Tetrahedron Letters No.47, pp. 4181-4186, 1965. Pergamon Press Ltd.
Printed in Great Britain.

A NOVEL RING CONTRACTION LEADING TO D-NORSTEROIDS

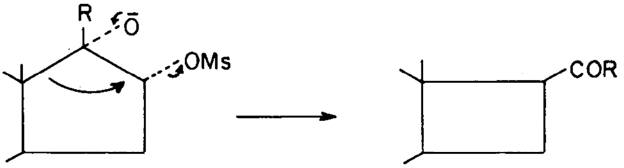
Eugene Ghera

Daniel Sieff Research Institute, The Weizmann
Institute of Science, Rehovoth, Israel

(Received 1 October 1965)

The contraction of a cyclopentane to a cyclobutane ring involves the conversion of a nonstrained to a strained ring. Perhaps for this reason there are almost no methods reported for performing such contractions, apart from the photolysis of diazoketones; this appears to be the only practical route for this type of transformation and has recently been used for the preparation of D-norsteroids (1). A few special cases of such contraction by Favorskii-type rearrangement are also known (2), but this process is not of general applicability (3).

We wish to report a new ring contraction to a four membered ring by way of a base catalyzed pinacol-type rearrangement (4). This method is used now for the preparation of D-norsteroids.

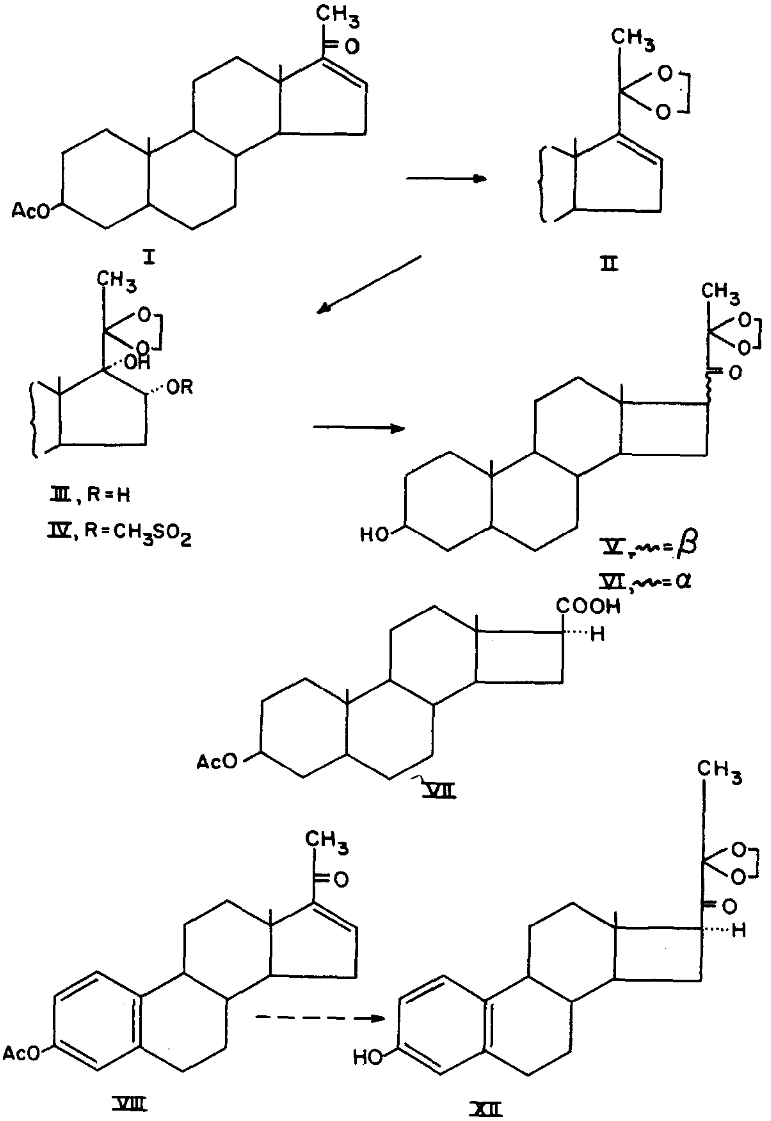


The reaction sequence started from the readily available (5) 5α-pregn-16-en-3β-ol-20-one acetate (I) which was converted to the ethylene ketal II* (m.p. 115-116°, $[\alpha]_D$ +2°). Hydroxylation of the double bond with osmium tetroxide in pyridine led to the compound III (m.p. 202-204°, $[\alpha]_D$ -6°), which on treatment with methanesulphonyl chloride in pyridine gave the corresponding methanesulphonate IV, m.p. 193-194°, $[\alpha]_D$ -51°, (47% over-all yield from I). The rearrangement of IV with 0.04N potassium t-butoxide (ca. 4 equiv.) in t-butyl alcohol (70°, 5 hours) yielded a crystallizable material which, although homogenous on t.l.c., consisted of two separable isomers to which the structures V and VI have been assigned. The main isomer, separated in 57% yield, had m.p. 170-171°, $[\alpha]_D$ +73°, mol. wt. (mass spectrum) 376, $\lambda_{max}^{CHCl_3}$ 5.83, 9.68μ, δ CDCl$_3$ 4 (4H, singlet, ethylene ketal), 3.16 (1H, double doublet, J= 9 c.p.s. and J'= 6 c.p.s., 16α-H) and 0.87 (3H, singlet, methyl at C-13). The 16α-isomer VI was isolated in small yield (m.p. 139-141°, $[\alpha]_D$ + 10°) and its C-13 methyl protons appear deshielded in the n.m.r. spectrum (δ 1.26) as compared with the corresponding protons in V (6). The ratio of V:VI after reaction was ca. 7:3** and each of the pure isomers could be converted by base treatment to the same equilibrium mixture. The side chain configuration has been assigned on the basis of o.r.d. curves. For compound V the curve shows a positive Cotton effect as does D-norpregnenolone,

---

* Satisfactory analyses were obtained for all compounds whose melting points (uncorrected) are reported. The optical rotations were determined in chloroform solution.

** This evaluation is based on the relative intensities of the methyl signals at C-13 in the n.m.r. spectrum and the optical rotation of the mixture as compared with the relevant values for the pure isomers.


CH₃
O
AcO
I
CH₃
O
O
II
CH₃
O
O
OH
OR
III, R=H
IV, R=CH₃SO₂
CH₃
O
O
O
HO
V, ∿=β
VI, ∿=α
COOH
H
AcO
VII
CH₃
O
AcO
VIII
CH₃
O
O
O
H
HO
XII

whereas isomer VI exhibits a negative Cotton effect curve (Ic).

Unequivocal proof for the proposed structures has been obtained by the conversion of V to the corresponding 16β-carboxylic acid VII, without purification of the intermediate products. The carbonyl group in V was reduced with sodium borohydride in methanol and the mixture of stereoisomers deketalized* by treatment with acid. Further reduction with lithium aluminum hydride gave a mixture of triols which on cleavage with sodium periodate yielded an air-sensitive aldehyde (absorption at 3.68 and 5.83 μ in infrared and δ 9.77 in n.m.r.) that appeared to be a single compound (t.l.c.). Acetylation of the 3-hydroxyl group followed by oxidation with Jones' reagent (7) afforded the acetate of 5α-D-norandrostan-3β-ol-16β-carboxylic acid (VII; m.p. 237-239°, $[\alpha]_D$ +27°), identical (infrared, t.l.c., rotation, mixed m.p.) with an authentic sample**(Ib).

In a parallel series of experiments, 3-acetoxy-17-acetyl-1,3,5,16-estratetraene (VIII) (8) was converted to the ethylene ketal IX (m.p. 104-105°, $[\alpha]_D$ +69°) and further to the triol acetate X (m.p. 210-212°, $[\alpha]_D$ +62°) and the methanesulphonate XI (m.p. 202-203°, $[\alpha]_D$ +12°). Base treatment of XI again involved rearrangement and gave a mixture of two isomers from which the 16β-derivative XII (m.p. 193-194°, $[\alpha]_D$ +114°) was separated in 52% yield. The structure and the configuration of the side chain have been assigned by analogy with the pregnane series, on the basis of spectral and analytical data.

---

* Direct acid treatment of V did not remove the ketal, probably because of the difficulty of formation of a cation α to the carbonyl group.

** Supplied by the Schering Corporation, by courtesy of Dr. Hans Reimann.

In both series no other rearrangement or elimination products, except the described D-norderivatives, have been observed.

Further investigation in other systems of this smooth ring contraction, which is undoubtedly conditioned by steric requirements, has been initiated.

Acknowledgements. The author wishes to thank Drs. H. Reimann, J. Mathieu and A. Hassner for samples of D-nor-steroids and Dr. N. Danieli for the mass spectral determination.

REFERENCES

1. Inter. al., see (a) M. P. Cava and E. Moroz, J. Amer. Chem. Soc., 84, 115 (1962); (b) J. Meinwald, G. G. Curtis and P. G. Gasman, ibid., 84, 116 (1962); (c) G. Muller, C. Huinh and J. Mathieu, Bull. Soc. Chim., 296 (1962); (d) A. Hassner, A. W. Coulter and W. S. Seese, Tetrahedron Letters, 17, 759 (1962); (e) J. L. Mateos, O. Chao and H. Flores, Tetrahedron, 1051 (1963); (f) H. Reimann, H. Schneider, O. Z. Sarre, C. Federbusch, C. Towne, W. Charney and E. P. Oliveto, Chem. and Ind. 334 (1963).

2. P. E. Eaton and T. W. Cole, J. Amer. Chem. Soc., 86, 962, 3157 (1964); K. W. Scherer, Jr., R. S. Lunt, III, and G. A. Ungefug, Tetrahedron Letters, 17, 1199 (1965).

3. M. Mousseron, R. Jaquier and A. Fontaine, Bull. Soc. Chim. 767 (1952).

4. See E. Ghera, J. Chem. Soc., in press and the references listed therein for this type of rearrangement.

5. Cf. P. Crabbé, M. Pérez and G. Vera, Can. J. Chem., 41, 156 (1963).

6. See M. Rubin and E. C. Blossey, J. Org. Chem., 1932 (1964), for similar downfield shifts of the methyl protons in 17α-20-ketosteroids.

7. K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, J. Chem. Soc., 39 (1946).

8. C. Djerassi, G. Rosenkranz, J. Iriarte, J. Berlin and J. Romo, J. Amer. Chem. Soc., 73, 1523 (1951).