The Claisen Rearrangement in Indole Alkaloid Synthesis. The Total Synthesis of (±)-Tabersonine[1]

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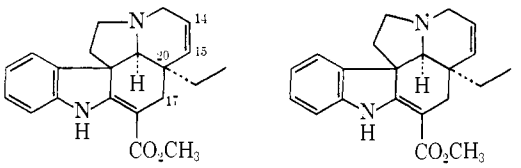
Abstract: The details of the total synthesis of (±)-tabersonine are discussed.

Tabersonine (**1**), first isolated from *Amsonia tabernaemontana*,[4] has since been found to be an *in vivo* progenitor[5] of catharanthine (*Iboga*) and vindoline (*Aspidosperma*), the latter being a precursor of the dimeric oncolytic alkaloids vinblastine (VLB) and vincristine (VCR).[6] The realization that tabersonine occurs in nature as its levorotatory enantiomer,[7] while vincadifformine (**2**) has been isolated in its racemic form in addition to enantiomeric forms,[7,8] implied a possible primary metabolic role for the dextrotatory enantiomer of tabersonine. Consequently, we considered developing a synthetic route to racemic tabersonine.



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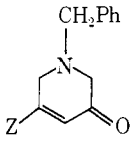
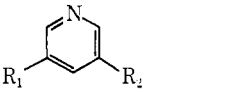
Our primary concern in devising a total synthesis of tabersonine lay in developing an effective means in establishing the C-14,15 double bond and the adjoining quaternary center at C-20. Since we had previously developed a technique for medium ring cyclization to form 2-acylindoles,[1a,9] it became apparent that the Claisen rearrangement would be admirably suited for the establisnment of the requisite functionality necessary to achieve our goal.

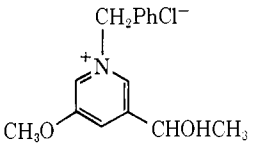
Our initial goal was the enone **3c**, which would serve as the immediate precursor of allylic alcohol **7a**, upon which the rearrangement would be effected. The first solution to this problem involved construction of the piperidine ring. Thus, ethyl *N*-benzylglycinate was alkylated with chloroacetone in aqueous tetrahydrofuran in the presence of sodium bicarbonate to produce ethyl *N*-benzyl-*N*-acetonylglycinate in 80% yield.[10] Subsequent Claisen cyclization with sodium hydride in ether as reported[10] met with mixed success. The use of a protic medium, *i.e.*, potassium *tert*-butoxide in *tert*-butyl alcohol–ether, provided crude diketone **3a** in high yield. The diketone was subsequently converted to the enol ether **3b** with diazomethane, albeit in moderate yield,



3a, Z = OH
b, Z = OCH_3
c, Z = C_2H_5



4a, R_1 = Br; R_2 = $CONH_2$
b, R_1 = Br; R_2 = NH_2
c, R_1 = Br; R_2 = OH
d, R_1 = Br; R_2 = OCH_3
e, R_1 = $CHOHCH_3$; R_2 = OCH_3



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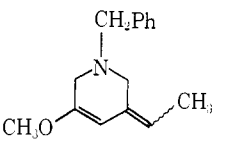

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but nonetheless it proved more successful than other standard techniques.[11] The extended conjugation of the enol ether was reflected in its low carbonyl frequency (1660 cm^{-1}), while the nmr spectrum revealed a methyl singlet at δ 3.74 and a vinyl proton at δ 5.45.

Treatment of the enol ether with ethereal ethylmagnesium bromide and subsequent acid hydrolysis provided the desired enone **3c** in high yield.[12] The crystalline amino ketone displayed a typical enone absorption (1670 cm^{-1}) in its infrared spectrum, while the nmr spectrum was in full accord with expectation.

Previous investigations in this laboratory led to selective techniques for the reduction of 3-α-hydroxyalkylpyridium salts.[13] By judiciously constructing an appropriately substituted pyridinium salt (*viz.*, **5**), reduction would, applying these techniques, lead to the enol ether of amino ketone **3c**. Hofmann rearrangement of 5-bromonicotinamide (**4a**)[14,15] with sodium hypobromite provided the known[16] 3-amino-5-bromopyridine (**4b**). It was necessary to keep the reaction medium at high pH in order to avoid protonation of the

(1) For preliminary communications of this work, see (a) F. E. Ziegler and G. B. Bennett, *Tetrahedron Lett.*, 2545 (1970); (b) *J. Amer. Chem. Soc.*, **93**, 5930 (1971).
(2) National Institutes of Health Career Development Awardee, 1973–1978.
(3) National Institutes of Health Predoctoral Fellow, 1968–1971; taken in part from the Ph.D. thesis of G. B. B., Yale University, 1971.
(4) M.-M. Janot, H. Pourrat, and J. LeMen, *Bull. Soc. Chim. Fr.*, 707 (1954).
(5) For a comprehensive review, see A. I. Scott, *Accounts Chem. Res.*, **3**, 151 (1970).
(6) I. S. Johnson, J. F. Wright, G. H. Svoboda, and J. Vlantes, *Cancer Res.*, **20**, 1016 (1960); G. H. Svoboda, *Llodia*, **24**, 173 (1961).
(7) M. Hesse, "Indolalkaloide in Tabellen," Springer-Verlag, Berlin, 1964, p 30; 1968, p 56.
(8) B. Zsadon and P. Kaposi, *Tetrahedron Lett.*, 4615 (1970).
(9) F. W. Ziegler, J. A. Kloek, and P. A. Zoretic, *J. Amer. Chem. Soc.*, **91**, 2342 (1969).
(10) *Cf.* F. Zymalkowski and P. Messinger, *Arch. Pharm. (Weinheim)*, **300**, 91 (1967).
(11) *Cf.* W. F. Gannon and H. O. House, *Org. Syn.*, 40, 41 (1960); E. G. Meek, J. H. Turnbull, and W. Wilson, *J. Chem. Soc.*, 811 (1953); G. Büchi, P. Kulsa, and R. Rosati, *J. Amer. Chem. Soc.*, **90**, 2448 (1968); and G. F. Wood and J. W. Tucker, *ibid.*, **70**, 2174 (1948).
(12) G. F. Woods, P. H. Griswold, B. H. Armbrecht, D. L. Blumenthal, and K. Plapinger, *ibid.*, **71**, 2028 (1949).
(13) F. E. Ziegler and J. G. Sweeny, *J. Org. Chem.*, **32**, 3216 (1967); *cf.* F. Bohlmann and R. Mayer-Mader, *Tetrahedron Lett.*, 171 (1965).
(14) E. E. Garcia, C. V. Greco, and I. M. Hunsberger, *J. Amer. Chem. Soc.*, **82**, 4431 (1960).
(15) E. Graf, E. Lederer-Ponzer, M. Kopetz, R. Rukrert, and P. Lazlo, *J. Prakt. Chem.*, **138**, 244 (1934).
(16) W. Czuba, *Recl. Trav. Chim. Pays-Bas.*, **82**, 988 (1963).

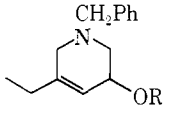
intermediate sodiocarbamic acid, thereby circumventing the premature generation of the free amine, which could be destroyed by bromine.

The initial route to ether **4d**[17] involved hot aqueous sulfuric acid decomposition of the diazonium salt of amine **4b**, followed by low temperature etherification of the resultant 3-bromo-5-hydroxypyridine (**4c**)[18] with diazomethane. With an obvious desire to avoid using copious quantities of diazomethane, conditions were developed for the formation and decomposition of the diazonium salt in methanol, which permitted the direct transformation **4b** → **4d**, although it was never possible to totally avoid the formation of hydroxypyridine **4c**.[19]

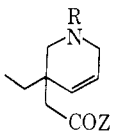
The bromo ether **4d** was converted to its Grignard reagent by entrainment[20] in ether–tetrahydrofuran followed by the addition of acetaldehyde to produce the secondary alcohol **4e**. This reaction proved to be somewhat capricious in that appreciable precipitation occurred upon addition of acetaldehyde, necessitating efficient mechanical agitation to disperse the precipitate. Failure to adhere to this requirement resulted in diminished yields in favor of the production of 3-methoxypyridine. In some instances, 3-ethyl-5-methoxypyridine could be isolated, arising from coupling of the two halides. Near quantitative quaternization of the secondary alcohol **4e** was achieved with benzyl chloride in refluxing acetone.

Reduction of the salt **5** was accomplished with lithium aluminum hydride in tetrahydrofuran at room temperature yielding the enol ether **6** as a mixture of double bond isomers. Direct hydrolysis with 10% aqueous hydrochloric acid provided enone **3c**, identical with the material synthesized by the former route. Although the latter route involved more steps, the overall yields of the two sequences were comparable, with the latter sequence avoiding the use of diazomethane.

With the enone in hand, our efforts were directed toward investigating the Claisen rearrangement. Reduction of enone **3c** with lithium aluminum hydride proceeded without complication, providing the allylic alcohol **7a**.



7a, R = H
b, R = COC_2H_5



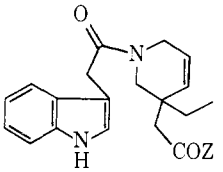
8a, R = $PhCH_2$; Z = $N(CH_3)_2$
b, R = CO_2Ph; Z = $N(CH_3)_2$
c, R = H; Z = OCH_3
d, R = $PhCH_2$; Z = OC_2H_5
e, R = $CO_2C_2H_5$; Z = OC_2H_5

Employing the technique of Eschenmoser,[21] the allylic alcohol was refluxed in dry diglyme in the presence of dimethylacetamide dimethyl acetal which provided the amide **8a** in 45% yield. The infrared spectroscopic data revealed an amide absorption (1635 cm^{-1}), while the nmr exhibited appropriate vinyl absorption and a distinct quaternary ethyl pattern. Moreover, the mass spectrum displayed a molecular ion (*m/e* 286) which gave conspicuous signals in agreement with the loss of ethyl and dimethylcarboxamidomethyl fragments.

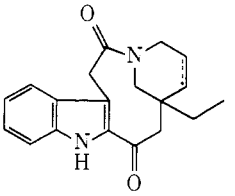
Whereas in the past we have depended upon catalytic hydrogenation for the removal of benzyl groups, the presence of an olefin rendered this method useless. Treatment of the amide with phenyl chloroformate[22] in methylene chloride at room temperature selectively effected debenzylation with no apparent sign of allyl cleavage. Vigorous saponification of the amide urethan **8b** with potassium hydroxide in Methyl Cellosolve followed by esterification with methanolic hydrogen chloride provided the secondary amino ester **8c** as a nondistillable oil.

Because of the vigorous conditions necessary to saponify the amide moiety coupled with the necessity of having to prepare the amide acetal, the possibility of utilizing the Johnson[23] orthoacetate Claisen variant was considered. When the allylic alcohol **7a** was heated at 140° in ethyl orthoacetate in the presence of pivalic acid,[24] the ester **8d** was obtained in 74% yield. Although phenyl chloroformate had been employed in the cleavage of amide **8a**, ethyl chloroformate in refluxing benzene cleanly transformed ester **8d** into its carbamate **8e**, which, because of its lower molecular weight, allowed for the product to be purified by distillation. Subsequent conversion to the secondary amine **8c** was accomplished in the aforementioned fashion.

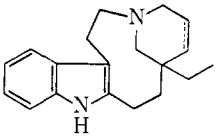
In a sequence which had been applied in other work,[9] amine **8c** was condensed under modified Schotten–Baumann conditions providing amide ester **9a** as



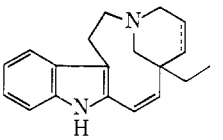
9a, Z = OCH_3
b, Z = OH



10a, 14,15-dehydro
b, 14,15-dihydro



11a, 14,15-dehydro
b, 14,15-dihydro



12a, 14,15-dehydro
b, 14,15-dihydro

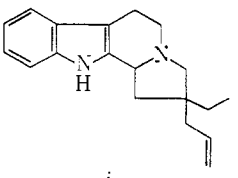
an oil readily characterized by amide (1630 cm^{-1}) and ester (1730 cm^{-1}) absorption. Selective saponification of the ester function was accomplished with 5% aqueous methanolic sodium hydroxide producing the amide acid

(17) K. Clark and K. Rothwell, *J. Chem. Soc.*, 1885 (1960).
(18) H. J. den Hertog, F. R. Schepman, J. de Bruyen, and G. J. E. Thysse, *Recl. Trav. Chim. Pays-Bas*, **69**, 1281 (1950).
(19) These experiments were conducted by Dr. Michael Condon, to whom we are grateful.
(20) J. Overhoff and W. Proost, *Recl. Trav. Chim. Pays-Bas*, **57**, 179 (1938).
(21) D. Felix, K. Gschwend-Steen, A. E. Wick, and A. Eschenmoser, *Helv. Chim. Acta*, **52**, 1030 (1969).
(22) J. O. Hobson and J. G. McClusky, *J. Chem. Soc. C*, 2015 (1967).
(23) W. S. Johnson, L. Werthmann, W. R. Bartlett, T. J. Brocksom, T.-t. Li, D. J. Faulkner, and M. R. Petersen, *J. Amer. Chem. Soc.*, **92**, 741 (1970).
(24) The use of propionic acid gave appreciable esterification[25] (**7b**); *cf.* W. S. Johnson, T. J. Brocksom, P. Loew, D. H. Rich, L. Werthemann, R. A. Arnold, T. Li, and J. D. Faulkner, *J. Amer. Chem. Soc.*, **92**, 4463 (1970), footnote 5. In our experience this problem is more acute in rearrangements wherein the termini of the allylic alcohol are contained in a ring.
(25) L. Brandsma, H. J. T. Bos, and J. F. Arens, "Chemistry of Acetylenes," H. G. Viehe, Ed., Marcel Dekker, New York, N. Y., 1969, p 780, and references cited therein.

9b. Ring closure was effected with polyphosphoric acid at 85° to provide the crystalline tetracyclic ketolactam **10a** in 66% yield.[26] The ultraviolet spectrum revealed a typical 2-acylindole chromophore while the mass spectrum indicated a parent ion, *m/e* 308. Moreover, catalytic reduction of the ketolactam **10a** provided its dihydro derivative **10b**, identical in all respects with a previously[9] prepared sample.

Reduction of ketolactam **10a** with lithium aluminum hydride in refluxing dioxane provided two amines, one of which was identified as 14,15-dehydroquebrachamine (parent *m/e* 280) (**11a**), a degradation product of tabersonine.[27,28] Catalytic reduction of **11a** provided quebrachamine (**11b**). The other product of the hydride reduction was assigned the tetradehydro structure **12a** on the following grounds. The mass spectrum displayed a parent peak at *m/e* 278 with a base peak at M − 29, indicating facile loss of an ethyl fragment. The uv spectrum indicated a simple indole chromophore, which is in accord with expectations, since molecular models demonstrate that the indole ring and the adjacent olefin must be orthogonal. This feature is exemplified in two other spectra observations. The infrared spectrum is devoid of E bands,[29] indicating that the electron pair of the basic nitrogen is equatorial to the dehydropiperidine ring. The nmr spectrum revealed the C-14,15 vinyl protons as a doublet of doublets centered at δ 5.85, while the other olefinic resonances were located in the aromatic region[30] based upon integration and the distinct dissimilarity between this region in **12a** compared with **11a** and **11b**. Prolonged catalytic hydrogenation of **12a** only reduced the C-14,15 double bond leaving the other linkage untouched because of its sterically hindered environment. Thin layer chromatographic analysis showed the absence of quebrachamine **11b** and a single product to which could be assigned structure **12b**.[31]

Returning to the synthesis, reduction of ketolactam **10a** with lithium aluminum hydride in tetrahydrofuran provided amino alcohol **13a** as a mixture of diastereomers, which were directly converted to the quaternary mesylate with methanesulfonyl chloride in pyridine at 0°.[32-35] The mass spectrum of this salt was the same



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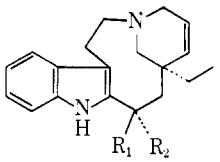
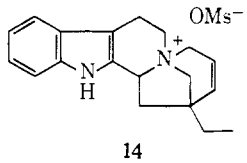


13a, $R_1 = H$; $R_2 = OH$
b, $R_1 = H$; $R_2 = CN$
c, $R_1 = H$; $R_2 = CO_2CH_3$



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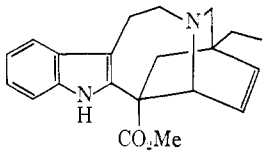
as that of tetracyclic **12a**, resulting from Hofmann elimination in the spectrometer inlet at 300°. Introduction of the one-carbon residue was accomplished by the method of Harley-Mason[32,36] as modified by Kutney;[33,37] employing potassium cyanide in hot dimethylformamide provided as its major reaction product a material less polar (tlc) than other substances present.[38] This substance contained an unconjugated nitrile function (2250 cm^{-1}, strong) and a molecular ion at *m/e* 305.[37] Saponification of the nitrile with potassium hydroxide in diethylene glycol and subsequent esterification with diazomethane provided a crystalline ester (1725 cm^{-1}; *m/e* 338), identical (R_f value and color reaction with Ce^{IV}/H_3PO_4 spray) with the less polar ester obtained from the formic acid–formamide reduction of tabersonine,[28] namely, 14,15-dehydro-16-epivincadine (**13c**).[39]

Exposure of ester **13c** to freshly reduced platinum in the presence of oxygen[41] in ethyl acetate solution effected oxidative cyclization to tabersonine identical by thin layer chromatography, mass, solution infrared, and ultraviolet spectroscopy with natural material.[42] Comparison of the thin layer chromatogram of the total reaction mixture showed other substances, none of which were identical with allocatharanthine (**15**). The



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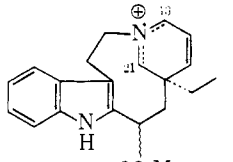

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formation of allocatharanthine requires the presence of the C-13 immonium salt **16** and the ability of the medium to deconjugate the indole double bond exocyclic. These conditions are met in hot acetic acid during

(26) For a discussion of the mechanism of this reaction, see ref 10.
(27) M. Plat, J. Le-Men, M.-M. Janot, J. M. Wilson, H. Budzikiewicz, L. J. Durham, Y. Nakagawa, and C. Djerassi, *Tetrahedron Lett.*, 271 (1962).
(28) M. J. Hoizey, L. Oliver, J. Levy, and J. Le-Men, *ibid.*, 1011 (1971).
(29) E. Wenkert and D. K. Roychandhuri, *J. Amer. Chem. Soc.*, **78**, 6417 (1956); F. Bohlmann, *Chem. Ber.*, **92**, 1798 (1959).
(30) T. Hayashi, *J. Org. Chem.*, **31**, 3253 (1966).
(31) This material was not identical (nmr, tlc) with a product which was previously[9] assigned this structure, the latter being reassigned the structure represented by i. *Cf.* M. Narisada, F. Watanabe, and W. Nagata, *Tetrahedron Lett.*, 3681 (1971).
(32) J. Harley-Mason and A. Ur-Rahman, *Chem. Commun.*, 208 (1967).
(33) J. P. Kutney, W. J. Cretney, P. LeQuesne, B. McKague, and E. Piers, *J. Amer. Chem. Soc.*, **92**, 1712 (1970).
(34) J. P. Kutney, N. Abdurahman, C. Gletsos, P. LeQuesne, E. Piers, and L. Vlattas, *ibid.*, **92**, 1727 (1970).
(35) It is presumably the same type of intermediate (*i.e.*, **14**) which produces i *via* Hofmann elimination ($\Delta^{13,14}$) and can only produce **12a** *via*[16,17] elimination during the lithium aluminum hydride–dioxane reduction of **10b** and **10a**, respectively.
(36) G. H. Foster, J. Harley-Mason, and W. R. Waterfield, *Chem. Commun.*, 21 (1967); G. H. Foster and J. Harley-Mason, *ibid.*, 1440 (1968).
(37) J. P. Kutney and F. Bylsma, *J. Amer. Chem. Soc.*, **92**, 6090 (1970).
(38) A second nitrile (2235 cm^{-1}, weak; *m/e* 305) could be isolated which was converted to its ester (1735 cm^{-1}; *m/e* 338), whose mass spectrum did not agree with that of 14,15-dehydrovincadine (epi C-16, **13c**) (*vide infra*). In addition, the substance failed to oxidize with $Pt-O_2$. In view of the complications which can arise in these displacements,[32,36] a structural assignment could not be made with certainty.
(39) This alkaloid has recently[40] been isolated from *Amsonia tabernaemontana*, constituting another case of a natural product being synthesized prior to its isolation.
(40) B. Zsadon, J. Tamás, and M. Szilasi, *Chem. Ind. (London)*, 229 (1973).
(41) D. Schumann and H. Schmid, *Helv. Chim. Acta*, **46**, 1996 (1963); *cf.* J. P. Kutney, E. Piers, and R. T. Brown, *J. Amer. Chem. Soc.*, **92**, 1700 (1970).
(42) We would like to extend our appreciation to Professors J. Le-Men and A. I. Scott for samples of (−)-tabersonine.

the equilibration of tabersonine and allocatharanthine.[43] Treatment of the total oxidation mixture with acetic acid at room temperature failed to provide allocatharanthine. If indeed deconjugation could be achieved under these conditions, the presence of the C-13 immonium salt would be precluded. It appears that ester **13c**, as is the case with related systems,[44] undergoes kinetic oxidation to form the unconjugated immonium salt.

Experimental Section

Microanalyses were performed by Galbraith Laboratories and Bernhardt Microanalytische Laboratorium. Melting points were obtained on a Fisher-Johns apparatus and are corrected. Infrared (ir) spectra were recorded on Perkin-Elmer Models 421 and 236B spectrometers; in general only bands characteristic of the functional groups present are listed. The nuclear magnetic resonance (nmr) spectra were obtained with a Jeolco Model JNM-MH-100 and Varian Models A-60, A-60A, and HA-100 spectrometers. Ultraviolet (uv) spectra were taken on a Bausch and Lomb Spectronic 505 recording spectrometer. Mass spectra were determined on a Hitachi RMU-6E instrument.

Except where noted, solvents were reagent grade and were used as received. Thin layer chromatograms (tlc) were made with Brinkman silica gel G and developed with 20% methanol in benzene unless otherwise noted. Florisil (60–100 mesh) and Fisher neutral alumina (activity I, 80–200 mesh) were used in preparing column chromatograms unless otherwise indicated. In all work-up procedures the drying process involved swirling over anhydrous magnesium sulfate and filtering prior to evaporation.

1-Benzyl-3-oxo-5-methoxy-1,2,3,6-tetrahydropyridine (3b). To a solution of potassium *tert*-butoxide [prepared by dissolving potassium (8.75 g, 0.22 mol) in a dry *tert*-butyl alcohol (500 ml) and dry ether (500 ml)] at 0° was added dropwise a solution of 50.0 g (0.20 mol) of ethyl *N*-benzyl-*N*-acetonylglycinate[11] in 50 ml of dry ether. After stirring at 0° for 2 hr and room temperature for 18 hr, the mixture was evaporated to dryness at reduced pressure.[45] The residue was triturated with 500 ml of ether, filtered, and quickly dissolved in 150 ml of 2 *N* aqueous acetic acid. Immediately following dissolution, the diketone began to precipitate out of solution. The mixture was treated with 50 ml of water and was refrigerated overnight to promote further crystallization.

After drying to constant weight in a vacuum desiccator over phosphorus pentoxide, the diketone (42.6 g crude) was dissolved in 150 ml of dry methanol and to the cold stirred solution was added an ethereal solution of excess diazomethane. The mixture was stirred for 0.5 hr and the excess diazomethane decomposed with glacial acetic acid. After evaporation to dryness, the residue was boiled overnight with 1 l. of dry ether. The ether solution was decanted and evaporated to yield the crude product. Recrystallization from ether–hexane led to 16.5 g (38%) of light yellow crystals: mp 109.5–110°; ir ($CHCl_3$) 1660 and 1620 cm^{-1}; nmr ($CDCl_3$) δ 3.18 (2 H, s), 3.25 (2 H, s), 3.67 (2 H, s), 3.74 (3 H, s), 5.45 (1 H, s), and 7.33 (5 H, s).

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.85; H, 6.97; N, 6.45. Found: C, 71.67; H, 6.94; N, 6.30.

1-Benzyl-3-oxo-5-ethyl-1,2,3,6-tetrahydropyridine (3c) (from 3b). To a stirred solution of 33 ml of 0.10 *N* ethereal ethylmagnesium bromide maintained at 0° under nitrogen was added dropwise a solution of 4.50 g (0.021 mol) of enol ether **3b** in 20 ml of tetrahydrofuran. After 0.5 hr of additional stirring, the mixture was treated with 40 ml of 10% aqueous hydrochloric acid and stirred for several hours at room temperature.

The aqueous layer was removed, washed twice with ether, neutralized with 50% aqueous sodium hydroxide at 0°, and extracted with ether. The extracts were dried and evaporated to give a yellow oil which solidified on standing. Recrystallization from ether–hexane afforded 3.35 g (80%) of light yellow needles: mp 89–89.5°; ir (KBr) 1670 and 1625 cm^{-1}; nmr ($CDCl_3$) δ 1.05 (3 H, t, J = 7 Hz), 2.12 (2 H, q, J = 7 Hz), 3.06 (4 H, s broad), 3.50 (2 H, s), 5.75 (1 H, m), and 7.05 (5 H, s).

Anal. Calcd for $C_{14}H_{17}NO$: C, 78.09; H, 7.97; N, 6.51. Found: C, 78.30; H, 7.73; N, 6.48.

3-Amino-5-bromopyridine (4b). To a solution of 79 g (1.98 mol) of sodium hydroxide in 660 ml of water at 20° was successively added 63.0 g (0.39 mol) of bromine and 66 g (0.33 mol) of 5-bromonicotinamide, **4a**,[14] and the mixture was stirred until homogeneous. The solution was subsequently heated at 70–80° for 0.75 hr, cooled, acidified, and washed with ether. After neutralization, the aqueous phase was extracted with ether, and the extracts were dried and evaporated affording 45.5 g (79%) of tan crystals, mp 64–67° (lit.[16] mp 66–67°).

3-Bromo-5-hydroxypyridine (4c). A mixture of 6.4 ml of concentrated sulfuric acid, 8.7 ml of water, 15 g of crushed ice, and 5.0 g (0.03 mol) of 3-amino-5-bromopyridine (**4b**) was stirred at 0–5° until homogeneous. A solution of 2.04 g (0.03 mol) of sodium nitrite in 5 ml of water was added, and after an additional 10 min stirring, the cold solution was added dropwise to a boiling mixture containing 20 ml of concentrated sulfuric acid and 15 ml of water. The resulting solution was cooled, poured onto ice water, neutralized with 5% aqueous sodium hydroxide to pH 8, saturated with brine, and extracted thoroughly with ethyl acetate. The extracts were combined, dried, and evaporated to give 4.92 g (98%) of a light brown solid, mp 165–167° (lit.[18] mp 166.5–167.5°).

3-Bromo-5-methoxypyridine (4d). To an excess of ethereal diazomethane at −15° was added dropwise a solution of 4.0 g (0.023 mol) of hydroxypyridine **4c** in 40 ml of dry *tert*-butyl alcohol. The solution was allowed to warm slowly to room temperature and the excess diazomethane was decomposed with glacial acetic acid. After evaporation at reduced pressure the residue was dissolved in chloroform, and the resulting solution was washed with 5% aqueous sodium hydroxide, dried, and evaporated to yield a light brown oil. Distillation (bp 80–82° (2 mm)) provided 2.77 g (74%) of a clear viscous liquid which crystallized uponn standing at room temperature, mp 30–32° (lit.[17] mp 33.5–34°).

3-Bromo-5-methoxypyridine (4d) Directly from Amine 4b. To a cooled stirred solution of 26.0 g (0.15 mol) of 3-amino-5-bromopyridine (**4b**) in 200 ml of MeOH was added 16.5 ml of concentrated sulfuric acid at such a rate to maintain the reaction temperature between 0 and 5°. To the resulting suspension was added 11.80 g (0.16 mol) of solid sodium nitrite and the reaction mixture was stirred at 0–5° for 2 hr. The cooling bath was removed as the reaction mixture was allowed to warm on its own as gas evolution commenced and the reaction mixture became exothermic. The temperature was maintained between 35 and 40° with external cooling to moderate the reaction. When gas evolution had subsided the mixture was refluxed for 45 min. The reaction mixture was poured onto ice and adjusted to pH 10 with concentrated aqueous sodium hydroxide, saturated with salt, and thoroughly extracted with chloroform. The combined extracts were dried and concentrated to yield 17.5 g (62%) of crude 5-bromo-5-methoxypyridine. Distillation (bp 65–67° (0.3 mm)) afforded 13.1 g (46%) of pure ether **4d**: mp 30–32°, mmp 30–33°.

The alkaline aqueous solution was adjusted to pH 7–8 with hydrochloric acid and thoroughly extracted with ethyl acetate. The combined extracts were dried and evaporated to give 8.64 g (31%) of crude solid 5-bromo-3-hydroxypyridine, mp 164–167°.

3-(1′-Hydroxyethyl)-5-methoxypyridine (4e). Several drops of ethyl bromide were added to 3.2 g (0.13 mol) of magnesium turnings covered with 15 ml of dry ether. Once reaction had begun, a solution of 5.0 g (0.026 mol) of bromopyridine **4d** and 7.0 g (0.064 mol) of ethyl bromide in 60 ml of dry 2:1 ether–tetrahydrofuran was added at such a rate as to maintain a gentle reflux. After the addition was complete, a solution of 4.65 g (0.043 mol) of ethyl bromide in 20 ml of dry ether was added at such a rate as to maintain reflux. After 1 hr of additional refluxing, the mixture was cooled to 0° and 11.7 g (0.267 mol) of dry acetaldehyde was added in 40 ml of dry 1:1 ether–tetrahydrofuran with vigorous stirring. Following an additional hour of stirring at room temperature, the reaction mixture was extracted thoroughly with 10% aqueous hydrochloric acid and the acid extracts were washed several times with ethyl acetate.

The aqueous solution was basified in the cold with 50% aqueous sodium hydroxide, neutralized with saturated aqueous ammonium chloride solution, and thoroughly extracted with chloroform, the combined extracts being dried and evaporated to give a dark liquid. Distillation afforded a forerun of 3-methoxypyridine (bp 29–30° (30 μ)) in 5–20% yield and 3.06 g (75%) of 3-(1′-hydroxyethyl)-5-methoxypyridine: bp 113–122° (30 μ); mp 44.5–45.5°; nmr ($CDCl_3$) δ 1.45 (3 H, d, J = 6.5 Hz), 3.82 (3 H, s), 4.70 (1 H, broad s,

(43) A. I. Scott and C. C. Wei, *J. Amer. Chem. Soc.*, 94, 8266 (1972), and references cited therein.

(44) For selective oxidations in related systems, see G. C. Crawley and J. Harley-Mason, *Chem. Commun.*, 685 (1971).

(45) Failure to evaporate all the *tert*-butyl alcohol resulted in substantially lower yields.

concentration dependent), 5.10 (1 H, q, J = 6.5 Hz), 7.15 (2 H, d, J = 3 Hz) and 8.12 (1 H, t, J = 3 Hz).

Anal. Calcd for $C_8H_{11}NO_2$: C, 62.72; H, 7.24; N, 9.14. Found: C, 62.96; H. 7.48; N, 8.95.

In some experiments a small quantity of material was obtained by preparative gas chromatography and identified by nmr as 3-ethyl-5-methoxypyridine; nmr ($CDCl_3$) δ 1.27 (3 H, t, J = 7.5 Hz), 2.65 (2 H, q, J = 7.5 Hz), 3.83 (3 H, s), 7.05 (1 H, m), and 8.14 (2 H, m).

1-Benzyl-3-(1′-hydroxyethyl)-5-methoxypyridinium Chloride (5). A mixture of 26.0 g (0.17 mol) of pyridine **4e** and 22.7 g (0.18 mol) of benzyl chloride in 250 ml of acetone was refluxed overnight. Evaporation of the solvent followed by trituration of the residue with ether gave 47.5 g (98%) of a white solid, mp 144.5–145°. Recrystallization from acetone provided an analytical sample, mp 149.5–150°.

Anal. Calcd for $C_{15}H_{18}ClNO_2$: C, 64.40; H, 6.48; N, 5.01. Found: C, 54.32; H, 6.66; N, 4.88.

1-Benzyl-3-ethylidene-5-methoxy-1,2,3,6-tetrahydropyridine (6). To a cooled solution of 5.0 g (0.018 mol) of pyridinium chloride **5** in 500 ml of dry tetrahydrofuran was slowly added 6.8 g (0.018 mol) of solid lithium aluminum hydride portionwise, after which the mixture was stirred at room temperature for 4 hr. After decomposition of the excess hydride with saturated aqueous sodium sulfate solution, the inorganic salts were removed by filtration and washed well with hot tetrahydrofuran. The combined filtrates were dried and evaporated to afford 4.02 g (97.5%) of a crude light yellow oil (single spot on tlc) as a mixture of ethylidene isomers; ir ($CHCl_3$) 1660 and 1625 cm^{-1}; nmr ($CDCl_3$) δ 1.95 (3 H, m), 3.14 (4 H, s), 3.40–3.95 (2 H, m), 3.61 (3 H, s), 5.10 (1 H, q, J = 7 Hz), 5.35 (0.2 H, s), 5.60 (0.8 H, s), and 7.37 (5 H, m).

1-Benzyl-3-oxo-5-ethyl-1,2,3,6-tetrahydropyridine (3c) from 6. A solution of 0.50 g (2.18 mmol) of crude enol ether was refluxed for 18 hr in a mixture of 25 ml of methanol and 2 ml of 10% aqueous hydrochloric acid. After evaporation of the solvent, the residue was dissolved in chloroform and washed with saturated aqueous sodium bicarbonate solution. The organic phase was dried and evaporated to give 0.48 g (100%) of light yellow needles. Recrystallization from ether–hexane gave light yellow needles identical with the material prepared from enol ether **3b**; mp 89–90°; mmp 88–90°.

1-Benzyl-3-hydroxy-5-ethyl-1,2,3,6-tetrahydropyridine (7a). To a cold stirred solution of 1.74 g (0.046 mol) of lithium aluminum hydride in 20 ml of dry tetrahydrofuran was slowly added a solution of 5.0 g (0.023 mmol) of ketone **3c** in 20 ml of dry tetrahydrofuran and the mixture stirred at room temperature for 1 hr. Following decomposition with saturated, aqueous sodium sulfate solution and filtration, the filter cake was washed several times with hot tetrahydrofuran. The combined filtrates were dried and evaporated to afford 5.08 g (100%) of a crude pale yellow oil which showed one spot with trace contaminants on an analytical thin layer plate. The material was used without further purification: ir ($CHCl_3$) 3550–3100 cm^{-1}; nmr ($CDCl_3$) δ 0.98 (3 H, t, J = 7.5 Hz), 1.92 (2 H, q, J = 7.5 Hz), 5.47 (1 H, m, vinyl), and 7.25 (5 H, s).

1-Benzyl-3-(*N*-*N*-dimethylcarboxamidomethyl)-3-ethyl-1,2,3,6-tetrahydropyridine (8a). A mixture of 10.2 g (0.046 mol) of allylic alcohol **7a** and 30 ml of 1-dimethylamino-1,1-dimethoxyethane in 30 ml of dry diglyme was heated with stirring in a 100-ml flask fitted with a variable takeoff distilling head. The distillate was removed until a vapor temperature of 161° was attained, and after 48 hr of additional refluxing, the solvent was removed at reduced pressure. Distillation (bp 162–167° (100 μ)) gave 6.0 g (45%) of a clear yellow liquid: ir ($CHCl_3$) 1635 cm^{-1}; nmr ($CDCl_3$) δ 0.83 (3 H, t, J = 7.5 Hz), 1.68 (2 H, q, J = 7.5 Hz), 2.10–2.80 (6 H, m), 2.85 (3 H, s), 2.95 (3 H, s), 3.55 (2 H, s), 5.65 (2 H, s), and 7.32 (5 H, s).

Anal. Calcd for $C_{18}H_{26}N_2O$: C, 75.48; H, 9.15; N, 9.78. Found: C, 75.72; H, 9.34; N, 9.53.

1-Benzyl-3-(carbethoxymethyl)-3-ethyl-1,2,3,6-tetrahydropyridine (8d). A mixture of 50.0 g (0.23 mol) of alcohol **7a**, 300 ml of triethyl orthoacetate, and 1.25 g (12.2 mmol) of pivalic acid was heated in a 500-ml flask fitted with a variable takeoff distilling head. The distillate was removed until a vapor temperature of 140° was achieved. After an additional 20 hr of refluxing, the solvent was evaporated and distillation (bp 127–129° (0.01 mm)) afforded 49.0 g (74.5%) of a light yellow oil; nmr ($CDCl_3$) δ 0.80 (3 H, t, J = 7.5 Hz), 1.16 (3 H, t, J = 7 Hz), 1.52 (2 H, q, J = 7.5 Hz), 2.28 (1 H, d, J = 11 Hz), 2.44 (2 H, s), 2.54 (1 H, d, J = 11 Hz), 2.78 (1 H, d, J = 17 Hz), 3.00 (1 H, d, J = 17 Hz), 3.52 (2 H, s), 4.05 (2 H, q, J = 7 Hz), 5.62 (2 H, s), and 7.26 (5 H, m).

Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.14; H, 8.97; N, 4.76.

1-Carbophenoxy-3-(*N*,*N*-dimethylcarboxamidomethyl)-3-ethyl-1,-2,3,6-tetrahydropyridine (8b). To a stirred solution of 8.45 g (0.03 mol) of amide **8a** in 80 ml of methylene chloride at 0° under nitrogen was added a solution of 5.5 g (0.035 mol) of redistilled phenyl chloroformate in 20 ml of methylene chloride. After stirring for an additional 3 hr at room temperature, the solution was successively washed with 8% aqueous sodium hydroxide, water, and 10% aqueous hydrochloric acid, dried, and evaporated to yield a yellow oil. Distillation (bp 210–215° (0.02 mm)) gave 4.57 g (49%) of a clear yellow liquid which crystallized upon standing, mp 66.5–67°.

If instead of distillation the crude oil was chromatographed on Florisil (20:1) eluting first with hexane and benzene to remove impurities, and subsequently with 10% ether–benzene, evaporation of the solvent provided 6.61 g (71%) of the desired carbamate: ir ($CHCl_3$) 1717 and 1645 cm^{-1}; nmr ($CDCl_3$) δ 0.94 (3 H, t, J = 7.5 Hz), 1.77 (2 H, q, J = 7.5 Hz), 2.47 (2 H, s), 2.97 (3 H, s), 3.05 (3 H, s), 3.62 (2 H, m), 4.10 (2 H, s), 5.80 (2 H, m), and 7.29 (5 H, m);

Anal. Calcd for $C_{18}H_{24}N_2O_3$: C, 68.31; H, 7.65; N, 8.86. Found: C, 68.53; H, 7.53; N, 8.78.

1-Carbethoxy-3-(carbethoxymethyl)-3-ethyl-1,2,3,6-tetrahydropyridine (8e). To a solution of 10.4 g (0.036 mol) of ester **8d** in 200 ml of dry benzene at 0° was added a solution of 5.86 g (0.054 mol) of ethyl chloroformate in 20 ml of benzene, and the resulting solution was refluxed for 18 hr. After evaporation of the solvent, distillation (bp 133–134° (1 mm)) afforded 8.63 g (90%) of a clear liquid: ir ($CHCl_3$) 1730 and 1695 cm^{-1}; nmr ($CDCl_3$) δ 0.93 (3 H, t, J = 7.5 Hz), 1.28 (6 H, t, J = 7 Hz), 1.44 (2 H, q, J = 7.5 Hz), 2.36 (2 H, s), 3.47 (2 H, s), 3.90 (2 H, s), 4.14 (2 H, q, J = 7 Hz), 4.17 (2 H, q, J = Hz), and 5.73 (2 H, s).

Anal. Calcd for $C_{14}H_{23}NO_4$: C, 62.41; H, 8.61; N, 5.20. Found: C, 62.29; H, 8.72; N, 5.35.

3-(Carbomethoxymethyl)-3-ethyl-1,2,3,6-tetrahydropyridine (8c). A mixture of 3.43 g (10.4 mmol) of carbamate **8b** and 2.65 g (0.065 mol) of potassium hydroxide was refluxed under nitrogen in 40 ml of Methyl Cellosolve for 48 hr. After evaporation of the solvent at reduced pressure and addition of 40 ml of dry methanol, the solution was saturated with hydrogen chloride gas and subsequently stirred under nitrogen at room temperature for 18 hr. A suspension of excess sodium bicarbonate in methylene chloride was added slowly followed by the evaporation of the solvent. The residue was thoroughly extracted with chloroform, and the extracts were washed with 5% aqueous sodium hydroxide, dried, and evaporated to yield 1.633 g (82.5%) of a tan liquid whose spectral properties were in accord with the desired product. All attempts at purification by chromatography or crystallization met with failure. The crude amino ester could not be distilled without extensive decomposition and was used in the subsequent reaction without further purification: ir ($CHCl_3$) 3450 and 1730 cm^{-1}; nmr ($CDCl_3$) δ 0.88 (3 H, t, J = 7 Hz), 1.52 (2 H, q, J = 7 Hz), 2.40 (2 H, s), 2.85 (2 H, m), 3.28 (2 H, s), 3.63 (3 H, s), and 5.67 (2 H, s).

Carbamate **8e** was converted to amino ester **8c** in 94% yield in the manner described (*vide supra*) for carbamate **8b**.

1-(Indol-3′-ylacetyl)-3-(carbomethoxymethyl)-3-ethyl-1,2,3,6-tetrahydropyridine (9a). To a cold stirred solution of 3.3 g (0.018 mol) of crude amino ester **8c** in 80 ml of tetrahydrofuran was added 1.00 g (0.019 equiv) of sodium carbonate in 40 ml of water followed by 3.65 g (0.019 mol) of 3-indoleacetyl chloride.[46] After stirring at 0° for 0.5 hr, an additional 2.0 g of sodium carbonate was added, and the mixture was stirred an additional 2 hr at 0° and 0.5 hr at room temperature. Removal of the aqueous phase, drying, and evaporation at reduced pressure led to a residue which was dissolved in 150 ml of chloroform and washed successively with 5% aqueous sodium hydroxide, water, and 10% hydrochloric acid. The chloroform was dried and evaporated to give 5.32 g (87%) of a dark liquid which showed one spot on an analytical thin layer plate which was used without further purification: ir ($CHCl_3$) 3490, 1730, and 1630 cm^{-1}.

1-(Indol-3′-ylacetyl)-3-(carboxymethyl)-1,2,3,6-tetrahydropyridine (9b). A mixture of 2.26 g (6.67 mmol) of crude lactam ester **9a** and 50 ml of 5% aqueous sodium hydroxide was refluxed in 80 ml of methanol for 2.5 hr. After evaporation of the methanol, the basic aqueous solution was washed with methylene chloride, acidified with 10% aqueous hydrochloric acid, and thoroughly extracted with methylene chloride. The organic washes were combined,

(46) E. Shaw and D. W. Wooley, *J. Biol. Chem.*, 203, 979 (1953).

dried, and evaporated to yield 1.30 g (60%) of a light yellow foam. All attempts to crystallize the crude product met with failure. Consequently, the crude material was used without further purification: ir ($CHCl_3$) 3480, 3150–2800, 1715, and 1635 cm^{-1}.

5,16-Dioxo-14,15-dehydroquebrachamine (10a). An intimate mixture of 0.90 g (2.76 mmol) of lactam acid and 90 g of polyphosphoric acid was heated with stirring at 85° for 20 min, during which time the color of the reaction mixture went from yellow to plum red. After the addition of ice water, the solution was extracted with chloroform, and the extracts were washed with 5% aqueous sodium hydroxide, dried, and evaporated to yield a light yellow foam. Recrystallization from a minimum of acetone gave 0.545 g (66%) of white crystals, mp 220–221°. An analytical sample was recrystallized from acetone as colorless crystals: mp 225–226°; ir ($CHCl_3$) 3465 and 1640 cm^{-1}; uv max (CH_3OH) 243 (18,100) and 319 (20,400) nm; mass spectrum (70 eV) *m/e* (rel intensity) 308 (37.3), 280 (10), 279 (5.6), 265 (5.6), 251 (4), 237 (5), 223 (3.3), 222 (3.9), 210 (3.5), 208 (3.9), 201 (6), 196 (5), 194 (3.7), 184 (7.6), 173 (13.6), 172 (15.5), 171 (13.6), 168 (10), 159 (26.4), 158 (16.3), 157 (21.8), 156 (23.6), 155 (7.6), 154 (5.5), 152 (5.1), 150 (10), 149 (43.6), 143 (36.4), 131 (12.7), 130 (34.6), 129 (43.6), 128 (25.5), 122 (11.8), 121 (40.9), 109 (23.6), 108 (100).

Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 73.74; H, 6.43; N, 8.87.

5,16-Dioxoquebrachamine (10b). A solution of 30.8 mg (0.10 mmol) of ketolactam **10a** in 3 ml of 40% acetone–ethanol was reduced at atmospheric pressure under hydrogen using 5 mg of 10% palladium on charcoal as catalyst. After filtration through Celite, the solvent was evaporated to give 30.9 mg (100%) of white solid which was recrystallized from acetone: mp 226–228°, mmp 226–228°.[9]

14,15-Dehydroquebrachamine (11a) and 14,15,16,17-Dehydroquebrachamine (12a). To a stirred suspension of 1.0 g (0.026 mol) of lithium aluminum hydride in 200 ml of refluxing dry 1,4-dioxane was added dropwise a solution of 0.50 g (1.62 mmol) of ketolactam **10a** in 50 ml of dry 1,4-dioxane and the reaction mixture was refluxed for 18 hr. After cooling and decomposition of the excess hydride with saturated aqueous sodium sulfate solution, the mixture was filtered through Celite, and the filter cake was washed thoroughly with hot tetrahydrofuran. The combined filtrates were dried and evaporated to yield 0.45 g of a yellow oil which was chromatographed on a Brinkman F-254 2-mm preparative thin layer plate using 20% methanol–benzene as the moving phase. Isolation of the products was accomplished by extraction of the silica gel with methanol, filtration, and evaporation of the solvent.

The material with the larger R_f value (0.90), 14,15-dehydroquebrachamine **11a**, was obtained as an amorphous solid, 0.225 g (41%). Attempts at crystallization or sublimation were unsuccessful: ir ($CHCl_3$) 3480, 3020, 2830, 2760, 2710, and 1465 cm^{-1}; nmr ($CDCl_3$) δ 0.69 (3 N, t, J = 6.5 Hz), 0.95 (2 H, q, J = 6.5 Hz), 1.62 (2 H, m), 2.20–3.80 (10 H, m), 5.29 (1 H, d, J = 10 Hz), 5.80 (1 H, dd, J = 3 and 10 Hz), 7.10 (3 H, m), and 7.50 (2 H, m); uv λ_{max} (CH_3OH) 231 (ϵ 30,750), 287 (6200), and 295 (5700) nm; mass spectrum (70 eV) *m/e* (rel intensity) 280 (38), 251 (19.8), 223 (15.7), 210 (15.7), 205 (8.4), 185 (9.2), 157 (30.5), 156 (31), 150 (19), 145 (40), 144 (20.5), 143 (100), 135 (11.6), 129 (12.5), 124 (27), 122 (31), 115 (16.2), 107 (35), 101 (17.5), 85 (8.4), 79 (17.5). This material was identical on tlc analysis (R_f and 1% ceric ammonium nitrate–85% H_3PO_4 color response) with material prepared by the degradation of tabersonine.[27,28]

A second product (R_f value 0.50), 14,15,16,17-dehydroquebrachamine (**12a**), was crystallized from ethanol–water to give 0.168 g (30.5%) of a white crystalline solid: mp 151–152°; ir ($CHCl_3$) 3480, 3020, and 1470 cm^{-1}; nmr ($CDCl_3$) δ 0.96 (3 H, t, J = 7 Hz), 5.55 (1 H, d, J = 10 Hz), 5.80 (1 H, d, J = 10 Hz), and 6.90–7.30 (7 H, m); uv λ_{max} (CH_3OH) 226 (ϵ 37,200), 282 (8900), and 291 (6820) nm; mass spectrum (70 eV) *m/e* (rel intensity) 279 (20.9), 277 (6.6), 253 (7.8), 250 (20.9), 249 (100), 248 (6.9), 247 (4.6), 237 (32), 235 (36), 234 (8.8), 233 (4.3), 221 (4.3), 209 (3.6), 208 (7), 207 (5.9), 206 (5.3), 205 (4.2), 204 (3.9), 183 (3.2), 155 (1.9), 154 (3.6), 143 (1.9), 115 (3.4), 111 (3.9), 110.5 (6.6), 110 (3.7), 77 (3.6).

Anal. Calcd for $C_{19}H_{22}N_2$: C, 81.97; H, 7.97; N, 10.06. Found: C, 81.74; H, 8.20; N, 9.84.

14,15-Dehydro-16-hydroxyquebrachamine (13a). To a stirred suspension of 1.20 g (31.8 mmol) of lithium aluminum hydride in 40 ml of dry tetrahydrofuran at 0° was slowly added a solution of 0.60 g (1.94 mmol) of ketolactam **10a** in 40 ml of dry tetrahydrofuran. After 2 hr of stirring at room temperature, the excess hydride was decomposed with saturated aqueous sodium sulfate solution, and the inorganic salts were removed by filtration and washed several times with hot tetrahydrofuran. The combined filtrates were evaporated to give 0.550 g of a viscous yellow oil.

Chromatography on Florisil (20:1), eluting first with hexane and hexane–benzene to remove impurities, gave upon elution with benzene 0.11 g (19.5%) of one diastereomeric alcohol (**3a**) as a yellow oil: ir ($CHCl_3$) 3475, 3600–3200, 3065, 3015, 2975, 2930, 2815, 2790, and 2740 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 296 (100), 280 (7), 279 (6), 278 (9), 277 (5.5), 267 (14.5), 251 (15), 249 (11.5), 237 (15.5), 173 (22.5), 172 (20), 168 (21.5), 167 (19.5), 158 (25.5), 156 (45), 154 (34), 144 (71), 143 (29), 138 (24), 136 (27.5), 135 (31.5), 130 (45), 124 (30), 123 (32.5), 122 (56.5), 108 (31.5), 107 (22), 95 (28).

Elution with 1–5% ether–benzene provided 0.257 g (44.5%) of a second diastereomeric alcohol as a light yellow foam: ir ($CHCl_3$) 3460, 3500–3150, 2985, 2950, 2905, 2860, 2840, 2790, 2780, 2735, 2715, and 2650 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 296 (22.7), 280 (1.9), 279 (2.3), 278 (1.9), 267 (1.5), 173 (23.8), 168 (38.2), 167 (32.2), 166 (23.5), 165 (31.8), 155 (20), 154 (100), 153 (48.5), 152 (42), 124 (36), 123 (19.3), 97 (29.2), 96 (19.7), 95 (38).

16-Cyano-14,15-dehydroquebrachamine (13b). To an ice-cooled solution of 2.44 g (8.24 mmol) of alcohols **13a** in 2 ml of pyridine was added 1.13 g (9.8 mmol) of ice-cold methanesulfonyl chloride, and the mixture was allowed to stand at 0° for 18 hr.[33] The solvent was evaporated under a stream of nitrogen with the aid of slight warming, with the last traces removed at reduced pressure. The residue was washed twice with ether, treated with 3 ml of water and 6 ml of 6 *N* aqueous ammonium hydroxide, and thoroughly extracted with chloroform. Drying and evaporation of the chloroform extracts provided a dark red semisolid. Decolorization with activated charcoal in refluxing methanol afforded after filtration, evaporation, and crystallization from methanol–acetone 1.22 g (39.5%) of a light tan solid, mp 285 dec; the mass spectrum was identical with that displayed by amine **12a**. No attempt was made at further characterization or purification but rather was used as obtained in the cyanide cleavage.

To a mixture of 1.1 g (0.017 mol) of potassium cyanide in 150 ml of dimethylformamide was added 1.27 g (3.4 mmol) of crude mesylate salt **14** and the mixture heated at 145° for 2 hr. After evaporation of the solvent at reduced pressure, 10 ml of 10% aqueous potassium carbonate was added and the solution thoroughly extracted with ether. The ether extracts were dried and evaporated to yield a dark oil. Chromatography on Florisil (20:1) gave upon elution with ether a fraction containing nitrile which was rechromatographed on a 200 × 200 × 2 mm Brinkman F-254 preparative silica gel plate with 40% ether–pentane as the moving phase. The material (R_f 0.85) was isolated by ether extraction providing 455 mg of nitrile (one spot tlc) as a clear oil (44%) homogeneous by tlc: ir ($CHCl_3$) 3465, 3450–3250, 2250 (CN), and 1610 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 306 (10), 305 (39), 223 (6), 205 (7), 182 (10), 181 (8), 152.5 (3), 124 (100), and 95 (57).

14,15-Dehydro-16-epivincadine (13c). A mixture of 260 mg (0.85 mmol) of nitrile **13b** and 0.5 g of potassium hydroxide was heated in 2.5 ml of diethylene glycol at 145° for 6 hr. The solution was cooled, diluted with 10 ml of methanol, and subsequently treated with saturated methanolic hydrogen chloride until slightly acidic. An ethereal solution of excess diazomethane was immediately added and the resulting mixture was allowed to stand in an ice–water bath for 15 min. This sequence of acidification with methanolic hydrogen chloride and subsequent treatment with excess ethereal diazomethane was performed two more times, after which the excess diazomethane was removed with the aid of a nitrogen stream and a warm-water bath. The resulting residue was shaken with 10% aqueous potassium carbonate (10 ml) and extracted thoroughly with ether. The extracts were dried and evaporated and the residue was chromatographed over neutral alumina (20:1). Elution with ether provided 253 mg (88%) of ester **13c** as a clear oil, homogeneous by tlc, which crystallized upon standing at 0°. Recrystallization from ether–hexane gave a white solid: mp 138–140°; ir ($CHCl_3$) 1725 cm^{-1}; mass spectrum *m/e* 338 (parent).

This substance was identical (tlc) with material prepared from tabersonine.[27,28]

(±)-Tabersonine (1). To a suspension of platinum, liberated by the hydrogenation of 150 mg of platinum oxide in 2 ml of ethyl acetate, was added a solution of 50.0 mg (0.144 mmol) of ester **13c** in 4 ml of ethyl acetate, and the mixture was stirred at atmospheric pressure of oxygen for 3 hr. The platinum catalyst was removed by filtration and the solvent evaporated to give a yellow wax which was separated on a Brinkman F-254 200 × 200 × 2 mm silica gel preparative thin layer plate using 40% ether–pentane as the moving

phase. Isolation of the products was accomplished by extraction of the silica gel with ether, filtration, and evaporation of the ether. The material with the largest R_f value (0.91), ester **3c**, was recovered in 6% yield (3 mg). The material with the second largest R_f value (0.73), (±)-tabersonine, was isolated as a clear semisolid, 15 mg (30.2%), and was identical with a sample of natural origin by comparative tlc, solution infrared, ultraviolet, and mass spectrometry.

When the polar material isolated from the preparative tlc plate (25 mg) was stirred overnight in 5% aqueous acetic acid, an additional 7 mg (total yield of 44.5%) of tabersonine was obtained.

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A Carbon-13 Magnetic Resonance Study of Aminoglycoside Pseudotrisaccharides. The Gentamicin Antibiotics

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Abstract: The ^{13}C nmr spectra of some gentamicin aminoglycosides are tabulated, assigned, and discussed. Methods of assignment are detailed. The chemical shifts of many carbon nuclei are shown to be reasonably constant among the different compounds. The reproducibility of ^{13}C nmr data obtained under varying experimental conditions is demonstrated.

Within recent years, carbon-13 magnetic resonance (cmr) techniques have been applied to the study of carbohydrates by a number of workers. The chemical shifts of oxygenated carbons, substitution, and proximity effects have been noted by earlier workers, especially Hall, Dorman, and Roberts.[3-5] Perlin, Casu, and Koch have studied configurational and conformational effects on chemical shifts in some detail and have demonstrated the existence of several consistent patterns in the dependence of these shifts on carbohydrate stereochemistry.[6] These studies have been extended to disaccharides.[7] The cmr of an aminoglycoside, hygromycin B, has been described, although this spectrum was not fully assigned.[8] Extension of these results to more complex systems such as antibiotics is a matter of obvious interest and practical value. As is well known, cmr spectra provide many advantages over proton spectra in the characterization of such complex molecules, principally due to the relatively much greater range (up to 200 ppm) of ^{13}C chemical shifts.[9]

The goal of the present study was the complete assignment of all resonances in a series of gentamicin antibiotics. As has been reported by other workers,[7,8] the present study demonstrates that the chemical shifts for certain positions of carbon nuclei are sufficiently invariant to allow assignments to be made with a considerable degree of confidence. Accordingly, we have utilized the comparisons of shifts among similar aminoglycosides and with the mono- and pseudodisaccharide fragments of these antibiotics. This approach has been supplemented by the use of such spectroscopic techniques as specific frequency proton decoupling and single frequency off-resonance decoupling (SFOR).

The particular series of compounds studied here include gentamicins C_1, C_{1a}, and C_2 and sisomicin, as well as several one- and two-ring fragments from these aminoglycosides. These antibiotics have been described previously and are representative of a large family of aminoglycosides.[10-13] The gentamicin antibiotics are the subject of considerable chemical and biological research. The successful outcome of the present investigation suggests that cmr will be a routine and reliable instrumental method for the elucidation of similar structures.

The cmr data currently found in the literature have been generated on a variety of instruments operated in both the pulsed and continuous wave mode. It was, therefore, important to determine the dependence of the present data on the experimental conditions employed. The results presented in this paper have been obtained from three different laboratories, each using significantly different experimental techniques. The agreement among the data so obtained gives assurance that these data are truly independent of the technique by which they were obtained.

(1) Schering Corporation.
(2) Emory University.
(3) L. D. Hall and L. F. Johnson, *Chem. Commun.*, 509 (1969).
(4) D. E. Dorman, S. J. Angyal, and J. D. Roberts, *J. Amer. Chem. Soc.*, **92**, 1351 (1970).
(5) D. E. Dorman and J. D. Roberts, *J. Amer. Chem. Soc.*, **92**, 1355 (1970).
(6) A. S. Perlin, B. Casu, and J. J. Koch, *Can. J. Chem.*, **48**, 2596 (1970).
(7) E. Breitmaier, G. Jung, and W. Voelter, *Chimia*, **25**, 362 (1971).
(8) N. Neuss, K. R. Koch, B. B. Molloy, W. Day, L. L. Huckstep, D. E. Dorman, and J. D. Roberts, *Helv. Chim. Acta*, **53**, 2314 (1970).
(9) A brief comparison of carbon-13 and proton data is given by W. O. Crain, Jr., W. C. Wildman, and J. D. Roberts, *J. Amer. Chem. Soc.*, **93**, 990 (1971).
(10) D. J. Cooper, M. D. Yudis, R. D. Guthrie, and A. M. Prior, *J. Chem. Soc. C*, 960 (1971).
(11) D. J. Cooper, M. D. Yudis, H. M. Marigliano, and T. Traubel, *J. Chem. Soc. C*, 2876 (1971).
(12) D. J. Cooper, P. J. L. Daniels, M. D. Yudis, H. M. Marigliano, R. D. Guthrie, and S. T. K. Bukhari, *J. Chem. Soc. C*, 3126 (1971).
(13) D. J. Cooper, R. S. Jaret, and H. Reimann, *Chem. Commun.*, 285, 924 (1971).