[FROM THE SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH]

Some Reactions of Epoxides of Steroid Enol Acetates[1]

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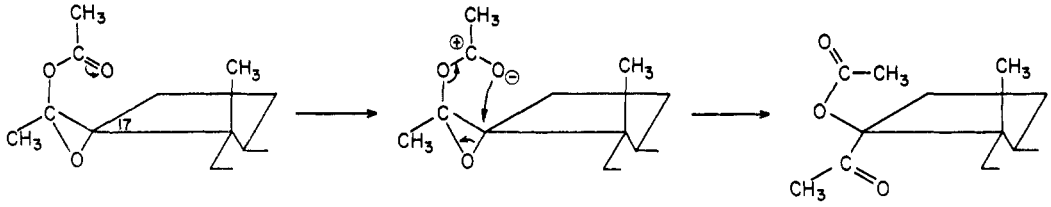
Epoxides prepared from enol acetates of 20-ketosteroids undergo rearrangement when chromatographed on silica gel or when heated above the melting point. From 17α,20β-epoxyallopregnane-3β,20α-diol diacetate the product obtained was 3β,17β-diacetoxyallopregnane-20-one; 3β,21-diacetoxyallopregnane-20-one was obtained when Δ[20]-allopregnene-3β,20-diol diacetate was oxidized with perbenzoic acid and chromatographed on silica gel. Evidence for the configurations assigned to the epoxides was provided by acetolysis and by reduction with lithium aluminum hydride. The preparation and acetolysis of 3α,21-diacetoxy-17α,20β-epoxypregnane-11-one is reported.

The preparation of side chain ketols characteristic of the corticosterone type of adrenocortical hormones from Δ[20]-steroid enol acetates has been described.[3] Because of the unexpected difficulties encountered in the conversion of these enol esters by peracid oxidation, it was desired to study the properties of a purified 20-acetoxy-20,21-epoxide. When Δ[20]-allopregnene-3β,20-diol diacetate (I) was treated with perbenzoic acid and the crude oxidation product was chromatographed on silica gel, the principal product obtained proved to be 3β,21-diacetoxyallopregnane-20-one (III). This compound must have resulted from acetoxyl migration and rearrangement of the intermediate epoxyacetate II, although the oxide was not isolated as such for this experiment. A similar rearrangement was also observed with 16α,17α-epoxyandrostane-3β,17β-diol diacetate which was converted to 3β,16α-diacetoxyandrostane-17-one when chromatographed on silica gel.[4] These facile rearrangements prompted an investigation of the scope and stereochemical course of the reaction.

The compound chosen for investigation was 17α,20-epoxyallopregnane-3β,20-diol diacetate (IV), a readily obtained substance of well-established structure.[5] When this oxide was allowed to remain upon a column of silica gel for 2 days and was then eluted, the product obtained proved to be 3β,17β-diacetoxyallopregnane-20-one (V). Since the oxide ring in IV was unquestionably attached to C-17 in the α-orientation, the formation of a 17β-acetoxy group in the reaction must have occurred with inversion by migration of the C-20 acetoxy group to the rear of the oxide ring. The same rearrangement can be effected by heating the epoxyacetate IV above its melting point. The acetoxyl migration with rearrangement of the carbon skeleton can be depicted as



IV V

CHART A

Although the evidence for the α-orientation of the oxide ring in IV was strong, the fact that a similar rearrangement in a ring D epoxyacetate was achieved without inversion made it desirable to buttress the structure assigned by further experimental evidence. This was provided by the formation of 3β-acetoxy-17α-hydroxyallopregnane-20-one (VI) (acetate of Reichstein's "Substance L") when IV was heated with glacial acetic acid, a reaction readily interpreted as acetolysis of the epoxide ring followed by reconstitution of the 20-ketone. This finding together with the earlier report[5] that IV upon alkaline hydrolysis was converted to Reichstein's "Substance L," seemed conclusive evidence for the structure assigned. Nevertheless, additional confirmation was provided by the finding that reduction of IV with lithium aluminum hydride followed by acetylation afforded allopregnane-3β,17α,20α-triol 3,20-diacetate (VII) (diacetate of Reichstein's "Substance O") in good yield. The conclusion that the 17,20-epoxide was in the α-orientation of C-17 was therefore inescapable.

The orientation of the epoxide ring at C-20 can likewise be assigned both on the basis of analogy and upon the accepted mechanisms for its known reactions. When 3α,21-diacetoxy-Δ[17]-pregnene-11-one was treated with perbenzoic acid, an oxide VIII was isolated. The orientation of the epoxide ring at C-17 was demonstrated by acetolysis to 3α,20α,-21-triacetoxy-17α-hydroxypregnane-11-one (IX), from which it can be deduced that, (a) the oxide was in the α-orientation of C-17 and, (b) that the attachment to C-20 was in the β-configuration of that carbon atom. The latter conclusion follows from the formation of a 20α-acetoxy derivative by a mechanism involving inversion. The conclusion about the orientation of the oxide at C-20 is in complete agreement with the analogous oxidation of the

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(3) (a) H. Vanderhaeghe, E. R. Katzenellenbogen, K. Dobriner and T. F. Gallagher, THIS JOURNAL, **74**, 2810 (1952); (b) R. B. Moffett and D. I. Weisblat, *ibid.*, **74**, 2183 (1952).

(4) N. S. Leeds, D. K. Fukushima and T. F. Gallagher, *ibid.*, **76**, 2943 (1954).

(5) T. H. Kritchevsky and T. F. Gallagher, *ibid.*, **73**, 184 (1951).

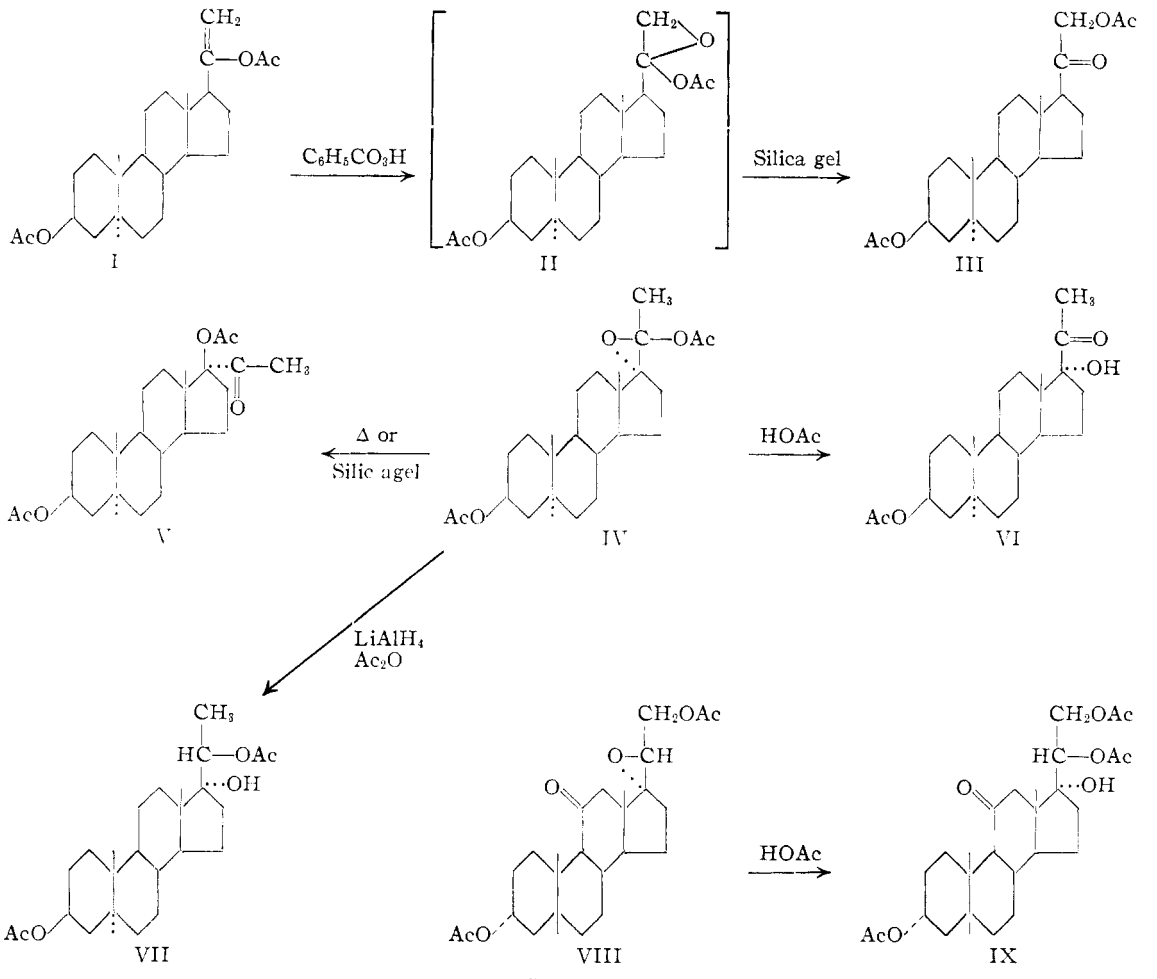

CHART B

same unsaturated side chain with osmium tetroxide to yield a 17α,20β,21-trihydroxy derivative. Since acetolysis of 17α,20-epoxyallopregnane-3β,20-diol diacetate (IV) yielded 3β-acetoxy-17α-hydroxyallopregnane-20-one, it is reasonable to assume that the oxide ring was similarly oriented in both substances. Accordingly, IV is properly formulated as 17α,20β-epoxyallopregnane-3β,20α-diol diacetate.

From these facts the mode of attack of lithium aluminum hydride on the epoxyacetate IV can be developed. This reaction would involve opening of the epoxide between the oxygen and C-20 followed by reduction without inversion. A similar mechanism would account for the products obtained from the related epoxyacetates of ring D, described in the accompanying report.

It could be argued that in the enol ester from which IV was prepared, the acetoxy group was *trans* to the angular C-18 methyl group, although this is the more hindered isomer according to the molecular models. The oxide derived from this hindered isomer should then be a 17α,20α-epoxide, and reduction with lithium aluminum hydride of this structure to yield Reichstein's "Substance O" would require a mechanism involving inversion. Since this would in turn necessitate two dissimilar mechanisms for the reduction of the side chain epoxyacetates and the ring D epoxyacetates, the interpretation previously set forth is preferred.

Experimental[6]

3β,21-Diacetoxyallopregnane-20-one (III) from Δ20-Allopregnene-3β,20-diol Diacetate (I).—A solution of 193 mg. of Δ20-allopregnene-3β,20-diol diacetate[2] (m.p. 91–92°; the purest product obtained melted 94.5–95.5°) in 4 ml. of benzene was mixed with 6.4 ml. of a 3.12 *M* benzene solution of perbenzoic acid. After 5.5 hours at room temperature, ether was added and the organic phase was extracted with dilute sodium hydroxide and water. The ether solution was dried over sodium sulfate and the solvent was removed *in vacuo* to yield an oily residue. Upon chromatography on silica gel 78 mg. of product, m.p. 144–146°, was obtained. Recrystallization from methanol yielded 3β,21-diacetoxyallopregnane-20-one (III) in the form of needles, m.p. 151–151.5°, alone and when admixed with an authentic sample; the infrared spectrum was identical in all respects with the known compound.

3β-Acetoxy-17α-hydroxyallopregnane-20-one (VI) by Acetolysis of 17α,20β-Epoxyallopregnane-3β,20α-diol Diacetate (IV).—A solution of 65 mg. of IV in 25 ml. of glacial acetic acid was heated under reflux for 16 hours, and the solvent was then removed under diminished pressure. The solid residue was recrystallized from acetone–petroleum ether and 3β-acetoxy-17α-hydroxyallopregnane-20-one (VI), m.p. 188–190°, was obtained; the infrared spectrum was identical with that of an authentic sample.

3β,17β-Diacetoxyallopregnane-20-one (V) from 17α,20β-Epoxyallopregnane-3β,20α-diol Diacetate (IV).—A solution of 214 mg. of IV in petroleum ether was adsorbed on a column

(6) All melting points are corrected.

of silica gel and allowed to remain on the adsorbent for 2 days. Elution with ether–petroleum ether mixtures yielded 187 mg. of crude product which after successive recrystallizations from acetone–petroleum ether yielded 102 mg. of pure 3β,17β-diacetoxyallopregnane-20-one (V), m.p. 226–229°, reported 227–229°[7]; the infrared spectrum was identical with that of an authentic sample.[8]

Twenty-seven mg. of IV was heated to 235° for 10 minutes. The product solidified upon cooling and was recrystallized from acetone–petroleum ether to yield 22 mg. of 3β,17β-diacetoxyallopregnane-20-one (V) identical in infrared spectrum and melting point with the known compound.

Allopregnane-3β,17α,20α-triol 3,20-Diacetate (VII) from 17α,20β-Epoxyallopregnane-3β,20α-diol Diacetate (IV).—Approximately 100 mg. of lithium aluminum hydride was added to a solution of 58 mg. of IV in 1 ml. of benzene and 9 ml. of ethyl ether. The solution was stirred for 1 hour and then was heated to boiling for 5 minutes. Ethyl acetate was added followed by dilute hydrochloric acid. The organic phase was washed successively with water and dilute sodium hydroxide, again with water and dried over sodium sulfate. After removal of the solvent, 47 mg. of product was obtained and this was acetylated with acetic anhydride and pyridine at room temperature for 16 hours. The acetate was isolated in the usual manner and was recrystallized from petroleum ether containing a trace of acetone. Two crops were obtained: the first, 26 mg., m.p. 247–250°; the second, 10 mg., m.p. 240–245°. Chromatography of the mother liquors upon silica gel followed by recrystallization yielded 8 mg., m.p. 240–245°. All the products exhibited an infrared spectrum indistinguishable from that of an authentic sample of allopregnane-3β,17α,20α-triol 3,20-diacetate (diacetate of Reichstein's "Substance O").

(7) C. W. Shoppee and D. Prins, *Helv. Chim. Acta*, **26**, 185 (1943).

(8) We are indebted to Dr. R. B. Turner of Rice Institute, Houston, Texas, for this reference compound.

3α,21-Diacetoxy-17α,20β-epoxypregnane-11-one (VIII).—A solution of 65 mg. (0.156 mm.) of 3α,21-diacetoxy-Δ^{17}-pregnene-11-one[9] in 1 ml. of benzene was mixed with 1 ml. of a 0.398 *M* benzene solution of perbenzoic acid (0.785 mm.). After 4 days at room temperature the solution was diluted with ether, washed with dilute sodium carbonate solution and water, and was dried over sodium sulfate. After removal of the solvent and crystallization from petroleum ether, 42 mg., m.p. 156–165°, together with a second crop of 11 mg., m.p. 150–162°, was obtained. Recrystallization from petroleum ether yielded 3α,21-diacetoxy-17α,20β-epoxypregnane-11-one (VIII) as needles, m.p. 168–170°, $[\alpha]^{26}D$ +77.6° (chloroform).

Anal. Calcd. for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.44; H, 8.41.

17α-Hydroxy-3α,20α,21-triacetoxypregnane-11-one (IX) from VIII.—A solution of 32 mg. of 3α,21-diacetoxy-17α,-20β-epoxypregnane-11-one (VIII) in 11 ml. of redistilled glacial acetic acid was heated under reflux for 24 hours. The solvent was removed under diminished pressure and the residue oil was chromatographed upon a partition column in which silica gel acted as the support for 95% ethanol. Solution was achieved with 1:1 methylene chloride–petroleum ether containing 1% ethanol. The product was recrystallized and 11 mg. of crude product was obtained. Recrystallization yielded 4 mg. of m.p. 211–214°, 3 mg., m.p. 208–213°, and 2 mg., 201–209°; the infrared spectra of these products was indistinguishable from an authentic sample of 3α,20α,21-triacetoxy-17α-hydroxypregnane-11-one, m.p. 213–214°.[9,10]

(9) We wish to express our gratitude to Dr. L. H. Sarett, Merck & Co., Inc., Rahway, New Jersey, for his generosity in supplying us with this compound.

(10) L. H. Sarett, THIS JOURNAL, **71**, 1169 (1949).

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Studies of Steroid Ring D Epoxides of Enol Acetates; A New Synthesis of Estriol and of Androstane-3β,16α,17β-triol[1]

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A generally applicable method for the preparation of steroid ring D glycols in good yield and with a high degree of stereospecificity has been developed. The procedure consists in the formation of an enol acetate of a 17-ketosteroid followed by epoxidation with perbenzoic acid. The oxide ring is attached to C-16 and C-17 in the α-configuration. With or without prior acid hydrolysis, the epoxyacetate is reduced with lithium aluminum hydride and the principal product obtained is the 16α,17β-glycol. The method is illustrated by the preparation of estriol from estrone enol acetate in 66% yield without isolation of any intermediates, and by the preparation of androstane-3β,16α,17β-triol from isoandrosterone. By alkaline hydrolysis of the intermediary ketol acetate the procedure can be altered to afford an equally successful synthesis of 16β,17β-ring D glycols. The rearrangement of ring D epoxyacetates by chromatography or heating above the melting point is shown to proceed with retention of configuration at C-16.

Because of the interest in steroid ring D ketols as metabolites of hormones and potentially useful intermediates in the synthesis of ring D glycols, it was desired to provide a generally applicable and simple synthesis for these compounds. In particular, an efficient synthesis of estriol, one of the metabolites of the estrogenic hormone estradiol was sought. It seemed reasonable to anticipate that epoxidation of the enol ester of estrone would proceed as with the C-20 ketosteroids[2] and would furnish a key intermediate, X, that could be readily reduced to estriol. This, indeed, proved to be the fact. Two other essentially identical procedures for the partial synthesis of estriol from estrone have been reported.[3,4] The present method has the advantage of a higher yield and greater simplicity in that the whole operation can be accomplished without isolation of any intermediates.

For reasons that will be clear, it was preferable to carry out the initial studies on a neutral compound and 3β-hydroxyandrostane-17-one (isoandrosterone, (I)) was chosen as the starting material. Upon treatment with isopropenyl acetate, in the presence of catalytic amounts of sulfuric acid, the enol acetate II was obtained in better than 80% yield. With dilute perbenzoic acid in benzene at room temperature, II was readily converted to 16α,-17α-epoxyandrostane-3β,17β-diol diacetate (III).

(1) This investigation was supported by grants from the Anna Fuller Fund, the Lillia Babbitt Hyde Foundation, the Teagle Foundation, and the National Cancer Institute, United States Public Health Service (C-440).

(2) T. H. Kritchevsky and T. F. Gallagher, *J. Biol. Chem.*, **179**, 507 (1949); THIS JOURNAL, **73**, 184 (1951).

(3) M. N. Huffman and W. R. Miller, *Science*, **100**, 312 (1944); M. N. Huffman, *J. Biol. Chem.*, **169**, 167 (1947).

(4) A. Butenandt and E. L. Schäffler, *Z. Naturforsch.*, **1**, 82 (1946).