[CONTRIBUTION FROM THE DIVISION OF CHEMICAL RESEARCH, G. D. SEARLE AND CO.]

Product Development Control in the Hydride Reduction of 17-Keto-C/D *cis*- and *trans*-Steroids

LELAND J. CHINN

Received July 12, 1961

The hydride reduction of a 17-keto-C/D *trans*-steroid proceeds from the backside while a similar reduction of a 17-keto-C/D *cis*-steroid (either 13β,14β or 13α,14α) involves a frontal approach. These results are explained on the basis that the reductions are product development controlled, affording as the predominant product the more stable epimer in each case.

The concepts of steric approach control and product development control on the hydride reduction of a carbonyl group have been propounded by Dauben and his associates.[1] Based upon these concepts they concluded that the reduction of an unhindered ketone with lithium aluminum hydride will yield a mixture of epimers whose composition will closely resemble that obtained under equilibrating conditions, and that when sodium borohydride in methanol is used in place of lithium aluminum hydride, the product will be richer in the unstable epimer.

Applying the concept of product development control to the hydride reduction of the 17-ketosteroids, both those in which rings C and D are fused *cis* as well as *trans*, and assuming that the energy-level spacings of the alcohols epimeric at C-17 are nearly identical,[2] we have reached a set of conclusions pertaining to the relative stability of the reduction products, the epimeric 17-ols, which agrees with the results obtained by conformational analysis.

It is a well documented fact that the reduction of a 17-keto-13β,14α-steroid yields overwhelmingly the 17-ol having the β-configuration. If the 17-keto group is unhindered, then the 17β-ol must be the more stable epimer in keeping with the concept of product development control. Although Elks and Shoppee[3] were unable to equilibrate the epimeric androstan-17-ols with sodium ethoxide, which would have provided direct evidence as to the relative stability of the two epimers, the greater stability of the 17β-ol can be inferred from the equilibration studies of the normal (17β) 20-ketosteroids, which have been shown to be more stable than the 17α-compounds.[4]

St. André *et al.*[5] reported that the reduction of 17-keto-5α,14β-androstan-3β-ol with sodium borohydride gives the 17α-ol as the principal product. As it has been shown that derivatives of 20-keto-14β,17α-pregnane are more stable than the corresponding derivatives of 20-keto-14β-pregnane,[6] the 17α-ol must be regarded as the more stable epimer.

When a 17-keto-13α,14α-steroid is reduced with lithium aluminum hydride, the 17α-ol is obtained as the predominant product.[7] Although experimental support is lacking, the 17α-ol can be assumed to be the more stable epimer on the basis that the course of the hydride reduction of the 17-keto-13α,14α-steroid,[8] just as of the 17-keto-13β,14α- and 17-keto-13β,14β-steroids, is product development controlled.

According to Brutcher and Bauer[9] there are three important conformations to be considered for ring D of the steroids. Two of these conformations are envelope forms and the third is a half-chair. For a 13β,14α-steroid the envelope conformations are I and II. Examination of conformations I–III reveals that a substituent at the 17β-position would be on a bisectional bond in I, an equatorial bond in II, and a pseudoequatorial bond in III. A substituent at the 17α-position would be on a bisectional

(1) W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Am. Chem. Soc.*, **78**, 2579 (1956); W. G. Dauben, E. J. Blanz, Jr., J. Jiu, and R. A. Micheli, *J. Am. Chem. Soc.*, **78**, 3752 (1956).

(2) L. P. Hammett, *Physical Organic Chemistry*, McGraw-Hill, New York, 1940, p. 78.

(3) J. Elks and C. W. Shoppee, *J. Chem. Soc.*, 241 (1953).

(4) A. Butenandt and L. Mamoli, *Ber.*, **68**, 1847 (1937); A. Butenandt and G. Fleischer, *Ber.*, **70**, 96 (1935); A. Butenandt, J. Schmidt-Thomé, and H. Paul, *Ber.*, **72**, 1112 (1939).

(5) A. F. St. André, H. B. MacPhillamy, J. A. Nelson, A. C. Shabica, and C. R. Scholz, *J. Am. Chem. Soc.*, **74**, 5506 (1952).

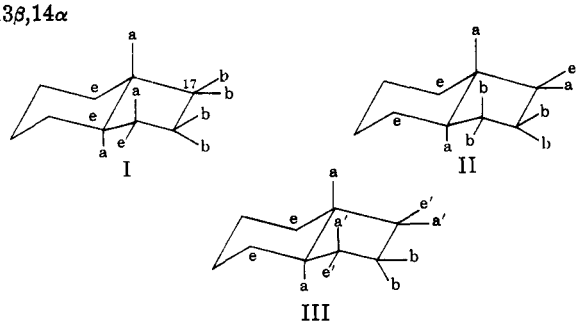
(6) K. Meyer, *Helv. Chim. Acta*, **30**, 2024 (1947); A. Lardon, *Helv. Chim. Acta*, **32**, 1517 (1949).

(7) J. P. L. Bots, *Rec. des Trav. Chim. des Pays-Bas*, **77**, 1010 (1958). 13α-Androst-5-ene-3,17-dione was first reduced with lithium aluminum hydride and then oxidized with manganese dioxide to yield 13α-testosterone in *ca.* 10% yield and 13α,17α-testosterone in *ca.* 20% yield. Independently, we observed that the lithium aluminum hydride reduction of the 3-enol ether of 13α-androstenedione gave, after acidification, 13α-testosterone and 13α,17α-testosterone in 7.6% and 44.3% yields, respectively (*cf.* Experimental).

(8) Although the β-side of the carbonyl group of a 17-keto-13α,14α-steroid is doubly shielded by the methenyl and methylene groups at C-8 and C-11, respectively, in the manner that the β-side of the 11-keto group of cortisone is shielded by the two angular methyl groups, the methenyl and methylene groups, lacking the bulk of the methyl groups, will not hinder the approach of an entering group to the same extent as the latter groups.

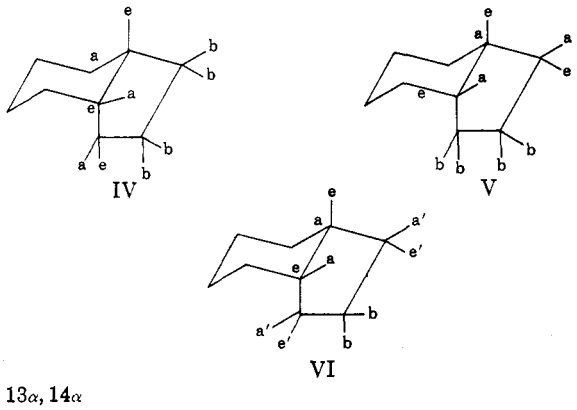
(9) F. V. Brutcher, Jr., and W. Bauer, *Science*, **132**, 1489 (1960).

13β,14α



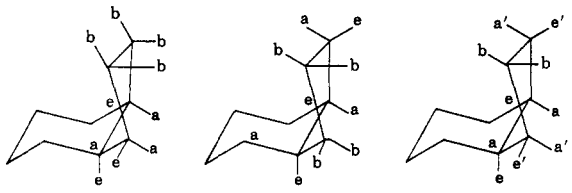
I II III

13β, 14β



IV V VI

13α, 14α



VII VIII IX

a = axial
a′ = pseudo-axial
b = bisectional
e = equatorial
e′ = pseudo-equatorial

bond in I, an axial bond in II, and a pseudo-axial bond in III. As either a 17β- or a 17α-substituent in I would be eclipsed by a hydrogen atom at C-16, conformation I would be energetically less favorable than II or III. Hence, a consideration of II and III would lead to the conclusion that a substituent at the 17β-position is more stable than if it were attached to the 17α-bond.[10]

For a 13β,14β-steroid the three important conformations are IV–VI, of which IV and V are the two envelope forms. For reasons outlined above, conformation IV may be omitted from consideration. An examination of V and VI indicates that the 17α-position (equatorial in V and pseudoequatorial in VI) is more stable than the 17β.

The argument that the 17α-position is more stable than the 17β in a 13β,14β-steroid is also valid for a 13α,14α-steroid. The three important conformations for the latter substance are represented by VII–IX, of which VII and VIII are the envelope forms and VII is energetically the least favorable when a substituent is located at C-17.

EXPERIMENTAL[11]

13α-Testosterone and 13α,17α-testosterone. A solution of 3.590 g. (0.0125 mole) of 13α-androst-5-ene-3,17-dione,[7] 5 ml. (0.0303 mole) of freshly distilled ethyl orthoformate, 0.25 g. (0.00132 mole) of *p*-toluenesulfonic acid monohydrate, 0.2 ml. of absolute ethanol, and 30 ml. of purified dioxane was allowed to stand at room temperature in an atmosphere of nitrogen for 4 hr. To the dark green reaction mixture was added 2 ml. of pyridine, whereupon it turned to an orange-brown color. The reaction mixture was then added over a period of 10 min. to a mixture of 0.65 g. (0.0171 mole) of lithium aluminum hydride in 60 ml. of anhydrous ether, which was heated under reflux. After the addition was complete, an additional 50 ml. of anhydrous ether was added to the reaction mixture. Heating was discontinued, and the mixture was stirred at room temperature for 15 hr. After the reaction mixture was decomposed with the successive addition of acetone and water and acidified with 5% hydrochloric acid, the organic phase was separated and washed successively with 5% hydrochloric acid and water. The solvents were removed by evaporation on the steam bath in a stream of nitrogen, and the residue was dissolved in 10 ml. of methanol containing 0.2 ml. of 6*N* hydrochloric acid. The reaction mixture was heated under reflux for 10 min., diluted with water, and cooled in an ice bath. The resulting viscous brown oil was extracted with benzene. The benzene solution was dried over anhydrous potassium carbonate and chromatographed on 200 g. of alumina. The column was eluted with varying proportions of benzene and ethyl acetate. Elution with 10% ethyl acetate in benzene gave *ca.* 3 g. of a solid mixture. The mixture was fractionally crystallized from ether-hexane, and the residual mother liquor was rechromatographed on alumina. In this manner a total of 1.603 g. (44.3% yield) of 13α,17α-testosterone, melting in the region of 124–127° to 130–132.5°, and a total of 0.273 g. (7.6% yield) of 13α-testosterone, melting from 156.5–158.5° to 162–164°, were obtained.

The analytical sample of 13α,17α-testosterone was obtained as colorless stout rods from ether-hexane, m.p. 129.5–131°; $[\alpha]_D$ +39°; (0.5% dioxane); reported[7] m.p. 129–130°; $[\alpha]_D^{20}$ +48.9° (ethanol).

The analytical sample of 13α-testosterone was obtained as colorless needles from ether-hexane, m.p. 162.5–164.5°; $[\alpha]_D$ +78° (0.5% dioxane); reported[7] m.p. 153–155°; $[\alpha]_D$ +90.5° (ethanol).

13α,17α-Testosterone acetate. A solution of 115 mg. of 13α,17α-testosterone, m.p. 127–129°, 1 ml. of pyridine, and 1 ml. of acetic anhydride was allowed to stand at room temperature for 48 hr. Then it was poured into water and cooled in an ice bath. The solid was collected, washed well with water, and dried, m.p. 99–102.5°, yield 121 mg. (91.6%). Repeated crystallizations from acetone-water gave colorless rhombs, m.p. 103.5–104.5°; $[\alpha]_D$ +55° (1% dioxane); $\Delta[M]_D^{OAc-OH}$ +69.5°.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.44; H, 9.00.

13α-Testosterone acetate. A solution of 53 mg. of 13α-testosterone, m.p. 162.5–164.5°, 0.3 ml. of pyridine, and 0.3 ml. of acetic anhydride was allowed to stand at room temperature for 16 hr. The reaction mixture was worked up as

(10) *Cf.* D. H. R. Barton, *Experientia*, 6, 316 (1950); L. F. Fieser and M. Fieser, *Steroids*, Reinhold, New York, 1957, p. 468.

(11) Melting points were taken on a Fisher-Johns melting block and optical rotations were determined at 23°.

before to afford a crude solid product, m.p. 134.5–138°. The solid was crystallized from hexane, m.p. 136–138°, yield 44 mg. (72.6%). The analytical sample was obtained as colorless dense crystals after two more crystallizations from hexane, m.p. 136–137.5°; $[\alpha]_D$ +89° (1% dioxane); $\Delta[M]_D^{OAc-OH}$ +69°.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9 15. Found: C, 76.22; H, 8.99.

CHICAGO 80, ILL.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PENNSYLVANIA]

Hydrogen Transfers from 1-Substituted Dihydropyridines. I. Reduction of Nitro Groups[1-3]

DONALD C. DITTMER AND JOHN M. KOLYER[4]

Received July 19, 1961

1-Benzyl-1,4-dihydronicotinamide reduces nitrobenzene at 139° in the absence of added solvent. The intermediate, nitrosobenzene, is trapped, presumably as a nitrone which is identified by its hydrolysis to benzaldehyde. The reaction products, after hydrolysis of the reaction mixture, are aniline, nicotinamide, benzaldehyde, phenylhydroxylamine, and hydrazobenzene. Hydroquinone had no effect on the yields of products. A *p*-nitro group facilitates the reduction; a *p*-dimethylamino group hinders it. *o*-Nitrophenol and *o*-nitroanisole are reduced in comparable yields. 2,6-Dimethylnitrobenzene was reduced with difficulty. Other compounds reduced were nitrosobenzene, *p*-nitroso-*N*,*N*-dimethylaniline, phenylhydroxylamine, azoxybenzene, and azobenzene. Aliphatic nitro compounds were not reduced.

Dihydropyridines play an important role in biological reductions, and the study of model reactions which may simulate an enzymic reaction may lead to an understanding of the catalytic action of enzymes. Dihydropyridine derivatives have been reported to reduce a variety of substances nonenzymically: thio ketones,[5] keto acids,[6] quinones,[7] dyes,[7c,8] benzil,[9] derivatives of maleic and fumaric acids,[9] and bromotrichloromethane.[10]

Enzymic reductions of nitro groups may directly or indirectly involve dihydrodiphosphopyridine nucleotide (dihydronicotinamide-adenine-dinucleotide).[11]

Nitrobenzene has been used frequently as an oxidizing agent for organic compounds.[12] Several reductions of nitro groups by dihydropyridines have been reported. There is a photochemically induced intramolecular reduction of 4-(2′-nitrophenyl)-1,4-dihydropyridine.[13] *trans*-4-Nitrostilbene is reduced to 4-aminostilbene (16% yield) and nitrobenzene is reduced to aniline (yield greater than 8%) by the Hantzsch dihydropyridine (1,4-dihydro - 2,6 - dimethyl - 3,5 - dicarbethoxypyridine).[9] There have been no published reports of the nonenzymic reduction of nitro groups by a dihydronicotinamide.[14]

Reduction of nitrobenzene. When nitrobenzene and 1-benzyl-1,4-dihydronicotinamide were heated at 139° under nitrogen the following products were identified after hydrolysis of the reaction mixture by dilute aqueous acid: nicotinamide (30%), aniline (60–68%), benzaldehyde (11%), phenylhydroxylamine and hydrazobenzene. Aniline was shown to be present before hydrolysis, whereas benzaldehyde was not. Small amounts of carbon dioxide and ammonia were produced also.

The carbon dioxide and ammonia are formed presumably by opening of the pyridinium ring,[15] hydrolysis of the amide group and decarboxylation

(1) We wish to acknowledge the support of the National Science Foundation (Grant 7582) for part of this work.

(2) For complete experimental details see John M. Kolyer, Ph.D. Thesis, University of Pennsylvania, 1960.

(3) Reported in part at 136th Meeting, American Chemical Society, Atlantic City, N. J., September 1959.

(4) Walter T. Taggart Memorial Fellow, 1959–60.

(5) R. H. Abeles, R. F. Hutton, and F. H. Westheimer, *J. Am. Chem. Soc.*, **79**, 712 (1957).

(6) R. Abeles and F. H. Westheimer, *J. Am. Chem. Soc.*, **80**, 5459 (1958); K. Wallenfels and D. Hofmann, *Tetrahedron Letters*, No. 15, 10 (1959).

(7)(a) H. Kühnis, W. Traber, and P. Karrer, *Helv. Chim. Acta*, **40**, 757 (1957); (b) E. A. Braude, J. Hannah, and R. Linstead, *J. Chem. Soc.*, 3249 (1960); (c) K. Wallenfels and M. Gellrich, *Ann.*, **621**, 149 (1959).

(8) D. Mauzerall and F. H. Westheimer, *J. Am. Chem. Soc.*, **77**, 226 (1955); P. Karrer, G. Schwarzenbach, F. Benz, and U. Solmssen, *Helv. Chim. Acta*, **19**, 824 (1936); S. J. Leach, J. H. Baxendale, and M. G. Evans, *Australian J. Chem.*, **6**, 395 (1953).

(9) E. A. Braude, J. Hannah, and R. Linstead, *J. Chem. Soc.*, 3257 (1960).

(10) J. L. Kurz, R. Hutton, and F. H. Westheimer, *J. Am. Chem. Soc.*, **83**, 584 (1961).

(11) W. A. Müller, *Z. physiol. Chem.*, **311**, 155 (1958); A. Saz and R. B. Slie, *J. Biol. Chem.*, **210**, 407 (1954).

(12) There are many examples in the literature of which may be mentioned the oxidation of dihydroquinolines (Skraup reaction) [R. H. F. Manske and M. Kulka, *Org. Reactions*, **7**, 59 (1953); H. Gilman, J. Eisch, and T. S. Soddy, *J. Am. Chem. Soc.*, **81**, 4000 (1959)], the acid-catalyzed dehydrogenation of 9,10-dihydroanthracene and the dihydro adducts formed in the Scholl reaction [C. D. Nenitzescu and A. Balaban, *Chem. Ber.*, **91**, 2109 (1958); R. Scholl and C. Seer, *Ber.*, **55**, 330 (1922)], the oxidation of benzyl alcohol in alkaline solution [L. T. Smith and R. E. Lyons, *J. Am. Chem. Soc.*, **48**, 3165 (1926)] and the oxidation of eugenol to vanillin [E. Mayer, *Österr. Chemiker-Ztg.*, **50**, 40 (1949); *Chem. Abstr.*, **44**, 1451 (1950)].

(13) J. A. Berson and E. Brown, *J. Am. Chem. Soc.*, **77**, 447 (1955).

(14) Professor F. H. Westheimer has informed us that his co-workers have observed an apparent reduction of the nitro group in *p*-nitrothiobenzophenone by 1-benzyl-1,4-dihydronicotinamide.