ELECTROPHILIC ADDITION TO THE Δ^{14}-DOUBLE BOND OF A STEROID

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The preparation and reactions of 14β,15β-epoxy-steroids in the androstane, etiocholanic acid, pregnane, and cardenolide series have been well elaborated in the literature. Whereas in the C19 series, a 14β,15β-epoxy-17-one may be prepared simply by perbenzoic acid treatment of a Δ^{14}-17-one,[1] it is necessary to treat Δ^{14}-compounds in the other series with a hypohalous acid to form halohydrins followed by cyclization conditions to prepare the 14β,15β-epoxy compounds.[2,3] It is not clear from the cited literature as to the exact formulation of the intermediate halohydrin compounds. The patent literature[2a,b] strongly suggests that the compounds are 14α-halo-15β-hydroxysteroids. Indeed, in one of the patents[2a] this type of intermediate is purported to give 15β-hydroxydeoxycorticosterone by reductive dehalogenation treatment with deactivated Raney nickel. It may also be noted, however, that Lardon and Reichstein,[2c] although acknowledging the suggestion of one of the patents,[2b] have not disregarded the possibility that the intermediate halohydrin might be a 14β-hydroxy-15α-halo-steroid.[4] Furthermore, in their determi-

nation of the structure of resibufogenin, a naturally occurring 14β, 15β-epoxybufadienolide, Linde and Meyer[5] opened the epoxide ring with hydrochloric acid and recyclized the halohydrin to starting material. It has been formulated by Fieser and Fieser[6] that the chlorhydrin so formed was the 14β-hydroxy-15α-chlorobufadienolide. It was thought that a definitive contribution might be made toward elucidating this structural problem by utilizing compounds readily available in this Laboratory.

For this purpose 3β-acetoxy-20-ethylenedioxypregn-14-en-21-ol (Ia)[7] was acetylated to give the 3, 21-diacetate Ib which, in turn, was treated with N-bromoacetamide and perchloric acid in dioxane to form the intermediate bromohydrin II. The latter compound was not purified but was cyclized with potassium acetate to form 14β, 15β-epoxy-20-ethylenedioxypregnane-3β, 21-diol diacetate (III). Treatment of the bromohydrin II with deactivated Raney nickel[8] afforded a mono-alcohol IVb. The mono-alcohol IVb could also be prepared by reaction of the 14β, 15β-epoxide III with lithium aluminum hydride to give a solvated triol IVa which was acetylated to the diacetate-mono-alcohol IVb. Since it has been shown unequivocally by Linde and Meyer[5] that lithium aluminum hydride reduction of a 14β, 15β-epoxy-steroid gives a 14β-ol, compound IVa must be 20-ethylenedioxypregnane-3β, 14β, 21-triol and IVb its 3β, 21-diacetate. In this manner it follows that the bromohydrin II has the structure 3β, 21-diacetoxy-15α-bromo-20-ethylenedioxypregnan-14β-ol,

necessitating a Markownikoff addition of hypobromous acid.

To establish further that IVa and IVb are 14β-hydroxysteroids, the triol IVa was deketalized with acetic acid, and the resultant impure gum was acetylated to yield the known 3β, 21-diacetoxy-14β-hydroxypregnan-20-one (V). The latter compound was identical to an authentic specimen prepared according to Meyer and Reichstein[9] from digitoxigenin.

It is interesting to speculate on the Markownikoff addition of the hypobromous acid to the $\Delta^{14,15}$-compound Ib, and the reductive cleavage of the 14β, 15β-epoxide III to form a 14β-hydroxy compound. Superficially, both of these reactions could be considered as violations of the many examples of ionic addition to olefins[10] and reductive cleavage of epoxides[11] in steroids wherein diaxial products are obtained. Thus, a prediction of the products of the ionic addition might suggest a 14α-halo-15β-hydroxy-bromohydrin product, which is respectively axial at C14 and pseudo-axial at C15 to Ring C. Similarly, reduction of the 14β, 15β-epoxide would be expected to give a 14α-hydrogen-15β-hydroxy-monoalcohol which would be axial at C14 and pseudo-axial at C15. Countering these considerations must be the obviously important effect that a cis C/D ring junction is usually favored thermodynamically.[12,13] Furthermore, inspection of Dreiding models of these systems reveals that the severe 1, 3 interaction of the C13-methyl group with a 15β-halogen or hydroxy grouping in a C/D trans junction may be effectively relieved by the preferred formation of the C/D cis junction.

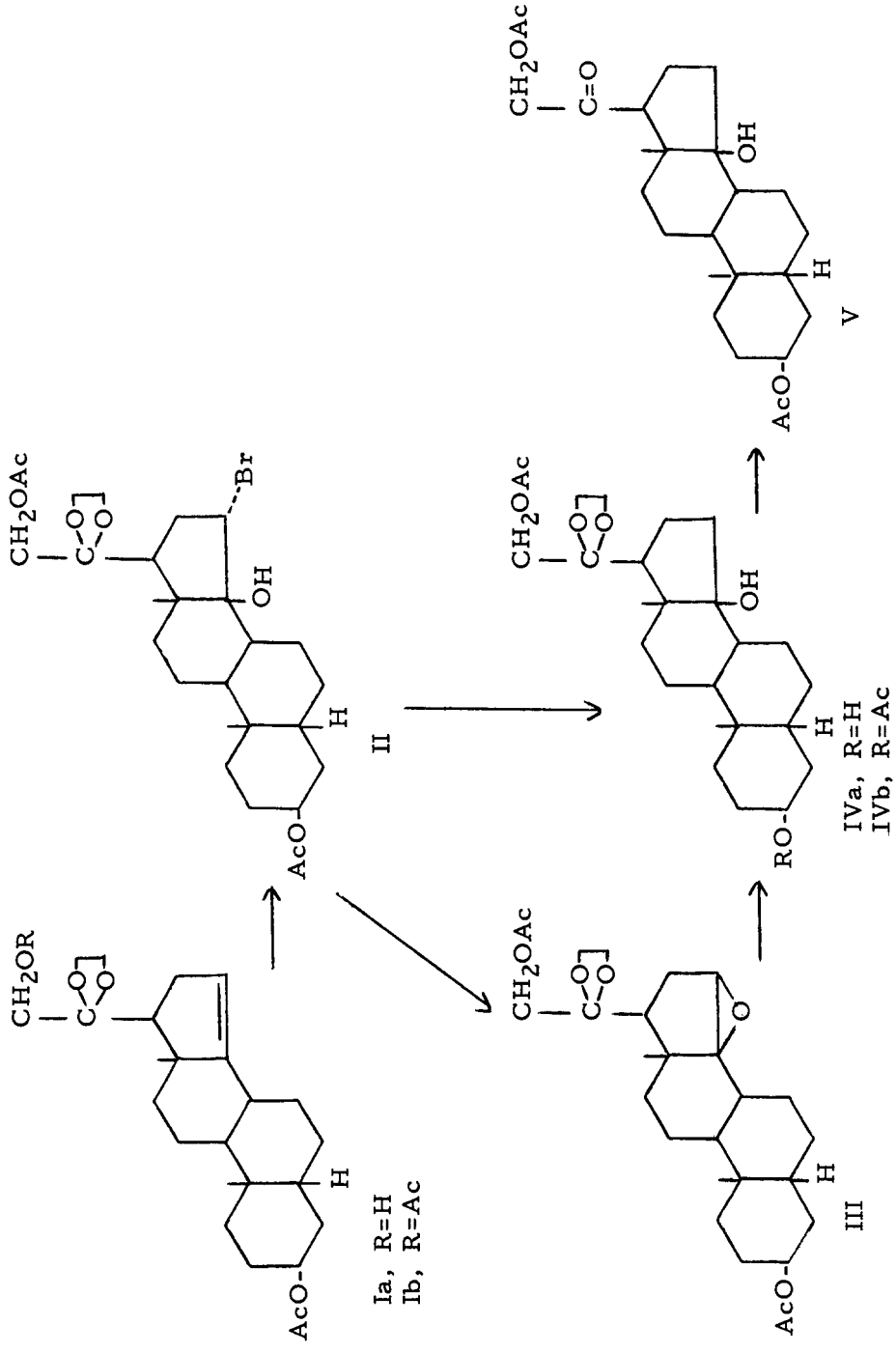
Finally, it is well known, generally in cases not affected by the rigid stereochemistry such as exists in the steroid molecule, that lithium aluminum hydride attacks secondary-tertiary epoxides with hydride ion at the secondary carbon atom.[14]

It should also be noted that if desired, a preparation of a 14β-hydroxy-20-ethylene ketal compound (i.e. IVa and IVb) is now available. This could not be done by direct ketalization of a 14β-hydroxy-20-one as reported previously.[7]

Experimental[15]

3,21-Diacetoxy-20-ethylenedioxypregn-14-ene. (Ib). - A sample of the alcohol Ia[7] was acetylated in the usual manner with acetic anhydride in pyridine to afford the diacetate IIb. This could not be crystallized and was used as a gum in the following experiment.

3,21-Diacetoxy-14β,15β-epoxy-20-ethylenedioxypregnane-(III). - To a solution of Ib (370 mg.) in peroxide-free dioxane (10 ml.) and water (2 ml.) was added N-bromoacetamide (113 mg.) and 3 N perchloric acid (0.21 ml.). The solution was allowed to stand at room temperature for 15 min., diluted with water and extracted with ethyl acetate. The extract was washed with sodium bicarbonate solution, dried and evaporated *in vacuo* with minimal heating. The crude bromohydrin II thus obtained was dissolved in absolute ethanol (25 ml.) and excess anhydrous potassium acetate was added. The mixture was heated under reflux for 18 hr., then diluted with water and extracted with ethyl acetate. The dried


CH2OR
C
O
O
AcO
H
Ia, R=H
Ib, R=Ac
CH2OAc
C
O
O
Br
OH
AcO
H
II
CH2OAc
C
O
O
O
AcO
H
III
CH2OAc
C
O
O
OH
RO
H
IVa, R=H
IVb, R=Ac
CH2OAc
C=O
OH
AcO
H
V

extract was evaporated *in vacuo*, and the residue was acetylated with acetic anhydride and pyridine in the usual manner. The resultant gum was submitted to chromatography on a Florisil[16] column. The product was obtained as a gum from the 5% acetone-methylene chloride eluates. Crystallization from acetone-water afforded a white solid (116 mg.), m.p. 178-180°. Two additional crystallizations from the same solvent pair raised the melting point to 182-183°; ν_{max} 1750, 1250, 1043 cm.$^{-1}$; $[\alpha]_D^{25}$ + 35° (methanol).

Anal. Calcd. for $C_{27}H_{40}O_7$ (476.59): C, 68.04; H, 8.46. Found: C, 68.29; H, 8.53.

20-Ethylenedioxypregnane-3β, 14β, 21-triol (IVa). - To a solution of 14β, 15β-epoxide III (258 mg.) in ether (130 ml.) was added lithium aluminum hydride (1.3 g.). The mixture was stirred and heated under reflux for 3 hr. The mixture was cooled in an ice-bath and saturated sodium potassium tartrate solution (10 ml.) was added dropwise. The mixture was filtered, and the ether layer was separated and dried. Evaporation *in vacuo* produced 100 mg. of white solid. Several additional extracts of the inorganic filter-cake with hot ethyl acetate (100 ml.) afforded additional white solid (70 mg.). The combined solids were crystallized from acetone-water and yielded white crystals (139.5 mg.), m.p. 184-186°. Two additional crystallizations served only to lower the melting point to 181-182°, and IVa was obtained in a solvated state.

Anal. Calcd. for $C_{23}H_{38}O_5$ (394.53): C, 70.01; H, 9.71.

Found: C, 69.10; H, 9.90.

3,21-Diacetoxy-20-ethylenedioxypregnan-14β-ol (IVb). - A. The triol Va was acetylated with acetic anhydride-pyridine to give the product IVb, from acetone-water, m.p. 176-177°; ν_{max} 3540, 1745, 1722, 1262, 1240, 1020 cm.$^{-1}$; $[\alpha]_D^{25}$ + 13° (methanol).

Anal. Calcd. for $C_{27}H_{42}O_7$ (478.61): C, 67.75; H, 8.85; OAc, 17.97. Found: C, 67.68; H, 8.83; OAc, 16.86.

B. A solution of crude bromohydrin (II, 1.0 g.) in methanol (50 ml.) was stirred and heated under reflux with deactivated Raney nickel[8] (8 g.) for 4 hr. The cooled mixture was filtered through diatomaceous earth, and the filtrate was evaporated in vacuo. The residual gum (760 mg.) was dissolved in methylene chloride and chromatographed on a Florisil[16] column. The product was obtained as a gum from the 4% acetone-petroleum ether (60-70°) eluates and crystallized from acetone-water to afford white crystals (120 mg.), m.p. 177-178°. Comparison of the infrared spectra and no depression on admixture melting point determination showed this material to be identical with that prepared in A above.

3β,21-Diacetoxy-14β-hydroxypregnane-20-one (V). - To a solution of 20-ethylenedioxypregnane-3β,14β,21-triol (IVa, 150 mg.) in acetic acid (3.0 ml.) was added water (3.0 ml.). The solution was heated on the steam bath for 90 min., diluted with water and extracted with ethyl acetate. The extract was washed with sodium bicarbonate solution, dried and evaporated in vacuo. The residual amber gum was acetylated

in pyridine (2 ml.) and acetic anhydride (0.2 ml.). The residual gum from the acetylation was chromatographed on a Florisil[16] column. The 7% acetone-petroleum ether (60-70°) eluates on evaporation in vacuo yield a gum which was crystallized from acetone-water giving V (22.3 mg.), m.p. 183-184°. Admixture melting point with a sample prepared according to the method of Reichstein[9] showed no depression. The infrared spectra of the two samples were identical.

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13. See reference 6, p. 211-216.

14. Gaylord, N. G., Reduction with Complex Metal Hydrides, Interscience Publishers, New York, N. Y., p. 646, and following pages.

15. All melting points are uncorrected. The infrared spectra were determined in a potassium bromide disk. The analytical data were provided by Louis M. Brancone and associates, and the spectral and optical rotational data by William Fulmor and associates.

16. Florisil is the Floridin Co.'s registered trademark for a synthetic magnesium silicate.