A New Approach to the Synthesis of [17α,16α-*d*]Oxazolino-Corticosteroids

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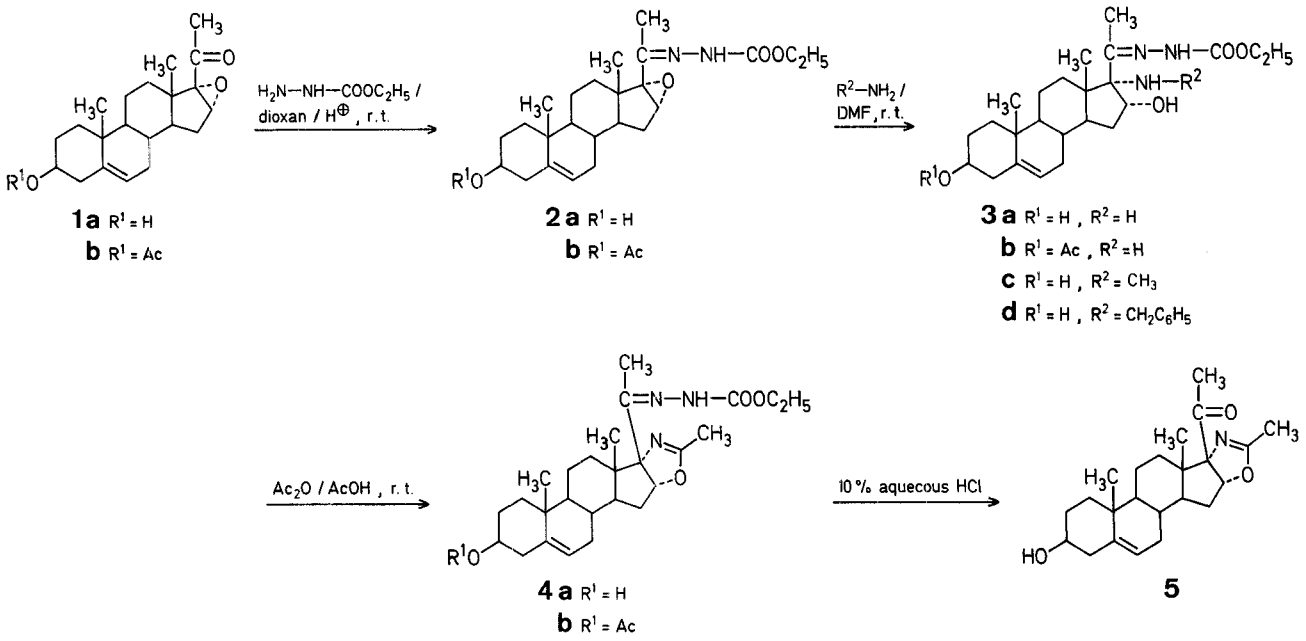
There are three methods known for the preparation of 16α-hydroxy-17α-aminopregnanes and hence [17α,16α-*d*]oxazolinopregnanes. The cleavage of 16β,17β-epoxides with alkali azides in the presence of acids[1,2,3] gives 17α,16α-azidohydrins which are reduced to aminoalcohols. This unusual *cis*-opening of an epoxide proceeds actually through a retro-aldol condensation of the intermediate 17α-azido-16β-hydroxy derivative[2]. In a second method, [17α,16α-*d*]oxazolinopregn-5-en-3β-ol-20-one **(5)** was obtained directly from the corresponding 16α,17α-aziridine[3,4]. In the first step of this sequence, methoxyamine is added to the Δ^{16}-20-keto system[5], the resulting 16α-methoxyamine is converted to 16α,17α-aziridine and is then acetylated. In the last method, the C_{17}—O bond of 3β-acetoxy-16α,17α-epoxypregn-5-en-20-ethoxycarbonylhydrazone is cleaved by azide ions, with retention of the configura-



tion, to yield the desired 17α-16α-azidohydrin[6]. This reaction, which implies the participation of the neighbouring hydrazone[7], was performed with different acidic nucleophiles, e.g. acetic acid[8], methanol[9], and thioacetic acid[6].

For the bulk production of Deflazacort® (pregna-1,4-diene-11β,21-diol-3,20-dione[17α,16α-*d*]-2′-methyloxazoline)[10], neither of these methods appeared suitable because of the complexity and of the explosion risks linked with the use of both sodium azide and methoxyamine[11]. The present paper describes the successful attempt to obtain the oxazoline **5** in high yield and under safe conditions according to the above scheme.

The ethoxycarbonylhydrazone **2a**, prepared by known methods[6], was dissolved in dimethylformamide and treated with gaseous ammonia yielding 90% of the crude aminoalcohol **3a** which was quantitatively cyclized to the oxazoline **4a** with acetic anhydride in acetic acid. Without purification, **4a** was treated with dilute hydrochloric acid in order to restore the 20-keto group. The final compound **5**[3] was crystallized to yield the pure product with an overall yield of 76% from **1a**. It is worthwhile to note that the whole procedure is carried out at room temperature and without purification of the intermediates. The synthesis of **5** starting from the 3-acetate **1b** gave similar results.

This sterically abnormal epoxide ring opening of the 20-ethoxycarbonylhydrazones is not limited to ammonia. As examples of the extension of the reaction to primary amines, the preparations of the 16α-hydroxy-17α-methylamine **3c** and -benzylamine **3d** are described in the experimental part.

16α,17α-Epoxypregn-5-en-3β-ol-20-one Ethoxycarbonylhydrazone (2a):
To a solution of the epoxide **1a** (100 g) in dioxan (800 ml), ethyl carbazate (50 g) is added at room temperature. A solution of conc. sulfuric acid (2 ml) in dioxan (50 ml) is added and stirring is continued for 30 h. The final solution is poured into ice/water (3000 ml). Crude **2a** is collected by filtration (122 g, 97%) and recrystallized from ethyl acetate; yield: 88 g (70%); m.p. 178–180°C; $[\alpha]_D^{20}$: +40.1° (1% in $CHCl_3$).

$C_{24}H_{36}N_2O_4$	calc.	C 69.20	H 8.71	N 6.72
(416.6)	found	69.48	9.00	6.61

^{1}H-N.M.R. ($CDCl_3$): δ = 1.01 (s, 3H, 18-CH_3); 1.70 (s, 3H, 21-CH_3); 3.53 (m, 1H, 16-H); 7.80 ppm (s, 1H, NHCO).

17α-Aminopregn-5-en-3β,16α-diol-20-one Ethoxycarbonylhydrazone (3a):
Dry ammonia is bubbled until saturation into a solution of the crude epoxide **2a** (122 g) in dimethylformamide (975 ml) at 22°C. After 30 h, the mixture is poured into ice/water (4000 ml). Crude **3a** is obtained by filtration (114 g, 90%) and recrystallized from ethyl acetate; yield: 91 g (72%); m.p. 174–176°C; $[\alpha]_D^{20}$: −146° (1% in CH_3OH).

$C_{24}H_{39}N_3O_4 \cdot 0.25H_2O$	calc.	C 65.12	H 9.10	N 9.49
(442.6)	found	65.22	9.21	9.65

^{1}H-N.M.R. (DMSO-d_6): δ = 0.60 (s, 3H, 18-CH_3); 1.83 (s, 3H, 21-CH_3); 4.97 (m, 1H, 16-H); 9.50 ppm (s, 1H, NHCO).

3β-Acetoxy-17α-aminopregn-5-en-16α-ol-20-one Ethoxycarbonylhydrazone (3b):
Dry ammonia is bubbled until saturation into a suspension of the epoxide **2b**[6] (10 g) in dimethylformamide (100 ml). After 48 h at room temperature, the reaction mixture is diluted with ice/water (200 ml), crude **3b** is collected by filtration (9.7 g, 94%) and recrystallized from ethanol; yield: 7.53 g (73%); m.p. 287–289°C; $[\alpha]_D^{20}$: −123° (1% in $CHCl_3$).

$C_{26}H_{41}N_3O_5 \cdot 0.5H_2O$	calc.	C 64.43	H 8.73	N 8.67
(484.6)	found	64.38	8.64	8.86

^{1}H-N.M.R. (DMSO-d_6): δ = 0.58 (s, 3H, 18-CH_3); 1.82 (s, 3H, 21-CH_3); 4.93 (m, 1H, 16-H); 9.43 ppm (s, 1H, NHCO).

17α-Methylaminopregn-5-en-3β,16α-diol-20-one Ethoxycarbonylhydrazone (3c):
Dry methylamine is slowly bubbled into a solution of the epoxide **2a** (0.833 g) in dimethylformamide (7 ml) at 25°C. After 4 h the mixture is poured into ice/water (35 ml), the solid **3c** is collected and crystallized from ethyl acetate; yield: 0.25 g (28%); m.p. 201–202°C; $[\alpha]_D^{20}$: −15° (1% in CH_3OH).

$C_{25}H_{41}N_3O_4$	calc.	C 67.08	H 9.23	N 9.39
(447.6)	found	66.85	9.43	9.34

^{1}H-N.M.R. ($CDCl_3$): δ = 0.74 (s, 3H, 18-CH_3); 1.88 (s, 3H, 21-CH_3); 2.36 (s, 3H, N—CH_3); 4.91 (m, 1H, 16-H); 7.64 ppm (s, 1H, NHCO).

17α-Benzylaminopregn-5-en-3β,16α-diol-20-one Ethoxycarbonylhydrazone (3d):
To a stirred suspension of the epoxide **2a** (2 g) in toluene (50 ml), benzylamine (2 g) is added and the mixture is heated at 65°C for 8 h. After cooling crystalline **3d** is obtained (2.2 g, 88%), and recrystallized from ethyl acetate; yield: 1.78 g (71%); m.p. 125–128°C; $[\alpha]_D^{20}$: −123° (1% in $CHCl_3$).

$C_{31}H_{45}N_3O_4$	calc.	C 71.09	H 8.66	N 8.02
(523.7)	found	70.70	8.96	7.77

^{1}H-N.M.R. ($CDCl_3$): $\delta = 0.77$ (s, 3 H, 18-CH_3); 1.83 (s, 3 H, 21-CH_3); 3.62 and 3.90 (2 d, 2 H, N—CH_2); 4.93 (m, 1 H, 16-H); 7.30 (s, 5 H_{arom}); 7.57 ppm (s, 1 H, NHCO).

Pregn-5-en-3β-ol-20-one[17α,16α-*d*]-2′-methyloxazoline Ethoxycarbonylhydrazone (4a):

The crude aminoalcohol **3a** (114 g) is dissolved in acetic acid (570 ml). Acetic anhydride is added (114 ml) and the temperature is maintained at 25 °C for 5 h. Under vigorous stirring the mixture is poured into ice/water (3000 ml) and 10% aqueous sodium hydroxide solution (4000 ml) is added with cooling after 1 h. Crude **4a** is collected (119 g, 99%) and recrystallized from ethyl acetate; yield: 95.5 g (81%); m.p. 190–193 °C; $[\alpha]_D^{20}$: +17.4° (1% in $CHCl_3$).

$C_{26}H_{39}N_3O_4$	calc.	C 68.24	H 8.59	N 9.18
(457.6)	found	68.46	9.06	9.30

^{1}H-N.M.R. ($CDCl_3$): $\delta = 0.67$ (s, 3 H, 18-CH_3); 1.92 (s, 3 H, 21-CH_3); 1.94 (s, 3 H, 2′-CH_3); 5.70 (m, 1 H, 16-CH_3); 7.53 ppm (s, 1 H, NHCO).

3β-Acetoxypregn-5-en-20-one[17α,16α-*d*]-2′-methyloxazoline Ethoxycarbonylhydrazone (4b):

The crude aminoalcohol **3b** (9.7 g) is treated as in the previous example. Neutralization of the reaction mixture is carried out with conc. ammonia solution while cooling. Crude **4b** is collected (9.5 g, 95%) and recrystallized from ethanol; yield: 7.0 g (70%); m.p. 254–255 °C; $[\alpha]_D^{20}$: +7.8° (1% in $CHCl_3$).

$C_{28}H_{41}N_3O_5$	calc.	C 67.31	H 8.27	N 8.41
(499.7)	found	67.41	8.48	8.30

^{1}H-N.M.R. ($CDCl_3$): $\delta = 0.68$ (s, 3 H, 18-CH_3); 1.93 (s, 3 H, 21-CH_3); 1.97 (s, 3 H, 2′-CH_3); 5.73 (m, 1 H, 16-H); 7.70 ppm (s, 1 H, NHCO).

Pregn-5-en-3β-ol-20-one [16α,17α-*d*]-2′-methyloxazoline (5):

The crude carbazone **4a** (119 g) in 10% hydrochloric acid (1190 ml) is stirred at room temperature for 24 h. The mixture is poured into ice/water (2400 ml) and neutralized, while cooling, with aqueous sodium hydroxide solution (1310 ml). Crude **5** (96.5 g) is collected and crystallized from ethanol; yield: 84.9 g (88%); m.p. 200–204 °C; $[\alpha]_D^{20}$: +6.0° (1% in $CHCl_3$) (Ref.[3], m.p. 198–200 °C; $[\alpha]_D^{22}$: +10°).

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[11] Methoxyamine was found by our Reactive Chemical Hazard Lab to be extremely shock sensitive! (Technoproducts dropo weight tester).