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A SYNTHETIC APPROACH TO THE 9(10→19)*ABEO*-PREGNANE SYSTEM, INVOLVING CARBOCYCLIC RING CLEAVAGE DURING WOLFF-KISHNER REDUCTION

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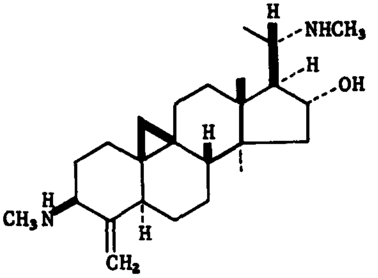
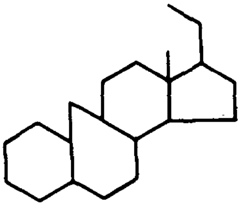
In the course of studies on the synthesis of 9β,19-cyclosteroid analogs of *Buxus* alkaloids such as cyclobuxine (I) (1), an unusual Kishner reduction which involves cleavage



I



II

of a carbocyclic ring has been observed. The reaction constitutes a synthetic approach to derivatives of the 9(10→19)*abeo*-pregnane[a] ring system (II), which has recently been shown to occur in buxenine-G (2,3) and related alkaloids (3).

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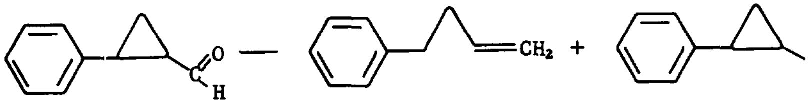
[a] A discussion of "*abeo*" nomenclature has appeared in Appendix B, *Tentative* Recommendations of Steroid Nomenclature Subcommittee, Information Bulletin No. 11, IUPAC (reprint available from Dr. R. Morf, Hoffmann-La Roche & Co., Basle 2, Switzerland).

When 9β,19-cyclo-5α-pregnane-3,11,20-trione-3,20-diethylene ketal (III) (4) was subjected to the Huang-Minlon modification of the Wolff-Kishner reduction, the expected 11-deoxo-compound was not obtained. Two crystalline products, A, $C_{25}H_{38}O_4$, m.p. 109-110°; $[\alpha]_D^{29}$ -12° (c 0.5, chf.), 20% yield, and B, $C_{25}H_{38}O_4$, m.p. 124-126°; $[\alpha]_D^{27}$ -46° (c 0.59, chf.), 10% yield, were obtained after adsorption chromatography on neutral Woelm grade II alumina, followed by preparative thick layer chromatographic separation. The infrared spectra of A and B each showed a strong band at 11.60μ and no carbonyl absorption. The n.m.r. spectra[a] of A and B indicated that each had two tertiary C-methyl groups (9.27 τ, 3H, s; 8.81 τ, 3H, s), eight ethylene ketal protons (6.15 τ, 8H, s), one vinyl proton (4.84 τ, 1H, m), and no cyclopropane methylene protons. Compounds A and B each decolorized bromine solution, gave a positive test with tetranitromethane, and consumed one mole of hydrogen (Pt, ethanol) accompanied by the disappearance of the vinyl proton signal in the n.m.r. spectrum.

It has been reported that when 2-phenylcyclopropanecarboxaldehyde (IV) is subjected to the Wolff-Kishner reaction, 4-phenylbutene-1 (V) is one of two products obtained (5). This



IV V VI

type of elimination reaction was first observed by Kishner in his work on 2,6-dimethyl-2-hydroxy-3-octanone (6), and similar reactions of α-amino ketones, α-substituted pinacolones, α-epoxy- and α-halo ketones have also been reported (7-10). Analogy with the precedents and the chemical and spectral characteristics of A and B led to the conclusion that ring B enlargement had taken place during Wolff-Kishner reduction of

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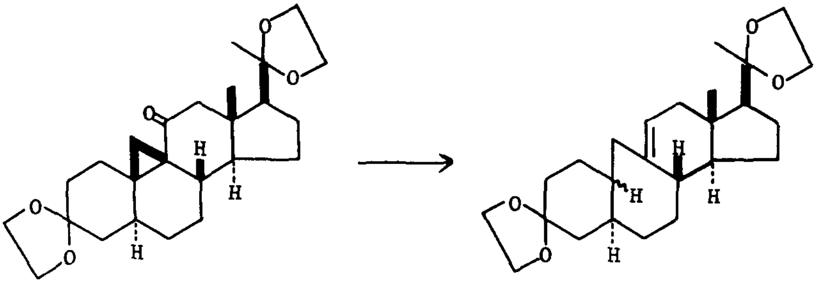
[a] N.m.r. spectra were measured in deuterochloroform solution on a Varian A-60 spectrometer with TMS as the internal standard.

III, affording C-10 epimers which could be represented as VIIa, and VIIb.

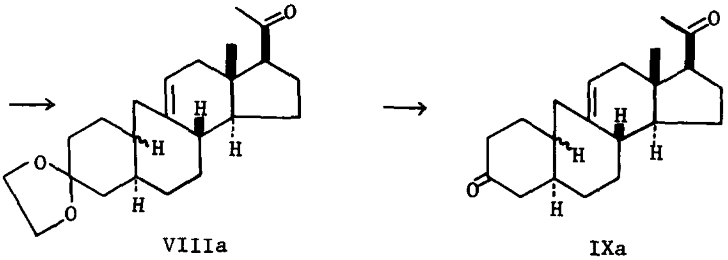
The configurations at C-10 in VIIa and VIIb were determined by optical rotatory dispersion studies of appropriate derivatives. Selective ketal hydrolysis of VIIa, with boron



III

VIIa and VIIb

VIIa $\longrightarrow$



VIIIa

IXa

VIIb $\longrightarrow$ VIIIb $\longrightarrow$ IXb

trifluoride etherate, yielded VIIIa, $C_{23}H_{34}O_3$, m.p. 134-136°; $[\alpha]_D^{30}$ + 36° (c 0.7, chf.); $\lambda_{max.}^{chf.}$ 5.90μ. The n.m.r. spectrum showed the presence of one tertiary C-methyl group (9.37 τ, 3H, s), the expected downfield shift of the C-21 methyl group (7.98 τ, 3H, s), four ketal protons (6.13 τ, 4H, s), and one vinyl proton (4.86 τ, 1H, m). Hydrolysis of VIIIa in acetone-p-toluenesulfonic acid mixture at room temperature produced IXa, m.p. 169-171°, $\lambda^{KBr}_{max.}$ 5.90μ, 80% yield. Boron trifluoride hydrolysis of VIIb yielded VIIIb, $C_{23}H_{34}O_3$, m.p. 90-92°; $[\alpha]_D^{29}$ + 35° (c 0.1, chf.); $\lambda^{chf.}_{max.}$ 5.90μ. The n.m.r. spectrum indicated the presence of one tertiary C-methyl group (9.37 τ, 3H, s), one α-carbonyl methyl (7.87 τ, 3H, s), four ketal protons (6.0, 4H, s), and one vinyl proton (4.65 τ, 1H, m). p-Toluenesulfonic acid hydrolysis of VIIIb gave IXb, m.p. 159-161°, $\lambda^{KBr}_{max.}$ 5.90μ, 80% yield.

The optical rotatory dispersion curves of VIIIa and VIIIb were positive (see FIG. 1), as expected (11). p-Toluenesulfonic acid hydrolysis of VIIIa caused no change in amplitude of rotation, indicating that the O.R.D. curve for the C-3 carbonyl group in IXa is essentially plain. Acid treatment of VIIIb, on the other hand, resulted in a two-fold increase in amplitude, indicating a strong positive Cotton effect for the C-3 carbonyl group in IXb. It has been shown that the O.R.D. curves of 19-nor-5α,10α-androstan-17α-ethyl-17-ol-3-one (X) (12), and 19-nor-

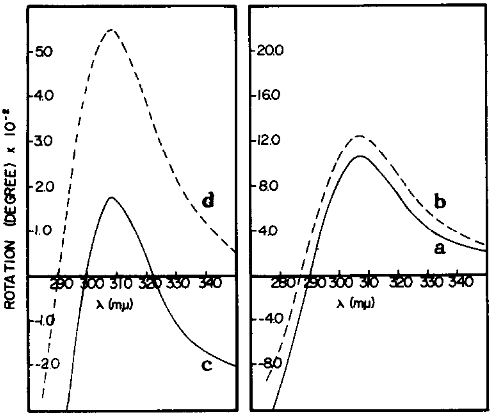
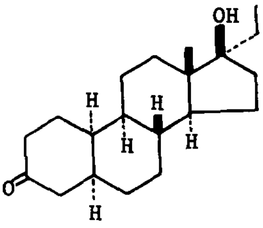
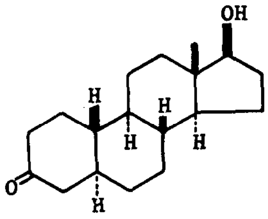
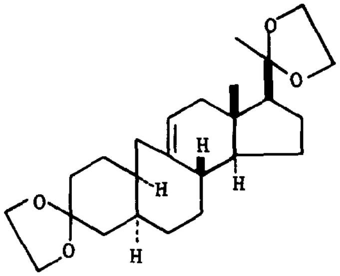


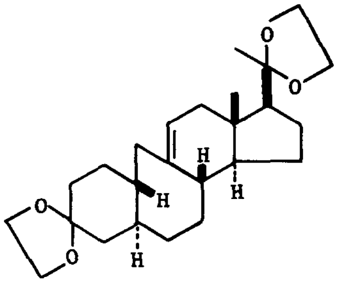
FIG. 1 - O.R.D. curves for: (a) VIIIa, 2.1 mg. in 5 ml. methanol; (b) product of acid treatment of (a); (c) VIIIb, 1.2 mg. in 5 ml. methanol; (d) product of acid treatment of (c).

5α-androstan-17β-ol-3-one (XI) (13) exhibit plain and strong single positive Cotton effects, respectively. By analogy, isomer VIIa was assigned structure XII, 9(10→ 19)*abeo*-$\Delta^{9(11)}$-5α,10α-pregnene-3,20-dione-3,20-diethylene ketal, and isomer VIIb was assigned structure XIII, 9(10→ 19)*abeo*-$\Delta^{9(11)}$-5α,10β-pregnene-3,20-dione-3,20-diethylene ketal.

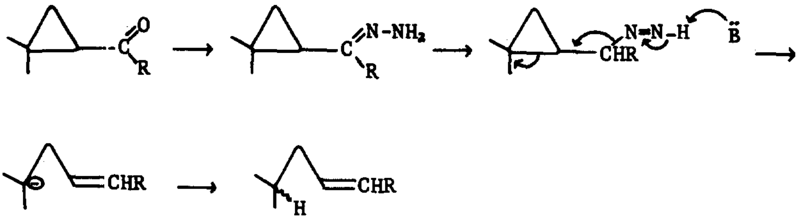

X


XI


XII


XIII

Wolff-Kishner reduction of α,β-unsaturated carbonyl compounds has been shown to be accompanied by migration of the double bond. A cyclic intermediate has been suggested to account for this shift (14). Non-cyclic stepwise mechanisms have been advanced for other Kishner eliminations (15-18). We suggest that the Kishner reduction of III may proceed *via* a stepwise mechanism to a C-10 carbanion, followed by protonation to the observed products.



Goutarel and co-workers have recently reported isolation of a new *Buxus* alkaloid, baleabuxine, which possesses the same conjugated cyclopropyl ketone system as in III (19). By analogy with the work reported herein, Kishner reduction of baleabuxine-like alkaloids may lead to chemical interrelation with alkaloids of the buxenine-G type.

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REFERENCES

(1) K. S. Brown, Jr. and S. M. Kupchan, *J. Am. Chem. Soc.*, **84**, 4590, 4592 (1962).

(2) S. M. Kupchan and W. L. Asbun, *Tetrahedron Letters*, 3145 (1964).

(3) D. Stauffacher, *Helv. Chim. Acta*, **47**, 968 (1964).

(4) H. Wehrli, M. S. Heller, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **44**, 2162 (1961).

(5) C. L. Bumgardner and J. P. Freeman, *Tetrahedron Letters*, 737 (1964).

(6) N. Kishner, *J. Russ. Phys. Chem. Soc.*, **45**, 973 (1913).

(7) N. J. Leonard and S. Gelfand, *J. Am. Chem. Soc.*, **77**, 3269 (1955).

(8) Idem., Ibid., 77, 3272 (1955).

(9) P. S. Wharton and D. H. Bohlen, J. Org. Chem., 26, 3615 (1961); W. R. Benn and R. M. Dodson, Ibid., 29, 1142 (1964).

(10) P. S. Wharton, S. Dunny, and L. Soto Krebs, Ibid., 29, 958 (1964).

(11) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, p. 55.

(12) R. T. Rapala and E. Farkas, J. Org. Chem., 23, 1404 (1958).

(13) C. Djerassi, O. Halpern, and B. Riniker, J. Am. Chem. Soc., 80, 4001 (1958).

(14) G. Lardelli and O. Jeger, Helv. Chim. Acta, 32, 1817 (1949); R. Fischer, G. Lardelli, and O. Jeger, ibid., 33, 1335 (1950); R. Fischer, G. Lardelli, and O. Jeger, ibid., 34, 1577 (1951).

(15) T. D. Perrine and L. F. Small, J. Org. Chem., 17, 1540 (1952).

(16) D. H. R. Barton, N. J. Holness, and W. Klyne, J. Chem. Soc., 2456 (1949).

(17) D. E. Ames and R. Bowman, ibid., 2572 (1951).

(18) D. H. R. Barton and C. H. Robinson, ibid., 3045 (1954).

(19) D. Gaulier, F. Khuong-Huu-Laine, E. Stanislas, and R. Goutarel, Bull Soc. Chim.France, 657 (1965).