The catalyst was filtered and the resulting solution was concentrated and freeze-dried. Three grams of a light yellow, amorphous powder was obtained. It contained less than 0.2% residual filipin and was inactive against *S. pastorianus*. The 2,4-dinitrophenylhydrazine and ferric chloride tests were negative.

Anal. Calcd. for $C_{30}H_{58}O_{10}$: C, 62.25; H, 10.11. Found: C, 62.88; H, 10.26.

Preparation of the Degradation Product.—Five grams of crystalline filipin was suspended in 350 ml. of 95% ethanol, stirred, and filtered. The filtrate was concentrated in a nitrogen stream to 220 ml. and the clear solution was placed in the deepfreeze overnight. The feathery, white crystals were filtered, washed with ice cold ethanol, ether, and air-dried. Successive crops were obtained totaling 705 mg. (m.p. 195–205°; specific rotation, 0).

Anal. Calcd. for $C_{30}H_{50}O_{11}$: C, 61.41; H, 8.59. Found: C, 61.28; H, 8.75.

Acknowledgment.—The authors are indebted to the members of the staff of The Upjohn Company and of the Chemistry Department, University of Illinois, and, in particular, to Miss Evelyn Webber for early purification studies; to Drs. J. L. Johnson, John W. Shell and Mrs. Anne Fonken for the physical measurements and interpretation; Messrs. G. F. Crum and W. H. DeVries for large-scale extractions, and to Mr. W. A. Struck for chemical analyses.

KALAMAZOO, MICH.
URBANA, ILLINOIS

[JOINT CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE UNIVERSITY AND THE INSTITUTO DE QUIMICA DE LA UNIVERSIDAD NACIONAL AUTONOMA DE MEXICO]

Alkaloid Studies. VIII.[1] The Structures of the Diterpenoid Alkaloids Laurifoline and Cuauchichicine

BY CARL DJERASSI, C. R. SMITH,[2] A. E. LIPPMAN,[3] S. K. FIGDOR[3] AND J. HERRAN

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The isolation and structure elucidation of two new diterpenoid alkaloids, laurifoline and cuauchichicine from *Garrya laurifolia* Hartw. is described. Laurifoline (VI) is 19-epiveatchine and its ready isomerization with acid to cuauchichicine (V) and with hot alcohol to isolaurifoline (VII) is reported.

Garrya laurifolia Hartw., a tree, commonly known as "cuauchichic," is widely distributed throughout Mexico[4] and extracts of the bark are used in indigenous medical practice as an antidiarrhetic agent.[4] Our interest in this plant was stimulated by an earlier report[5] in which it was indicated that it contained one or more unidentified alkaloids and by Oneto's publication[6] on the isolation of two new alkaloids, veatchine and garryine, from the related *Garrya veatchii* Kellogg as well as from five other *Garrya* species.

Our initial isolation experiments, patterned after those of Oneto[6] and proceeding *via* the hydrochlorides, suggested that the alkaloid composition of *G. laurifolia* was quite similar to that of the other *Garrya* species. Shortly thereafter, the first of a series of outstanding papers appeared by Wiesner and collaborators[7a] culminating in the structure elucidation[7c,d] of veatchine (I) and garryine (II).[8] The Canadian investigators,[7c] recognizing the close similarity between the *Garrya* alkaloids and the atisines,[9] also proposed a skeletal structure for the latter class of alkaloids and supporting experimental evidence has recently been provided by Pelletier and Jacobs.[10]

The facile and nearly quantitative separation of the isomeric alkaloids veatchine (I) and garryine (II) by countercurrent distribution[7a] prompted us to apply a similar procedure to the crude alkaloids of *Garrya laurifolia*, which had been extracted with ethanol and subsequently separated with dilute *hydrochloric acid* (*vide infra*). From such a separation scheme, there was isolated a crystalline alkaloid, $C_{22}H_{33}NO_2$, which proved to be isomeric but not identical with veatchine and garryine. We have named this alkaloid "cuauchichicine" after the indigenous name ("cuauchichic") of the plant and our original structure studies were carried out with this substance.[11]

The most important difference between cuauchichicine and the other *Garrya* alkaloids (I, II) is demonstrated by the infrared spectrum (Fig. 1) which shows the complete absence of NH or OH absorption but a strong carbonyl band at 5.78 μ, which can be attributed to a five-membered ring ketone. The carbonyl group is moderately reactive, as shown by preparation of an oxime (of isocuauchichicine X); semicarbazone or 2,4-dini-

(1) Paper VII, C. Djerassi and J. Fishman, *Chemistry & Industry*, 627 (1955).

(2) Eli Lilly Predoctorate Research Fellow, 1953–1955.

(3) Postdoctorate Research Fellow.

(4) M. Martinez, "Las Plantas Medicinales de Mexico," Ediciones Botas, Mexico, D. F., 1944, 3rd edit., pp. 92–95.

(5) C. Olguin H., Thesis, Facultad de Ciencias Quimicas, Mexico, D. F., 1932.

(6) J. F. Oneto, *J. Am. Pharm. Assoc.*, **35**, 204 (1946).

(7) (a) K. Wiesner, S. K. Figdor, M. F. Bartlett and D. R. Henderson, *Can. J. Chem.*, **30**, 608 (1952); (b) K. Wiesner, W. I. Taylor, S. K. Figdor, M. F. Bartlett, J. R. Armstrong and J. A. Edwards, *Ber.*, **86**, 800 (1953); (c) K. Wiesner, R. Armstrong, M. F. Bartlett and J. A. Edwards, *Chemistry & Industry*, 132 (1954); (d) K. Wiesner, R. Armstrong, M. F. Bartlett and J. A. Edwards, THIS JOURNAL, **76**, 6068 (1954).

(8) We are proposing a numbering system which follows as closely as possible that of abietane (W. Klyne, *J. Chem. Soc.*, 3072 (1953)) in order to emphasize the structural similarity to the diterpenes.

(9) *Cf.* E. S. Stern, in R. H. F. Manske and H. L. Holmes, 'The Alkaloids," Vol. IV, Academic Press, Inc., New York, N. Y., 1954, chapter 37.

(10) S. W. Pelletier and W. A. Jacobs, THIS JOURNAL, **76**, 4496 (1954).

(11) For preliminary communication see C. Djerassi, C. R. Smith, S. K. Figdor, J. Herran and J. Romo, *ibid.*, **76**, 5889 (1954). The constants (m.p. and $[\alpha]D$) for cuauchichicine reported in that communication have to be changed slightly since that material was probably contaminated with isocuauchichicine, which is described in the present paper.

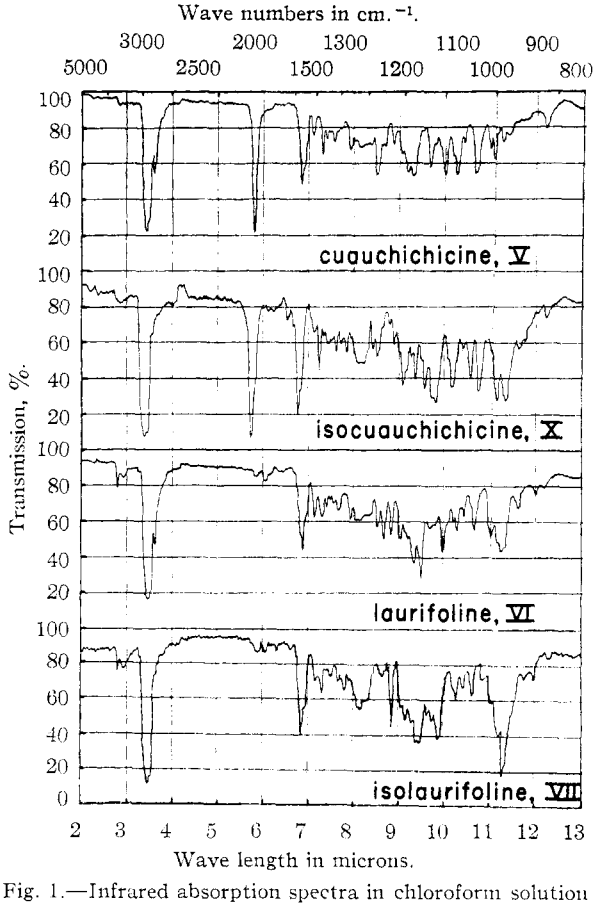
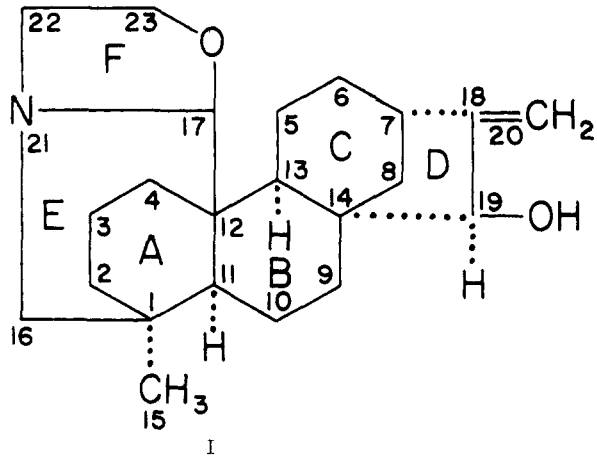


Fig. 1.—Infrared absorption spectra in chloroform solution (0.1 mm. thickness).

trophenylhydrazone formation was unsuccessful. Another important difference between cuauchichicine and the other *Garrya* alkaloids (I, II) is the absence of the exocyclic methylene group at C-18; thus ozonization did not yield formaldehyde and a Kuhn–Roth determination carried out parallel with veatchine (I) indicated that cuauchichicine possessed two rather than one C-methyl group as is the case with veatchine. The nature of five of the six rings present in the alkaloid was defined by the course of the selenium pyrolysis at 290–300° which yielded *pyrolysis base A* (III), identical with a specimen[12] obtained earlier by similar treatment[7b] of veatchine (I). Reduction of cuauchichicine with lithium aluminum hydride or sodium borohydride led to tetrahydroepiveatchine (IV), which had been synthesized earlier by Wiesner, *et al.*,[7b] from *pyrolysis base A*. It follows, that the carbonyl group of cuauchichicine must be located at C-19 and that the oxazolidine ring was opened by hydride reduction in the conventional manner.[13] The termination point (C-16 or C-17) of the oxazolidine ring could be assigned on the basis of the basicity of the alkaloid since it had already been observed earlier[7a] that veatchine (I) (*pK* 11.5) and garryine (II) (*pK* 8.7) differ enormously in that respect. Cuauchichicine was found to exhibit a *pK* of 11.15[14] and is, therefore, assigned structure V.



I

In the countercurrent distributions from which cuauchichicine (V) was isolated, there was always encountered in the earlier fractions a non-crystalline substance which did not possess any carbonyl band in the infrared. The amount of this material appeared to vary, apparently in inverse proportion to the length of time that the crude alkaloids (prior to countercurrent distribution) remained in hydrochloric acid solution. On the assumption that this substance might be labile to mineral acid, an isolation scheme was employed which involved extraction of the bark with ethanol and partitioning of the ethanol extract between dilute acetic acid and methylene dichloride. The crude alkaloids, recovered from the acetic acid extraction, showed essentially no infrared carbonyl band and were subjected to countercurrent distribution. In this manner, there was obtained a second crystalline alkaloid, which has now been named laurifoline.

Laurifoline proved to be isomeric with cuauchichicine (V) and hence veatchine (I) and garryine (II). It was of the same order of basicity (*pK* 11.8) as observed for I and V, but its infrared spectrum (Fig. 1) showed only hydroxyl absorption, thus resembling veatchine (I). A further similarity was demonstrated by the course of the ozonization, from which formaldehyde was isolated, thus establishing the presence of an exocyclic methylene group. When laurifoline was dissolved in dilute hydrochloric acid solution and allowed to stand overnight, the recovered product possessed a strong infrared carbonyl band and pure cuauchichicine (V) could be recovered in good yield.

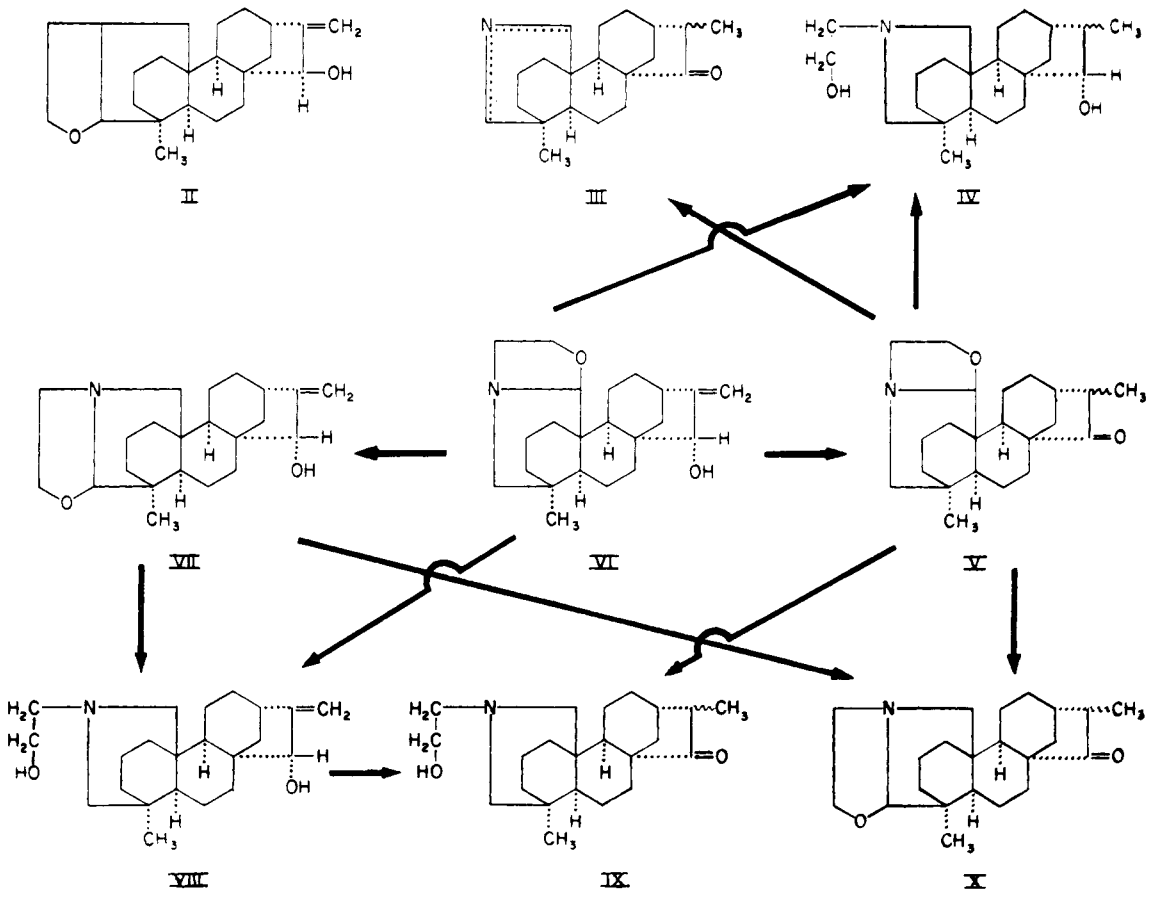
The following sequence demonstrated that only ring D could be involved in this isomerization and that laurifoline (VI) should be considered the C-19 epimer of veatchine (I). Lithium aluminum hydride reduction of laurifoline (VI) resulted in opening of the oxazolidine ring[13] and the formation of F-dihydrolaurifoline (VIII),[15] which in turn

(12) We are greatly indebted to Prof. K. Wiesner of the University of New Brunswick for this material.

(13) E. D. Bergmann, *Chem. Revs.*, **53**, 309 (1953); N. G. Gaylord, *Experientia*, **10**, 351 (1954).

(14) This value is obtained only when the alkaloid (in cellosolve–20% water) is titrated immediately with 0.1 *N* HCl. If the solution is permitted to stand overnight in an atmosphere of nitrogen prior to titration, two breaks (11.15 and 8.80) are observed in the titration curve indicating partial isomerization to isocuauchichicine (X).

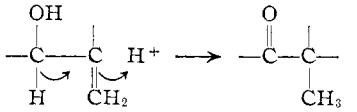
(15) In the absence of a systematic nomenclature for these alkaloids, we are employing the prefix F in order to indicate that reduction occurred in ring F rather than in ring D.



could be isomerized with dilute hydrochloric acid to F-dihydrocuauchichicine (IX),[15] also obtainable by catalytic hydrogenation of cuauchichicine (V). Furthermore, lithium aluminum hydride reduction of F-dihydrocuauchichicine (IX) gave tetrahydroepiveatchine (IV), which also was produced in the catalytic hydrogenation of laurifoline (VI) itself.

These transformations are only consistent with formulation VI for laurifoline. It is interesting to note that in parallel experiments, veatchine (I)[12] was recovered completely unchanged when treated with dilute hydrochloric acid, even on heating. The amazing difference in the behavior of these two epimers must, therefore, be due to an unusual stereochemical feature. The attachment of ring E to ring A must involve two axial bonds (at positions 1 and 12) and the assumption of an α-configuration at positions 11 and 13 seems justified on the basis of biogenetic analogy to the diterpenes. This would leave only two alternatives for the stereochemistry at C-14 (and hence C-7) and Wiesner and Edwards[16] have recently presented cogent arguments in favor of the α-attachment of ring D as expressed in formulations I and II for veatchine and garryine. Cuauchichicine (V) must exhibit precisely the same stereochemical features as veatchine (I) since it has been inter-related with it *via* tetrahydroepiveatchine (IV). Consequently, barring an unlikely rupture of the 14-19 bond in the acid isomerization of laurifoline (VI) to cuauchichicine (V), the former also must possess the same stereochemistry at these centers leaving only the assignment of the C-19 hydroxyl group in veatchine (I) and laurifoline (VI) open for consideration.

The laurifoline (VI) → cuauchichicine (V) isomerization can be depicted as XI → XII, the axially oriented hydrogen presumably being the one which undergoes facile elimination. From the available information, it was not possible to deduce the configuration of the C-19 hydroxyl group in laurifoline (VI) (and hence tetrahydroepiveatchine IV) as compared with that of veatchine (I).



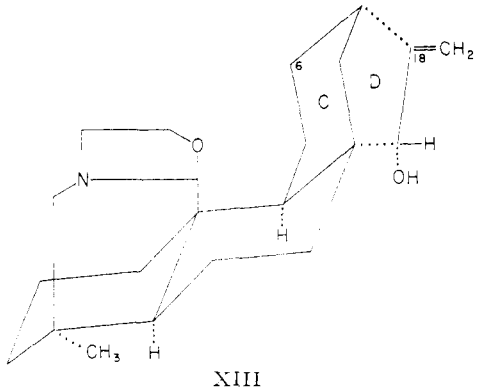
XI XII

Lithium aluminum hydride reduction of *reactive* ketones generally gives the corresponding equatorial alcohol,[17] but such a generalization cannot readily be applied to the present case, since (a) the carbonyl group of cuauchichicine (V) is at best moderately reactive and (b) the terms *equatorial* and *axial* lose their precise meaning since we are dealing with a five-, respectively, seven-membered ring ketone and a point of reference has first to be chosen. The conformational representation of laurifoline (VI) is shown in XIII and that of rings D and E in XIV. Using C-19 as an example, the

(16) K. Wiesner and J. A. Edwards, *Experientia*, **11**, 255 (1955).

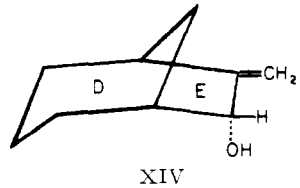
(17) *Cf.* D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).

latter expression clearly shows that a quasi-equatorial substituent with respect to the seven-membered ring becomes quasi-axial with respect to the five-membered D ring and *vice versa*.

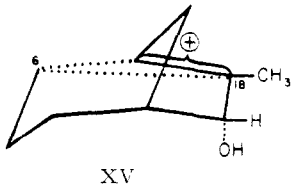


XIII

In order to determine whether lithium aluminum hydride reduction of cuauchichicine (V) or dihydrocuauchichicine (IX) indeed yields the more stable alcohol, we have undertaken the lithium–liquid ammonia–alcohol reduction of dihydrocuauchichicine (IX) since such a reduction procedure[17,18] invariably leads to the thermodynamically more stable epimer. The major product of the reduction proved to be tetrahydroepiveatchine (IV), previously obtained by hydride reduction of V and IX or by catalytic hydrogenation of laurifoline (VI), thus demonstrating that the C-19 hydroxyl group of laurifoline rather than of veatchine (I) exists in the more stable conformation. Facile ionic 1,2-elimination requires that the four centers involved should lie in one plane[17] and this would appear most readily rationalized in the present case if one invoked a non-classical carbonium ion intermediate[19] (XV), in which the quasi-axial (with respect to the five-membered D ring) C-19 hydrogen atom lies in one plane with the 6-18 bond (dotted line). This leads to the complete stereochemistry for laurifoline depicted in VI and XIII, from which it follows that the hydroxyl group in veatchine (I) must be quasi-axial (with respect to ring D).

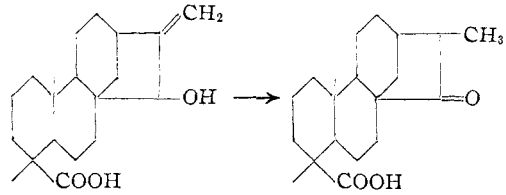


XIV



XV

While no simple examples of the laurifoline → cuauchichicine rearrangement appear to exist in the literature,[19a] it is of obvious biogenetic significance that the recently proposed structures[20] for the diterpene steviol (XVI) and its acid-catalyzed rearrangement product isosteviol (XVII) are completely analogous to the present examples (VI → V, VIII → IX). There is little doubt that this rearrangement proceeds by the same mechanism and that the same stereochemical driving force is also involved in the steviol → isosteviol rearrangement.



XVI XVII

In view of the lability of laurifoline, its purification was always followed by infrared spectral analysis. It was noted that when laurifoline (VI) was recrystallized from methanol, the finger print region of the spectrum changed (*cf.* Fig. 1) and that ultimately another isomer was obtained with markedly different physical constants. This isomerization could be accomplished by refluxing laurifoline with methanol for several hours and the resulting product has been named isolaurifoline (VII). That this isomerization was strictly analogous to the change veatchine (I) → garryine (II) and thus involved only the attachment of the oxazolidine ring was established by the course of the lithium aluminum hydride reduction of isolaurifoline (VII) which yielded F-dihydrolaurifoline (VIII). The reduced basicity (*pK* 8.6) of VII is also comparable to that observed[7a] (*pK* 8.7) for garryine (II). A similar isomerization upon boiling with methanol could be accomplished with cuauchichicine (V) and the resulting isocuauchichicine (X) (*cf.* Fig. 1) was also produced when isolaurifoline (VII) was subjected to mild hydrochloric acid treatment. As was to be anticipated, reduction of isocuauchichicine (X) with lithium aluminum hydride afforded tetrahydroepiveatchine (IV).

The isomerization of veatchine (I) to garryine (II) has previously been carried out[7a] with methanolic potassium hydroxide but it is clear that the alkali is superfluous since veatchine itself is a sufficiently strong base. The question may arise as to how it was possible to isolate laurifoline (VI) and cuauchichicine (V)[21] from the plant since the extraction scheme involved prolonged heating with alcohol, conditions under which these alkaloids are isomerized to the "iso"-series (VII, X). The simplest explanation is to assume that the isomeriza-

(18) *Cf.* F. Sondheimer, O. Mancera, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **75**, 1282 (1953).

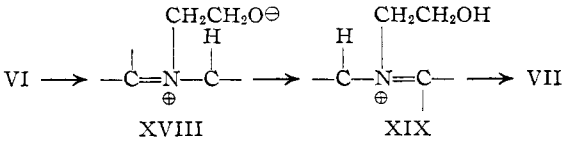
(19) Such an intermediate was first suggested by Prof. R. B. Woodward (Harvard University) to Prof. K. Wiesner and we are indebted to both of them for this information. It is pertinent to mention that similar intermediates have been proposed recently by E. Wenkert (*Chemistry & Industry*, 282 (1955)) in a theoretical discussion of certain biogenetic schemes in the diterpene series, which are also relevant to the case under discussion.

(19a) NOTE ADDED IN PROOF.—A simple example of this type of rearrangement has been encountered recently by A. Dreiding and J. A. Hartman (private communication), who observed the acid-catalyzed transformation of 2-methylenecycloalkanols to the corresponding methyl ketones (e.g., 2-methylenecyclohexanol → 2-methylcyclohexanone).

(20) E. Mosettig and W. R. Nes, *J. Org. Chem.*, **20**, 884 (1955). We are greatly indebted to Drs. E. Mosettig and W. R. Nes (National Institutes of Health) for an advance copy of this manuscript.

(21) It cannot be stated at this time whether cuauchichicine (V) exists as such in the plant or is produced by acid isomerization of laurifoline (VI). When the latter is removed from the plant extract with dilute acetic acid, subsequent extraction with dilute hydrochloric acid yields some cuauchichicine (V). The latter is, of course, the major product when the initial extraction is carried out *directly* with hydrochloric acid.

tion involves as an intermediate XVIII,[22] the alkoxide anion acting as an internal base in the abstraction of the proton thus permitting the shift of the double bond, the last step being recyclization of XIX to the "iso"-derivative. It is suggested that in the plant, these alkaloids exist as salts of organic acids, which prevent the formation of the internal anion (XVIII) required for the isomerization.



Acknowledgment.—We are grateful to Eli Lilly and Co., Indianapolis, Indiana, for a predoctorate research fellowship. This investigation was carried out as part of a joint research program, financed by the Rockefeller Foundation, on Latin-American plant products between Wayne University and the National University of Mexico. We should also like to express our indebtedness to Prof. K. Wiesner of the University of New Brunswick for furnishing several comparison samples and for informing us of work in his Laboratory prior to publication.

Experimental[23]

Extraction of Alkaloids. (a) With Hydrochloric Acid.—The bark of *Garrya laurifolia* Hartw. was collected near Huixquilucan (Estado de Mexico) and identified botanically by Prof. M. Martinez, Instituto de Biologia, Mexico, D. F. After drying and powdering, the bark (15 kg.) was extracted exhaustively with boiling ethanol and the solvent removed *in vacuo*, yielding approximately 800 g. of sirupy residue which was used in the subsequent extraction experiments.[24]

A portion (97 g.) of the extract was warmed with 500 cc. of 10% hydrochloric acid, undissolved material was removed by filtration and the filtrate was made alkaline with sodium hydroxide solution and extracted continuously overnight with ether. The residue (4.7 g.) after evaporation of the ether was again partitioned between chloroform and 10% hydrochloric acid yielding 4.3 g. of crude alkaloids. A ten-stage countercurrent distribution was carried out with 15 g. of such crude alkaloid fractions, using 200 cc. each of chloroform and citric acid–disodium phosphate buffer of *p*H 7.4 with the following results.

Fract.	Wt. (g.)	Fract.	Wt. (g.)
1	1.89	6	1.32
2	2.00	7	1.52
3	2.11	8	0.85
4	1.40	9	0.76
5	1.29	10	1.54

Fractions 1–3 were amorphous and by infrared analysis were shown to consist chiefly of laurifoline (no carbonyl band). Fractions 5–8 were crystalline and contained chiefly cuauchichicine, as demonstrated by infrared examination. This order of movement in the countercurrent distribution is in agreement with the observed *pK* values of the two alkaloids.

(b) With Acetic Acid.—A second portion (394 g.) of the crude *Garrya* extract was partitioned between methylene chloride and 10% acetic acid, the acid extract was made basic and extracted continuously with ether. The ether residue (28 g.) was again partitioned between methylene chloride and 10% acetic acid yielding 21 g. of nearly colorless, amorphous solid which was principally laurifoline as indicated by infrared analysis.

The original methylene chloride solution was then extracted with 10% hydrochloric acid and after the usual processing, 1.4 g. of nearly pure, crystalline cuauchichicine was isolated.

Characterization of Cuauchichicine (V).—Cuauchichicine, obtained by countercurrent distribution, was recrystallized several times from ether and dried carefully at 65° *in vacuo;* m.p. 152–155° (very dependable on rate of heating and degree of drying) $[\alpha]_D$ −71.4°, no high selective absorption in the ultraviolet, $\lambda_{max}^{CHCl_3}$ 5.78 μ (see Fig. 1), pK^{14} 11.15.

Anal. Calcd. for $C_{22}H_{33}NO_2$: C, 76.92; H, 9.68; N, 4.08; 1-(C)-CH_3, 4.37. Found: C, 77.04; H, 9.60; N, 3.93; (C)-CH_3,[25] 5.04.

The **hydrochloride** was prepared in methanol solution and recrystallized from methanol–ether; m.p. 259–262° after drying *in vacuo* at 100°.

Anal. Calcd. for $C_{22}H_{34}ClNO_2$: C, 69.53; H, 9.02; N, 3.69; Cl, 9.33. Found: C, 69.44; H, 9.32; N, 3.89; Cl, 9.47.

Isocuauchichicine (X).—Cuauchichicine (0.5 g.) was refluxed for 24 hours with 10 cc. of methanol and then evaporated to dryness. The crude product (m.p. 114–120°) exhibited an infrared spectrum which was nearly identical with that of the pure product (Fig. 1) obtained after two recrystallizations from methanol; m.p. 134–136°, $[\alpha]_D$ −84°, *pK* 8.10.

Anal. Calcd. for $C_{22}H_{33}NO_2$: C, 76.92; H, 9.68; N, 4.08. Found: C, 76.79; H, 9.82; N, 4.16.

The **oxime**[26] was prepared in pyridine–ethanol solution (3 hours, steam-bath) and recrystallized first from carbon tetrachloride and then from dilute methanol; m.p. 192–194°.

Anal. Calcd. for $C_{22}H_{34}N_2O_2$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.27; H, 9.89; N, 7.60.

Characterization of Laurifoline (VI).—The above 21 g. of crude laurifoline was subjected to countercurrent distribution between 200 cc. each of methylene dichloride and buffer[27] (*p*H 9.6) with the following results.

Fract.	Wt. (g.)	Fract.	Wt. (g.)
1	0.14	6	2.95
2	0.39	7	4.01
3	0.60	8	4.83
4	1.15	9	0.79
5	2.00	10	3.72

Fractions 1–9 showed the infrared spectrum of laurifoline, while a small carbonyl band was noticeable in fract. 10. Initial attempts to crystallize laurifoline were abortive and a middle fraction was sublimed at 0.01 mm. and analyzed (found: C, 77.23; H, 9.77; N, 4.14). Once seed crystals were obtained from a very concentrated acetone solution, recrystallization proved possible although the very considerable solubility of laurifoline prevented high recoveries. The infrared spectra of amorphous and crystalline material (Fig. 1) were indistinguishable. The analytical sample of laurifoline was obtained after recrystallization from ether and then hexane; m.p. 130–133°, $[\alpha]_D$ −60°, *pK* 11.81.

Anal. Calcd. for $C_{22}H_{33}NO_2$: C, 76.92; H, 9.68; N, 4.08. Found: C, 77.07; H, 9.63; H, 4.36.

Ozonolysis of laurifoline in glacial acetic acid followed

(22) This is essentially the mechanism proposed by Wiesner and coworkers (ref. 7b) except that it does not require an external base as assumed by them.

(23) All melting points were determined on the Kofler block. We are indebted to Mrs. Dolores Phillips for the infrared spectra which were measured in chloroform solution with a Baird Associates double beam recording infrared spectrophotometer. All rotations were measured in chloroform solution in 1 dcm. tubes. The microanalyses were carried out by Geller Laboratories, Hackensack, New Jersey, while the potentiometric titrations (cellosolve–20% water) are due to Dr. R. Dietrich, Zurich, Switzerland.

(24) We are grateful to Mr. B. T. Jackson for assistance in the early stages of this extraction.

(25) A Kuhn–Roth determination carried out at the same time with veatchine (I) showed 2.87 C-CH_3.

(26) The oxime mentioned in our preliminary communication (ref. 11) is actually isocuauchichicine oxime.

(27) W. R. G. Atkins and C. F. A. Pantin, *Biochem. J.*, **20**, 102 (1926).

by steam distillation into an ethanolic dimedon solution furnished 20–25% of the dimedon derivative of formaldehyde in two separate runs. No formaldehyde was encountered in a parallel ozonization of cuauchichicine.

Acetylation of 0.21 g. of laurifoline with acetic anhydride–pyridine (room temperature, 45 hours) yielded a basic monoacetate, which could not be crystallized even after chromatography and countercurrent distribution. The amorphous material gave a fairly satisfactory analysis (found: C, 74.76; H, 9.15) and could be converted into a crystalline oxalate by treatment with an ethereal solution of oxalic acid; m.p. 161–165° after recrystallization from methanol–ether.

Anal. Calcd. for $C_{26}H_{37}NO_7$: C, 65.66; H, 7.84; N, 2.95. Found: C, 65.55; H, 8.24; N, 3.31.

Isolaurifoline (VII).—Laurifoline (VI) was refluxed with methanol exactly as described above for cuauchichicine and gave in quantitative yield a crude product, whose infrared spectrum was nearly identical with that of pure isolaurifoline (Fig. 1) obtained by recrystallization (concentrated solution) from acetone and then hexane; m.p. 140–144°, $[\alpha]_D$ −57°, pK 8.60.

Anal. Calcd. for $C_{22}H_{33}NO_2$: C, 76.92; H, 9.68; N, 4.08. Found: C, 77.09; H, 9.83; N, 4.15.

Isomerization of Laurifoline (VI) to Cuauchichicine (V).—Laurifoline (0.75 g.), purified by countercurrent distribution, was allowed to stand overnight at room temperature in 10 cc. of 10% hydrochloric acid. Addition of sodium hydroxide, extraction with methylene chloride and evaporation furnished 0.69 g. of crude cuauchichicine which was purified by countercurrent distribution. Crystallization from methanol yielded 0.41 g. of cuauchichicine, m.p. 146–149°, $[\alpha]_D$ −72.5°, infrared spectrum superimposable with that of the analytical sample (Fig. 1). The hydrochloride melted at 256–258° and no depression in mixture m.p. was observed.

Veatchine (I)[12] was recovered unchanged after similar treatment or when refluxed for 3 hours in 0.75 N methanolic hydrochloric acid.

Isomerization of Isolaurifoline (VII) to Isocuauchichicine (X).—Isolaurifoline (0.2 g.) was treated in the above described manner with dilute hydrochloric acid to furnish 0.15 g. of isocuauchichicine (X), identified by infrared spectrum, m.p. 132–136° and undepressed mixture m.p.

Selenium Pyrolysis of Cuauchichicine (V).—Following Wiesner's[7b] procedure for the pyrolysis of veatchine (I), 3.6 g. of cuauchichicine (V) was heated with 7.2 g. of red selenium for 8 hours at 290–300° in a current of dry nitrogen. The crushed residue was extracted continuously in a Soxhlet extractor with chloroform, basic material was extracted with dilute sulfuric acid and recovered by the addition of sodium hydroxide and chloroform extraction. Evaporation of the solvent and chromatography of the residue (1.6 g.) on alumina followed by elution with benzene and recrystallization from hexane yielded 0.4 g. of *pyrolysis base A* (III),[7b] m.p. 133–36°; identity with authentic material,[7b,12] was established by mixture melting point determination and infrared comparison.

F-Dihydrolaurifoline (VIII).[15]—Laurifoline (VI) (0.97 g.) was reduced with 1 g. of lithium aluminum hydride in ether solution by the soxhlet technique (6 hours), saturated sodium sulfate solution was added followed by anhydrous sodium sulfate, the inorganic salts were filtered and the filtrate was evaporated; yield 0.78 g., m.p. 110–120°. The analytical sample was recrystallized from dilute methanol and from dilute acetone; m.p. 127–130° (after drying at 65° *in vacuo*), $[\alpha]_D$ −79°, no carbonyl absorption in the infrared.

Anal. Calcd. for $C_{22}H_{35}NO_2$: C, 76.47; H, 10.21; N, 4.05. Found: C, 76.24; H, 10.34; N, 4.33.

F-Dihydrolaurifoline (0.17 g.) was also obtained when 0.23 g. of isolaurifoline (VII) was reduced in a similar manner with lithium aluminum hydride.

F-Dihydrocuauchichicine (IX). (a) By Acid Isomerization of F-Dihydrolaurifoline (VIII).—F-Dihydrolaurifoline (0.48 g.) was allowed to stand in 10% hydrochloric acid solution overnight, sodium hydroxide was added and the product was extracted with chloroform, dried, washed and evaporated; yield 0.56 g., m.p. 103–109°, strong infrared carbonyl band. Recrystallization from ether and from hexane yielded colorless crystals, m.p. 113–117°, $[\alpha]_D$ −102°, $\lambda_{max}^{CHCl_3}$ 5.79 μ.

Anal. Calcd. for $C_{22}H_{35}NO_2$: C, 76.47; H, 10.21; N, 4.05. Found: C, 76.46; H, 10.29; N, 4.36.

(b) By Catalytic Hydrogenation of Cuauchichicine (V).—A sample (0.2 g.) of cuauchichicine (V) was hydrogenated in glacial acetic acid solution with 0.05 g. of platinum oxide catalyst[28] overnight at room temperature. Filtration of the catalyst, addition of sodium hydroxide until alkaline, extraction with chloroform and evaporation of the chloroform extract furnished 0.17 g. of F-dihydrocuauchichicine, m.p. 99–109°. Further recrystallization from hexane yielded 0.12 g. of IX, which was identified with material prepared according to procedure (a) by mixture melting point and infrared comparison.

Tetrahydroepiveatchine (IV). (a) By $NaBH_4$ or $LiAlH_4$ Reduction of Cuauchichicine (V).—A solution of 0.3 g. each of cuauchichicine and sodium borohydride in 30 cc. of ethanol was left at room temperature for 48 hours, diluted with water and extracted with ether. Evaporation of the ether yielded 0.25 g. of tetrahydroepiveatchine, m.p. 172–177°, raised to 175–177° after several recrystallizations from methanol, $[\alpha]^{29}_D$ −86.7°; pK 6.84. Identity with an authentic specimen[7b,12] (observed values in our laboratory: m.p. 175–178°, $[\alpha]^{29}_D$ −85.2°) was established by undepressed mixture melting point and superimposition of the infrared spectra.

Anal. Calcd. for $C_{22}H_{37}NO_2$: C, 76.03; H, 10.73; N, 4.03; equiv. wt., 347.5. Found: C, 76.11; H, 10.71; N, 4.53; equiv. wt., 357.

Lithium aluminum hydride reduction of 0.2 g. of cuauchichicine in the customary manner yielded a crude product having m.p. 155–163°; recrystallization furnished 0.070 g. of pure tetrahydroepiveatchine.

The hydrochloride, prepared in methanol solution, was recrystallized from ether–methanol; m.p. 292–300° dec.

Anal. Calcd. for $C_{22}H_{38}ClNO_2$: C, 68.81; H, 9.97; N, 3.65; Cl, 9.24. Found: C, 68.54; H, 10.10; N, 3.71; Cl, 9.32.

(b) By $NaBH_4$ or $LiAlH_4$ Reduction of Isocuauchichicine (X).—Reduction of 0.2 g. of X with 0.1 g. of lithium aluminum hydride in ether solution for 30 minutes and decomposition with moist ether, yielded after one recrystallization from methanol–ether 0.16 g. of tetrahydroepiveatchine, m.p. 169–173°, infrared spectrum identical with that of an authentic specimen.[12] Similar results were obtained when sodium borohydride was employed as described under (a).

(c) By $LiAlH_4$ Reduction of F-Dihydrocuauchichicine (IX).—Reduction of 88 mg. of IX with 300 mg. of lithium aluminum hydride in ether solution (3 hours) gave 82 mg. of tetrahydroepiveatchine, m.p. 166–172°, raised to 175–177° after two recrystallizations from ether and one from methanol. Identity was established in the usual manner.

(d) By Lithium–Ammonia–Methanol Reduction of F-Dihydrocuauchichicine (IX).—Liquid ammonia (100 cc.) was distilled from sodium into a three-necked flask cooled in a Dry Ice bath followed with continuous stirring by the addition of 0.5 g. of lithium and 4 cc. of methanol. A solution of 0.48 g. of IX in 60 cc. of ether was added dropwise and after 30 minutes the reaction was quenched, by the addition of 6 g. of ammonium chloride and excess water. The product was extracted with chloroform and after evaporation of the solvent, there was obtained 0.46 g. of solid, m.p. 134–155°, which proved difficult to purify by recrystallization and which was, therefore, chromatographed on 10 g. of alumina (activity III). Elution with benzene and recrystallization from the same solvent yielded 0.18 g. of tetrahydroepiveatchine, m.p. 175–176°.

(e) By Catalytic Hydrogenation of Laurifoline (VI).—Laurifoline (0.5 g.) was hydrogenated at room temperature for 2.5 hours with 0.05 g. of platinum oxide in 25 cc. of absolute ethanol. The product was chromatographed on 15 g. of alumina (activity III). Elution with benzene furnished 170 mg. of amorphous material, the infrared spectrum of which closely resembled that of F-dihydrocuauchichicine (IX). This fraction was not investigated further although it suggested that the rearrangement of the allylic alcohol to the methyl ketone (VIII → IX) could also be accomplished on a catalyst surface. Elution with benzene–ether (9:1)

(28) The resistance of the C-19 carbonyl group to these hydrogenation conditions has already been observed earlier (ref. 7b) in the case of pyrolysis base A (III).

and recrystallization from methanol produced 0.16 g. of tetrahydroepiveatchine, m.p. 174–177°, undepressed upon admixture with authentic material. This almost certainly must have involved direct hydrogenation of VI rather than proceeding *via* the ketone IX, since the C_{19} carbonyl group is not reducible under those conditions.

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Alkaloids of the Amaryllidaceae. V. Alkaloids of *Nerine falcata* Barker and *N. laticoma* (Ker) Dur. and Schinz.[1]

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Nerine falcata Barker and *N. laticoma* (Ker) Dur. and Schinz. have been found to contain lycorine, caranine and a new alkaloid which has been named falcatine. The empirical formula and functional groups of falcatine have been determined. Evidence is presented that the aromatic ring contains methylenedioxy and methoxyl groups.

The genus *Nerine* (Amaryllidaceae) recently was investigated by Boit,[2] who found in *N. sarniensis* tazettine, lycorine and a new alkaloid of empirical formula $C_{19}H_{25}NO_5$, named nerinine. This paper deals with the alkaloids of two *Nerine* species which were collected two years ago in South Africa. To date, the alkaloids of this genus appear to vary considerably with the species, since the alkaloids of *N. falcata* and *N. laticoma* are quite different from those found in *N. sarniensis*. Moreover, we have found that *N. kreigii* contains lycorine and two additional new alkaloids which will be reported in another paper.

The isolation procedures were similar to those of our previous work. The yields of lycorine, caranine and falcatine from the two *Nerine* species are shown in Table I. Lycorine and caranine were identified by melting point and comparison of infrared spectra with those of authentic samples.

TABLE I

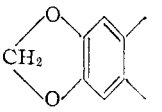
ALKALOIDAL CONTENT OF *Nerine* SPECIES BASED ON FRESH BULB WEIGHT

	N. falcata	*N. laticoma*
Lycorine, %	0.046	0.024
Caranine, %	.021	.006
Falcatine, %	.216	.042

The new alkaloid, falcatine, was shown by analysis to have the molecular formula $C_{17}H_{19}NO_4$. Although relatively unstable to oxygen and light, the alkaloid showed no decomposition when stored for two months under nitrogen at 0° in a brown bottle. Analysis of the functional groups showed the presence of one methoxyl. The N-methyl group was absent. A band at 2.80 μ in the infrared spectrum of falcatine showed the presence of a hydroxyl group. An aliphatic hydroxyl was verified when it was found that falcatine gave a basic monoacetate showing carbonyl absorption at 5.81 μ. Bands at 9.55 and 10.70 μ indicated the presence of a methylenedioxyphenyl function. A positive Labat[3] test gave further proof of the methylenedioxyphenyl group. Upon catalytic reduction, falcatine absorbed one mole of hydrogen to give a crystalline dihydro derivative. No evidence of a second isomer was obtained. The relatively low yield of dihydrofalcatine is attributed to partial decomposition during purification. Falcatine gave two methiodides when treated with methyl iodide. The α-isomer, m.p. 250–255° dec., was formed in smaller amount. The β-isomer was non-crystalline.

Falcatine is isomeric with natalensine, coccinine, montanine and crinamine.[1,4] However, spectral comparisons of falcatine with these isomers show two important differences. It has been our observations that most alkaloids containing the methylenedioxyphenyl chromophore show ultraviolet maxima near 240 mμ (log ϵ ~3.6) and 295 mμ (log ϵ ~3.7) when no unsaturated group is conjugated with the aromatic ring. Crinamine and caranine differ slightly in the respect that the low wave length band appears as a shoulder near 235 mμ. The ultraviolet spectrum of falcatine clearly resembles that of hydrocotarnine (λ_{max} 287 mμ, log ϵ 3.23) more closely than those of crinamine and its isomers.

A study of the infrared spectra between 6.0 and 6.5 μ of compounds containing the system I shows very weak C=C stretching absorption near 6.25 μ when no unsaturation is conjugated with the phenyl group.



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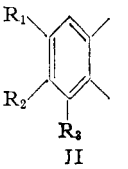

II

a, $R_1R_2 = O_2CH_2$ b, $R_1R_2 = OCH_3$ c, $R_1, R_2, R_3 = OCH_3$
$R_3 = OCH_3$ $R_3 = H$

Strong absorption appears at 6.25 μ if conjugation is introduced. Oxyhydrastinine and piperonal show absorption at 6.25 μ almost as intense as that of the carbonyl band.[5] A similar intensification appears to occur in compounds of the type II even though no conjugation is present. Lycorenine, hydrocotarnine, mescaline, homoveratrylamine, 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and its 2-methyl derivative all show relatively strong bands

(1) Previous paper, L. H. Mason, E. R. Puschett and W. C. Wildman, THIS JOURNAL, **77**, 1253 (1955).

(2) H.-G. Boit, *Chem. Ber.*, **87**, 1704 (1954).

(3) J. A. Labat, *Bull. soc. chim. biol.*, **15**, 1344 (1932).

(4) W. C. Wildman and C. J. Kaufman, THIS JOURNAL, **77**, 1248 (1955).

(5) A more general discussion of this phenomenon is found in L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, pp. 59–63.