liquid nitrogen temperature. After allowing the bulb and its contents to warm to and remain at room temperature for at least 3 hr., the mixture was exposed to ultraviolet irradiation from a 125-w. Hanovia lamp. The irradiation was discontinued at the end of 16 hr. and the mixture was analyzed by vapor phase chromatography. The ratio of the isobutylene–difluorocarbene adduct to the *cis*-butene-2 product was found to be 12.8:1 by area measurements. It had previously been determined that the vapor phase chromatography sensitivities of the pure components were essentially equal.

Acknowledgment. The author is indebted to Mr. D. P. Babb for technical assistance, Dr. J. J. McBrady and Mr. R. A. Meiklejohn for infrared and nuclear magnetic resonance measurements and interpretation, and Mr. B. W. Nippoldt and Mr. P. B. Olson for various analytical determinations. The author also wishes to thank Dr. J. G. Erickson for reviewing and editing the manuscript.

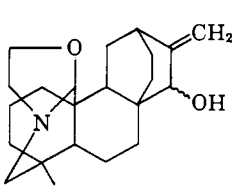
The Diterpene Alkaloids. Correlation of the Atisine and Garrya Series of Alkaloids[1]

S. William Pelletier[2] and David M. Locke

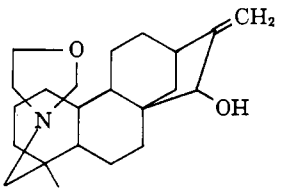
Contribution from the Department of Chemistry, The University of Georgia, Athens, Georgia, and the Laboratories of the Rockefeller Institute, New York, New York. *Received October 15, 1964*

This paper reports the details of the correlation of atisine and veatchine via the bisnor ester V. Two reaction pathways from atisine to V and one from veatchine to V are described. Thus one pathway from atisine involves the sequence I → VIII → IX → VI → VII → X → XI → XII → XIII → V and the other route, the sequence XVI → XVII → XVIII → XIX → XX → XXI → XXII → XXIII → XXIV → XIV → XXIX → V. The route from veatchine (II) involves intermediates XXX → XXXI → XXXII → XXXIII → XXXIV → XXXV → XXXVI → XXXVII → XXXVIII → XXXIX → XL → V. The structures of certain byproducts encountered in the course of these degradations are discussed. This correlation provides the first unequivocal evidence for the common stereochemistry of the atisine- and garrya-type alkaloids.

Several years ago structures I and II were assigned to the diterpene alkaloids[3,4] atisine[5,6] [*Aconitum heterophyllum* Wall (*Ranunculaceae*)] and veatchine[5,7] [*Garrya veatchii* Kellogg (*Garryaceae*)], respectively. At the time, little was known about the precise stereochemistry of the compounds, and the question of whether they possessed the same stereochemistry was an interesting one since the alkaloids occur in unrelated plant families. Subsequent information indicated that in veatchine the five-membered ring bearing the allylic alcohol moiety was *trans* to the heterocycle ring.[8,9] The failure to interrelate atisine and veatchine by vigorous acid isomerization of dihydroveatchine[10] underscored the need for further experimental studies to determine whether the allyl alcohol grouping in atisine occupies the *trans* (as in veatchine) or the *cis* bridge (with respect to nitrogen) of the bicyclo[2.2.2]octane system. Since evidence from this[11] and another laboratory[12] indicated



I



II

that atisine, like veatchine, has the allyl alcohol group in a *trans* relationship to the nitrogen ring, we were prompted to undertake an unambiguous correlation of atisine and veatchine. This paper reports the successful correlation of atisine (III)[13] and veatchine (IV)[13] *via* the bisnor ester V. A preliminary account of this

(1) This investigation was supported in part by Grants RG 5807, RG 5807(C1), GM 10921-01, and GM 10921-02 from the National Institutes of Health, U. S. Public Health Service.

(2) The Department of Chemistry, The University of Georgia, Athens, Ga.

(3) Recent review articles on the diterpene alkaloids are: (a) S. W. Pelletier, *Experientia*, 20, 1 (1964); (b) S. W. Pelletier, *Tetrahedron*, **14**, 76 (1961).

(4) See also (a) H. G. Boit, "Ergebnisse der Alkaloid-Chemie bis 1960," Academie-Verlag, Berlin, 1961, pp. 851–905, 1009–1011; (b) E. S. Stern in "The Alkaloids," Vol. VII, R. H. F. Manske, Ed., Academic Press, Inc., New York, N. Y., 1960, pp. 473–503; (c) K. Wiesner and Z. Valenta, "Progress in the Chemistry of Organic Natural Products," Vol. XVI, Springer-Verlag, Vienna, 1958, pp. 26–63.

(5) K. Wiesner, J. R. Armstrong, M. F. Bartlett, and J. A. Edwards, *Chem. Ind.* (London), 132 (1954).

(6) S. W. Pelletier and W. A. Jacobs, *J. Am. Chem. Soc.*, **76**, 4496 (1954).

(7) K. Wiesner, R. Armstrong, M. F. Bartlett, and J. A. Edwards, *ibid.*, **76**, 6068 (1954).

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

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

(10) Ref. 4c, p. 52.

(11) S. W. Pelletier, *Chem. Ind.* (London), 1116 (1958).

(12) D. Dvornik and O. E. Edwards, *ibid.*, 623 (1958).

(13) Since the detailed stereochemistry of atisine[3b,14–18] and veatchine[17] is now well known, the correct absolute stereochemistry is indicated from formula III on.

(14) A. J. Solo and S. W. Pelletier, *Chem. Ind.* (London), 1108 (1960).

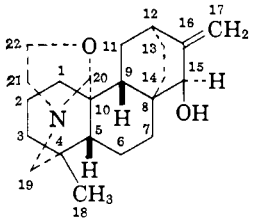
(15) A. J. Solo and S. W. Pelletier, *Proc. Chem. Soc.*, 14 (1961).

(16) D. Dvornik and O. E. Edwards, *Tetrahedron*, **14**, 54 (1961).

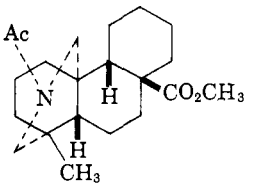
(17) H. Vorbrueggen and C. Djerassi, *J. Am. Chem. Soc.*, **84**, 2990 (1962).

(18) J. W. ApSimon and O. E. Edwards, *Can. J. Chem.*, **40**, 896 (1962).

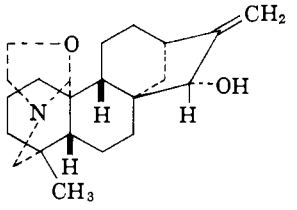
work was outlined[19] and it is the purpose of this paper to disclose the details of the correlation.



III

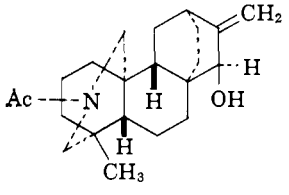


V

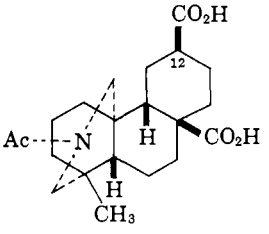


IV

The envisioned reaction path from atisine to V involved the use of the very stable N-acetate VI[20] which may be readily prepared from atisinium chloride.[21] The plan was to degrade VI by a suitable means to the dicarboxylic acid VII, and devise a means of selectively decarboxylating or otherwise removing the secondary carboxyl group at position 12. If successful in the case of atisine, application of the same reaction sequence to veatchine would be expected to complete the correlation.

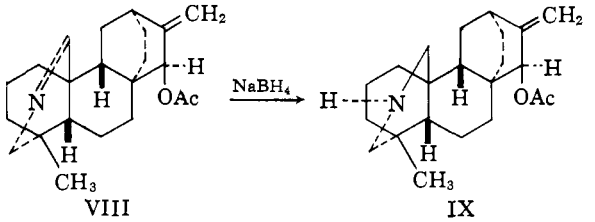


VI



VII

The route to the starting material VI was shortened over the published procedure[20] by reduction of the imine acetate VIII[22] with sodium borohydride and acetylation of the crude product IX with acetic anhydride–pyridine. Saponification of the resulting O,N-diacetate[20] gave the N-acetate VI in an over-all yield of 85%.



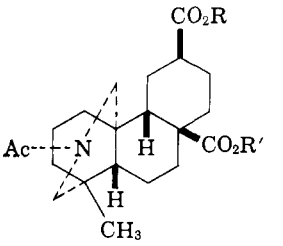
VIII IX

↓

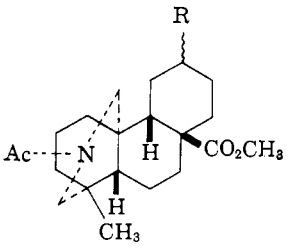
VI

(19) S. W. Pelletier, *J. Am. Chem. Soc.*, **82**, 2398 (1960).
(20) S. W. Pelletier and W. A. Jacobs, *ibid.*, **78**, 4139, 4144 (1956).
(21) Atisinium chloride is the so-called "atisine hydrochloride." Since the salts resulting from the addition of HX acids to atisine and veatchine exist really as ternary iminium salts rather than as hydrohalide salts, they will be referred to hereafter as atisinium and veatchinium salts.
(22) D. Dvornik and O. E. Edwards, *Can. J. Chem*, **35**, 860 (1957). We thank Dr. Edwards for providing experimental directions, prior to publication, for the preparation of compound VIII.

Degradation of VI to the noracid VII was effected by oxidation with sodium metaperiodate–potassium permanganate[23] in high dilution. The reaction conditions were very critical, but with proper care the noracid VII, m.p. 285–289,°, $[\alpha]D$ +11.3°, could be obtained in one step from VI in 40% yield. VII was converted to the diester X, m.p. 196–198.5°, $[\alpha]D$ +13°, with diazomethane in acetone. Selective saponi-



VII, R = R′ = H
X, R = R′ = CH_3
XI, R = H; R′ = CH_3
XII, R = Ag; R′ = CH_3



XIII, R = Br
V, R = H

fication with aqueous sodium hydroxide afforded the N-acetyl monoester acid XI, m.p. 248–251.5°, $[\alpha]D$ +15°.

Conversion of XI to the corresponding silver salt XII required careful attention to reaction conditions. An attempt to prepare the salt by reaction of the acid with freshly prepared silver oxide[24] failed. Treatment of the ammonium salt of XI with 1 equiv. of sodium hydroxide, followed by addition of exactly 1 equiv. of silver nitrate, gave a low yield of unstable product. The best procedure appeared to involve neutralization of XI with 1 equiv. of sodium hydroxide, followed by addition of exactly 1 equiv. of silver nitrate in the cold and dark. The salt was rather soluble in water and therefore was washed only sparingly with ice–water. The crude salt was dried *in vacuo* at 60° and used immediately in the Hunsdiecker reaction.

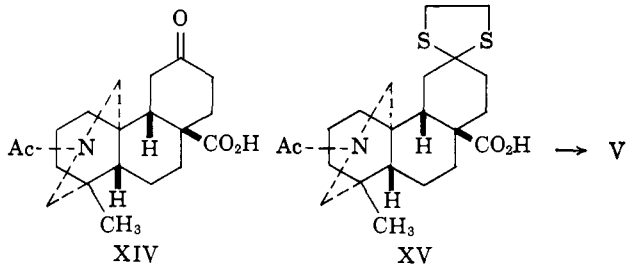
Though all the usual precautions were observed in carrying out the Hunsdiecker[25] reaction on XII, the yields of bromo derivative XIII were uniformly poor. In every case less than the theoretical amount of bromine reacted and about one-third of the product consisted of parent acid XI. After careful chromatography the bromo derivative XIII was obtained as an amorphous resin.

Attempts to remove the bromine in XIII by hydrogenation in the presence of palladium on calcium carbonate in either neutral or basic media were unsuccessful. Adams catalyst was also ineffective. Likewise unsuccessful was the use of palladium on charcoal with hydrazine hydrate. However, reduction by zinc in glacial acetic acid[26] containing a few drops of hydrochloric acid gave a halogen-free semicrystalline product. Preliminary chromatography over silicic acid and alumina afforded a nicely crystalline bisnor ester, m.p. 154–156°, $[\alpha]D$ −35°. Interestingly, material prepared from veatchine by a similar degradative sequence (*vide infra*) showed the same melting point and infrared spectrum but a different rotation, $[\alpha]D$ −17°. Repeated crystallization of the atisine- and veatchine-

(23) R. U. Lemieux and E. von Rudloff, *Can. J. Chem.*, **33**, 1701, 1710 (1955); E. von Rudloff, *ibid.*, **33**, 1714 (1955).
(24) H. Hunsdiecker and C. Hunsdiecker, *Ber.*, **75B**, 291 (1942).
(25) C. V. Wilson, *Org. Reactions*, **9**, 332 (1957).
(26) N. G. Brink, D. M. Clark, and E. S. Wallis, *J. Biol. Chem.*, 162, 695 (1946).

derived bisnor esters failed to alter the rotations. However, careful chromatography of the atisine-derived sample revealed the presence of a few milligrams of material with $[\alpha]_D$ −68°. Elimination of this contaminant gave the pure bisnor ester V, m.p. 156–157°, $[\alpha]_D$ −18.9°.

While we were investigating the degradative sequence from atisine to V which is described above, it appeared desirable to explore an alternate route in case of failure of the first pathway. What appeared to be an attractive scheme involved conversion of the bisnor keto acid (XIV), the preparation of which had just been reported in a preliminary communication,[27] to the thioketal XV and desulfurization of the latter with Raney nickel. The reaction sequence to XIV is described below since several modifications in the published sequence were used.



XIV XV

Hydration of azomethine (XVI)[20] at room temperature with 10% hydrochloric acid gave poor yields of the azomethinediol XVII.[27] The use of a slightly higher temperature (32°), however, gave a much improved yield (51%) of the desired product, m.p. 262–264° (lit.[27] 264–264.5°). It is interesting to note that attempts to hydrate the O-acetate (VIII) with sulfuric acid or sulfuric acid–acetic acid mixtures produced only ketonic products, resulting presumably from the rearrangement of the allyl alcohol system.[28]

Reduction of the azomethinediol XVII was accomplished with sodium borohydride in preference to the catalytic procedure.[27] The crude product XVIII was acetylated with acetic anhydride–pyridine and isolated as the crystalline diacetate XIX, m.p. 217–219° (lit.[27] 214°), in a yield of 84% for the two steps.

Saponification of the diacetate XIX gave a crude N-acetyl diol (XX) which was oxidized directly with Kiliani reagent[31] to the 15,16-secomethyl keto acid XXI, m.p. 223–226° (lit.[27] 218°). The yield for the two steps was 63%. This same product could be obtained, but in a much poorer yield, from the N-acetate VI. Hydration of this compound followed by oxidation of the crude product XX with Kiliani reagent gave a small yield of a crystalline seco acid which was identical with XXI.

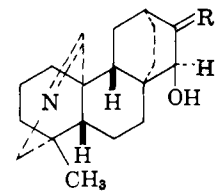
(27) (a) D. Dvornik and O. E. Edwards, *Chem. Ind.* (London), 623 (1958). We are grateful to Dr. O. E. Edwards for kindly providing a prepublication copy of this communication, for physical constants of several of the compounds mentioned in it, and for the experimental directions for the hydration of the imine alcohol (XVI). (b) D. Dvornik and O. E. Edwards, *Can. J. Chem.*, **42**, 137 (1964).

(28) Several examples of the acid-induced allyl alcohol → methyl ketone rearrangement are known in the diterpenes.[9,11,29] A simple example involving the transformation of 2-methylenecyclohexanol to 2-methylcyclohexanone has also been described.[30]

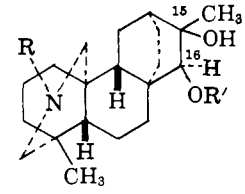
(29) E. Mosettig and W. R. Nes, *J. Org. Chem.*, **20**, 884 (1955).

(30) A. Dreiding and J. A. Hartman, *J. Am. Chem. Soc.*, **78**, 1216 (1956).

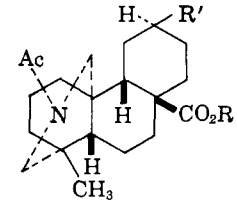
(31) H. Kiliani and B. Merck, *Ber.*, **34**, 3562 (1901). Kiliani reagent consists of 53 g. of chromium trioxide and 80 g. of sulfuric acid in 400 ml. of water.



XVI, R = CH_2
XVII, R = $<^{CH_3}_{OH}$



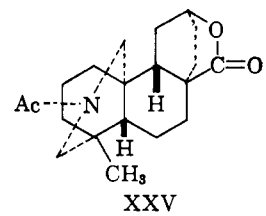
XVIII, R = R′ = H
XIX, R = R′ = Ac
XX, R = Ac, R′ = H



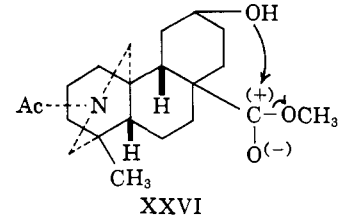
XXI, R = H; R′ = $COCH_3$
XXII, R = H; R′ = $OCOCH_3$
XXIII, R = CH_3; R′ = $OCOCH_3$
XXIV, R = H; R′ = OH
XXVII, R = CH_3; R′ = OH

Oxidation of this seco acid by the Baeyer–Villiger reaction using peroxytrifluoroacetic acid[32] gave the bisnor acetoxy acid XXII,[27] m.p. 306–308°, in good yield. It was found that in our hands 0.5-g. batches appeared to be optimum for this reaction. The bisnor acetoxy acid XXII was converted by the action of diazomethane to a methyl ester (XXIII), previously unreported, m.p. 165–167°, $[\alpha]^{26}_D$ −26°. Saponification of the acetoxy acid XXII gave a 65% yield of the bisnor hydroxy acid XXIV, m.p. 207–208° (lit.[27] 203°). If acidification was not carried out under carefully controlled conditions in the cold, a crystalline lactone (XXV),[27] m.p. 164–166°, was obtained, ν_{max} 1742 (δ-lactone) and 1645 $cm.^{-1}$ (NAc).

Surprisingly it was discovered that saponification of the methyl ester XXIII of the acetoxy acid gave the same bisnor hydroxy acid XXIV. Apparently saponification of the tertiary ester was accomplished by participation of the hydroxyl group across the ring (XXVI) to give lactone XXV which was in turn hydrolyzed to the bisnor hydroxy acid XXIV. The hydroxy acid XXIV was converted by the action of diazomethane to a previously unreported methyl ester (XXVII), m.p. 190–196°, $[\alpha]^{26}_D$ −35°.



XXV

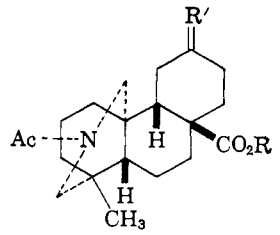


XXVI

It was considered at this point that an attractive route from XXIV to the desired bisnor ester V might well involve dehydration of the hydroxy acid XXIV, or its methyl ester XXVII, to an olefinic compound followed by hydrogenation to one of the desired products (XXVIII or V). Extensive testing of this hypothesis produced a lactone (XXV) as the only identified product.

Oxidation of the hydroxy acid XXIV with sodium dichromate gave in our hands a 46% yield of the bisnor

(32) W. D. Emmons and G. B. Lucas, *J. Am. Chem. Soc.*, **77**, 2287 (1955).



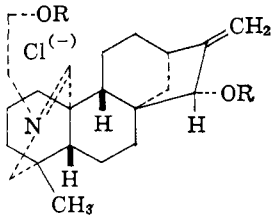
XXVIII, R = H; R′ = H_2
V, R = CH_3; R′ = H_2
XIV, R = H; R′ = O
XXIX, R = CH_3; R′ = O

keto acid XIV,[27] m.p. 254–258°, while oxidation of the methyl ester XXVII with chromic acid gave a 95% yield of the previously unreported keto ester XXIX.

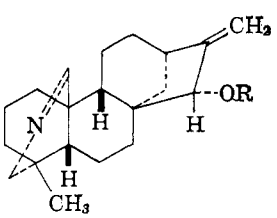
The keto acid XIV could be converted to the thioketal with ethanedithiol and boron trifluoride etherate[33] and reduced with Raney nickel catalyst to give a very small yield of product which appeared to contain the desired bisnor acid XXVIII, although it was not positively identified. Reduction of the methyl ester XXIX of the keto acid by the same method produced a 25% yield of recrystallized bisnor ester V which was identical with material obtained from the previously described sequence (VI, VII, X, XI, XII, XIII, and V) as indicated by nondepression of mixture melting point and identity of the infrared spectra. Thus, atisine has been converted to the bisnor ester V by two independent routes.

An attempt to convert veatchine to the same bisnor ester V by the route just described failed at the first stage when it was found impossible to hydrate the double bond in veatchine azomethine under conditions found successful with the azomethine from atisine (or even under more drastic conditions). Fortunately, conversion of veatchine to the bisnor ester V was successful by a sequence of reactions (VI, VII, X, XI, XII, XIII, and V) paralleling the first route described for conversion of atisine to V. Since most of the products of these reactions are new, the sequence will be outlined briefly.

Veatchinium chloride[21,34] (XXX) was prepared in the usual way from veatchine[35] and converted by re-

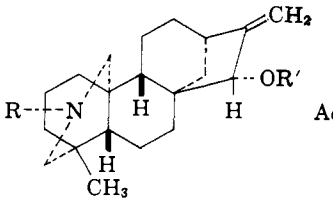


XXX, R = H
XXXI, R = Ac

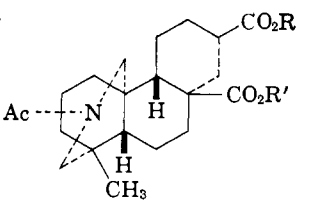


XXXII, R = Ac
XXXIII, R = H

fluxing in acetic anhydride–acetic acid to the iminium diacetate chloride XXXI,[19] m.p. 254–257°, $[\alpha]^{31}D$ −56°, ν_{max}^{Nujol} 1739 and 1238 (OAc), and 1669 $cm.^{-1}$ (>C=N). Treatment of this material with strong base under nonhydrolytic conditions effected removal of the β-acetoxyethyl group to give the imine acetate XXXII,[19] m.p. 122.5–124°, in good yield. Saponification afforded the corresponding alcohol XXXIII,[19,36] m.p. 186–188°, which was reduced smoothly with sodium borohydride in methanol to the secondary amine XXXIV,[19,36] m.p. 166–169°. Acetylation of XXXIV followed by mild saponification gave an amorphous N-acetate (XXXV),[7] ν_{max} 3571 (OH) and 1653 $cm.^{-1}$ (NAc). The intermediate O,N-diacetate crystallized as feathery needles: m.p. 122–123°; ν_{max} 1730 and 1253 (OAc), 1618 (NAc), and 893 $cm.^{-1}$ (>C=CH_2). In large-scale preparations of XXXV it was convenient to subject veatchine azomethine acetate (XXXII)



XXXIV, R = R′ = H
XXXV, R = Ac; R′ = H



XXXVI, R = R′ = H
XXXVII, R = R′ = CH_3
XXXVIII, R = H; R′ = CH_3
XXXIX, R = Ag; R′ = CH_3

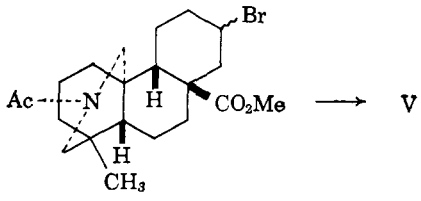
successively to reduction, acetylation, and saponification without the isolation of the intermediate products.

Oxidation of XXXV with permanganate–periodate[23] under conditions developed for the oxidation of the corresponding atisine derivative proceeded smoothly to give dicarboxylic acid XXXVI,[19] m.p. 254–256°, $[\alpha]D$ +20° (EtOH), in a yield of 36.5%. The compound could also be prepared, though in poorer yield, by oxidation of XXXV with powdered potassium permanganate in acetone. Compound XXXVI was converted to the dimethyl ester XXXVII with diazomethane and thence by mild saponification to the monoester acid XXXVIII.[19] The latter was converted to the silver salt (XXXIX), taking precautions to exclude light, and the silver salt was subjected to the Hunsdiecker[24] reaction. As experienced in the atisine series, the Hunsdiecker reaction gave a poor yield of an amorphous bromo derivative (XL). Reductive debromination with zinc and acetic acid[26] containing a small amount of hydrochloric acid gave a bisnor ester (V) of m.p. 153.5–155.5°, $[\alpha]^{27}D$ −17°. The infrared spectra in chloroform and Nujol were identical with those of the corresponding product prepared by the two degradative routes from atisine (*vide supra*).

This correlation[19] of atisine and veatchine provides the first unequivocal evidence for the common stereochemistry of the atisine and garrya alkaloids. Since several interconversions among various alkaloids in the above groups have been effected, the following alkaloids are now known to have the same stereochemistry of their carbon skeletons: atisine, veatchine, garryfoline,[9] atidine,[37–39] ajaconine,[16,39] and cuauchichicine.[9]

By-Products of Permanganate–Periodate Oxidation. During the course of correlating atisine and veatchine

(33) L. F. Fieser, *J. Am. Chem. Soc.*, 76, 1945 (1954).
(34) K. Wiesner, S. K. Figdor, M. F. Bartlett, and D. R. Henderson, *Can. J. Chem.*, 30, 608 (1952).
(35) In the Experimental section is described a simplified procedure for the isolation of veatchine from *Garrya veatchii* bark. The method involves basification of the crude acidified extracts and filtration through Celite. Almost all of the alkaloid fraction is retained by the Celite, from which it can be obtained by extraction with chloroform. The procedure gives a high yield of veatchine without recourse to countercurrent distribution[34] and obviates a tedious extraction of an emulsion-prone system.
(36) *Cf.* M. F. Bartlett, W. I. Taylor, and K. Wiesner, *Chem. Ind.* (London), 173 (1953); K. Wiesner, *et al.*, *Ber.*, **86**, 800 (1953).
(37) S. W. Pelletier, *Chem. Ind.* (London), 1016 (1956).
(38) S. W. Pelletier, *ibid.*, 1670 (1957).
(39) D. Dvornik and O. E. Edwards, *Proc. Chem. Soc.*, 280 (1958).

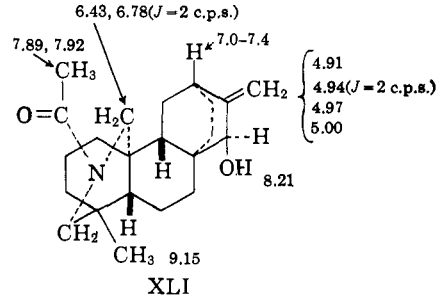


XL

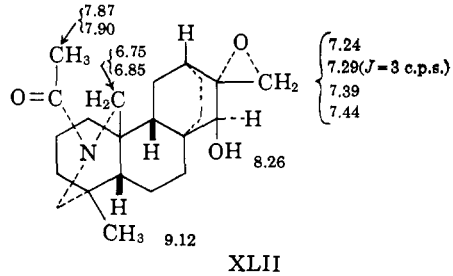
two interesting by-products were encountered which will now be described. Oxidation of the N-acetate VI with periodate–permanganate led to two other products, one neutral and one acidic.

The neutral product was produced in small yield and after repeated crystallization and chromatography it melted at 272–282°. Analysis indicated a molecular formula of $C_{22}H_{33}NO_3$. The infrared spectrum contained bands for a hydroxyl (3632 cm.$^{-1}$) and an N-acetate group (1629 cm.$^{-1}$). Since no bands attributable to an exocyclic methylene group are apparent in the spectrum and the analysis requires addition of one oxygen atom to the N-acetate VI, it seems reasonable to assign an epoxide structure (XLII) to this product. In agreement with this assignment is the fact that high-resolution infrared spectra[40] of the N-acetate VI and O,N-diacetate XLIII[20] show typical bands for the exocyclic methylene at 3070 and 3080 cm.$^{-1}$, respectively. In the epoxide this peak disappears and is replaced by a small but real peak, at 3045 cm.$^{-1}$, which accords well with the C–H stretching frequency of two hydrogens in a methylene group of an epoxide. Though absorption in this region is not unique for epoxide hydrogens, in the context of the present problem it is strong support for the epoxide structure.

The n.m.r. spectra of the N-acetate XLI and compound XLII further confirm the assignment of an epoxide structure to the neutral by-product. The exocyclic methylene in XLI is clearly indicated by the AB quartet with peaks at τ 4.91, 4.94, 4.97, and 5.00 (J = 2 c.p.s.). The protons have slightly different chemical shifts because of their different geometry and the values



XLI



XLII

are about 0.4 p.p.m. lower than for isolated methylene protons due to the adjacent hydroxyl. In the neutral by-product XLII olefinic hydrogen peaks are absent. Instead, a quartet centered about τ 7.35 occurs in the spectrum of this compound. The position is that expected for the methylene of an epoxide. Since Jackman[41] quotes τ 7.71 for the methylene of propylene oxide, the downward shift of about 0.4 p.p.m. in XLII is reasonable due to the effect of the adjacent hydroxyl. The AB-type quartet at τ 7.35 with peaks at 7.24, 7.29, 7.39, and 7.44 (J = 3 c.p.s.) fits the epoxide methylene group, since the hydrogens are in a slightly different environment and will split each other. It is pertinent to note that the diffuse signal in the τ 7.0–7.4 region of XLI attributed to the C-12 proton will have gone well upfield into the band envelope when the olefin is converted to an epoxide. Thus the quartet centering about τ 7.35 in the product is definitely new and in the context of the problem can only fit an epoxide methylene. For any other sized ring the bands should be below τ 6.5. The band at τ 8.21 in XLI and at τ 8.26 in XLII is assigned to the hydroxyl hydrogen since it disappears after shaking a $CDCl_3$ solution of the compounds with a drop of D_2O for 1 min.

A consideration of the infrared frequencies of the hydroxyl groups in compounds XLI and XLII is informative.[40] The O–H stretching frequency in the epoxide is at 3632 cm.$^{-1}$—normal for a secondary hydroxyl which is not hydrogen bonded. In compound XLI the hydroxyl absorption is at 3615 cm.$^{-1}$, the lower frequency probably indicating H-bonding to the π-orbital of the exocyclic double bond. Lack of hydrogen bonding in XLII is significant stereochemically, because if the epoxide oxygen and alcohol groups had a *cis* relative configuration on ring D, one would predict from models that weak hydrogen bonding should occur between the alcohol hydrogen and a pair of electrons on the epoxide oxygen. Therefore, the groups have a *trans* configuration which is not particularly surprising since attack of the epoxidizing agent might be expected on the side of ring D remote from the adjacent hydroxyl.

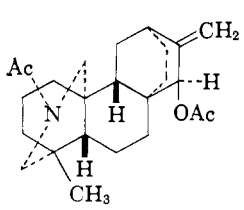
Several attempts were made to synthesize XLII from XLI or the corresponding O,N-diacetate XLIII. Treatment of XLII with peracetic acid in chloroform in the presence of sodium acetate led to recovered starting material. Treatment with peroxytrifluoroacetic acid gave resins which did not crystallize. In subsequent work the O,N-diacetate XLIII was treated with peroxytrifluoroacetic acid according to the Emmons procedure.[42] Work-up under mild conditions gave a mixture from which the dihydroxyacetate (XLIV) could be isolated by repeated crystallization or chromatography. The other component of the mixture was not identified but may be a mixture of XLIV and some epoxide. Saponification of XLIV gave a crystalline triol (XLV).

The acidic by-product referred to earlier was isolated as the methyl ester from the mother liquors remaining after separation of the crystalline N-acetyl dicarboxylic acid VII. The methyl ester, m.p. 236–240°, had an analysis agreeing with the formula $C_{22}H_{33}NO_4$, and an infrared spectrum suggestive of

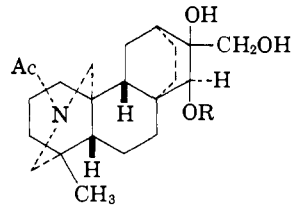
(40) These infrared spectra were taken on a Beckman IR-7 spectrometer and the n.m.r. spectra on Varian DP-60 and A-60 spectrometers.

(41) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press Inc., New York, N. Y., 1959.

(42) W. D. Emmons and A. S. Pagono, *J. Am. Chem. Soc.*, 77, 89 (1955).

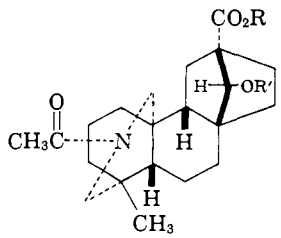


XLIII

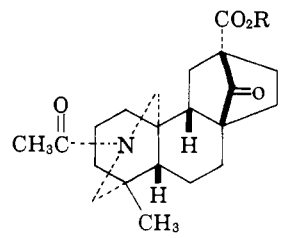


XLIV, R = Ac
XLV, R = H

the presence of hydroxyl (3378 cm.$^{-1}$), N-acetyl (1621 s. cm.$^{-1}$), and —CO_2Me groups (1730 cm.$^{-1}$). The n.m.r. spectrum was also in agreement with the presence of an $NCOCH_3$ group (τ 7.90, 3H, singlet) and a $COOCH_3$ group (τ 6.27, 3H, singlet) in the molecule. Saponification of the ester with methanolic sodium hydroxide furnished an amorphous carboxylic acid, $C_{21}H_{31}NO_4$, ν_{max} 3448 (OH), 2857–2703, 1712 (—CO_2H), and 1603 cm.$^{-1}$ ($NCOCH_3$), which regenerated the methyl ester when treated with diazomethane. The presence of the hydroxyl group was confirmed by formation of an acetate, m.p. 181–183.5°, and oxidation with Jones reagent to a keto ester, m.p. 186–189.5°, $\nu_{max}^{CCl_4}$ 1783 cm.$^{-1}$ (>C=O). These data lead to structure XLVI for the ester and XLVII for the parent acid. The carbonyl absorption of the keto ester XLIX at 1783 cm.$^{-1}$ is consistent with the value reported for a bicyclo[2.2.1]heptanone with a keto group in the small

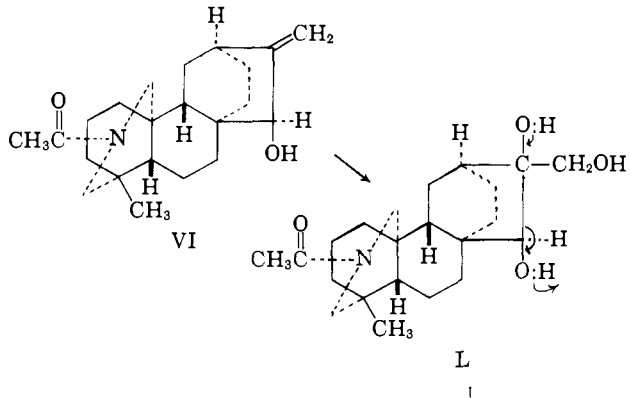


XLVI, R = CH_3; R′ = H
XLVII, R = R′ = H
XLVIII, R = CH_3; R′ = Ac



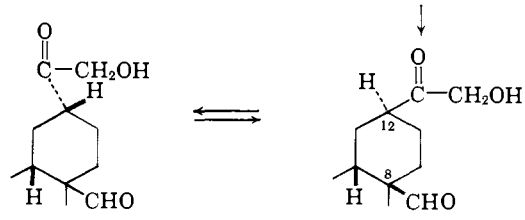
XLIX, R = CH_3

bridge.[43] Moreover, the proton on the carbon bearing the acetoxyl in XLVIII appears at τ 5.00 and



VI

L

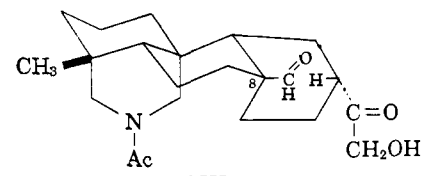


LII

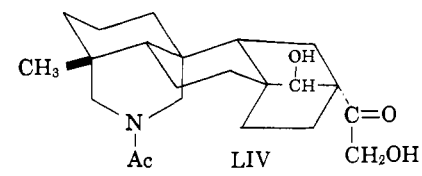
LI

(43) C. H. DePuy and B. W. Ponder, *J. Am. Chem. Soc.*, 81, 4629 (1959).

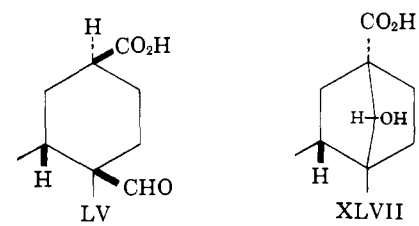
is unsplit. The formation of acid XLVII by oxidation of VI is interesting. A plausible reaction sequence leading to XLVII is given below (VI, L, LI, LII ≡ LIII, LIV, XLVII). Epimerization at C-12 can occur through the enol form of LI. This must precede cyclization by aldolization, which can take place only with ring C in the boat form (LIII → LIV); this conformation (LIII) is favored by the absence of the 1,4-flagpole and the 1,3-diaxial interactions of the 8-formyl group with the 11β- and 13β-hydrogens present in the chair form. Oxidation to the carboxyl XLVII must occur after epimerization at C-12, and possibly after cyclization, since epimerization of a C-12 COOH as in LV is contraindicated under the mild experimental conditions. It is pertinent to note that the analogous carboxylic ester XI shows no tendency to epimerize even in boiling 0.25 *N* methanolic sodium hydroxide.



LIII



LIV



LV

XLVII

Experimental

General Experimental Procedures. Melting points are corrected and were taken on a hot stage equipped with a microscope and polarizer. Finely powdered samples were placed on the stage 15° below the melting point and the temperature was raised at a rate of about 4°/min. Rotations were taken in chloroform unless otherwise noted. Ultraviolet spectra were determined in 95% ethanol on a Beckman Model DU spectrophotometer and infrared spectra on Perkin-Elmer Model 21 and Infracord-137 spectrophotometers. Certain high-resolution spectra were taken on a Beckman IR-7 spectrometer.[40] N.m.r. spectra were taken on Varian DP-60[40] and A-60 spectrometers in deuteriochloroform with tetramethylsilane as an internal standard. Petroleum ether refers to a light petroleum fraction of b.p. 30–70°. Ligroin refers to a light petroleum fraction of b.p. 60–70°. The removal of solvents *in vacuo* was accomplished with a Craig-type rotating flash evaporator at 15–20 mm. and with the water bath usually at 35–50°.

Reduction of Atisine Imine Acetate (VIII)[22] *to Secondary Amine O-Acetate (IX).* A solution of 280 mg. of VIII in 25 ml. of methanol was treated at 30° with

390 mg. of sodium borohydride and allowed to stand at room temperature for 5 hr. and overnight in the refrigerator. Evaporation *in vacuo* gave a gum which was partitioned between water and chloroform. Evaporation of the chloroform phase gave a residue which crystallized from ether as prisms, 131 mg., m.p. 165–168°. Recrystallization gave heavy rods; 78 mg.; m.p. 168–169°; $[\alpha]^{27}D$ −79° (*c* 1.3); ν_{max}^{Nujol} 1733 (OAc) and 1647 cm.$^{-1}$. NH absorption was not evident in the 3-μ region though conversion to the O,N-diacetate (*vide infra*) demonstrated the presence of the -NH group.

Anal. Calcd. for $C_{22}H_{33}NO_2$: C, 76.92; H, 9.68; Ac, 12.53. Found: C, 77.27, 77.09; H, 9.80, 9.74; Ac, 12.25.

For a large-scale preparation the following directions are typical. A solution of 11.65 g. of VIII in 250 ml. of methanol was treated with 8.0 g. of sodium borohydride with cooling and allowed to stand overnight. The mixture was evaporated to dryness *in vacuo*, taken up in water, and extracted several times with chloroform. Evaporation of the chloroform gave a semicrystalline mass (11.25 g.) which was used directly for the preparation of compound VI.

Saponification of Atisine Imine Acetate (VIII) from Atisine to Imine (XVI). A solution of 12.1 g. of the azomethine acetate in 150 ml. of methanol and 20 ml. of water was treated with 10 g. of potassium hydroxide and boiled under reflux for 15 min. After removal of the methanol under reduced pressure, the mixture was diluted with water and extracted with chloroform. The residue crystallized from acetone to give 10.5 g. of the azomethine alcohol XVI, m.p. 176.5–178.5°. Recrystallization from acetone afforded the pure compound as flat, pointed blades which sublimed under the microscope to scimitar-shaped blades, m.p. 178.5–180°, $[\alpha]^{31}D$ −22° (*c* 1.13, $CHCl_3$). The infrared spectrum was identical with that of the same compound obtained as a by-product of the permanganate oxidation of atisine[20]: ν_{max}^{Nujol} 892 (>C=CH_2), 1653 (>C=N—), and 3448 cm.$^{-1}$ (OH).

Anal. Calcd. for $C_{20}H_{29}NO$: C, 80.22; H, 9.76. Found: C, 80.23; H, 9.73.

Conversion of Secondary Amine O-Acetate (IX) to O,N-Diacetate (XLIII). A solution of 37 mg. of the amine in 1.0 ml. of acetic anhydride and 1.0 ml. of dry pyridine was allowed to stand overnight. The mixture was diluted with methanol and evaporated *in vacuo* several times to remove acetic acid. The residue in benzene was washed successively with dilute sulfuric acid, dilute sodium carbonate, and water. Evaporation *in vacuo* gave a residue which crystallized from ether to give flat blades. Recrystallization afforded 27 mg. of the known O,N-diacetate,[20] m.p. 166.5–169.0° cor., undepressed with an authentic sample. The infrared spectrum of the product in Nujol was identical with that of an authentic sample.

N-Acetyl-des-(β-hydroxyethyl)dihydroatisine (VI).[20] A solution of 11.25 g. of crude IX in 50 ml. of dry pyridine and 50 ml. of acetic anhydride was allowed to stand for 72 hr. The mixture was evaporated to dryness *in vacuo* and let stand for 0.5 hr. in methanol to decompose remaining traces of acetic anhydride. The residue remaining after evaporation of the methanol was dissolved in benzene and extracted with dilute sulfuric acid to remove pyridine and any unacetylated alkaloid. Evaporation of the benzene phase gave 12.8 g. of the O,N-diacetate (XLIII)[20] which was saponified without further purification. A solution of 12.8 g. of the crude O,N-diacetate in 100 ml. of methanol was treated with 10 ml. of 50% sodium hydroxide and 10 ml. of water and boiled under reflux for 45 min. The solvent was removed *in vacuo*, and the residue taken up in dilute sulfuric acid and extracted with chloroform. Evaporation of the chloroform phase gave 10.64 g. of crude N-acetate VI. Crystallization from acetone afforded 9.01 g. of m.p. 219–222°, which was pure enough for the preparation of VII. On careful processing, the mother liquors afforded an additional 1.02 g., m.p. 219–221°. An analytical sample melted at 229–230.5° (lit.[20] 222–225°).

Anal. Calcd. for $C_{22}H_{33}NO_2$: C, 76.92; H, 9.68. Found: C, 76.99, 76.97; H, 9.69, 9.67.

Oxidation of VI to N-Acetyl Dicarboxylic Acid (VII). A solution of 3.4 g. of VI in 300 ml. of pyridine and 600 ml. of water at 32° was treated with 400 ml. of 0.2 *M* sodium metaperiodate (stock solution, 10.74 g./250 ml. water) and 200 ml. of 0.01 *M* potassium permanganate[23] (stock solution, 0.790 g./500 ml. of water). When the solution had turned orange after a few minutes a charge of 200 ml. of periodate solution and 100 ml. of permanganate was added. After each color change more periodate–permanganate was added until a total of 900 ml. of periodate and 450 ml. of permanganate had been added. No further uptake of reagent was noted. The total aqueous mixture was extracted 12 times with 200-ml. portions of chloroform. The solvent was removed *in vacuo* and the residue was flashed several times to remove pyridine. The residue (3.55 g.) in chloroform was extracted with 10% sulfuric acid to remove any bases and then with 5% sodium carbonate solution. Evaporation of the chloroform phase gave 298 mg. of neutral product (N) which was reserved. The carbonate extract was chilled with ice, acidified to congo red with dilute sulfuric acid, and extracted with chloroform. The chloroform extract yielded 2.96 g. of resin. After standing overnight in acetone, the material crystallized as heavy rosettes, 1.49 g., m.p. 281–287° (40% yield). Recrystallization from 500 ml. of boiling acetone afforded 1.10 g.: m.p. 285.5–289°; $[\alpha]^{29}D$ +11.3° (*c* 1.08); ν_{max}^{Nujol} 1727, 1692 (CO_2H), and 1610 cm.$^{-1}$ (NAc).

Anal. Calcd. for $C_{21}H_{31}NO_5$: C, 66.82; H, 8.28. Found: C, 66.86; H, 8.23.

Recrystallization of material from the mother liquors afforded 362 mg. of m.p. 283.5–288°.

N-Acetyl Dicarboxylic Ester (X). A solution of 1.0 g. of the dicarboxylic acid (VII) in acetone was treated with an excess of diazomethane. Evaporation of the solvent gave a residue which crystallized from acetone to give 852 mg. of prisms; m.p. 196–198.5°; $[\alpha]^{29}D$ +13°; ν_{max}^{Nujol} 1724 (—CO_2CH_3) and 1639 cm.$^{-1}$ (NAc). An analytical sample showed m.p. 196–200°.

Anal. Calcd. for $C_{23}H_{35}NO_5$: C, 68.14; H, 8.70. Found: C, 68.17; H, 8.86.

N-Acetyl Monoester Acid (XI). A solution of 1.149 g. of dicarboxylic ester (X) in 50 ml. of methanol was treated with 1.0 ml. of 50% sodium hydroxide and boiled under reflux for 15 min. Evaporation of the solvent gave a residue which was dissolved in water;

made acidic to congo red, and extracted with chloroform. Evaporation of the solvent *in vacuo* gave a white resin which crystallized slowly as fine needles, 1.015 g., m.p. 248–251.5°. Recrystallization from acetone gave material of the same melting point: $[\alpha]^{29}D$ +15°, ν_{max}^{Nujol} 1712 (—CO_2H, —CO_2CH_3) and 1603 cm.$^{-1}$ (NAc).

Anal. Calcd. for $C_{22}H_{33}NO_5$: C, 67.49; H, 8.50. Found: C, 67.42, 67.79; H, 8.41, 8.89.

N-Acetyl Monoester Acid Silver Salt (XII). The N-acetyl monoester acid XI (255 mg.) was exactly neutralized with 6.70 ml. of 0.098 *N* sodium hydroxide solution, filtered, and evaporated to dryness *in vacuo*. The residue in 4.0 ml. of distilled water was cooled to 0° and treated (protected from light) with 1 equiv. (111 mg.) of silver nitrate in 2.0 ml. of water. The curdy white precipitate was collected and washed once with a small amount of ice–water. Drying *in vacuo* in the dark at 60° gave 300 mg. of the silver salt. This material was used immediately in the Hunsdiecker reaction.

N-Acetyl Bromo Ester (XIII). A finely pulverized mixture of 300 mg. of XII and 100 mg. of silver acetate was dried for 1 hr. at 60° at 0.01 mm. and added to 5.0 ml. of carbon tetrachloride which had been previously dried over P_2O_5. A 1.0-ml. portion of carbon tetrachloride was distilled over to ensure dryness. The mixture was cooled to room temperature and, while protected from light, 1.60 ml. of stock bromine solution in carbon tetrachloride (62 mg./ml.) was added. After refluxing a few minutes the bromine color was discharged. Another 1.0 ml. of bromine solution was added and refluxing was continued for 1 hr. Excess bromine was distilled over and the mixture allowed to stand overnight. The mixture was filtered through sintered glass and the silver bromide washed well with chloroform. The filtrate was extracted with sodium bicarbonate solution to remove any XI present. Acidification of the bicarbonate solution and extraction with chloroform gave 100 mg. of recovered XI. Evaporation of the organic phase remaining from the bicarbonate extract gave 166 mg. of yellow foam which still showed the presence of strong —OH and —CO_2H bands in the infrared. The material was dissolved in benzene and extracted two times with dilute sodium bicarbonate. Evaporation of the benzene phase gave 153 mg. of resin which showed the absence of —OH or —CO_2H bands in the infrared. The material was chromatographed in benzene over 4.0 g. of silicic acid (100 mesh). The first 350 ml. of benzene eluted 2.9 mg. which was discarded. Chloroform (250 ml.) eluted 118 mg. of resin which gave an approximate analysis for the required bromo derivative. Rechromatography over 3.0 g. of silicic acid gave 85 mg. of the amorphous bromo derivative XIII, ν_{max}^{film} 1730 (—CO_2CH_3) and 1647 cm.$^{-1}$ (NAc).

Anal. Calcd. for $C_{21}H_{32}NO_3Br$: C, 59.15; H, 7.57; Br, 18.74. Found: C, 59.11, 58.38; H, 7.32, 7.62; Br, 18.83, 20.74.

Reductive Debromination[26] of XIII to N-Acetyl Bisnor Acid Methyl Ester (V). Preparations of the crude bromo derivative (XIII) from several runs were combined to give 317 mg. A solution of this material in 10 ml. of acetic acid was treated with 1.5 g. of granulated zinc (30 mesh) and 5 drops of concentrated HCl. After each 10 min. of refluxing, 5 drops of concentrated HCl was added until a total of 0.5 ml. of HCl had been added. The mixture was filtered, evaporated to dryness *in vacuo*, and taken up in water. Extraction with chloroform gave 233 mg. of resin which showed some tendency to crystallize from acetone. Preliminary purification by chromatography over silicic acid (100 mesh) and crystallization from acetone gave 65 mg., m.p. 152–155°, $[\alpha]^{27}D$ −35° (*c* 0.63). Similar material prepared by the degradation of veatchine (*vide infra*) showed m.p. 154–156° and an identical infrared spectrum. However, since rotations on the two samples were different further purification was effected. The 65-mg. sample was chromatographed in chloroform over 2.0 g. of silicic acid. Material eluted from fractions 3 and 4 totaled 55.6 mg. and was rechromatographed in benzene over 1.56 g. of Woelm neutral alumina. The first three fractions gave 48 mg. with $[\alpha]^{26}D$ −31.2° (*c* 2.19). This material was rechromatographed over 2.0 g. of Woelm neutral alumina as shown in Table I. Material from fractions 2–9 (26.2 mg.) was combined and crystallized from hexane to give 20 mg., m.p. 153.5–157°. Recrystallization gave 16 mg. of V, m.p. 156–157°, $[\alpha]^{27}D$ −18.9° (*c* 0.61). The infrared spectra in Nujol and chloroform were identical with those of the corresponding degradation product prepared from veatchine.

Table I

Solvent	Tube	Ml.	Mg.	$[\alpha]D$, deg.
Benzene–hexane (1:1)	1	10	5.1	+ 1.5
Benzene–hexane (1:1)	2–6	170	11.9	−15.7
Benzene–hexane (1:1)	7–9	220	14.3	−17.6
Benzene–hexane (1:1)	10–13	400	12.0	−32.9
Benzene	14–18	765	8.0	−68.0

Anal. Calcd. for $C_{21}H_{33}NO_3$: C, 72.58; H, 9.57. Found: C, 72.87; H, 9.58.

Attempted Hydration of Atisine Azomethine (XVI) with Sulfuric Acid. A 50-mg. sample of the azomethine (XVI) from atisine was dissolved in 5 ml. of 60% sulfuric acid, warmed on the steam bath to dissolve, and allowed to stand at room temperature overnight. The reddish orange solution, when poured over crushed ice, became straw colored. Extraction with chloroform gave 3.1 mg. of material. Basification of the acidic solution and extraction produced 44.3 mg. of crude resin which showed a strong carbonyl band in the infrared (1721 cm.$^{-1}$, CS_2).

Attempted Hydration of Atisine Azomethine Acetate (VIII) with Sulfuric Acid. A 50-mg. sample of azomethine acetate (VIII) was treated with 35% sulfuric acid and allowed to stand overnight. After basification with 10% NaOH, several milliliters of ethanol were added to the solution as well as 0.5 g. of NaOH. The resulting solution was heated for 2 hr. on the steam bath (to saponify). Extraction with chloroform gave 40 mg. of crude product. Chromatography of the crude material over alumina furnished 35.5 mg. of material showing a strong carbonyl band in the infrared (1721 cm.$^{-1}$, CS_2).

Other experiments carried out in acetic acid–sulfuric acid mixtures produced either recovered starting material or ketonic products.

Hydration[27] *of Atisine Azomethine to Azomethinediol (XVII).* A 3.52-g. sample of atisine azomethine (XVI)[20,27] was dissolved in 60 ml. of 10% hydrochloric acid (by weight) and allowed to stand at 25° for 22 hr. The solution was then basified with sodium hydroxide, extracted repeatedly with chloroform, and the combined chloroform extracts were evaporated to dryness *in vacuo*. The resulting crude product (3.90 g.) was taken up in benzene and again evaporated to dryness *in vacuo*. Trituration with benzene and filtration of the resulting crystalline material plus washing with hot benzene gave 638 mg. of azomethinediol XVII, m.p. 262–264° (lit.[27] 264–264.5°).

The mother liquors were taken up in 40 ml. of 10% hydrochloric acid (by weight) and the temperature was maintained at 32° for 22 hr. Work-up as before furnished 1.28 g. (m.p. 255–262°) for a total of 1.91 g. or 51% yield.

N.B.: Comparable experiments at which the temperature was not raised to 32° did not show increased yield at this step; it was therefore concluded that the hydration proceeds better at the elevated temperature.

Iminodiol O,N-Diacetate (XIX). A 4.96-g. sample of diol XVII from the hydration of atisine azomethine was taken up in 200 ml. of 80% methanol and treated with 5 g. of sodium borohydride. After standing for 4 hr. the solution was concentrated *in vacuo* and taken up in chloroform and water. The aqueous phase was separated and extracted repeatedly with chloroform. Evaporation of the combined chloroform extracts *in vacuo* gave 5.12 g. of crude iminodiol XVIII.

Acetylation of the crude material XVIII was accomplished with 100 ml. of acetic anhydride in 100 ml. of dry pyridine. After standing overnight the solution was concentrated *in vacuo* and flashed repeatedly with mixtures of benzene and ethanol. Ultimately the residue was treated with acetone, and crystallization ensued giving 4.41 g. of diacetate XIX, m.p. 208–215°.

The mother liquor was evaporated several times with acetone, yielding two further crops of diacetate, 422 mg., m.p. 205–210°, and 161 mg., m.p. 205–213°, respectively.

The 1.04 g. of residue was chromatographed over 20 g. of alumina. Elution with benzene gave a noncrystalline fraction, while elution with chloroform–benzene mixtures gave crystalline fractions from which were obtained 218 mg. of crystalline material, m.p. 187–205°.

Combination of all crystalline material and recrystallization from acetone (containing a small amount of benzene to promote solubility) gave 4.0 g., m.p. 217–219° (lit.[27] 214°), 706 mg., m.p. 214–217°, and 243 mg., 211–215°, or a total yield of recrystallized diacetate of 4.95 g. (84%).

N-Acetyldiol (XX). A sample of 4.94 g. of recrystallized iminodiol O,N-diacetate XIX was taken up in 100 ml. of methanol containing 4 g. of NaOH. The resulting solution was refluxed for 1 hr. on the steam bath, concentrated *in vacuo*, diluted with water, and extracted repeatedly with chloroform. The chloroform extracts were washed with dilute hydrochloric acid and then with water and evaporated to dryness *in vacuo* to give 4.75 g. of crude N-acetyldiol XX which was used directly in the next step.

15:16-Secomethylketo Acid (XXI). A. Via the N-Acetyldiol (XX). A 4.69-g. sample of crude N-acetyldiol XX from the above reaction was taken up in 50 ml. of glacial acetic acid and cooled in an ice bath. To the cooled solution was added 50 ml. of Kiliani reagent.[31] The solution was allowed to come slowly to room temperature and to stand for 1 hr. It was then cooled in an ice bath, a small amount of methanol was added, and the solution was allowed to stand until it had turned green. After dilution with water the solution was extracted with chloroform. The chloroform extracts were evaporated to dryness *in vacuo* yielding 4.38 g. of crude product which on crystallization from benzene gave 2.65 g., m.p. 215–220°, and a second crop of 0.395 g., m.p. 213–219°. These factions were combined and recrystallized from methanol giving 2.90 g. in two crops, m.p. 223–226° (lit.[27] 218°).

Chromatography of the mother liquors over 30 g. of silicic acid gave on elution with chloroform containing a small amount of methanol various crystalline fractions. These, after crystallization from benzene and recrystallization from methanol, afforded 0.210 g., m.p. 215–220°. The total crystalline material obtained from the two steps amounted to 3.11 g. (63% yield).

B. By Hydration of N-Acetate (VI) from Atisine. A 400-mg. sample of N-acetate VI prepared from atisine was dissolved in 10 ml. of 10% hydrochloric acid (by weight) and 10 ml. of absolute ethanol with warming on the steam bath. When solution was complete, the reaction mixture was allowed to stand at room temperature overnight. It was then basified and extracted with chloroform. The chloroform extracts on evaporation to dryness furnished 432 mg. of crude material which was chromatographed over 10 g. of silicic acid. Elution with chloroform gave 250 mg. of crystalline material: m.p. *ca.* 150–200°; ν_{max} ($CHCl_3$) 1706 (ketone) and 1623 cm.$^{-1}$ (NAc). (This material apparently represents a mixture of epimeric ketones arising by rearrangement of the allyl alcohol.) Elution with 5% methanol in chloroform gave 135 mg. of resinous material showing strong hydroxyl absorption in the infrared.

Oxidation of the above crude diol in 2 ml. of glacial acetic acid was accomplished by means of 2 ml. of Kiliani reagent.[31] After standing at room temperature for 15 min. the reaction mixture was chilled in an ice bath, and 1 ml. of methanol was added. The solution was allowed to stand until green, diluted with water, and extracted with chloroform. The combined chloroform extracts were evaporated to dryness *in vacuo* and the residue was chromatographed over 5 g. of silicic acid. Elution with 1% methanol in chloroform gave 93.4 mg. of crude product which was taken up in benzene, a small amount of insoluble material being discarded. The benzene solution was evaporated to dryness *in vacuo* and crystallization of the resin from ether furnished 40 mg. (9% over-all yield) of crystals, m.p. 215–217° (mixture melting point with authentic 15:16-secomethylketo acid prepared by route A, 215–217°; infrared spectrum identical with material prepared by route A).

Baeyer–Villiger Oxidation[32] *of 15:16-Secomethylketo Acid (XXI) to Acetoxy Acid (XXII).*[27] Three 0.55-g. batches of keto acid XXI totaling 1.67 g. were separately dissolved (yield from *ca.* 0.5-g. batches appeared to be optimum) by warming in 6 ml. of methylene chloride. To each of these solutions was added 1.04 g. of Na_2HPO_4, followed by cooling in the cold room. After cooling, to each was added with swirling a solution prepared in the cold from 1 ml. of methylene chloride, 0.42 ml. of trifluoroacetic anhydride, and 0.067 ml. of 90% hydrogen peroxide. After standing for a short time in the cold room with occasional swirling, the solution was allowed to come to room temperature and then refluxed for 1 hr. The cooled solutions were then combined, treated with chloroform and water, and the organic layer was separated. The aqueous layer was repeatedly extracted with chloroform and all organic layers were combined and evaporated to dryness *in vacuo* to give 1.78 g. of crude product. Crystallization of the crude material from methanol furnished 1.02 g., m.p. 306–308° (lit.[27] 309°).

The mother liquor was combined with that from a similar run and chromatographed over 25 g. of silicic acid. Elution with 1% methanol in chloroform gave a first crystalline fraction followed by a large amount of resin. From the former was obtained by crystallization from benzene 218 mg. of crystals, m.p. 302–304°.

All the noncrystalline material from the column was reoxidized in 6 ml. of methylene chloride, using an oxidizing solution prepared from 0.63 ml. of trifluoroacetic anhydride and 0.1 ml. of hydrogen peroxide in 1.5 ml. of methylene chloride.

Work-up as before gave 820 mg. of crude product which on crystallization from methanol furnished two crops of 484 mg., m.p. 306–310°, and 23 mg., m.p. 297–305°, respectively.

Bisnor Acetoxy Acid Methyl Ester (XXIII). A 200-mg. sample of product from the Baeyer–Villiger reaction was dissolved in a minimum of hot absolute ethanol and then cooled to room temperature. To this solution was added diazomethane in ether until a yellow color persisted. After standing at room temperature for *ca.* 1 hr., the solution was evaporated on the steam bath and the residue was crystallized from petroleum ether to give 194 mg. (94%), m.p. 165–167°, $[\alpha]^{26}D$ −26° (*c* 1.53).

Anal. Calcd. for $C_{23}H_{35}NO_5$: C, 68.12; H, 8.70. Found: C, 68.07; H, 8.64.

Bisnor Hydroxy Acid (XXIV). A. By Saponification of Acetoxy Acid (XXII). A 2.40-g. sample of product XXII from the Baeyer–Villiger oxidation was taken up in 200 ml. of 1 *N* NaOH in methanol. After refluxing for 1 hr. the solution was concentrated *in vacuo* and diluted with water. (Extraction of this basic solution with $CHCl_3$ and evaporation to dryness *in vacuo* gave 124 mg. of crystals, m.p. 137–143°.)

The aqueous solution was then carefully acidified with dilute HCl *in the cold* and extracted with chloroform to give on evaporation to dryness *in vacuo* 1.83 g. of crude product. Crystallization from acetone gave 1.18 g., m.p. 201.5–203°, and a second crop of 0.21 g., m.p. 193–194°, for a total yield of 1.39 g. or 65%. Recrystallization from ethanol gave crops melting successively at 207–208° (XXIV, lit.[27] 196°; infrared, 1706 (CO_2H) and 1613 cm.$^{-1}$ (NAc)) and 200–202° and 193–194°; R.D. in methanol (*c* 0.057) $[\alpha]_{700}$ −60, $[\alpha]_{589}$ −10, and $[\alpha]_{305}$ −1100.

N.B.: Saponification of 282 mg. of XXIII during which the acidification step was not controlled gave a resinous product of 249 mg. showing a lactone band in the infrared. Crystallization of this material from ether gave 139 mg. of a lactone XXV, m.p. 164–166°; ν_{max}^{Nujol} 1742 (δ-lactone) and 1645 cm.$^{-1}$ (NAc).

The hydroxy acid XXIV was regenerated from the lactone by dissolving the crystalline lactone in 10 ml. of aqueous ethanolic NaOH, warming on the steam bath for 1 hr., and working up as above.

B. By Saponification of the Bisnor Acetoxy Acid Methyl Ester (XXIII). A 194-mg. sample of the methyl ester XXIII of the Baeyer–Villiger reaction product was dissolved in 10 ml. of methanol containing 400 mg. of NaOH. After refluxing for 1 hr. the solution was concentrated *in vacuo*, diluted with water, and extracted with chloroform. Evaporation of the extracts to dryness furnished 6.4 mg.

Acidification of the aqueous solution was followed by extraction with chloroform and evaporation to dryness. Crystallization of the crude product from acetone gave 129 mg., m.p. 208–209°, mixture melting point with sample from A 207–208°. A second crop of 17 mg., m.p. 206–208°, was obtained for a total yield of 146 mg., 85%.

Bisnor Hydroxy Acid Methyl Ester (XXVII). A 250-mg. sample of hydroxy acid XXIV was taken up in methanol and treated with diazomethane in ether until a yellow color persisted. Evaporation to dryness on the steam bath and addition of ether resulted in the separation of 243 mg. of crystals, 190–196° (93% yield), $[\alpha]^{26}D$ −3.5° (*c* 1.28).

Anal. Calcd. for $C_{21}H_{33}NO_4$: C, 69.39; H, 9.15. Found: C, 69.22; H, 9.08.

Attempted Dehydration of Hydroxy Acid XXIV. To a solution of 147 mg. of hydroxy acid XXIV in 10 ml. of pyridine cooled in an ice bath was added 2 ml. of phosphorus oxychloride. The solution was allowed to come slowly to room temperature over a period of 2 hr. and was then poured onto ice. The resultant mixture was extracted exhaustively with chloroform and the chloroform extracts were evaporated to dryness *in vacuo* to give a total of 87.7 mg. of crude material. Chromatography over 2.5 g. of silicic acid and elution with chloroform gave 68.8 mg. of resin.

The crude material from the above chromatogram was taken up in acetone and treated with diazomethane in ether until a slight excess was indicated by a yellow color. After standing for 2 hr. the solution was evaporated to dryness *in vacuo*.

The esterified material was taken up in 5 ml. of methanol (containing 6 drops of acetic acid) and hydrogenated in the presence of 30 mg. of platinum oxide catalyst prereduced in 3 ml. of methanol. After approximately 2 hr., 2.8 ml. of hydrogen (theoretical uptake 5.5 ml.) was taken up and no more appeared to be absorbed. The catalyst was removed by filtration and washed with methanol and the combined filtrate and washings were evaporated to dryness *in vacuo*. The crude residue was chromatographed over 2.5 g. of alumina. Elution with benzene gave several crystalline fractions, which after several recrystallizations from

petroleum ether showed m.p. 163–164°. The infrared spectrum was identical with that of the lactone XXV previously obtained by saponification of XXIII, followed by acidification. Rechromatography of the mother liquors from this crystalline material failed to give any other definite product.

Attempted Dehydration of Hydroxy Acid Methyl Ester XXVII. To a solution of 100 mg. of hydroxy ester XXVII in 5 ml. of pyridine cooled in an ice bath was added 1 ml. of phosphorus oxychloride. The solution was allowed to come slowly to room temperature and then heated for 1 hr. on the steam bath. The resulting solution was poured onto ice and extracted with chloroform. Evaporation of the chloroform to dryness *in vacuo* gave a crude resin which was taken up in hot ether, leaving a 20-mg. sample of insoluble material.

The soluble portion (92 mg.) was evaporated to dryness, taken up in methanol, and hydrogenated over 50 mg. of platinum oxide catalyst prereduced in methanol. Uptake of hydrogen amounted to 3 ml. before levelling off (theoretical uptake, 8.0 ml.) The catalyst was removed by filtration, washed with methanol, and the combined filtrates and washings were evaporated to dryness *in vacuo* and chromatographed over 3 g. of aluminum.

Elution with increasing amounts of benzene in ligroin gave several crystalline fractions which were combined into two portions and recrystallized separately from petroleum ether (28 mg., 6 mg.), both melting 170–173° but strongly depressed on admixture, and both giving strong Beilstein tests. The infrared spectra of the two fractions were similar but not identical and appeared to represent similar mixtures (1724 $cm.^{-1}$, ester; 1634 $cm.^{-1}$, lactone). Neither appeared to contain the desired bisnor acid methyl ester V. Analysis of the larger component confirmed the presence of chlorine, but in insufficient amount to represent 1 mole of chloro ester.

Anal. Calcd. for $C_{21}H_{32}ClNO_3$ (chloro ester): C, 66.03; H, 8.45; Cl, 9.28. $C_{20}H_{29}NO_3$ (lactone): C, 72.47; H, 8.82. $C_{21}H_{33}NO_3$ (bisnor acid, methyl ester): C, 72.58; H, 9.57. Found: C, 72.00; H, 9.10; Cl, 1.43.

Bisnor Keto Acid (XIV).[27] To a solution of 185 mg. of the hydroxy acid XXIV in 3 ml. of glacial acetic acid was added 58 mg. of sodium dichromate in 2 ml. of glacial acetic acid. After standing overnight (17 hr.) the deep green solution was diluted with water and extracted with chloroform. The chloroform layer was evaporated to dryness *in vacuo* giving 187 mg. of crude product.

Chromatography of the crude material over 4 g. of silicic acid with 1% methanol in chloroform gave several crystalline fractions which were combined and crystallized from acetone–ether to give 84 mg. (46% yield): m.p. 254–258° (lit.[27] 256°); ν_{max}^{Nujol} 1712 and 1592 $cm.^{-1}$ (lit.[27] 1712 and 1602 $cm.^{-1}$ in $CHCl_3$); R.D. in methanol (*c* 0.023): $[\alpha]_{700}$ +130, $[\alpha]_{589}$ +40, $[\alpha]_{305}$ −1560 (trough), and $[\alpha]_{295}$ −1050.

Anal. Calcd. for $C_{20}H_{29}NO_4$: C, 69.13; H, 8.41. Found: C, 69.10; H, 8.58.

Bisnor Keto Acid Methyl Ester (XXIX). To 98 mg. of hydroxy ester XXVII dissolved in 3 ml. of glacial acetic acid was added a solution of 22.8 mg. of chromic acid dissolved in a minimum of water and diluted to 3 ml. with glacial acetic acid. After standing for 4 hr. the green solution was diluted with water and extracted repeatedly with chloroform. The chloroform extracts were evaporated to dryness *in vacuo* to give 106 mg. of crude product which was chromatographed over 2.5 g. of alumina. Elution with chloroform furnished 92.8 mg. of resinous product (95% yield); R.D. in methanol (*c* 0.020): $[\alpha]_{700}$ −35, $[\alpha]_{589}$ −20, $[\alpha]_{305}$ −1000 (trough), and $[\alpha]_{290}$ +260.

Anal. Calcd. for $C_{21}H_{31}NO_4$: C, 69.77; H, 8.65. Found: C, 69.79; H, 8.54.

N-Acetyl Bisnor Acid Methyl Ester (V). A. By Reduction of Keto Acid XIV via the Thioketal, Followed by Esterification. To a suspension of 41.3 mg. of keto acid XIV in 0.5 ml. of ethanedithiol was added, with shaking, 0.1 ml. of boron trifluoride etherate.[33] After standing at room temperature for 3.5 hr. the solution was diluted with water and extracted repeatedly with chloroform. The chloroform solution was evaporated at room temperature under reduced pressure and the residue was chromatographed over 5 g. of silicic acid. Elution with benzene yielded strongly smelling materials, while 1% methanol in chloroform gave 51 mg. of resinous product.

The chromatographed thioketal (51 mg.) was treated with *ca.* 1.5 g. of Raney nickel catalyst in 2.5 ml. of ethanol on the steam bath for 19 hr. The catalyst was removed by filtration and washed with ethanol. The combined ethanol extracts were evaporated to dryness *in vacuo* to give 28.2 mg. Exhaustive extraction of the catalyst with hot ethanol gave an additional 10.6 mg.

The combined crude material was taken up in chloroform and extracted with sodium carbonate. Acidification of the aqueous layer and extraction with chloroform gave a crude product which on chromatography over 1 g. of silicic acid and elution with benzene gave 19.1 mg. of partly crystalline material (m.p. *ca.* 190–200°).

This fraction was crystallized from acetone in three successive crops by concentrating in a tiny test tube, cooling until crystallization ensued, and then removing the mother liquor with a micropipet. These combined crystalline fractions were chromatographed in benzene over 4 g. of silicic acid. The crystalline product (13.4 mg.) was recrystallized by the same technique as above to give two fractions, m.p. 217–219° and 210–225°. (N.B.: An analysis was obtained at this point on material from a separate run.)

Anal. Calcd. for $C_{20}H_{31}NO_3$: C, 72.03; H, 9.37. Found: C, 72.22; H, 9.42.

The higher melting fraction from this run was taken up in chloroform and extracted three times with sodium bicarbonate. The chloroform layer was evaporated to dryness *in vacuo* to give 5.1 mg.

The aqueous layer was acidified with dilute hydrochloric acid and extracted with chloroform giving 6.4 mg. This material was crystallized from acetone as before and the crystalline material in acetone was treated with diazomethane in ether. The solution was evaporated to dryness *in vacuo* and the crude material was chromatographed over 1 g. of alumina and eluted with 20% chloroform–benzene, giving 3.2 mg. which crystallized in the tube: m.p. *ca.* 120–140° (N.B. birefringent needles formed on cooling, m.p. 148°);

ν_{max}^{film} 1724 (CO_2CH_3) and 1639 cm.$^{-1}$ (NAc), not identical with the spectrum of material formed in B.

B. V. By Reduction of Keto Ester XXIX via Thioketal. To a solution of 63.9 mg. of keto ester XXIX in 1 ml. of ethanedithiol was added 0.1 ml. of boron trifluoride etherate. After standing at room temperature for 2.5 hr., the solution was evaporated on the water pump at room temperature and chromatographed over 2 g. of silicic acid.

Benzene readily eluted excess ethanedithiol and other odorous contaminants, and chloroform eluted 65.4 mg. of resinous thioketal.

The crude thioketal was dissolved in 2 ml. of ethanol and to this solution was added 2.5 ml. of Raney nickel catalyst in 10 ml. of ethanol. After being heated at reflux for 18 hr. the solution was filtered to remove catalyst. After the catalyst was washed extensively with acetone, the combined solution and washings were evaporated to dryness *in vacuo* giving 48 mg. of crude product. On chromatographing the crude product over 2 g. of alumina, it was found that crystalline material was eluted with benzene–petroleum ether mixtures. Combination of the first portion of these followed by crystallization from hexane gave 17 mg. of crystals (V, 25% yield): m.p. 154–156°; $[\alpha]^{30}D$ −20 (*c* 1.57); mixture melting point with material prepared by an alternate route from both atisine and veatchine, 154–156°; ν_{max}^{Nujol} 1721 (CO_2CH_3) and 1639 cm.$^{-1}$ (NAc). The infrared spectrum (Nujol) was identical with that of material from the alternative routes.

Anal. Calcd. for $C_{21}H_{33}NO_3$: C, 72.58; H, 9.57. Found: C, 72.36; H, 9.59.

Crystallization from hexane of the subsequent fractions from the chromatogram gave 6 mg., m.p. 141–143°.

Isolation of Veatchine from Garrya veatchii Bark. The bark was stripped from Bear Castle bush (quinine bush) (*Garrya veachii* Kellogg) collected in the Angeles Forest of the Mount Baldy district in Glendora, Calif. Semidry bark (43 lb.) on drying to constant weight at 80° gave 33.43 lb. (15.2 kg.). The dried bark was finely ground and worked up in about 3-kg. batches as described below.

Three kilograms of finely ground bark was percolated slowly with 34.6 l. of 80% ethanol. The eluent was collected in batches, concentrated *in vacuo* to a thick sirup, and each concentrate was worked up separately.

Batch A. (5 l. of Extract). The thick, dark sirup was diluted with 1 l. of water, acidified with 25% sulfuric acid (congo red), and filtered through a layer of Hy Flo Celite (Johns Manville). The celite bed was washed with 1% sulfuric acid and the filtrate and washings were combined and extracted ten times with chloroform to remove neutral and acidic components. The dark aqueous phase was chilled to 10° and treated with 700 ml. of 25% sodium hydroxide solution. The cold mixture was quickly filtered through a fresh bed of Hy Flo Celite. Practically all the alkaloids are retained by the Celite. It is important *not* to wash the Celite at this point or the alkaloids will pass into the aqueous filtrate. Extraction of the aqueous filtrate with chloroform yielded only 589 mg. of bases. If the Celite filtration is omitted and the base fraction isolated by extraction with chloroform, very troublesome emulsions form and the extract is of a dirty brown color. The product obtained by the Celite method is much cleaner and easier to process.

The Celite was pressed dry and dried *in vacuo*. Extraction with four portions of hot chloroform and concentration to dryness gave 19.76 g. of basic fraction.

The other batches were processed in an identical manner. A summary of the total base fraction obtained from each batch appears in Table II.

Table II

Batch	Vol. extract, l.	Dry wt. of base, g.
A	5.0	20.34
B	5.0	24.98
C	8.0	12.05
D	15.6	1.75
	33.6	59.12

The 59.12 g. of bases was dissolved in 500 ml. of warm benzene and the benzene solution was extracted several times with 5% sulfuric acid. The benzene solution containing a small amount of neutral material was reserved. The acidic phase was covered with a layer of benzene, cooled to 10° with ice, and basified to pH 6 with cold, dilute sodium hydroxide and to pH 8.3 with cold, dilute sodium carbonate. Extraction with ten portions of benzene gave a weak base fraction of 6.79 g. The aqueous phase was treated with ice and made strongly basic by addition of 100 ml. of cold 50% sodium hydroxide. The solution was extracted quickly with chloroform until no more alkaloid was obtained. The strong base fraction amounted to 47.37 g.. The latter on crystallization from acetone by the triangle scheme gave the following fractions of veatchine[34]: 35.0 g., m.p. 125.5–128.5°; 4.3 g., m.p. 122–125.5°; 1.45 g., m.p. 124–127°; 0.40 g., m.p. 124–126°; or a total of 41.1 g.; $[\alpha]^{30}D$ −67.5° (*c*, 1.35).

Anal. Calcd. for $C_{22}H_{33}NO_2$: C, 76.92; H, 9.68. Found (dried *in vacuo* at 60°): C, 76.86, 77.04; H, 9.65, 9.65.

Processing the other 12.2 kg. of bark by the procedure described above gave 137.6 g. of crude basic fraction. From this was obtained 7.92 g. of weak base fraction and 124.1 g. of strong base fraction. From the latter was obtained 104 g. of crystalline veatchine. Reprocessing the weak base fraction along with veatchine mother liquors gave an additional 2.67 g. of veatchine. The yield of basic fraction from some of the earlier batches was low due to inadvertent loss when the Celite was discarded without extraction.

Veatchinium Chloride (XXX).[21] A solution of 31.1 g. of veatchine in 500 ml. of acetone was cooled to 10° and treated gradually with a solution of 8.8 ml. of concentrated HCl in 200 ml. of cold acetone until acid to congo red. The chloride crystallized rapidly as fine needles: 33.6 g.; m.p. 273–276° (lit.[34] 267–271°); $[\alpha]^{27}D$ −65.5° (*c* 0.56) and $[\alpha]^{29}D$ −56.2°(*c* 1.45, EtOH); ν_{max}^{Nujol} 3290 (OH), 1678 (>C=$\overset{+}{N}$<), and 916 cm.$^{-1}$ (>C=CH_2).

Anal. Calcd. for $C_{22}H_{34}ClNO_2$: C, 69.55; H, 9.02. Found: C, 69.55, 69.67; H, 8.93, 9.28.

Veatchinium Diacetate Chloride (XXXI).[19] A suspension of 26.6 g. of veatchinium chloride (XXX) in

100 ml. of acetic anhydride and 30 ml. of acetic acid was boiled under reflux for 30 min. The solution was taken to dryness *in vacuo* and flashed several times with methanol to remove most of the acetic acid. The residue was dissolved in 50 ml. of methanol and diluted slowly with 500 ml. of boiling ether. The salt crystallized rapidly as fine needles: 30.45 g., m.p. 251–252°. An analytical sample showed m.p. 254.5–257°; $[\alpha]^{31}D$ −56° (*c* 1.06); ν_{max}^{Nujol} 1739 and 1238 (OAc) and 1669 cm.$^{-1}$ (>C=$\overset{+}{N}$<).

Anal. Calcd. for $C_{26}H_{38}ClNO_4$: C, 67.29; H, 8.25; Ac, 18.55. Found: C, 66.72; H, 8.29; Ac, 18.71.

Veatchine Azomethine Acetate (XXXII).[19] To a solution of 13.6 g. of veatchinium diacetate chloride (XXXI) in 25 ml. of water was added 50 ml. of cold chloroform and 60 g. of crushed ice. A 10-ml. portion of cold 50% sodium hydroxide solution was added and the mixture was shaken vigorously for 1 min. Three more portions of sodium hydroxide solution were added followed by vigorous shaking after each addition. The chloroform layer was separated and the aqueous phase was extracted with three 50-ml. portions of chloroform. The chloroform extract was boiled under reflux for 45 min. during which time a strong odor of acetaldehyde was apparent. Evaporation *in vacuo* and repeated flashing with chloroform gave a yellow resin. This material was dissolved in petroleum ether and a small amount of insoluble material was discarded. Evaporation gave 7.75 g. of light yellow resin which was chromatographed in benzene over 150 g. of neutral Woelm alumina. The veatchine azomethine acetate XXXII was present in the early fractions and crystallized from petroleum ether as heavy, well shaped tetrahedra, 5.88 g., m.p. 122–123.5°. An analytical sample showed m.p. 122.5–124°; $[\alpha]^{26}D$ −87.4° (*c* 1.61); ν_{max}^{Nujol} 1730 and 1233 (OAc), and 1647 cm.$^{-1}$ (>C=N—).

Anal. Calcd. for $C_{22}H_{31}NO_2$: C, 77.37; H, 9.15; N, 4.10; Ac, 12.60. Found: C, 77.25, 77.03; H, 9.27, 9.08; N, 4.24; Ac, 12.57.

Veatchine Azomethine Alcohol (XXXIII).[19] A solution of 2.16 g. of the azomethine acetate XXXII in 10 ml. of 90% methanol was treated with 0.5 g. of potassium hydroxide and boiled under reflux for 15 min. The mixture was diluted with water and extracted with chloroform. Evaporation of the organic phase gave a resin which crystallized from acetone, 1.48 g., m.p. 184–186°; Recrystallization afforded material: m.p. 186–188°, $[\alpha]^{29}D$ −109.7° (*c* 1.31); ν_{max}^{Nujol} 3300 (OH), 1656 (>C=N—), and 897 cm.$^{-1}$ (>C=CH_2).

Anal. Calcd. for $C_{20}H_{29}NO$: C, 80.22; H, 9.76; N, 4.68. Found: C, 80.40, 80.30; H, 9.79, 9.79; N, 4.69.

Attempted Hydration of Azomethine (XXXIII) from Veatchine. An 80-mg. sample of veatchine azomethine XXXIII was dissolved in 2 ml. of 10% hydrochloric acid (by weight) and allowed to stand at room temperature for 21.5 hr. The solution was then basified with sodium carbonate and extracted repeatedly with chloroform. The combined chloroform extracts were evaporated to dryness *in vacuo* to give 82.6 mg. of crude material, m.p. 183–185° (melting point of material recrystallized from acetone was undepressed when admixed with starting material).

The total crude recovered material was then taken up in 2 ml. of 1:1 hydrochloric acid–water and allowed to stand at room temperature for 3 days. Work-up as before furnished 81 mg. of crude material which was taken up in acetone leaving a small amount of insoluble material, m.p. *ca.* 260°.

The acetone solution was evaporated to dryness *in vacuo*, and the residue showed in the infrared two strong carbonyl bands, 1712 (six-membered ketone) and 1645 cm.$^{-1}$ (>C=N—).

The material was chromatographed over 2 g. of silicic acid. Elution with chloroform gave 32.7 mg. of crude material from which was obtained by crystallization from ligroin and recrystallization from acetone a small amount of recovered starting material, m.p. 184.5–186.5° (not depressed on admixture with authentic material). The mother liquor was rechromatographed over 1 g. of alumina and various fractions were treated with hydroxylamine hydrochloride. No crystalline oxime was obtained.

Elution with methanol in chloroform gave 25.2 mg. of material which was rechromatographed giving only small irregular fractions with no evidence for appreciable amounts of hydrated materials.

Reduction of Veatchine Azomethine Alcohol (XXXIII) to Secondary Amine XXXIV. A solution of 321 mg. of veatchine azomethine alcohol (XXXIII) in 25 ml. of 90% methanol was treated with 400 mg. of sodium borohydride. After 3 hr. the solution was evaporated to dryness *in vacuo* and the residue was taken up in water and extracted with chloroform. Evaporation gave a resin which crystallized from methanol–ether, 210 mg., m.p. 165–170°. Recrystallization afforded material of m.p. 166–169°, $[\alpha]^{27}D$ −98.6° (*c* 0.66). Analysis consistently gave low carbon values until the material was sublimed at 210° (0.3 mm.), m.p. 162–165°.

Anal. Calcd. for $C_{20}H_{31}NO$: C, 79.67; H, 10.37. Found: C, 79.20; H, 10.36.

When a sublimed sample was recrystallized from ether it melted at 164–167° and again gave low carbon values, indicating retention of solvent. *Anal.* Found: C, 77.40, 77.17; H, 10.06, 10.04.

Conversion of Veatchine Azomethine Acetate (XXXII) to N-Acetyldes(β-hydroxyethyl)dihydroveatchine (XXXV). A solution of 3.48 g. of XXXII in 75 ml. of methanol and 15 ml. of water was treated with 2.74 g. of sodium borohydride and allowed to stand at room temperature for 5 days. The methanol was removed *in vacuo* and the residue was taken up in water and extracted with chloroform. The product from the chloroform phase was directly acetylated by boiling for 30 min. in a mixture of 30 ml. of acetic anhydride and 10 ml. of acetic acid. On work-up the O,N-diacetate was obtained as a gum. A small quantity was chromatographed over neutral alumina to give material which crystallized from ether as needles: m.p. 122–123°; ν_{max}^{Nujol} 1730 and 1253 (O-Ac), 1618 (N-Ac), and 893 cm.$^{-1}$ (>C=CH_2).

Anal. Calcd. for $C_{24}H_{35}O_3N$: C, 74.76; H, 9.15. Found: C, 75.29; H, 9.35.

The remainder of the crude O,N-diacetate was dissolved in methanol and boiled under reflux for 15

min. with an excess of sodium hydroxide. The methanol was removed *in vacuo*, and the aqueous phase was extracted several times with chloroform. The chloroform extract was washed with 2% sulfuric acid to remove any unacetylated base and evaporated to dryness to give the crude N-acetyldes(β-hydroxyethyl)-dihydroveatchine (XXXV) as an amorphous resin, 3.25 g.. This material was used directly without further purification for oxidation to the dicarboxylic acid XXXVI: ν_{max} 3571 (OH), 1653 (NAc), and 905 cm.$^{-1}$ (>C=CH$_2$).

Oxidation of N-Acetyldes(β-hydroxyethyl)dihydroveatchine (XXXV) to the Dicarboxylic Acid (XXXVI). A. To a solution of 4.20 g. of XXXV in 300 ml. of pyridine and 600 ml. of water at 32° were added 200 ml. of 0.2 *N* sodium metaperiodate (stock solution, 10.74 g. of sodium metaperiodate in 250 ml. of water) and 100 ml. of 0.01 *N* potassium permanganate solution (stock solution, 0.790 g. of $KMnO_4$ in 500 ml. of water). After the intervals of time shown below additional quantities of oxidizing agent were added as indicated in Table III. After standing overnight at 10°, another 200

Table III

Time, min., at 32°	0.2 *N* $NaIO_4$, ml.	0.01 *N* $KMnO_4$, ml.	Color change
3	200	100	Purple to orange
3	200	100	Purple to orange
6	200	100	Purple to orange
8	200	100	Purple to orange

ml. of periodate and 100 ml. of permanganate solution were added and the mixture allowed to stand for 45 min. at 32°. No further color change was noted. In all, 1200 ml. of periodate and 600 ml. of permanganate were consumed. The mixture was extracted 21 times with 250-ml. portions of chloroform to give 3.50 g. of resin. The 3.50-g. sample was dissolved in chloroform and extracted six times with dilute sodium carbonate solution. Evaporation of the chloroform phase gave 0.618 g. of neutral product. Acidification of the carbonate extract with 25% sulfuric acid and subsequent extraction with chloroform gave an acidic fraction of 2.584 g.. The latter crystallized from hot acetone as a fine powder, 1.689 g., (36.5%), m.p. 252.5–254°. An analytical sample prepared by crystallization from a large volume of acetone showed m.p. 254–256°; $[\alpha]^{27}D$ +20° (*c* 0.6 in EtOH); ν_{max}^{Nujol} 1757 (CO_2H) and 1650 cm.$^{-1}$ (NAc).

Anal. Calcd. for $C_{21}H_{31}NO_5$: C, 66.82; H, 8.28, N, 3.71; neut. equiv., 188.7. Found: C, 66.73, 66.71; H, 8.48, 8.47; N, 3.60; neut. equiv., 200.2.

B. A solution of 435 mg. of XXXV in 400 ml. of acetone was treated with finely powdered potassium permanganate over a period of 2 hr. Excess permanganate was destroyed with a few drops of hydrazine and the mixture was filtered. Evaporation of the filtrate gave a residue of 99 mg.. The MnO_2 precipitate was suspended in water and treated with sodium sulfite and sulfuric acid until dissolved. Extraction of the solution with chloroform gave a resin which was combined with the 99-mg. fraction and partitioned between chloroform and dilute sodium carbonate solution. Acidification of the carbonate extract and extraction with chloroform gave 187 mg. which crystallized slowly from acetone, 125 mg., 247.5–249°. The infrared spectrum was identical with that of the dicarboxylic acid prepared by the procedure in part A above.

Dimethyl Ester XXXVII. Treatment of a solution of 174 mg. of XXXVI in 25 ml. of methanol with excess diazomethane gave a quantitative yield of the dimethyl ester XXXVII as a resin: ν_{max} (film from benzene) 1721 (CO_2CH_3) and 1627 cm.$^{-1}$ (NAc).

Anal. Calcd. for $C_{23}H_{35}NO_5$: C, 68.12; H, 8.70. Found: C, 68.30; H, 8.44.

Monoester Acid XXXVIII. A solution of 2.8 g. of dimethyl ester XXXVII in methanol was treated with 10 ml. of 50% sodium hydroxide and boiled under reflux for 5 min. The solvent was removed *in vacuo* and the residue was taken up in water, acidified with dilute sulfuric acid, and extracted with chloroform. Evaporation gave a resin which crystallized from acetone, 2.04 g., sinters, 117–132°, m.p. 180–185°. Concentration of the mother liquors afforded an additional 0.594 g., m.p. 170–180°. An analytical sample also showed a double melting point, m.p. 117–135, then 182–186; $[\alpha]^{28}D$ +16.5° (*c* 1.46); ν_{max}^{Nujol} 1730 and 1709 (CO_2H, CO_2Me), and 1597 cm.$^{-1}$ (NAc). The compound appeared to retain solvent. Titration of several samples against 0.1 *N* sodium hydroxide gave neutralization equivalents of 425–429 indicating retention of about 0.5 mole of acetone.

Anal. Calcd. for $C_{22}H_{33}NO_5$: C, 67.49; H, 8.50. Calcd. for $C_{22}H_{33}NO_5 \cdot C_3H_6O$: C, 66.79; H, 8.75. Found: C, 66.75, 66.80, 66.57; H, 8.90, 8.76, 8.58.

Recrystallization from ethyl acetate gave material of m.p. 177–182°. *Anal.* Found: C, 66.92; H, 8.50.

Monoester Acid Silver Salt XXXIX. A solution of 1.282 g. of monoester acid XXXVIII in water was exactly neutralized (phenolphthalein) with 0.098 *N* sodium hydroxide (32.0 ml. required). The solution was evaporated to dryness *in vacuo*, taken up in 6.0 ml. of distilled water in actinic glass, cooled, and treated with a solution of 527.0 mg. of silver nitrate in 4 ml. of water. The silver salt was collected and dried *in vacuo* at room temperature in the absence of light, 1.33 g. It was used immediately in the Hunsdiecker reaction.

Veatchine Bromo Derivative (XL). A finely ground mixture of 1.33 g. of the silver salt XXXIX and 440 mg. of silver acetate was dried at 60° under high vacuum and added to 50 ml. of dry carbon tetrachloride. A solution of bromine in carbon tetrachloride (62 mg./ml.) was added gradually during refluxing until the color persisted for 15 min. A total of 10 ml. of bromine solution was added (theoretically 13.76 ml.). Excess bromine was distilled over, the mixture was cooled and filtered, and the precipitate of silver bromide was well washed with chloroform. The filtrate was extracted with sodium bicarbonate solution, and the bicarbonate extract was acidified and extracted with chloroform. Evaporation gave 115 mg. of recovered acid XXXVI. The chloroform phase from the bicarbonate wash on evaporation gave 867 mg. of neutral product which was chromatographed in benzene over 11.4 g. of Woelm neutral alumina. The first 40 ml. of benzene eluted 1.6 mg. of spurious material which was

discarded. The next 150 ml. of chloroform eluted 461.0 mg. of resin which proved to be the desired bromo derivative.

Anal. Calcd. for $C_{21}H_{32}BrNO_3$: C, 59.15; H, 7.57. Found: C, 58.98; H, 7.47.

Reduction of XL to the Bisnor Ester (V). A solution of 253 mg. of bromo derivative (XL) in 10 ml. of glacial acetic acid was treated with 1.5 g. of activated zinc granules (30 mesh) and 0.5 ml. of concentrated hydrochloric acid and boiled under reflux for 1 hr. After the mixture was filtered and the filtrate was evaporated *in vacuo*, the residue was taken up in water and extracted with chloroform. The product (200 mg.) was chromatographed over 3.0 g. of silic acid (100 mesh). Chloroform eluted 110 mg. which crystallized from acetone, m.p. 251–257°. This material was combined with material obtained from another run (total 167 mg.) and chromatographed in benzene over Woelm neutral alumina (see Table IV).

Table IV

Solvent	Tube	Ml.	Wt., mg.	Rotation, deg.
Benzene	1	10	8.5	−11.8
	2	10	17.5	−17.5
	3–6	35	16.6	−16.2
	7–8	75	14.3	−17.1
Benzene–MeOH	9	20	23.9	−18.3
(200:1)	10	25	82.9	−18.5
	11	50	3.4	...

Fractions 2–10 were combined (146 mg.) and crystallized twice from hexane, m.p. 153–155.5°; from ether, m.p. 155–156°; and from hexane to give 98.7 mg. of m.p. 153.5–155.5°, $[\alpha]^{27}D$ −17° (*c* 0.71). The infrared spectra in chloroform and Nujol were identical with those of the bisnor ester derived from atisine (*vide supra*).

Anal. Calcd. for $C_{21}H_{33}NO_3$: C, 72.58; H, 9.57. Found: C, 72.56; H, 9.32.

Neutral Product (XLII). The neutral fractions from several experiments on the permanganate–periodate oxidation of VI were combined (0.60 g.) in acetone and allowed to stand. A portion of the material crystallized slowly to give 345 mg., m.p. 238–245°. Recrystallization from methanol–acetone gave material of m.p. 267.5–276°. The material appeared to be a mixture of epoxides.

Anal. Calcd. for $C_{22}H_{33}NO_3$: C, 73.50; H, 9.25. Found: C, 73.34, 73.07; H, 9.27, 9.01.

Recrystallization of a sample from methanol gave flat flakes of m.p. 272–278°. The melting point was highly dependent on the rate of heating and the temperature at which the sample was placed on the hot stage. Repeated crystallization from methanol gave fine needles which were transformed on standing to plates, m.p. 279–284°.

Anal. Found: C, 73.30, 73.38; H, 8.82, 9.05.

Chromatography of a 235-mg. sample in chloroform over Woelm neutral alumina gave fractions of XLII crystallizing from methanol or ethyl acetate with melting points of 272–282°; ν_{max}^{Nujol} 3632 (OH), 3045 (>C—O—CH_2), and 2960, 2936, 2874, 2852, and 1629 cm.$^{-1}$ (NAc).

Anal. Found: C, 73.43, 73.26; H, 9.17, 9.21.

The n.m.r. spectrum in $CDCl_3$ showed bands at τ 9.12 (C—CH_3); 7.87 and 7.90 (—NCOCH_3); quartet at 6.75, 6.85 (CH_2—N—CH_2); 7.24, 7.29, 7.39, 7.44 (J = 3 c.p.s.) (>C—O—CH_2); and 8.26 (—OH). After exchange with deuterium oxide, the 8.26 band disappeared.

Treatment of O,N-Diacetate (XLIII) with Peroxytrifluoroacetic Acid. To a suspension of 0.7 ml. of fresh 90% hydrogen peroxide in 5.0 ml. of methylene chloride at ice bath temperature was added dropwise 4.5 ml. of trifluoroacetic anhydride. The mixture was stirred well for 15 min. and used immediately.

To a solution of 542 mg. (0.0014 mole) of the O,N-diacetate in 5.0 ml. of methylene chloride was added 840 mg. of anhydrous Na_2HPO_4 (dried at 80°). While the mixture was stirred at reflux, 0.75 ml. of the freshly prepared solution of peroxytrifluoroacetic acid was added dropwise, and refluxing was continued for 30 min. The mixture was diluted with water and neutralized with sodium bicarbonate solution while maintained at 5° with cracked ice. Extraction with chloroform gave 602 mg. of yellow resin which crystallized from acetone to give two fractions, 162 mg., 217.5–222.0° and 34 mg., m.p. 209–215.5°. The mother liquors were evaporated to give 369 mg. which was reserved for chromatography. Recrystallization of the combined crystalline fractions from methanol–acetone gave fine birefringent needles of the dihydroxyacetate XLIV: 142 mg., m.p. 220.5–225°; ν_{max}^{Nujol} 3460 and 3257 (OH), 1745 and 1245 (OAc), and 1626 cm.$^{-1}$ (NAc).

Anal. Calcd. for $C_{24}H_{37}NO_5$: C, 68.70; H, 8.89. Found: C, 68.84; H, 8.83.

A 300-mg. portion of resin from the mother liquors was chromatographed in benzene over 15 g. of Woelm neutral alumina. The first 565 ml. of benzene eluted 206 mg. of resin which after saponification crystallized from acetone as feathery needles, m.p. 206–208°. Two more crystallizations raised the melting point to 210.5–211.5°; ν_{max}^{Nujol} 3584 and 3279 (OH) and 1629 cm.$^{-1}$ (NAc). This material appeared to be a mixture of the epoxide and triol XLV. *Anal.* Found: C, 70.90; H, 9.54.

Chloroform eluted 85 mg. of the dihydroxy acetate XLIV which crystallized from acetone as birefringent prisms, m.p. 218–223°. The infrared spectrum in Nujol was identical with the previously described sample.

Saponification of Dihydroxyacetate (XLIV) to Triol (XLV). A solution of 50 mg. of XLIV in 5 ml. of methanol was treated with an excess of 50% sodium hydroxide solution and allowed to stand for 90 min. After removal of methanol *in vacuo*, the residue was taken up in water and extracted with chloroform. The product crystallized from acetone as tiny blades, m.p. 219–220°. Recrystallization gave thin, wedge-shaped leaflets of the triol XLV: 30 mg.; m.p. 218–220°; ν_{max}^{Nujol} 3636 and 3401 (OH), and 1600 cm.$^{-1}$ (NAc).

Anal. Calcd. for $C_{22}H_{35}NO_4$: C, 69.99; H, 9.35. Found: C, 70.08; H, 9.17.

Isolation of By-Product Ester XLVI from Oxidation of VI. The mother liquors remaining after separation of the crystalline N-acetyl dicarboxylic acid VII from

several runs were combined, evaporated to dryness (3.26 g.), taken up in acetone, and treated with an excess of diazomethane. After concentration to a small volume and standing overnight, the solution deposited 268 mg. of crystals, m.p. 225.5–237°. Recrystallization from acetone gave 188 mg., m.p. 232.5–239°. An analytical sample melted at 236–240°, $[\alpha]$ 5.8°; ν_{max}^{Nujol} 3378 (OH), 1730 (CO_2CH_3), and 1621 cm.$^{-1}$ (NAc); n.m.r., τ 9.08 (3H singlet, CCH_3), 7.90 (3H singlet, $NCOCH_3$), and 6.27 (3H singlet, $COOCH_3$).

Anal. Calcd. for $C_{22}H_{33}NO_4$: C, 70.37; H, 8.86. Found: C, 70.54, 70.47, 70.50; H, 9.01, 8.70, 8.89.

Saponification of XLVI to Carboxylic Acid XLVII. A solution of 50 mg. of XLVI in 9 ml. of methanol and 1 ml. of water was treated with 0.1 ml. of 50% sodium hydroxide and then heated under reflux for 10 min. After evaporation to dryness *in vacuo*, the residue was taken up in water and extracted with chloroform. The aqueous phase was cooled to 5°, made acid to congo red by the dropwise addition of dilute sulfuric acid, and quickly extracted with chloroform. Evaporation gave 47.4 mg. of a white foam. This was dissolved in benzene and filtered from a small amount of residue. Evaporation gave an amorphous carboxylic acid which did not crystallize from ether, benzene, or acetone: ν_{max} (film, $CHCl_3$) 3448 (OH), 2857–2703, and 1712 broad (—CO_2H), and 1603 s cm.$^{-1}$ (NAc).

Anal. Calcd. for $C_{21}H_{31}NO_4$: C, 69.77; H, 8.65. Found: C, 69.88, 69.84; H, 8.49, 8.54.

Methylation of XLVII to Regenerate XLVI. A solution of 42 mg. of XLVII in 2 ml. of acetone was treated with an excess of diazomethane in ether. After concentration, the ester XLVI crystallized as needles, m.p. 234–239.5°. Recrystallization gave material melting at 236–240° with an infrared spectrum in Nujol identical with that of the ester prior to saponification.

Anal. Calcd. for $C_{22}H_{33}NO_4$: C, 70.37; H, 8.86; N, 3.73. Found: C, 70.35; H, 8.76; N, 3.87.

Acetylation of XLVI to XLVIII. A solution of 23 mg. of XLVI in 1.0 ml. of dry pyridine and 1 ml. of acetic anhydride was allowed to stand over the weekend. The mixture was evaporated to dryness *in vacuo*, taken up in benzene, and washed with cold sodium carbonate solution. Evaporation to dryness gave 23 mg. of resin which crystallized slowly from acetone–petroleum ether as rosettes, 20 mg., m.p. 180.5–183°. Recrystallization gave 15 mg. of m.p. 181–183.5°; ν_{max}^{Nujol} 1745, 1733, 1266, and 1245 (OAc and CO_2CH_3), and 1634 cm.$^{-1}$ (NAc); n.m.r., τ 9.13 (3H singlet, CCH_3), 7.90 (6H singlet, $OCOCH_3$ and $NCOCH_3$), 6.30 (3H singlet, CO_2CH_3), and 5.0 [1H singlet, $R_3C—CH(OAc)—CR_3$].

Anal. Calcd. for $C_{24}H_{35}NO_5$: C, 69.03; H, 8.45. Found: C, 69.20; H, 8.30.

Oxidation of XLVI to Keto Ester XLIX. A solution of 20 mg. of XLVI in 3.0 ml. of acetone was cooled to 0° and treated with 3 drops of 8 *N* Jones reagent. After 15 min. at 0° the mixture was allowed to warm to room temperature. The mixture was diluted with water and extracted with chloroform to give 18.8 mg. of resin. This was combined with 20 mg. of product from a duplicate run and crystallized from ethyl acetate to give 21 mg. of round rosettes, m.p. 182–186°. Repeated crystallization and processing of mother liquors gave 19 mg. of the keto ester XLIX: m.p. 186–189.5°; ν_{max}^{Nujol} 1776 (>C=O), 1733 (—CO_2CH_3), and 1639 cm.$^{-1}$ (NAc); $\nu_{max}^{CCl_4}$ 1783 (>C=O), 1733 (—CO_2CH_3), and 1642 cm.$^{-1}$ (NAc).

Anal. Calcd. for $C_{22}H_{31}NO_4$: C, 70.75; H, 8.37. Found: C, 70.60; H, 8.35.

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