SYNTHESIS OF 17α-20-KETOPREGNANES[1]

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The use of freshly activated zinc in the Serini-Logemann reaction of 17α-hydroxy-20-acetoxypregnanes provides a convenient method for the preparation of 17α-20-ketopregnanes. Reproducibly high yields were obtained with 16-unsubstituted compounds; 16α- or 16β-methyl substituents caused marked reduction in yield.

For part of a study of steric effects in 20-ketosteroids, a convenient preparation of 17α-20-ketopregnanes was desired. Two methods are described in the literature for synthesis of such compounds. The first, initially reported by Butenandt and coworkers[3a,b] and most recently used by Glick and Hirschman[4], involves refluxing the commonly available 17β-steroids in alkaline solution followed by separation of the minor product[5] of the equilibration, the desired 17α-isomer, by fractional crystallization or other techniques. In cases where side reactions are unimportant, recovered starting material can be recycled to accumulate moderate quantities of desired product, but at best this method is time-consuming, tedious and inefficient except in rare cases where the 17α-isomer predominates at equilibrium (v.i.).

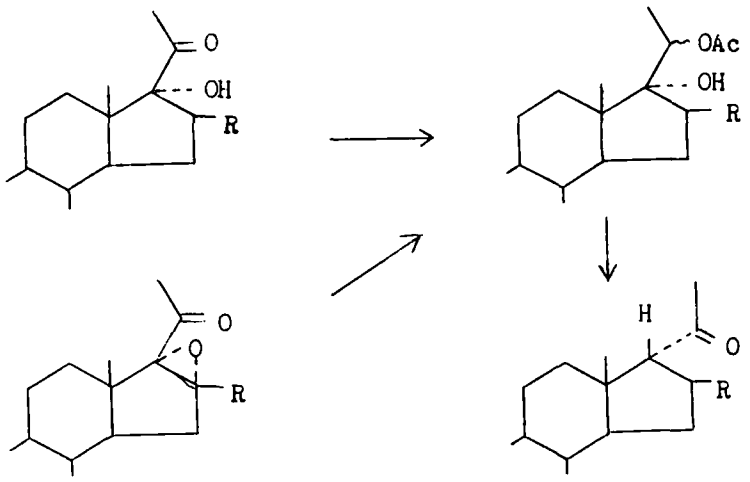
A more promising approach involved use of the Serini-Logemann reaction[6,7]. This reaction, formally analogous to the pinacol rearrangement, involves heating secondary-tertiary or primary-tertiary glycol monoacetates with zinc, and leads to ketones with

inverted configuration at the tertiary carbon atom. Reaction of 17α-hydroxy-20-acetoxypregnanes, readily available from 17α hydroxy- or 16α,17α-epoxy-20-ketones. would provide the desired 17α-20-ketopregnanes. The original report[8] of the Serini-Logemann reaction described sublimation of the reaction product under high vacuum from a heated mixture of zinc dust and the glycol monoacetate; other investigators[6] have obtained the rearranged ketones by refluxing the glycol monoacetate and a suspension of zinc in a variety of high boiling solvents. The reported yields range from 30-60%.

Following a suggestion of Wagle[9], we have employed freshly activated zinc in refluxing xylene with vigorous stirring for 20-24 hrs. to obtain a number of 17α-20-ketopregnanes in yields ranging from 68% to nearly quantitative. Using a standarized procedure for activating the zinc, reproducible results have consistently been obtained and quantities of several grams or more[10] of the desired 17α-steroids obtained without difficulty. In some cases the product could be crystallized directly from the crude reaction mixture; in others it was contaminated with starting glycol monoacetate, separable by Florisil or alumina chromatography. Pilot experiments with pure C-20 epimers indicated that the yield of the reaction did not depend on the stereochemistry at C-20. Accordingly, no attempt was made to separate the mixture of C-20 epimers (presumably predominantly 20β) which resulted from hydride reduction of 17α-hydroxy- or 16α,17α-epoxy-20-ketones. Syntheses of 17α-pregnenolone acetate (17α-Δ^4-pregnene-3β-ol-20-one acetate) and 17α-progesterone

(17α-Δ^4-pregnene-3,20-dione) are described in the experimental section.

The presence of a 16-methyl substituent had a considerable effect, presumably steric in origin, on the yield of 17α-steroid. Increasing the reaction time from the usual 24 hrs. to 160 hrs. afforded, reproducibly, approximately 25% of 16β-methyl-17α-pregnenolone acetate (16β-methyl-Δ^5-17α-pregnene-3β-ol-20-one acetate) from the corresponding glycol monoacetate. In this case the base-catalyzed isomerization is clearly superior since it leads to isolation of 17α-isomer from 16β-methylpregnenolone[11] in 52% yield.



However, in the case of 16α-methyl-20-ketopregnanes where no detectable amount of 17α-isomer is obtained by base-catalyzed equilibration[11], the Serini-Logemann reaction provided the desired isomer in 25% yield after 120 hrs. reaction time. The starting material for the synthesis of 16α-methyl-17α-

progesterone (16α-methyl-17α-Δ^4-pregnene-3,20-dione) was 16α-methyl-17α-hydroxyprogesterone which was selectively converted to the pyrollidine-3-enamine[12]. This was reduced with lithium aluminum hydride to the 17α,20-diol which, after hydrolysis of the enamine and acetylation, gave 16α-methyl-Δ^4-pregnene-3-one-17α,20-diol-20-acetate required for the Serini-Logemann reaction.

In contrast to earlier reports[7], we have observed little or no effect of oxygen or added hydroquinone on yields of the Serini-Logemann reaction. The importance of a tertiary hydroxyl group is suggested by recovery of unchanged starting material when the glycol monoacetate obtained by sodium borohydride reduction of desoxycorticosterone acetate followed by manganese dioxide oxidation (to regenerate the Δ^4-3-keto function) was subjected to the usual reaction conditions.

EXPERIMENTAL PART[13]

Activated zinc: A suspension of zinc (30-60 mesh) in concentrated sulfuric acid (4 ml. per gram of zinc) and a few drops of fuming nitric acid was heated on the steam bath for 30 minutes with occasional swirling. The acid was decanted after cooling and the residue allowed to react with ice-cold distilled water (25 ml. per g. of zinc) for one minute. The water was decanted and the zinc washed with distilled water until the washings were neutral, then twice with 95% ethanol and twice with acetone. It was used directly after drying at 100-120° for 40 minutes.

General Serini-Logemann reaction procedure: A 1% solution of the glycol monoacetate in distilled xylene was refluxed in a

nitrogen atmosphere with 20 times its weight of freshly activated zinc while stirring vigorously. After the appropriate reaction time, the solution was cooled, and the zinc filtered and washed with benzene. The combined filtrates were concentrated under reduced pressure on the steam bath and the residue taken up in ethyl acetate and water. The layers were separated and the organic layer washed with water and saturated salt solution, dried over anhydrous sodium sulfate, and concentrated under reduced pressure on the steam bath. The resulting crude reaction product was crystallized directly or chromatographed on Florisil.

17α-Progesterone: Serini-Logemann reaction of 2.83 g. of Δ^4-pregnene-17α,20-diol-3-one-20-acetate (m.p. 186-191°, α_D^{30} + 124°) for 20 hrs. yielded 2.70 g. of oil which was chromatographed on 136 g. of Florisil. Fractions eluted with 2% and 3% acetone-benzene (1.82 g.) were combined and recrystallized from isopropyl ether to give 1.50 g. (68%) of white needles, m.p. 142-144°, α_D^{31} + 2 ± 2° (reported[14] m.p. 145°, α_D 0° (alcohol)).

Yields ranging from 60-80% were obtained in five similar runs.

17α-Pregnenolone acetate: Reaction of 2.35 g. of Δ^5-pregnene-3β,17α,20-triol-3,20-diacetate (m.p. 155-161°, α_D -41°) for 24 hrs. furnished 2.14 g. of crude, crystalline product, m.p. 140-169°, α_D^{31} -112 ± 3°. Crystallization from acetone-methanol yielded, in two crops, 1.11 g. (55%), m.p. 170-170.5°, α_D^{30} -120 ± 1° (reported[14] m.p. 170-171°, α_D^{20} -126° (ethanol)).

16α-Methyl-Δ^4-pregnene-3-one-17α,20-diol-20-acetate: The solvent was slowly distilled from a mixture of 1.00 g. of 16α-methyl-

Δ^4-pregnene-17α-ol-3,20-dione, 1.36 ml. of freshly distilled pyrollidine and 30 ml. of isopropyl alcohol so that 7 ml. of distillate was collected in one hr. After cooling and concentration 1.20 g. of crude 16α-methyl-3-(N-pyrollidyl)-$\Delta^{3,5}$-pregnadiene-17α-ol-20-one was obtained, m.p. 130-170° (dec.) λ_{max} (ether) 279mμ (20,200); (KBr) 2.90, 3.03, 5.90, 6.10, 6.21μ.

The crude enamine was reduced directly with 0.28 g. of lithium aluminum hydride in 25 ml. of tetrahydrofuran at room temperature. After careful addition of 3 ml. of water in 3 ml. of methanol, 31 ml. of methanol, 5 ml. of glacial acetic acid, 6 ml. of water and 8 g. of sodium acetate were added and the solution refluxed for 1.5 hrs. The organic solvents were removed under reduced pressure, the residue diluted with 250 ml. of water and the solution acidified to pH 1 by addition of conc. hydrochloric acid. This was then extracted three times with methylene chloride and the combined extracts washed with water, saturated sodium bicarbonate solution and water to give, after drying over sodium sulfate and concentration, 0.91 g. (91%) of solid, m.p. 150-185°. The analytical sample of 16α-methyl-Δ^4-pregnene-3-one-17α,20-diol was obtained by crystallization from acetone-ether, m.p. 190-192°, α_D^{30} +66°. λ_{max} 242mμ (17,000); (KBr) 2.80, 6.00, 6.20μ.

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.34; H, 10.17.

Acetylation of 0.90 g. of crude diol with acetic anhydride and pyridine in the usual manner gave 0.998 g. of yellow white solid, m.p. 150-177°. Chromatography of 200 mg. of this material on 8 g. of Florisil gave 154 mg. of solid, m.p. 155-183°, eluted

with 3% ethyl acetate in benzene. The analytical sample of mixed C-20 epimers of 16α-methyl-Δ^4-pregnene-3-one-17α,20-diol-20-acetate was obtained by crystallization from acetone-petroleum ether, m.p. 161-181°, α_D^{30} +101°. λ_{max} 242mμ (17,600); (KBr) 2.75, 5.77, 5.97, 8.10μ.

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.40; H, 9.20.

16α-methyl-17α-progesterone: Serini-Logemann reaction of 413 mg. of glycol monoacetate described above for 120 hrs. gave 410 mg. of yellow oil, α_D^{31} 30°, which was chromatographed on 20 g. of Florisil. Elution with 1-1.5% ethyl acetate in benzene gave 129 mg. of solid which could not be satisfactorily recrystallized and was rechromatographed on 6.5 g. of Florisil. Elution with 1% ethyl acetate in benzene gave 88 mg. (25%) of solid, m.p. 136-139°. The analytical sample was obtained by crystallization from ether as needles, m.p. 139-140°, α_D^{30} +13°. λ_{max} 242mμ (18,000); (KBr) 5.88, 5.99, 6.19μ.

Anal. Calcd. for $C_{22}H_{32}O_2$: C, 80.44; H, 9.83. Found: C, 80.39; H, 9.53.

16β-Methyl-17α-pregnenolone acetate: Serini-Logemann reaction of 3.00 g. of 16β-methyl-Δ^5-pregnene-3β,17α,20-triol-3,20-diacetate (obtained by lithium aluminum hydride reduction of 16β-methyl-16α,17α-oxido-Δ^5-pregnene-3β-ol-20-one acetate followed by acetylation with acetic anhydride-pyridine) for 160 hrs. gave 3.00 g. of yellow semi-solid melting to 145°, α_D^{30} -103°, which was chromatographed on 150 g. of Florisil. Elution with benzene gave 1.22 g. of material which was crystallized from methanol-

acetone to give 736 mg. (27%) of 16β-methyl-17α-pregnenolone acetate, m.p. 170-194°, α_D^{29} -124°. Further crystallization gave glistening plates, changing to needles at 175° and melting at 198-199°, α_D^{29} -126° λ_{max} (KBr) 5.78, 5.86, 8.05μ. (reported[11] m.p. 178-180°, α_D -115° (dioxane)).

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