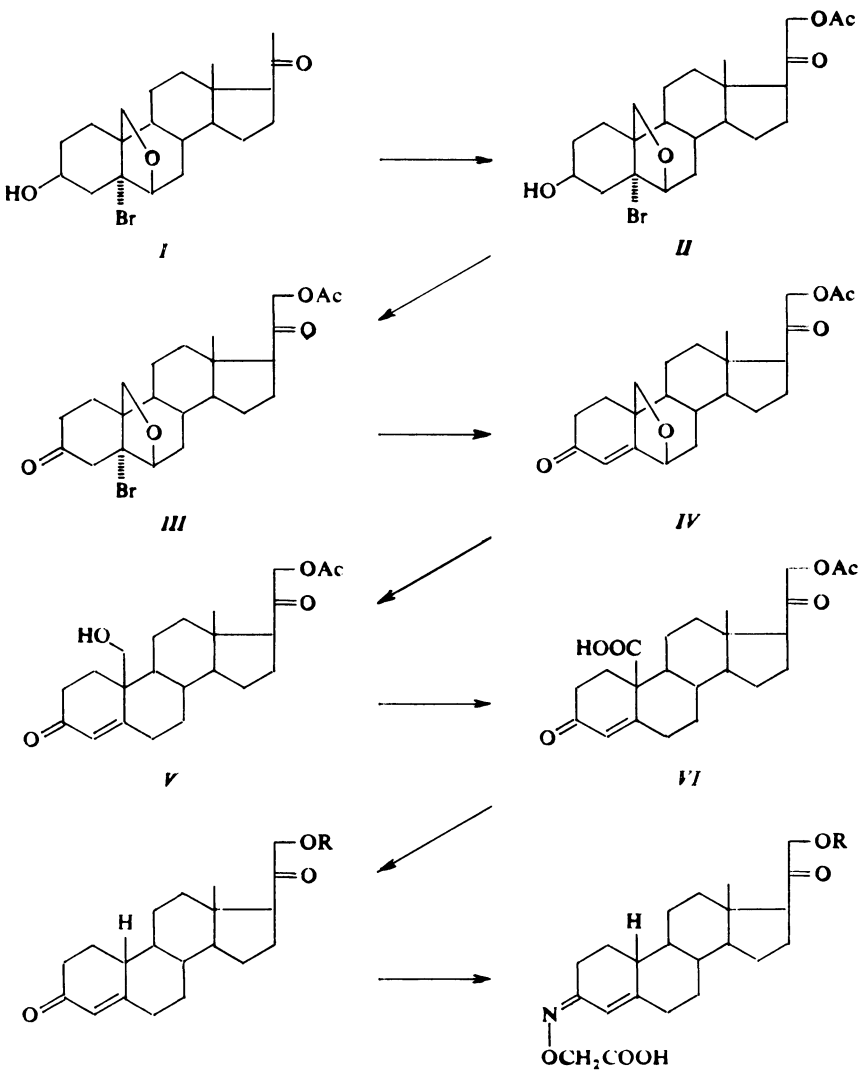

EXPERIMENTAL

Melting points were determined on a Kofler block. Optical rotations were carried out in chloroform, unless otherwise stated, with an error of $\pm 3°$. The infrared spectra were recorded on a Zeiss UR 20 spectrometer in tetrachloromethane. Usual working up of a solution implies washing the solution with 5% aqueous hydrochloric acid, water, 5% aqueous sodium hydrogen carbonate,

water, drying over magnesium sulphate and evaporation of the solvent under reduced pressure. Ligroin refers to the fraction of b.p. 40—60°C.

5-Bromo-3β,21-dihydroxy-6β,19-epoxy-5α-pregnan-20-one 21-Acetate (*II*)

The ketone[5] *I* (10 g) in benzene (380 ml) was treated with methanol (25 ml), lead tetraacetate (17 g) and boron trifluoride etherate (60 ml) and agitated at room temperature for 4 h. The solids were filtered off, the filtrate was diluted with ether and washed with hydrochloric acid, a sodium hydrogen carbonate solution, water, dried over magnesium sulphate, and the solvents were removed under reduced pressure. The residue was chromatographed on a silica gel column (500 mg) in benzene–ether (3 : 1). Fractions containing the desired product were worked up and the crude product was crystallised from methanol to yield 7·85 g of the acetate *II*, m.p. 162—163°C, $[\alpha]_D^{20}$ +35° (*c* 1·8). For $C_{23}H_{33}BrO_5$ (469·4) calculated: 58·85% C, 7·09% H, 17·03% Br; found: 58·76% C, 6·94% H, 17·32% Br.

21-Acetoxy-5-bromo-6β,19-epoxy-5α-pregnane-3,20-dione (*III*)

The alcohol *II* (6·2 g) in acetone (200 ml) was treated with excess Jones' reagent and allowed to stand for 15 min at room temperature. The oxidising reagent was removed with methanol, the reaction mixture was diluted with water and the product was isolated with ethyl acetate. The extract was washed with diluted hydrochloric acid, a sodium hydrogen carbonate solution, water, and dried over magnesium sulphate. Evaporation of the solvent afforded the ketone *III*, which was pure on TLC and was used for further step without crystallisation. An analytical sample was obtained on crystallisation from methanol and showed a m.p. of 184—186°C and $[\alpha]_D^{20}$ +108° (*c* 1·3). For $C_{23}H_{31}BrO_5$ (467·4) calculated: 59·09% C, 6·68% H, 17·09% Br; found: 59·22% C, 6·67% H, 17·62% Br.

21-Acetoxy-6β,19-epoxypregn-4-ene-3,20-dione (*IV*)

The bromo ketone *III* (9 g) was dissolved in pyridine (180 ml), treated with sodium hydrogen carbonate (20 g) and water (60 ml) and pyridine was removed from the reaction mixture by steam distillation. After cooling off the product was taken into ethyl acetate, the solution was worked up and the residue (8 g) was acetylated with acetic anhydride (30 ml) in pyridine (40 ml) at room temperature for 16 h. The reaction mixture was decomposed with ice and water and the product was isolated with ether. Usual working up afforded a crude product which was essentially pure on TLC. Chromatography over silica gel (400 g) in benzene–ether (3 : 1) and working up of the corresponding fractions gave 7 g of a bromine free product which on crystallisation from ethyl acetate yielded 6·2 g of the ketone *IV*, m.p. 198—199°C, $[\alpha]_D^{20}$ +2° (*c* 1·4). For $C_{23}H_{30}O_5$ (386·5) calculated: 71·48% C, 7·82% H; found: 71·39% C, 7·75% H.

19,21-Dihydroxypregn-4-ene-3,20-dione 21-Acetate (*V*)

Activated zinc dust (60 g) was prepared by washing it twice with 50% acetic acid and three times with glacial acetic acid. The epoxide *IV* (12 g) in 80% acetic acid (400 ml) was agitated with the activated zinc dust in boiling water bath for 30 min. After cooling off the metal was removed by suction and washed with ethanol. The volume of the filtrate was reduced to about 100 ml *in vacuo* at 35°C. The residue was diluted with chloroform, the solution was washed with hydrochloric acid, water, a sodium hydrogen carbonate solution, water, and worked up as usual. The product was chromatographed on a silica gel column (700 g) in benzene–ether (1 : 1). Working up of the corresponding fractions and crystallisation from acetone afforded 8·5 g of the alcohol *V*, m.p. 200—201°C, $[\alpha]_D^{20}$ +181° (*c* 1·8), in accordance with the literature[8].

21-Acetoxypregn-4-ene-3,20-dione-19-oic Acid (*VI*)

The alcohol *V* (13·2 g) in acetone (70 ml) was treated with excess Jones' reagent and the reaction mixture was kept at 35°C for 1 h. The oxidising agent was removed with methanol, water was added and the product was isolated with ethyl acetate. The extract was washed well with water, dried over magnesium sulphate, and the solvent was distilled off. The residue was crystallised from ethyl acetate–ligroin to yield 10·2 g of the acid *VI*, m.p. 170—175°C (decarboxylation), $[\alpha]_D^{20}$ +221° (*c* 1·5). For $C_{23}H_{30}O_6$ (402·5) calculated: 68·63% C, 7·51% H; found: 68·56% C, 7·42% H.

21-Hydroxy-19-norpregn-4-ene-3,20-dione (*VII*)

A solution of the acid *VI* (10·5 g) in methanol (1 200 ml) was treated with conc. hydrochloric acid (18 ml) and refluxed for 1 h. The mixture was neutralised with a sodium hydrogen carbonate solution and methanol was distilled off *in vacuo*. The residue was diluted with water and the product was taken into ethyl acetate. Usual working up and evaporation of the solvent yielded a crude product which was chromatographed on a silica gel column (400 g) in benzene–ether (4 : 1) to yield after working up of the corresponding fractions and crystallisation from ethyl acetate–ether 7·8 g of *VII*, m.p. 134—135°C, $[\alpha]_D^{20}$ +138° (*c* 2·1), in accordance with the literature[1].

21-Acetoxy-19-norpregn-4-ene-3,20-dione 3-(O-carboxymethyl)-oxime (*X*)

The acetate[1] *VIII* (3 g) in pyridine (30 ml) was treated at 0°C with aminooxyacetic acid (1 g) and allowed to stand at 0°C for 8 h. The mixture was poured on ice containing 50 ml of conc. hydrochloric acid and the product was extracted into ethyl acetate. The extract was washed with water, dried over magnesium sulphate and the solvent was distilled off under reduced pressure. The residue contained traces of the dioxime according to the TLC. It was purified by column chromatography over silica gel (60 g) in a chloroform–ether (6 : 4) mixture containing methanol (2%) and acetic acid (0·5%). Working up of the corresponding fractions and crystallisation from ether–ligroin yielded 2·6 g of the oxime *X*, m.p. 142—143°C, $[\alpha]_D^{20}$ +181° (*c* 1·9 in methanol), IR spectrum: 3 500—2 400, 1 725 (carboxyl), 1 725 (carbonyl), 1 749, 1 248 (acetate), 1 645, 1 632 cm^{-1} (C=C—C=N—O—). For $C_{22}H_{31}NO_5$ (389·5) calculated: 67·84% C, 8·02% H, 3·60% N; found: 67·73% C, 7·88% H, 3·54% N.

21-Hydroxy-19-norpregn-4-ene-3,20-dione 3-(O-carboxymethyl)-oxime (*IX*)

The acetate *X* (2·1 g) in methanol (18 ml) was treated in an argon atmosphere with a solution of potassium hydroxide (300 mg) in methanol (4 ml) and allowed to stand at room temperature for 1 h. The mixture was acidified with hydrochloric acid and diluted with ethyl acetate (150 ml). The solution was washed well with water, dried over magnesium sulphate and solvent was removed *in vacuo*. The residue was crystallised from ether–ligroin to afford 1·4 g of the oxime *IX*, m.p. 180—182°C (decomposition), $[\alpha]_D^{20}$ +124° (*c* 1·3 in methanol). IR spectrum: 3 500—2 400, 1 765, 1 712 (carboxyl), 1 712 (carbonyl), 1 631, 1 106 cm^{-1} (=N—O—). For $C_{20}H_{29}NO_4$ (347·4) calculated: 69·14% C, 8·41% C, 8·41% H, 4·03% N; found: 69·05% C, 8·36% H, 3·95% N.

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 Mrs K. Matoušková under the direction of Dr J. Smolíková.*

REFERENCES

1. Sandoval A., Thomas G. A., Djerassi C., Rosenkranz G., Sondheimer F.: J. Amer. Chem. Soc. *77*, 148 (1955).
2. Zaffaroni A., Casac Campillo C., Cordoba F., Rosenkranz G.: Experientia *11*, 219 (1955).
3. Halton P. G.: U.S. 3 196 170; Chem. Abstr. *66*, 55 662 (1967).
4. Chang-Yon Byon, Gut M.: J. Org. Chem. *45*, 4404 (1980).
5. Bowers A., Villotti R., Edwards J. A., Denot E., Halpern O.: J. Amer. Chem. Soc. *84*, 3204 (1962).
6. Cocker J. D., Henbest H. B., Phillipps G. H., Slater G. P., Thomas D. A.: J. Chem. Soc. *1961*, 4472.
7. Kalvoda J., Heusler K., Anner G., Wettstein A.: Helv. Chim. Acta *46*, 1017 (1963).
8. Deghenghi R.: J. Org. Chem. *31*, 2427 (1966).
9. Hagiwara H., Noguchi S., Nichikawa M.: Chem. Pharm. Bull. *8*, 84 (1960).

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