

that the observed unusually high stereoselectivity, 99.98% *exo*, is explicable only in terms of the unique stereochemical requirements of a σ -bridged intermediate.^{6,7}

Evidence was previously presented that the presence of 7,7-dimethyl substituents in norbornene either forces such concerted *cis* additions to go preferentially *endo*, or prevents such additions from occurring.¹⁹ Both acetic acid and trifluoroacetic acid readily add to 7,7-dimethylnorbornene at rates not very different from those exhibited by norbornene itself to give stereoselectively *exo-cis* addition products.³ Consequently, the postulate of competing concerted *cis* additions of acetic acid and trifluoroacetic acid appears highly improbable.

There is a third possibility to consider. It could be assumed that the transfer of the proton from these acids to norbornene proceeds to the initial formation of the classical norbornyl cation. This cation then undergoes a closure to the nonclassical cation at a rate that is competitive with the capture of the nucleophile.²⁰ Thus, in the case of acetic acid, 40% of the product (nonhydride shifted) would be formed *via* the σ -bridged intermediate and 50% *via* the classical norbornyl cation captured prior to the conversion to the nonclassical ion. This mechanism could account for the isotopic distribution (eq 2). However, it requires that capture of the nucleophile by the classical norbornyl cation must proceed with stereoselectivity of essentially 99.98% *exo*. This again would be incompatible with the argument that such a high stereoselectivity is inexplicable save in terms of the unique steric requirements of a σ -bridged cation.^{6,7}

These considerations suggest that the simplest, most consistent interpretation of these addition reactions²¹ is that they proceed through rapidly equilibrating classical norbornyl cations and that such cations react with nucleophiles with a high preference for *exo* capture. It follows that the high stereoselectivity observed in the acetolysis of norbornyl derivatives cannot be used to support the proposal that such solvolyses proceed with σ bridging.

(19) H. C. Brown and J. H. Kawakami, *J. Amer. Chem. Soc.*, **92**, 201 (1970).

(20) Such a mechanism has been proposed to account for the formation of *exo*-norbornanol with 10% retention of optical activity in the elimination of optically active *exo*-norbornylamine: E. J. Corey, J. Casanova, Jr., P. A. Vatakencherry, and R. Winter, *ibid.*, **85**, 169 (1963).

(21) Including the addition of deuterium chloride previously studied: H. C. Brown and K.-T. Liu, *ibid.*, **89**, 466, 3898, 3900 (1967).

(22) (a) To whom correspondence should be addressed. (b) Graduate assistant on a grant (GP 6492X) provided by the National Science Foundation.

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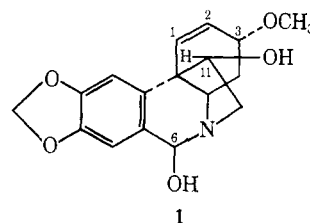
Stereospecific Synthesis of Haemanthidine and Tazettine

Sir:

Most of the large family (>70 members) of alkaloids of the *Amaryllidaceae* belong to one of two biosynthetically related structural groups, characterized by the skeletons of lycorine and crinine.¹ The most pro-

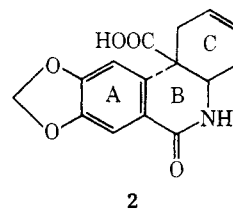
(1) W. C. Wildman in "The Alkaloids," Vol. VI, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1960.

ductive synthetic challenge of the latter group appeared to be the most complex, *i.e.*, haemanthidine (**1**),



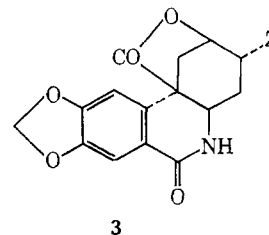
since removal of the functions at C-6 and C-11 (and alteration at C-3) should concurrently afford easy routes to many of the simpler members, while syntheses of the latter do not so readily also lead to haemanthidine. There is further synthetic challenge in the stereochemical control of five asymmetric centers and the reactivity of haemanthidine to both mild acids and bases.

A system for synthesis design² reveals that creation of quaternary carbons is the most limited construction operation. We selected cycloaddition for this operation here since it also provides ring construction with stereochemical control over up to four adjacent asymmetric centers. This choice virtually dictates the synthesis from the available starting material, piperonal, to the lactam acid **2**, in eight operations and 14%



overall yield, as previously reported.³ This intermediate possesses a rigid *trans*-decalin skeleton, assured by the cycloaddition, with a sterically dominant axial carboxyl for steric control of ring-C functionalization as well as for bridge formation to nitrogen. When the latter operation was carried out first, the crinine skeleton was formed,³ but in the subsequent functionalization of ring C full steric control was not achieved.⁴ This communication reports prior functionalization of ring C and the stereospecific conversion to haemanthidine (**1**) and tazettine, a closely related isomeric alkaloid.¹

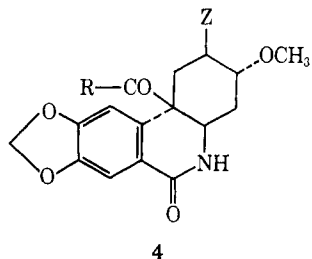
The less stable axial orientation of methoxyl at C-3 can reliably be created by the opening of the more hindered, 2,3-epoxide *cis* to the carboxyl in **2**. Such an epoxide was created by iodolactonization of **2** (KI₃ in NaHCO₃ solution) to **3**, Z = I, mp 270° (92%),



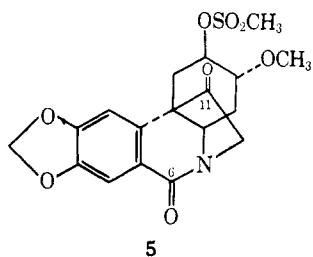
(2) J. B. Hendrickson, manuscript in preparation.
(3) J. B. Hendrickson, C. Foote, and N. Yoshimura, *Chem. Commun.*, **9**, 165 (1965); the overall yield has been improved since this report.
(4) Unpublished work by Dr. S. Grossert in these laboratories.

followed by heating with 0.1 *N* NaOH solution and cooling to crystallize the epoxy acid salt (82%). The methoxy lactone **3**, *Z* = OCH₃, mp 279° (70%), was then prepared by stirring in BF₃·CH₃OH overnight.

Hydrolysis of **3**, *Z* = OCH₃, and normal esterification did not serve to free the C-2 hydroxyl for reaction owing to preferential re-lactonization, but saponification followed by displacement in phenacyl bromide by the carboxylate anion (in DMF) did afford an ester, **4** (*Z* = OH, *R* = OCH₂COC₆H₅), mp 157° (85%), which could be mesylated in cold pyridine to **4** (*Z* =



OSO₂CH₃, *R* = OCH₂COC₆H₅), mp 233° (66%), containing a leaving group appropriate for later trans elimination only to the desired Δ^{2,3}-olefin.⁵ The bridge to nitrogen was now prepared by saponification to **4**, *R* = OH, acid chloride formation with thionyl chloride, and treatment with diazomethane to the diazo ketone **4** (*Z* = OSO₂CH₃, *R* = CHN₂), mp 180° (90%). The bridge was closed with dry HCl to yield **5**, mp 194° (55%). The carbonyl at C-6 in **5** is essentially un-



available for stabilizing amide resonance with nitrogen owing to Bredt's rule (*cf.* ref 3 and 6) and hence is readily solvolyzed, or reduced by cold NaBH₄ to a carbinolamine still containing the C-11 ketone. This carbinolamine, like haemanthidine,⁷ is self-equilibrated

(5) Eliminations at this stage resulted in concomitant decarboxylation.

(6) S. Uyeo, H. M. Fales, R. J. Highet, and W. C. Wildman, *J. Amer. Chem. Soc.*, **80**, 2590 (1958).

(7) R. W. King, C. F. Murphy, and W. C. Wildman, *ibid.*, **87**, 1912 (1965).

(*via* C-6 aldehyde) to an equilibrium configuration at C-6.

Since reduction at C-11 in natural 11-oxo derivatives yields predominantly the wrong 11-epimer,⁸ our retention of the axial mesylate at C-2 was intended to reverse this trend by steric hindrance. Indeed, reduction of **5** with NaBH₄ (in boiling isopropyl alcohol) followed by hot alkaline elimination yielded exclusively nortazettine, identical with a sample obtained from haemanthidine in base;⁹ no 11-epimer was formed. As methylation of nortazettine yields tazettine,¹ this constitutes a synthesis of the latter alkaloid.

The internal Cannizzaro hydride transfer that converts haemanthidine to nortazettine occurs in mild base and it was established that the same reaction had occurred here in the hot NaBH₄ reduction of **5**.¹⁰ Accordingly, acid reduction with a hindered borane (refluxing diisiamylborane-THF) was used to avoid this further conversion. The crude diol was acetylated to prevent the Cannizzaro transfer in the subsequent elimination of mesylate with base (hot 1,5-diazabicyclo[3.4.0]nonene-5), and the products were deacetylated with LiAlH₄ and chromatographed to yield *d,l*-haemanthidine, mp 195° (20%), and 5% of the 11-epimer. The alkaloids were identical with natural samples by spectral comparisons and thin layer chromatograms in five different solvent systems.^{9,11} Although stereospecificity in the borane reduction is not as complete as with hot NaBH₄, nevertheless the stereochemical distinction between the C-11 epimers formed may be established independently of their identification with natural material since only haemanthidine can form the cyclic ether, apohaemanthidine, in acid.¹ Conversion of several of these synthetic materials to other alkaloids of the crinine family is being investigated.

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(8) H. M. Fales and W. C. Wildman, *ibid.*, **82**, 197 (1960); W. C. Wildman and D. T. Bailey, *ibid.*, **91**, 150 (1969); and independent examinations in these laboratories.

(9) We wish to thank Professors W. C. Wildman (Iowa State) and F. L. Warren (Capetown) for generous gifts of natural alkaloids.

(10) This was shown by acetylation directly following reduction, which yielded an acetamide, reduced by LiAlH₄ to an *N*-ethyl derivative.

(11) Analyses and spectra of all the intermediates were consistent with the formulations given.

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Book Reviews

Separation Methods in Organic Chemistry and Biochemistry. By FRANK J. WOLF, Merck Sharp and Dohme Research Laboratories, Rahway, New Jersey. Academic Press, Inc., 111 Fifth Ave., New York, N. Y. 1969. vii + 237 pp. 23.5 × 16 cm. \$11.50.

One of the most tedious chores facing the nonchemist working in biological-medical fields is the search through multitudes of pub-

lications dealing in a specialized way with the numerous techniques and procedures utilized by chemists, in order to select procedures which are suitable for his problem. Books which present a survey of methods are indeed rare and for this reason this volume will be welcomed not only by chemists but biologists and medical investigators as well. Not so comprehensive as to overwhelm the nonchem-