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STEROIDS LXXVI (1). STEREOSPECIFIC FORMATION OF α- AND β-EPOXIDES IN THE REACTION OF DIMETHYLSULFONIUM METHYLIDE AND DIMETHYLSULFOXONIUM METHYLIDE WITH DIHYDROTESTOSTERONE (2)

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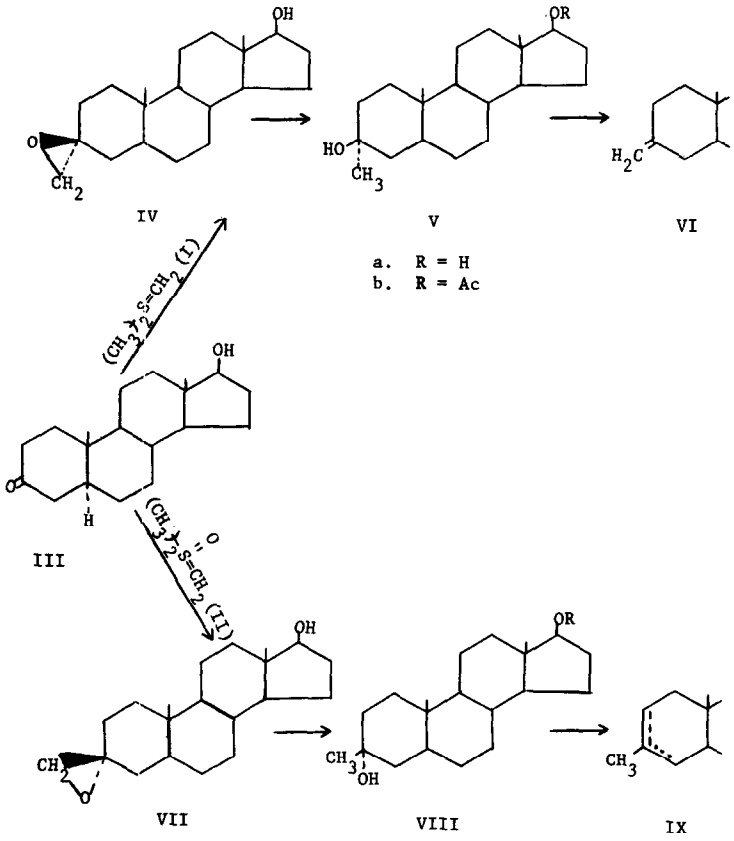
We wish to report unequivocal evidence that the methylene transfer reagents dimethylsulfonium methylide (I) (3) and dimethylsulfoxonium methylide (II) (4) react stereospecifically and in opposite directions with the relatively unhindered 3-ketone moiety of dihydrotestosterone (III) to give, respectively, the β- and α- oxides IV and VII. This reversal of stereospecificity in the formation of carbon-carbon bonds is novel and may have considerable utility in synthesis.

Dihydrotestosterone (III) reacted readily with the sulfonium ylide I to give a 90% yield of the β-oxide IV, m.p. 193-195°, $[\alpha]_D$ +6°.* Reduction of IV with lithium aluminum hydride gave the 3α-methyl-3β, 17β-diol Va, m.p. 193-195°, $[\alpha]_D$ +19°, in 85% yield. Acetylation of Va yielded Vb,

*A 7% yield of the 17-methyl ether of IV was also obtained. Any epimeric oxide must have been present in less than 3% yield and even this much is unlikely.


OH
OR
O
CH2
HO
CH3
H2C
IV
V
VI
a. R = H
b. R = Ac
(CH3)2S=CH2 (I)
OH
O
H
III
(CH3)2S=CH2 (II)
O
OH
OR
CH2
O
CH3
OH
CH3
VII
VIII
IX
a. R = H
b. R = Ac

m.p. 207.5-208°, $[\alpha]_D$ +10°. In contrast, the sulfoxonium ylide II reacted with III to give a 79% yield of the α-oxide VII, m.p. 173-175°, $[\alpha]_D$ +7°.** *** Reduction of VII gave the 3β-methyl-3α, 17β-diol VIIIa, m.p. 168-170°, $[\alpha]_D$ +8°, in 86% yield. Acetylation of VIIIa yielded VIIIb, m.p. 214-215°, $[\alpha]_D$ +6°.****

The orientation of the hydroxyl and methyl groups at C-3 was proved by subjecting mono-acetates Vb and VIIIb to the dehydration conditions (phosphorus oxychloride in pyridine) used by Barton in a study of epimeric 3-methylcholestanols (5). The crude products were examined by n.m.r. spectroscopy. The product from Vb was clearly shown to have the exo-methylene structure VI by an n.m.r. peak at 275 c.p.s. (relative to internal tetramethylsilane at 60 Mc), while that from VIIIb had peaks at 98 c.p.s. (CH_3-C=) and 317 c.p.s. (tri-substituted olefin) clearly demonstrative of the endocyclic structure IX (6).*** ** Infrared spectra were in agreement with these assignments.

As Barton has pointed out (5), a trans, coplanar elimination in a 3α-methyl-3β-hydroxy-5α-steroid is only possible if the hydrogens of the

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**No evidence could be found for any of the epimeric compound in the mother liquor.

***In a very recent paper [M. E. Wolff, W. Ho, and R. Kwok, J. Med. Chem., 7, 577 (1964)], mention is made of the reaction of II and III to yield an epoxide, m.p. 173-175°, $[\alpha]_D$ +3°. These authors assigned to it the β-oxide structure IV, without any formal structure proof. Our results demonstrate that this assignment was incorrect.

****B. Pelc, Coll. Czechoslav. Chem. Comm., 25, 1624 (1960), reports m.p. 186-188°, $[\alpha]_D$ +12°, for Va, m.p. 194-195°, $[\alpha]_D$ +12°, for Vb, m.p. 168-170°, $[\alpha]_D$ +8°, for VIIIa, and m.p. 205-207°, $[\alpha]_D$ +5°, for VIIIb. Although Pelc's assumptions as to configuration at C-3 appeared reasonable, we felt that an unequivocal demonstration was necessary.

***Olefins IX and X were not purified. N.m.r. of the crude olefins did ** not indicate the presence of a mixture of endo and exo double bonds in either case.

methyl group participate to yield an exo-methylene compound, whereas a 3α-hydroxyl group is trans to and coplanar with axial hydrogens at C-2 and C-4 and thus dehydrates to an endocyclic olefin. Therefore it follows that alcohols V and VIII have the stereochemistry shown. Since no attack at C-3 was involved in the formation of alcohols V and VIII from their respective epoxides IV and VII, epoxide IV must be 3β- and epoxide VII must be 3α-, as shown.

The reversal in stereochemistry on changing from dimethylsulfonium methylide (I) to the sulfoxonium reagent (II) has not been previously noted. We suggest that it may be due to the greater stability, lesser reactivity, and greater bulk of II relative to I.*** ****
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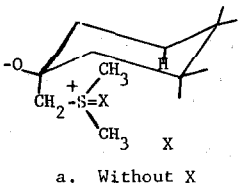
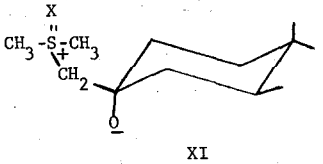
***The observed effects may be rationalized by the following assumptions: (a) Steric control of approach of each reagent would favor initial backside attack with formation of intermediates (Xa,b) having the methylene group α. (b) The intermediate Xa from the ketone and the much more reactive, less stable sulfonium ylide I would for thermodynamic reasons be less likely to undergo reversal to starting materials than the intermediate (Xb) formed by the less reactive, more stable sulfoxonium ylide II. (The stability and reactivity of I and II have been compared in reference 3). (c) The mechanism proposed by Johnson [A. W. Johnson, V. G. Hruby, and J. S. Williams, J. Am. Chem. Soc., 86, 918 (1964)] for the similar reaction of benzaldehydes with diphenylsulfonium benzylide (S_N2 backside displacement of sulfonium group by oxyanion) applies. This requires the trans-coplanar relationship between oxygen and sulfur indicated in structure X--an arrangement which results in severe non-bonded interactions between groups attached to sulfur and the axial 1α and 5α hydrogens. These interactions are more severe in the intermediate Xb from the sulfoxonium ylide II. Intermediate XI is relatively free of non-bonded interactions. Thus while the same intermediate X may be initially formed in each case, only Xa goes to products. Intermediate Xb participates in an equilibrium among starting materials, Xb, and XIb. Only the latter can readily assume the configuration necessary to go on to products.



X

a. Without X
b. X = O



XI

a. Without X
b. X = O

**** Sufficient data (elemental analyses, infrared and n.m.r. spectra) were obtained to identify new compounds. Optical rotations were determined in chloroform solution, n.m.r. spectra in deuteriochloroform, and melting points on a Kofler apparatus.

References

(1) Steroids LXXV. S. G. Levine, N. H. Eudy, and E. C. Farthing, Tetrahedron Letters 1517 (1963).

(2) (a) This research was carried out under contract SA-43-ph-4351 of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health.

(b) Abstracted from work done by Robert C. Corley in partial fulfillment of the requirements for the Ph.D. degree at North Carolina State of the University of North Carolina at Raleigh.

(3) E. J. Corey and M. Chaykovsky, J. Am. Chem. Soc., 84, 3782 (1962).

(4) E. J. Corey and M. Chaykovsky, J. Am. Chem. Soc., 84, 867 (1962).

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(6) L. M. Jackman, Nuclear Magnetic Resonance Spectroscopy, Pergamon Press, New York, N. Y., 1959, p. 61. Compare, e. g., α-pinene (310 cps) and β-pinene (276 cps). N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, NMR Spectra Catalog, Varian Associates, 1962, Spectra 272, 274.