Structures of Cuauchichicine, Garryfoline, Lindheimerine, and Ovatine. Chemical Correlation of Cuauchichicine with (-)-"β"-Dihydrokaurene

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Received November 13, 1980

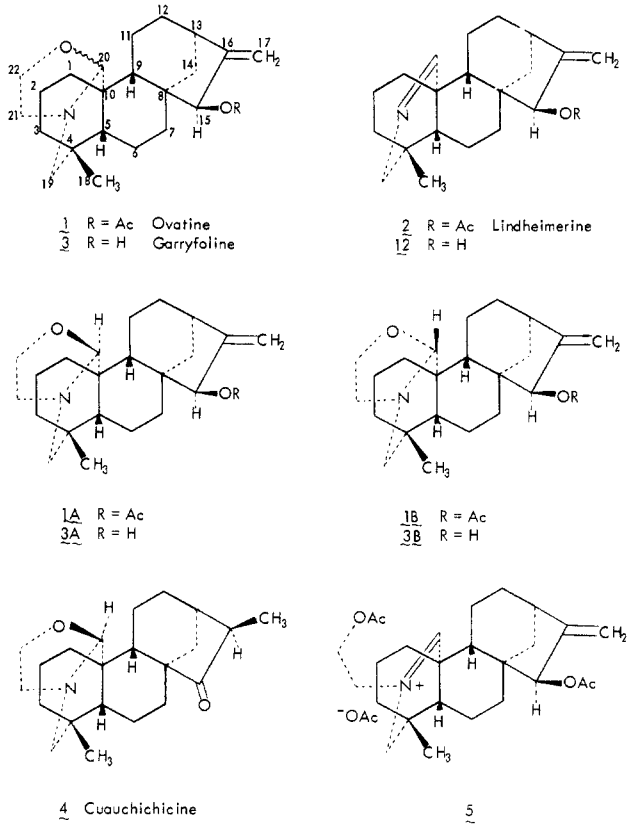
Chemical examination of the alkaloids of *Garrya ovata* var. lindheimeri Torr. has led to the isolation and characterization of two new C_{20}-diterpenoid alkaloids, ovatine (**1**) and lindheimerine (**2**), as well as two known alkaloids, garryfoline (**3**) and cuauchichicine (**4**). ^{13}C NMR spectral analysis of ovatine and garryfoline reveals that each alkaloid exists as a mixture of C(20) epimers in solution. The structure of lindheimerine was confirmed by synthesis from ovatine or garryfoline via an internal Hofmann degradation. Ovatine was also prepared from lindheimerine by treatment with ethylene oxide in acetic acid. Several derivatives of ovatine and garryfoline were prepared for their ^{13}C NMR spectral analysis. The earlier assignments of stereochemistry of the C(16) methyl group and the oxazolidine ring at C(20) in cuauchichicine have been revised by ^{13}C NMR spectral analysis and subsequently confirmed by X-ray crystallography; cuauchichicine is the first "normal-type", oxazolidine-ring-containing, C_{20}-diterpenoid alkaloid which does not exist as a pair of epimers at C(20) in solution as well as in the solid state. Certain of the previously published conclusions drawn from the correlation of cuauchichicine with (-)-"β"-dihydrokaurene are in error because of an unanticipated epimerization of the C(16) methyl group during Wolff–Kishner reduction of the intermediate ketone **23**. On the basis of the revised structure of cuauchichicine, several structures assigned to derivatives of cuauchichicine have been revised.

In our search for tumor-inhibitory compounds from plants, we found that the crude extracts from the bark and leaves of *Garrya ovata* var. lindheimeri Torr.,[1] a plant native to Texas, have shown confirmed antitumor activity in vivo. This result prompted us to investigate the alkaloidal constituents of this plant. To our knowledge no systematic investigation of the constituents of this plant has been reported. This paper reports the isolation and structure elucidation of two new alkaloids, ovatine (**2**) and lindheimerine (**2**),[2] and the structure revision of two well-known alkaloids, garryfoline (**3**) and cuauchichicine (**4**,[3] Chart I), which had been isolated earlier from the Mexican tree *G. laurifolia*.[4,5]

A 7.5-kg batch of the finely powdered stembark of *G. ovata* var. lindheimeri was first defatted with petroleum ether and then further extracted with acetone by percolation at room temperature. After extracting with acetone, the plant material was thoroughly extracted with 85% ethanol at room temperature until the last portion of the extract gave a negative Mayer's test for alkaloids. The petroleum ether extract gave a negative Mayer's alkaloid test, and the acetone extract gave a weak positive test for alkaloids. The alcoholic extracts were evaporated in vacuo at 40 °C to yield 650 g of dark brown residue. The alkaloids were isolated from this brown residue by a combination of gradient pH separation, column chromatography, and fractional crystallization methods. The alkaloids were fractionated into a weak-base and a strong-base fraction at pH ~8 and ~12, respectively.

The total weak-base fraction yielded 6.2 g of crude alkaloid mixture which when crystallized several times from acetone gave 1.12 g of large, rhombic crystals of ovatine, mp 113–114 °C (corr). Ovatine [$C_{24}H_{35}NO_3$ (elemental analysis and mass spectrum), $[\alpha]^{22}_D$ -79.4° (*c* 1.0, $CHCl_3$)] showed IR bands at 1735 and 1235 (acetate), 1660 (double bond), and 1100 (ether) cm^{-1}. The ^1H NMR spectrum in $CDCl_3$ exhibited two sharp singlets of unequal intensity at δ 0.72 and 0.80 in 1:3 ratio, respectively, for the C(4) CH_3 group, a three-proton singlet at δ 2.15 for an acetoxy group, a broad two-proton singlet at δ 2.60 for the NCH_2C group, two singlets at δ 3.95 and 4.25 in a 1:3 ratio, respectively, for the C(20) proton, and two broad doublets centered at δ 4.88 and 5.14 for the exocyclic double bond. The ^{13}C NMR spectrum of ovatine revealed the presence of one methyl, one acetoxyl, nine methylene, four methine groups, and three quaternary carbons together with two olefinic carbons and one carbonyl carbon (Table I). Comparison of the ^{13}C NMR spectrum of ovatine with that of garry-

Chart I



(1) This plant is also known as *Garry lindheimeri* Torr. Cf. D. S. Correll and M. C. Johnston, "Manual of the Vascular Plants of Texas", Vol. 6, Texas Research Foundation, Renner, TX, 1970, p 1171.

(2) S. W. Pelletier, N. V. Mody, and D. S. Seigler, *Heterocycles*, **9**, 1409 (1978).

(3) S. W. Pelletier, H. K. Desai, J. Finer-Moore, and N. V. Mody, *J. Am. Chem. Soc.*, **101**, 6741 (1979).

(4) C. Djerassi, C. R. Smith, A. E. Lippman, S. K. Figdor, and J. Herran, *J. Am. Chem. Soc.*, **77**, 4801, 6633 (1955).

(5) H. Vörbrueggen and C. Djerassi, *J. Am. Chem. Soc.*, **84**, 2990 (1962).

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Table I. ^{13}C Chemical Shifts and Assignments for Ovatine, Garryfoline, Lindheimerine, and Their Derivatives

	1A	1B	3A	3B	8	2	12[a]	11	9
C(1)	41.9	41.6	41.9	41.6	40.7	42.4	43.2	41.5	41.4
C(2)	18.2	19.5	19.3	20.0	21.3	18.0	18.7	18.0	18.1
C(3)	37.6	37.6	37.6	37.6	40.5	36.5	37.4	41.1	40.7
C(4)	34.2	34.1	34.2	34.1	39.9	33.0	33.8	33.9	33.8
C(5)	52.2	53.2	52.3	53.1	48.7	47.0	47.4	49.9	49.7
C(6)	18.5	17.2	18.9	17.5	18.2	20.5	21.4	19.2	19.1
C(7)	35.3	35.1	35.1	35.1	37.2	35.2	35.7	37.1	37.1
C(8)	45.7	46.0	45.4	45.7	45.5	45.6	46.5	45.8	45.4
C(9)	45.4	44.8	43.9	43.2	42.8	43.6	43.4	44.3	42.6
C(10)	40.8	40.3	40.2	40.1	36.1	45.2	46.3	40.1	39.8
C(11)	22.8	21.9	22.8	21.9	22.4	21.3	22.5	23.7	23.5
C(12)	32.2	30.9	32.0	30.9	33.0	34.0	35.2	33.3	32.9
C(13)	40.6	40.2	40.4	40.4	39.7	40.7	41.5	40.4	39.8
C(14)	37.6	37.6	37.4	37.4	37.6	34.8	36.0	37.4	36.9
C(15)	82.1	82.4	83.1	83.1	82.6	81.6	82.6	81.8	82.4
C(16)	154.5	154.9	159.3	159.8	158.1	153.8	158.7	153.7	158.1
C(17)	105.7	105.5	104.4	106.0	105.2	106.8	105.5	106.7	105.1
C(18)	26.0	26.6	26.0	26.5	24.5	26.2	26.4	26.7	26.6
C(19)	56.6	56.1	56.6	56.1	98.6	59.7	59.8	60.6	60.4
C(20)	93.2	94.4	93.2	94.5	51.3	167.1	170.4	56.5	56.2
C(21)	50.5	49.5	50.5	49.4	54.9			58.2	58.0
C(22)	64.6	59.0	64.6	59.0	58.7			61.1	60.8
$CH_3C{=}O$	171.7	171.7				171.3		171.8	
$CH_3C{=}O$	21.3	20.4				21.2		21.4	

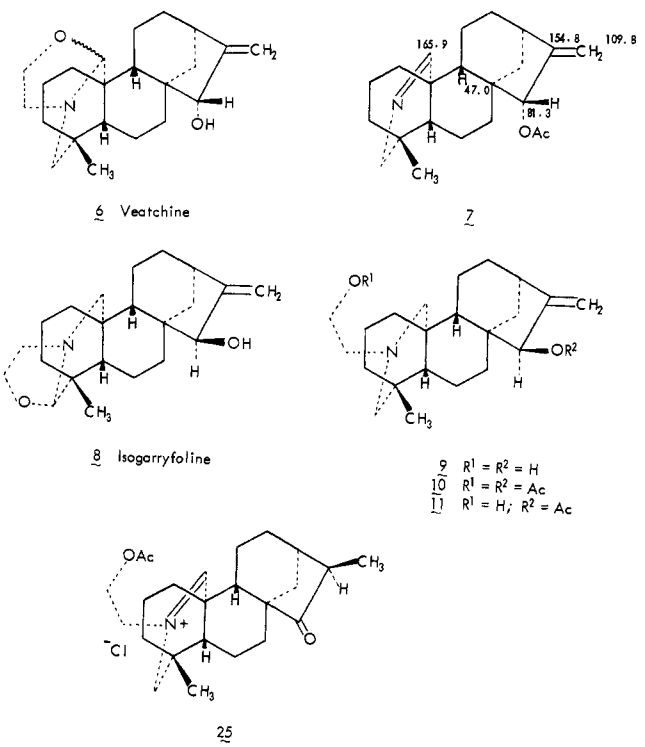
[a] Garryfoline azomethine (12) is sparingly soluble in chloroform; the spectrum was taken in CD_3OD.

foline (3) showed that the only difference between these two alkaloids was the presence of an additional acetoxyl group at the C(15) position in ovatine.

The ^{13}C NMR spectra of ovatine and garryfoline in $CDCl_3$ at room temperature showed the presence of two different sets of signals for the oxazolidine ring, the piperidine ring, the C(4) methyl group, and certain other carbon atoms, a result which indicates the existence of a mixture of epimers at the C(20) position in these alkaloids. The ^{13}C NMR assignments of ovatine and garryfoline were based on the earlier assignments for the closely related alkaloid veatchine. Ovatine and garryfoline each showed a ^{13}C NMR pattern similar to that of veatchine. The ^{13}C NMR spectrum of veatchine was analyzed by relating the models of the C(20) epimers to the ease of formation of the oxazolidine ring. Because the epimer with the C(20) α-hydrogen can be formed easily, we assigned this structure to the major epimer.[6] Later, this assignment was confirmed by X-ray analysis.[8] The structures of ovatine (1) and garryfoline (3) can be represented as an epimeric mixture at C(20) of **1A** and **1B** and of **3A** and **3B**, respectively, with the **A** epimer predominating in both alkaloids just as in the case of the closely related alkaloids veatchine (**6**)[6,8] and atisine.[6] It is worth noting that early workers assumed a β-configuration for the C(20) hydrogen in garryfoline.[5,7]

Treatment of ovatine (1) with a 5% saturated solution of potassium carbonate in methanol *or* in methanol at room temperature, without external base, afforded the known alkaloid garryfoline (3), indicating the presence of the acetoxyl group at C(15) in ovatine. Acetylation of garryfoline with acetic anhydride in pyridine at room temperature gave compound **5** in quantitative yield instead of ovatine, the desired acetylation product. Ovatine also afforded compound **5** upon treatment with acetic anhydride in pyridine. For confirmation of the structure of ovatine, garryfoline was converted into ovatine in two steps

Chart II



in an overall yield of 88%. Compound **5** was heated at reflux temperature in chloroform to afford lindheimerine (**2**) in 90% yield.[9] Treatment of the latter with ethylene oxide in acetic acid at room temperature for 48 h afforded ovatine in a yield of 98%.[10] When a similar reaction was performed with methanol instead of acetic acid as solvent, compound **2** gave garryfoline (3) within 15 h in 96% yield.

Garryfoline was isolated from the strong-base fraction of alkaloids by a combination of column chromatographic and crystallization techniques. The spectral data of gar-

(6) N. V. Mody and S. W. Pelletier, *Tetrahedron*, **34**, 2421 (1978).
(7) W. Klyne and J. Buckingham, "Atlas of Stereochemistry. Absolute Configuration of Organic Molecules", Vol. 1, Oxford University Press, New York, 1978 p 169 and references cited therein.
(8) S. W. Pelletier, W. H. DeCamp, and N. V. Mody, *J. Am. Chem. Soc.*, **100**, 7976 (1978).
(9) N. V. Mody and S. W. Pelletier, *Tetrahedron Lett.*, 3313 (1978).
(10) S. W. Pelletier, J. Nowacki, and N. V. Mody, *Synth. Commun.*, **9**, 201 (1979).

ryfoline and ovatine are similar except for the absence of the C(15) acetoxy group in garryfoline (see Experimental Section). Several derivatives of garryfoline and ovatine have been prepared and their ^{13}C NMR spectra analyzed (Table I). Ovatine was converted into isogarryfoline (**8**) by being heated in methanol at reflux temperature for 7 h. During this reaction, hydrolysis of the C(15) acetoxyl group and isomerization of the normal-type oxazolidine ring occurred simultaneously. Reduction of isogarryfoline (**8**, Chart II) with sodium borohydride in methanol afforded dihydrogarryfoline (**9**), which is unstable. Acetylation of **9** with acetic anhydride in pyridine gave the diacetate **10**. Dihydroovatine (**11**) was prepared in quantitative yield from ovatine by reduction with sodium cyanoborohydride at pH 5–6.[11]

The minor alkaloid, lindheimerine (**2**), was isolated in an amorphous state from the mother liquor accumulated during the isolation of ovatine from the weak-base fraction.[2] Lindheimerine [$C_{22}H_{31}NO_2$; $[\alpha]^{24}_D$ −113.8° (*c* 2.0, $CHCl_3$)] exhibited IR absorptions at 1735 and 1230 (acetate), 1660 (double bond), and 1645 (imine) cm^{-1}. The ^1H NMR spectrum of **2** revealed the presence of the C(4) methyl group (3 H, s) at δ 0.82, an acetoxy group (3 H, s) at δ 2.18, the NCH_2C group as a singlet at δ 3.42, broad doublets at δ 4.98 and 5.28 for the exocyclic double bond, and a broad singlet at δ 8.0 for the C(20) imine proton. The ^{13}C NMR spectrum of lindheimerine indicated the presence of one methyl, one acetoxy, one imine, three methine, and seven methylene groups and of three tetrasubstited carbons together with two olefinic carbons and one carbonyl carbon (Table I). The pattern of chemical shifts in lindheimerine is similar to that of the known compound **7** (Table I) except for a few changes. Comparison of the chemical shifts of C(8), C(15), C(16), and C(17) in lindheimerine with those of compound **7**[6] gave evidence for the presence of a β-acetoxy group at C(15) and led to structure **2** for lindheimerine. Finally, the structure was confirmed by comparison with the internal Hofmann degradation product of **5**, which was found to be identical with lindheimerine (**2**).[9] The latter was also prepared in quantitative yield from garryfoline azomethine (**12**) by treatment with acetic anhydride in pyridine at room temperature.

Along with ovatine, lindheimerine, and garryfoline, we have also isolated the known alkaloid cuauchichicine from a crude extract which had been treated with 5% H_2SO_4 at room temperature during one of the extraction procedures. When the acidic extraction of alkaloids was carried out at 5–10 °C, we did not encounter cuauchichicine. This result indicates that cuauchichicine was formed as an artifact from garryfoline by the acid-catalyzed rearrengement during extraction. This observation suggests that the reported occurrence of cuauchichicine in the Mexican tree *G. laurifolia*[4] probably results from the acid-catalyzed rearrangement of garryfoline during extraction. The structure of cuauchichicine was established as **13** on the basis of chemical correlation with (−)-"β"-dihydrokaurene (**14**).[4,5,12] The structure of the latter, a minor hydrogenation product of *ent*-kaurene (**15**), was assigned on the basis of the behavior of *ent*-kaurene during hydrogenation. We now have revised the structure of cuauchichicine to **4** on the basis of ^{13}C NMR spectral analysis and X-ray crystallography.[3]

Cuauchichicine [$C_{23}H_{33}NO_2$, mp 152–154 °C, $[\alpha]^{18}_D$ −69° (*c* 1.0, $CHCl_3$)] isolated from *G. ovata* var. lindheimeri, was identified by comparison with an authentic specimen prepared by the acid-catalyzed rearrangement of garryfoline. The 100-MHz ^1H NMR spectrum in $CDCl_3$ shows a sharp singlet at δ 0.81 for the C(4) methyl group, a doublet centered at δ 1.11 for the C(16) methyl group, a broad singlet at δ 2.65 for the C(19) methylene group, and a broad singlet at δ 4.29 for the C(20) proton. Comparison of the ^{13}C NMR spectrum of cuauchichicine in $CDCl_3$ with that of garryfoline revealed the presence of a *single set of signals* for the oxazolidine ring, the piperidine ring, and the methyl groups at C(4) and C(16) (Table II). This result indicates that cuauchichicine exists as a single C(20) epimer with the C(20) proton in the α-configuration. Early work on the configuration of garryfoline assumed, without evidence, a β configuration for the C(20) proton.[5,7] Since cuauchichicine had been chemically correlated with garryfoline, the β configuration was presumed for the C(20) proton in cuauchichicine also.[12]

Table II. ^{13}C Chemical Shifts and Assignments for Cuauchichicine and Its Derivatives

	4	17	18	22	23	21
C(1)	41.6	40.6	40.8	42.4	41.1	42.2
C(2)	18.4	20.1	20.2	20.4	18.8	19.1
C(3)	38.4	39.7	39.9	35.8	38.4	44.1
C(4)	34.0	40.6	40.6	33.1	42.0	33.3
C(5)	52.4	50.6	50.7	46.9	51.1	57.2[a]
C(6)	17.9	18.0	18.3	18.5	18.1	20.8
C(7)	32.6	33.0	32.9	32.0	32.7	37.9
C(8)	52.0	54.4	52.8	52.0	52.2	43.0
C(9)	47.7	47.9	47.8	47.6	49.8	56.1[a]
C(10)	40.5	35.9	36.0	45.6	33.1	45.8
C(11)	22.7	22.3	30.1	20.4	22.1	22.5
C(12)	22.4	24.9	22.3	25.1	23.1	23.8
C(13)	33.7	38.5	37.0	35.2	33.5	35.4
C(14)	34.7	34.6, 34.2	36.5	34.2	34.9	34.8
C(15)	224.7	224.7	225.3	224.1	224.7	30.9
C(16)	49.5	48.8	46.3	48.1	47.9	52.2
C(17)	10.0	10.1	15.9	9.8	10.0	19.1
C(18)	25.5	24.3	24.3	26.2	23.1	34.4
C(19)	56.7	98.4, 96.8	98.4	59.8	96.0	18.9
C(20)	92.7	48.4	48.4	166.3	71.9	61.8
C(21)	50.5	54.9, 56.5	54.8			
C(22)	64.5	58.8, 64.9	58.8			

[a] These assignments may be reversed, but those given here are considered to be most likely.

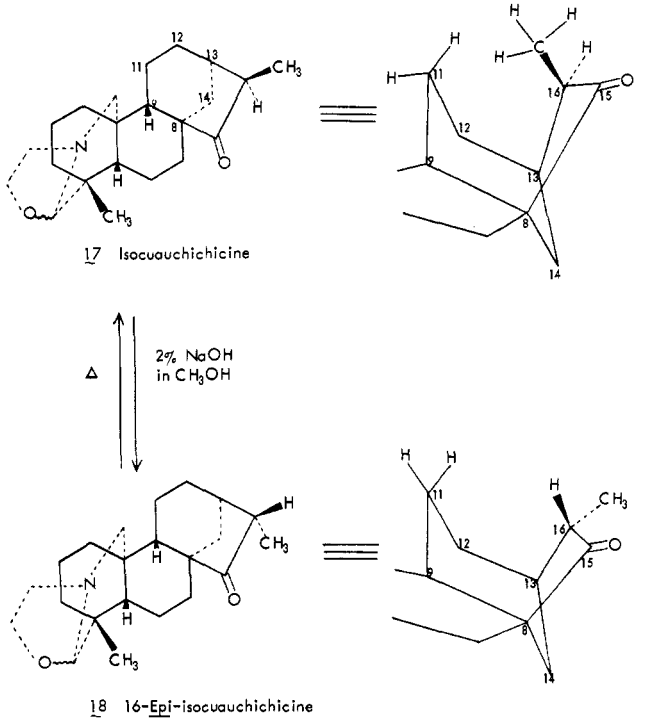
To establish the stereochemistry of the C(16) methyl group in cuauchichicine by ^{13}C NMR spectral anlaysis, isocuauchichicine (**17**) and its C(16) methyl epimer (**18**; see Scheme I) were prepared from cuauchichicine by boiling in a solution of 2% sodium hydroxide in methanol. These epimers were separated by chromatography over alumina using hexane and benzene as eluents. Comparison of molecular models of compound **17** and its epimer **18** revealed that the methyl group at C(16) is spatially crowded in the β-position in contrast to the α-position. The chemical shift of the β-methyl group should appear at higher field than that of α-methyl group because of steric compression. Accordingly, we have assigned the chemical shift at 10.15 ppm to the β-methyl group (**17**) and the shift at 15.95 ppm to the α-methyl group (**18**, Table II). Since the chemical shift in cuauchichicine is at 10.0 ppm, structure **4** with a β-methyl at C(16) may be assigned to this alkaloid. Subsequently, this assignment was confirmed by a single-crystal, X-ray analysis of cuauchichicine.[3]

The incorrect structure (**13**) originally assigned[5] to cuauchichicine requires that the epimerization of the C(16) methyl group occur somewhere in the six-step correlation sequence (see Scheme II), or the structure of the final degradation product, (−)-"β"-dihydrokaurene (**14**), is in-

(11) S. W. Pelletier, N. V. Mody, A. P. Venkov, and H. K. Desai, *Tetrahedron Lett.*, 4939 (1979).

(12) J. R. Hanson, "The Tetracyclic Diterpenes", Pergamon Press, Oxford, 1968, Chapter 5, p 68.

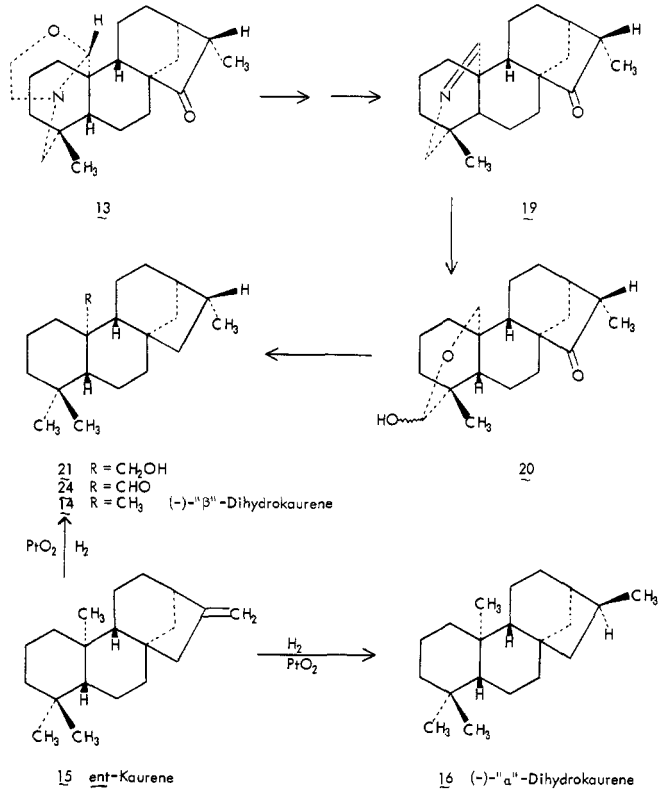
Scheme I



17 Isocuauchichicine

18 16-Epi-isocuauchichicine

Scheme II

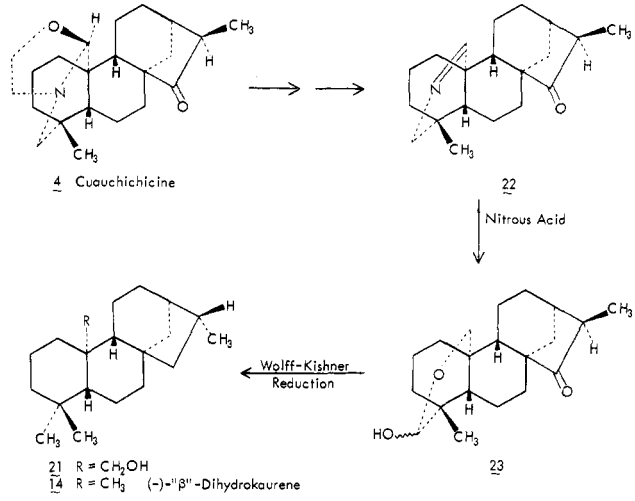


21 R = CH_2OH
24 R = CHO
14 R = CH_3 (−)-"β"-Dihydrokaurene

15 ent-Kaurene

16 (−)-"α"-Dihydrokaurene

Scheme III



4 Cuauchichicine

22

23

21 R = CH_2OH
14 R = CH_3 (−)-"β"-Dihydrokaurene

correct. Because the structural assignments of almost 100 natural products depend on (−)-"β"-dihydrokaurene, we have reinvestigated the structure of this important diterpene hydrocarbon. Hydrogenation of a small sample of *ent*-kaurene afforded a mixture of *ent*-kauranes consisting mainly of (−)-"α"-dihydrokaurene (stevane A) (**16**). The "β" epimer was produced in too small a yield to permit isolation in a pure state. Since X-ray crystallography[3] of (−)-"α"-dihydrokaurene confirmed the structure to be **16**, the structure previously assigned[13] for (−)-"β"-dihydrokaurene is correct. These results demonstrate that epimerization of the C(16) methyl group must have occurred during the degradation of cuauchichicine to (−)-"β"-dihydrokaurene. To establish the point of epimerization during the degradation, we have carried out the degradation of cuauchichicine by the previously published method.[5] Cuauchichicine azomethine was prepared from cuauchichicine by an internal Hofmann degradation. Treatment of the azomethine with nitrous acid afforded the hemiacetal, which on Wolff–Kishner reduction gave the primary alcohol **21**. Carbon-13 NMR analysis of cuauchichicine azomethine and the hemiacetal demonstrates that the C(16) methyl group is in the "β" configuration in both compounds (Table II). Therefore, the structures of cuauchichicine azomethine and the hemiacetal must be revised to **22** and **23**, respectively. ^{13}C NMR analysis of the primary alcohol **21** indicates that the C(16) methyl group is indeed in the "α" configuration as assigned earlier. These results confirm that unanticipated epimerization occurred during Wolff–Kishner reduction of the hemiacetal **23**, a fact which accounts for the error in the assigments of configuration of the C(16) methyl group in cuauchichicine azomethine, in the hemiacetal, and, therefore, in cuauchichicine. Scheme III displays the correct structures for compounds involved in the correlation of cuauchichicine with (−)-"β"-dihydrokaurene. Since the stereochemistry of the C(16) methyl group in cuauchichicine is reassigned, the previously assigned structures for the following degradation products of cuauchichicine are revised as shown: cuauchichicine acetate chloride (**25**), cuauchichicine azomethine (**22**) and the hemiacetal (**23**).

Interestingly, lindheimerine occurrs in an extremely small quantity in comparison with ovatine. Since lindheimerine and ovatine can be easily interconverted, we postulate that lindheimerine may be a biogenetic precursor of ovatine. It is of interest that cuauchichicine is the first "normal-type" oxazolidine-ring-containing alkaloid which does not exist in the epimeric form at C(20) in solution or in the solid state.

Experimental Section

Melting points are corrected and were taken on a Thomas-Kofler hot stage equipped with a microscope and polarizer. Rotations were taken in $CHCl_3$ unless otherwise noted on a Perkin-Elmer polarimeter, Model 141. Infrared spectra were recorded on a Perkin-Elmer Model 237 B spectrophotometer. Proton NMR measurements were made on $CDCl_3$ solutions, unless otherwise mentioned, on a Varian T-60 spectrometer with Me_4Si as an internal standard, and all the signals are reported in as δ

values. The following abbreviations are used to express the multiplicity of the signals: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; m, multiplet. ^{13}C NMR spectra were taken at 15.03 MHz in the Fourier mode by using a JEOL FX-60 spectrometer. ^{13}C chemical shifts are reported in parts per million downfield from Me_4Si. Spectra were determined in $CDCl_3$ solution (which also provided the lock signal). Thin-layer chromatography (TLC) of the alkaloids was accomplished on Merck aluminum oxide GF-254 (type E or 60/E), and the compounds were visualized in UV light and by spraying with Dragendorff reagent. Column chromatography was conducted on Merck neutral aluminum oxide (activity state III, 70–230 mesh ASTM). Preparative layer chromatography (PLC) was carried out on 20 × 40 cm plates coated with a 2.5-mm layer of Merck aluminum oxide 150 PF-254-366 (Type T), and compounds were visualized in UV light. The solvent system used for TLC and PLC was mainly hexane–benzene–ethyl acetate–diethylamine (4.25:4.25:10.0:0.5) unless otherwise mentioned.

Processing of the Plant Material. The leaves and stembark of *Garrya ovata* var. lindheimeri were extracted and processed for the isolation of alkaloids separately. Air-dried and finely powdered plant material (7.5 kg) was first defatted with petroleum ether (bp 35–60 °C) at room temperature in a stainless-steel percolater (3 × 14 L). The extract was evaporated to dryness in vacuo. The residue (157.8 g) gave a negative alkaloid test and was reserved. After defatting, the plant material was further extracted at room temperature with acetone (3 × 14 L). The total acetone extract when evaporated to dryness in vacuo gave a dark brown residue (200.34 g) which tested faintly positive against Mayer's reagent. The acetone extract was triturated with cold 2% sulfuric acid, and the filtered acid extract was worked up for the alkaloids as described below for the alcoholic extract. The total basic residue (0.285 g) consisted mainly of a mixture of ovatine and garryfoline as indicated by TLC and ^{13}C NMR analysis.

Finally, the plant material was extracted exhaustively with 85% ethanol (9 × 13 L) until the last portion of the extract gave a negative Mayer's test. The combined alcohol extract was evaporated in vacuo below 40 °C to give a dark brown gummy residue (650 g). The residue was made into a thick slurry with alcohol–water (1:1, 150 ml), and the mechanically stirred and chilled slurry was acidified to pH 1 with a cold solution of 1% H_2SO_4. The acidic solution was stirred for another 0.5 h and then filtered through a bed of Celite. The filtrate was kept in an ice bath during filtration. The cold acidic layer was quickly extracted with $CHCl_3$ (3 × 150 mL) to remove nonbasic material and then basified (cold) to pH ~8.0 with solid $NaHCO_3$. The basic solution was extracted with $CHCl_3$ (5 × 1.0 L), and the extract was dried over anhydrous Na_2SO_4 and evaporated to dryness in vacuo to afford 6.2 g of a weak-base fraction which was processed separately. The aqueous layer at pH 8.0 was further basified in the cold to pH ~12 with 20% NaOH solution and extracted with $CHCl_3$ (4 × 1.0 L). The combined $CHCl_3$ extract was washed with cold water, dried over anhydrous Na_2SO_4, and evaporated to dryness in vacuo at room temperature to give 7.3 g of a strong base fraction.

In one experiment, during extraction of the bases from the crude extract, we found that if the crude extract was treated with 5% H_2SO_4 at room temperature overnight, a mixture was obtained which had the same TLC pattern (SSA) as that of the above-reported $CHCl_3$ fractions. However, when the compound corresponding to ovatine on TLC was isolated from this mixture, it proved to be cuauchichicine instead of ovatine. This experiment indicates that cuauchichicine is an artifact formed during extraction by the acid-catalyzed rearrangement of garryfoline.

Alkaloids of the Weak-Base Fraction: Isolation of Ovatine (1). The dark-colored residue (6.2 g) was dissolved in acetone and the solution left for 4 days in the dark when large rhombic crystals of ovatine were collected (1.12 g) and washed with cold acetone. The washings were combined with the mother liquor. Recrystallization from acetone afforded crystals: mp 113–114 °C; $[\alpha]^{22}_D$ −79.4° (*c* 1.0); IR ν_{max} (KBr) 1735, 1235 (acetate), 1660 (double bond), 1100 (ether) cm^{-1}; ^1H NMR δ 0.72 and 0.80 (combined 3 H, s, C(4) CH_3), 2.15 (3 H, s, $OCOCH_3$), 2.60 (br s, NCH_2C), 3.95 and 4.25 (2 br s, C(20) H), 4.88 and 5.14 (2 br d, $C{=}CH_2$). *Anal.* Calcd for $C_{24}H_{35}NO_3$: C, 74.77; H, 9.15; N, 3.63. Found: C, 74.74; H, 9.18; N, 3.65.

Transformation of Ovatine (1) into Lindheimerine (2). A solution of 100 mg of ovatine in 5 mL of dry pyridine and 3 mL of acetic anhydride was stirred for 14 h at room temperature. Excess pyridine and acetic anhydride were removed completely in vacuo at 50 °C by flashing with absolute ethanol and dry benzene several times to afford the salt **5** in quantitative yield. Without further purification, compound **5** was refluxed in 25 mL of chloroform for 8 h to give lindheimerine (**2**) as an amorphous compound in 90% yield. The TLC pattern and ^1H and ^{13}C NMR data were identical with those of naturally occurring lindheimerine.

Conversion of Lindheimerine (2) into Ovatine (1). A 50-mg sample of lindheimerine, 1 mL of ethylene oxide, and 5 mL of glacial acetic acid were allowed to react for 48 h at 25 °C. The colorless solution was cooled in an ice bath, basified with 25 mL of 20% sodium hydroxide solution, and extracted with chloroform. The extract was dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo to give, after crystallization from acetone, 56 mg of ovatine, mp 113–114 °C. The ^1H and ^{13}C NMR spectral data of synthetic ovatine were identical with those of the naturally occurring alkaloid.

Preparation of Garryfoline (3) from Lindheimerine (2). A 25-mg sample of lindheimerine was treated with an excess of ethylene oxide in 5 mL of methanol at 25 °C. After 15 h, removal of excess ethylene oxide and methanol gave garryfoline: yield 96%; mp 134–136 °C; $[\alpha]^{27}_D$ −48.8° (*c* 1.0).

Hydrolysis and Isomerization of Ovatine to Isogarryfoline (8). A solution of ovatine (0.25 g) in methanol (13 mL) was refluxed for 7 h on a steam bath. Workup gave a gum which, after purification through a small column of neutral alumina and crystallization from petroleum–ether (bp 35–60 °C), afforded platelets of isogarryfoline: 0.19 g; mp 140–143 °C; $[\alpha]^{18}_D$ −50.2° (*c* 1.0) (lit.[4] mp 140–144 °C; $[\alpha]_D$ −57°); IR (Nujol) ν_{max} 3400 (OH), 1662 ($C{=}CH_2$) cm^{-1}; ^1H NMR δ 1.05 (3 H, s, C(4) CH_3), 2.66 (2 H, br s, C(20) H_2), 3.78 (2 H, m, C(22) H_2), 3.98 (1 H, br s, C(19) H), 5.0 and 5.18 (2 H, br s, $C{=}CH_2$).

Reduction of Isogarryfoline with Sodium Borohydride: Dihydrogarryfoline (9). Isogarryfoline (0.275 g) in methanol (25 mL) was treated overnight with sodium borohydride (100 mg). The usual workup gave a gum (0.25 g) which was purified by PLC. The amorphous product was identified as dihydrogarryfoline (**9**) by its ^{13}C NMR spectrum (Table I). This compound[4] is unstable in solution as well as in the solid state.

Acetylation of Dihydrogarryfoline. A solution of dihydrogarryfoline (0.05 g) in dry pyridine (0.5 mL) and acetic anhydride (0.5 mL) was left overnight and then worked up in the usual manner. The gum (0.052 g) obtained was further purified by PLC on Al_2O_3 (hexane/5% ethanol) to give the major product (0.031 g) as a noncrystalline compound which was identified as the diacetate of dihydrogarryfoline (**10**)[4] by spectral analysis: IR (Nujol) ν_{max} 1739 (C=O), 1665, 890 ($C{=}CH_2$); ^1H NMR δ 0.76 (3 H, s, C(4) CH_3), 2.06 (3 H, s, C(22) $OCOCH_3$), 2.16 (3 H, s, C(15) $OCOCH_3$), 2.70 (3 H, br s, NCH_2C), 4.96 and 5.18 (3 H, unequal br d, C(15) H and $C{=}CH_2$).

Preparation of Dihydroovatine (11). The pH of a solution of ovatine (0.07 g) in methanol (3 mL) was adjusted between 5 and 6 with dilute HCl. Sodium cyanoborohydride (0.1 g) in methanol (3 mL) was added, and the resulting solution was stirred for 3 h at room temperature while the pH was maintained between 5 and 6 throughout the reaction. The usual workup gave amorphous dihydroovatine (0.065 g) which showed a single spot on TLC: IR (Nujol) ν_{max} 3450 (OH), 1742 (C=O) and 1665 ($C{=}CH_2$) cm^{-1}; ^1H NMR δ 0.76 (3 H, s, C(4) CH_3), 2.15 (3 H, s, $OCOCH_3$), 3.66 (2 H, t, CH_2OH), 4.90 and 5.18 (3 H, unequal d and t, C(15) H, $C{=}CH_2$). Dihydroovatine was characterized as its HCl salt which crystallized from a mixture of acetone and ether: mp 190–194 °C; mass spectrum obsd *m/z* 387, required *m/z* 387. Anal. Calcd for $C_{24}H_{37}NO_3{\cdot}HCl$: C, 67.98; H, 9.03; N, 3.30. Found: C, 67.74; H, 9.06; N, 3.28.

Isolation of Lindheimerine (2) from the Mother Liquor of the Weak Base Fraction. The tarry residue (4.95 g) from the mother liquor was dissolved in the minimum volume of benzene and loaded on a column of 170 g of neutral alumina (activity III). The column was protected from light and the fractions (50–60 mL each) shown in Table III were collected.

Fractions 7–13: Lindheimerine (2). TLC (hexane–3% ethanol) of the amorphous fraction (0.192 g) showed a single spot

Table III

fraction	eluent	wt, g
1-3	hexane	
4-6	hexane-benzene (3:1)	
7-13	hexane-benzene (1:1)	0.192
14-17	hexane-benzene (1:1)	
18-20	benzene	
21-30	benzene	0.215
31-50	99% benzene-1% methanol	1.033
51-60	80% benzene-20% methanol	0.072

Table IV

fraction	eluent	amt residue, g
1-7	benzene	
8-9	benzene-1% ethanol	
10-18	benzene-1% ethanol	1.84
19-23	benzene-2% ethanol	0.02
24-27	methanol	
28-32	methanol-2% acetic acid	

(R_F 0.9): $[\alpha]^{24}_D$ −113.8° (c 1.0); IR (KBr) ν_{max} 1735, 1230 (acetate), 1645 (imine), 1660 (double bond) cm^{-1}; ^1H NMR δ 0.82 (3 H, s, C(4) CH_3), 2.18 (3 H, s, $OCOCH_3$), 3.42 (2 H, s, NCH_2C), 4.98 and 5.28 (2 H, br d, $C{=}CH_2$), 8.0 (1 H, s, C(20) H); mass spectrum obsd m/z 341, required m/z 341.

Fractions 21–60. The residue (1.32 g) showed the presence of ovatine and garryfoline by TLC and ^{13}C NMR analysis.

Acetylation of Garryfoline Azomethine (12). A solution of garryfoline azomethine (0.05 g) in pyridine (1 mL) and acetic anhydride (1 mL) was allowed to stand overnight. The usual workup gave an amorphous solid which was identified as lindheimerine by TLC and IR, ^1H NMR, and ^{13}C NMR spectra.

Isolation of Garryfoline from the Strong-Base Fraction. The residue (7.3 g) of the strong-base fraction on TLC showed one major spot (R_f ~0.65). This fraction was dissolved in ice-cold 1% H_2SO_4, and the solution was extracted with $CHCl_3$ (3 × 100 mL). The $CHCl_3$ extract was washed with cold water (2 × 25 mL), and the washings were combined with the aqueous acid layer. This acidic fraction was basified to pH ~12 with 10% NaOH solution under cooling and was extracted with $CHCl_3$ (5 × 150 mL). The combined $CHCl_3$ extract was washed with cold water (2 × 30 mL), dried over anhydrous Na_2SO_4, and evaporated in vacuo to give a gum (2.4 g). The latter was dissolved in the minimum volume of benzene and loaded on a column of neutral alumina (70 g, activity III). The 50–60-mL fractions shown in Table IV were collected.

Fractions 10–23: Garryfoline (3). The gummy residue (1.86 g) was found to be a mixture of ovatine (1) and garryfoline (3) by TLC. A sample (0.32 g) was separated by PLC into two compounds. The polar compound (0.19 g) when repeatedly crystallized from acetone gave white, powdery crystals of garryfoline [mp 124–126 °C; $[\alpha]^{23}_D$ −46° (c 1.0)] which showed a weak ketonic absorbtion (1730 cm^{-1}) in the IR spectra, indicating the presence of cuauchichicine as an impurity.

Cuauchichicine (4) from the Mixture of Garryfoline and Ovatine. A sample (0.15 g) from fractions 10–23 was treated with 10% hydrochloric acid (13 mL) and the mixture stirred mechanically at room temperature. After some time the mixture dissolved, and the stirring was continued overnight at room temperature. The solution was filtered to remove some turbidity, and the filtrate was basified with 20% sodium hydroxide solution with cooling. The precipitated semisolid was extracted with chloroform (3 × 20 mL), and the chloroform extract was washed with water (2 × 15 mL), dried (anhydrous Na_2SO_4), and evaporated in vacuo to give a gum (0.12 g). Crystallization of the latter from aqueous acetone (long standing) gave large rhombic crystals of cuauchichicine: mp 152–154 °C; $[\alpha]^{18}_D$ −69.0° (c 1.0) (lit.[4] mp 152–155 °C; $[\alpha]_D$ −71.4°); IR (Nujol) ν_{max} 1730 cm^{-1} (C=O); 100-MHz ^1H NMR δ 0.81 (3 H, s, C(4) CH_3), 1.11 (3 H, d, C(16) CH_3), 2.65 (2 H, br s, NCH_2C), 4.29 (1 H, br s, C(20) H).

The remainder of fractions 10–23 was used for preparing derivatives of ovatine and garryfoline.

Fractions 28–32: Garryfoline (3). This fraction (0.42 g) on trituration with acetone gave a white crystalline solid (0.25 g) which was recrystallized from a large volume of acetone to afford a salt: mp 265–267 °C dec; $[\alpha]^{24}_D$ −28.2° (c 1.0, MeOH).

A solution of the above salt (0.14 g) in cold water (3 mL) was basified to pH ~12 with 10% NaOH solution to yield a gum (0.11 g) which when crystallized from aqueous acetone afforded white crystals (0.082 g) of garryfoline: mp 133–136 °C; $[\alpha]^{27}_D$ −48.8° (c 1.0) (lit.[4] mp 130–133 °C; $[\alpha]_D$ −60°); IR (Nujol) ν_{max} 3460 (OH), 1660 ($C{=}CH_2$) cm^{-1}; ^1H NMR δ 0.76 and 0.81 (combined 3 H, s, C(4) CH_3), 2.60 (2 H, br s, NCH_2C), 3.82 (2 H, m, C(22) CH_2), 4.43 (1 H, s, C(20) H), 5.0 and 5.1 (2 H, d, $C{=}CH_2$).

Isomerization of Cuauchichicine (4) to Isocuauchichicine (17). A solution of cuauchichicine (0.11 g) in methanol (10 mL) was refluxed on a steam bath for 7 h. After the reaction was completed (TLC monitering every hour), methanol was removed in vacuo to give a residue (0.1 g) which crystallized from acetone as needles of isocuauchichicine: 0.09 g; mp 132–134 °C; $[\alpha]^{24}_D$ −79.3° (c 0.89) (lit.[4] mp 134–136 °C; $[\alpha]_D$ −84°); IR (Nujol) ν_{max} 1731 (C=O), 1370 (CCH_3) cm^{-1}; 100-MHz ^1H NMR δ 1.07 and 0.91 (3 H, s, C(4) CH_3), 1.11 (3 H, d, C(16) CH_3), 3.95 (1 H, s, C(19) H).

Isocuauchichicine was also obtained by treatment of isogarryfoline with 10% HCl overnight at room temperature.

Preparation of 16-Epiisocuauchichicine (18). Isocuauchichicine (0.4 g) in methanol (37 mL) containing 2% NaOH was refluxed overnight. Workup of the reaction mixture gave a residue (0.37 g) showing a single spot on TLC (various solvent systems). The ^{13}C NMR spectrum of this fraction revealed the presence of two compounds (viz. C(16) CH_3 epimers) which were successfully separated by chromatography over alumina (activity III, 27 g) with hexane and hexane–benzene mixtures as eluant (Table V).

Table V

fraction	eluent	vol, mL	amt residue, g
1-9	hexane	500	
10-12	hexane-25% benzene	200	
13-17	50% hexane-50% benzene	60	0.083
18-20	50% hexane-50% benzene	160	0.087
21-27	50% hexane-50% benzene	260	0.071

Fractions 13–17: 16-Epiisocuauchichicine (18). The ^{13}C NMR spectrum of this fraction showed chemical shifts which are different from those of isocuauchichicine. Recrystallization from acetone gave the title compound as clusters of needles: mp 141–143 °C; $[\alpha]^{24}_D$ −83.0° (c 0.65); IR (Nujol) ν_{max} 1725 (C=O); 1367 (CCH_3) cm^{-1}; 100-MHz ^1H NMR δ 1.07 and 0.92 (3 H, s, C(4) CH_3), 1.08 (3 H, d, J = 4.15 Hz, C(16) CH_3), 3.91 (1 H, s, C(19) H).

Fractions 18–20. The ^{13}C NMR spectrum of this mixture showed two sets of signals for isocuauchichicine and 16-epiisocuauchichicine.

Fractions 21–27: Isocuauchichicine (17). Crystallization of this fraction from acetone afforded isocuauchichicine with physical and spectral data identical with that reported earlier in this paper.

Preparation of Cuauchichicine Azomethine (22) and Garryfoline Azomethine (12). The crude basic residue (3 g) from extraction of a fresh batch of leaves containing mainly lindheimerine, ovatine, and garryfoline was dissolved in 10% HCl and the solution stirred for 24 h in order to effect the hydrolysis of the acetate group of ovatine and rearrangement to cuauchichicine. The reaction mixture was filtered and the cooled filtrate basified with 20% NaOH. The precipitated bases were extracted with $CHCl_3$ (3 × 150 mL), and the extract was washed with water (2 × 100 mL), dried (anhydrous Na_2SO_4), and evaporated in vacuo to give a residue (2.7 g). The well-dried residue was dissolved in pyridine (17 mL) and acetic anhydride (17 mL) and the solution allowed to stand overnight. Acetic anhydride and pyridine were removed in vacuo by flashing several times with ethanol and benzene, and the resulting residue was refluxed in 200 mL of $CHCl_3$ for 2 days. Removal of chloroform in vacuo and TLC examination of the residue showed the presence of at least three compounds, the major product having R_f 0.45 (Al_2O_3, hexane–3% ethanol). This compound was isolated in a pure crystalline state by column chromatography on alumina. Initial fractions eluted

with hexane and hexane–0.5% ethanol gave the less polar impurity. Further elution with the same solvent system gave garryfoline azomethine (**12**) as a white solid (1.7 g), which crystallized from acetone in prismatic rods: mp 176–178 °C; $[\alpha]^{25}_D$ −79.8° (*c* 1.0, Et OH). IR (Nujol) ν_{max} 3200, 3070 (OH), 1648 (sh, double bonds) cm^{-1}; ^1H NMR δ 0.81 (3 H, s, C(4) CH_3), 3.38 (2 H, s, NCH_2C), 3.81 (1 H, s, CHOH), 4.96 and 5.06 (each 1 H, s, $C{=}CH_2$) and 7.8 (1 H, s, N=CH). Anal. Calcd for $C_{20}H_{29}NO$: C, 80.22; H, 9.76; N, 4.68. Found: C, 80.13; H, 9.76; N, 4.66.

A solution of 1.65 g of garryfoline azomethine in ethanol containing 8% HCl was refluxed 30 h when it was completely rearranged to cuauchichicine azomethine (**22**). The usual workup gave a residue (1.6 g) which crystallized from acetone in clusters of needles: mp 135–137 °C; $[\alpha]^{29}_D$ −114.4° (*c* 1.0) (lit.[5] mp 137–138 °C; $[\alpha]_D$ −114°); IR (Nujol) ν_{max} 1740 (C=O), 1650 and 1660 (sh, double bonds); ^1H NMR δ 0.81 (3 H, s, C(4) CH_3), 1.12 (3 H, d, $CHCH_3$), 3.43 and 3.48 (2 H, s, NCH_2C), 7.93 (1 H, br s, N=CH).

Isolation of *ent*-Kaurene from the Extract of *Cryptomeria japonica*. Examination of the crude extract (0.8 g) on an alumina TLC plate showed the presence of several components. Column chromatography of this extract on alumina with petroleum ether–ether (20 mL, 35–60 °C) gave a fraction (0.395 g) which showed mainly one spot on TLC. Crystallization of this fraction from acetonitrile afforded white crystals (0.17 g) of *ent*-kaurene: mp 49–50 °C; $[\alpha]^{26}_D$ −71.4° (*c* 1.0) [lit.[13] mp 51 °C; $[\alpha]^{11}_D$ −72° (*c* 1.0)]. Further elution of this column with more polar solvents gave fractions which showed the absence of *ent*-kaurene on TLC.

Hydrogenation of *ent*-Kaurene. A solution of *ent*-kaurene (0.18 g) in alcohol (70 mL) was hydrogenated at 31 psi of H_2 in the presence of PtO_2 (0.2 g) overnight. The usual workup of this solution afforded a mixture of "α"- and "β"-dihydrokaurenes which on crystallization from acetonitrile afforded long needles of "α"-dihydrokaurene: mp 84.5–85 °C; $[\alpha]^{25}_D$ −34.6° (*c* 0.479) (lit.[13] mp 83–84 °C; $[\alpha]^{21}_D$ −32°). The minor isomer, "β"-dihydrokaurene, could not be isolated in pure state as it was present in too small an amount.

Acknowledgment. This work was supported in part by Grant CA 24180 from the National Cancer Institute, Department of Health, Education, and Welfare. We thank Professor J. MacMillan, University of Bristol, for a sample of an extract of *Cryptomeria japonica* containing *ent*-kaurene and Dr. A. W. Stocklinski of the School of Pharmacy, University of Georgia, for providing the mass spectra. We also thank Dr. D. S. Siegler for collection of some of the plant material.

Registry No. 1A, 68719-14-2; **1B**, 76984-75-3; **2**, 68831-67-4; **3A**, 509-30-8; **3B**, 76984-76-4; **4**, 545-60-8; **5**, 68832-24-6; **8**, 467-92-5; **9**, 7096-94-8; **10**, 74232-41-0; **11**, 74613-52-8; **11**·HCl, 74260-92-7; **12**, 76946-28-6; **14**, 6714-12-1; **15**, 562-28-7; **16**, 1573-40-6; **17**, 467-93-6; **18**, 72580-08-6; **21**, 76946-29-7; **22**, 76915-15-6; **23**, 76900-43-1; **25**, 76900-44-2.

(13) L. H. Briggs, B. F. Cain, R. C. Cambie, B. R. Davis, P. S. Rutledge, and J. K. Wilmshurst, *J. Chem. Soc.*, 1345 (1963).

Synthesis of Aldosterone

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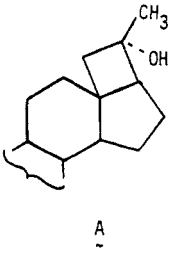
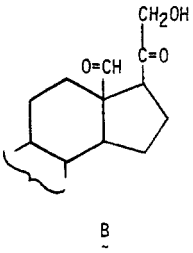
Received September 2, 1980

A convenient synthesis of 11-deoxyaldosterone (**11**) from 3β-acetoxy-20α-hydroxy-18,20-cyclopregn-5-ene (**1**) is described in Scheme I. The key steps were a selective epoxidation of **4** to **6**, base-catalyzed transformation of **6** to an allylic alcohol (**7**), and a selective oxidative cleavage of the 18(20) double bond of the acetate **8** to give 11-deoxyaldosterone acetate (**10**). Aldosterone was synthesized from 3-(ethylenedioxy)-11-oxo-20α-hydroxy-18,20-cyclopregn-5-ene (**16**) as summarized in Scheme II. The critical steps were kinetic addition of phenylselenyl bromide to **19a** followed by oxidative elimination to **20a** and acetate displacement to give **23a**. Subsequent selective oxidative cleavage of the 18(20) double bond of **23b** produced aldosterone acetate (**26a**). An efficient preparation of the starting material **16** is also described.

In connection with other projects, we required a transformation of 20-hydroxy-18,20-cyclo steroids A into 18,20-dioxo-21-hydroxy steroids B. A successful solution of this problem culminated in an efficient synthesis of 11-deoxyaldosterone (**11**) and aldosterone (**26b**).



A



B

Results and Discussion

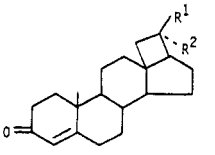
Synthesis of 11-Deoxyaldosterone (11). Pregnenolone acetate was photocyclized by a known procedure[1,2] to 20α-hydroxy-18,20-cyclo steroid **1**, which was dehydrated with phosphorus oxychloride in pyridine[1] to give a 4:1 mixture of exo olefin **2** and endo olefin **3** (Scheme I) as determined by gas chromatography. Saponification of the acetoxy group followed by Oppenauer oxidation afforded a 4:1 mixture of **4** and **5**, which were isolated[3] by a low-pressure column. The exo olefin **4** was epoxidized regioselectively with *m*-chloroperbenzoic acid to give a mixture of α- and β-epoxides **6**.[4] Treatment of **6** (X = H)

(1) Buchschacher, P.; Cereghetti, M.; Wehrli, H.; Schaffner, K.; Jeger, O. *Helv. Chim. Acta* **1959**, *42*, 2122.

(2) Cereghetti, M.; Wehrli, H.; Schaffner, K.; Jeger, O. *Helv. Chim. Acta* **1960**, *43*, 354.

(3) To the best of my knowledge, neither pure **4** nor **5** has been described in the literature, though these structures were disclosed in: U.S. Patent 3 211 759, 1965.

(4) Two epoxides were formed in comparable amounts and could not be separated by routine procedures. The pure α- and β-epoxides were prepared by indirect methods (see Experimental Section). The reduction of pure α-epoxide with lithium aluminum hydride followed by oxidation with pyridinium chlorochromate gave i, whereas the same treatment of β-epoxide gave ii. The configuration of i and ii has been known (Jeger, O.; et al. *Helv. Chim. Acta* **1960**, *43*, 315; see also related papers).



i R^1=Me, R^2=OH

ii R^1=OH, R^2=Me

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