

We have also completed the conversion of this alkaloid to atisine (II), which will be described separately.

The synthesis of 16-keto-10-carboxy-17,20-bisnor-kaurene (III) has already been described.¹ Treatment of the acid chloride of III, (–)-isomer, with anhydrous hydrazine afforded a crude acid hydrazide, m.p. 265–270°, which was further converted to an acid hydrazide ketal (IV), m.p. 256–258°, with ethylene glycol and three equivalents of *p*-toluenesulfonic acid. Compound IV exhibited an infrared spectrum identical with that of its *dl* compound described previously.¹ Reaction of IV with nitrous acid gave an unstable azide (V) (λ_{\max} (methylcyclohexane) 4.69, 5.80 μ) which was irradiated at $-10 \sim -15^\circ$ with a Hanovia 450-w. mercury lamp.³ Careful column chromatography separated a lactam fraction of the photolysis product, which was reduced with lithium aluminum hydride and then acetylated to give an acetamide ketal (VI), m.p. 185–186°, in approximately 5% yield in addition to other compounds. The acid hydrolysis of VI afforded a keto amide (VII), m.p. 164–165°, which proved to be identical with the compound prepared from veatchine azomethine acetate (VIII).⁴ Reaction of VII with methylene triphenylphosphorane in dimethyl sulfoxide⁵ led to an exocyclic methylene compound (IX), m.p. 147–148° ($\lambda_{\max}^{\text{chl}}$ 11.36 μ ; n.m.r. signal of two olefinic protons, 5.20 τ), which was isomerized to an endocyclic isomer (X),⁶ m.p. 148–149°, ($\lambda_{\max}^{\text{chl}}$ 12.24 μ , n.m.r. signal of one olefinic proton, 4.93 τ) with dry hydrogen chloride in cold acetic acid.⁷ The n.m.r. spectral analysis of an equilibrated mixture showed that it consisted of 75% of X and 20% of IX. The photosensitized (hematoporphyrin) oxygenation⁸ of X followed by the lithium aluminum hydride reduction of the resulting hydroperoxide ($\lambda_{\max}^{\text{chl}}$ 3.1, 11.0 μ) in diethyl ether⁸ gave an oily alcohol (XI) ($\lambda_{\max}^{\text{chl}}$ 2.8, 11.05 μ). The corresponding acetate (XII) melted at 85–86°. The von Braun reaction on XII proceeded smoothly to afford an N-cyano compound (XIII), m.p. 220–221° ($\lambda_{\max}^{\text{chl}}$ 4.51, 5.8, 11.0 μ). The lithium aluminum hydride reduction¹⁰ of XIII gave a cyclic secondary amine (XIV), m.p. 166–167°, which was identical in every respect with the compound obtained by the lithium aluminum hydride reduction⁴ of VIII.

Wiesner, *et al.*, have alkylated XIV with ethylene bromohydrin to give dihydroveatchine, which in turn was converted quantitatively into garryine by a unique oxidation reaction with osmium tetroxide.¹¹ Therefore, the work described herein completes the total synthesis of a Garrya alkaloid, garryine.^{12,13}

(3) Photolyses of model compounds have been performed in several places including this Laboratory. Some of the results have already been published: J. W. ApSimon and O. E. Edwards, *Can. J. Chem.*, **40**, 896 (1962); W. L. Meyer and A. S. Levinson, *Proc. Chem. Soc.*, 15 (1963).

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

(5) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963).

(6) X appears to be the same compound as that prepared from VIII by a different route, see ref. 4.

(7) L. H. Briggs and P. W. Cawley, *J. Chem. Soc.*, 1888 (1948). Although kaurene was converted to its hydrochloride under these conditions, IX rearranged directly to X.

(8) G. O. Schenk, *Angew. Chem.*, **69**, 579 (1957). For application to steroids and terpenes, see A. Nickon and J. F. Bagli, *J. Am. Chem. Soc.*, **83**, 1498 (1961); R. A. Bell and R. E. Ireland, *Tetrahedron Letters*, No. 4, 269 (1963).

(9) The over-all yield of XII from X was routinely more than 65%, and a by-product (less than 5%) appeared to be the epimeric acetate (garryfoline series).

(10) A. C. Curie, G. T. Newbold, and F. S. Spring, *J. Chem. Soc.*, 4693 (1961).

(11) K. Wiesner, W. I. Tayler, S. K. Figdor, M. F. Bartlett, J. R. Armstrong, and J. A. Edwards, *Chem. Ber.*, **86**, 800 (1953).

(12) Satisfactory analyses and spectra (infrared, n.m.r.) were obtained for all new compounds described herein.

(13) This investigation was supported by a grant (GM 10369) from the National Institutes of Health, Public Health Service.

Acknowledgment.—The author is grateful to Professor C. Djerassi for providing him with an abundant amount of crude alkaloids of *Garrya Laurifolia*.

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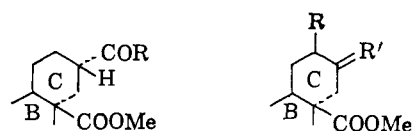
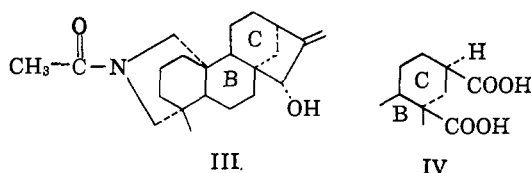
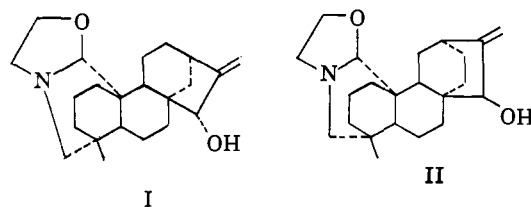
SATORU MASAMUNE

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Total Syntheses of Diterpenes and Diterpene Alkaloids. V.¹ Atisine

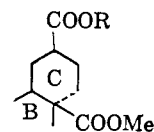
Sir:

In 1954 Wiesner first proposed the correct gross structures for dihydro derivatives of veatchine (I) and atisine (II), basing his argument on a limited amount of experimental data then available.² Since that time unsuccessful attempts³ apparently have been made to convert the former alkaloid to the latter. We have now accomplished such a conversion and report it herein.



V, R = OMe
VI, R = OH
VII, R = Me

VIII, R = H; R' = H, OAc
IX, R = H; R' = H, OH
X, R = H; R' = O
XI, R = COOMe; R' = O



XII, R = Me
XIII, R = H

Compound III, prepared from veatchine azomethine acetate,⁴ was oxidized with the Lemieux and Rudloff reagent⁵ to afford a dicarboxylic acid, m.p. 252–254° (IV).⁶ Treatment of the dimethyl ester of IV with sodium methoxide effected the epimerization of a carbomethoxy group and afforded a *trans* dimethyl ester (V), which was subsequently hydrolyzed to give

(1) Part IV: S. Masamune, *J. Am. Chem. Soc.*, **86**, 290 (1964).

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

(3) K. Wiesner and Z. Valenta, "Progress in the Chemistry of Organic Natural Products," Vol. XVI, Springer-Verlag, Vienna, 1958, p. 52.

(4) H. Vorbrueggen and C. Djerassi, *J. Am. Chem. Soc.*, **84**, 2990 (1962); K. Wiesner, J. R. Armstrong, M. F. Bartlett, and J. A. Edwards, *ibid.*, **76**, 6068 (1954).

(5) R. W. Lemieux and E. von Rudloff, *Can. J. Chem.*, **33**, 1701 (1955); E. von Rudloff, *ibid.*, **33**, 1714 (1955).

(6) S. W. Pelletier, *J. Am. Chem. Soc.*, **82**, 2398 (1960).

a monoester carboxylic acid (VI), m.p. 235–237°. Conversion of the carboxy group of VI to a hydroxy group was achieved by treatment of the acid chloride⁸ of VI with dimethylcadmium,⁹ followed by the Baeyer–Villiger reaction on the resulting methyl ketone (VII)¹⁰ (n.m.r. spectra: OMe (3) 6.29 τ , CO–CH₃ (3) 7.84, NCO–CH₃ (3) 7.93, C–CH₃ (3) 9.15) and finally mild alkaline hydrolysis of the acetate (VIII),¹⁰ ($\lambda_{\text{max}}^{\text{CH}_1}$ 5.81, 6.18, 8.05 μ). The resulting hydroxy compound (IX) melted at 205–206°. Oxidation of IX with chromic acid gave the corresponding ketone (X), m.p. 172–176°, which was carbomethoxylated with dimethyl carbonate and sodium methoxide¹¹ to provide a β -keto ester (XI) (amorphous, $\lambda_{\text{max}}^{\text{CH}_1}$ 5.82, 6.03, 6.20 μ ; $\lambda_{\text{max}}^{\text{EtOH}}$, 253 $\mu\mu$ (ϵ 9800)). Reduction of XI with sodium borohydride and treatment of the resulting epimeric alcohols with tosyl chloride provided an unsaturated ester, m.p. 175–180°. This unsaturated ester was hydrogenated and the resulting mixture was treated with sodium methoxide. Chromatography of the saturated compounds separated a dimethyl ester (XII), m.p. 197–199°, and the alkaline hydrolysis of XII gave a monomethyl ester carboxylic acid (XIII), m.p. 248–250°. The identity of XII and XIII with those obtained from atisine^{6,12} was confirmed by means of mixture melting point and infrared spectra, respectively. Conversion of XIII to atisine has recently been reported.¹³ Thus, the first conversion of Garrya alkaloids, veatchine and garryine, to atisine has been achieved. Since garryine has been synthesized,¹ we have now completed in a formal sense the synthesis of atisine also.^{14–16}

Acknowledgment.—The author is grateful to Mr. N. T. Castellucci for his technical assistance throughout this work.

(7) The direct alkaline hydrolysis of the dimethyl ester of IV at room temperature gave a *cis* ester carboxylic acid, m.p. 184–186°. See ref. 6.

(8) The amide group was found to react with oxalyl chloride slowly. Therefore, addition of this reagent was carefully controlled.

(9) D. A. Shirley, "Organic Reaction," Vol. VIII, R. Adams, Ed., John Wiley and Sons, Inc., New York, N. Y., 1954, Chapter 2.

(10) We have experienced difficulties in crystallizing intermediates of this series. The homogeneity of these compounds was confirmed by the identical infrared spectra of every fraction, resulting from two kinds of chromatography (silicic acid and alumina). In addition, thin layer chromatography gave only one spot in every case.

(11) Part II of this series, ref. 8.

(12) The author wishes to thank Professor Pelletier for providing him with an authentic sample.

(13) S. W. Pelletier and P. C. Parthasarathy, *Tetrahedron Letters*, No. 4, 205 (1963).

(14) An elegant synthesis of atisine has recently been reported: W. Nagata, T. Sugasawa, M. Narisada, T. Wakabayashi, and Y. Hayase, *J. Am. Chem. Soc.*, **85**, 2342 (1963).

(15) All new crystalline compounds gave satisfactory elementary analyses.

(16) This investigation was supported by a grant (GM 10369) from the National Institutes of Health, Public Health Service.

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Photoisomerization of Diazirine

Sir:

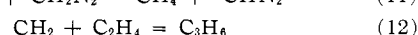
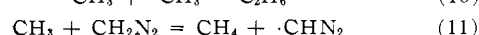
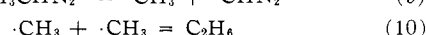
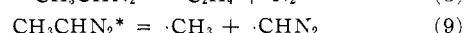
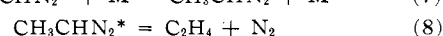
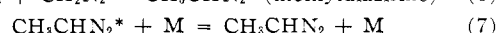
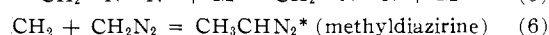
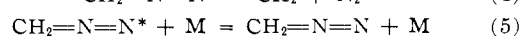
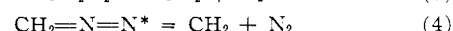
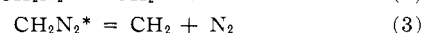
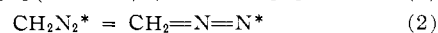
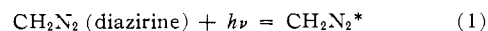
We wish to report the results of preliminary experiments on the photolysis of mixtures of diazirine (cyclic diazomethane), 5–30 mm., and nitrogen, 0–600 mm. The emission from a 200-w., high-pressure Hg lamp (PEK), passing through a Bausch and Lomb monochromator (Catalog No. 33-86-01) set at 3200 Å. (entrance slit, 1.8 mm.; exit slit, 1.0 mm.) and a Corning, CS 7-54, filter, is focused at the center of 10-cm. quartz photolysis cells. We follow the reaction by intermittent ultraviolet analysis of the reaction mixture and by gas chromatographic analysis of the final reaction mixture using a flame ionization detector.

The quantum yield for the initial disappearance of diazirine (spectrophotometric determination), based on ferrioxalate actinometry, is 2.0 ± 0.5 . A chain reaction which results in the formation of polymer on the walls is probably responsible for the scatter in quantum yield data.

The most significant feature of the spectrophotometric analysis is the identification of diazomethane as a product of photolysis. Diazomethane has a broad, very weak absorption with a maximum at 4100 Å. and a molar decadic extinction coefficient of 3.¹ At shorter wave lengths there are three much stronger absorption maxima (with extinction coefficients, based on the above value of 3 at 4100 Å.) at 2295 (3000), 2175 (10,000), and 2135 (7600) Å. The amount of diazomethane produced in the photolyses is estimated on the basis of this short wave-length absorption; the quantum yield for its formation is about one-tenth that for diazirine disappearance. The concentration of diazomethane builds up initially as a run proceeds, but then it levels off and finally begins to decline as the reactant diazirine is depleted. Scattered light, present in substantial amount in the exit beam from the monochromator, probably causes photolysis of the diazomethane and is responsible for the leveling off and decline of diazomethane concentration with increasing time of photolysis.

Frey and Stevens² have reported the photolysis of diazirine, presumably at higher pressures than reported here, and find ethylene and nitrogen as the major products of the reaction. Methane, ethylene, ethane, and propylene are the major products of the reaction we detect by the chromatographic analyses. At a constant initial pressure of diazirine, the ratio of ethane to ethylene in the products increases with decreasing pressure of added nitrogen. The effect of changing the initial pressure of diazirine is complicated because the photolysis light then penetrates the cell to different extents and the effective reactor volume differs; the product ratios are sensitive to the resulting diffusion effects.

We suggest the following mechanism, which is consistent with the results.



The designation of any product as "activated" does not imply anything concerning the type of activation; electronic or vibrational or both. Reactions 6–12 are written to be analogous to those observed in other systems in which methylene is produced.³ The radicals produced in reactions 9 and 11 probably go on to cause polymerizations. There is no spectrophotometric or chromatographic evidence for the methyldiazirine postulated in reaction 7. Its absorption spectrum must be similar to that of diazirine, but shifted

(1) R. K. Brinton and D. H. Volman, *J. Chem. Phys.*, **19**, 1394 (1951).

(2) H. M. Frey and I. D. R. Stevens, *Proc. Chem. Soc.*, 79 (1962).

(3) J. A. Bell and G. B. Kistiakowsky, *J. Am. Chem. Soc.*, **84**, 3417 (1962).