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D-HOMOSTEROIDS

BOAT CONFORMATION OF THE D-RING[1]

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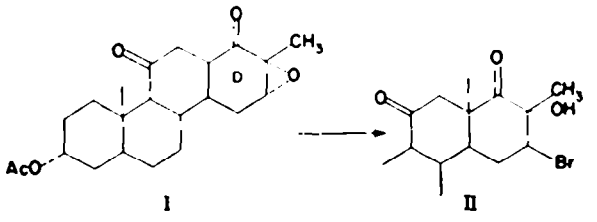
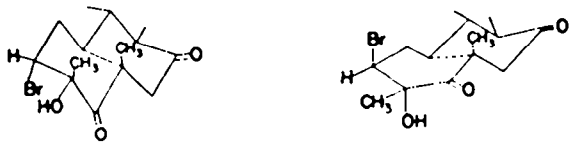
Abstract –Chemical evidence is cited in support of the boat conformation of ring-D in certain D-homosteroids. The interconversion of ketolic isomers ostensibly by methyl migration is presented.

THE observation was made several years ago that the D-homosteroid oxide (I) undergoes scission with hydrogen bromide in acetic acid to give the bromohydrin II.[2] In the latter compound the functionality, Br and OH, becomes equatorially disposed in the chair conformation of ring-D (IIa)– a consequence in contradiction to the rule of axial opening of oxides.[3] If, on the other hand, the conformation of the oxide (I) is based on a distorted boat form of ring-D (cf. Ref. 4) then the bromohydrin correspondingly will have as its immediate structural consequence the boat form IIb in conformity with the diaxial opening rule.[3] (See later discussion.)



I II



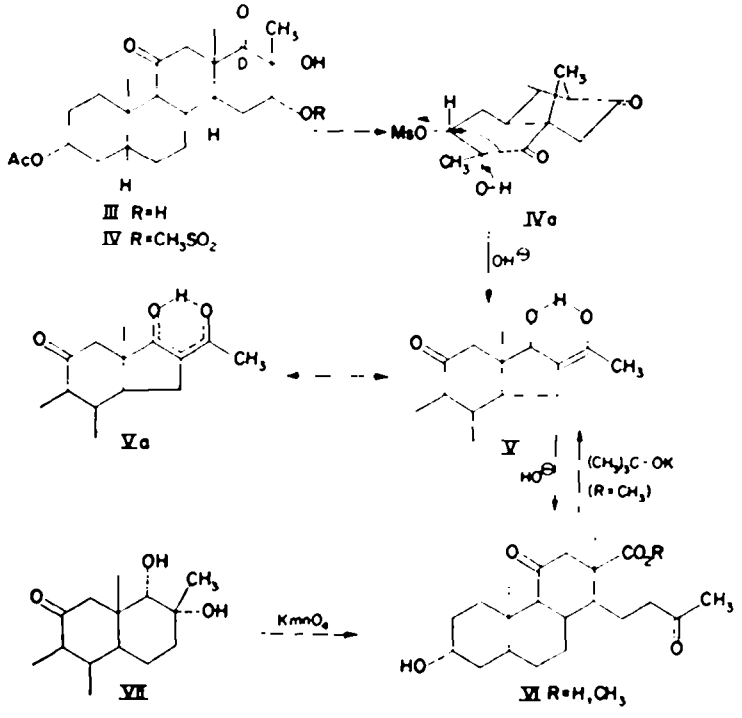
IIa IIb

Recently, Barton *et al.*[4] were able to isolate conformationally isomeric bromoketones in the triterpenoid field wherein one isomer was found to possess the A-ring in the boat form. A further conformational anomaly was also found in the reactions of the 2β,3β-epoxides of lanost-8-ene and lanostane. In this connection these authors made reference to the anomalous opening of the oxide (I) and suggested that this anomaly might be conformational in nature. As a result of studies in a related series

[1] For preliminary reports of this work see N. L. Wendler, *Chem. & Ind.* 1662 (1958); *Ibid.* 20 (1959).
[2a] N. L. Wendler and D. Taub, *Chem. & Ind.* 505 (1955); [b] N. L. Wendler, D. Taub, S. Dobriner and D. K. Fukushima, *J. Amer. Chem. Soc.* **78**, 5027 (1956).
[3] A. Fürst and P. L. Plattner, *Helv. Chim. Acta* **32**, 275 (1949); A. Fürst and R. Scotoni, *Ibid.* **36**, 1410 (1953).
[4] D. H. R. Barton, D. A. Lewis and J. F. McGhie, *J. Chem. Soc.* 2907 (1957).

we arrived at experimental findings which indicate the probability of the boat conformation of ring-D in certain D-homosteroids substituted at C-17.

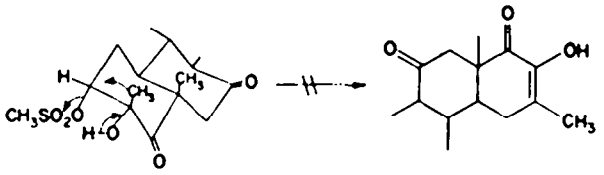
The D-ring dihydroxyketone (III), of established structure,[5] was converted with methanesulfonyl chloride in pyridine at 0–5° to its 16-mesylate derivative (IV).[6] The latter on warming with 5 per cent methanolic potassium hydroxide was transformed with attending ring contraction to the β-diketone (V), m.p. 170–172°, $\lambda_{max}^{CH_2OH}$ 282 mμ (ε = 8300). The infrared spectrum of V possessed bands at 5·75 μ (5-ring C=O), 5·84 μ (6-ring C=O) and at 5·99 and 6·18 μ (conj C=O). Strong hydrogen bonding in the infrared spectrum of V together with its isolation as an apparently single isomeric species, strongly suggests the geometry indicated by formula V; a completely symmetrical electron distribution structure is represented by Va. Proof of structure of the β-diketone (V) was provided by its quantitative cleavage with 20 per cent methanolic potassium hydroxide to the acid VI from which it could be re-synthesized by Dieckmann condensation of its methyl ester. The structure of the acid VI in turn was secured by comparison with an authentic specimen obtained by permanganate oxidation of the known diol VII.[6]



If the D-homo derivative (IV) possesses the chair conformation of the D-ring as in VIII then the C-17 methyl group, which is disposed *trans*-antiparallel with respect to the departing mesylate function, would be expected to migrate to give the known diosphenol (IX).[7] Since, however, ring contraction takes place instead to give the

[5a] N. L. Wendler and D. Taub, *Chem. & Ind.* 1237 (1957); [5b] *J. Amer. Chem. Soc.* In press.
[6] N. L. Wendler and D. Taub, *J. Org. Chem.* 23, 953 (1958).
[7] N. L. Wendler and D. Taub, *Chem. & Ind.* 415 (1958); N. L. Wendler, D. Taub and R. P. Graber, *Tetrahedron* 7, 173 (1959).

β-diketone (V), it is suggested that the D-ring possesses the boat-conformation (IVa) in order to accommodate this change in conformity with the geometrical prerequisities of *trans*-antiparallelism of the moving and departing groups. In this event the oppositional forces, arising from non-bonded interactions between the C-18 methyl group and the axial substituent at C-17 present in the chair structure could be responsible for conformational inversion.

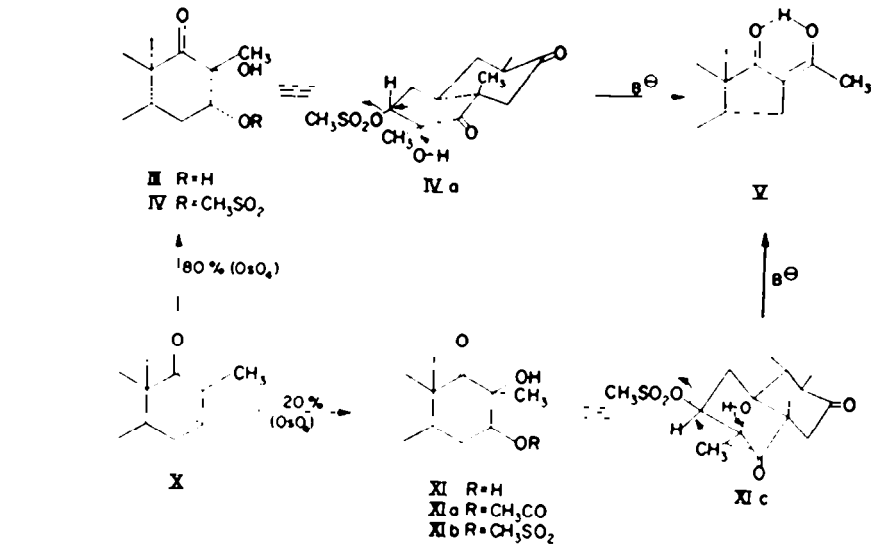


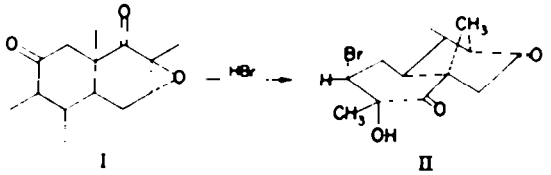
VIII IX

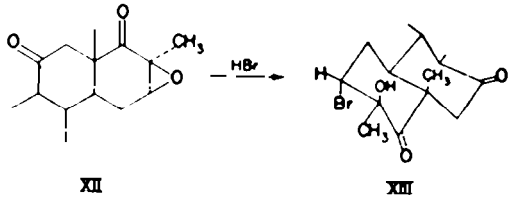
The hydroxylation of the $\Delta^{1,3}$-ketone (X) with osmium tetroxide has been described previously as giving the 16α,17α-diolone (III) as major product.[6] Chromatography of the mother liquors from the osmylation reaction revealed the presence of 20 per cent of the 16β,17β-diolone (XI). The latter as its 16-mesylate derivative XIb undergoes rearrangement with alkali to give the same β-diketone (V) as that obtained from its isomer IV. Consequently, since both isomers (IV and XIb) rearrange to the same product (V) they should have different conformations. These findings taken in consideration with the theoretical assumptions discussed above provide mutual support for the boat-conformation of the α-diolone (III) and the chair conformation of the β-diolone (XI). The foregoing is also in agreement with and, in fact, provides the interpretative basis for the directional course of opening of the α- and β-oxides I and XII.[2] The role of electronic factors *per se* in controlling the directional course of oxide scission in the case of I were considered earlier;[2b] these would now appear to be of minor significance in view of Shaw and Stevenson's demonstrated conversion of 4,5β-oxido coprostane-3-one to 4-bromo cholestenone.[8] Rather the stereo-electronic factors implicit in the diaxial opening rule would seem to be as determining here as in the established cases of simpler oxido systems. This signifies that the transition state to the formation of II from I resembles the product boat conformation. It further appears suggested that the non-bonded interaction of 1,3-axial methyl vs. methyl is greater than the corresponding 1,3-axial methyl vs. hydroxyl; further, the former in contrast to the latter appears sufficiently great by the foregoing considerations to cause conformational inversion, whereby the boat conformation provides the more stable species.

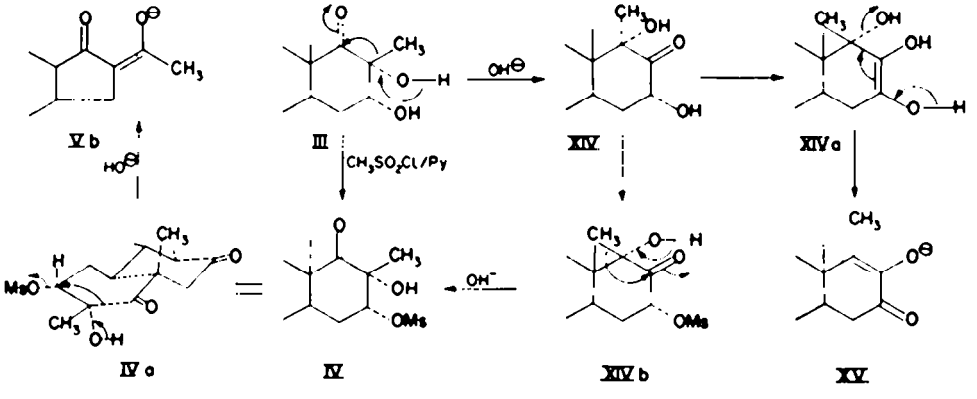
In an earlier account[6] the fate of the isomeric D-homo diolones III and XIV with alkali was discussed. The conversion of the diolone III to the diosphenol XV is considered to proceed by way of a C-17 → C-17a methyl migration to form XIV as a transitory intermediate wherein the latter can undergo β-elimination via its enediol (XIVa) to give XV. In fact, not only does the isomeric diolone XIV give the diosphenol XV on treatment with alkali but its 16-mesylate derivative (XIVb) in turn also is converted to the β-diketone (V). The latter transformation must, presumably, take

[8] J. I. Shaw and R. Stevenson, *J. Chem. Soc.* 3549 (1955). cf. Ref. 4; also W. Bergmann and M. B. Meyers, *Liebigs Ann.* **620**, 46 (1959).


III R=H
IV R=CH3SO2
IV a
V
80 % (OsO4)
20 %
(OsO4)
X
XI R=H
XI a R=CH3CO
XI b R=CH3SO2
XI c


HBr
I
II


HBr
XII
XIII


V b
III
CH3SO2Cl/Py
XIV
XIV a
IV a
IV
XIV b
XV

place by methyl migration in the sense opposite to that leading to diosphenol formation from IV, namely C-17a → C-17 to give IV as a transitory intermediate, which in turn undergoes ring contraction to the β-diketone V. The latter sequence is again uniquely defined by the structure and stereochemistry of the diolone (XIV). The apparent interconversion of the isomeric ketols via methyl migration may be considered to derive its promotional energy from the eventual collapse of each system to its respective stable enolate namely, Vb and XV.

EXPERIMENTAL

3α-Hydroxy-16-acetyl-5β-androstane-11,17-dione (V)

(a) *Alkaline rearrangement of 3α-acetoxy-16α-methanesulfonyloxy-17α-hydroxy-17β-methyl-D-homo-5β-androstane-11,17a-dione* (IV). A solution of 4 g IV[5] in 40 cc methanol was treated under nitrogen with a solution of 4 g potassium hydroxide[6] in 4 cc water and refluxed for 1 hr. The reaction mixture was cooled, acidified with 20 cc of 50% HCl aq and the methanol removed *in vacuo*. The residue was extracted with ethyl acetate and the ethyl acetate extract washed 3 times with dil $KHCO_3$ aq. Acidification of the bicarbonate extracts precipitated acid VI. The neutral ethyl acetate layer was evaporated to dryness and the residue crystallized slowly from ether to deposit the β-diketone (V) 1st crop 1 g m.p. 165–170°, recrystallization from ether m.p. 170–172° λ_{max}^{EtOH} 282 mμ ε 8300 λ_{max}^{Nuj} 5.75 μ (5-ring C=O), 5.84 μ (6-ring C=O), 5.99 μ and 6.18 μ (conj C=O). (Found: C, 72.83; H, 8.66. Calc. for $C_{21}H_{30}O_4$: C, 72.83; H, 8.67%).

Cleavage of the β-diketone (V) *to the acid* (VI). A solution of 500 mg β-diketone (V) in 15 cc methanol was treated with 5 g KOH in 5 cc water and refluxed in a nitrogen atmosphere for 18 hr. The reaction product was cooled, acidified with dil HCl aq and the methanol removed *in vacuo*. The residue was taken up in ethyl acetate and the ethyl acetate extracted thoroughly with $KHCO_3$ solution. Acidification of the potassium bicarbonate extract precipitated the acid VI. The latter was extracted with ethyl acetate, the solvent evaporated and the residue crystallized from ether m.p. 145–148° (cap.). This acid retained solvent of crystallization tenaciously and the latter affected the m.p. of the acid variously. For analysis a sample was pigged at 130° for 2 hr (wt. loss 5.3%). (Found: C, 69.11; H, 8.79. Calc. for $C_{21}H_{32}O_5$: C, 69.23; H, 8.79%).

The infrared spectrum of this acid was identical with an authentic sample prepared as in part B.

(b) *Preparation of* VI *by oxidative cleavage of 3α,17α,17aα-trihydroxy-17β-methyl D-homo 5β-androstane-11-one* (VII). A solution of 600 mg VII[4] in 50 cc acetone was treated with 1 g potassium permanganate and stirred for 3 hr at room temp. At the end of this period the acetone was removed in a stream of nitrogen and replaced with an equal volume of water. The reaction mixture was acidified with H_2SO_4, treated with sodium bisulfite and extracted with ether. The ether layer was washed thoroughly with $KHCO_3$ solution and the extract acidified. The precipitated acid was taken up in ethyl acetate concentrated and the residue crystallized from ether. The acid VI thus obtained was identical in m.p., mixed m.p. and infrared spectrum with the acid obtained in part A.

Resynthesis of the β-diketone (V) *from the cleavage acid* (VI). A 100 mgs ample of the acid VI was methylated in ether solution with diazomethane. The crude ester in 10 cc benzene was treated with a 1.5 cc aliquot from a solution of 1 g potassium in 30 cc t-butanol, and the reaction mixture refluxed for 2 hr. The reaction was worked up as previously described and afforded the β-diketone (V) from ether, m.p. and mixed m.p. with a sample obtained from alkaline rearrangement of IV 169–172°; the infrared spectra of the two samples were identical.

3α-Acetoxy-16β,17β-dihydroxy-17α-methyl D-homo-5β-androstane-11,17a-dione (XI)

Osmylation of the $\Delta^{16,17}$*-ketone* (X). A solution of 2 g of the $\Delta^{16,17}$-ketone (X)[3] was treated with 2.5 g osmium tetroxide in 15 cc dioxane and allowed to stand 48 hr at room temp. At the end of this period the osmate ester was decomposed with hydrogen sulfide and the reaction mixture filtered through celite. The filtrate was concentrated and chromatographed on 50 g neutral alumina employing mixtures of chloroform and ethylacetate for elution. Eluates consisting of chloroform afforded 1·1 g

[6] In practice, potassium t-butoxide (see later examples) is superior to potassium hydroxide for the rearrangement to the β diketone (V) since the latter is not further cleaved to the acid VI with t-butoxide as it is with hydroxide.

(79%) of the known α-diolone[4] m.p. 174–176°. Eluates consisting of 10–50% ethylacetate in chloroform gave 0·3 g (21%) of the β-diolone (XI) m.p. 180–182° phase change 205–207°. (Found: C, 68·25; H, 8·28. Calc. for $C_{23}H_{34}O_6$: C, 67·98; H, 8·37%).

Acetylation of XI at room temp with acetic anhydride in pyridine gave the 3,16 *diacetate derivative* XIa m.p. 238–243° λ_{max}^{Nj} 2·84 μ (OH), 5·73 and 8·1 μ (OAc) and 5·84 μ (11 C=O). (Found: C, 66·79; H, 8·25. Calc. for $C_{23}H_{30}O_7$: C, 66·96; H, 8·04%).

Rearrangement of the β-diolone XI *as its* 16-*mesylate* (XIb) *to the β-diketone* (V). A 400 mg sample of the β-diolone XI was converted to its 16-mesylate derivative XIb with 0·25 cc methanesulfonyl chloride in 2·5 cc pyridine solution. The latter was obtained amorphous and could not be induced to crystallize, λ_{max}^{Nj} 2·8–2·9 μ (OH), 5·78 + 8·0 μ (OAc), 5·84 μ (11 C=O) and 7·3 & 8·5 μ (CH_3SO_3O).

A solution of 500 mg of the amorphous mesylate derivative XIb in 10 cc t-butanol was refluxed for 2 hr under nitrogen with potassium t-butoxide prepared from 1 g potassium metal and 20 cc t-butanol. The reaction mixture was worked up as previously described by acidification, removal of the solvent *in vacuo* and extraction of the residue into ethyl acetate. The ethyl acetate extract was washed free of all acid by $KHCO_3$ solution. Evaporation of the ethylacetate and crystallization from ether afforded the β-diketone (V), m.p. 169–172°. Mixed m.p. with authentic V not depressed. The infrared spectrum of V thus obtained was identical with previous preparations.

Rearrangement of the diolone (XIV) *as its mesylate* (XIVb) *to the β-diketone* (V). A 500 mg sample of the diolone XIV[1,3] was converted to its 16-mesylate derivative (XIVb) with 0·5 cc methanesulfonyl chloride in 5 cc pyridine. This derivative was obtained non-crystalline λ_{max}^{Nj} 2·76–2·95 μ (OH), 5·79 · 5·84 μ ; 7·98 μ (OAc + 11 C=O), 7·31 + 8·49 μ (CH_3SO_3O).

The above mesylate derivative was refluxed for 2 hr with 30 cc 1 M potassium t-butoxide in t-butanol solution. The reaction product was worked up in the same manner described above. The product crystallized from ether m.p. 165 170°, mixed m.p. with authentic V not depressed. The infrared spectrum of this sample of V was identical with previous preparations.