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The Syntheses of the Corticoid Side-chain. II. A New Synthesis of 17α,21-Dihydroxypregna-1,4-diene-3,20-dione 21-Acetate from 21-Hydroxy-20-methylpregna-1,4-dien-3-one

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Synopsis. 17α,21-Dihydroxypregna-1,4-diene-3,20-dione, a potentially useful intermediate of prednisolone, can be prepared from 21-hydroxy-20-methylpregna-1,4-dien-3-one, a biodegradation product of cholesterol.

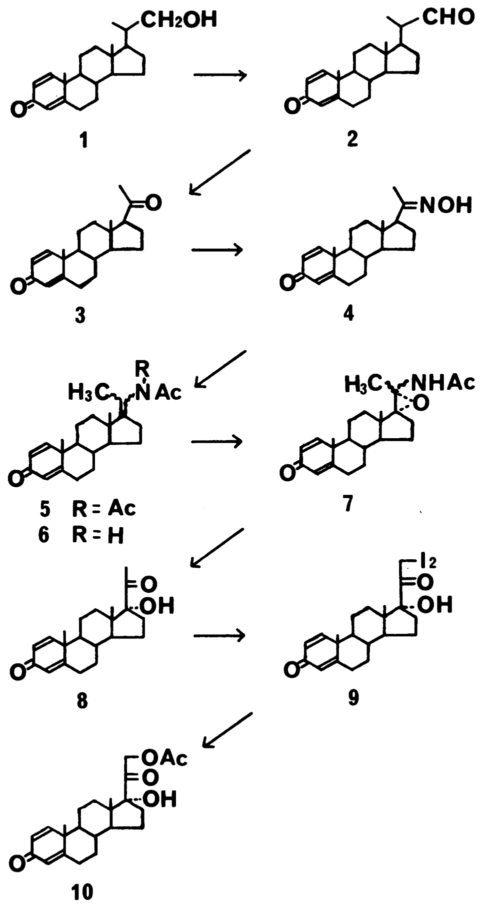
Corticosteroids are commercially produced from deoxycholic acid, stigmasterol or diosgenin. Recently, it was reported that cholesterol could be degraded to 21-hydroxy-20-methylpregna-1,4-dien-3-one (**1**) by a mutant of *Mycobacterium* sp.[1] Compound **1** may be one of the ideal starting materials for prednisolone synthesis. We present here a new conversion of **1** into 17α,21-dihydroxypregna-1,4-diene-3,20-dione 21-acetate (**10**), a precursor of prednisolone.

Results and Discussion

The methods employed in this conversion are summerized in Scheme 1. The first step is the oxidation of **1** to the aldehyde **2**. The oxidation of **1** was conducted by using the complex obtained from dimethyl sulfide and *N*-chlorosuccinimide[2] in toluene-dichloromethane to give **2** in 90% yield. The conversion of **2** into the ketone **3** was followed by a known oxidative decarboxylation procedure.[3] By bubbling air through a mixture of **2**, DBU and copper (II) acetate-2,2′-bipyridyl complex in DMF, the ketone **3** was obtained in 90% yield. The ketone **3** was converted to the oxime **4** easily in 92% yield.

Modifying the synthetic method of 3-acetylamino-5α-cholest-2-ene,[4] the oxime **4** was heated in acetic anhydride–pyridine for 40 h. The resulting solution was evaporated to dryness and the black tarry residue was partitioned into benzene and aqueous sodium hydrogencarbonate solution layers. Further processing including chromatography on silica gel yielded the enamide **5**. The NMR spectra of **5** showed that **5** was a 4:1 mixture of E and Z isomers. The hydrolysis of **5** in aqueous potassium hydrogencarbonate–methanol gave the enamide **6** as an amorphous product. Without further purification, **6** was treated with peracetic acid in the presence of sodium acetate in dichloromethane in the usual way.[5] After usual treatment, **8** was obtained in 43% yield from **4**. This was identified with the authentic sample which was derived from 17α-hydroxyprogesterone by the dehydrogenation with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone.

The 21-acetoxy introduction into **8** was accomplished by Stork's iodination procedure.[6] Iodination of **8** in THF–methanol with an excess of iodine in the presence of calcium oxide gave the iodide **9**, which was converted directly to **10** by treatment with triethylammonium acetate in acetone. Overall yield of **10** was 88% from **8** and 28% from **1**. The transformation of **10** into prednisolone can be followed by a microbiological process.



Scheme 1.

Experimental

20-Methyl-3-oxopregna-1,4-dien-21-al (2). To a stirred solution of *N*-chlorosuccinimide (8.0 g) in toluene (150 ml), dimethyl sulfide (6.0 ml) in toluene (50 ml) was added at 0 °C under nitrogen atmosphere. The mixture was cooled to −25 °C and a solution of 21-hydroxy-20-methylpregna-1,4-dien-3-one (**1**) (6.0 g) in dichloromethane (100 ml) was added dropwise. The stirring was continued for 2 h at −25 °C and then a solution of triethylamine (3.0 g) in dichlomethane (5.0 ml) was added dropwise. The cooling bath was removed and after 5 min, ether was added. The organic layer was washed with 1% hydrochloric acid and then with water. Removal of dried (sodium sulfate) solvents produced **2** in 90% yield. Recrystallization from ethyl acetate–hexane afforded the analytically pure sample; mp 154.4—154.8 °C dec., NMR ($CDCl_3$) δ=0.91 (s, 3H), 1.14 (d, 3H, J=4 Hz), 1.24 (s, 3H), 6.08 (s, 1H), 6.22 (d, 1H, J=10 Hz), 7.06 (d, 1H, J=10 Hz), 9.54 (d, 1H, J=4 Hz); m/z 326 (M^+).

Found: C, 81.03; H, 9.25%. Calcd for $C_{22}H_{30}O_2$: C, 80.98; H, 9.20%.

Pregna-1,4-diene-3,20-dione (3). Through a rapidly stirring mixture of **2** (0.5 g), DBU (0.1 g), $Cu(OAc)_2\cdot H_2O$ (8 mg), and 2,2′-bipyridyl (7 mg) in *N,N*-dimethylformamide (10 ml), air was bubbled at 20 °C for 14 h. The reaction mixture was extracted with chloroform and the organic layer was washed with 1% hydrochloric acid and then with water. Removal of solvents afforded **3** in 89.6% yield. Recrystallization from tetrahydrofuran–octane provided the analytically pure sample; mp 152.0—152.3 °C; NMR ($CDCl_3$) δ=0.7 (s, 3H), 1.24 (s, 3H), 2.12 (s, 3H), 6.08 (s, 1H), 6.24 (d, 1H, J=10 Hz), 7.06 (d, 1H, J=10 Hz).

Found: C, 80.93; H, 9.03%. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03%.

Pregna-1,4-diene-3,20-dione 20-Oxime (4). To a stirred solution of **3** (10.0 g) and sodium acetate (5.0 g) in aqueous methanol (90%, 150 ml), hydroxylamine hydrochloride (2.3 g) was added at 3—5 °C and stirred for 1.5 h. Water was added and the resultant precipitate was separated by filtration to give **4** (10.3 g) in 91.9% yield. Recrystallization from tetrahydrofuran–octane afforded the analytically pure sample; NMR ($CDCl_3$) δ=0.72 (s, 3H), 1.24 (s, 3H), 1.88 (s, 3H), 6.08 (s, 1H), 6.24 (d, 1H), 7.06 (d, 1H); m/z 327 (M^+).

Found: C, 77.24; H, 8.83; N. 4.28%. Calcd for $C_{21}H_{29}NO_2$: C, 77.02; H, 8.93; N, 4.28%.

20-(Diacetylamino)pregna-1,4,17(20)-trien-3-one (5). The oxime **4** (2.91 g) in dry pyridine (75 ml) and acetic anhydride (50 ml) was refluxed under nitrogen atmosphere for 40 h. The solvent was evaporated off under reduced pressure, the resultant black tar was taken up in benzene and saturated sodium carbonate solution.

The mixture was shaken and then filtered through a Celite pad, which was washed thoroughly with benzene. The benzene layer was separated, washed with water, dried and evaporated. The product in benzene was chromatographed on silica gel (Wakogel C-100, 15 g). The elution with benzene afforded **5** (3.77 g). This product was a mixture of *E*:*Z*=4:1, which was determined by NMR. NMR ($CDCl_3$) δ(*E*-form)=1.00 (s, 3H), 1.24 (s, 3H), 2.28 (s, 3H), 2.32 (s, 3H), 6.06 (s, 1H), 6.22 (d, 1H, J=10 Hz), 7.06 (d, 1H, J=10 Hz), δ(*Z*-form)=0.88 (s), 1.24 (s), 2.26 (s), 2.38 (s), 6.04 (s), 6.20 (d, J=10 Hz), 7.04 (d, J=10 Hz); m/z 395 (M^+).

20-(Acetylamino)pregna-1,4,17(20)-trien-3-one (6). Diacetylamino compound **5** (3.77 g) was added to methanol (60 ml) and potassium hydrogencarbonate (3.5 g) and refluxed for 1.5 h. The reaction mixture was extracted with dichloromethane and the organic layer was washed with water, dried and evaporated to give **6** (3.14 g). NMR ($CDCl_3$) δ(*E*-form)=0.96 (s, 3H), 1.24 (s, 3H), 2.00 (s, 6H), 6.06 (s, 1H), 6.22 (d, 1H, J=10 Hz), 6.56 (broad, 1H), 7.06 (d, 1H, J=10 Hz), δ(*Z*-form)=0.94 (s), 1.22 (s), 1.98 (s), 6.06 (s), 6.20 (d, J=10 Hz), 6.76 (broad), 7.04 (d, J=10 Hz); m/z 353 (M^+).

17α-Hydroxypregna-1,4-diene-3,20-dione (8). To a mixture of **6** (1.54 g) and sodium acetate (0.22 g) in dichloromethane (5 ml), 40% peracetic acid (0.99 g) in dichloromethane (15 ml) was added dropwise at 3—5 °C. After 1 h, sat. sodium hydrogencarbonate solution was added and the organic layer was separated, washed successively with 5% potassium iodide solution, sodium thiosulfate solution and water, dried and evaporated. To the residue, methanol (20 ml) and 0.3 M(1 M=1 mol dm^{-3}) sodium hydroxide solution (20 ml) were added and the mixture was heated under reflux for 1.5 h. After cooling, the mixture was neutralized with acetic acid and then concentrated. The products were extracted with dichloromethane and the organic layer was washed with water and dried. Removal of solvents afforded crude **8** (1.39 g), which was chromatographed on a column of silica gel with benzene–methanol (85:15) to give **8** (0.61 g) in 43% yield from **4**. Recrystallization from octane–tetrahydrofuran (1:1) afforded the analytically pure sample; mp 258.0—258.7 °C, NMR ($CDCl_3$) δ=0.8 (s, 3H), 1.26 (s, 3H), 2.28 (s, 3H), 2.96 (s, 1H), 6.08 (s, 1H), 6.22 (d, 1H, J=10 Hz), 7.06 (d, 1H, J=10 Hz).

Found: C, 76.95; H, 8.48%. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59%.

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