were those expected, with the rearrangement ion (*m/e* 74) the most abundant. Again the diester gave M + 1 (*m/e* 217) considerably more abundant than M.

Registry No.—**1**, 30409-26-8; **2**, 30345-96-1; deuterated methyl tetradecapentaenoate, 30345-97-2.

Acknowledgment.—We wish to express our appreciation to Dr. C. R. Smith, Jr., Northern Regional Research Laboratory, Peoria, Ill., who, when the manuscript was originally submitted, included in his referee report recommendations which led to our establishing the correct structures for the ajenoic acids.

Structural Modifications of Isosteviol. Partial Synthesis of Atiserene and Isoatiserene[1]

ROBERT M. COATES* AND EDWARD F. BERTRAM

Department of Chemistry, University of Illinois, Urbana, Illinois 61801

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By means of functional interconversions in ring D of the tetracyclic diterpene isosteviol (*ent*-16-oxobeyeran-19-oic acid, **1**), various 15- and 16-substituted methyl *ent*-beyeran-19-oates (**3**–**7**) have been prepared. Ring C functionalization at positions 12 and 14 has been accomplished by degradation of isosteviol to the unsaturated tricyclic tosylate esters **14c** and **15c** [methyl *ent*-8α-(2′-tosyloxyethyl)-13-methyl-12-podocarpen-19-oate and its Δ^{13} double bond isomer] followed by recyclization. Buffered formolysis of **14c** at room temperature affords after partial hydrolysis methyl *ent*-16β-hydroxyatisan-19-oate (**16a**), which at 85° in formic acid rearranges to methyl *ent*-12β-formyloxybeyeran-19-oate (**18d**). Formolysis of **15c** at 80° gives a tetracyclic formate formulated as methyl *ent*-14β-formyloxybeyeran-19-oate (**17d**). Dehydration of **16a** produces the exocyclic and endocyclic unsaturated esters **21** and **22** which were separately converted into atiserene (**25**) and isoatiserene (**28**).

In order to examine the biogenetic-like rearrangements within the kaurene and atiserene family of tetracyclic diterpenes,[2] we needed synthetic access to both 12β- and 16β-beyerane (hibaane) derivatives with functional groups suitable for the generation of carbonium ion intermediates. This paper describes the conversion of the relatively available diterpene, isosteviol (**1**, *ent*-16-oxobeyeran-19-oic acid),[3–6] into the 12β-hydroxy (**18a**), 16β-hydroxy (**7a**), and 16-amino (**4**) esters. The synthetic route to the 12β-hydroxy ester, proceeding by way of methyl *ent*-16β-hydroxyatisan-19-oate (**16**), opened the way to a partial synthesis of atiserene (**25**) and isoatiserene (**28**).[2b,7]

Since sodium borohydride reduction of the 16-carbonyl group of isosteviol methyl ester **2** affords exclusively the undesired endo (α) hydroxy ester **5a**,[8] the investigation of other approaches was necessary. Hydroboration of the unsaturated ester **8** with disiamylborane[9] in tetrahydrofuran gave rise to a 2:3 mixture of the two exo (β) hydroxy esters **6a** and **7a**. A 3:2 distribution of the 15β and 16β isomers has been reported for hydroboration of hibaene (*ent*-15-beyerene, **8** with CH_3 in place of CO_2CH_3) with diborane.[10] Although a partial separation of the mixture could be achieved by column chromatography of the corresponding acetates **6b** and **7b**, the purification was both tedious and inefficient. Reduction of isosteviol methyl ester by the Meerwein–Ponndorf–Verley method under equilibrating conditions[11] for prolonged periods afforded a mixture (about 1:1) of **5a** and **7a**, which again was partially separated by repeated chromatography of the acetate derivatives **5b** and **7b**. However, by recycling the undesired endo isomer along with mixed factions, a satisfactory yield (59%) of **7b** was realized. Amino ester **4** was prepared by reduction of the oxime **3** of isosteviol methyl ester with sodium in isopropyl alcohol (Scheme I).

The stereochemistry of the hydroxyl group in **5**, **6**, and **7** is assigned on the assumption that attacking reagents in irreversible reactions will approach the 15 or 16 positions of the beyerane nucleus from the exo (β) direction. Although there exists extensive precedent for high stereoselectivity in a wide variety of reactions involving several D ring functional groups in tetracyclic diterpenoids,[12] independent stereochemical evidence is, to our knowledge, limited to recent nmr data (car-

(1) Taken in part from the Ph.D. thesis of E. F. B., University of Illinois, 1970.

(2) (a) R. M. Coates and E. F. Bertram, *Tetrahedron Lett.*, 5145 (1968); (b) R. M. Coates and E. F. Bertram, *Chem. Commun.*, 797 (1969); (c) manuscript in preparation.

(3) Isolation: (a) H. B. Wood, Jr., R. Allerton, H. W. Diehl, and H. G. Fletcher, Jr., *J. Org. Chem.*, **20**, 875 (1955); (b) M. Ruddat, E. Heftmann, and A. Lang, *Arch. Biochem. Biophys.*, **110**, 496 (1965).

(4) Source of *Stevia Rabaudiana* Bertoni (dried leaves and stems or extract): Mr. Luis Enrique de Gesperi, Empresas Ago-Industrales, Asuncion, Peru. We are grateful to Mr. de Gesperi for a sample of the extract.

(5) Structure: (a) E. Mosettig, U. Beglinger, F. Dolder, H. Lichti, P. Quitt, and J. A. Waters, *J. Amer. Chem. Soc.*, **85**, 2305 (1963); (b) J. R. Hansen, "The Tetracyclic Diterpenes," Pergamon Press, Oxford, England, 1968, pp 23–25.

(6) The numbering system used throughout this paper conforms to the recommendations ("The Common and Systematic Nomenclature of Cyclic Diterpenes," 3rd revision, Oct 1968; Adenda and Corrigenda, Feb 1969) prepared by J. W. Rowe (Forest Products Laboratory, Forest Service, U. S. Department of Agriculture, Madison, Wisc. 53705). Both common and systematic names are used in the text as appropriate; complete systematic names appear in the Experimental Section. We are grateful to Dr. Rowe for copies of these recommendations.

(7) A. A. Kapadi, R. R. Sobti, and S. Dev, *Tetrahedron Lett.*, 2729 (1965); A. A. Kapadi and S. Dev, *ibid.*, 2751 (1964).

(8) J. R. Hanson, *Tetrahedron*, **23**, 793 (1967).

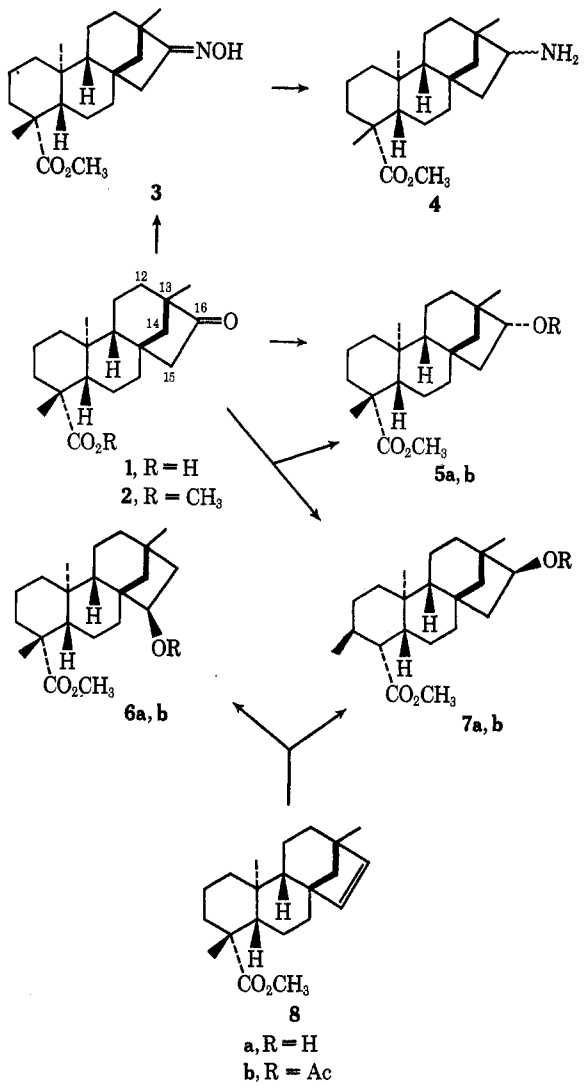
(9) (a) G. Zweifel, K. Nagase, and H. C. Brown, *J. Amer. Chem. Soc.*, **84**, 190 (1962); (b) H. C. Brown and G. Zweifel, *ibid.*, **83**, 1241 (1961).

(10) R. R. Sobti and S. Dev, *Tetrahedron Lett.*, 3939 (1966).

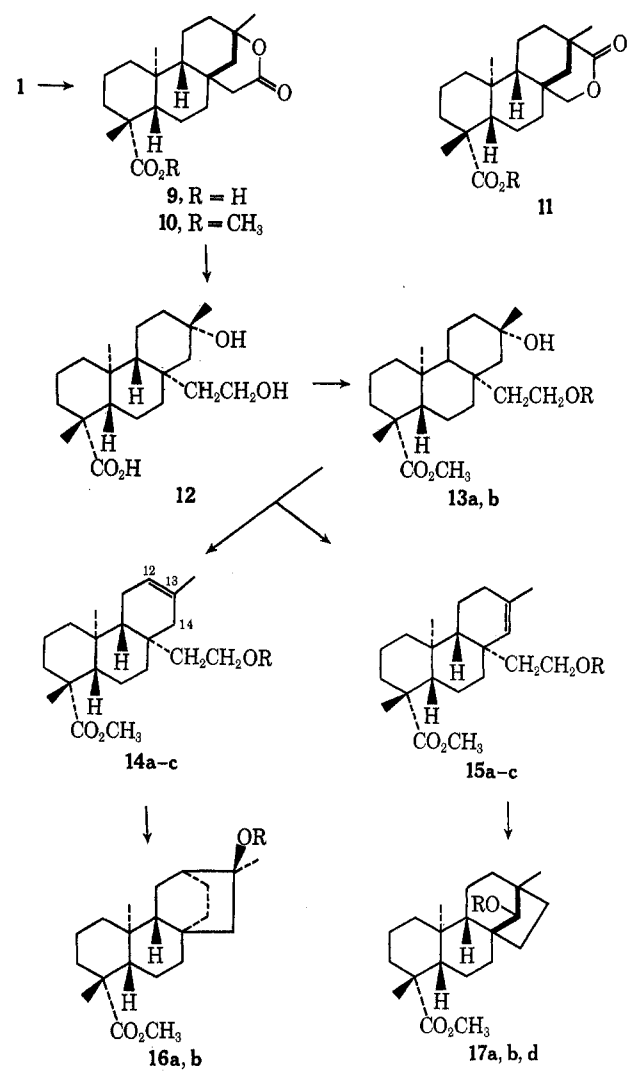
(11) C. F. Wilcox, Jr., M. Sexton, and M. F. Wilcox, *J. Org. Chem.*, **28**, 1079 (1963).

(12) The following selection of references include osmium tetroxide oxidation, epoxidation, hydride reduction, catalytic hydrogenation, sensitized oxygenation, hydroboration, and Grignard addition: (a) P. K. Grant and R. Hodges, *Tetrahedron*, **8**, 261 (1960); (b) J. R. Hanson, *J. Chem. Soc.*, 5061 (1963); (c) L. H. Briggs, B. F. Cain, R. C. Cambie, B. R. Davis, P. S. Rutledge, and J. K. WilmsHurst, *ibid.*, 1345 (1963); (d) R. A. Finnegan, *J. Org. Chem.*, **26**, 3057 (1961); (e) L. H. Briggs, R. C. Cambie, and P. S. Rutledge, *J. Chem. Soc.*, 5374 (1963); (f) L. H. Briggs, B. F. Cain, R. C. Cambie, and B. R. Davis, *ibid.*, 1840 (1962); (g) H. Vorbreugen and C. Djerassi, *J. Amer. Chem. Soc.*, **84**, 2990 (1962); (h) B. E. Cross, R. H. B. Galt, and J. R. Hanson, *J. Chem. Soc.*, 2944 (1963); (i) M. Barnes and J. MacMillan, *ibid.*, *C*, 361 (1967); (j) J. R. Hanson, *Tetrahedron* **23**, 801 (1967); (k) K. Mori and M. Matsui, *ibid.*, **24**, 3095 (1968); (l) R. A. Appleton, P. A. Gunn, and R. McCrindle, *J. Chem. Soc.*, 1148 (1970), and ref 5 8, and 10.

SCHEME I



SCHEME II



binyl proton half-widths) for the epimeric 17-norkauran-16-ols and 17-norphyllocladanols[12j,l] and the X-ray crystallographic structure determination on the alkaloid lucidusculine.[13,15]

The introduction of a substituent at the 12β position was accomplished by an indirect route (Scheme II) in which ring D is first opened and then reclosed by solvolytic cyclization. Baeyer–Villiger oxidation of isosteviol with sodium acetate buffered peroxyacetic acid[17] furnished the lactone acid **9**. The absence of absorptions expected for the $-CH_2OCO-$ group (τ ~6.0) in the nmr spectrum of this substance decisively excludes the isomeric lactone **11**. Lithium aluminum hydride effected selective reduction of the lactone leaving the hindered C-4 carboxyl group unchanged. Esterification with diazomethane and selective acetylation gave the diol monoacetate **13b**. Dehydration of **13b** under a variety of conditions (see Experimental Section) gave a mixture of the Δ^{12} and Δ^{13} double bond isomers **14a** and **15a**. The best conditions found (thionyl chloride in methylene chloride–collidine at 0°) produced a 2:1 ratio of the isomers, a selectivity rather less favorable than might have been expected.[18] The nmr spectrum of the mixture shows two distinct vinyl protons (τ 4.67 and 4.90) for the major and minor isomers, respectively.[19] The greater breadth of the lower field absorption band ($W_{1/2}$ = 9 *vs.* 4 Hz at 60 MHz) forms the basis for the isomer assignments in view of the additional vicinal coupling expected for the vinyl proton of **14a**. Since the two isomers could not be separated, the mixture was

(13) (a) A. Yoshino and Y. Itaki, *Acta Crystallogr.*, **21**, 57 (1966). (b) Lithium aluminum hydride reduction of isonapelline (15-ketone) gives dihydronapelline B; thus hydride attacks from the exo direction to produce the endo hydroxyl group at C-15 as in natural napelline (luiciculine).[14]

(14) (a) K. Wiesner and Z. Valenta, *Fortschr. Chem. Org. Naturst.*, **16**, 26 (1958); (b) S. W. Pelletier and L. H. Keith in "The Alkaloids," Vol. XII, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1970, Chapter 2.

(15) Although predictions that the exo isomer will be thermodynamically more stable than the endo in an equilibratable epimeric pair have been used to assign the orientation of various C-17 substituents,[12j,g,16] in the one case for which the position of equilibrium has actually been measured (kauran-15-ones), the endo isomer predominates by a 3:2 margin.[12i] (The equilibration of **5a** and **7a** to a 1:1 mixture is another example.) Kauran-17β-al is reported to isomerize to a mixture of epimers[12i] while methyl kaurane-17β-19-dioate,[12k] and kauran-17β-oic acid[12i] on the other hand, are converted to the 17α epimers. Thus, the stability predictions seem to be equivocal at present.

(16) G. V. Baddeley, P. R. Jefferies, and R. W. Retallack, *Tetrahedron*, **20**, 1983 (1964).

(17) R. R. Sauers, *J. Amer. Chem. Soc.*, **81**, 925 (1959).

(18) (a) D. H. R. Barton, A. da S. Campos-Neves, and R. C. Cookson, *J. Chem. Soc.*, 3500 (1956); see also R. M. Carman and H. C. Deeth, *Aust. J. Chem.*, **23**, 1053 (1970); (b) R. B. Turner, W. R. Meador, and R. E. Winkler, *J. Amer. Chem. Soc.*, **79**, 4122 (1957).

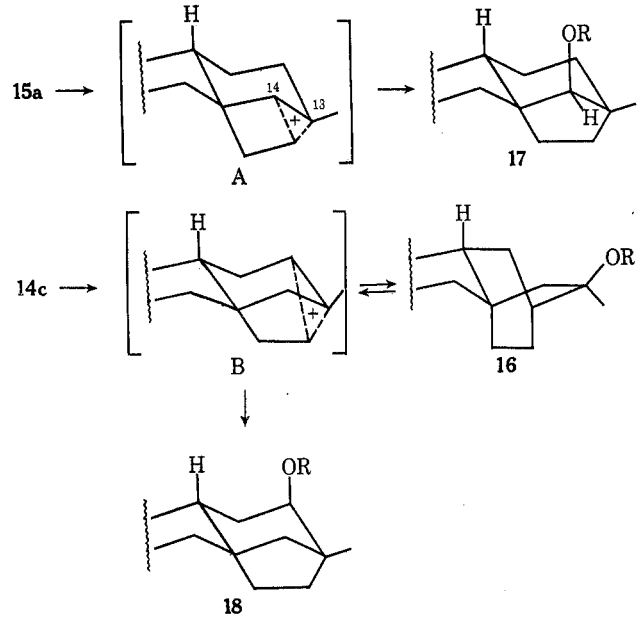
(19) The presence of a small amount (*ca.* 5%) of the exocyclic double bond isomer could also be detected in the nmr spectrum (τ 5.3, $=CH_2$).

carried on to the tosylates (**14c** + **15c**) by partial hydrolysis to the hydroxy esters (**14b** + **15b**) followed by reaction with tosyl chloride.

Solvolysis of the tosylate mixture in buffered formic acid under relatively mild conditions (23–25°, 3.5 hr) effected cyclization of **14c** to the tetracyclic ring system of atiserene. After alkaline hydrolysis and chromatography, the hydroxy ester **16a** and unchanged **15c** were isolated in high yield. At higher temperature (80°, 5 hr), the Δ^{13} toslyate underwent solvolytic cyclization to a secondary formate, which was purified and characterized after partial hydrolysis to the hydroxy ester. This substance is tentatively formulated as methyl *ent*-14β-hydroxybeyeran-19-oate (**17a**). The nmr spectra of **17a** and **17b** showed singlets ($W_{1/2}$ = 2 Hz) for the carbinyl protons (τ 7.06 and 5.53). These data as well as the position of the C-13 methyl group (τ 9.07 and 9.12) are in rather good agreement with nmr data reported for beyeran-14β-ol[20] and beyerane-14β,19-diol (*i.e.*, enantiomers of **17a** with $-CH_3$ and $-CH_2OH$ in place of CO_2CH_3).[20a] The fact that tosylate **15c** leads to the same tetracyclic system as is produced in the formic acid cyclization of manool[20a,b] and agathadiol[20a] provides additional support[21] for the mechanism suggested.[20a,b] Both reactions proceed through the common cationic intermediate A.[22]

The difference in the solvolytic reactivity of the two unsaturated tosylates **14c** and **15c** was not unexpected since acetolysis of 2-(2′-cyclohexenyl)ethyl brosylate results only in direct substitution[23] while 2-(3′-cyclohexenyl)ethyl brosylate gives mainly cyclization to bicyclic products.[24] Although methyl group substitution is known to facilitate double bond participation in solvolysis reactions,[25] in order for the methyl group of **15c** to stabilize the developing positive charge in the transition state leading to ion A, there must be partial bond formation to C-14. However, this stabilization is offset by the simultaneous increase in the strain resulting from partial cyclobutane formation. On the other hand, double bond participation in the solvolysis of **14c** leads to a comparatively unstrained transition state on the way to B.[22]

Since a single isomer of the tertiary alcohol **16a** was isolated in high yield, it seems likely that the bridging carbon has directed the entering nucleophile (formate) to the opposite side, *i.e.*, syn to the C-9 proton as indicated. Nucleophilic attack upon an open (*i.e.*, symmetrically solvated) carbonium ion would appear to be relatively unhindered from either direction.[26] Similarly the hydroxyl group in **17a** is most probably β oriented, opposite to the two carbon side chain in **15c**.[20,28]



Exposure of hydroxy ester **16a** to more vigorous formolysis conditions (85°, 4 hr) induces Wagner–Meerwein rearrangement to the desired 12β-*ent*-beyerane derivative **18d**. The formate was converted by hydrolysis and acetylation to the corresponding acetate **18b** in order to facilitate chromatographic separation from recovered **16**. The structure of the rearrangement product was established by oxidation of the alcohol (**18a**) to the keto ester **19** (ν_{max}^{KBr} 1695, 1720 cm^{-1}) and Wolff–Kishner reduction to the saturated tetracyclic ester **20**. Authentic samples of **20** were obtained by Wolff–Kishner reduction of isosteviol methyl ester (**2**) and catalytic hydrogenation of **8**.

The relatively narrow breadth ($W_{1/2}$ = 5.5 Hz at 60 MHz) of the C-12 carbinyl proton in the nmr spectrum of **18b** indicates that the acetoxyl group is β and axial to the six-membered C ring. If the acetoxyl group were equatorial (α), the width of this peak should be considerably broader ($W_{1/2}$ > 10 Hz) from the larger axial–axial coupling.[29] Thus, the formate group has again been introduced on the side opposite to the participating carbon–carbon bond (Scheme III).

The Wagner–Meerwein rearrangement of **16a** to **18d** thus evidently proceeds through the same cation B as is produced in the formolysis of the unsaturated tosylate **14c**. At the lower temperature of the latter reaction, kinetic control results in attack at the more highly

(20) (a) O. E. Edwards and R. S. Rosich, *Can. J. Chem.*, **46**, 1113 (1968). (b) E. Wenkert and Z. Kumazawa, *Chem. Commun.*, 140 (1968). (c) The chemical shift reported in ref a for the C-14 carbinyl proton of beyeran-14β-ol (τ 7.58) appears to be in error since the same proton in beyerane-14β,19-diol is given as τ 7.09 and ref b reports τ 7.10 for beyeran-14β-ol. Furthermore, ref 21a gives τ 7.08.

(21) (a) O. E. Edwards and B. S. Mootoo, *Can. J. Chem.*, **47**, 1189 (1969); (b) J.-L. Fourrey, J. Polonsky, and E. Wenkert, *Chem. Commun.*, 714 (1969); (c) S. F. Hall and A. C. Oehlschlager, *ibid.*, 1157 (1969).

(22) The bridged ions depicted in A and B may be taken to represent either nonclassical carbonium ions or transition states between a pair of classical Wagner–Meerwein isomers, according to the reader's preference.

(23) A. A. Youssef and S. M. Sharaf, *J. Org. Chem.*, **33**, 2581 (1968).

(24) (a) S. Winstein and P. Carter, *J. Amer. Chem. Soc.*, **83**, 4485 (1961); (b) see also W. Herz, A. K. Pinder, and R. N. Mirrington, *J. Org. Chem.*, **31**, 2257 (1966).

(25) P. D. Bartlett and G. D. Sargent, *J. Amer. Chem. Soc.*, **87**, 1297 (1965); P. G. Gassman and D. S. Patton, *ibid.*, **91**, 2160 (1969); O. L. Chapman and P. Fitton, *ibid.*, **85**, 41 (1963); H. Felkin and C. Lion, *Chem. Commun.*, 60 (1968).

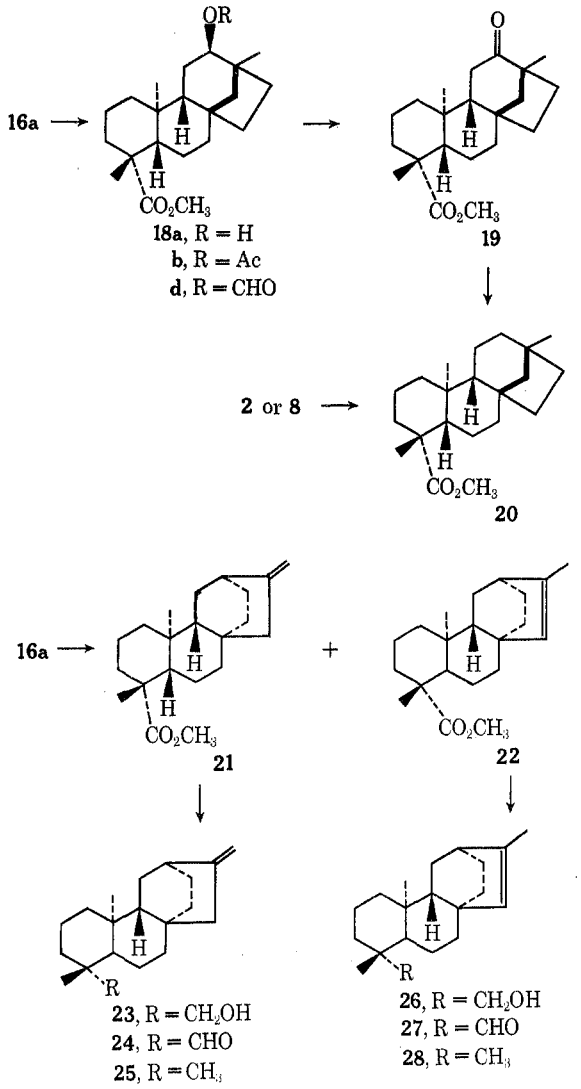
(26) In contrast to the high exo stereoselectivity observed in reactions at positions 15 and 16 in diterpenes having a bicyclo[3.2.1]octane for the C and D rings,[12] the diterpenes with a bicyclo[2.2.2]octane show little selectivity.[14b,27]

(27) (a) L. H. Zalkow and N. N. Girota, *J. Org. Chem.*, **29**, 1299 (1964); (b) R. A. Bell, R. E. Ireland, and L. N. Mander, *ibid.*, **31**, 2536 (1966); (c) S. W. Pelletier, *Quart. Rev., Chem. Soc.*, **21**, 525 (1967).

(28) Since hydride reduction of beyeran-14-one produces a single alcohol with the same C-14 configuration as the solvolysis product,[20a,b] the formate group is evidently entering from the more hindered side. Thus, the stereochemical influence of the carbon bridging prevails over the existing steric effects.

(29) (a) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, pp 79–80; (b) R. H. Bible, Jr., "Interpretation of NMR Spectra," Plenum Press, New York, N. Y., 1965, pp 109–111.

SCHEME III



substituted position (16), while at the higher temperature **16** (a or d) reionizes to B allowing the thermodynamically more stable **18d** to accumulate slowly. Similar interconversions have been observed in the rearrangements of substituted norbornyl derivatives.[30]

Dehydration of the tertiary alcohol **16a** with thionyl chloride in methylene chloride–pyridine affords a mixture of the exocyclic (37%) and endocyclic (50%) unsaturated esters, **21** and **22**, separable by chromatography on silica gel impregnated with silver nitrate. Both **21** and **22** were converted to atiserene (**25**) and isoatiserene (**26**) by the sequence—lithium aluminum hydride reduction, chromium trioxide–dipyridine complex oxidation,[31] and Wolff–Kishner reduction. The melting points, optical rotations, and nmr data are in good agreement with the literature data for atiserene[7,27a,32] and isoatiserene.[7] In addition, the complete ir and nmr spectra of natural atiserene proved to be superimposable upon the corresponding spectra of **25** obtained from isosteviol. This correlation provides further support for the structure and absolute configuration of these new tetracyclic diterpenes[33] and, in addition, constitutes a total synthesis[32] in view of the recent synthesis of steviol.[34]

(30) J. A. Berson in "Molecular Rearrangements," P. de Mayo, Ed., Wiley, New York, N. Y., 1963, pp 133–138.

(31) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968).

(32) For another total synthesis, see R. A. Bell, R. E. Ireland, and R. A. Partyka, *J. Org. Chem.*, **31**, 2530 (1966), and ref 27b.

Experimental Section[35]

Isosteviol (*ent*-**16-Oxobeyeran-19-oic Acid, 1**).—A 100-g sample of dried and ground leaves and stems of *Stevia Rabuadiana* Bertoni[4] was extracted with five portions of alcohol according to the procedure of Ruddat, Heftmann, and Lang.[3b] The residual syrupy liquid after leaching with ether was dissolved in 25 g of 48% hydrobromic acid and allowed to stand at 23–25° for 15 hr. This treatment liberates the aglycone and also effects pinacol rearrangement of steviol to isosteviol.[5a] Filtration through sintered glass separated a black solid which after chromatography on silica gel with chloroform as eluent yielded 2.7 g (2.7%) of isosteviol (**1**), mp 227–228° (lit.[3a] mp 230–231°).

Isosteviol Methyl Ester (**Methyl** *ent*-**16-Oxobeyeran-19-oate, 2**).—Stevioside was isolated from both a dried extract (250 g) and powdered and sifted leaves and stems (280 g or 3.2 kg) of *Stevia Rabaudiana* Bertoni,[4] using the procedure of Fletcher,[3a] and then hydrolyzed as above with 48% hydrobromic acid.[5a] Esterification of the isosteviol so obtained with diazomethane in methanol and crystallization from acetone afforded the ester **2** (1.9% from the dried extract, 2.1% from the leaves and stems): mp 202–203° (lit.[3a] mp 202–203°); τ 6.40, 8.81, 9.02, 9.30 (all s, 3 H); $[\alpha]^{25}D$ −69.0° (*c* 1.02).

Methyl *ent*-**16-Aminobeyeran-19-oate** (**4**).—A 988-mg (3 mmol) portion of isosteviol methyl ester (**2**) was allowed to react with 2 g (28.5 mmol) of hydroxylamine hydrochloride in 50 ml of pyridine for 15 hr at 23–25°. The pyridine was then evaporated and the crude product extracted from a dilute hydrochloric acid suspension with hexane. The hexane extract was washed with water, dried (Na_2SO_4), and evaporated. A small portion of the oxime **3** was recrystallized from hexane and chloroform: mp 153–155°; τ 9.23, 8.92, 8.83, and 6.40 (all s, 3 H).

Anal. Calcd for $C_{21}H_{33}NO_3$: C, 72.58; H, 9.57; N, 4.03. Found: C, 72.27; H, 9.50; N, 3.94.

The remainder of the crude oxime was dissolved in 100 ml of isopropyl alcohol and 6 g (0.26 mmol) of sodium was added to the solution at reflux temperature over a 5-hr period. Water was then added and the product isolated by extraction with hexane. After recrystallization of the hydrochloride salt of **4** from chloroform and ethyl acetate (52.5%), the free amine **4** was regenerated by extraction from a dilute sodium hydroxide suspension and was crystallized from chloroform and hexane: mp 110°; τ 9.28, 9.14, 8.83, and 6.37 (all s, 3 H), 7.16 (m, ~1 H, $CHNH_2$); ν_{max} 3600, 3280, 3160 sh (NH_2), 1720 cm^{-1} (C=O).

Anal. Calcd for $C_{21}H_{35}NO_2$: C, 75.63; H, 10.58; N, 4.20. Found: C, 75.78; H, 10.78; N, 4.12.

Methyl *ent*-**16a-Hydroxybeyeran-19-oate** (**2**).—Isoteviol methyl ester (**2**, 200 mg, 0.5 mmol) was reduced with excess sodium borohydride in methanol at room temperature. The product was isolated by extraction with hexane and recrystallized from hexane affording alcohol **5a** (190 mg, 95%): mp 164–165° (lit.[8] mp 164–165°); τ^{CCl_4} 9.28, 9.10, 8.84, and 6.36 (all s, 3 H), 6.11 (t, 1 H, J = 7.5 Hz).

The acetate **5b** was prepared by treatment of **5a** with acetic anhydride and pyridine (1:3) for 15 hr at 23–25°. Crystalliza-

(33) For other correlations see (a) ref 12l and 27a; (b) R. A. Appleton, A. J. McAlees, A. McCormick, R. McCrindle, and R. D. H. Murray, *J. Chem. Soc. C*, 2319 (1966); (c) G. Hugel, L. Lods, J. M. Mellor, and G. Ourisson, *Bull. Soc. Chim. Fr.*, 2894 (1965).

(34) K. Mori, Y. Nakahara, and M. Matsui, *Tetrahedron Lett.*, 2411 (1970).

(35) Melting points were taken in open capillary tubes on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were determined as potassium bromide pellets (unless specified to the contrary) on Perkin-Elmer spectrophotometers Model 137, Model 237, or Model 521. The nmr spectra were taken in chloroform-*d* (unless specified otherwise) using tetramethylsilane as internal standard on Varian Associates Model A160A, Model A-56-60, or Model HA-100 spectrophotometers. The mass spectra were determined on an Atlas CH_4 mass spectrometer. Microanalyses were performed by Mr. J. Nemeth and associates. The gas chromatograph used was Varian Aerograph Hi-Fi Model 600-D with a 6 ft × 0.25 in. column of 5% SE-30 silicone rubber on 60–80 mesh DMCS Chromosorb W at 230°. The optical rotations were taken with a Zeiss polarimeter using $CHCl_3$ as solvent. The ultraviolet spectra were taken on a Cary Model 14 spectrophotometer using ethanol as solvent.

tion from methanol gave acetate **5b** in 90% yield: mp 110°; mp 110°; τ^{CCl_4} 9.31, 9.10, 8.86, 8.00, and 6.40 (all s, 3 H), 5.29 (t, 1 H, J = 7.5 Hz).

Hydroboration of Methyl *ent*-15-Beyeren-19-oate (8) with Disiamylborane. Methyl *ent*-15β-Acetoxybeyeran-19-oate (6b) and Methyl *ent*-16β-Acetoxybeyeran-19-oate (7b).—A solution of disiamylborane was prepared from the reaction of boron trifluoride etherate (16.0 g), sodium borohydride (3.0 g, 0.079 mol), and 2-methyl-2-butene (15.27 ml, 0.146 mol) in 70 ml of tetrahydrofuran (freshly distilled from lithium aluminum hydride).[9] A 2.0-g (6.1 mmol) portion of **8**[2a,c] in 30 ml of tetrahydrofuran was added to the disiamylborane solution. After 5 hr of stirring at 23–25°, 50 ml of 20% sodium hydroxide in water was added slowly with rapid stirring. After an additional 1 hr of stirring, 50 ml of 30% hydrogen peroxide was added. This mixture was stirred for 2 hr more and then 200 ml of water was added and the cloudy white mixture was stirred for approximately 5 hr. The product (2.0 g) was separated by ether extraction and then acetylated with acetic anhydride (3 ml) and pyridine (20 ml) for 24 hr at 23–25°. A glpc analysis of the acetate mixture showed three main peaks. The two peaks of longer retention times were separated from the shorter retention time product on a silica gel column using chloroform as eluent, but repeated chromatography was necessary to achieve a 90:10 enriched mixture from the previous 70:30 mixture. The enriched fractions were then recrystallized several times, first from methanol and water and then proceeding to pure methanol as solvent. A 650-mg (28%) yield of **7b** greater than 99% pure was obtained: mp 91–92°; τ 9.25, 9.12, 8.85, 8.04, and 6.39 (all s, 3 H), 5.4 (dd, 1 H, J = 1.5, 3, 7 Hz); $[\alpha]^{24}D$ −10.6° (*c* 5.6); $\nu_{max}^{CCl_4}$ 1710 (C=O), 1240 cm^{-1} (CO).

Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.37; H, 9.64. Found: C, 73.25; H, 9.25.

The other major component **6b** was recrystallized from methanol: 525 mg (23%); mp 122–123.5°; τ 9.19, 9.02, 8.85, 7.96, and 6.39 (all s, 3 H), 4.71 (broad d, 1 H, J = 6 Hz); ν_{max} 1718 (C=O), 1250 cm^{-1} (CO).

Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.37; H, 9.64. Found: C, 73.68; H, 9.57.

A 600-mg portion of acetate **7b** was hydrolyzed in 25 ml of 5% sodium hydroxide in 85% ethanol for 2 hr at reflux. Recrystallization from hexane gave the 16β-hydroxy ester **7a**: 400 mg; mg 109–111°; τ 9.38, 9.06, 8.84, 6.38 (all s, 3 H), and 6.33 (br d, CHOH, masked partly by signal at 6.38); ν_{max} 3500 and 3350 (OH), 1720 cm^{-1} (C=O).

Meerwein–Pondorf–Verly Reduction of Isosteviol Methyl Ester (2). Methyl *ent*-16β-Acetoxybeyeran-19-oate (7b).—A 3.35-g (10 mmol) portion of **2** was added to 80 ml of isopropyl alcohol, 10 ml of acetone, and 30 g (146 mmol) of aluminum isopropoxide.[11] The mixture was heated at reflux temperature and then the acetone was distilled over a 24-hr period by adding isopropyl alcohol, keeping the volume of solvent approximately constant. The mixture was then heated at reflux temperature for an additional 16 hr. The alcohol was evaporated and dilute hydrochloric acid was added, and the product was isolated by extraction with hexane. The alcohol mixture was acetylated with 10% acetic anhydride in pyridine for 24 hr at 23–25° and then chromatographed on silica gel using 1% ethyl acetate and benzene. A series of five successive column chromatographies was performed, each yielding 10–20% of the two isomers **5b** and **7b** as pure components (by glpc analysis) after crystallization from methanol. The mixed fractions were then rechromatographed. The total yield of **7b** was 1.2 g. The remaining mixture of **5b** and **7b** and the pure **5b** were combined, hydrolyzed, and recycled in a second Meerwein–Pondorf–Verly reduction yielding 1.0 g of **7b** (total yield 2.2 g, 59%).

***ent*-8α-Carboxymethyl-13α-hydroxy-13β-methylpodocarpan-19-oic Acid Lactone (9).**—A 6.0-g (18 mmol) portion of isosteviol (**1**) was added to 400 ml of 25% peracetic acid and 20 g (0.24 mol) of sodium acetate in a 1-l. erlenmeyer flask.[17] Cooling was necessary to prevent foaming during the addition of the sodium acetate. The solution was stirred for 48 hr at 23–25°, concentrated by evaporated to ~50 ml, and poured into a chloroform and water mixture. The chloroform extract was washed twice with water, once with 5% ferric sulfate in 5% hydrochloric acid, again with water and then dried (Na_2SO_4) and evaporated. Crystallization from chloroform and hexane afforded 5.6 g (89%) of **9** (mp 262–264°): the melting point improved to 264–265° on recrystallization from acetone; τ 9.12, 8.75, and 8.66 (all s, 3 H), 6.89 and 7.99 (AB, J = 19 Hz, CH_2CO_2); $[\alpha]^{23}D$ −46.9° (*c* 3.2); ν_{max} 1695–1705 (C=O), 1230 cm^{-1} (CO).

Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 72.06; H, 8.93.

A 100-mg portion of the methyl ester **10** was formed using diazomethane and crystallized from chloroform and hexane: mp 192–194°; τ 9.23, 8.82, 8.65, and 6.35 (all s, 3 H), 7.97 and 6.92 (AB, J = 19 Hz, lower field peak shows additional coupling, J = 21 Hz).

Methyl *ent*-8α-(2′-Acetoxyethyl)-13α-hydroxy-13β-methylpodocarpan-19-oate (15b).—Lithium aluminum hydride (3 g) in 200 ml of dry tetrahydrofuran was added to a rapidly stirred solution of the lactone acid **9** (5.5 g, 16 mmol) in 500 ml of tetrahydrofuran. The reaction mixture was stirred for 3 hr at 23–25° and then 5 ml of water in 25 ml of tetrahydrofuran was added dropwise with continued stirring. The tetrahydrofuran was removed by evaporation and the remaining mixture was added to 5% hydrochloric acid and extracted with chloroform. The chloroform extract was washed with water, dried (Na_2SO_4), and evaporated. A small portion of the diol acid **12** was crystallized from acetone: mp 205–209°; $\tau^{C_5H_5N}$ 8.93, 8.70, and 8.64 (all s, 3 H), 6.05 (m, 2 H).

The remainder of the crude diol acid was treated with excess diazomethane in chloroform and then chromatographed on silica gel using methanol in chloroform as eluent; 1 l. of 2% methanol in chloroform eluted 4.97 g (90%) of the diol methyl ester **13a**. The product was crystallized from acetone: mp 220–221°; τ 9.31 and 6.3 (both s, 3 H), 8.84 (2 s, 6 H), 6.28 (t, 2 H, J = 5 Hz), 6.43 (s, 3 H); $[\alpha]^{23}D$ −30.2° (*c* 4.0); $\nu_{max}^{CHCl_3}$ 1713 (C=O), 3525 and 3595 cm^{-1} (OH).

Anal. Calcd for $C_{21}H_{36}O_4$: C, 71.55; H, 10.29. Found: C, 71.82; H, 10.02.

A 5-g (14 mmol) portion of the diol methyl ester **13a** was acetylated with acetic anhydride (10 ml) and pyridine (45 ml) overnight at 23–25°. The product **13b** (5.3 g, 90%) was crystallized from acetone and hexane: mp 145–145.5°; τ 9.28, 7.98, and 6.38 (all s, 3 H), 8.83 (2 s, 6 H), 5.82 (m, 2 H); $[\alpha]^{25}D$ −15.8° (*c* 3.8); $\nu_{max}^{CHCl_3}$ 1710–1720 (C=O), 3595 and 3530 cm^{-1} (OH).

Anal. Calcd for $C_{23}H_{38}O_5$: C, 70.02; H, 9.71. Found: C, 7.07; H, 9.59.

Methyl *ent*-8α-(2′-Tosyloxyethyl)-13-methyl-12-podocarpen-19-oate (14c) and Methyl *ent*-8α-(2′-Tosyloxyethyl)-13-methyl-13-podocarpen-19-oate (15c).—γ-Collidine (20 ml) was added to a solution of the diol monoacetate **13b** (4.5 g, 11.5 mmol) in 200 ml of methylene chloride. A solution of thionyl chloride (3.5 ml, 20 mmol) in 25 ml of methylene chloride was added quickly (*ca.* 1 min) with rapid stirring under a nitrogen atmosphere. After 1 min more, the mixture was added to cold dilute hydrochloric acid and extracted with ether. A quantitative recovery (4.3 g) was obtained of a product showing two peaks upon a glpc analysis with retention times 7.3 and 8.0 min and relative areas 1:2. The nmr spectrum has bands at τ 8.82, 7.97, and 6.35 (all s, 3 H), 8.40 (broad s, 3 H), 9.28 (s, 2 H), 9.31 (s, 1 H), 5.98 (m, 2 H), 4.67 (m, 2/3 H, $W_{1/2}$ = 9 Hz), 4.90 (m, 1/3 H, $W_{1/2}$ = 4 Hz). The bands at τ 9.28 and 4.67 are assigned to the Δ^{12-13} isomer **14b** and those at τ 9.31 and 4.90 are assigned to the Δ^{13-14} isomer **15b**.[19] The following alternative methods for dehydration gave less favorable results according to glpc analysis: phosphorus oxychloride–pyridine, 24 hr at 25° (**14b**:**15b**, 30:70), thionyl chloride–ethyl diisopropyl amine–methylene chloride (50:50), thionyl chloride–γ-collidine at various temperatures (65:35), thionyl chloride–pyridine (50:50), thionyl chloride–quinoline (40:60), tosyl chloride–pyridine, reflux 5 hr (72:25, but incomplete and poor recovery).

The mixture (4.5 g, 12 mmol) of olefins **14b** and **15b** was added to 100 ml of 5% sodium hydroxide in 95% ethanol and allowed to stand overnight at 23–25°. The ethanol was partially removed by rotary evaporation, and the product, a mixture of **14a** and **15a**, was isolated by ether extraction (4.0 g, 100%): τ 6.37 (s, 3 H), 6.2–6.6 (m, 2 H), 8.83 (s, 3 H), 8.41 (broad s, 3 H), 9.28 (s, 2 H), 9.32 (s, 1 H), 4.88 (m, 1/3 H), 4.67 (m, 2/3 H).

The mixture (4.0 g, 12 mmol) of hydroxy olefins **14a** and **15a** in 50 ml of pyridine was treated with 5 g (26 mmol) of *p*-toluenesulfonyl chloride at 23–25° for 24 hr. A 2-ml portion of water was then added over a 0.5-hr period with cooling. After work-up by ether extraction the tosylate mixture of **14c** and **15c** (5.7 g) was obtained: τ 8.83, 7.54, and 6.35 (all s, 3 H), 9.37 (s, 2 H), 9.40 (s, 1 H), 6.03 (τ, 2 H, J = 6.5 Hz), 5.08 (m, 1/3 H), 4.73 (m, 2/3 H) 2.21 and 2.66 (AB, 2 H, J = 9 Hz). The nmr bands

at τ 9.37 and 4.73 are assigned to **14c** and those at τ 9.49 and 5.08 to **15c**.

Methyl *ent*-16β-Hydroxyatisiran-19-oate (16a).—A solution of sodium formate in formic acid was prepared by dissolving 2.5 g (24 mmol) of sodium carbonate in 125 ml of formic acid. The tosylate mixture containing **14c** and **15c** (5.7 g, 11.5 mmol)[19] was added, requiring about 30 min to dissolve completely. After 3.5 hr at 23–25° the solvent was evaporated at room temperature under reduced pressure (required about 30 min) and the residue hydrolyzed with 5% sodium hydroxide in 95% ethanol (*ca.* 12 hr at room temperature). The ethanol was removed with a rotary evaporator. The residue was partitioned between hexene and water, and the water layer extracted two or three more times with hexane. The combined hexane extracts were dried (Na_2SO_4) and evaporated. The residue (4.3 g) was chromatographed on silica gel using ether and hexane as eluent. With 20% ether and hexane the tosylate **15c** and the exocyclic double bond isomer were eluted (2.4 g, 40%): τ 9.40, 8.84, 8.43, 7.53, and 6.35 (all s, 3 H), 5.91 (t, 2 H, J = 7.5 Hz), 5.09 (m, $^4/_5$ H), 5.41 and 5.63 (both m, $^1/_5$ H), 2.23 and 2.65 (AB, 2 H, J = 9 Hz). The nmr band at τ 5.09 is assigned to **14c** while those at 5.41 and 5.63 are assigned to the exocyclic double bond isomer.

Elution with 40–100% ether and hexane mixtures gave the tertiary alcohol **16a** (2.3 g, 60%) which was then recrystallized from hexane: mp 148–148.5°; τ 9.21, 8.84, 8.71, and 6.35 (all s, 3 H); $[\alpha]^{23}D$ −42.7° (*c* 3.3); ν_{max} 3505 (OH), 1708 cm^{-1} (C=O).

Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25. Found: C, 75.60; H, 10.18.

Methyl *ent*-14β-Hydroxybeyeran-19-oate (17a).—An 80-ml portion of buffered formic acid, prepared as above, was added to the unsaturated tosylate (3.2 g, 6.4 mmol) recovered from the preceding low temperature formolysis (**15c** containing *ca.* 20% of the exocyclic double bond isomer) and the solution heated at 80° for 5 hr. The product was isolated as above and the solid residue (2.0 g, 93%, mp 233–245°) recrystallized twice from acetone to give pure **17a**: mp 248–249°; τ 9.25, 9.07, 8.83, and 6.36 (all s, 3 H), 7.06 (s, $W_{1/2}$ = 2 Hz, 1 H); ν_{max} 3520 (OH), 1700 cm^{-1} (C=O).

Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25. Found: C, 75.12; H, 10.25.

A small sample of **17a** was treated with acetic anhydride–pyridine (1:3) for 2 hr at 100°. The solvent and excess reagent were removed by evaporation and the residue was crystallized twice from methanol to give **17b**: mp 141–142°; τ 9.22, 9.12, 8.82, 7.83, and 6.36 (all s, 3 H), 5.53 (s, 1 H, $W_{1/2}$ = 2 Hz); ν_{max} 1710 and 1717 cm^{-1} (C=O).

Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.37; H, 9.64. Found: C, 73.39; H, 9.61.

Methyl *ent*-12β-Hydroxybeyeran-19-oate (18a).—The hydroxy ester **16a** (1.4 g, 4.2 mmol) was dissolved in buffered formic acid as described above for the preparation of **16a** and the solution heated at 85° for 4 hr. The product, isolated in the same manner as before, was dissolved in pyridine containing 10% acetic anhydride and heated at steam bath temperature for 3 hr. The excess reagents were removed under reduced pressure and the resulting white residue was chromatographed on silica gel using ether–hexane mixtures as eluent. The first components eluted were 25 mg (2%) of olefins according to glpc analysis. Elution with 10% ether and hexane gave a fraction containing acetate **18b** (1.16 g, 71%) which was crystallized from methanol: mp 137–139°; τ 9.28, 9.08, 8.82, 7.96, and 6.39 (all s, 3 H), 5.30 (br, $W_{1/2}$ = 5.5 Hz, 1 H); $[\alpha]^{23}D$ −77.6° (*c* 5.4); ν_{max} 1720 (C=O), 1250 cm^{-1} (CO). Later fractions (30–100% ether and hexane) afforded 0.25 g (18%) of alcohol **16a**.

Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.37; H, 9.64. Found: C, 73.14; H, 9.56.

The acetoxy methyl ester **18b** (0.670 g, 1.8 mmol) was hydrolyzed with potassium hydroxide (2 g) in ethanol (70 ml) for 1 hr at 70°. The hydroxy ester **18a** was isolated by ether extraction and recrystallized from hexane (0.46 g, 70%): mp 104–105.5°; τ 9.25, 9.04, 8.83, and 6.35 (all s, 3 H), 6.48 (br s, 1 H); $[\alpha]^{23}D$ −57.8° (*c* 2.9); ν_{max} 1700 and 1720 (C=O), 3480 and 3520 cm^{-1} (OH); $\nu_{max}^{CHCl_3}$ 3500 (OH), 1720 cm^{-1} (C=O). Evaporation of the mother liquid afforded another 0.100 g of **18a** which was pure according to glpc analysis.

Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25. Found: C, 75.49; H, 10.29.

Methyl *ent*-12-Oxobeyeran-19-oate (19).—Hydroxy ester **18a** (0.826 g, 0.86 mmol) was dissolved in 25 ml of methylene chloride, a 2-g portion of chromium trioxide–dipyridine complex[31] was added, and the mixture was swirled for 5 min. The mixture was diluted with 50 ml of hexane and applied to a silica gel column. The keto ester **19** (0.280 g, 99%) was eluted with 10% ether in hexane and crystallized from acetone: mp 205–206° [mmp (with isosteviol methyl ester **1**) 193–196°]; τ 9.22, 8.93, 8.82, and 6.36 (all s, 3 H); $[\alpha]^{23}D$ −113° (*c* 1.4); ν_{max}^{KBr} 1695 and 1720 cm^{-1} (C=O).

Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.67; H, 9.56.

Methyl *ent*-Beyeran-19-oate (20). A.—Isosteviol methyl ester (**2**) (0.200 g, 0.6 mmol) was dissolved in 15 ml of diethylene glycol and 3 ml of hydrazine hydrate (99%). The solution was heated at reflux temperature for 13 hr and the suspension was extracted with ether. The ether extract was washed four times with water, dried (Na_2SO_4), and evaporated. The residue (presumably hydrazone) was then transferred to a glass high-pressure reaction tube along with 20 ml of 30% sodium methoxide and 0.2 ml of hydrazine hydrate (99%). The tube was sealed and heated at 200° for 3–4 hr. The product was isolated by extraction with ether and then esterified with diazomethane. Crystallization from methanol gave 0.165 g (83%) of the saturated ester **20**, mp 142–143° (lit.[3a] mp 143°).

B.—A similar procedure to the reduction of **2** given above was followed using 0.178 g (0.55 mmol) of keto ester **19**. A yield of 92 mg (50%) of **20** was obtained after recrystallization: mp 142°; τ 9.25, 0.04, 8.83, and 6.38 (all s, 3 H); $[\alpha]^{23}D$ −46° (*c* 4.5); ν_{max} 1720 cm^{-1} (C=O).

Anal. Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 78.85; H, 10.82.

C.—A 125-mg (0.4 mmol) sample of the unsaturated ester **8**[2a,c] was dissolved in 100 ml of 95% ethanol and 0.200 g of palladium on carbon was added. The mixture was then shaken in a Parr apparatus under 50-lb hydrogen pressure for 3 hr. The ethanol suspension was filtered and the ethanol removed by evaporation. Crystallization from methanol yielded 0.113 g (88%) of **20**, mp 142–143°.

A mixture melting point of 142–143° for mixtures of **20** obtained from all three procedures was observed. The ir and nmr spectra as well as the glpc behavior were also identical.

Methyl *ent*-16-Atisen-19-oate (21) and Methyl *ent*-15-Atisen-19-oate (22).—A 1.0-ml portion of thionyl chloride was quickly added to a solution of the hydroxy ester **16a** (1.05 g, 3.1 mmol) in 10 ml of pyridine and 20 ml of methylene chloride over a 1-min period. After 1 min more, this solution was poured into dilute hydrochloric acid and the suspension was extracted three times with ether. The combined ether extracts were washed twice with water, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was chromatographed on 15% silver nitrate–silica gel with 3–4% ether in hexane as eluent. Unsaturated ester **22** (0.505 g, 50%) was eluted first and was crystallized from methanol: mp 90–91°; τ 9.20, 8.83, and 6.37 (all s, 3 H), 8.28 (d, 3 H, J = 1.7 Hz), 4.42 (m, 1 H); $[\alpha]^{23}D$ −79.5° (*c* 6.2); ν_{max} 1720 cm^{-1} (C=O).

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.35; H, 10.15.

The isomeric ester **21** (0.360 g, 37%) was eluted with 4% ether in hexane and was crystallized from methanol: mp 126–127°; τ 9.22, 8.83, and 6.37 (all s, 3 H), 5.28 and 5.42 (2, 2 H, J = 2 Hz); $[\alpha]^{23}D$ −62.5° (*c* 0.96); ν_{max} 1720 (C=O), 3035, 870, and 865 (C=CH_2), 1650 cm^{-1} (C=C).

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.50; H, 10.16.

***ent*-15-Atisene (Isoatiserene, 28).**—Lithium aluminum hydride (1.2 g) was added with stirring to a solution of the unsaturated ester **22** (0.50 g, 1.57 mmol) in 100 ml of tetrahydrofuran under a nitrogen atmosphere. After 1 hr at reflux, the solution was cooled and 2 ml of water in 20 ml of tetrahydrofuran was added cautiously with cooling. The tetrahydrofuran was then removed under reduced pressure and the residue was added to dilute hydrochloric acid. The resulting suspension was extracted three times with ether, and the combined ether extracts were washed twice with water, dried (Na_2SO_4), and evaporated. A yield of 0.445 (95%) of alcohol **26** was obtained: mp 138.5–139.5°; τ 9.04 and 9.02 (both s, 3 H), 8.26 (d, 3 H, J = 1.7 Hz), 6.27 and 6.53 (AB, 2 H, J = 11.5 Hz), 4.42 (m, 1 H); ν_{max} 3360 cm^{-1} (OH).

Anal. Calcd for $C_{20}H_{32}O$: C, 83.27; H, 11.18. Found: C, 83.00; H, 11.26.

An 0.360-g (1.25 mmol) portion of **26** was added to 35 ml of dichloromethane and 1 g (5 mmol) of pyridine–chromium trioxide complex[31] was added with stirring. After 3 min the reaction was terminated by addition of 50 ml of hexane. The suspension was chromatographed on a silica gel column; 10% ether and hexane eluted 0.315 g (88%) of aldehyde **27**: τ 9.17 and 8.98 (both s, 3 H), 6.40 (m, 1 H), 8.26 (d, 3 H, J = 1.5 Hz), and 0.27 (s, 1 H). The glpc retention time was different from that of the starting material.

The aldehyde **27** (0.315 g, 1.1 mmol) was dissolved in 30 ml of diethylene glycol and 5 ml of 99% hydrazine hydrate was added. The solution was heated under nitrogen for 5 hr at 120–130°, 3.5 g (90 mmol) of sodium hydroxide was added, and the hydrazine and water were distilled from the reaction. The solution was then heated at 185° for 15 hr. The product was isolated by ether extraction and chromatographed on silica gel. Hexane eluted 0.280 g (90%) of an unsaturated hydrocarbon (**28**) which was crystallized from methanol: mp 81.5–82.5° (lit.[7] mp 84–85°); τ 9.17, 9.13, and 9.03 (all s, 3 H), 8.26 (d, 3 H, J = 1.5 Hz), 4.40 (m, 1 H); $[\alpha]^{23}D$ −75° (*c* 9.0) (lit.[7] −73.99°); ν_{max} 3025 cm^{-1} (C=CH). The spectral data correspond to those reported for natural isoatiserene.[7]

Anal. Calcd for $C_{20}H_{32}$: C, 88.16; H, 11.84. Found: C, 88.26; H, 11.77.

ent-16-Antisene (Atisirene, 25).—The same reduction procedure as described above was followed using 0.353 g (1.1 mmol) of unsaturated ester **21** and 0.5 g of lithium aluminum hydride. Alcohol **23** was recrystallized from hexane (0.330 g, 99%): mp 139–140°; τ 9.02 (s, 6 H), 5.29 and 5.46 (both quartets with $J \sim 2$ Hz, 1 H), 6.28 and 6.53 (AB, 1 H, J = 11 Hz); ν_{max} 3390 (OH), 3070, 1650, and 870 cm^{-1} (C=CH$_2$).

Anal. Calcd for $C_{20}H_{32}O$: C, 83.27; H, 11.18. Found: C, 82.71; H, 11.21.

Alcohol **23** (0.245 g, 0.84 mmol) was then added to 30 ml of dry dichloromethane and 2 g of chromium trioxide–dipyridine complex[31] was added. After 3 min, the suspension was diluted with 50 ml of hexane and then poured on to a column of silica gel; elution with hexane containing 10% ether gave 0.230 g (95%) of aldehyde **24** (glpc retention time different from that of **23**).

The aldehyde **24** (0.230 g, 0.8 mmol) was subjected to Wolff–Kishner reduction as above, with 15 ml of diethylene glycol and 3 ml of 99% hydrazine hydrate. Column chromatography of the product on silica gel using hexane as eluent gave 0.083 g (38%) of atisirene (**25**), which after crystallization from methanol had mp 58–58.5° [lit.[7,27a] mp 57–58°; 60–61° (for enantiomer)]; τ 9.16, 9.14, and 9.02 (all s, 3 H), 5.29 and 5.46 (both m, 2 quartet, 1 H, J = 2 Hz); $[\alpha]^{23}D$ −41.20° (*c* 5.0) (lit.[7] −40.46°]; ν_{max} 3080, 1648, 880, and 870 cm^{-1} (C=CH$_2$). The spectral data are in reasonable agreement with the corresponding literature data for natural atiserene,[7] its enantiomer,[27a] and synthetic racemic antiserene.[32] In addition, the complete ir and nmr spectra are superimposable upon those of natural atiserene.[7]

Anal. Calcd for $C_{20}H_{32}$: C, 88.16; H, 11.84. Found: C, 87.92; H, 11.82.

Registry No.—**1**, 27975-19-5; **2**, 30217-41-5; **3**, 30217-42-6; **4**, 21682-55-3; **5b**, 30288-12-1; **6b**, 30217-44-8; **7a**, 30217-45-9; **7b**, 21682-20-2; **9**, 23963-60-2; **10**, 30217-48-2; **12**, 30217-49-3; **13a**, 24022-50-2; **13b**, 24022-51-3; **14a**, 30217-52-8; **14b**, 23963-18-0; **14c**, 23963-59-9; **15a**, 30217-54-0; **15b**, 23963-19-1; **15c**, 30288-14-3; **16a**, 23963-20-4; **17a**, 30217-57-3; **17b**, 30217-58-4; **18a**, 30217-59-5; **18b**, 23963-23-7; **19**, 23963-24-8; **20**, 19898-49-8; **21**, 23963-21-5; **22**, 23963-22-6; **23**, 30217-65-3; **25**, 20230-48-2; **26**, 30217-67-5; **28**, 5975-29-1.

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Cycloserine Dimer Hydrolysis and Its Equilibration with Cycloserine

F. O. LASSEN[1] AND C. H. STAMMER*

Department of Chemistry, University of Georgia, Athens, Georgia 30601

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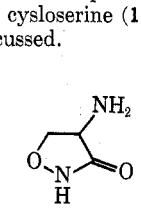
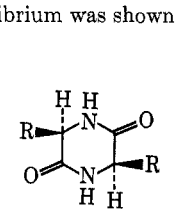
A kinetic investigation of the hydrolysis of three cis-3,6-disubstituted 2,5-piperazinediones (**2**, **3**, and **4**) at several HCl concentrations has been completed. The relative rates are compared to the unsubstituted 2,5-piperazinedione (**5**). In solutions of pH 1–2, a cycloserine dimer **2** ⇆ cysloserine (**1**) equilibrium was shown to be rapidly established. The mechanism of this interconversion is discussed.

It has been well established[2] that the broad-spectrum antibiotic cycloserine (**1**) is converted into its dimer, (+)-*cis*-3,6-bis(aminoxymethyl)-2,5-piperazinedione (**2**) even in the solid state.[3] This present investigation indicates that in solution **2** is also converted into cycloserine and that the establishment of an equilibrium between **1** and **2** is pH dependent. Our recent kinetic study[4] of the acid-catalyzed hydrolysis of **2** indicated that the side-chain aminoxy groups do not anchimerically assist the reaction at low pH. Such participation would necessarily lead to the intermediate formation of



1



2, R = CH_2ONH_2
3, R = CH_2OH
4, R = CH_3
5, R = H

a cycloserine peptide which further hydrolysis would convert into the observed product, β-aminoxy-D-alanyl-β-aminoxy-D-alanine (see Scheme I). Table I summarizes the results of more recent studies on the hydrolysis of **2** and analogous 2,5-piperazinediones **3** and **4** at various concentrations of HCl. The results confirm the previous hypothesis that the aminoxy groups do not participate at low pH.

Table II shows the activation parameters for the hydrolyses of **2**, **3**, **4**, and the unsubstituted compound **5**. It was primarily the small differences in hydrolysis rates

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