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Improved Synthesis of 18-Hydroxydeoxycorticosterone

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Abstract □ Hypoiodite photolysis of 3β-acetoxy-5-pregnen-20β-ol gave 3β-acetoxy-5-pregnene-18,20-lactone in 46% yield. Lithium aluminum hydride reduction of the latter afforded 3β,18,20β-trihydroxy-5-pregnene (91% yield) which, on Oppenauer oxidation, was converted to 18-hydroxyprogesterone (66%). Lead tetraacetate oxidation followed by mild saponification gave 18-hydroxydeoxycorticosterone (58% yield).

Keyphrases □ 18-Hydroxydeoxycorticosterone—synthesis □ 18,-20-Oxido-20-hydroxy-4-pregnen-3-one—synthesis □ 18-Hydroxyprogesterone—synthesis

Because recent evidence suggests that 18-hydroxydeoxycorticosterone (I) may be an important causative agent in hypertension (1–6), considerable interest recently has been shown in the synthesis of this compound. Syntheses reported to date have either been overly long (7), low in yield (7, 8), or lacking in needed experimental detail (9). The details of a short, reproducible, high yield synthesis of I from 3β-acetoxy-5-pregnen-20-one (II) are now reported (Scheme I).

DISCUSSION

3β-Acetoxy-5-pregnen-20β-ol (III), prepared in 69% yield by borohydride reduction of pregnenolone acetate (II), was subjected to photolysis in the presence of lead tetraacetate and iodine (10) to afford 3β-acetoxy-5-pregnene-18,20-lactone (IV) in a yield of 46%. Lithium aluminum hydride reduced IV to 3β,18,20β-trihydroxy-5-pregnene (V) in a yield of 91%. Oppenauer oxidation converted V to 18,20-oxido-20-hydroxy-4-pregnen-3-one (VI) in 66% yield.

The latter hemiketal (VI) was oxidized by lead tetraacetate in acetic acid (9) and then hydrolyzed with dilute hydroxide to form I. Reaction for 18 hr with excess tetraacetate caused the intermediate 21-acetoxy Compound VII to cleave to form the lactone VIII. However, by limiting the reaction time to 6 hr, VI could be transformed to I in 58% yield. An attempt to improve this yield by limiting the amount of tetraacetate proved futile.

In summary, the reported procedure has permitted the reproducible preparation of I from a cheap and readily available starting material in an overall yield of 11%.

EXPERIMENTAL[1]

3β-Acetoxy-5-pregnen-20β-ol (III)—Pregnenolone acetate (20 g) in tetrahydrofuran (100 ml) was added to sodium borohydride (3 g) in water (10 ml) and stirred at room temperature for 72 hr. Acetic acid was added and then the mixture was diluted with water. The solvent was concentrated under reduced pressure.

The solid was filtered, dried, and then chromatographed on a column of 200 g of acidic alumina. Elution with benzene–ethyl acetate (100:20) afforded III in a yield of 14 g (69%); mp 167° [lit. (11) mp 165°]; IR ($CHCl_3$): ν 3610 and 1720 cm^{-1}; NMR: δ 0.78 (s, C-18 H), 1.04 (s, C-19 H), 2.03 [s, $O(O{=})CCH_3$], and 5.39 (d, $J \approx 4$ Hz, C-5 H).

3β-Acetoxy-5-pregnene-18,20-lactone (IV)—To a stirred suspension of lead tetraacetate (15 g) and calcium carbonate (5 g) in cyclohexane (500 ml) at 80° were added iodine (4 g) and III (5 g). The stirred mixture was refluxed and irradiated with a 250-w tungsten lamp for 150 min and then was cooled and filtered. The filter cake was washed with cyclohexane, and the filtrate was washed with aqueous sodium thiosulfate (5%) and water. After pyridine (1.25 ml) was added, the filtrate was concentrated under reduced pressure.

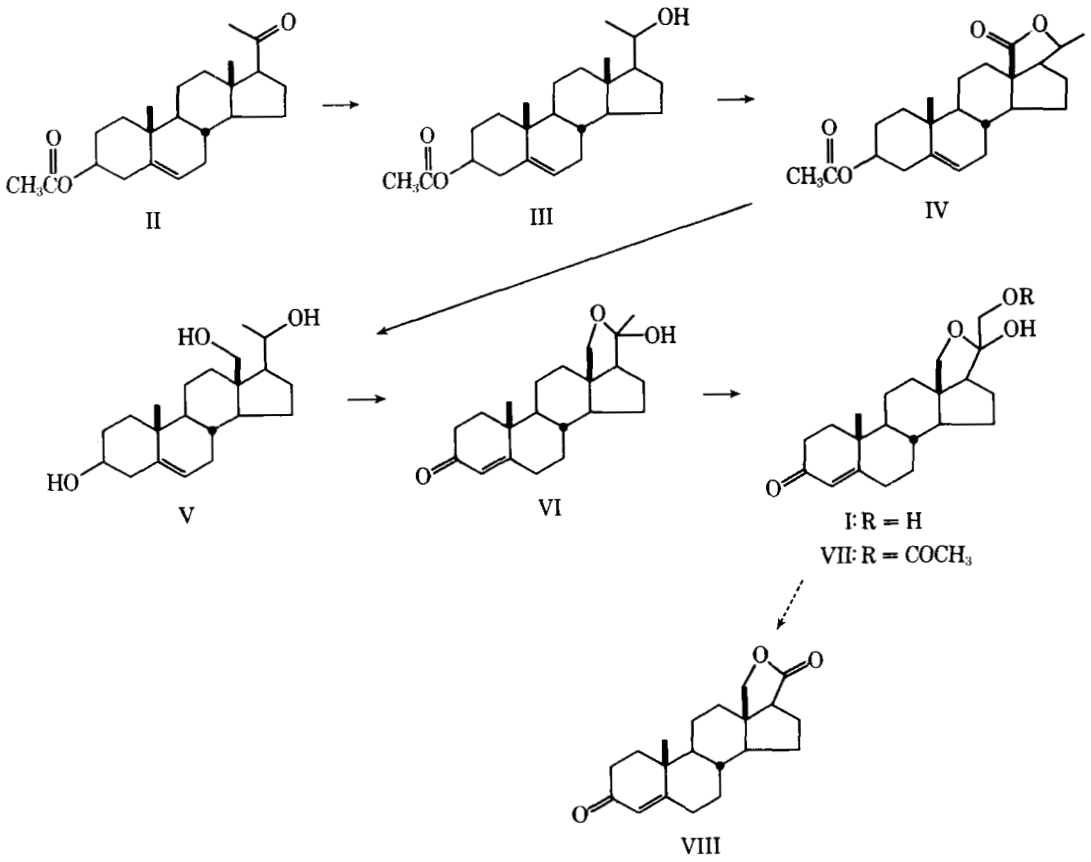
The residue was dissolved in acetone (100 ml), and silver chromate (2.5 g) was added. The mixture was cooled to 0°, and 5.7 ml of a solution prepared by dissolving chromium trioxide (13.3 g) in sulfuric acid (11.5 ml) and diluting to 50 ml with water was added slowly. After 60 min a solution of sodium acetate (60 g) in water (100 ml) was added. The mixture was extracted two times with benzene.

The organic layer was washed (water), dried (magnesium sulfate), and concentrated under reduced pressure. Crystallization from benzene–ether gave IV in a yield of 2.4 g (46%), mp 208–210°; IR ($CHCl_3$): ν 1745 and 1720 cm^{-1}; NMR: δ 1.13 (s, C-19 H), 2.02 [s, $O(O{=})CCH_3$], and 5.40 (s, C-5 H).

Anal.—Calc. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.23; H, 8.66.

3β,18,20β-Trihydroxy-5-pregnene (V)—A mixture of IV (1 g) and lithium aluminum hydride (1 g) in tetrahydrofuran (60 ml)

[1] Melting points were determined in an open capillary tube on a Mel-temp apparatus and are uncorrected. IR spectra were recorded on a Beckman IR-8. NMR spectra were determined on a Varian A-60 spectrometer in deuterochloroform solution and are reported in parts per million downfield from a tetramethylsilane internal standard. Elemental analyses were determined by Atlantic Microlab, Inc.



Scheme I

was stirred overnight at room temperature. Standard work-up afforded V which, when recrystallized from acetone, afforded an analytical sample, 0.82 g (91%); IR (mineral oil): ν 3370 cm^{-1}.

Anal.—Calc. for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25. Found: C, 75.18; H, 10.08.

18,20-Oxido-20-hydroxy-4-pregnen-3-one (VI)—Ten milliliters was distilled from a mixture of toluene (80 ml), cyclohexanone (25 ml), and V (0.80 g). Then aluminum isopropoxide (0.80 g) was added, and the resulting mixture was heated under reflux for 5 hr. Standard work-up afforded VI, which crystallized from methylene chloride–ether in a yield of 0.50 g (66%), mp 172–175° [lit. (7) mp 173–182°]; IR ($CHCl_3$): ν 3440, 1660, and 1610 cm^{-1}; NMR: δ 1.11 (s, C-19 H), 1.47 (s, C-21 H), 3.71 (s, C-18 H), and 4.67 (s, C-4 H).

18,20-Oxido-20,21-dihydroxy-4-pregnen-3-one (I)—A mixture of VI (100 mg), lead tetraacetate (100 mg), and acetic acid (1.5 ml) was stirred at room temperature for 6 hr. The solution was poured on ice, extracted with ethyl acetate, washed with water, dried over magnesium sulfate, and concentrated under reduced pressure. The residue, consisting of a mixture of VI, VII, and VIII, was dissolved in methanol (10 ml). To the solution was added 1 ml of 0.1 *N* potassium hydroxide. The mixture was stirred for 2 hr at room temperature and then was neutralized with acetic acid and concentrated under reduced pressure.

The residue was dissolved in ethyl acetate, washed with water, dried over magnesium sulfate, concentrated, and purified by thick-layer chromatography on silica gel. Acetone–benzene (18:82) was used to develop the plate. The most polar band afforded I, in a yield of 60 mg (58%), mp 191–193° [lit. (7) mp 191–195°]; IR ($CHCl_3$): ν 3415, 1660, and 1610 cm^{-1}.

A slightly less polar band contained VI and an appreciably less polar band contained the lactone VIII, IR ($CHCl_3$): ν 1760 cm^{-1}. The NMR spectrum showed loss of acetate CH_3 and the C-18 protons appeared as an *AB* pattern centered at δ 4.05.

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