[CONTRIBUTION FROM THE METCALF CHEMICAL LABORATORIES OF BROWN UNIVERSITY]

The Reaction of α- and β-Cholestanyl p-Toluenesulfonates with Methanol

BY HAROLD R. NACE

RECEIVED MAY 22, 1952

The reaction of α-cholestanyl p-toluenesulfonate with methanol yields Δ^2- and Δ^3-cholestene and β-cholestanyl methyl ether. β-Cholestanyl p-toluenesulfonate gives Δ^2- and Δ^3-cholestene and α-cholestanyl methyl ether.

The introduction of double bonds by the elimination of p-toluenesulfonyl groups has been applied to a number of steroids.[1] In the case of eliminations involving the 3-position of steroids with saturated A-rings, the structures of the products have not been rigorously established.[2,3] More exact information on the nature of the products would be helpful in extending the synthetic value, in the steroid field, of the elimination reactions of sulfonate esters.

Stoll[3] studied the reaction of methanol with the p-toluenesulfonate esters of α- and β-cholestanol (hereafter referred to as α- or β-cholestanyl tosylate). The α-tosylate was reported to react rapidly to yield only "neo-cholestene." This was ozonized to a dicarboxylic acid, which was then pyrolyzed to a ketone stated to be identical with Windaus' pyroketone of m.p. 100–100.5°,[4] thus establishing the 2,3-position of the double bond. Stoll gave no experimental details on this degradation other than the melting point of the olefin. He also stated that the β-tosylate reacted slowly with methanol to form a cholestanyl methyl ether which was characterized only by a methoxyl determination on a non-crystalline product.

Reports in the literature on the reaction of tosyl esters with alcohols indicated that both of the compounds studied by Stoll should yield olefins. Hückel, *et al.*,[5] found that a number of decalyl tosylates containing *trans*-hydrogens gave olefins in high yield on heating in ethanol.

The formation of ethers by the alcoholysis of tosylates has also been reported.[6]

Since both the α- and β-cholestanyl tosylates possess *trans*-hydrogens on the 2- and 4-carbons, reaction with methanol might be expected to yield a one to one mixture of Δ^2- and Δ^3-cholestene.

The reaction of β-cholestanyl tosylate with methanol proceeded slowly (3 days) and gave a 17% yield of a one to one mixture of Δ^2- and Δ^3-cholestene and a 73% yield of the previously unreported α-cholestanyl methyl ether. No β-methyl ether could be isolated, although a small amount may have been present in the mother liquors.

The reaction of the α-cholestanyl tosylate proceeded rapidly (6 hours) and gave a 69% yield of the same olefin mixture and a 23% yield of β-cholestanyl methyl ether. No α-methyl ether could be isolated.

The relative rates for the reaction of the two isomers are in accord with present concepts[7,8] of the stereochemistry of the A-ring in the cholestane molecule and of *trans*-eliminations. If the A-ring has the chair conformation the 3β-tosylate group and the 2- and 4α-hydrogens all have equatorial linkages in β-cholestanyl tosylate and the elimination should proceed with difficulty.[10] Conversely, the 3α-tosylate group and the 2- and 4β-hydrogens all have polar linkages in α-cholestanyl tosylate and the elimination should take place more readily, as indeed it does.

The yields of ethers in the two cases can perhaps be explained on the basis that a substitution reaction competes with the elimination reaction.[6] When elimination is difficult (β-tosylate) substitution takes place to a greater extent (75% yield of ether) and, conversely, when elimination is facilitated (α-tosylate) substitution is the secondary reaction (23% yield of ether).

Acknowledgment.—The author wishes to express his appreciation to the Corporation of Brown University for a Faculty Summer Research Fellowship which enabled the completion of this work.

Experimental[11]

β-Cholestanyl Tosylate.—This compound was prepared according to Stoll's procedure[12] in 88% yield, m.p. 136.5–137.5° (dec.) (reported[12] m.p. 134–135°), $[\alpha]_D$ +6.5°.

α-Cholestanyl Tosylate.—Modifications of Stoll's procedure[12] were made in order to obtain pure material. To a mixture of 200 mg. (0.52 millimole) of α-cholestanol and 270 mg. (1.42 millimoles) of p-toluenesulfonyl chloride was added 2 ml. of anhydrous pyridine. The mixture was allowed to stand at room temperature. Solution was complete in 24 hours. After 5 days, the orange solution was poured into 100 g. of a mixture of ice and dilute sodium bicarbonate solution. The precipitated white solid was washed well with water and dried overnight over calcium chloride. The dried solid (240 mg.) was dissolved in benzene (the use of anhydrous ether gave an impure product), the solution filtered to remove suspended material, the benzene removed under reduced pressure, and the residue crystallized from petroleum ether (b.p. 30–60°) (the use of acetone[3] gave an impure product) to yield 153 mg. (54%) of fibrous white needles, $[\alpha]_D$ +12°. Further recrystallization from petroleum ether did not change the rotation. The

(1) *Cf.* J. von Euw and T. Reichstein, *Helv. Chim. Acta*, **29**, 654 (1946), and references cited there.

(2) (a) P. A. Plattner and A. Fürst, *ibid.*, **26**, 2266 (1943); (b) A. Ruff and T. Reichstein, *ibid.*, **34**, 70 (1951).

(3) W. Stoll, *Z. physiol. Chem.*, **246**, 1 (1937).

(4) A. Windaus and O. Dalmer, *Ber.*, **52**, 162 (1919).

(5) W. Hückel, W. Tappe and G. Legutke, *Ann.*, **543**, 191 (1940).

(6) *Cf.* S. Winstein, M. Brown, K. C. Schreiber and A. H. Schlesinger, THIS JOURNAL, **74**, 1140 (1952), and references cited there.

(7) D. H. R. Barton and E. Miller, *ibid.*, **72**, 1066 (1950).

(8) D. H. R. Barton and W. S. Rosenfelder, *J. Chem. Soc.*, 1048 (1951).

(10) In the boat form the hydrogens and the tosylate group have polar linkages, and if this form is readily available in solution, the elimination should proceed as readily as in the case of the α-compound. Inspection of models shows, however, that there is considerable interference between the tosylate group and the methyl group at C-10, making the boat form a high energy form, and therefore less available.

(11) Melting points corrected (Hershberg apparatus, Anschütz thermometers) unless stated otherwise. Rotations at room temperature, approximately 1% chloroform solutions. Merck and Co., Inc. Alumina (Suitable for Chromatographic Adsorption) used for chromatography. Analyses by S. M. Nagy and associates, Microchemical Laboratory, Massachusetts Institute of Technology.

(12) W. Stoll, *Z. physiol. Chem.*, **207**, 147 (1932).

m.p. appeared to be sensitive to trace impurities. The m.p.'s were sharp (less than 0.5° range) and were accompanied by decomposition, but values for the same sample or different samples ranged between 105 and 130°.

Anal. Calcd. for $C_{34}H_{54}O_3S$: C, 75.23; H, 10.03. Found: C, 75.18; H, 10.19.

The compound decomposed to *p*-toluenesulfonic acid and a one to one mixture of Δ^2- and Δ^3-cholestene when dissolved in petroleum ether and passed over a column of alumina. The same type of reaction was obtained with the tosylate of 12(α)-hydroxypregnane-3,20-dione by Ruff and Reichstein.[2b]

Reaction of β-Cholestanyl Tosylate with Methanol.—A suspension of 500 mg. (0.92 millimole) of β-cholestanyl tosylate in 38 ml. of methanol (Baker and Adamson, A.C.S. Reagent Grade) was heated under reflux. Solution was complete in approximately 20 hours. After 73 hours the solvent was removed under reduced pressure and the residue taken up in water and ether. The ether layer was washed with water, dilute sodium carbonate solution, water and saturated sodium chloride solution, and then filtered through anhydrous sodium sulfate. After removal of the ether 352 mg. of colorless oil was obtained, which crystallized on standing. (Crystallization of the product of another experiment from 3 to 1 methanol–acetone gave needles, m.p. 45–70°.) The solid was taken up in 15 ml. of petroleum ether (b.p. 30–60°) and chromatographed on 16 g. of alumina in a column 20 × 70 mm. Fractions of 10 ml. were collected.

Fractions 1 (8 mg.) and 2 (43 mg.) crystallized spontaneously. Fraction 3 (40 mg., colorless oil, $[\alpha]_D$ +31°) was taken up in 10 ml. of petroleum ether and rechromatographed on 3 g. of alumina in a column 12 × 37 mm. Fractions of 5 ml. were collected. Fraction 1-A (8 mg. $[\alpha]_D$ +63°) was combined with fractions 1 and 2 above to give 57 mg. (17%) of Δ^2- and Δ^3-cholestene, $[\alpha]_D$ +65°. One half was crystallized from dilute ethanol to give 22 mg. of needles, m.p. 70.5–72°, $[\alpha]_D$ +64°; reported[3,13] for this olefin mixture from β-cholestanyl benzoate pyrolysis, 67–68°, $[\alpha]_D$ +62°. The second half was taken up in 5 ml. of carbon tetrachloride and a 5% solution of bromine in carbon tetrachloride was added until the straw color persisted. After the solution had stood overnight the solvent was removed under reduced pressure, and the residue flushed once with carbon tetrachloride to give 50.2 mg., $[\alpha]_D$ +46° (calculated[13] for 1-1 mixture of 2,3- and 3,4-dibromide, +41°).

(13) D. H. R. Barton and W. J. Rosenfelder, *J. Chem. Soc.*, 2459 (1949).

Fraction 2-A (15 mg., $[\alpha]_D$ +45°) was a colorless oil and was not investigated further. Fractions 3-A to 5-A (22 mg.) were combined with fractions 4–11 (246 mg.) to yield 272 mg. (73% calculated as α-cholestanyl methyl ether) of dendritic crystals, $[\alpha]_D$ +20°. One recrystallization from acetone gave 204 mg., m.p. 62.5–63.5°; and 26 mg., m.p. 58–61.5°. The analytical sample (one additional recrystallization) had m.p. 62.8–63.8°, $[\alpha]_D$ +18°.

Anal. Calcd. for $C_{28}H_{50}O$: C, 83.51; H, 12.52; CH_3O–, 7.71. Found: C, 83.61; H, 12.63; CH_3O–, 7.22.

A one to one mixture with β-cholestanyl methyl ether softened from 50–59°, and melted at 59–75°.

Reaction of α-Cholestanyl Tosylate with Methanol.—A mixture of 200 mg. (0.37 millimoles) of α-cholestanyl tosylate and 15 ml. of methanol was heated under reflux for 6 hours. (Solution was complete after 5 hours.) The reaction product was worked up as above to yield 141 mg. of colorless oil, $[\alpha]_D$ +44°. The oil was dissolved in 10 ml. of petroleum ether (b.p. 30–60°) and the solution chromatographed on 7 g. of alumina in a column 13 × 82 mm. The column was developed with petroleum ether and 5-ml. fractions were collected. Fractions 2–6 were combined to give, after removal of the solvent, 91.4 mg. of oil which crystallized spontaneously in rosettes of needles (yield 69%, calculated as Δ^2- and Δ^3-cholestene), $[\alpha]_D$ +59°. The entire sample was dissolved in carbon tetrachloride, a slight excess of a 5% solution of bromine in carbon tetrachloride was added, and the resulting solution allowed to stand overnight. The solvent was then removed from the light straw-colored solution, and the residue flushed twice under reduced pressure with carbon tetrachloride. The resulting light-yellow oil weighed 135 mg. (69% yield calculated for Δ^2- and Δ^3-cholestene dibromides) and had rotation $[\alpha]_D$ +45° (calculated[13] for one to one mixture, +41°).

Fractions 7–10 yielded only traces of colorless oils.

Fractions 11–22 were combined and the solvent removed to yield 34 mg. (23% yield calculated as β-methoxycholestane) of colorless oil which crystallized spontaneously and had rotation $[\alpha]_D$ +24°. Recrystallization from acetone gave 23.5 mg. of white blades, m.p. 81–82° (substage heater, not corrected), $[\alpha]_D$ +20°; and 7 mg., m.p. 68–73° (substage heater, not corrected); reported for β-methoxycholestane, m.p., 82–83°[14], $[\alpha]_D$ +20°.[15]

(14) J. L. Dunn, I. M. Heilbron, R. F. Phipers, K. M. Samant and F. S. Spring, *ibid.*, 1576 (1934).

(15) T. Wagner-Jauregg and L. Werner, *Z. physiol. Chem.*, **213**, 123 (1932).

PROVIDENCE 12, R. I.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

A New Route to 11-Ketosteroids by Fission of a $\Delta^{9(11)}$-Ethylene Oxide. II

BY HANS HEYMANN AND LOUIS F. FIESER

RECEIVED JULY 29, 1952

3α-Hydroxy-20-keto-$\Delta^{9(11)}$-pregnene has been prepared. This ketone and methyl 3α-hydroxy-$\Delta^{9(11)}$-etiocholanate have been converted into the corresponding 11-keto derivatives. The synthesis made use of the 9,11-oxides and the 3β-hydroxy-3α-9α-oxido-11-keto derivatives.

The conversion of $\Delta^{9(11)}$-lithocholenic acid to 3-hydroxy-11-ketocholanic acid in a novel fashion *via* the ethylene oxide has been described in our first paper.[1] At present we wish to report application of the procedure to 3α-acetoxy-20-keto-$\Delta^{9(11)}$-pregnene (V) and to 3α-acetoxy-$\Delta^{9(11)}$-etiocholenic acid (I). Introduction of the C_{11}-oxygen function into the last-named compound (I) served to correlate a synthetic steroid[2] with an intermediate to cortisone, and this conversion has been the subject of a preliminary communication.[3]

The requisite olefins were prepared from a sample of 3α-hydroxy-11-ketoetiocholanic acid.[4] Sodium borohydride reduction[1] followed by acetylation furnished the 3α-acetoxy-11β-hydroxy acid, which was dehydrated with boron fluoride etherate to give 3α-acetoxy-$\Delta^{9(11)}$-etiocholenic acid (I). Methyl 3α-acetoxy-11β-hydroxyetiocholanate[5] by analogous

(1) Hans Heymann and L. F. Fieser, THIS JOURNAL, **73**, 5252 (1951).

(2) R. B. Woodward, F. Sondheimer and D. Taub, *ibid.*, **73**, 4057 (1951).

(3) Hans Heymann and L. F. Fieser, *ibid.*, **73**, 4054 (1951).

(4) The material was kindly supplied by Dr. Max Tishler, Merck and and Company, Inc., Rahway, New Jersey.

(5) T. Reichstein and A. Lardon, *Helv. Chim. Acta*, **26**, 705 (1943).