Reaction of III with Maleic Anhydride.—Compound III (0.24 g., 1.0 mmole) and 0.11 g. (1.1 mmoles) of resublimed maleic anhydride were dissolved in 10 ml. of dry ether. The solution was deaerated with nitrogen and allowed to stand at room temperature for 20 hr. Evaporation of the ether left a tan semi-solid residue. Recrystallization from benzene–hexane gave the adduct V as white needles, m.p. 148–150°. Two additional recrystallizations gave 0.185 g. (54%) of pure V, m.p. 150–151°. The n.m.r. spectrum of V showed a single olefinic proton resonance centered at 3.65 τ. Comparison of its relative area with that of the combined signals of the methyl protons of the α-cyanoisopropyl groups showed these were in the ratio of 1:12.

Anal. Calcd. for $C_{20}H_{22}N_2O_8$: C, 70.98; H, 6.55; N, 8.28. Found: C, 71.16; H, 6.44; N, 8.33.

Hydrogenation of III.—Compound III (0.118 g.) was hydrogenated in 9 ml. of 95% ethanol at atmospheric pressure. Initially 39 mg. of 10% palladium-on-charcoal was added. Two 20-mg. portions of fresh catalyst were added during the course of the hydrogenation. Hydrogen uptake ceased after 25.6 ml. (102% of two double bonds) of hydrogen was taken up. A fourth portion of catalyst led to no further consumption of hydrogen. Filtration of the catalyst and evaporation of the solvent gave a colorless oil which could not be induced to crystallize.

Reaction of III with Dimethyl Acetylenedicarboxylate and Pyrolysis of the Resulting Adduct.—A solution of 0.24 g. of III and 0.42 g. of dimethyl acetylenedicarboxylate in 5 ml. of dry xylene was refluxed for 6 hr. under nitrogen. The xylene and excess dimethyl acetylenedicarboxylate were evaporated at 1 mm. pressure on the steam-bath. The residue, a viscous, almost colorless oil, amounted to 0.36 g. (94%). Its infrared spectrum showed strong bands at 5.82, 6.96, 7.90 and 8.8–8.9 μ, as in the spectrum of the adduct of dimethyl acetylenedicarboxylate and 7,8-dichlorobicyclo[4.2.0]octa-2,4-diene.[3b]

The adduct was pyrolyzed by heating it for 4 hr. at 200–210° in a flask equipped with an air condenser. The cooled, dark brown reaction mixture was chromatographed directly on a 20 × 300 mm. alumina column. Elution with benzene gave a colorless oil whose infrared spectrum indicated it was mainly an α-cyano-

isopropyl-substituted phthalate ester. This material was evaporatively distilled in a Hickman still at 0.2 mm., bath temp. 170–180°, to give 0.14 g. (57%) of dimethyl 4-(α-cyanoisopropyl)-phthalate (IV) as a colorless oil which set to a glass at −40°.

Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.37; H, 5.79; N, 5.36; mol. wt., 261. Found: C, 63.98; H, 5.93; N, 5.28; mol. wt., 244 (osmometric in $CHCl_3$).

The infrared spectrum of IV in the 4–15 μ region showed bands at 4.49(w), 5.83(vs), 7.19(w), 7.28(w), 7.7–8.2(vs), 8.91(s), 9.41(s), 11.42(m), 11.80(m), 12.20(m), 12.33(sh), 12.69(m), 12.99(m), 13.76(w), 14.21(m), and 14.75(m) μ. The n.m.r. spectrum consisted of a closely spaced multiplet at 2.36 τ (rel. area, 1), a singlet at 6.18 τ (rel. area 2) and a singlet at 8.29 τ (rel. area 2). The infrared spectrum of IV, except for the −CN band at 4.49 μ, was very similar to that of dimethyl 4-*t*-butylphthalate.[18a] In the key 10–15 μ region the 4-*t*-butyl ester showed bands at 10.32(m), 11.41(m), 11.80(m), 12.23(m), 12.65(m), 12.97(m), 13.78(w) and 14.20(w) μ. In contrast, dimethyl 3-ethylphthalate[18b] had bands at 10.04(m), 10.50(m), 11.53(m), 12.11(m) and 14.39(m) μ.

Reaction of AIBN with 1,3-Cyclooctadiene.—A solution of 4.1 g. of AIBN in 25 ml. each of 1,3-cyclooctadiene and benzene was deaerated with nitrogen and then heated at reflux under nitrogen for 8 hr. The benzene and excess cyclooctadiene were evaporated under reduced pressure, and the residue was chromatographed on a 35 × 350 mm. column of acid-washed alumina. Elution with benzene and ether–benzene mixtures gave, first, 0.95 g. of tetramethylsuccinonitrile, and then in later fractions, 3.84 g. of colorless viscous oil. All attempts to isolate a crystalline isomer from this oil failed. Its infrared spectrum was almost identical with that of tetrahydro-I. The n.m.r. spectrum was also very similar to that of tetrahydro-I, the principal difference being that the olefinic proton lines at 4.4 τ were a complex multiplet instead of a pair of doublets. Models suggest that the cis- and trans-1,4-adducts should be of comparable stability. It therefore seems quite reasonable that radical addition to cyclooctadiene should give substantial amounts of both stereoisomers. Separation of tetrahydro-I, which is thought to be the *trans* isomer, from the *cis* isomer could well be difficult, particularly since both may be contaminated with some 1,2-addition product.

(17) G. Fraenkel, private communication. We wish to thank Dr. Fraenkel for this and other valuable discussions of the interpretation of the various n.m.r. spectra.

(18) (a) B. W. Larner and A. T. Peters, *J. Chem. Soc.*, 680 (1952); (b) prepared from the anhydride [K. Alder and W. Vogt, *Ann.*, **571**, 137 (1951)] by the same procedure as used in ref. 18a.

[Contribution from the Department of Chemistry, University of California, Berkeley 4, Calif.]
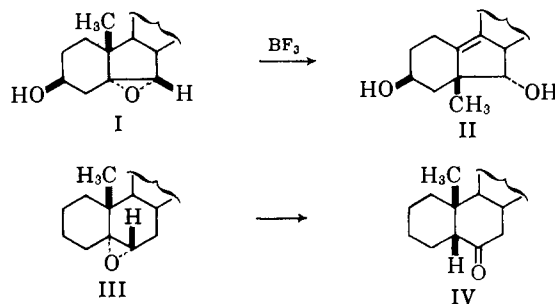
The Preparation of 8α-B-Norsteroid Derivatives[1,2]

By William G. Dauben, George A. Boswell, Jr.,[3] William Templeton and James W. McFarland

The effect of changes in bond hybridization at C-3 in a B-norsteroid on the thermodynamic stability of a remote center has been investigated in the B-norcoprostane-3,6-dione (V) series. In dione V an *anti*-B/C-ring juncture was found to be the stable form whereas a *syn*-B/C-ring juncture was favored in the 3-ol-6-one series. The chemistry of the various compounds was investigated.

In the course of a study directed toward the establishment of the stereochemistry of various B-norsteroid derivatives,[4] the boron trifluoride etherate-catalyzed rearrangement of 5α,6α-oxido-B-norcholestane-3β-ol (I) was studied. It was found that migration of the C-10 methyl group took place to form a Westphalen type of diol II. This result is in contrast to the usual rearrangement of 5α,6α-oxidocholestane (III) to 6-oxocoprostane (IV).[5] This marked change in the reaction course of a B-nor oxide must be due to indefinite long range conformational effects[6] which, in turn, may affect the steric strain introduced into the B-nor molecule by the presence of the methyl group at C-10. Since bond angle changes tend to bring about these

(1) For a preliminary publication of a portion of these results see W. G. Dauben, *Bull. soc. chim. France*, 1338 (1960).

(2) This work was supported, in part, by U. S. Public Health Grant CY-4284.

(3) General Electric Co. Fellow in Chemistry, 1958–1959.

(4) W. G. Dauben, G. A. Boswell, Jr., W. Templeton, J. W. McFarland and G. H. Berezin, *J. Am. Chem. Soc.*, **85**, 1672 (1963).

(5) H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.*, 4596 (1957).

(6) D. H. R. Barton, F. McCapra, P. J. May and T. Thudium, *ibid.*, 1297 (1960), and earlier papers.

long range conformational effects, it was of interest to see if modifying the bond angles in ring A by changing the hydridization at C-3 from tetrahedral to trigonal could also introduce a similar effect.

Earlier it had been found that the diketone V, possessing the *cis-anti-trans* orientation, was the most thermodynamically stable configuration of the molecule.[7,8] If conversion of C-3 to a tetrahedral state

(7) L. F. Fieser, *J. Am. Chem. Soc.*, **75**, 4386 (1953).

(8) W. G. Dauben and G. J. Fonken, *ibid.*, **78**, 4736 (1956).

changes the strain in the molecule, the configuration of C-5 or C-8 or both might well adopt a different configuration in the thermodynamically stable molecule.

When coprostane-3,6-dione (V) was allowed to react at zero degrees with a slight excess of sodium borohydride, selective reduction of the six ring ketone was achieved.[9,10] The reduction product was separated into a difficultly crystallizable material which readily formed a crystalline acetyl derivative and a crystalline solid. When analyzed by paper chromatography, the more difficultly crystallizable isomer VIa was found to be a pure material, but the readily crystallizable product was found to be a 1:1 complex of two materials, one of them being VIa, and was not further investigated. Wolff–Kishner reduction of VIa yielded B-

V
VIa, R = H
b, R = Ac
VII

X
IX
VIII
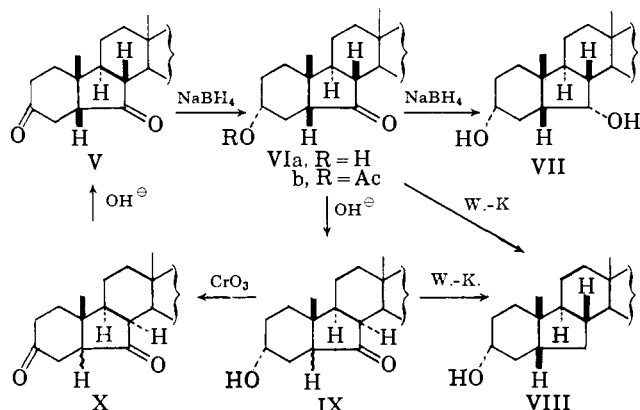
norcoprostane-3α-ol (VIII), indicating that VIa is 3α-hydroxy-B-norcoprostane-6-one. In order to make sure that the hydroxy group and the ring junctures were not epimerized under these strong alkaline conditions, VIa also was reduced with either sodium borohydride or lithium aluminum hydride to give B-nor-coprostane-3α,6α-diol (VII) and its 6β-isomer.[4]

3α-Hydroxy-B-norcoprostane-6-one (VIa) upon reaction with acetic anhydride was converted to its 3-acetyl derivative VIb and under the reaction conditions there was no change in stereochemistry of the molecule since the acetate VIb upon reduction with lithium aluminum hydride gave the same mixture of the 3α,6α- and 3α,6β-diols as did the starting olone VIa. In an attempt to reconvert the acetate back to its strongly dextrorotatory alcohol by saponification it was found that in addition to the parent olone VIa, an isomeric olone IX possessing a strong negative rotation was formed in about equal amounts. The isomeric olone IX upon Wolff–Kishner reduction, however, yielded B-norcoprostane-3α-ol (VIII). This result clearly indicated that during the reduction reaction, the isomeric olone IX first was reconverted to VIa which, in turn, underwent reduction. The interconversion of isomers in a Wolff–Kishner reduction finds an analogy in the reduction of a thermodynamically more stable C/D-cis-15-ketosapogenin to a C/D-trans-sapogenin,[11] a result which shows that the rate of reaction of hydrazine with the carbonyl group in the more stable isomer is slower than is the rate of reaction of the less stable isomer. The rate difference has been interpreted in steric hindrance terms and a similar explanation appears also to apply in this B-nor case. The carbonyl function in the new isomer IX is more hindered than is the similar group in VIa as shown by the complete reduction by lithium aluminum hydride of the latter

(9) W. G. Dauben and G. A. Boswell, Jr., *J. Am. Chem. Soc.*, **83**, 5003 (1961).

(10) H. C. Brown and K. Ichikawa, *Tetrahedron*, **1**, 221 (1957).

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

material in 5 hr. while in the former compound less than 50% of the carbonyl group was reduced in 24-hr.

The isomeric compound IX upon oxidation yielded a new diketone X which in contrast to its olone precursor was thermodynamically unstable and was isomerized back to the starting B-norcoprostane-3,6-dione (V) in base. Thus the conversion of the carbonyl group at C-3 to the corresponding alcohol (*i.e.*, changing C-3 from sp² to sp³) affects the normally stable configuration of the backbone of the B-nor molecule.

In such an isomerization reaction it always is possible that interaction between the hydroxyl and the carbonyl group can play a role. To establish that such an interaction was not functioning in the present case and only a bond hybridization change was responsible for this change in stability, B-norcoprostane-6-one (XI) was shown to change to the isomeric ketone XII upon alkaline treatment. Thus, this type of stereochemical modification is due to a change in internal strain caused

XI
XII
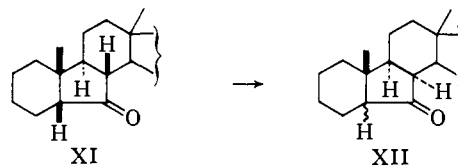
by conversion of a C-3 of a B-norsteroid from a trigonal to a tetrahedral state.

In this stereochemical change either the configuration of C-5, C-8, or both could have been affected. That more than a simple change from A/B-*cis* to A/B-*trans* had occurred was shown by the preparation of the authentic *trans-anti-trans*-dione XIV. B-Norcholesterol (XIII) was hydroborated in the standard fashion[12] to give B-norcholestane-3β-6α-diol (XIV) which upon oxidation yielded B-norcholestane-3,6-dione (XV). This latter material, in contrast to the dione X, which possesses a negative rotation, displayed a strong positive


XIII
XIV
V
XV
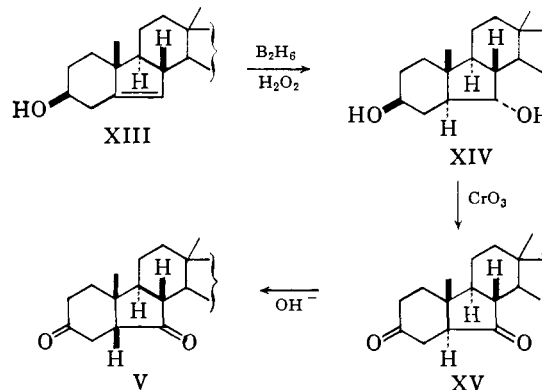
rotation. Upon reaction with alkali, XV was converted to B-norcoprostane-3,6-dione (V), again showing the thermodynamic stability of the latter material.

It follows that in the alkali-induced isomerizations of the B-norcoprostane-6-ones, the configuration of C-8 was changed from β to α to yield a compound with an 8,9-*syn* arrangement. From the present experiments the stereochemistry of the A/B-junctures in the 8-iso materials cannot be assigned. Examination of models show that the *cis-anti-cis* isomer can exist in an all-chair conformation while the *trans-anti-cis* tends to prefer ring C as a boat; only by undue strain can an all chair conformation be accommodated. This feature would suggest that the A/B *cis* configuration had remained in the new isomer but this conclusion is open

(12) S. Wolfe, M. Mussim, Y. Mazur and F. Sondheimer, *J. Org. Chem.*, **24**, 1034 (1959).

to question since it is difficult to assess strain energies in hydrindanes from models.

The change in the B/C ring juncture would not have been expected since such a change moves rings C and D from an extended form (XVI) to a conformation (XVII) in which there is crowding of the angular

XVI

XVII
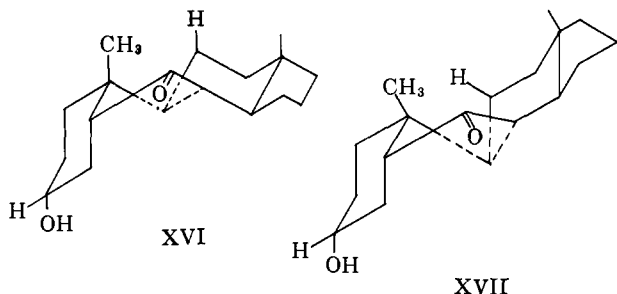
methyl group on C-10 and the C-11 methylene group. Also, in this form there exists a 1,3-diaxial arrangement between the carbon substituents on C-8 and C-13. The substitution of a carbonyl group for a methyl group is known not to lower appreciably this interaction.[13] Since about equal amounts of the two C-8 isomers were formed, these isomers must differ little in energy. It would be estimated that an energy change of about 1–2 kcal. took place when the hydridization of C-3 was changed. These long range conformational effects most likely have their origin in a distortion of bond angles and the present case seems to exhibit one of the more dramatic examples of this phenomenon.[6]

The alkaline isomerization of the backbone configuration is not limited to the B-nor steroids but it also has been found by Reichstein[14] to occur with A/B-cis-steroids. Their study of the 7-keto-etiocholanic acids has not been extensive and it is not possible at this time to evaluate the effect of bond angle change on the reactions in this series. The results do suggest that perhaps the energy difference between various stereochemical arrangements may be smaller than had heretofore been expected.

Experimental[15]

Reduction of B-Norcoprostane-3,6-dione (V) with Sodium Borohydride.—To a stirred solution of 1.50 g. (3.9 mmoles) of B-norcoprostane-3,6-dione[7] in 100 ml. of 95% ethanol, cooled to 0°, there was added 44 mg. (1.19 mmoles) of sodium borohydride in one portion. The suspension was stirred vigorously and after 20 min. the sodium borohydride had dissolved. The reaction mixture was allowed to react for 2 hr. at 0°, 15 ml. of glacial acetic acid was added, and after 30 min. the reaction mixture was poured into 1000 ml. of ice-water. The mixture was extracted three times with ether and the ether extract was washed with water and dried. The solvent was evaporated and the 1.48 g. of residual colorless oil ($\nu_{max}^{CS_2}$ 1730, 3390 cm.$^{-1}$) chromatographed on 60 mg. of Woelm neutral alumina (Activity III).

Elution with petroleum ether and petroleum ether-benzene (1:1) gave 115 mg. of crystalline starting dione. Elution with benzene yielded 630 mg. of oily 3α-hydroxy-B-norcoprostane-6-one (VIa). Continued elution with benzene-ether (2:1 and 1:1) gave 425 mg. of a crystalline complex (see below), elution with ether yielded 20 mg. of B-norcoprostane-3α,6α-diol, and finally ether gave 16 mg. of the 3β,6α-diol.

3α-Hydroxy-B-norcoprostane-6-one could be obtained as a solid by slow crystallization from pentane; m.p. 90–92°, [α]²⁰D +44° (c 0.5). The compound was more readily handled as the acetate which could be prepared by dissolving the 630 mg. of oil in 20 ml. of acetic anhydride and warming the solution at 100° for 1 hr. After the usual processing, the crude solid was recrystallized from methanol to yield 390 mg. (56%) of 3α-acetoxy-B-

(13) B. Rickborn, J. Am. Chem. Soc., 84, 2414 (1962).

(14) R. Jungmann, O. Schinder and T. Reichstein, Helv. Chim. Acta, 41, 1234 (1958).

(15) All melting points are corrected. All optical rotations were determined in chloroform. Paper chromatograms, using Whatman No. 1 paper, were run in phenyl Cellosolve-n-heptane and were developed with a 10% ethanolic solution of phosphomolybdanic acid. Analyses were performed by the Microanalytical Laboratory, College of Chemistry, University of California.

B-norcoprostane-6-one (VIb) as large, colorless needles, m.p. 110.5–111.0°, [α]²⁵D +77° (c 0.54).

Anal. Calcd. for $C_{28}H_{46}O_3$ (430.65): C, 78.09; H, 10.77. Found: C, 77.92; H, 10.78.

The crystalline complex from the above chromatography was recrystallized from petroleum ether and from aqueous methanol to yield the 1:1 complex as fine, white needles, m.p. 116–118°, [α]²⁰D +47° (c 1.99). Upon paper chromatography, there were obtained two spots of equal intensity at R_f 0.25 and 0.35. The former spot was shown to be due to the 3α-isomer VIa.

Anal. Calcd. for $C_{26}H_{44}O_2$ (388.61): C, 80.35; H, 11.41. Found: C, 80.75; H, 11.63.

Wolff–Kishner Reduction of 3α-Acetoxy-B-norcoprostane-6-one (VIb).—A solution of 0.225 g. (0.52 mmole) of VIb, 5.0 g. of potassium hydroxide, 5 ml. of 85% hydrazine hydrate, and 25 ml. of diethylene glycol was heated under reflux for 1 hr. The excess hydrazine and water were allowed to distil by removal of the reflux condenser and raising the bath temperature to 210°. When the temperature of the reaction mixture had reached 200°, the condenser was replaced, and the remaining solution was heated under reflux for 3 hr. The reaction mixture was cooled to room temperature, diluted with water, and extracted with ether. The ethereal extracts were washed successively with dilute hydrochloric acid, water, dilute sodium bicarbonate solution, and saturated sodium chloride solution and then dried over magnesium sulfate. The solvent was removed under reduced pressure and the 0.158 g. of residual oil was chromatographed on Woelm neutral alumina (Act. III). Elution with petroleum ether-benzene (1:1) gave 0.124 g. (63.5%) of crystalline alcohol, m.p. 85–88°. Recrystallization from methanol gave 0.084 g. (43%) of B-norcoprostane-3α-ol as long, silk-like needles, m.p. 95–96°, [α]²⁰D +16° (c 1.01). The literature values[4] are identical with those just found and the sample possessed an identical infrared spectrum as found with an authentic sample.

Anal. Calcd. for $C_{26}H_{46}O$ (374.63): C, 83.35; H, 12.38. Found: C, 83.31; H, 12.10.

Sodium Borohydride Reduction of 3α-Hydroxycoprostane-6-one (VIa).—To a stirred solution of 0.180 mg. (0.41 mmole) of olone VIa (purified by chromatography and analyzed by paper chromatography) in 30 ml. of methanol-ether (3:1) there was added 0.5 g. of sodium borohydride and the reaction mixture was stirred at room temperature for 10 hr. The mixture was decomposed with dilute hydrochloric acid and processed in the usual manner; yield 0.150 g. The total crude product was chromatographed on Woelm neutral alumina (Act. III). Elution with benzene and benzene-ether gave 86 mg. (49%) of B-norcoprostane-3α,6α-diol, m.p. 138–140°, [α]²⁰D ± 0° (c 1.42), identical in all respects with an authentic sample.[4] Further elution with ether gave 30 mg. (21%) of B-norcoprostane-3α,6β-diol, m.p. 170–173°, identical in all respects with an authentic sample.[4]

Lithium Aluminum Hydride Reduction of 3α-Acetoxy-B-norcoprostane-6-one (VIb).—A solution of 96 mg. (0.22 mmole) of the acetate VIb in 10 ml. of tetrahydrofuran was treated with a slurry of 0.2 g. of lithium aluminum hydride in 10 ml. of tetrahydrofuran. The reaction mixture was heated under reflux for 5 hr. and processed in the usual fashion. Chromatography as described above gave 29 mg. of B-norcoprostane-3α,6α-diol, m.p. 138–140°, and 31 mg. of the B-norcoprostane-3α,6β-diol, m.p. 172–173°. Both materials were identical with authentic samples.[4]

Alkali Isomerization of 3α-Acetoxy-B-norcoprostane-6-one (VIb).—A solution of 400 mg. (0.91 mmole) of VIb and 1 g. of potassium hydroxide in 25 ml. of methanol was allowed to stand for 10 hr. at room temperature. The solution was poured into water and the organic materials isolated by ether extraction. The solvent was removed under reduced pressure and the residue chromatographed on Woelm neutral alumina (Act. III). Elution with hexane-benzene (1:1) and recrystallization from methanol gave 160 mg. of 3α-hydroxy-8-iso-B-norcoprostane-6-one (IX), m.p. 113–114°, [α]²⁵D −43° (c 0.53). Further recrystallization gave material, m.p. 118.0–118.5°, [α]²⁵D −52° (c 2.44).

Anal. Calcd. for $C_{26}H_{44}O_2$ (388.61): C, 80.35; H, 11.41. Found: C, 80.43; H, 11.50.

Elution with benzene-ether (9:1 and 4:1) gave 220 mg. of 3α-hydroxy-B-norcoprostane-6-one (VIa), which was recrystallized from hexane; m.p. 90–92°, [α]²⁰D +44° (c 0.50).

Wolff–Kishner Reduction of 3α-Hydroxy-8-iso-B-norcoprostane-6-one (IX).—A solution of 120 mg. (0.31 mmole) of iso-olone IX, 2.5 g. of potassium hydroxide and 3 ml. of hydrazine hydrate in 25 ml. of diethylene glycol was treated in the usual manner as described above for the similar reaction. After chromatography there was obtained 50 mg. (44%) of B-norcoprostane-3α-ol as white needles, m.p. 95–96°, undepressed on admixture with an authentic sample, [α]²⁰D +16° (c 0.86). The infrared spectra of this material and of the authentic sample were identical.

8-Iso-B-norcoprostane-3,6-dione (X).—To a stirred solution of 100 mg. (0.26 mmole) of iso-olone IX in 20 ml. of purified acetone, in a nitrogen atmosphere, there was added dropwise 0.25 ml. of a

2.67 M solution of chromic acid in sulfuric acid.[16] The reaction mixture was stirred for 10 min. at room temperature, at the end of which time excess oxidizing agent was still present. Methanol was added until the solution turned green, the mixture was diluted with water, and the product isolated with ether. Evaporation of the ether gave 100 mg. of a colorless oil which crystallized upon trituration with petroleum ether. The crude product was recrystallized from ether–petroleum ether; yield 80 mg. (72%), m.p. 135–137°, $[\alpha]^{20}D$ −61° (c 1.11); $\nu_{max}^{CS_2}$ 1730, 1705 cm.$^{-1}$. In contrast to V, this 8-iso-dione crystallized poorly from methanol.

Anal. Calcd. for $C_{26}H_{42}O_2$ (386.58): C, 80.83; H, 10.97. Found: C, 80.76; H, 11.17.

Alkali Isomerization of 8-Iso-B-norcoprostane-3,6-dione (X).—In a nitrogen atmosphere, 2.0 g. of potassium hydroxide was added to a solution of 124 mg. (0.32 mmole) of X in 50 ml. of methanol and the solution was allowed to stand under a nitrogen atmosphere for 18 hr. The excess alkali was neutralized with hydrochloric acid and the product isolated in the usual way with ether. The ether was removed under reduced pressure and the residual yellow crystals chromatographed on Woelm neutral alumina (Act. III). There was obtained 95 mg. (77%) of crystalline dione (m.p. 90–95°) which was recrystallized from petroleum ether to yield B-norcoprostane-3,6-dione, m.p. 104–107°, $[\alpha]^{20}D$ −42° (c 1.41). The infrared spectra of this material and of an authentic sample were superimposable.

8-Iso-B-norcoprostane-6-one (XII).—A solution of 121 mg. (0.32 mmole) of B-norcoprostane-6-one[17] in 20 ml. of 5% potassium hydroxide in methanol was heated under reflux for 41 hr. The solution was kept under a nitrogen atmosphere for the entire period. The reaction solution was concentrated under reduced pressure and the oily residue dissolved in ether. The ethereal solution was washed with water, the solution dried, and the solvent removed to yield 114 mg. (94%) of a clear oil. The entire product was chromatographed on Woelm neutral alumina (Act. I) and 70 mg. of a clear oil was obtained by elution with petroleum ether–benzene (9:1 and 4:1). The material could not be obtained crystalline, but it possessed an infrared spectrum grossly different from that of the starting ketone. The material had $[\alpha]^{20}D$ −42.5° (c 1.40) as compared[17] to $[\alpha]D$ +34° for the starting material.

Anal. Calcd. for $C_{26}H_{44}O$ (372.61): C, 83.80; H, 11.90. Found: C, 83.35; H, 11.60.

B-Norcholestane-3β,6α-diol (XIV).—A solution of 0.5 g. (1.35 mmoles) of B-norcholesterol and 0.75 g. of boron trifluoride etherate in 20 ml. of dry ether was added dropwise, over a 1-hr.

period, to a stirred solution of 0.15 g. of lithium aluminum hydride in 10 ml. of dry ether. The entire reaction was conducted at room temperature under a nitrogen atmosphere. The mixture was stirred for one additional hour, excess saturated magnesium sulfate solution added, the mixture filtered, and the ether evaporated. The residue was dissolved in tetrahydrofuran and stirred for 30 min. with an excess of 10% aqueous potassium hydroxide and 30% hydrogen peroxide. The solution was poured into water and the organic material extracted with ether. Upon removal of the ether the product crystallized, m.p. 178–183°. The product was recrystallized from methanol; yield 450 mg. (86%), m.p. 191–192°, $[\alpha]^{20}D$ +7.4° (c 0.89). Upon chromatography on paper, the compound showed one spot and the R_f was different from that shown by B-norcholestane-3β,6β-diol.

Anal. Calcd. for $C_{26}H_{46}O_2$ (390.63): C, 79.94; H, 11.87. Found: C, 79.66; H, 11.66.

B-Norcholestane-3,6-dione (XV).—To a stirred solution of 200 mg. (0.51 mmole) of B-norcholestane-3β,6α-diol in 25 ml. of purified acetone at −25°, under a nitrogen atmosphere, there was added 0.4 ml. of a 2.67 M solution of chromic acid in sulfuric acid.[16] After 20 min., excess methanol was added, the mixture was poured into water, and the mixture extracted with ether. The ethereal extract was evaporated and the residual yellow crystals (190 mg., m.p. 110–115°) were recrystallized from methanol; m.p. 138–140°, $[\alpha]^{20}D$ +129° (c 1.09); $\nu_{max}^{CHCl_3}$ 1730, 1715 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{42}O_2$ (386.58): C, 80.83; H, 10.97. Found: C, 80.63; H, 10.89.

Alkali Isomerization of B-Norcholestane-3,6-dione (XV).—In a nitrogen atmosphere, 2.0 g. of potassium hydroxide was added to a solution of 125 mg. (0.32 mmole) of B-norcholestane-3,6-dione in 50 ml. of methanol and the solution allowed to stand under a nitrogen atmosphere for 18 hr. The solution was poured into dilute hydrochloric acid and the resulting mixture extracted with ether. The ether extract was evaporated and the yellow oily residue was dissolved in methanol and allowed to stand for 2 days in a refrigerator. During this time 17 mg. of $\Delta^{2,4,6}$-B-norcholestatriene-3,6-diol[18] crystallized and was removed. The methanol was removed from the filtrate, the residue dissolved in hexane, and the solution placed on a column of Woelm neutral alumina (Act. III). Elution with hexane–benzene (3:1) gave 17 mg. of an oil. Elution with hexane–benzene (1:1) yielded 42 mg. of an oil which crystallized as yellow needles, m.p. 100–103°. The product was recrystallized from methanol to yield colorless needles, m.p. 112–114°, $[\alpha]^{20}D$ −35° (c 0.9). The infrared spectrum was identical with that of B-norcoprostane-3,6-dione. and when the two materials were mixed there was no depression in the melting point.

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The Absolute Configuration of Steviol and Isosteviol

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Steviol (I) was degraded to stevane A (XVII) which was identical with (−)-α-dihydrokaurene. A similar transformation was carried out on steviol (I) *via* 19-hydroxystevane B (XXIV) to stevane B (XVIII). Stevane B (XVIII), the C-16 epimer of stevane A (XVII), was found to be identical with the hydrocarbon derived from garryfoline; however, alcohol XXIV and the primary alcohol from garryfoline were different. These chemical interconversions with the phyllocladene-type diterpenes and the diterpene alkaloids of the Garrya, coupled with various optical rotatory dispersion and other physical measurements, have resulted in the establishment of the complete absolute configuration of the diterpene acids steviol (I) and isosteviol (II).

A series of recent communications[2] has described correlations of steviol (I) and isosteviol (II) with other diterpenes and diterpene alkaloids,[3] the results of which

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(2) (a) F. Dolder, H. Lichti, P. Quitt and E. Mosettig, *J. Am. Chem. Soc.*, **82**, 246 (1960); (b) E. Mosettig, P. Quitt, U. Beglinger, J. A. Waters, H. Vorbrueggen and C. Djerassi, *ibid.*, **83**, 3163 (1961); (c) C. Djerassi, P. Quitt, E. Mosettig, R. C. Cambie, P. S. Rutledge and L. H. Briggs, *ibid.*, **83**, 3720 (1961).

(3) For a complete discussion of the correlations existing between the diterpene alkaloids (Garrya and Atisine) and the diterpenes of the phyllocladene-type (*e.g.*, kaurene and steviol–isosteviol) see H. Vorbrueggen and C. Djerassi, *ibid.*, **84**, 2990 (1962).

have enabled us to assign the absolute configuration of our diterpene acids as depicted in structures I and II.

Stevioside,[4] the principal constituent of *Stevia Rebaudiana* Bertoni, on enzymatic hydrolysis yields steviol (I),[5] while treatment of the glucoside with 48% hydrobromic acid gives isosteviol (II). Isosteviol (II) can also be obtained by acid treatment of steviol (I) *via* a Meerwein rearrangement.

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