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STEROIDS CCXC.(1) THE HYDROBORATION OF A TETRACYCLIC DIENE

J. P. Turnbull(2) and J. H. Fried

Institute of Steroid Chemistry
Syntex Research, Palo Alto, California

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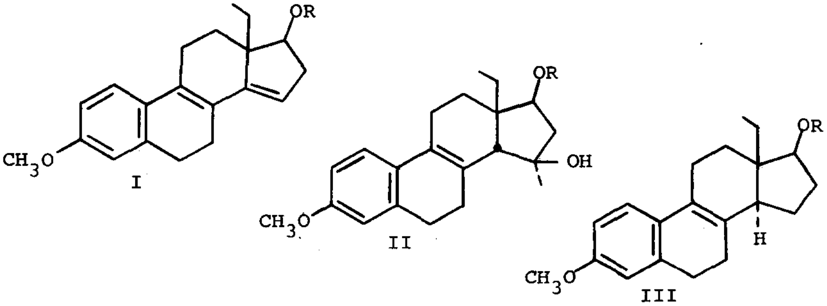
The stereochemistry of hydroboration of rigid systems can usually be predicted from steric parameters which direct the reagent to the less hindered side of the molecule(3a,b) We wish to report that hydroboration of the synthetic (±) tetracycle Ia(4,5) carried out with tert-2,3-dimethylbutylborane(6) followed by oxidation with hydrogen peroxide affords stereospecifically the unsaturated 14-iso-15β-alcohol IIa(7,8,9) [m.p. 135-136°; λ_{max} 273 mμ (log ε 4.23). <u>Anal</u>. Calcd. for $C_{25}H_{34}O_4$: C, 75.34; H, 8.60. Found: C, 75.32; H 8.47]. The



I

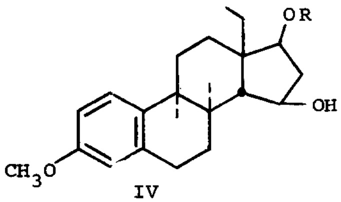
II

III

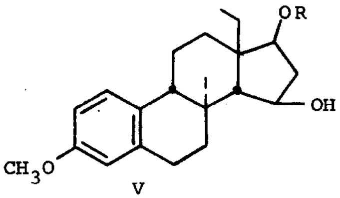
a - R:THP
b - R:H
c - R:CH$_2$Ø

formation of the cis-fused ring system, vide infra., is unexpected and is opposite to that predicted from simple steric considerations as exemplified by catalytic hydrogenation of two derivatives of I, the 17-ketone and the corresponding ketal, which yields products with the 14α-stereochemistry.(10) The bulky 17β-tetrahydropyranyloxy function in Ia would be expected to favor reaction from the α-side to an even greater extent. Indeed, the hydroboration of the nonconjugated 14-enes, 5α-cholest-14-en-3β-ol and 5α-androst-14-ene-3β,17β-diol, studied by Nussim et al.(11) affords products with the 14α-stereochemistry.

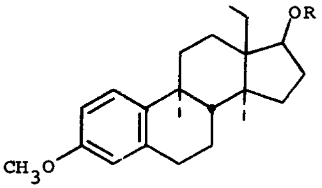
Reduction of the crystalline tetrahydropyranyl ether, IIa, with potassium and aniline in liquid ammonia affords a ca. 1:3 mixture of two dihydroderivatives IVa [m.p. 106-107°; λ_{max} 278 and 287 mμ (log ε 3.35 and 3.32). Anal. Calcd. for $C_{25}H_{36}O_4 \cdot 1/2\ C_2H_5OH$: C, 73.74; H, 9.28. Found: C, 73.84; H, 9.11], and Va [m.p. 160-162°; λ_{max} 278 and 287 mμ (log ε 3.35



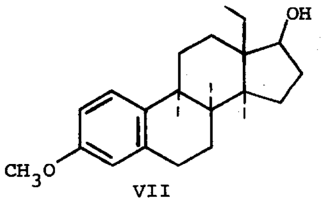
IV



V



VI



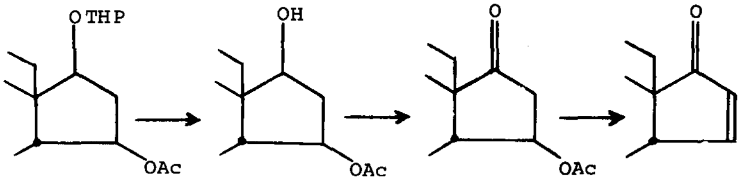
VII

and 3.33). Anal. Calcd. for $C_{25}H_{36}O_4$: C, 74.86; H, 9.06. Found: C, 74.82; H, 8.58] while hydrogenation of IIa over platinized charcoal yields the previously obtained compound IVa.

This result can only be accommodated by assigning the 14β-stereochemistry to IIa since (a) metal ammonia reduction of the 14α-steroid IIIb affords a single product VIb with the *trans-anti-trans* stereochemistry(10) while hydrogenation of IIIb affords only the *cis-syn-trans* product VII(12) [m.p. 129-130°; λ_{max} 278 and 287 mμ (log ε 3.75, 3.78). Anal. Calcd. for $C_{20}H_{28}O_2$: C, 79.97; H, 9.39. Found: C, 79.66; H, 9.21].

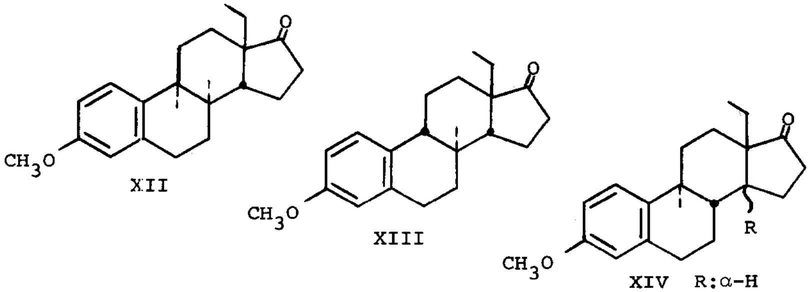
However, in agreement with the results of the present study, Smith, *et al.*,(13) have demonstrated that 8-dehydro-14β-estrone methyl ether affords both the *cis-anti-cis* and *trans-anti-cis* products on metal-ammonia reduction, the former being identical with the major product of catalytic hydrogenation.

Both IV and V were converted in turn to the corresponding estrone derivatives by acetylation of the C-15 carbinol, hydrolysis of the C-17 tetrahydropyranyl ether, Jones oxidation of the derived C-17 carbinol, acid catalyzed elimination of acetic acid and catalytic reduction to yield from IV, *via* intermediates VIII - XI, 13β-ethyl-3-methoxy-8α,9α,14β-gona-1,3,5(10)-trien-17-one, XII [m.p. 110-111°; λ_{max} 278 and 287 mμ (log ε 3.32 and 3.30); ν_{max} 1737 cm^{-1}. Anal. Calcd. for $C_{20}H_{26}O_2$: C, 80.49;



VIII IX X XI

H, 8.78. Found: C, 80.29; H, 8.64] and from V, 13β-ethyl-3-methoxy-8α,9β,14β-gona-1,3,5(10)-trien-17-one, XIII [m.p. 146-147°; λ_{max} 278 and 287 mμ (log ε 3.30 and 3.28); ν_{max} 1724 cm^{-1}. Anal. Calcd. for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78. Found: C, 80.61; H, 8.77].



XII

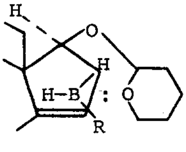
XIII

XIV R:α-H

XV R:β-H

Comparison of XII and XIII with XIV and XV$^{(14)}$ both by melting point analysis and gas liquid chromatography$^{(15)}$ demonstrated the expected non-identity.

A possible explanation for the steric course of hydroboration is the formation of a complex with the reagent and the oxygen in the tetrahydropyranyl ring which would then be in a position to deliver the hydroborating species to the β-face of the molecule. This hypothesis was investigated by hydroboration of benzyl ether Ic$^{(16)}$, followed by the sequence described above.$^{(18)}$ In this case a complex, if formed, is not within



bonding distance of the C-14 double bond. Analysis of the isomeric 18-homoestrones by g.l.c. indicated a 7:3 ratio of β-face to α-face hydroboration. This result suggests the operation of several other factors including a more facile than expected direct β-face hydroboration or, possibly, rearrangement of an initially formed α-hydroboration product to the thermodynamically more stable β-product.

References

1. Steroids CCLXXXIX. J. B. Siddall, G. V. Baddeley, J. Edwards, Chem. & Ind. (in Press).
2. Syntex Postdoctoral Fellow, 1964-1965.
3. (a) For a recent survey cf. H. C. Brown, Hydroboration, W. A. Benjamin, Inc., New York (1962).
   (b) For hydroboration of steroid dienes cf. M. Nussim, Y. Mazur and F. Sondheimer, J. Org. Chem., **29**, 1131 (1964).
4. Structural formulas depict one asymmetric center but racemates were used throughout this work. Subsequently, the (±) prefix will be omitted.
5. Prepared by D. Green from 13-ethyl-3-methoxygona-1,3,5(10), 8,14-pentaen-17-one(10) by reduction of the C-17 ketone with sodium borohydride and formation of the tetrahydropyranyl ether [m.p. 106-107°; λ_{max} 312 (log ε 4.58). Anal. Calcd. for $C_{25}H_{32}O_3$: C. 78.91; H, 8.48. Found: C, 78.34; H, 8.46].
6. Diborane gave a mixture of mono and bishydroboration products and sec-(bis-3-methylbutyl)-borane was unreactive under mild conditions.
7. Ultraviolet and infrared spectra were determined in methanol solution and potassium bromide disks respectively. We wish to thank Dr. L. Throop and his associates for the physical measurements herein reported.

8. An oily second component isolated from this reaction is isomeric at the 17-tetrahydropyranyl ether. This was demonstrated by mild hydrolysis of both products to the same 17β-carbinol IIb [m.p. 128-130°; λ_{max} 273 mμ (log ε 4.23). *Anal*. Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.37; H, 8.40].

9. The 15β-stereochemistry is assigned to the newly introduced hydroxyl function on the basis of *cis*-hydroboration and retention of configuration during oxidation.(3a)

10. H. Smith, G. A. Hughes, G. H. Douglas, G. R. Wendt, G. C. Buzby, Jr., R. A. Edgren, J. Fisher, T. Foell, B. Gadsby, D. Hartley, D. Herbst, A. B. A. Jansen, K. Ledig, B. J. McLoughlin, J. McMenamin, T. W. Pattison, P. C. Phillips, R. Rees, J. Siddall, J. Siuda, L. L. Smith, J. Tokolics and D. H. P. Watson, *J. Chem. Soc.*, 4472 (1964).

11. M. Nussim, Y. Mazur and F. Sondheimer, *J. Org. Chem.*, **29**, 1120 (1964).

12. The stereochemistry assigned to VII is based upon the analogous reduction in the 8-dehydroestrone series affording 8α-estrone methyl ether.(13)

13. G. H. Douglas, J. M. H. Graves, D. Hartley, G. A. Hughes, B. J. McLoughlin, J. Siddall and H. Smith, *J. Chem. Soc.*, 5072 (1963) and references cited.

14. The synthesis of this compound will be the subject of a separate publication.

15. We wish to thank D. Askerman for carrying out the g.l.c. analysis.

16. Prepared(17) from Ib with benzylchloride and sodium hydride [m.p. 89-90°; λ_{max} 312 mμ (log ε 4.49). *Anal*. Calcd. for $C_{27}H_{30}O_2$: C, 83.90; H, 7.82. Found: C, 84.02; H, 7.98].

17. We wish to thank I. Jamieson for carrying out this preparation.

18. We wish to thank D. Green for carrying out this procedure.