Tetrahedron, 1960, Vol. 8, pp. 145 to 149. Pergamon Press Ltd. Printed in Northern Ireland

CIS–TRANS ISOMERISM OF STEROIDAL $\Delta^{17(20)}$ ENOL ACETATES

A. L. NUSSBAUM and F. E. CARLON
Natural Products Research Department, Schering Corporation, Bloomfield, New Jersey

(*Received* 18 *May* 1959)

Abstract—Structures are assigned to two pairs of geometrical isomers of steroidal $\Delta^{17(20)}$ enol acetates, based on their conversion by catalytic hydrogenation to products of known stereochemistry. The structures of 17,20-epoxides derived from one of these isomer pairs are discussed.

ENOLIZATION of a 20-ketosteroid may be directed toward one of two positions. Depending upon conditions, either an α-hydrogen at C-21 or that on the cyclopentane ring participates, so that derived enol esters have either a terminal[1] or an exocyclic double bond. In the latter case, *cis–trans* isomerism can be envisaged, and indeed it has been possible to isolate two individual isomeric $\Delta^{17(20)}$ enol acetates in some cases. Fieser and Huang-Minlon[2] separated two enol acetates (m.p. 144–146° and 171–172°) derived from 3β-acetoxy-Δ^5-pregnen-20-one (I,Δ^5), established the fact that they were geometrical isomers around a $\Delta^{17(20)}$ double bond, but did not assign absolute structures. Marshall *et al.*[3] had also obtained a corresponding isomer pair from 3β-acetoxy-5α-pregnan-20-one (I), m.p. 121·5–122·5 and 172·5–173·5. These authors arbitrarily assigned a *trans*-structure[4] to the higher melting compound.

It seemed desirable, however, to obtain direct evidence concerning this assignment, if only to clear up the interrelationship between the enol acetates in question and certain reaction products derived therefrom. Thus, the structure of an epoxide[5] obtained from the mixture of the *cis* and *trans* enol acetates of 3β-hydroxy-5α-pregnan-20-one was considered to be the 17α, 20β-oxido-20α-acetate.[6] Assignment was made on the basis of certain steric considerations from molecular models and because of the following facts: When the epoxide in question was subjected to reduction with lithium aluminum hydride followed by acetylation, 3β,17α,20α-trihydroxy-5α-pregnane 3,20-diacetate was obtained. By analogy with a state of affairs postulated in a similar situation in ring D,[7] it was considered that this reaction involved oxide opening *without inversion* at C-20.[8] Hence the epoxide structure was proposed.

It is now possible to arrive at an assignment concerning the geometrical isomerism of the pairs of $\Delta^{17,20}$ enol acetates: When the *lower* melting isomer of Fieser's

---

[1] R. B. Moffett and D. I. Weisblat, *J. Amer. Chem. Soc.* **76**, 2183 (1952), H. Vanderhaege, E. R. Katzenellenbogen, K. Dobriner and T. F. Gallagher, *Ibid.* **74**, 2810 (1952).

[2] L. F. Fieser and Huang-Minlon, *J. Amer. Chem. Soc.* **71**, 1840 (1949).

[3] C. W. Marshall, T. H. Kritchevsky, S. Liebermann, and T. F. Gallagher, *J. Amer. Chem. Soc.* **70**, 1837 (1948).

[4] C-21 bears a *trans* relationship to the quaternary C-13.

[5] T. H. Kritchevsky and T. F. Gallagher, *J. Amer. Chem. Soc.* **73**, 184 (1951).

[6] A. H. Soloway, W. J. Considine, D. K. Fukushima and T. F. Gallagher, *J. Amer. Chem. Soc.* **76**, 2941 (1954).

[7] N. S. Leeds, D. K. Fukushima and T. F. Gallagher, *J. Amer. Chem. Soc.* **76**, 2943 (1954).

[8] D. K. Fukushima and E. D. Meyer, *J. Org. Chem.* **23**, 174 (1958) exclude the intermediate formation of a C-20 ketone, since a control reduction of this same ketone gives a different yield of 20-ols than does the epoxy-acetate here discussed. However, the reaction path proposed by these authors postulates an intermediate trigonal C-20, and the sequence of events to be described below is not inconsistent with this picture. We should like to acknowledge an interesting discussion of this point with Prof. D. H. R. Barton.

$\Delta^{5,17(20)}$-pregnadiene-3β,20-diol diacetate[2] was catalytically hydrogenated to completion,[9] 5α-pregnane-3β, 20α-diol diacetate (B in Fig. 1, V in the chart) was isolated in fair yield. The same compound was obtained by an analogous hydrogenation of the *lower* melting enol acetate[3] of the Sloan–Kettering group. In both cases, therefore,

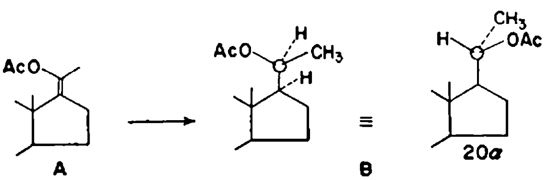

FIG. 1.

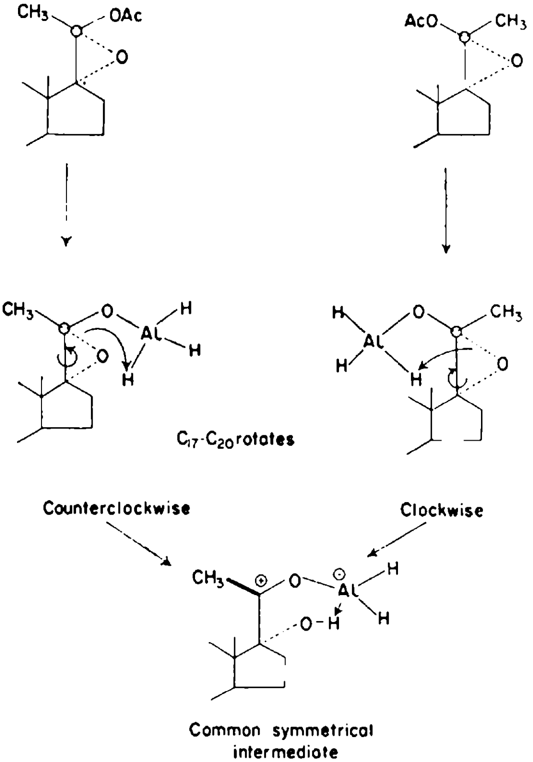

FIG. 2.

if the saturation of the enolic double bond is granted to proceed via *cis*-hydrogenation, the enol acetates in question must have the geometrical *trans* structure (A in Fig. 1, IIa in Chart 1) and, *per exclusionem*, their higher melting partners must be *cis* (IIb in the chart), accordingly.

Application of the procedures of Kritchevsky and Gallagher[5] to the individual enol acetates in the saturated series (derived from 1) resulted in the following interesting observations: When the lower melting enol acetate—now known to be the *trans*

---

[9] For hydrogenation of steroidal enol acetates, see R. Hirschmann, M. Brown and N. L. Wendler, *J. Amer. Chem. Soc.* 73, 5073 (1951); J. Fajkos, *Chem. Listy.* 52, 1320 (1958). We are indebted to Dr. Hans Reimann of these laboratories for suggesting this reaction.

isomer IIa—was subjected to the action of peracid, an oxido-acetate IIIa was obtained which differed from that obtained by the Sloan–Kettering investigators.[10] A like peroxidation of an enol acetate mixture rich in the higher melting *cis* (IIb) isomer furnished another oxido-acetate (IIIb) which appeared more similar to that recorded in the literature.[5] Reduction of the latter, followed by acetylation, furnished the known 3β,17α,20α-trihydroxy-5α-pregnane (IV) as its 3,20-diacetate, in agreement with the reported facts.[6,8] If the hydride reduction step does indeed involve an oxide opening without inversion at C-20,[6] an identical series of reactions performed on the former oxido-acetate (IIIa) possessing an epimeric situation at C-20 should produce the 3β,17α,20β-triol[11] as its 3,20-diacetate.

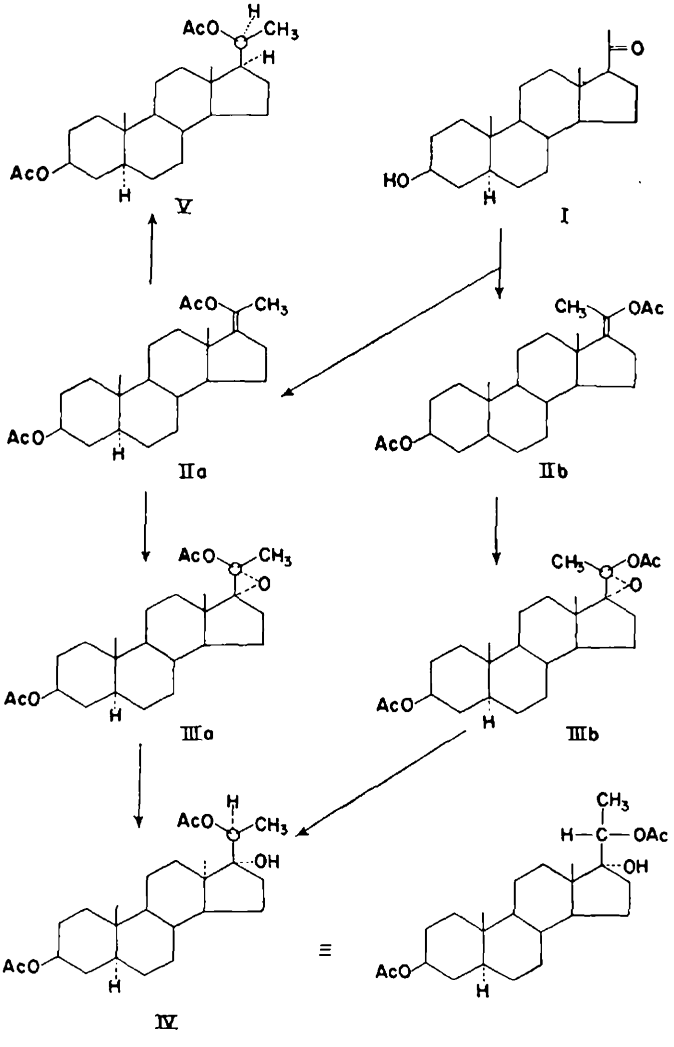

Fig. 3.

---

[10] We found optical rotation a more helpful criterion for characterization than melting point: the latter varies with the method of its measurement, perhaps due to thermal instability of the oxido-acetate structure.

[11] The possibility that the two oxido-acetates react via different mechanisms with lithium aluminum hydride is not considered likely.

When the experiment was carried out, however, the same 20α-ol IV was obtained as had been isolated from the C-20 isomer IIIb.

It appears thus that the course of the metal hydride reduction does not involve oxide opening without inversion at C-20, but rather that there exists a common symmetrical intermediate such as the one proposed by Fukushima and Meyer.[8] No matter from which isomeric oxido-acetate one starts, the formation of a coordination complex involving the oxygen on C-20 and the hydroxyl group at C-17 results in the existence of the common intermediate depicted in Fig. 2. The subsequent reduction occurs stereospecifically from the less hindered side opposite the angular methyl group at C-13. It follows that no argument concerning the structures of the oxido-acetates here discussed can be based on the hydride reduction. The latter follow, however, from the course of the catalytic hydrogenation.

It seems pertinent to discuss the infrared spectra of the isomeric oxido-acetates IIIa and IIIb. That of IIIb shows a single carbonyl absorption band for both its acetate groups at C-3 and at 5·76 C-20. Isomer IIIa, however, has two resolved bands, at 5·66 and 5·75. This is interpreted to be in agreement with the assigned structures since the acetyl group at C-20, being closer in space to the angular methyl group C-18 and the C-12 methylene might well be sterically strained and thus give rise to an absorption at higher frequency.

EXPERIMENTAL[*]

5α-Pregnane-3β, 20α-diol diacetate (V)

(a) *From* $\Delta^{5,17(20)}$ *pregnadiene-3β,20-diol diacetate* (trans). The lower melting isomer[8] from the enol acetylation reaction (IIa, Δ^5, 200 mg) was dissolved in ethyl acetate (10 ml) and hydrogenated at room temperature over palladium on charcoal (5%) 100 mg. After 4 hr, uptake had ceased (more than one equivalent of hydrogen had been taken up, suggesting some hydrogenolysis). The catalyst was removed by filtration and the filtrate concentrated to dryness. Chromatography over alumina gave a single eluate peak with benzene–petroleum ether. The central fractions (89 mg), having the highest melting points were combined and recrystallized from methanol to give 53·0 mg, m.p. 164–167°, $[\alpha]_D^{25}$ −0·9 ($CHCl_3$).[12]

(b) *From* $\Delta^{17(20)}$*-pregnene-3β,20-diol diacetate* (trans). The lower melting isomer from the enol acetylation reaction (IIa, 200 mg) was hydrogenated over 100 mg of platinum oxide and worked up as before. Product V (48 mg) was identical with that from A in melting point, rotation and infrared spectrum.

17α,20β-*Oxido-5α-pregnane-3β,20α-diol diacetate* (IIIa)

Lower melting enol acetate IIa[8] (200 mg) was dissolved in 15 ml ethereal perphthalic acid (39 mg/ml) and allowed to stand overnight at room temp. The solution was worked up by washing with iodide, thiosulfate, carbonate and water, drying and crystallization. From ether, 138 mg of m.p. 158–166° were obtained. Several recrystallizations from ether gave an analytical sample, m.p. 162–167°, $[\alpha]_D^{24}$ +14·8°, tetranitromethane test negative (starting material reacts to strong yellow color), λ^{Nujol} at 5·65 5·76, 8·00 and 8·16 μ. (λ^{CS_2} at 5·66 and 5·76 μ). (Found: C, 72·10; H, 9·15, $C_{25}H_{38}O_5$ requires: C, 71·74; H, 9·15%)

17α,20α-*Oxido-5α-pregnane-3β,20β-diol diacetate* (IIIb)

The more polar fractions of the chromatogram from the enol acetylation of I had wide melting ranges up into the 160°s. Although not pure, they were undoubtedly rich in the *cis*-isomer IIb, and

---

[*] All melting points were taken on a Kofler Block, except where indicated, and are uncorrected. Rotations were carried out in a 1-dm. tube at a concentration of ca. 1% in the solvent specified. Analyses and spectral data were obtained by the Microanalytical and Physical Chemistry Department of the Schering Corporation.

[12] R. B. Turner and D. M. Voitle report m.p. 165–167°, $[\alpha]_D$ ±0.

1·9 g of combined eluates were treated with perphthalic acid and worked up as before. From ether, 970 mg having m.p. 170–186° were obtained. Several recrystallizations from ether gave an analytical sample, m.p. 174–187° (a capillary m.p. was 174–176°), $[\alpha]_D^{25}$ −44·2° ($CHCl_3$)[18] λ^{Nujol} at 5·74–5·76 and 8·08 μ (λ^{CS_2} at 5·76 μ).

(Found C, 71·92; H, 9·00. $C_{25}H_{38}O_6$ requires: C, 71·74; H, 9·15%).

5α-*Pregnane*-3β,17α,20α-*triol* 3,20-*diacetate* (IV)

Reduction of oxido-acetates IIIa and IIIb with lithium aluminum hydride and subsequent reacetylation were carried out as described by Soloway *et al.*[6]

Trans oxido-acetate IIIa (125 mg) gave a first crop of 57 mg, m.p. 245–247°, $[\alpha]_D^{23}$ −32, and a second crop of 24 mg, m.p. 241–246°. The remaining mother liquors were still crystalline and, upon paper chromatography in the heptane–methyl cellosolve system, were shown to consist of ca. 60% of the same product as the first two crops, plus ca. 30% of a slightly more polar substance—presumably the 20-epimer—plus some trace impurities.

Cis oxido-acetate IIIb (50 mg) gave 18·1 mg of the same material, m.p. 245–247^{c}, and a second crop of 5·4 mg, m.p. 240–245°. The remaining mother liquors were shown to be largely the same material by paper chromatography; only a very small amount was attributable to the 20-epimer.

---

[18] The Sloan–Kettering product has m.p. 173–176°, upon recrystallization m.p. 190–193°, $[\alpha]_D^{28}$ −37° ($CHCl_3$).