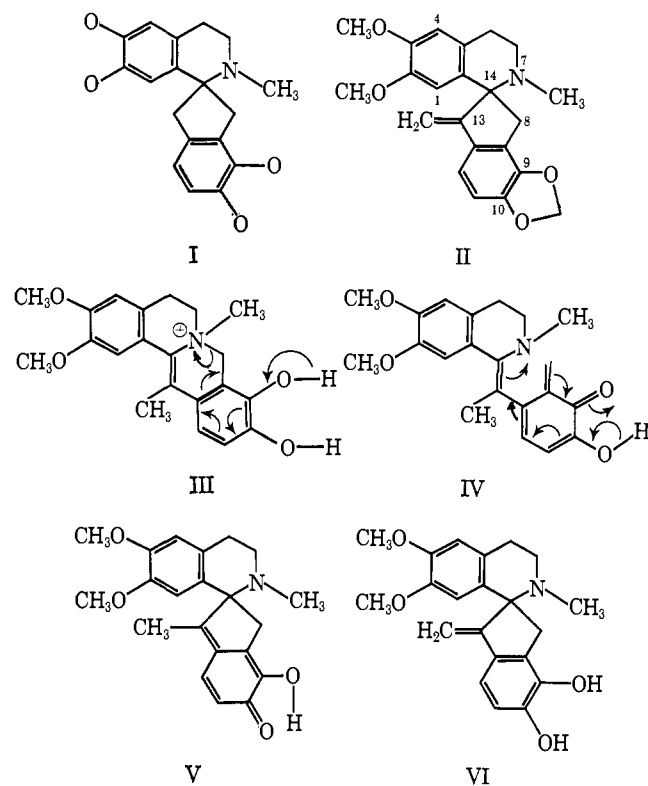


A Model for the Biogenesis of the Spirobenzylisoquinoline Alkaloids

Sir:

The spirobenzylisoquinolines are a group of five bases each possessing the features represented by partial expression I.¹⁻⁴ The alkaloid ochotensimine (II) was the first member of this class to have its structure elucidated.^{1,2}

We speculated that ochotensimine is formed in the plant from an enamine N-metho salt such as III. In a basic medium, this precursor can undergo cleavage to the quinonoid intermediate IV, which by the electrocyclic process indicated forms the spirane V. A tautomeric shift then yields the diphenol VI which is easily convertible to ochotensimine (II).



In order to test the above hypothesis, the dibenzylxyprotoberberinium iodide VII was synthesized,⁵ mp 140–145° dec; $\lambda_{\text{max}}^{\text{EtOH}}$ 218, 265, 288, 308, 340 sh, and 370 m μ (log ϵ 4.57, 4.28, 4.41, 4.34, 4.08, and 3.67). This 10,11-substituted system is much more readily prepared than the 9,10 analog, yet lends itself equally well to the aims of our investigation.

Partial reduction of VII with LiAlH₄ in ether followed by immediate treatment with excess MeI afforded the methiodide salt VIII in 65% over-all yield for the two steps; C₃₅H₃₆O₄N⁺I⁻; mp 165–170° dec. Debenzylation of VIII with refluxing aqueous HBr–ethanol produced the key intermediate IX in 92% yield; C₂₁H₂₄O₄NBr; mp

(1) S. McLean and M.-S. Lin, *Tetrahedron Letters*, 3819 (1964).

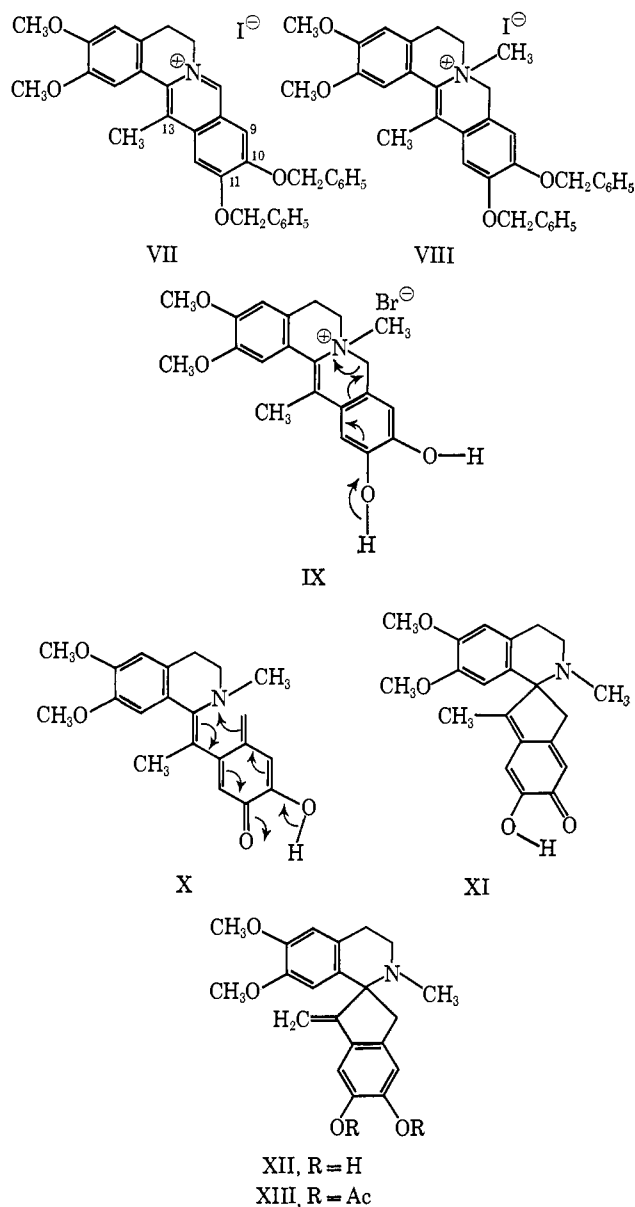
(2) S. McLean, M.-S. Lin, and R. H. F. Manske, *Can. J. Chem.*, **44**, 2449 (1966).

(3) S. McLean, M.-S. Lin, A. C. Macdonald, and J. Trotter, *Tetrahedron Letters*, 185 (1966).

(4) J. K. Saunders, R. A. Bell, C.-Y. Chen, D. B. MacLean, and R. H. F. Manske, *Can. J. Chem.*, **46**, 2873, 2876 (1968).

(5) The details of the synthesis of the dibenzylxyprotoberberinium iodide salt VII will be reported at a later date. No unusual steps were involved in this preparation.

235° dec; $\lambda_{\text{max}}^{\text{EtOH}}$ 232 and 330 m μ (log ϵ 4.18 and 4.20); nmr in DMSO-*d*₆ with DMSO as internal reference at δ 2.50: 13-CH₃ (3 H singlet, δ 2.26), N⁺CH₃ (3 H singlet, δ 2.94), two OCH₃ (6 H superimposed singlets, δ 3.82).



The methobromide IX was refluxed for 12 hr in aqueous ethanolic NaOH. Acidification with aqueous HCl followed by basification with NaHCO₃ afforded an oily yellow-green oil which was taken up in CHCl₃ and a little DMSO. Evaporation of the solvent furnished in 75% yield the desired phenolic spirobenzylisoquinoline XII as an oil. The nmr spectrum in DMSO-*d*₆ with DMSO at δ 2.50 exhibited NCH₃ (3 H singlet, δ 2.02), CH₂CH₂ (4 H broad multiplet, δ 2.8), 8-methylene (2 H pair AB doublets, centered δ 3.33, internal chemical shift 39 Hz and J = 19 Hz), two OCH₃ (6 H singlets, δ 3.45 and 3.70), two vinylic protons (2 H singlets, δ 4.60 and 5.36), and four aromatic protons (4 H singlets, δ 6.16, 6.54, 6.61, and 6.92). The mass spectrum demonstrated an intense M⁺ at m/e 353 for C₂₁H₂₃O₄N.

The diacetate derivative of XII, corresponding to species XIII, was a light yellow oil with a strong M⁺

peak at m/e 437 for $C_{25}H_{27}O_6N$. The nmr spectrum in $CDCl_3$ showed NCH_3 (3 H singlet, δ 2.10), acetoxy protons (6 H singlet, δ 2.28), CH_2CH_2 (4 H multiplet, δ 2.9), 8-methylene (2 H broad singlets, δ 3.11 and 3.34), two OCH_3 (6 H singlets, δ 3.62 and 3.80), two vinylic protons (2 H singlets, δ 4.97 and 5.63), and four aromatic protons (4 H, δ 6.24, 6.50, 7.02, and 7.29).

The exocyclic double bond in diacetate XII was readily reduced with Adams catalyst. The resulting oily dihydrodiacetate, M^+ m/e 439 for $C_{25}H_{29}O_6N$, exhibited an nmr spectrum whose most salient feature was a C-13 methyl doublet, centered at δ 0.95, $J = 6.5$ Hz.

The rearranged product XII must have been formed from the methobromide IX through intermediates X and XI, *i.e.*, by a route that may very well parallel the biogenetic sequence for ochotensimine (II).^{6,7}

Acknowledgments. The authors are grateful to Professor J. E. Baldwin for useful discussions, to the National Institutes of Health for research fellowship 2 F01 GM-33,013-03 to C. D. J., and for research grant GP-9359 from the National Science Foundation.

(6) Two syntheses of ochotensimine by classical routes have been reported; see (a) S. McLean, M.-S. Lin, and J. Whelan, *Tetrahedron Letters*, 2425 (1968); (b) T. Kametani, S. Takano, and S. Hibino, *J. Pharm. Soc. Japan*, **88**, 1123 (1968); (c) H. Irie, T. Kishimoto, and S. Uyeo, *J. Chem. Soc., C*, 3051 (1968).

(7) Satisfactory elemental analyses were obtained for all key intermediates.

Maurice Shamma, C. D. Jones

Department of Chemistry, The Pennsylvania State University
University Park, Pennsylvania 16802

Received April 7, 1969

Deuterium Tracer Studies of Tricarbahexaborane(7) Formation. Synthesis of the 2,4- $(CH_3)_2C_3B_3H_4^-$ Ion and 2,4- $(CH_3)_2-\mu-D-C_3B_3H_4$

Sir:

The characterization of a C-methyl derivative and two C,C'-dimethyl derivatives of the open-cage carborane $C_3B_3H_7$ (*nido*-2,3,4-tricarbahexaborane(7)) as the principal volatile products in the vapor-phase reaction of tetraborane(10) with acetylene at 25–50° has been reported.^{1–3} We now present some additional findings on the formation and chemistry of this carborane cage system. The vapor-phase reaction of C_2D_2 with an equimolar amount of B_4H_{10} at 50° in a sealed Pyrex bulb yields three major volatile products whose infrared and mass spectra² and glpc retention times clearly identify them as deuterated tricarbahexaborane(7) derivatives corresponding to those obtained from the $C_2H_2-B_4H_{10}$ reaction, *e.g.*, 2-methyl-, 2,3-dimethyl-, and 2,4-dimethyl-2,3,4-tricarbahexaborane(7). Significantly, all deuterium incorporated into these products appears to be bound to carbon; no evidence for either terminal or bridge B–D bonds can be detected in the infrared spectra of the carboranes or in those of the B_2H_6 and B_4H_{10} recovered from the reaction. Cage C–H bands (~ 3020 cm^{-1}), which are present in the ir spectra of isotopically normal $C_3B_3H_7$ derivatives,² are absent in the products of this study, and the methyl C–H band (normally a

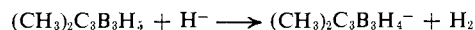
multiplet) is a single strong absorption at 2940 cm^{-1} in all three spectra. Medium absorptions at 2270 and 2170 cm^{-1} in each spectrum (not present in the nondeuterated compounds) are attributed to cage C–D and methyl C–D stretch, respectively.

The mass spectra of all three tricarbahexaborane products exhibit sharp cutoffs corresponding to the tetradeuterated species, *e.g.*, at m/e 94 for the monomethyl derivative ($^{12}C_4^{11}B_3^1H_5^2D_4^+$) and at m/e 108 for each of the dimethyl derivatives ($^{12}C_5^{11}B_3^1H_7^2D_4^+$). The presence of trideuterated species is also indicated, however, by comparison of the fragmentation patterns with those of the isotopically normal compounds. When the $C_2D_2-B_4H_{10}$ reaction is carried out with a 10:1 excess of C_2D_2 , the relative abundance of tetradeuterated *vs.* tri-deuterated species in each spectrum increases approximately fourfold compared to the 1:1 reaction, as estimated from the cutoff peak intensities.

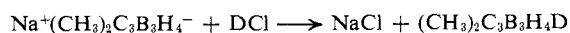
The possibility that some incorporation of deuterium into the carborane products may occur *via* direct exchange of the latter with C_2D_2 has been examined by exposing 2- $CH_3C_3B_3H_6$, 2,3- $(CH_3)_2C_3B_3H_5$, and 2,4- $(CH_3)_2C_3B_3H_5$ to a 100-fold excess of C_2D_2 at 50°. After 10 days mass spectroscopic analysis of all compounds involved gave no evidence of deuterium exchange.

These data point to a minimum of C–D bond breaking during formation of the tricarbahexaborane derivatives, and in this respect parallel the synthesis⁴ of $C_2D_2-B_4H_6$ (2,3-dicarbahexaborane(8)-*d*₂) from C_2D_2 and B_3H_9 . However, while the formation of the dicarbahexaborane requires no C–C breakage, such cleavage is clearly involved³ in the preparation of both $(CH_3)_2C_3B_3H_5$ derivatives from C_2H_2 . Rate studies of this reaction are now in progress and may provide additional clues to the reaction mechanism.

The reaction of either isotopically normal C,C'-dimethyl derivative with excess sodium hydride in dry diglyme or tetrahydrofuran (THF) proceeds smoothly at room temperature, producing a volume of H_2 consistent with the reaction



Typically, 0.930 mmole of the carborane reacted with 1.17 mmoles of NaH suspended in mineral oil to yield 0.923 mmole of H_2 (collected in a Toepler pump). The ions apparently produced (2,3- and 2,4-dimethyl-2,3,4-tricarbahexaborate(–1)) are readily hydrolyzed on exposure to moist air and slowly decompose even in dry diglyme solution. It is clear that the $(CH_3)_2C_3B_3H_4^-$ ions are formed by removal of a bridge proton from the neutral carborane, since treatment of a THF solution of sodium 2,4-dimethyltricarbahexaborate(–1) with excess deuterium chloride produces 2,4-dimethyl- μ -deuterio-tricarbahexaborane(7).



The infrared spectrum of the carborane product is very close to that of 2,4- $(CH_3)_2C_3B_3H_5$,² except for the virtual absence of the B–H–B stretch at 1950 cm^{-1} and the appearance of a medium band at 1550 cm^{-1} which is assigned to B–D–B absorption. No terminal B–D or C–D bands are observed. The mass spectrum has a sharp cutoff at m/e 105, corresponding to the $^{12}C_5^{11}B_3-$

(1) C. L. Bramlett and R. N. Grimes, *J. Am. Chem. Soc.*, **88**, 4269 (1966).

(2) R. N. Grimes and C. L. Bramlett, *ibid.*, **89**, 2557 (1967).

(3) R. N. Grimes, C. L. Bramlett, and R. L. Vance, *Inorg. Chem.*, **7**, 1066 (1968).

(4) J. R. Spielman, R. Warren, G. B. Dunks, J. E. Scott, Jr., and T. Onak, *ibid.*, **7**, 216 (1968).