Tetrahedron Letters No.26, pp. 3063-3067, 1966. Pergamon Press Ltd.
Printed in Great Britain.

A NEW ROUTE TO RING C-BENZENOID STEROIDS

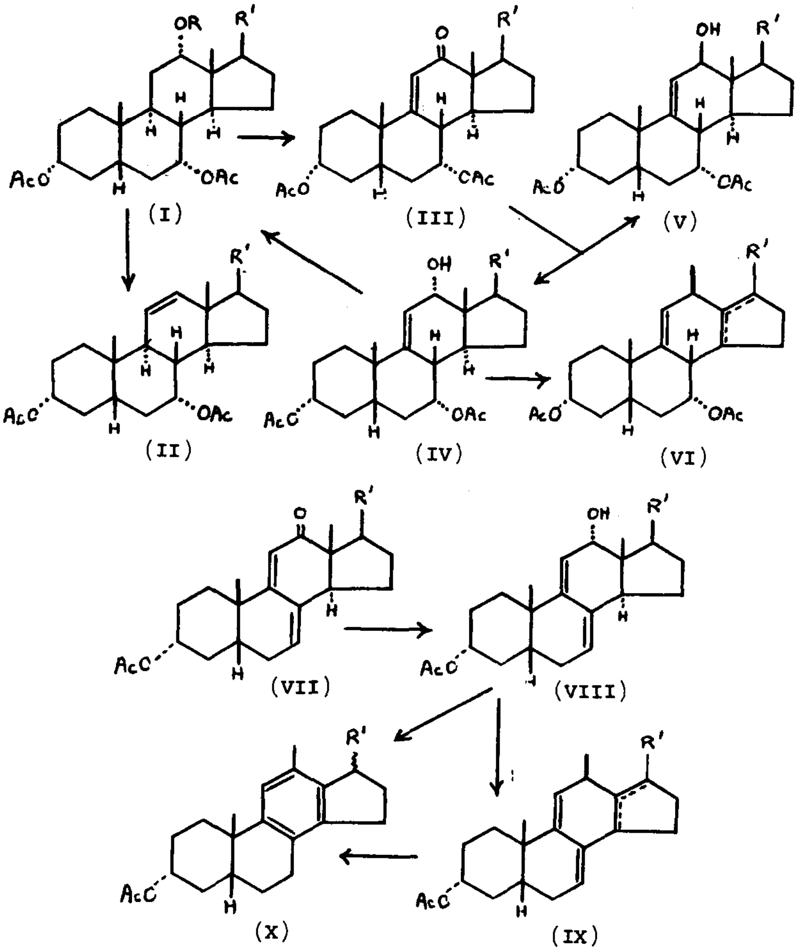
Daniel Levy and Robert Stevenson
Department of Chemistry, Brandeis University,
Waltham, Massachusetts.

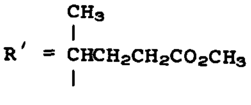
(Received 2 April 1966)

A synthetic pathway to ring C-benzenoid allo (A/B trans) steroids has been described[1]. We have found that this procedure is inapplicable to normal (A/B cis) steroids, since the required intermediate 7,11-dibromo-8-ethylene, produced by the action of bromine on Δ^7-allo steroids is not obtained on similar treatment of Δ^7-normal steroids. We have consequently sought an alternative route, applicable to the latter case; for this purpose, we have devised a procedure for effecting a Wagner-Meerwein shift of the blocking angular C-18 methyl group from C-13 to C-12.

The solvolysis of sulphonate esters of the epimeric C-12 alcohols has previously been extensively investigated with reference to conformation and stereoelectronic principles of elimination. Thus the 12β-equatorial epimers undergo the C-nor-D-homo rearrangement[2] and the 12α-axial epimers undergo simple elimination to yield the corresponding Δ^{11}-ethylene[3]. Of pertinence to this study, dehydration of methyl 3α,7α-diacetoxy-12α-hydroxycholanate (I,R=H)[4] with phosphorus oxychloride in pyridine or treatment of the derived mesylate (I,R=Ms, $C_{30}H_{48}O_8S$, m.p. 88-90°, $[\alpha]_D$ + 53°) with potassium t-butoxide gave the known methyl 3α,7α-diacetoxychol-11-enate (II)[5]. We considered that in the absence of a readily removed proton at C-11, the elimination of the 12α-axial group might instead occur with a 1,2-shift of the trans antiparallel C-18 angular methyl group. To test this hypothesis, methyl 3α,7α-diacetoxy-12α-hydroxychol-9(11)-enate(IV) was prepared. Reduction of methyl 3α,7α-diacetoxy-12-ketochol-9(11)-enate (III)[4] with sodium borohydride in aqueous methanol gave a mixture of two alcohols (in a 3,2 ratio) separated by thin layer chromatography. Consideration of order of elution on chromatography, molecular rotation differences and nuclear magnetic resonance spectra indicated that the major product was the quasi-axial isomer, methyl 3α,7α-diacetoxy-12α-hydroxychol-9(11)-enate(IV,$C_{29}H_{44}O_7$, m.p. 139-140°, $[\alpha]_D$ + 71°), and the minor product the 12β-epimer(V,$C_{29}H_{44}O_7$, m.p. 169-171°, $[\alpha]_D$ + 24°). The configurational assignment of IV was confirmed by catalytic hydrogenation to give I(R=H). Dehydration of IV by phosphorus oxychloride in pyridine or on attempted methanesulphonate formation yielded a <u>non-conjugated</u> diene which we formulate as methyl 3α,7α-diacetoxy-12β-methyl-18-norchola-9(11),13[or 13(17)]-dienate(VI, $C_{29}H_{42}O_6$, m.p. 163-165°, $[\alpha]_D$ + 80°, λ210 mμ(ε7200)). This assignment is supported by the nuclear magnetic resonance spectrum which indicates the absence of a vinyl methyl group and the presence of one vinyl proton (τ4.25, H-11), a tertiary methyl group (τ8.93, singlet, C-19) and a secondary methyl group (τ8.76, doublet, J=7c.p.s., C-18).

With this encouraging result, we turned attention to





$$R' = \overset{\displaystyle CH_3}{\underset{|}{\overset{|}{C}}}HCH_2CH_2CO_2CH_3$$

the corresponding dienol(VIII). On reduction of the dienone (VII)[4] with sodium borohydride, a single alcohol was isolated in 85% yield and is assigned the desired structure, methyl 3α-acetoxy-12α-hydroxychola-7,9(11)-dienate(VIII,$C_{27}H_{40}O_5$, m.p. 125-127°, $[\alpha]_D$ + 169°) since it yielded methyl 3α-acetoxy-12α-hydroxycholanate[6] on platinum catalysed hydrogenation in acetic acid solution containing hydrogen chloride. Dehydration of VIII with phosphorus oxychloride in collidine[7] gave in excellent yield a triene for which we propose the structure methyl 3α-acetoxy-12β-methyl-18-norchola-7,9(11), 13[or 13(17)]-trienate(IX,$C_{27}H_{38}O_4$, m.p. 121-123°,$[\alpha]_D$ + 140°). The ultraviolet absorption spectrum, λ225 sh. (10,200), 231(12,200), 238 sh. (10,200) and 284 (broad) mμ (4,400) indicated that the triene was not linearly conjugated[8], and the nuclear magnetic resonance spectrum indicated the presence of two vinyl proton multiplets (at τ4.17 and 4.57), a tertiary methyl group (τ9.02, singlet) and a secondary methyl group (τ9.12, doublet J=7.5 c.p.s.). Isomerization of this stable triene with formic acid in benzene yielded the benzenoid steroid, methyl 3α-acetoxy-12-methyl-18-norchola-8,11,13-trienate(X,$C_{27}H_{38}O_4$, non-crystalline, $[\alpha]_D$ + 78° with $\lambda^{\text{iso-octane}}$ 220(12,600),261(300),268(325) and 275 sh. mμ (280) in excellent agreement with the corresponding benzenoid chromophore reported in the ergosterol series[1]. In addition, the infrared spectrum (in $CHCl_3$) showed absorption at 869 cm^{-1}, typical of a pentasubstituted benzene, and the nuclear magnetic resonance spectrum showed the presence of one aromatic proton (τ3.14) and a methyl group attached to a benzene ring(τ7.77).

The benzenoid steroid(X) was also obtained directly from the dienol(VIII) in over 50% yield by dehydration with phosphorus pentoxide in benzene solution. Satisfactory analyses have been obtained for all new compounds[9] (indicated by molecular formulae). The structure recently proposed[10] for the mould metabolite, viridin, indicates that it is the first naturally occurring ring C-benzenoid steroid.

The award of a research grant (AM-03439) from the National Institute of Arthritis and Metabolic Diseases, Public Health Service is gratefully acknowledged.

REFERENCES

1 C. F. Hammer, D. S. Savage, J. B. Thomson and R. Stevenson, Tetrahedron, 20, 929 (1964).

2 Reviewed by N. L. Wendler in "Molecular Rearrangements" (Ed., de Mayo) Interscience, New York, 1964. p. 1094.

3 F. C. Chang and N. F. Wood, Steroids, 4, 55 (1964) provides recent examples.

4 L. F. Fieser, S. Rajagopalan, E. Wilson and M. Tishler, J. Amer. Chem. Soc., 73, 4133 (1951).

5 F. Nakada, Steroids, 2, 45 (1963).

6 T. F. Gallagher, W. P. Long, J. Biol. Chem., 162, 521 (1946).

7 With pyridine, the reaction of VIII with phosphorus oxychloride or methanesulfonyl chloride took a different course.

8 The ultraviolet absorption spectrum is rather unusual. The three principal maxima (λ225, 231 and 238 mμ) suggest a transoid heteroannular diene system, although at lower wavelength and intensity than customarily found for $\Delta^{7,9,(11)}$-diene systems: This may be a consequence of steric crowding (interaction of 12β-methyl group and C-20 substituents) in the $\Delta^{7,9(11),13(17)}$-formulation.

9 Specific rotations were determined in $CHCl_3$, nuclear magnetic resonance spectra in $CDCl_3$ and ultraviolet spectra in 95% C_2H_5OH solution unless otherwise indicated.

10 J. F. Grove, P. McCloskey and J. S. Moffatt, Chem. Comm. 343 (1965).