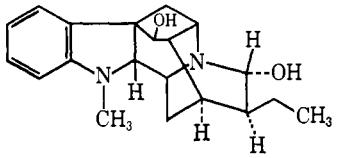
The Biogenetic-Type Total Synthesis of Ajmaline[1]

Sir:

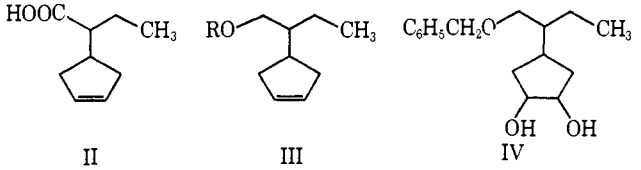
Possessing a total of six rings and nine asymmetric centers, the singular indole alkaloid ajmaline (I) presents a distinct challenge to the organic chemist con-



I

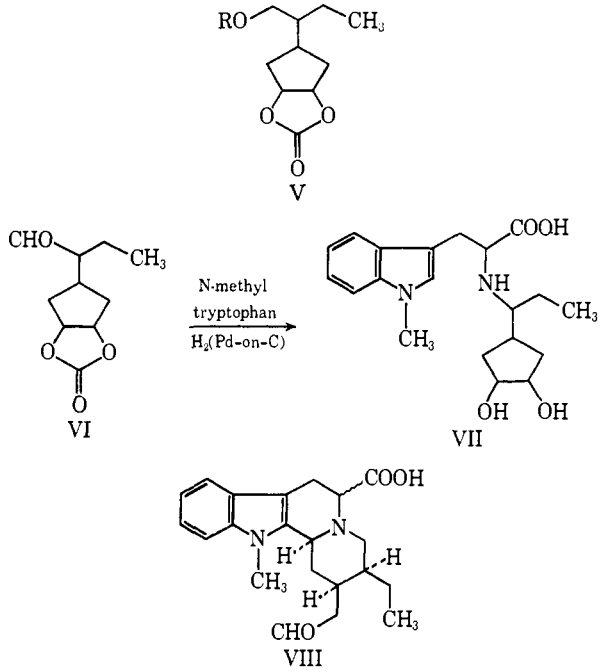
cerned with the development of meaningful biogenetically patterned syntheses of complex, naturally occurring systems.[2,3] Outlined below is an ajmaline construction which, starting from N-methyltryptophan and a suitable C_9 precursor, features several chemical changes of obvious relation to obligatory key steps in the biosynthesis of I.[4]

Preparation of the C_9 unit needed for juncture with N-methyltryptophan started with *dl*-α(Δ^3-cyclopentenyl)butyric acid (II), obtained[5] by alkylation of ethyl cyanoacetic ester with Δ^3-cyclopentenyl tosylate, followed by (1) saponification to the cyanoacid, (2) decarboxylation, and (3) hydrolysis. Lithium aluminum hydride reduction of II, carried out in refluxing THF, provided the expected unsaturated alcohol III (R = H), bp 112–115° (25 mm) (94–97%). After O benzylation (benzyl chloride at 100° in the presence of powdered KOH) (83%) the cyclopentene III (R = $C_6H_5CH_2$–) was hydroxylated at room temperature



II III IV

by a slight excess of osmium tetraoxide in pyridine–THF (79%).[6] The resulting diol (IV) (ir ν_{max}^{film} 3400, 3080–3020, 2960–2860, 1590, 1493, 1480, 1450, 1440, 1358, 1065–1110, 1024, 740, 733, and 695 cm^{-1}; nmr 60 MHz ($CDCl_3$) τ 2.65, 5.50, 5.87, and 6.58, higher field envelope for CH_3, CH_2, and CH), was subjected to transesterification conditions (refluxing dimethyl carbonate in the presence of sodium methoxide) giving the cyclic carbonate V (R = $C_6H_5CH_2$–) (87%) (ir $\nu_{max}^{CCl_4}$ 3080–3075, 2960–2850, 1815, 1452, 1367, 1280, 1148, 1110, 1080, 1045, and 692 cm^{-1}; nmr 60 MHz (CCl_4) τ 2.80, 5.10, 5.64, and 6.68, higher field envelope for CH_3, CH_2, CH).



V VI VII VIII

Subsequent to removal of the benzyl group by catalytic hydrogenolysis (Pd-on-C in EtOH) (95%), the primary alcohol V (R = H) was oxidized in CH_2Cl_2 with chromic acid–pyridine[7] to aldehyde VI (98%) (ir $\nu_{max}^{CHCl_3}$ 3000–2850, 2705, 1800, 1718, 1368, 1210, 1165, 1100, 1073, 1040, 900, 750, and 660 cm^{-1}; nmr 60 MHz ($CDCl_3$) τ 0.37, 4.87, and higher field envelope for CH_3, CH_2, CH).

Reductive alkylation of N-methyltryptophan with aldehyde VI, carried out in ethanol with H_2–Pd-on-C, provided the N-substituted amino acid (51%), which without purification was saponified (KOH–MeOH) to the required diol VII (ir ν_{max}^{KBr} 3400–2800, 1660–1600, 1400, 1305, 1075, and 736 cm^{-1}; nmr 60 MHz (D_2O–NaOD) highly complex except for indolic hydrogens at τ 2.48–2.07 and NCH_3 at 5.80). The dialdehyde resulting from 1,2-glycol cleavage,[8] brought about in VII by a dilute solution of metaperiodate (1 mol in aqueous sodium acetate buffer at room temperature) spontaneously ring closed (53%) to tetracyclic aldehyde in a step which clearly has biosynthetic parallel.[4] At this point, the desired C-3, -15, -20 all-*cis* material (VIII) was not separated from stereoisomeric congeners, but the mixture (ir ν_{max}^{KBr} ~3400, 2820, 1726, 1465, 1380, 1280, 1120, 1070, and 740 cm^{-1}) was carried through the succeeding fragmentation–cyclization process.

(1) First presented publicly in the Bachmann Memorial Lecture, Oct 31, 1969, at the University of Michigan, Ann Arbor, Mich.

(2) For a description and examples of this approach, see E. E. van Tamelen, *Fortschr. Chem. Org. Naturstoffe*, **19**, 242 (1961).

(3) The correct gross structure of ajmaline was established by R. B. Woodward and K. Schenker. See: R. B. Woodward, *Angew. Chem.*, **68**, 13 (1956). Stereoformula I was proposed by M. F. Bartlett, R. Sklar, W. I. Taylor, E. Schlittler, R. L. S. Anai, P. Beak, N. V. Bringi, and E. Wenkert, *J. Amer. Chem. Soc.*, **84**, 622 (1962).

(4) Tryptophan has been established as a biosynthetic precursor by E. Leete, *Chem. Ind.* (London), 692 (1960). Loganin is a progenitor of the nontryptamine portion, as demonstrated by D. Arigoni and coworkers, *Chem. Commun.*, 136, 137 (1968), and by A. R. Battersby and coworkers, *ibid.*, 131, 133, 134 (1968). For additional discussion of biogenetic mechanism, see ref 3 and E. E. van Tamelen, V. B. Haarstad, and R. L. Orvis, *Tetrahedron*, **24**, 687 (1968).

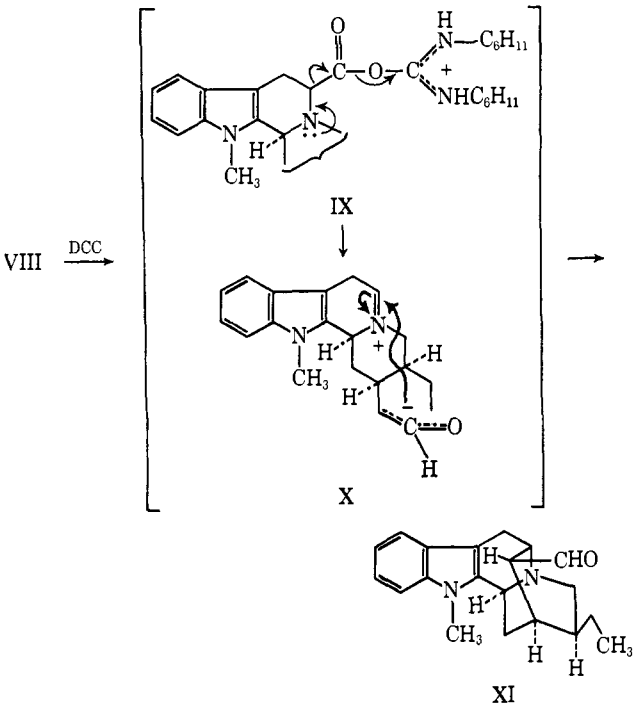
(5) E. E. van Tamelen, L. J. Dolby, and R. G. Lawton, *Tetrahedron Lett.*, 30 (1960).

(6) Each of the intermediates IV–VII was found to be a noncrystalline mixture of diastereomers, which, because of the impermanence of the asymmetric relationships present, we did not attempt to separate into pure components.

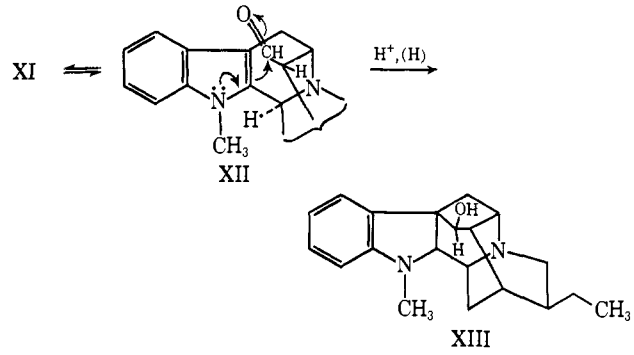
(7) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968).

(8) Alkaloid synthesis involving dialdehyde generation by cycloalkane-1,2-diol cleavage, followed by Pictet–Spengler cyclization involving a tryptamine residue, was first employed by E. E. van Tamelen, M. Shamma, A. W. Burgstahler, J. Wolinsky, R. Tamm, and P. E. Aldrich in the yohimbine synthesis, *J. Amer. Chem. Soc.*, **80**, 5006 (1958); **91**, 7315 (1969). For other examples see: (a) E. E. van Tamelen, J. P. Yardley, and M. Miyano, *Tetrahedron Lett.*, 1011 (1963), and (b) J. A. Webber, Ph.D. Dissertation, Stanford University, Stanford, Calif., 1966. This device was also applied in the ajmaline synthesis of S. Masamune, S. K. Ang, C. Egli, N. Nakatsuka, S. K. Sarkar, and Y. Yasunari, *J. Amer. Chem. Soc.*, **89**, 2506 (1967).

With the carboxyl in VIII properly positioned for directing formation of iminium ion which would permit requisite bond formation between C-5 and C-16,[9] a decarbonylation reaction (IX) was induced by treatment of the amino acid with 2 mol each of dicyclohexylcarbodiimide and *p*-toluenesulfonic acid in dioxane at 80°.[10] The dihydro-β-carboline X was not isolated, but allowed to generate spontaneously, in a bioorganic cyclization (X), *dl*-deoxyajmalal-B (XI) (mp 204–206°), isolated by tlc on silica gel (18%). The synthetic aldehyde was resolved by use of D-camphor-10-sulfonic acid, the resolved base (mp 212–213°) as well as its sulfonate salt (mp 236–240°) being identical with authentic specimens[11] in all respects, including mixture melting points.



Completion of the synthesis depends on certain relay operations. By means of appropriate experiments carried out with either deoxyajmalal-A (XII) or -B (XI) in room temperature acetic acid–sodium acetate or in refluxing benzene over alumina, it was demonstrated that there exists at equilibrium a mixture of ~15% A and ~85% B (by nmr analysis), from which mixture there can be isolated (tlc, silica gel GF) deoxyajmalal-A (mp 179–180°), identical with authentic base.[11] Reductive cyclization according to the method of Taylor, *et al.*,[11] brings about biogenetic-type conversion of aldehyde -A (XII), but not -B (XI), to deoxyajmaline (XIII). Functionalization of the latter at C-21 is achieved by the phenyl chloroformate ring opening–oxidative ring closure sequence innovated by Hobson and McCluskey,[12] with resultant formation of ajmaline itself.[13]



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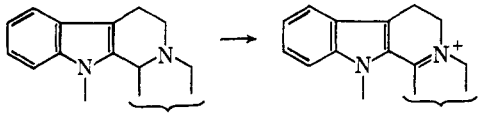
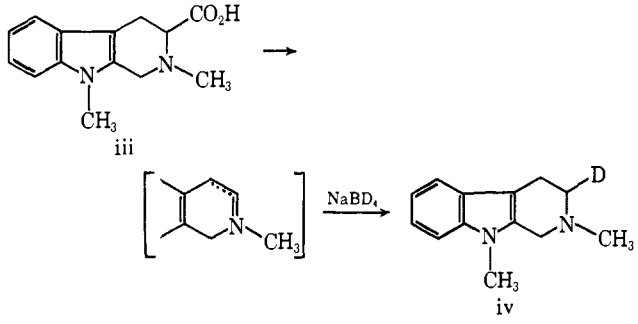
(9) It is evident that generation of the iminium salt (X) required for the critical C-5–C-16 bond formation would not be possible by dehydrogenation of a tryptamine-derived tetrahydrocarboline (i) with any known reagents (*e.g.*, mercuric acetate), since in such cases the thermodynamically more stable Δ³-dihydro-β-carboline (ii) results.



(10) The conditions for the decarbonylation reaction were worked out in a model case utilizing the tetrahydro-β-carboline carboxylic acid iii.



Under the conditions used with VIII, the model acid iii was converted to product, reduced *in situ* with $NaBD_4$ to 3-monodeuterio-N-methyl tetrahydro-β-carboline (iv). The latter possessed 60-MHz $CDCl_3$ nmr peaks at *inter alia* τ 6.39 (1 H, doublet, 16 Hz), 5.82 (1 H, doublet, 16 Hz) (C-1 hydrogens), and at 7.00–7.30 (3 H, multiplet) (C-3 and C-4 hydrogens), thus indicating the deuterium site and therefore the nature of the unsaturation in the precursor. For related decarbonylation processes, see V. I. Maksimov, *Tetrahedron*, 21, 687 (1965).

(11) M. F. Bartlett, B. F. Lambert, H. M. Werblood, and W. I. Taylor, *J. Amer. Chem. Soc.*, 85, 475 (1963).

(12) J. D. Hobson and J. G. McCluskey, *J. Chem. Soc.*, 2015 (1967).

(13) Structures of intermediates are supported by all other spectral and analytical data obtained.

(14) National Science Foundation Predoctoral Fellow (1965–1968), National Institutes of Health Predoctoral Fellow (1968–1969).

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Minimal Substrate Structural Requirements for Lanosterol–Squalene 2,3-Oxide Cyclase Action. 10′-Norsqualene 2,3-Oxide

Sir:

One aim of the Stanford investigations into substrate behavior during lanosterol squalene 2,3-oxide cyclase action is definition of the minimal structural requirements for (1) enzymic cyclization and (2) the ensuing methyl–hydrogen migration sequence. The accumulated set of prior preliminary findings has lacked a key case: all-*trans*-10′-norsqualene 2,3-oxide (I). We now wish to report that this oxide—although missing an important methyl group—is converted *in vitro* to 4,4-dimethyl-$\Delta^{8(9),24}$-cholestadienol (II), a