Tetrahedron Letters No.40, pp. 2955-2958, 1964. Pergamon Press Ltd.
Printed in Great Britain.

A 13,14-SECOSTEROID ANALOG (1)

Masato Tanabe and David F. Crowe

Life Sciences Research
Stanford Research Institute
Menlo Park, California

(Received 3 August 1964; in revised form 12 August 1964)

The recent report by Mihailović, Stefanović, Lorenc and Gašic (2) on the preparation of a 5,10 secosteroid, prompts us to report our results on the preparation of a 13,14-secosteroid.

We reported previously that base treatment of 3,5-cyclo-6β-methoxy 17β-tosyloxyandrostane-14α-ol (3) yielded instead of the 13,14-secosteroid fragmentation product, 3,5-cyclo-6β-methoxy-14-androstene-17α-ol. The formation of this product could be rationalized by the intermediate formation of a 14α,17α-oxide intermediate which underwent base catalyzed opening of the oxetane ring to yield the unsaturated inverted alcohol at C_{17}.

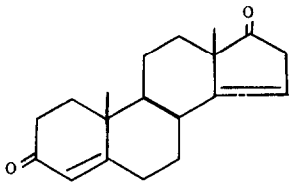
It was anticipated that the fragmentation to a 13,14-secosteroid could be accomplished with a 14β-hydroxy-17α-tosyloxyandrostane derivative. This arrangement of the C_{17}-tosyloxy leaving group and the 14β-hydroxy anion participating in the fragmentation of the $C_{13}C_{14}$ bond would preclude the formation of a 14β,17β-oxido compound, since the steric effect of the C_{18} angular methyl group would seriously interfere with this process. Corey (4) has recently reported on the fragmentation reaction of a pair of substituted 1,3-diol monotosylates in the hydrindane series to yield the cyclonene derivatives, di-caryophyllene and di-isocaryophyllene. In both examples of these fragmentation reactions the participating hydroxyl anion was cis to an angular methyl group.

To prepare the requisite androstane-14β-17α-diol a modification of the method of Sondheimer (5) for the inversion of a 14α-ol to a 14β-ol was employed with 4-androstene-3,17-dione-14α-ol (6). This was dehydrated with p-toluenesulfonic acid in toluene to 4,14-androstadiene-3,17-dione (7) structure I, m.p. 141-142; $\alpha]D$ + 248; $\lambda_{max.}^{Nujol}$ 5.75, 6.0 and 6.2 μ; $\lambda_{max.}^{MeOH}$ 239 mμ (16,900); n.m.r. 4.24 (C_4-H); 4.45 (C_{15}-H); 7.12 (C_{16}-H); 8.77 (C_{19}-H); and 8.86 τ (C_{18}-H).* Treatment of 4,14-androstadiene-3,17-dione with m-chloroperbenzoic acid afforded a mixture of the 14α,15α and 14β,15β oxides (8). Attempts to separate this mixture by chromatography on alumina afforded 4,15-androstadiene-3, 17-dione-14β-ol, m.p. 234-236; $\alpha]D$ + 262 (dioxane); $\lambda_{max.}^{Nujol}$ 2.87, 5.88, 6.0, 6.2, and 6.3 μ; $\lambda_{max.}^{MeOH}$ 239 mμ (18,000); 217 mμ (12,200); n.m.r. 3.8, doublet J = 3 cps (C_{16}-H); 4.23 (C_4-H); 4.53 doublet J = 3 cps (C_{15}-H); 8.81 (C_{19}-H) and 8.86 τ (C_{18}-H); and 14α,15α-oxido-4-androstene-3,17-dione; m.p. 220-222, $\alpha]D$ + 107; $\lambda_{max.}^{Nujol}$ 5.73, 6.0 and 6.17 μ; $\lambda_{max.}^{MeOH}$ 239 mμ (14,500). Reduction of (II) with sodium borohydride in methanol led to a crude triol (III) which was oxidized directly with manganese dioxide in chloroform to 4-androstene-3-one-14β,17α-diol (IV); $\lambda_{max.}^{Nujol}$ 2.85, 6.0 and 6.2 μ. Isolation of this product (IVa) indicates that sodium borohydride simultaneously reduces the C_{15}-C_{16} conjugated double bond and the C_{17}-ketone (9); m.p. 243-245; $\alpha]D$ + 66 (dioxane); $\lambda_{max.}^{MeOH}$ 240 mμ (14,800); $\lambda_{max.}^{Nujol}$ 2.85, 6.0 and 6.2 μ.

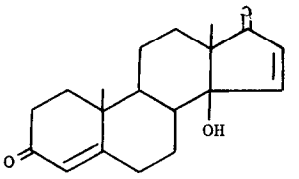
Treatment of the diol (IVa) with p-toluenesulfonylchloride in pyridine afforded the 17α-toluenesulfonate ester (IVb). Fragmentation of this 1,3-diol monotosylate by generation of the alkoxide ion with sodium hydride in tetrahydrofuran proceeded smoothly to afford the 13,14 seco ketone (V).

---

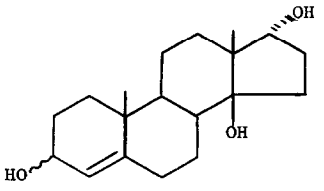
*Satisfactory analyses have been obtained for all new compounds reported. All rotations are reported in chloroform as 1% solutions unless otherwise noted. Nuclear magnetic resonance spectra were recorded in deuteriochloroform with tetramethylsilane as an internal reference on a Varian A-60 spectrometer.



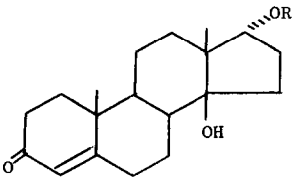
I



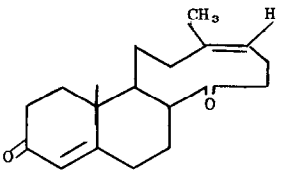
II



III



IVa R = H
IVb R = $C_7H_7SO_2$



V

The appearance of a new carbonyl band in the infrared spectrum at 5.92 μ, along with the disappearance of hydroxyl absorption is in accord with structure V. The nuclear magnetic resonance spectrum further confirms the nature of V with the C_{18} angular methyl group signal now appearing at 8.41τ and a single vinyl proton multiplet appearing at 4.5τ, characteristic of the grouping $-\overset{CH_3}{\underset{|}{C}}=\overset{H}{\underset{|}{C}}-$. The cis orientation of the double bond in the cyclononene ring is assigned on the basis of the

17α-configuration of the hydroxyl in IVa (10). The spectral data are thus in accord with the seco structure as 13,14-seco-4-cis-13,17-androstadiene-3,14-dione; m.p. 149-150°; $\lambda_{max.}^{Nujol}$ 5.92, 6.0 and 6.2 μ; $\lambda_{max.}^{MeOH}$ 238 mμ (14,900); n.m.r. 4.27 (C_4-H); 4.5 (C_{17}-H); 8.41 (C_{18}-H) and 8.86 (C_{19}-H).

Further studies are in progress to assess the effect of the incorporation of medium sized nine- and ten-membered rings in the steroid nucleus on biological activity.

REFERENCES

(1) It is a pleasure to acknowledge the support of the Public Health Service under Grant AM-05183 from the National Institute of Arthritis and Metabolic Diseases for support of this work.

(2) M. Y. Milhailović, M. Stefanvić, Y. Lorenc and M. Gašic, Tetrahedron Letters, 1867 (1964).

(3) M. Tanabe and D. F. Crowe, J. Org. Chem. 28, 3197 (1963).

(4) E. J. Corey, R. B. Mitra and H. Uda, J. Am. Chem. Soc. 86, 485 (1964).

(5) F. Sondheimer, S. Burstein and R. Mechoulam, J. Am. Chem. Soc. 82, 3209 (1960).

(6) S. H. Eppstein, P. D. Meister, D. H. Peterson, H. C. Murray, H. M. Leigh Osborn, A. Weintraub, L. M. Reineke, and R. C. Meeks, J. Am. Chem. Soc. 80, 3382 (1958).

(7) Isolated along with the β isomer was a considerable portion of the conjugated isomer, 4,15-androstadiene-3,17-dione. The details will be discussed in a forthcoming full publication.

(8) In Ref. 5 only the isolation of the 14,15 β-oxide from the peracid treatment of 14-androstene-3β-ol-17-one-acetate is reported.

(9) Reduction of the conjugated double bond in 3-keto-Δ^4 compounds was observed initially by F. Sondheimer, M. Velasco, E. Batres and G. Rosenkranz, Chem. and Ind., 1482 (1954).

(10) A. F. St. Andre, H. B. MacPhillamy, J. A. Nelson, A. C. Shabica and C. R. Scholz, J. Am. Chem. Soc. 74, 5506 (1952) described the reduction of C_{17} keto compounds to the 17α-ol in 14β steroids.