solved in hot chloroform containing only enough methanol to bring about solution. A small amount of gummy solid precipitated on cooling and was removed. The filtered solution was evaporated *in vacuo* and the residue was crystallized and recrystallized from ether–methylene chloride. There was obtained 69 mg. (29%) of solid, m.p. 115–116°. Admixture of the solid obtained in the previous experiment did not depress the m.p. The ultraviolet and infrared spectra of the two solids were identical.

PEARL RIVER, NEW YORK

[FROM THE DIVISION OF STEROID METABOLISM AND BIOCHEMISTRY, SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH, SLOAN-KETTERING DIVISION, CORNELL UNIVERSITY MEDICAL COLLEGE]

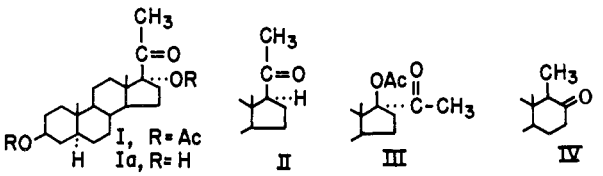
Tertiary Hydroxyl Group Elimination in Steroid Ketols[1]

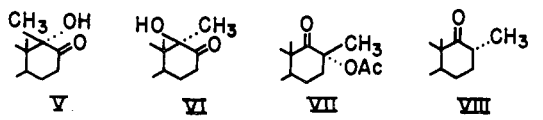
BY R. S. ROSENFELD

RECEIVED MAY 20, 1957

3β,17α-Diacetoxyallopregnane-20-one (I) reacted with zinc dust in refluxing glacial acetic acid to form 3β-acetoxyallopregnane-20-one (II) in 89% yield while 3β,17β-diacetoxyallopregnane-20-one (III) afforded 46% of II. Under identical conditions, 3β,17α-dihydroxyallopregnane-20-one (Ia) yielded 8% of II and 14% of 3β-acetoxy-17αβ-methyl-D-homoandrostane-17-one (IV). In the 17a-hydroxy-17-ketones, 3β-acetoxy-17aα-hydroxy-17aβ-methyl-D-homoandrostane-17-one (V) reacted with zinc–acetic acid to form 78% of IV while the 17aβ-hydroxy epimer VI was recovered unchanged. 3β,17α-Diacetoxy-17β-methyl-D-homoandrostane-17a-one (VII) yielded 88% of 3β-acetoxy-17α-methyl-D-homoandrostane-17a-one (VIII) under the same conditions. The results are discussed in terms of the conformation of the tertiary hydroxyl groups.

Treatment of steroid ketols or ketol acetates with divalent metals under reducing conditions has been shown to be an effective method for the removal of the hydroxyl or acetoxyl function provided a double bond, halogen atom or additional acetoxyl, is attached to a carbon alpha to the ketol structure.[2] Under these conditions, the ketone group is largely unattacked. However, when no such additional groups are present, deacetoxylation in good yield is dependent upon the steric requirements of the reaction. Thus, in ring C ketol ace-





tates of the bile acid series deacetoxylation proceeds in almost quantitative yields when these substances are refluxed with zinc dust in glacial acetic acid provided the acetoxyl function occupies the axial position, but in less than 30% yield when this group has the equatorial conformation.[3] Similar results were reported by Chapman, Elks, Phillips and Wyman[4] who found that in the preparation of 11-oxotigogenin, the corresponding 12α-acetoxy (axial) compound was more easily deacetoxylated with barium or calcium in liquid ammonia than was the epimeric 12β-compound. These results have been interpreted in the light of investigations of Barton and his group[5] who have shown that 1,2-eliminations takes place with greater ease if the substituents are coplanar, *trans* and axial.[3]

The epimeric 17-acetoxy-20-ketosteroids represent further examples of ketol acetates which should deacetoxylate in a way that would be influenced by the conformation of the acetoxyl group. Although the 17-acetoxyl group is attached to a 5-membered ring, inspection of molecular models shows that the 17α-acetoxyl is perpendicular to the D ring and is axial while the 17β-acetoxyl group is equatorial and lies almost in the plane of ring D. When 3β,17α-diacetoxyallopregnane-20-one (I)[6] was refluxed for 24 hours with zinc dust and glacial acetic acid, 3β-acetoxyallopregnane-20-one (II) was obtained in 89% yield accompanied by about 8% of the starting material. Under the same conditions, the epimeric 3β,17β-diacetoxyallopregonane-20-one (III) afforded 46% of 3β-acetoxyallopregnane-20-one (II) and 45% of the starting material III was recovered. It should be noted that inversion of the acetyl side chain had taken place in the formation of 3β-acetoxyallopregnane-20-one (II) from III while in the conversion of I to II the configuration occupied by the side-chain was unaffected. In both cases, no trace of the 17-epimer of 3β-acetoxyallopregnane-20-one was detected in the reaction products. This is explained by the formation of a common intermediate represented as an enol-zinc complex

(1) This investigation was supported in part by a grant from the American Cancer Society and a research grant (C-440) from the National Cancer Institute of the National Institutes of Health, United States Public Health Service.

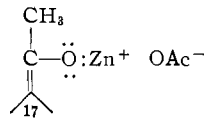
(2) J. K. Norymberski, *J. Chem. Soc.*, 517 (1956); J. Romo and A. R. de Vivar, *J. Org. Chem.*, **21**, 902 (1956); S. A. Knight, J. F. McGhie and M. J. Birchenough, *Chemistry & Industry*, 822 (1953); L. F. Fieser, THIS JOURNAL, **75**, 4377 (1953); F. Sondheimer, St. Kaufmann, J. Romo, H. Martinez and G. Rosenkranz, *ibid.*, **75**, 4712 (1953); M. Roth, G. Saucy, R. Anliker, O. Jeger and H. Heusser, *Helv. Chim. Acta*, **36**, 1908 (1953); W. R. Nes and H. L. Mason, THIS JOURNAL, **73**, 4765 (1951).

(3) R. S. Rosenfeld and T. F. Gallagher, *ibid.*, **77**, 4367 (1955).

(4) J. H. Chapman, J. Elks, G. H. Phillips and L. J. Wyman, *J. Chem. Soc.*, 4344 (1956).

(5) D. H. R. Barton, *Experientia*, **6**, 316 (1950); D. H. R. Barton and W. J. Rosenfelder, *J. Chem. Soc.*, 1048 (1951); D. H. R. Barton and E. Miller, THIS JOURNAL, **72**, 1066 (1950).

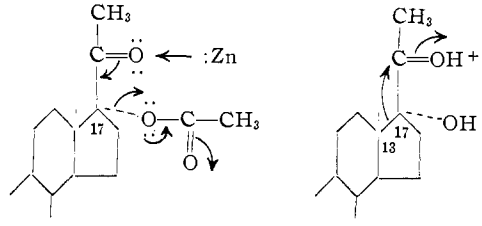
(6) R. B. Turner, *ibid.*, **75**, 3489 (1953).



It is known that enol acetates of 20-ketosteroids may exist in two geometrical isomeric forms provided that no bulky substituents are in the vicinity.[7] However, the comparatively large zinc molecule precludes the formation of two enol–zinc complexes and only the more stable would exist.

Recent studies on the mechanism of ketonization of enols[8,9] indicate that there is "a general and strong preference for axial attack in the protonation of steroid enols by acetic acid."[8] Therefore, acetolysis of the zinc complex might be expected to yield but one product and this, in fact, is 3β-acetoxyallopregnane-20-one (II) from the axial entry of the proton at C-17. This sequence of events is quite different from the partial isomerization of the side-chain of 20-ketosteroids by acid or base in hydroxylic solvents.[10]

When 3β,17α-dihydroxyallopregnane-20-one (Ia) was heated with zinc in acetic acid, only 8% represented elimination of the 17-hydroxyl group with the formation of II; 40% of starting material and 14% of 3β-acetoxy-17aβ-methyl-D-homoandrostane-17-one (IV) comprised the remainder of the isolated products. Acylation at the 17-hydroxyl is necessary for removal of this function in high yield since scission of the oxygen bonded to C-17 is favored by the electron-withdrawing capacity of the ester carbonyl group.



In Ia, this situation does not exist and the presence of IV as a reaction product may be explained by proton attack at the 20-ketone with the migration of C_{13-17} bond to the C-20 carbonium ion.[11] In contrast to this, Norymberski and Stubbs have reported that the 17α-hydroxyl group in 3α,17α-dihydroxypregnane-11,20-dione is inert to the action of zinc and acetic acid.[12]

The epimeric 17a-hydroxy-17-ketones in the D-homosteroids are conformationally similar to the ring C ketols[3] and possess comparable reactivity toward zinc and acetic acid. 3β-Acetoxy-17aα-hydroxy- 17aβ -methyl- D -homoandrostane- 17 -one (V) (17a-hydroxyl = axial) readily eliminated the tertiary alcohol in zinc–glacial acetic acid to yield 78% of 3β-acetoxy-17aβ-methyl-D-homoandrostane-17-one (IV); no 17aα-methyl epimer was found. In contrast, 3β-acetoxy-17aβ-hydroxy-17-aα-methyl-D-homoandrostane-17-one (VI) (17a-hydroxyl = equatorial) was recovered unchanged under the same conditions.

In the isomeric 17a-ketone, 3β,17α-diacetoxy-17β-methyl-D-homoandrostane-17a-one (VII), the 17α-acetoxy group has the equatorial conformation when ring D is in the chair form and might be expected to be inert to the action of zinc–acetic acid. However, in VII, ring D can exist in the boat form in which there is no steric interaction between the angular methyl group at C-13 and substituents at C-17. In this conformation the 17α-acetoxyl becomes axial and susceptible to reaction. In support of this it was found that VII deacetoxylated in zinc–acetic acid to form 3β-acetoxy-17α-methyl-D-homoandrostane-17a-one (VIII)[13] in 88% yield. This differs from V and VI where conversion of ring D into the boat form with reversal of the conformations at C17a probably does not take place since there would be interaction between the C-13 angular methyl group and the 17aβ-substituent. In the ring C ketol acetates[3] there is no chair–boat interconversion since the chair form is the only possible conformation.

Experimental[16]

The conditions for the deacetoxylation or dehydroxylation of each substance with zinc and glacial acetic acid were identical. The compound was refluxed with 100 times its weight of zinc dust and 500 times its weight of glacial acetic acid for 24 hours. The reaction mixture was cooled and filtered. The filtrate was concentrated to a small volume, diluted with ethyl ether, and the ether solution was washed with 5% sodium hydroxide and then with 10% sodium chloride until the washings were neutral. The ether solution was dried over sodium sulfate and the solvent was removed.

Reaction of 3β,17α-Diacetoxyallopregnane-20-one (I) with Zinc–Acetic Acid.—One hundred and thirty-two milligrams of I[5] yielded a crystalline product, m.p. 110–140°, $[\alpha]^{26}D$ +51°; the infrared spectrum was identical with that of 3β-acetoxyallopregnane-20-one. Two recrystallizations from acetone–methanol yielded 39 mg. of 3β-acetoxyallopregnane-20-one (II), m.p. 146–147°, $[\alpha]^{26}D$ +76°. The mother liquors were chromatographed on silica gel and eluted with mixtures of ether–petroleum ether. After 9 mg. of a mixture of I and II, 67 mg. of II, m.p. 145–147°, was obtained. The mother liquors from the recrystallization yielded a further 51 mg., m.p. 140–145°, $[\alpha]^{26}D$ +70°; infrared spectrum identical with authentic II.

Reaction of 3β,17β-Diacetoxyallopregnane-20-one (III)[17] with Zinc–Acetic Acid.—The product from 194 mg. of III was crystalline, m.p. 180–216°. After two recrystallizations from acetone–methanol, 33 mg. of starting material III was obtained, m.p. 224–226°, $[\alpha]^{26}D$ −6°; infrared spectrum identical with 3β,17β-diacetoxyallopregnane-20-

(7) C. W. Marshall, T. H. Kritchevsky, S. Lieberman and T. F. Gallagher, THIS JOURNAL, **70**, 1837 (1948); L. F. Fieser and Huang-Minlon, *ibid.*, **71**, 1840 (1949); T. H. Kritchevsky and T. F. Gallagher, *ibid.*, **73**, 184 (1951).

(8) E. J. Corey and R. A. Sneen, *ibid.*, **78**, 6269 (1956).

(9) H. E. Zimmermann and H. J. Giallombardo, *ibid.*, **78**, 6259 (1956).

(10) A. Butenandt and L. Mamoli, *Ber.*, **68**, 1847 (1935).

(11) D. K. Fukushima and T. F. Gallagher, *J. Biol. Chem.*, **220**, 951 (1956); D. K. Fukushima, S. Dobriner, M. S. Heffler, T. H. Kritchevsky, F. Herling and G. Roberts, THIS JOURNAL, **77**, 6585 (1955).

(12) J. K. Norymberski and R. D. Stubbs, *Biochem. J.*, **64**, 168 (1956).

(13) This compound is identical with the acetate of the "17β,17aβ-epoxy-17a-methyl-D-homoandrostane-3β-ol" of Prins and Shoppee[14] which was later shown by Klyne[15] to have the structure VIII. In this compound the methyl group has the equatorial conformation since it was unchanged after refluxing with ethanolic potassium hydroxide. When 3β-acetoxy-17β-methyl-D-homoandrostane-17a-one, prepared by Dr. D. K. Fukushima, was similarly treated, it epimerized to VIII.

(14) D. A. Prins and C. W. Shoppee, *J. Chem. Soc.*, 494 (1946).

(15) W. Klyne, *Nature*, **166**, 559 (1950).

(16) All melting points were taken on a micro-stage and are corrected. Optical rotations were measured in chloroform unless otherwise specified.

(17) A. H. Soloway, W. J. Considine, D. K. Fukushima and T. F. Gallagher, THIS JOURNAL, **76**, 2941 (1954).

one. The mother liquors were chromatographed on silica gel and two fractions were eluted. The first yielded 77 mg. of 3β-acetoxyallopregnane-20-one (II), after two recrystallizations from methanol, m.p. 144–145°; $[\alpha]^{26}D$ +78°; infrared spectrum identical with that of an authentic sample. The second fraction afforded 54 mg. of starting material, III.

Reaction of 3β,17α-Dihydroxyallopregnane-20-one (Ia) with Zinc–Acetic Acid.—One hundred and forty-five milligrams of Ia afforded a crystalline product which was acetylated with acetic anhydride–pyridine at room temperature. Chromatography on silica gel yielded three fractions. Fraction A was rechromatographed on 10 g. of silica gel and three compounds were eluted: 12 mg. of 3β-acetoxyallopregnane-20-one (II), infrared spectrum identical with authentic II, m.p. 145–146° after one recrystallization from methanol; 14 mg. of a mixture of II and 3β-acetoxy-17α-hydroxyallopregnane-20-one; 20 mg. of IV, infrared spectrum identical with that of 3β-acetoxy-17aβ-methyl-D-homoandrostane-17-one, m.p. 161–169° after one recrystallization from methanol. Fraction B was recrystallized once from methanol, m.p. 188–190°, and was shown by infrared spectrometry to be the 3-monoacetate of Ia. Fraction C was again chromatographed but was poorly resolved; the monoacetate of Ia was the only substance identified.

Reaction of 3β-Acetoxy-17aα-hydroxy-17aβ-methyl-D-homoandrostane-17-one (V) with Zinc–Acetic Acid.—From 140 mg. of V, after chromatography, 104 mg. (78%) was obtained. The infrared spectrum was identical with that of 3β-acetoxy-17aβ-methyl-D-homoandrostane-17-one (IV). One recrystallization from methanol yielded IV, m.p. 172–173°, $[\alpha]^{26}D$ −60° (Ramirez[18] reported m.p. 171–173° and $[\alpha]^{25}D$ −52° ($CHCl_3$)). The mother liquor afforded impure IV, m.p. 164–167°.

Treatment of 3β-Acetoxy-17aβ-hydroxy-17aα-methyl-D-homoandrostane-17-one (VI) with Zinc–Acetic Acid.—Of 250 mg. of VI subjected to the standard treatment, 221 mg. of unreacted VI was recovered. There was no evidence for any other product.

Reaction of 3β,17α-Diacetoxy-17β-methyl-D-homoandrostane-17a-one (VII) with Zinc–Acetic Acid.—From 300 mg. of VII after chromatography on silica gel, 227 mg. of VIII were obtained; the infrared spectrum was identical with 3β-acetoxy-17α-methyl-D-homoandrostane-17a-one (VIII).[15] The substance was recrystallized once from methanol, 174 mg., m.p. 170–171°, $[\alpha]^{26}D$ −30° (acetone) (Prins and Sloppee[14] report a melting point of 171° and $[\alpha]D$ −32° (acetone) for this compound). The mother liquors yielded impure VIII, m.p. 168–171°, $[\alpha]^{26}D$ −24° (acetone).

Acknowledgment.—The support and interest of Dr. T. F. Gallagher in this investigation is gratefully acknowledged.

(18) F. Ramirez and S. Stafiez, THIS JOURNAL, **78**, 644 (1956).

NEW YORK 21, N. Y.

[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE, THE WEIZMANN INSTITUTE OF SCIENCE]

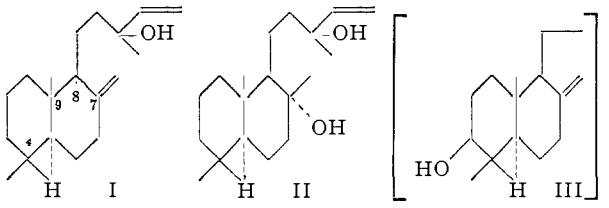
Syntheses in the Terpene Series. III.[1] A Synthesis of 4,4,9-Trimethyl-*trans*-decal-8-one

BY FRANZ SONDHEIMER AND DOV ELAD

RECEIVED MAY 31, 1957

4,4,9-Trimethyl-*trans*-decal-8-one (XIIa), a substance of potential utility for the synthesis of certain di- and triterpenes, has been synthesized from the readily accessible 9-methyl-Δ^4-octalin, -3,8-dione (VI) by a seven-step sequence. 9-Methyl-Δ^4-octal-7ξ-ol-3-one (XIX) has been prepared in the course of an investigation into routes to 4,4,9-trimethyl-*trans*-decal-7-one (XXa).

We have recently embarked upon the synthesis of certain of the di- and triterpene alcohols, such as manool (I),[2] sclareol (II)[2] and α-onocerin (I-II).[3] The carbon skeleton of all of these substances as well as of some of the diterpene acids such



as cativic acid,[4] eperuic acid[5] and labdanolic acid[6] contains the 4,4,9-trimethyl-*trans*-decalin system bearing alkyl or alkylidine substituents at the C-7 and C-8 positions. We considered that suitable starting materials would be the unknown 4,4,9-trimethyl-*trans*-decal-8-one (XIIa) and the corresponding 3β-hydroxy compound XIIb, or alternatively the C-7 ketones XXa and XXb, since the carbonyl group in ring B would make possible the introduction of an alkyl or alkylidine group in the adjacent position and could itself subsequently also be converted to an alkyl or alkylidine function. Such bicyclic ketones moreover could be of value as intermediates in the synthesis of the polycyclic di- and triterpenes containing more than two rings.[7] In the present paper we record the synthesis of 4,4,9-trimethyl-*trans*-decal-8-one (XIIa) by a method which should permit also the preparation of the corresponding 3β-hydroxy compound XIIb. After completion of this work (for a preliminary account, *cf.* footnote 1a), Cocker and Halsall[8] in a preliminary communication reported the synthesis of XIIa by a method similar to our own, while King, Ritchie and Timmons[9] announced the synthesis of the corresponding 3β-ol XIIb (as the benzoate) by a different method. We also undertook some exploratory experiments aimed at the synthesis of 4,4,9-trimethyl-*trans*-decal-7-one (XXa), an account of which is given.

(1) (a) The paper by D. Elad and F. Sondheimer, *Bull. Research Council Israel*, **5A**, 269 (1956), is to be considered Part I of this series; (b) for Part II, see D. Elad and F. Sondheimer, *Proc. Chem. Soc.*, 206 (1957).

(2) *Cf.* W. Klyne, *J. Chem. Soc.*, 3072 (1953).

(3) D. H. R. Barton and K. H. Overton, *ibid.*, 2639 (1955); K. Schaffner, R. Viterbo, D. Arigoni and O. Jeger, *Helv. Chim. Acta*, **39**, 174 (1956).

(4) F. W. Grant and H. H. Zeiss, THIS JOURNAL, **76**, 5001 (1954).

(5) F. E. King and G. Jones, *J. Chem. Soc.*, 658 (1955).

(6) J. D. Cocker and T. G. Halsall, *ibid.*, 4262 (1956).

(7) *Cf.* R. Rüegg, J. Dreiding, O. Jeger and L. Ruzicka (*Helv. Chim. Acta*, **33**, 889 (1950)), who prepared the optically active 7-methyl derivative of IIa by the degradation of α-amyrin.

(8) J. D. Cocker and T. G. Halsall, *Chemistry & Industry*, 1275 (1956).

(9) F. E. King, C. F. Ritchie and C. J. Timmons, *ibid.*, 1230 (1956).