The Preparation of AB-Dinor Steroids[1]

WILLIAM G. DAUBEN, DAVID J. ELLIS,[2] AND WILLIAM H. TEMPLETON

University of California, Berkeley, California 94720

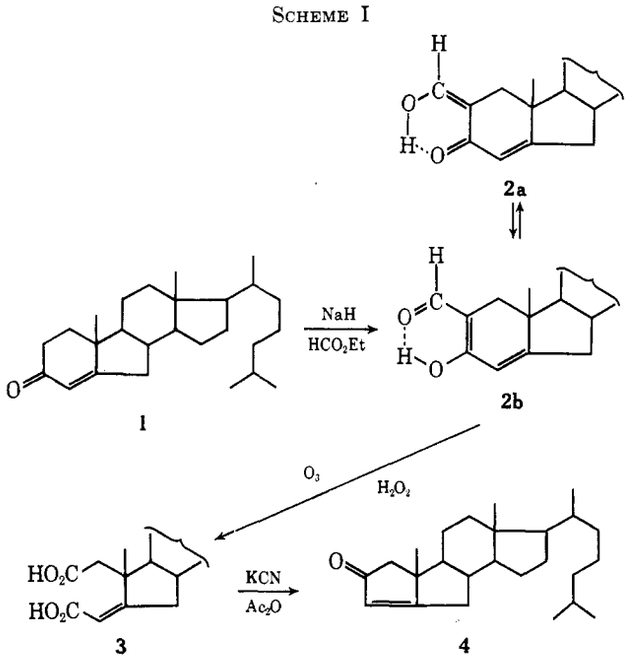
Received November 12, 1968

AB-Dinorcholestenone (**4**) and AB-dinortestosterone (**21**) have been synthesized to determine the chemical and biological consequences of contracting both the A and B rings of the steroid nucleus. The AB-dinor analogs were prepared from the corresponding B-nor steroids by formylation of B-norenone **1**, ozonization of 2-hydroxymethylene ketone **2**, and cyclization of the resulting diacid **3**. Catalytic or chemical reduction of enone **4** gave exclusively the 5β-saturated ketone **7**. Hydride reduction of *cis* ketone **7** gave predominantly 2α alcohol **12**, whereas lithium–ammonia reduction of **7** gave mostly the more stable 2β alcohol **13**.

An increasing number of ring-contracted steroids[3] have been reported to possess antihormonal activity.[4] At least one nor steroid, 17α-methyl-B-nortestosterone, has been used clinically as an antiandrogen.[5] It was therefore of considerable interest to see if antihormonal activity could be enhanced by further deviation from the normal steroid nucleus. Accordingly, our previous studies related to the A-nor[6] and B-nor steroids[7] have been extended to the AB-dinor steroids.

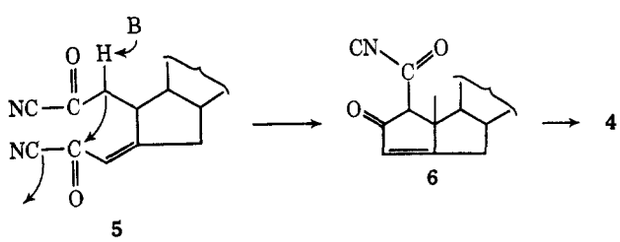
For initial chemical studies, cholesterol was transformed to an AB-dinor analog. The previously reported B-norcholestenone (**1**)[7] upon reaction with ethyl formate and sodium hydride gave an 85% yield of the 2-hydroxymethylene derivative **2**. The infrared (ir) and nuclear magnetic resonance (nmr) spectra of the product showed that it consists of a rapidly equilibrating mixture of the hydroxymethylene form **2a** and the formyl tautomer **2b** in the approximate ratio 75:25[8] (Scheme I).

SCHEME I



Treatment of **2** with 1 equiv of ozone at −15° resulted in the selective cleavage of the 2,3 bond to give the 2,3-seco diacid **3** in 93% yield after oxidative work-up with hydrogen peroxide.

The key step in the synthesis was the final cyclization of the seco diacid **3**. In the synthesis of A-nortestosterone, the corresponding seco diacid was readily cyclized by refluxing in acetic anhydride followed by pyrolysis of the resulting steroidal anhydride.[9] When the B-nor-seco diacid **3** was subjected to these conditions, only a 5% yield of the desired AB-dinorcholestenone (**4**) was obtained. Pyrolysis of the intramolecular lead salt of **3** gave only a 20% yield of **4**.[10] The cyclization was eventually effected in 50–60% yield by refluxing the seco diacid **3** in acetic anhydride containing potassium cyanide.[11] Substitution of potassium acetate or pyridine for potassium cyanide resulted in decreased yields of **4**. The cyanide is probably acting as a carbonyl-activating group by the formation of the acyl cyanide **5**, which can then undergo base-catalyzed cyclization. The β-keto acyl cyanide **6** can then be converted into **4**, either under the reaction conditions or during work-up. The spectral properties of **4** fully confirmed its assigned structure.



The enone **4** was subjected to a variety of reactions to learn more about the chemical behavior of the AB-dinor ring system. Hydrogenation of **4** over palladium on charcoal resulted in the rapid uptake of 1 equiv of hydrogen to give the saturated ketone **7**. The existence of more than one isomer could not be demonstrated and the product was assumed to be homogeneous. The 5β configuration would be expected since hydrogenation of either A-nor-[6a,12] or B-norcholestenones (**1**)[7] yields the 5β-saturated ketones.

(1) This work was supported in part by Grant No. CY-04284, National Cancer Institute, U. S. Public Health Service.

(2) National Science Foundation Graduate Fellow, 1961–1964.

(3) For a comprehensive review of ring contractions of steroids, see B. G. McFarland in "Steroids Reactions," C. Djerassi, Ed., Holden-Day, Inc., San Francisco, Calif., 1963, pp 427–455.

(4) R. I. Dorfman, J. Fajkos, and J. Joska, *Steroids*, **3**, 675 (1964); (b) H. L. Saunders, K. Holden, and J. F. Kerwin, *ibid.*, **3**, 687 (1964); (c) A. Segaloff and R. B. Gabbard, *ibid.*, **4**, 433 (1964); (d) S. M. Kupchan and S. D. Levine, *J. Amer. Chem. Soc.*, **86**, 701 (1964); (e) L. J. Lerner, A. Bianchi, and M. Dzelzkalns, *Acta Endocrinol.*, **44**, 398 (1963); (f) L. J. Lerner, A. V. Bianchi, and M. Dzelzkalns, *Steroids*, **6**, 215, 223 (1965).

(5) A. Zarate, V. B. Mahesh, and R. B. Greenblatt, *J. Clin. Endocrinol. Metab.*, **26**, 1394 (1966).

(6) (a) W. G. Dauben and G. A. Boswell, Jr., *J. Amer. Chem. Soc.*, **83**, 5003 (1961); (b) W. G. Dauben, G. A. Boswell, Jr., and W. H. Templeton, *ibid.*, **83**, 5006 (1961), and previous papers cited therein.

(7) W. G. Dauben, G. A. Boswell, Jr., W. H. Templeton, J. W. McFarland, and G. H. Berezin, *ibid.*, **85**, 1672 (1963), and references cited therein.

(8) E. W. Garbisch, Jr., *ibid.*, **87**, 505 (1965).

(9) F. L. Weisenborn and H. E. Applegate, *ibid.*, **81**, 1960 (1959).

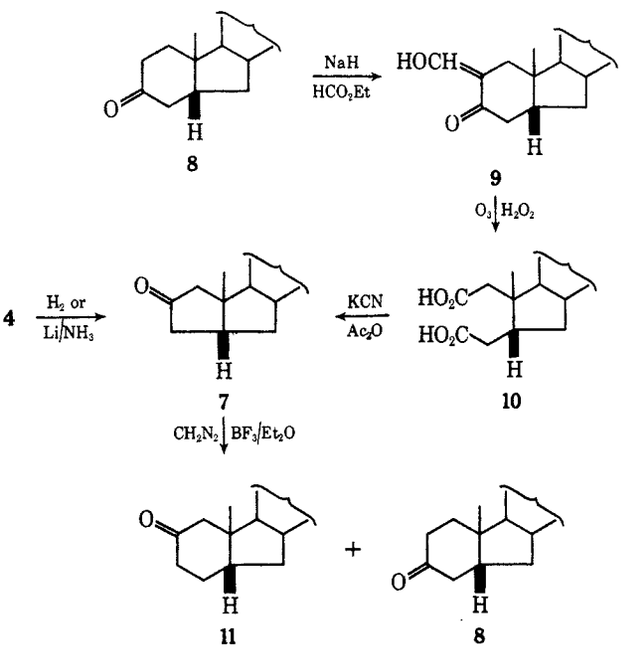
(10) H. Rapoport and J. Pasky, *ibid.*, **78**, 3788 (1956).

(11) F. Uhle, *ibid.*, **71**, 761 (1949).

(12) T. L. Jacobs and N. Takahashi, *ibid.*, **80**, 4865 (1958).

The stereochemistry of hydrogenation was proved by the synthesis of authentic AB-dinor-5β-cholestan-2-one (**7**) from B-nor-5β-cholestan-3-one (**8**) (Scheme II),

SCHEME II



whose C-5 configuration is well established.[7] Treatment of **8** with sodium hydride and ethyl formate gave the 2-hydroxymethylene derivative **9**,[13] which was ozonized to the 2,3-seco diacid **10**. The nmr spectrum of **10** clearly shows that the 2,3 bond had been cleaved, thus, firmly establishing that condensation had occurred at C-2. Cyclization of **10** with acetic anhydride and potassium cyanide gave a 35% yield of AB-dinor-5β-cholestan-2-one (**7**) that was identical with the hydrogenation product of **4**. A similar sequence was carried out with B-nor-5α-cholestan-3-one,[7] but the 5α-seco diacid could not be cyclized to the desired AB-dinor-5α-cholestan-2-one.

Additional chemical evidence for the 5β configuration of **7** was obtained by ring expansion of **7** to the known B-nor-5β ketone **8**. Treatment of **7** with a methylene chloride solution of diazomethane containing a trace of boron trifluoride etherate[14] gave a mixture of B-nor-5β-cholestan-2- and -3-ones (**11** and **8**) in approximately equal amounts. The equal migratory aptitudes of the 1,2 and 2,3 bonds of **7** are in contrast to the normal steroidal ketones, which usually show unequal migratory aptitudes.[15]

The 5β isomer **7** exhibited a negative Cotton effect ($a = -28$)[16] as does methyl-2-keto-A-nor-5β-cholanate ($a = -152$).[17] A-nor-5α-cholestan-2-one shows a strong positive Cotton effect ($a = +233$).[17] The increased planarity of the A ring in **7** relative to the A-nor ketones is probably responsible for the greatly reduced amplitude of its Cotton effect.[18,19]

The behavior of the AB-dinorenone **4** toward chemical reduction was of interest, since the factors governing product stereochemistry are still incompletely understood. Treatment of the enone **4** with an excess of lithium in ammonia gave a quantitative yield of the saturated alcohols **12** and **13**. Oxidation of the epimeric alcohols with chromic acid in acetone[20] gave the saturated AB *cis* ketone **7**. No trace of the 5α isomer could be found.[21]

The stereochemistry of reduction of the saturated AB-dinor ketone **7** was briefly studied. Chromatography of the alcohol mixture from lithium–ammonia reduction of **4** gave 80% more polar epimer and 20% less polar epimer. Although exceptions have been noted,[22] it appears reasonable to assume that lithium–ammonia reduction of **7** will yield predominantly the more stable epimer.[23,24] The *exo* epimer is the more stable in 1- and 2-substituted *cis*-bicyclo[3.3.0]octanes.[25] By analogy the 2β configuration is assigned to the major alcohol **13**. The 16β alcohol is also the more stable epimer in the closely related 14β steroids.[26] The 2β configuration of the major alcohol **13** is supported by the fact that it gave a precipitate with digitonin, whereas the minor alcohol **12** did not.[27] The chromatographic mobilities of the two epimers are also in the expected order.[28] Thus, the more exposed 2β epimer (*exo*) is less mobile than the hindered 2α alcohol (*endo*), which cannot interact as strongly with the adsorbent.

The hydride reduction of **7** was the final proof of stereochemistry. Hydride reduction of *cis*-bicyclo[3.3.0]octanones[25a,29] or of 2-keto-A-nor-5β steroids[6a,30] proceeds predominantly by topside attack to give the less stable α alcohols, and it was therefore anticipated that the product distribution from hydride reduction of **7** should be the reverse of that obtained from the lithium–ammonia reduction. Treatment of an ethanolic solution of **7** with sodium borohydride gave a mix-

(13) Formylation could also occur at C-4, but R. O. Clinton, R. Clarke, F. Stonner, A. Manson, K. F. Jennings, and D. Phillips, *J. Org. Chem.*, **27**, 2800 (1962), have shown that condensation usually occurs at C-2 in 5β-3 ketones.

(14) (a) W. S. Johnson, M. Neeman, and S. P. Birkeland, *Tetrahedron Lett.*, 1 (1960); (b) W. S. Johnson, M. Neeman, S. P. Birkeland, and N. A. Fedoruk, *J. Amer. Chem. Soc.*, **84**, 989 (1962); (c) H. O. House, E. J. Grubbs, and W. F. Gannon, *ibid.*, **82**, 4099 (1960).

(15) (a) N. A. Nelson and R. N. Schut, *ibid.*, **81**, 6486 (1959); (b) S. Hara, *Chem. Pharm. Bull.* (Tokyo), **12**, 1531 (1964).

(16) See C. Djerassi and W. Klyne, *Proc. Chem. Soc.*, 55 (1957), for a discussion of ORD nomenclature.

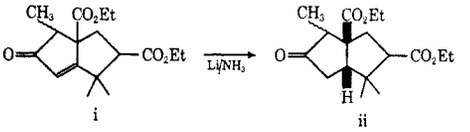
(17) C. Djerassi, R. Riniker, and B. Riniker, *J. Amer. Chem. Soc.*, **78**, 6362 (1956).

(18) (a) W. Klyne, *Tetrahedron*, **13**, 29 (1961); (b) P. M. Bourn and W Klyne, *J. Chem. Soc.*, 2044 (1960).

(19) C. Djerassi and J. E. Gurst, *J. Amer. Chem. Soc.*, **86**, 1755 (1964).

(20) (a) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); (b) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *ibid.*, 2548 (1953); (c) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(21) G. Stork and F. H. Clarke, Jr., *J. Amer. Chem. Soc.*, **83**, 3114 (1961), have obtained a similar result with a related enone i.



(22) (a) G. Ourisson and A. Rassat, *Tetrahedron Lett.*, 16 (1960); (b) J. W. Huffman, D. M. Alabran and T. W. Bethea, *J. Org. Chem.*, **27**, 3383 (1962).

(23) G. Stork and S. D. Darling, *J. Amer. Chem. Soc.*, **86**, 1761 (1964).

(24) D. H. R. Barton and R. C. Cookson, *Quart. Rev.* (London), **10**, 44 (1956).

(25) (a) R. Granger, P. Nau, and J. Nau, *Bull. Soc. Chim. Fr.*, 1350 (1960), and papers cited therein; (b) A. C. Cope and M. Brown, *J. Amer. Chem. Soc.*, **80**, 2859 (1958).

(26) T. Nambara and J. Fishman, *J. Org. Chem.*, **27**, 2131 (1962).

(27) Although digitonide formation with such a highly modified steroid may be questionable, it should be noted that A-norcholestanols behave normally with regard to digitonide formation.[6a]

(28) A. C. Cope and P. E. Peterson, *J. Amer. Chem. Soc.*, **81**, 1643 (1959).

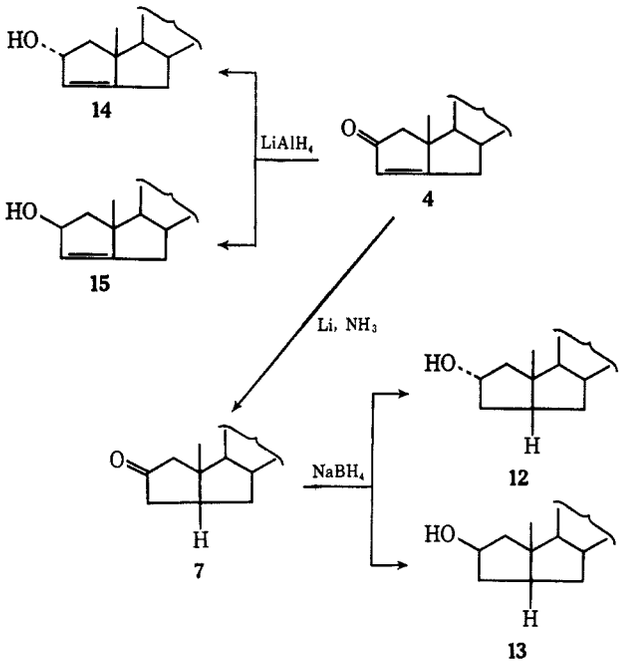
(29) A. C. Cope, M. Brown, and H. Petree, *ibid.*, **80**, 2852 (1958).

(30) K. Yoshida and T. Kubota, *Tetrahedron*, **21**, 759 (1965)

ture of the epimeric alcohols **12** and **13**. Chromatographic separation showed the mixture to consist of approximately 80% less polar α epimer **12** and 20% more polar β epimer **13**, thus confirming our prediction and providing compelling evidence for our assignment of stereochemistry.

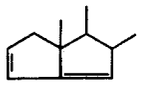
Lithium aluminum hydride reduction of the AB-dinorenone **4** gave a mixture of the epimeric allylic alcohols **14** and **15** (Scheme III) with the more polar

SCHEME III



epimer predominating. The major epimer was obtained in pure form after two recrystallizations from methanol, and was assigned the 2β configuration by analogy with A-norcholestenone[31] and because it formed a digitonide. The increase in α attack in comparison with the saturated ketone **7** is probably a result of the increased planarity of the A ring of **4** and the consequent reduction of hindrance on the α side of the A ring. In addition, the carbonyl group of **4** is more hindered by the 19-methyl group and topside attack is impeded. A similar effect is observed in the related 2-keto steroids.[32]

Treatment of the allylic alcohols **14** and **15** with refluxing ethanolic hydrochloric acid gave $\Delta^{2,5}$-AB-dinorcholestadiene (**16**) in quantitative yield. The



16

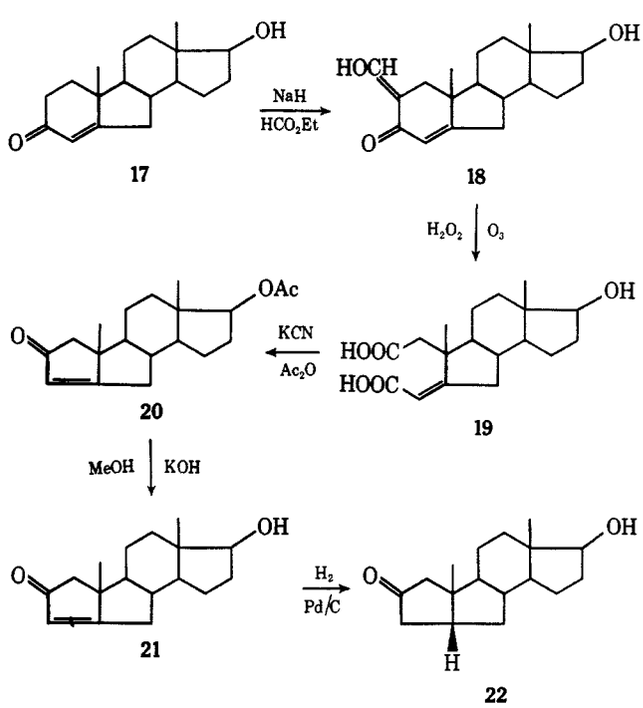
pattern of the vinyl protons in the nmr spectrum was very similar to that of $\Delta^{3,5}$-B-norcholestadiene and conclusively proved the position of the double bonds.

The AB-dinor ketone **7** was subjected to acid-catalyzed bromination to determine the direction of enolization of the 2 ketone. The ketone **7** was completely resistent to bromination. A similar lack of reactivity has been observed with 16-keto steroids[33] and 2-keto-A-nor steroids[6b,12] and is probably a reflection of the increased strain of the enol form.[34]

Although **7** was resistent to bromination it reacted with isopropenyl acetate under forcing conditions[6b] to give a quantitative yield of the Δ^1- and Δ^2-enol acetates in approximately equal amounts. It therefore appears that there is no great preference in the direction of enolization of the AB-dinor ketone **7**.

To determine the biological consequences of contraction of the A and B rings of a steroid hormone, the contraction sequence outlined above was applied to B-nortestosterone (**17**).[35] Treatment of **17** with sodium hydride and ethyl formate gave a 97% yield of the 2-hydroxymethylene derivative **18**, which was selectively ozonized to give the 2,3-seco diacid **19** in 70% yield. Cyclization of **19** in refluxing acetic anhydride containing potassium cyanide gave a 60% yield of AB-dinortestosterone acetate (**20**). Saponification gave AB-dinortestosterone **21**, whose spectral properties confirmed the assigned structure. Hydrogenation of **21** gave a quantitative yield of the 5β ketone **22** (Scheme IV). The ORD curve of **22** was very similar to that of AB-dinor-5β-cholestan-2-one (**7**) and supported the assigned stereochemistry.

SCHEME IV



Compounds **18**, **20**, and **21** were tested[36] for androgenic and antiandrogenic activity by the improved

(31) G. A. Boswell, "Doctoral Dissertation," University of California, Berkeley, Calif., 1959, p 50.

(32) W. G. Dauben, E. J. Blanz, Jr., J. Jiu, and R. A. Micheli, *J. Amer. Chem. Soc.*, **78**, 3752 (1956).

(33) J. Fajkos and J. Joska, *Coll. Czech. Chem. Comm.*, **25**, 2863 (1960).

(34) H. C. Brown, J. H. Brewster, and H. Shechter, *J. Amer. Chem. Soc.*, **76**, 467 (1954).

(35) Prepared according to T. Rull and G. Orisson, *Bull. Chim. Soc. Fr.*, 1581 (1958). In the later stages of our work we were kindly supplied with B-nortestosterone benzoate by the Cancer Chemotherapy National Service Center (CCNSC), which prepared the compound by the method of K. Tanabe and Y. Morisawa, *Chem. Pharm. Bull. (Tokyo)*, **11**, 536 (1963), and earlier papers cited therein.

(36) The authors are indebted to Dr. M. L. Hopwood, Dr. R. P. Martin, and G. S. Farnham, who carried out the biological testing at the Endocrine Section of the Department of Chemistry, Colorado State University, Fort Collins, Colo.

chick comb methods of Lerner.[4e,37] None of the compounds showed significant androgenic or antiandrogenic activity at the 95% confidence level. The antiandrogenic activity of the A- and B-nor analogs[4] is therefore not enhanced by further ring contraction. Apparently, the geometry of the AB-dinor analogs has been changed to the point where binding to the receptor can no longer occur. The A- or B-nor analogs are sufficiently similar to the hormone so that receptor binding still takes place, but their altered geometry does not cause the molecular changes leading to an androgenic response.[38] Thus, they are capable of blocking the effect of testosterone without causing an androgenic response themselves.

Experimental Section[39]

2-Hydroxymethylene-B-norcholest-4-en-3-one (2).—A benzene solution (470 ml) of 37.6 g of **1** was treated with ethyl formate (38 ml, 0.47 mol) and sodium hydride (5.64 g, 0.24 mol) according to the procedure of Weisenborn[9] to give 37.2 g (91%) of **2**, mp 100–102°. Three recrystallizations from hexane gave an analytical sample: mp 100–104°; $[\alpha]^{28}D$ −71° (*c* 0.496); λ_{max}^{EtOH} 250 mμ (ε 11,300) and 307 (6800); $\nu_{max}^{CCl_4}$ 2703, 1645, 1567, and 1195 cm.$^{-1}$, nmr (CCl_4) τ −3.87 (1 H, broad, enolic proton), 2.73 (1 H, d, *J* = 8 Hz, hydroxymethylene vinyl), and 4.23 (1 H, t, *J* = 1.5 Hz, C-4 vinyl).

Anal. Calcd for $C_{27}H_{42}O_2$: C, 81.35; H, 10.62. Found: C, 81.07; H, 10.44.

2,3-Seco-B-norcholest-4-ene-2,3-dioic Acid (3).—A solution of 33.2 g (83 mmol) of **2** in 700 ml of 1:1 glacial acetic acid–ethyl acetate was treated with 1 equiv of ozone at −15° and worked up by the method of Weisenborn[9] to give 32.4 g (93%) of **3**, mp 145–160°. Recrystallization from chloroform–hexane gave fine needles that melted with gas evolution at 160–161°: $[\alpha]^{25}D$ + 6.3° (*c* 0.473); λ_{max}^{EtOH} 225 mμ (ε 12,500); $\nu_{max}^{CHCl_3}$ 3484, 1702, 1642, and 1235 cm.$^{-1}$; nmr (CCl_4) τ 2.45 (2 H, broad, OH), 5.20 (1 H, broad, vinyl).

Anal. Calcd for $C_{26}H_{42}O_4$: C, 74.60; H, 10.4. Found: C, 74.82; H, 9.99.

AB-Dinorcholest-3-en-2-one (4).—A solution of 640 mg (1.53 mmol) of **3** and 110 mg (1.69 mmol) of potassium cyanide in 40 ml of acetic anhydride was allowed to reflux under nitrogen for 2 days. The dark brown mixture was evaporated under reduced pressure, and the residue was dissolved in ether and washed with water and 10% potassium hydroxide. The ether solution was evaporated to give 600 mg of a dark brown oil that was chromatographed on 20 g of Woelm neutral activity III alumina. Elution with petroleum ether–benzene (3:1) gave 372 mg (68%) of **4**, mp 50–53°. Four recrystallizations from methanol gave an analytical sample: mp 54–55°; $[\alpha]^{29}D$ −123° (*c* 0.494); λ_{max}^{EtOH} 235 mμ (ε 13,400); $\nu_{max}^{CCl_4}$ 1709 and 1629 cm^{-1}; nmr (CCl_4) τ 4.25 (1 H, t, *J* = 1.5 Hz, vinyl), 7.85 (2 H, s, C-1 methylene), and 7.74–7.98 (2 H, m, C-6 methylene); ORD (*c* 0.003, cyclohexane) $[\alpha]_{300}$ −1330°, $[\alpha]_{241}^{trough}$ −13,000°, $[\alpha]_{212}^{peak}$ +35,000° (*a* = −1710).

Anal. Calcd for $C_{25}H_{40}O$: C, 84.21; H, 11.31. Found: C, 84.16; H, 11.11.

AB-Dinor-5β-cholestan-2-one (7). A. From Hydrogenation of 4.—A solution of 400 mg (1.12 mmol) of **4** in 20 ml of 95% ethanol was hydrogenated at atmospheric pressure over 100 mg of 5% palladium on charcoal. After 20 min the reaction was complete and 400 mg (99%) of **7** was obtained. Recrystallization from methanol gave an analytical sample: mp 63–64°; $[\alpha]^{30}D$ + 4° (*c* 0.496); λ_{max}^{EtOH} 289 mμ (ε 14); $\nu_{max}^{CCl_4}$ 1742 and 1404 cm^{-1}; nmr (CCl_4) τ 7.79 (4 H, broad, C-1 and C-3 methylenes); ORD (*c* 0.182, methanol) $[\alpha]_{450}$ +8°, $[\alpha]_{312}^{trough}$ −297°, $[\alpha]_{270}^{peak}$ +489° (*a* = −28).

Anal. Calcd for $C_{25}H_{42}O$: C, 83.73; H, 11.81. Found: C, 83.71; H, 11.16.

B. From B-Nor-5β-cholestan-3-one (8).—A suspension of 712 mg (1.92 mmol) of **8**, 100 mg of sodium hydride (4.1 mmol, as a 54% mineral oil dispension), and 0.32 ml (4.0 mmol) of ethyl formate in 50 ml of benzene was allowed to reflux under nitrogen for 24 hr and then worked up as usual[9] to yield 624 mg (82%) of **9** as a yellow oil: $\nu_{max}^{CCl_4}$ 1661, 1590, and 1198 cm^{-1}; nmr (CCl_4) τ 2.84 (1 H, s, hydroxymethylene vinyl) and 7.98 (2 H, m, C-4 methylene).

A solution of 560 mg (1.40 mmol) of crude **9** in 30 ml of glacial acetic acid–ethyl acetate (1:1) was ozonized and worked up as usual[9] to yield 590 mg (99%) of the seco diacid **10**, mp 190–195°. Two recrystallizations from chloroform–hexane gave 420 mg (71%) of **10**: mp 190–201°; $[\alpha]^{28}D$ +26.7° (*c* 0.484); $\nu_{max}^{CCl_4}$ 3400–2500, 1706, and 1278 cm.$^{-1}$; nmr ($CDCl_3$) τ 0.71 (2 H, broad, –COOH) and 7.95 (4 H, m, C-1 and C-4 methylene).

Anal. Calcd. for $C_{26}H_{44}O_4$: C, 74.24; H, 10.54. Found: C, 74.18; H, 10.33.

A solution of 548 mg (1.31 mmol) of **10** and 340 mg of potassium cyanide (5.24 mmol) in 25 ml of acetic anhydride was allowed to reflux under a nitrogen atmosphere for 24 hr and worked up as described for **4** to yield 150 mg (33%) of **7**, mp 45–55°. Two recrystallizations from methanol gave material melting at 61–63° that was identical in all respects with that obtained from the hydrogenation of **4**.

Diazomethane Homologation of AB-Dinor-5β-cholestan-2-one (7).—A solution of 50 mg (0.14 mmol) of **7** (from hydrogenation of **4**) and 0.3 ml of catalyst solution[14b] (1 ml of boron trifluoride etherate in 25 ml of 3:1 methylene chloride–ether) in 10 ml of anhydrous methylene chloride was treated with 0.18 mmol of diazomethane for 1 hr at 0° and then worked up[14b] to give 77 mg of a clear oil: $\nu_{max}^{CCl_4}$ 1742 and 1718 cm^{-1}. Chromatography on 10 g of Woelm activity III neutral alumina gave 7 mg (13%) of homologated material upon elution with 1:1 petroleum ether–benzene. Gas chromatography on a 1% polyester column showed that the product consisted of approximately equal amounts of the 2- and 3-keto-B-nor-5β-cholestanes **11** and **8**.

Lithium–Ammonia Reduction of AB-Dinorcholest-3-en-2-one (4).—A solution of 103 mg (0.29 mmol) of **4** in 25 ml of liquid ammonia and 10 ml of ether was reduced with 200 mg of lithium to give 110 mg of a mixture of the 2α and 2β alcohols **12** and **13**. Chromatography on alumina showed the mixture to consist of approximately 80% 2β alcohol **13** which was recrystallized from methanol: mp 120–123°; $[\alpha]^{29}D$ +25° (*c* 0.489). The 2β alcohol (7.3 mg in 11 ml of 95% ethanol) gave a precipitate with digitonin (31.8 mg in 1.6 ml of 70% ethanol).

Anal. Calcd for $C_{25}H_{44}O$: C, 83.27; H, 12.30. Found: C, 83.40; H, 12.05.

Oxidation[20] of 17 mg of a 1:1 mixture of the alcohols **12** and **13** gave 15 mg (88%) of **7** that was identical with the material obtained from hydrogenation of **4**.

Sodium Borohydride Reduction of AB-Dinor-5β-cholestan-2-one (7).—A solution of 100 mg (0.28 mmol) of **7** in 50 ml of 95% ethanol was treated with 100 mg (2.63 mmol) of sodium borohydride to give 100 mg of a mixture of the 2α and 2β alcohols **12** and **13**, which was chromatographed on 20 g of alumina (activity III). Elution with benzene gave 66 mg (66%) of the 2α alcohol **12**: mp 89–91°; $[\alpha]^{25}D$ +15° (*c* 0.466). An insoluble digitonide was not formed.

Anal. Calcd for $C_{25}H_{44}O$: C, 83.27; H, 12.30. Found: C, 82.99; H, 12.18.

Continued elution with benzene gave 21 mg (21%) of the 2β alcohol **13**: mp 117–120°; $[\alpha]^{30}D$ +25° (*c* 0.489).

Lithium Aluminum Hydride Reduction of AB-Dinorcholest-3-en-2-one (4).—To a refluxing suspension of 38 mg (1.0 mmol) of lithium aluminum hydride in 25 ml of anhydrous tetrahydrofuran was added a solution of 250 mg (0.70 mmol) of **4** in 25 ml of anhydrous tetrahydrofuran over a period of 30 min. The mixture was allowed to reflux under N_2 for 5 hr and was then worked up with saturated ammonium chloride to give 242 mg of the 2α- and 2β-allylic alcohols **14** and **15**. Two recrystallizations of the crude reaction mixture from methanol gave the major epimer **15** in pure form: mp 105–107°; $[\alpha]^{26}D$ −22.4° (*c* 0.490).

Anal. Calcd for $C_{25}H_{42}O$: C, 83.73; H, 11.81. Found: C, 83.87; H, 11.70.

AB-Dinorcholesta-2,5-diene (16).—A solution of 70 mg (0.195 mmol) of a 1:1 mixture of **14** and **15** and 0.2 ml of concentrated

(37) L. J. Lerner and A. Bianchi, *Acta Endocrinol.*, **44**, 389 (1963).

(38) M. E. Wolff, W. Ho, and R. Kwok, *J. Med. Chem.*, **7**, 577 (1964).

(39) Melting points were determined with a Mel-Temp apparatus in evacuated, sealed capillaries and are uncorrected. Optical rotations were taken in chloroform. Infrared spectra were obtained with a Perkin-Elmer Model 137-B or Model 237 spectrometer. Ultraviolet spectra were recorded with a Perkin-Elmer Model 202 or a Cary Model 14 spectrometer. Nmr spectra were obtained with a Varian Associates Model A-60 spectrometer using tetramethylsilane as internal standard. ORD curves were recorded with a Cary Model 60 spectropolarimeter. Microanalyses were performed by the Microchemical Laboratory, College of Chemistry, University of California.

HCl in 20 ml of absolute ethanol was heated under reflux for 5 hr to give 65 mg (98%) of a pale yellow oil. Two recrystallizations from methanol gave 55 mg (80%) of **16**: mp 70–71°; $[\alpha]^{27}D$ −136° (*c* 0.472); $\nu_{max}^{CS_2}$ 837, 813, 734, and 698 cm^{-1}; $\lambda_{max}^{cyclohexane}$ 238 mμ (ε 9410), 245 (9860), and 253 (6570); nmr (CCl_4) τ 3.92 (1 H, doublet of triplets, $J_{2,3}$ = 10 Hz, $J_{1,3}$ = 2 Hz, C-3 vinyl), 4.38 (1 H, d, $J_{2,3}$ = 10 Hz, C-2 vinyl), 4.66 (1 H, s, C-7 vinyl), and 7.93 (3 H, m, allylic).

Anal. Calcd for $C_{25}H_{40}$: C, 88.16; H, 11.84. Found: C, 87.87; H, 11.60.

Enol Acetylation of AB-Dinor-5β-cholestan-2-one (7).—A solution of 2.00 g (5.58 mmol) of **7** and 0.40 g of *p*-toluenesulfonic acid in 200 ml of redistilled isopropenyl acetate was allowed to reflux for 3 days under forcing conditions.[6b] Chromatography of the crude product on silica gel gave 2.3 g of an oil that crystallized from methanol to give 2.10 g (97%) of an approximately 1:1 mixture of the Δ¹- and Δ²-enol acetates of **7**: mp 36–37°; $\nu_{max}^{CCl_4}$ 1766, 1665, 1645, and 1215 cm^{-1}; $\lambda_{max}^{cyclohexane}$ 193 mμ (ε 9680); nmr (CCl_4) τ 4.72 (1 H, m, vinyls) and 7.99 (3 H, s, acetyl).

Anal. Calcd for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found: C, 80.83; H, 11.30.

17β-Hydroxy-2-hydroxymethylene-B-norandrost-4-en-3-one (18).—A suspension of 1.79 g (6.53 mmols) of B-nortestosterone (**17**), 1.88 ml (23.5 mmol) of ethyl formate, and 0.56 g (23.6 mmol) of sodium hydride in 38 ml of benzene was stirred under N_2 for 3 days at room temperature and worked up as usual[9] to give 1.95 g (99%) of **18**. Recrystallization from methylene chloride–petroleum ether gave an analytical sample: mp 214–216°; $[\alpha]^{25}D$ −73° (*c* 0.430); $\nu_{max}^{CHCl_3}$ 3450, 1640, and 1562 cm^{-1}; λ_{max}^{EtOH} 250 mμ (ε 11,300) and 307 (6810).

Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.66. Found: C, 75.37; H, 8.66.

17β-Hydroxy-2,3-seco-B-norandrost-4-ene-2,3-dioic Acid (19).—A solution of 1.00 g (3.31 mmol) of **18** in 30 ml of 1:1 glacial acetic acid–ethyl acetate was treated with 3.31 mmol of ozone at −15° to give 0.74 g (69%) of crystalline seco diacid **19**, mp 212–214°. Recrystallization from aqueous methanol gave an analytical sample: mp 230–232°; $[\alpha]^{25}D$ −46° (*c* 0.450); ν_{max}^{KBr} 3330, 2597, 1712, and 1645 cm^{-1}; λ_{max}^{EtOH} 223 mμ (ε 12,600); nmr (CH_3OD) τ 5.30 (1 H, m, vinyl).

Anal. Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 66.86; H, 8.11.

17β-Hydroxy-AB-dinorandrost-3-en-2-one Acetate (20).—A solution of 4.75 g (14.75 mmol) of **19** and 3.82 g (59 mmol) of KCN in 250 ml of acetic anhydride was allowed to reflux under argon for 2 days and then worked up as described for **4**. Chromatography of the crude product on alumina gave 3.03 g (68%) of an oil, which was crystallized from methylene chloride–petroleum ether to give 2.64 g (60%) of crystalline **20**: mp 109–112°; $[\alpha]^{26}D$ −155° (*c* 0.491); ν_{max}^{CCl} 1742, 1712, and 1633 cm^{-1}; λ_{max}^{EtOH} 235 mμ (ε 13,500); nmr ($CDCl_3$) τ 4.25 (1 H, t, *J* = 1.5 Hz, vinyl), 5.40 (1 H, t, *J* = 7 Hz, 17α H), 7.97 (3 H, s, acetyl), 8.94 (3 H, s, C-19), and 9.13 (3 H, s, C-18).

Anal. Calcd for $C_{18}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.53; H, 8.45.

17β-Hydroxy-AB-dinorandrost-3-en-2-one (21).—A solution of 2.64 g (8.75 mmol) of **20** and 5 g of KOH in 125 ml of 95% methanol was allowed to reflux for 1 hr under nitrogen to give 1.9 g of crude **21** that was chromatographed on alumina to yield 1.70 g of crystalline **21**, mp 114–116°. Recrystallization from methylene chloride–petroleum ether gave an analytical sample: mp 116–117°; $[\alpha]^{25}D$ −150° (*c* 0.479); $\nu_{max}^{CCl_4}$ 3610, 3448, 1709, and 1626 cm^{-1}; λ_{max}^{EtOH} 235 mμ (ε 13,500); nmr ($CDCl_3$) τ 4.24 (1 H, t, *J* = 1.5 Hz, vinyl), 6.32 (1 H, t, *J* = 7.5 Hz, 17α H), and 7.78 (2 H, s, C-1 methylene); ORD (*c* 0.0024, ethanol) $[\alpha]_{400}$ −553°, $[\alpha]_{250}^{trough}$ −18,700°, $[\alpha]_{215}^{peak}$ +44,200° (*a* = −1636).

Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.40; H, 9.29. Found: C, 78.13; H, 9.27.

17β-Hydroxy-AB-dinor-5β-androtan-2-one (22).—A solution of 515 mg (1.98 mmol) of **21** in 50 ml of 95% ethanol was hydrogenated at atmospheric pressure over 50 mg of 5% palladium on charcoal to give 514 mg (99%) of **22**, mp 128–130°. Two recrystallizations from chloroform gave an analytical sample: mp 131–133°; $[\alpha]^{29}D$ −10° (*c* 0.460); $\nu_{max}^{CCl_4}$ 1739 cm^{-1}; nmr ($CDCl_3$) τ 8.93 (3 H, s, C-19) and 9.25 (3 H, s, C-18); ORD (*c* 0.085, methanol) $[\alpha]_{400}$ −24°, $[\alpha]_{311}^{trough}$ −530°, $[\alpha]_{272}^{peak}$ + 647° (*a* = −30.9).

Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.90. Found: C, 77.57; H, 9.82.

Registry No.—**2**, 19955-03-4; **3**, 19933-87-0; **4**, 19933-77-8; **7**, 19933-78-9; **7** (Δ¹-enol acetate), 19933-79-0; **7** (Δ²-enol acetate), 19933-80-3; **10**, 19933-89-2; **12**, 19955-04-5; **13**, 19933-81-4; **15**, 19955-05-6; **16**, 19933-82-5; **18**, 19933-83-6; **19**, 19933-88-1; **20**, 19933-86-9; **21**, 19933-84-7; **22**, 19933-85-8.

Photoisomerization of Acyclic Conjugated Cyclopropyl Carbonyl Compounds[1]

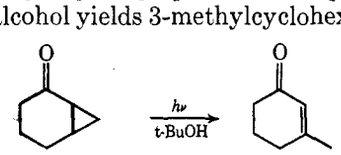
WILLIAM G. DAUBEN AND GARY W. SHAFFER[2]

University of California, Berkeley, California 94720, and Givaudan Corporation, Clifton, New Jersey 07014

Received December 30, 1968

The photochemistry of the acyclic vinylcyclopropane carbonyl chromophore has been studied. Using Corex-filtered light, dihydrofurans (**4**–**6**), δ,ε-unsaturated acids (**7** and **8**), and epoxycyclobutanes (**9** and **10**) were found. The mechanism for the formation of these materials are discussed, and all reactions involve conjugative opening of the cyclopropane ring (eq 6 and 7). The formation of a ketene from an acyclic aldehyde is a new process and it has been shown to proceed intramolecularly (eq 8).

The photoisomerization of the cyclopropyl carbonyl chromophore, when contained in a bicyclic system, has been shown generally to bring about the cleavage of the better overlapped bond of the cyclopropyl ring. For example, bicyclo[4.1.0]heptan-2-one upon photolysis in *t*-butyl alcohol yields 3-methylcyclohexenone (eq 1).[3]



(1)

When this chromophore is not geometrically constrained into a fused-ring system, isomerization to an α,β-unsaturated enone still occurs if the cyclopropyl ring is unsubstituted (eq 2);[4] however, when the cyclopropyl ring is substituted with an alkyl group *cis* to the carbonyl group, only a Norrish type II reaction is observed (eq 3).[5]

The related ene-cyclopropane-one chromophore when contained in a bicyclo[3.1.0]hexane ring system, the so-

(1) This work was supported in part by PHS Grant No. 00709, National Institutes of Arthritis and Metabolic Diseases, U. S. Public Health Service.

(2) National Institutes of Health Predoctoral Fellow, 1965–1967.

(3) W. G. Dauben and G. W. Shaffer, *Tetrahedron Lett.*, 4415 (1967).

(4) J. N. Pitts, Jr., and I. Norman, *J. Amer. Chem. Soc.*, **76**, 4815 (1954); L. D. Hess, J. L. Jacobsen, K. Schaffner, and J. N. Pitts, Jr., *ibid.*, **89**, 3684 (1967).

(5) W. G. Dauben, L. Schutte, and R. E. Wolf, *J. Org. Chem.*, **34**, 1849 (1969).