Synthesis of 3β-Hydroxyandrost-5-en-17-one-4-C^{14} and 3β-Hydroxypregn-5-en-20-one-4-C^{14} [1,2]

ZOFIA TARASIEJSKA GLAZER AND MARCEL GUT

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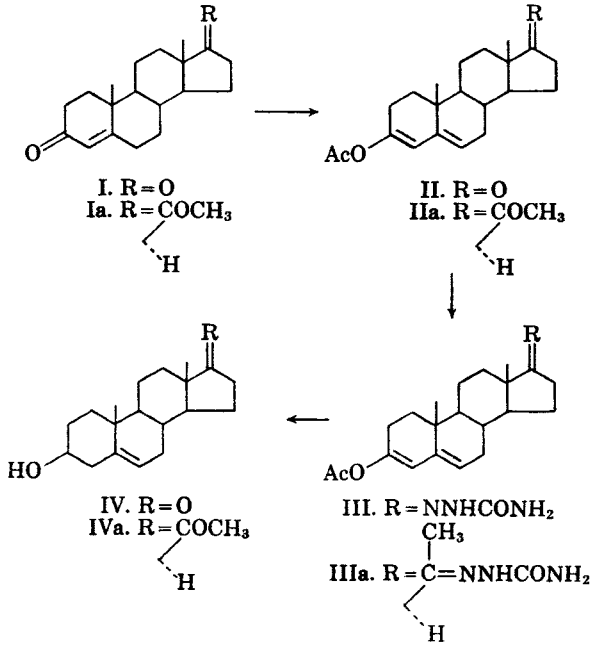
Since C^{14}-steroids labeled in ring A are originally obtained as 3-keto-Δ^4 compounds, the synthesis of dehydroepiandrosterone and pregnenolone requires the reduction of the 3-ketone and the shift of the double bond into the 5,6-position. Procedures for this transformation have already been described[3,4]. In a recent publication[5] a method has been outlined which permitted protection of the 3β-hydroxyl group of androst-5-en-3β,17β-diol during oxidation of its 17β-hydroxylic function, thereby making possible the transformation of testosterone to androstenolone.

In addition, this paper describes the application of known methods for the selective reduction of the 3-ketone and shifting of the double bond to the transformation of progesterone to Δ^5-pregnenolone.

The first approach[6] consists in blocking the conjugated ketone of I (Ia) by forming the enol acetate II, (IIa), which is then treated with semicarbazide under basic conditions to give III (IIIa). The 17- or 20-semicarbazone now makes possible the selective reduction of the 3-enol acetate with sodium borohydride after which the 17- or 20-keto group can be regenerated by treating it with pyruvic acid.[7]

The second approach is based on the observation[8] that the digitonide complex offers protection of the 3β-hydroxyl group towards chromic acid oxidation. In this case the conjugated ketone I (Ia) was converted to the enol ester II (IIa) and the reaction product was reduced with sodium borohydride in methanol. The crude reduced material was refluxed with methanolic hydrochloric acid (elimination of allylic alcohols), and the resulting product was treated with digitonin. The precipitated digitonin complex was filtered and oxidized with chromic acid in acetic acid. After oxidation the digitonin complex was cleaved in the usual manner and the desired dehydroepiandrosterone, and pregnenolone were isolated respectively.



The syntheses with radioactive materials (using androstenedione-4-C^{14} and progesterone-4-C^{14}, respectively) gave similar yields and products as those reported for the nonradioactive model run.

EXPERIMENTAL

Androst-4-ene-3,17-dione-3-enol acetate (II). This substance was prepared as described by Westphal.[9] The crude product was dissolved in benzene and filtered through a short column of alkaline aluminum oxide. The yield in crystalline material (m.p. 125°) was 82%.

Androst-4-ene-3,17-dione-3-enol acetate 17-semicarbazone (III). To a solution of 465 mg. of II in 60 ml. of ethanol and 6 ml. of pyridine was added 500 mg. of semicarbazide hydrochloride in 1 ml. of water. After refluxing the mixture for 30 min. a white precipitate formed. The heating was maintained for an additional 30 min.; then 5 ml. of water was added. After cooling, the semicarbazone was filtered and dried. The yield of crude material was 492 mg. (88%). Recrystallization from methanol, to which a trace of pyridine was added, gave white prisms melting at 264–265° dec. (introduced at 262°); $[\alpha]_D^{24}$ −114° (*c*, 0.18 in chloroform); λ_{max} 229 mμ (ε 33000).

Anal. Calcd. for $C_{23}H_{33}N_3O_3$: C, 68.54; H, 8.11; N, 10.90. Found: C, 68.36; H, 8.10; N, 10.67.

An alternative method consists in heating the ethanolic solution of the ketone containing a trace of pyridine with an ethanolic solution of semicarbazide acetate. However, for small scale work the first method is the preferred one.

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(2) This investigation was supported in part by a grant USPHS-A-3419.

(3) H. Reich and A. Lardon, *Helv. Chim. Acta*, 29, 671 (1946).

(4) For references see A. Murray, III and D. L. Williams, *Organic Syntheses with Isotopes*, Interscience, New York, 1958, I, p. 1056.

(5) M. Gut and M. Uskoković, *J. Org. Chem.*, 24, 673 (1959).

(6) For a similar procedure, compare S. G. Brooks, R. M. Evans, G. F. H. Green, J. S. Hunt, A. G. Long, B. Mooney, and L. J. Wyman, *J. Chem. Soc.*, 4614, (1958) and literature quoted.

(7) Note added in press: This method, namely the protection of a ketone during sodium borohydride reduction of the enol acetate, has been used for the preparation of 3β-hydroxypregn-5-en-20-one-4-C^{14} (P. N. Rao and L. R. Axelrod, *J. Org. Chem.*, 26, 1607 (1961)).

(8) D. Kupfer, E. Forchielli, and R. I. Dorfman, *J. Am. Chem. Soc.*, 82, 1257 (1960).

(9) U. Westphal, *Ber.*, 70, 2128 (1937).

Dehydroepiandrosterone (IV). To a warm solution of 374 mg. of III in 100 ml. of methanol and 70 ml. of pyridine was added 100 mg. of sodium borohydride in methanol. After standing for 20 hr. at room temperature the excess sodium borohydride was decomposed with acetic acid. The solvents were evaporated and the dry residue triturated with dilute hydrochloric acid, filtered and then dried.

The crude mixture of isomeric alcohols was suspended in 1 ml. of acetic acid, a mixture of 150 mg. of sodium acetate and 0.3 ml. of pyruvic acid in 1 ml. of acetic acid and a drop of water added, and heated for 1 hr. at 110°. During the heating period, 4 ml. of water was added to the solution. After cooling the mixture was extracted with ether, washed with a solution of sodium bicarbonate, water and dried over anhydrous sodium sulfate. The solvent was then evaporated. The 3β-alcohol was isolated through its digitonide which, after decomposition with pyridine, gave 117 mg. of crystalline IV, m.p. 139–141°, not depressed on admixture with authentic material.

This corresponds to an over-all yield, based on androstenedione, of 31%. The mother liquors of the digitonide were evaporated, extracted with ether and chromatographed over aluminum oxide. The benzene eluates gave 23 mg. (6% over-all yield) of crystalline androsta-3,5-dien-17-one [m.p. 87–89°; $[\alpha]_D^{24}$ −32° (*c*, 0.81 in ethanol); ultraviolet maxima at 228 mμ, 235 mμ, 247 mμ and infrared absorption spectrum identical with authentic material]. Mixtures of benzene-ethyl acetate (9:1) eluted first 68 mg. (17%) of crystalline androstenedione. Taking in account the recovery of the starting material, the over-all yield in 3β-hydroxyandrost-5-en-17-one was raised to 37%. Finally, 37 mg. (9%) of 3α-hydroxyandrost-5-en-17-one, m.p. 219–221°; $[\alpha]_D^{24}$ +1° (*c*, 1.1 in ethanol), infrared absorption spectrum identical with authentic material, was eluted with a mixture of benzene-ethyl acetate (9:1).

Progesterone-3-enol acetate-20-semicarbazone (IIIa). The 3-enol acetate of progesterone has been prepared as described by Westphal.[9] The 20-semicarbazone was obtained by the method used for preparation of III. The yield in crude semicarbazone was 63% (based on progesterone). Recrystallization from methanol to which a trace of pyridine was added gave light yellow crystals melting at 250–280° dec.; λ_{max} 233 mμ (ε 37000).

Anal. Calcd. for $C_{24}H_{35}O_3N_3$: C, 69.70; H, 8.53; N, 10.16. Found:, C 69.66; H, 8.61; N, 10.22.

3β-Hydroxypregn-5-en-20-one (IVa) *from* IIIa. The semicarbazone IIIa was reduced with sodium borohydride, the reduced product hydrolyzed with pyruvic acid and the hydrolyzed product isolated by precipitation with digitonin, as indicated for the conversion of III to IV. Thus, 628 mg. of IIIa yielded 198 mg. of IVa, m.p. 185–187° (26% based on progesterone).

The mother liquors, upon chromatography on aluminum oxide, furnished 4% of 3β-acetoxypregn-5-en-20-one, 6% of progesterone and 5% of 3α-hydroxypregn-5-en-20-one.

Taking in account the recovery of 6% of progesterone and the isolation of 4% of pregnenolone acetate, the over-all yield of IVa was raised to 32%.

3β-Hydroxypregn-5-en-20-one (IVa) *from pregn-5-en-3β,20β-diol.* To 190 mg. of pregn-5-ene-3β,20β-diol (obtained by sodium borohydride reduction of progesterone 3-enol acetate) were added 50 ml. of hot 90% ethanol and a hot solution of 800 mg. of digitonin in 80 ml. of 90% ethanol. After standing for 18 hr. at room temperature, 697 mg. of digitonide complex was filtered off, dried, dissolved in 40 ml. of glacial acetic acid, and oxidized with 60 ml. of a 1.2% solution of chromic acid in 60% acetic acid. After 30 min. a few drops of methanol were added. The solvent was evaporated *in vacuo*, and the dry residue heated for 1 hr. with pyridine. The digitonin was then precipitated by addition of ether and filtered off. The filtrate was concentrated *in vacuo* to a small volume, washed with water, dilute hydrochloric acid, water and then dried and chromatographed over neutral aluminum oxide. Mixtures of benzene–ethyl acetate (4:1) eluted 90 mg. (47% based on pregnenediol) of IVa, m.p. 185–187°, not depressed on admixture with authentic material.

THE WORCESTER FOUNDATION FOR EXPERIMENTAL BIOLOGY
SHREWSBURY, MASS.

Preparation of *cis*- and *trans*-4-*t*-Butyl-α,α-dimethylcyclohexanemethanol

ROBERT D. STOLOW AND CHARLES B. BOYCE

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As part of a study of conformational equilibria and reactivity of cyclohexane derivatives, we have prepared two stereoisomeric tertiary alcohols: *cis*- and *trans*-4-*t*-butyl-α,α-dimethylcyclohexanemethanol (*cis*-II and *trans*-II). These alcohols differ from *cis*- and *trans*-1,4-di-*t*-butylcyclohexane only in the replacement of one methyl group by a hydroxyl group. The *cis*-1,4-disubstituted cyclohexane derivatives which have bulky substituents, such as *cis*-1,4-di-*t*-butylcyclohexane and *cis*-II, would be expected to exist in non-chair conformations in significant populations at ordinary temperatures.[1,2]

Each alcohol, *cis*-II and *trans*-II, was prepared stereospecifically from the corresponding stereoisomer of 4-*t*-butylcyclohexanecarboxylic acid. Several methods have been reported recently for preparation of *cis*- and *trans*-4-*t*-butylcyclohexanecarboxylic acid.[2–7] The procedure for isolation of the *cis*-acid described by Lau and Hart[5] was repeated with excellent results. The *trans*-acid was prepared conveniently by use of the method of Tichý, Jonáš and Sicher.[6] Each pure acid was converted to its methyl ester (*cis*-I and *trans*-I) in excellent yield by use of diazomethane.[6,7] Addition to excess of the Grignard reagent, prepared from iodomethane and magnesium in ether, of each pure ester yielded the desired tertiary alcohols (*cis*-II and *trans*-II).

The *trans*-alcohol (*trans*-II) would be expected to exist in the chair conformation in which both bulky

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(7) E. A. S. Cavell, N. B. Chapman, and M. D. Johnson, *J. Chem. Soc.*, 1413 (1960).