

BIOMIMETIC SYNTHESIS OF THE DIBENZAZONINE ALKALOID LAURIFONINE

S. Morris Kupchan*, Chang-Kyu Kim, and Katsuji Miyano
 =====

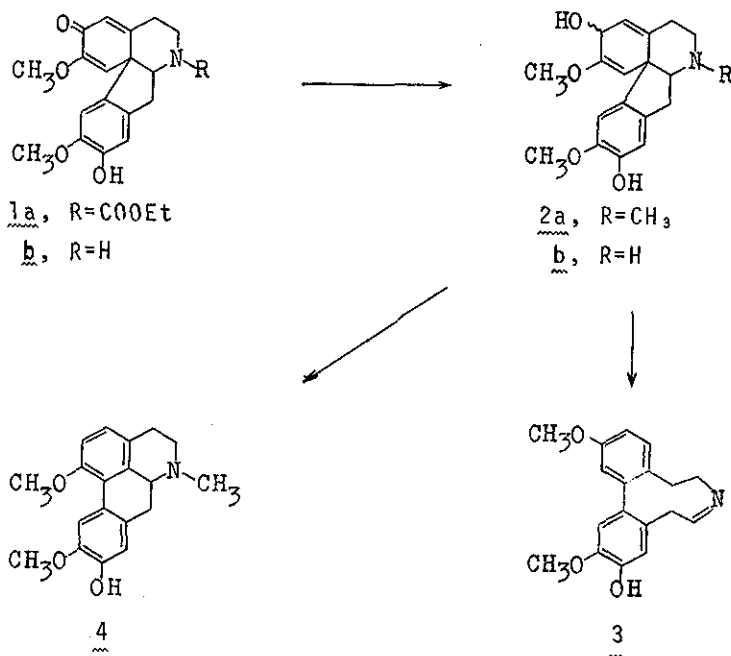
Department of Chemistry, University of Virginia,
Charlottesville, Virginia 22901, U.S.A.

A facile and efficient biomimetic synthesis of laurifonine (9a) is described. Reduction of (\pm)-0-methylflavinantine (5a) with sodium borohydride yielded a mixture of the epimeric dienols 6a, in 83% yield. Treatment of the dienol mixture with boron trifluoride-etherate followed by hydrogenation over platinum in methanol gave laurifonine (9a, 81%). When a mixture of (\pm)-proerythrina-dienols (2a) was subjected to acid-catalyzed rearrangement, the (\pm)-desoxyaporphine 4 was obtained, in 85% yield. Possible biogenetic implications of the observations are discussed.

Recently three new dibenzazonine alkaloids, laurifonine (9a), laurifinine (9b), and laurifine (9c) have been isolated from the leaves of Cocculus laurifolia D.C.¹ The occurrence of these trisubstituted dibenzazonine alkaloids is of particular biogenetic interest in view of the fact that a new group of erythrina-type alkaloids exemplified by cocculine (11a) and cocculidine (11b) also has been isolated from the same plants.² The biosynthesis of the new dibenzazonine alkaloids could be envisaged as proceeding either from norprotosinomenine (10a) via route A,¹

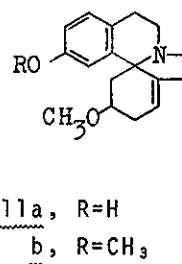
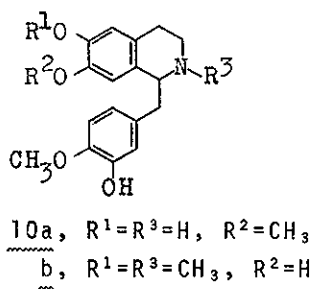
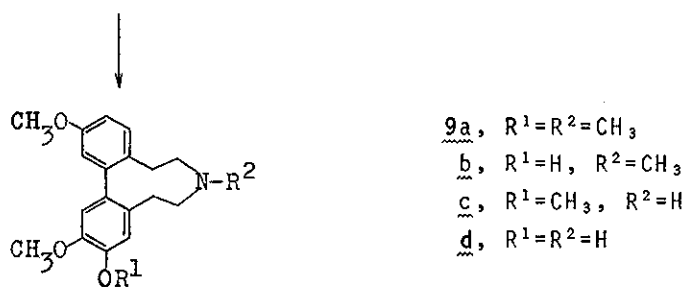
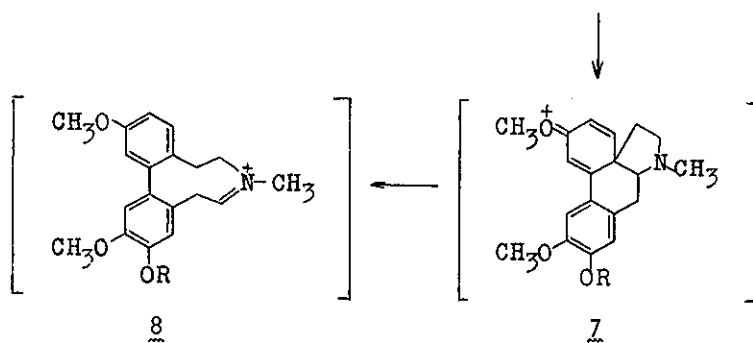
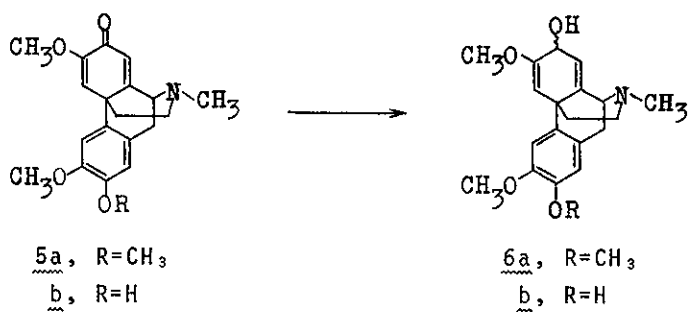
10a → 1b → 2b → 3 → 9d → 9a,b,c, analogous to the biosynthetic pathway proposed for *Erythrina* alkaloids,³ or from reticuline (10b) via the route B, 10b → 5b → 6b → 7 → 8 → 9b → 9a,c, analogous to the sequence of skeletal rearrangements proposed for dibenzazocine alkaloid biosynthesis in *Stephania japonica*.⁴ We report herein the results of biomimetic synthetic studies along both these lines, which have led to an efficient synthesis of the 1,9,10-trisubstituted aporphine 4 via a proerythrinadienone route and of laurifonine (9a) via the morphinandienone route (route B).

To evaluate the possible role of proerythrinadienones as trisubstituted dibenzazocine alkaloid precursors, (±)-N-ethoxycarbonylnorproerythrinadienone (1a)⁵ was treated with LiAlH₄ in THF under reflux for 16 hr, and a mixture of the epimeric dienols (2a) was obtained. This mixture could be separated by preparative tlc to give (±)-proerythrinadienol I⁶ (60%, mp 167.5-169°



(MeOH-Et₂O); uv $\lambda_{\text{max}}^{\text{EtOH}}$ (log ϵ) 291 (3.74), 235 (sh, 3.94) nm; ir $\lambda_{\text{max}}^{\text{CHCl}_3}$ 2.82, 6.04 μ ; nmr (CDCl₃) δ 6.80 and 6.30 (s, s, 2H, ArH), 5.84 (d, J=3 Hz, 1H, olefinic H), 4.64 (s, 1H, olefinic H), 4.72 (d, J=3 Hz, 1H, >CH-OH), 3.79 and 3.50 (s, s, 6H, 2-OCH₃), 2.33 (s, 3H, N-CH₃); mass spectrum m/e (%) 329 (10, M⁺), 312 (100), 311 (83), 296 (46), 281 (21)) and (\pm)-proerythrinadienol II (14%; mp 169.5-171° (MeOH-Et₂O); uv $\lambda_{\text{max}}^{\text{EtOH}}$ (log ϵ) 291 (3.72), 235 (sh, 3.94) nm; ir $\lambda_{\text{max}}^{\text{CHCl}_3}$ 2.82, 6.04 μ ; nmr (CDCl₃) δ 6.81 and 6.50 (s, s, 2H, ArH), 5.88 (d, J=4 Hz, 1H, olefinic H), 4.68 (s, 1H, olefinic H), 4.66 (d, J=4 Hz, 1H, >CH-OH), 3.80 and 3.48 (s, s, 6H, 2-OCH₃), 2.33 (s, 3H, N-CH₃); mass spectrum m/e (%) 329 (11, M⁺), 312 (100), 311 (83), 296 (45), 281 (21)). Upon treatment with concentrated hydrochloric acid in methanol or boron trifluoride-etherate at room temperature for 30 min, the mixture of (\pm)-proerythrinadienols I and II (2a) gave, in 85% yield, (\pm)-1,10-dimethoxy-9-hydroxyaporphine (4) as its hydrochloride salt, mp 218-221° dec., from which the free base was liberated; mp, initially melts at 101.5-102°, solidifies and remelts at 166-167° (MeOH-Et₂O); uv $\lambda_{\text{max}}^{\text{EtOH}}$ (log ϵ) 316 (4.18), 307 (4.19), 279 (4.04), 269 (sh, 3.92), 233.5 (4.59) nm; ir $\lambda_{\text{max}}^{\text{CHCl}_3}$ 2.82 μ ; nmr (CDCl₃) δ 7.89 (s, 1H, C-11 H), 6.98 (d, J=8.6 Hz, 1H, C-2 H or C-3 H), 6.88 (d, J=8.6 Hz, 1H, C-2 H or C-3 H), 6.80 (s, 1H, C-8 H), 3.90 and 3.86 (s, s, 6H, 2-OCH₃), 2.54 (s, 3H, N-CH₃); mass spectrum m/e (%) 311 (100), 310 (95), 296 (44), 281 (28), 268 (81), 253 (28), 237 (57). This result indicates that the acid-catalyzed dienol-benzene rearrangement of the (\pm)-proerythrinadienols (2a) favors the aporphine route (2a \rightarrow 4) instead of the dibenzazonine route (2a \rightarrow 3). Furthermore, the nitrogen free electron pair may participate in the rearrangement of the dienols to the aporphine, for acid-catalyzed rearrangement of an analogous amide derivative gave an aporphine in less than 1% yield.⁷⁻⁹

To evaluate the alternative route (via morphinandienone) (\pm)-0-methylflavinantine (5a)⁹ was reduced with NaBH₄ in methanol



to yield the epimeric dienols (6a) in 83% yield. These were also separable by preparative tlc, *i.e.*, (\pm)-0-methylflavinantiniol I as a crystalline material (mp 161-162.5° (MeOH-Et₂O); ir $\lambda_{\text{max}}^{\text{CHCl}_3}$ 2.73, 2.80, 6.04 μ ; uv $\lambda_{\text{max}}^{\text{EtOH}}$ (log ϵ) 285 (3.68), 232 (sh, 3.96) nm; nmr (CDCl₃) δ 6.77 and 6.58 (s, s, 2H, ArH), 5.78 (d, $J=4$ Hz, 1H, olefinic H), 5.30 (s, 1H, olefinic H), 4.68 (d, $J=4$ Hz, 1H, $>\text{CH-OH}$), 3.87, 3.85, and 3.73 (all s, 9H, 3-OCH₃), 2.45 (s, 3H, N-CH₃); mass spectrum m/e (%) 343 (54, M⁺), 328 (39), 326 (47), 325 (100), 310 (36)), and (\pm)-0-methylflavinantiniol II as an oil (ir $\lambda_{\text{max}}^{\text{CHCl}_3}$ 2.73, 2.80, 6.04 μ ; uv $\lambda_{\text{max}}^{\text{EtOH}}$ (log ϵ) 285 (3.68), 232 (sh, 3.98) nm; nmr (CDCl₃) δ 6.77 and 6.59 (s, s, 2H, ArH), 5.75 (d, $J=3$ Hz, 1H, olefinic H), 5.29 (s, 1H, olefinic H), 4.55 (d, $J=3$ Hz, 1H, $>\text{CH-OH}$), 3.87, 3.84, and 3.74 (all s, 9H, 3-OCH₃), 2.46 (s, 3H, N-CH₃); mass spectrum m/e (%) 343 (29, M⁺), 328 (20), 326 (37), 325 (100), 310 (36)). Treatment of the mixture of (\pm)-0-methylflavinantiniols (6a) with boron trifluoride-etherate at room temperature for 20 hr, followed by hydrogenation over Pt in methanol, gave laurifonine (9a),^{1,10} isolated as the perchlorate salt, in 81% yield. By analogy with the demonstrated favored rearrangement of morphinandienones to neospirinedienones (*e.g.*, 7) under the influence of strongly acidic catalysts,^{9,11} the conversion of 6a to 9a is presumed to proceed *via* the intermediacy of 7 and 8. This parallels the sequence of rearrangements proposed for the biosynthesis of the dibenzazone alkaloid, protostephanine, in Stephania japonica, as well as the biomimetic synthesis of the alkaloid.⁴

It is noteworthy that Cocculus and Stephania are both genera of the family Menispermaceae. It is conceivable that dibenzazone alkaloids which occur in plants of the family Menispermaceae may arise by a pathway similar to route B, whereas the dibenzazones of the family Fabaceae (*e.g.*, Erythrina species) may arise by a pathway analogous to route A.

ACKNOWLEDGEMENTS We thank the National Cancer Institute (CA-12059) and Hoffmann-La Roche Inc. for generous financial support.

REFERENCES

1. H. Uprety and D. S. Bhakuni, Tetrahedron Lett., 1975, 1201.
2. S. Yu Yunusov, Zhur. Obshchei. Khim., 1950, 20, 368; S. Yu Yunusov and R. Razakov, Khim. Prir. Soedin., 1970, 6, 74; Chem. Abstr., 1970, 73, 35585; R. Razakov, S. Yu Yunusov, S.-M. NasYROV, A. N. Chekhlov, V. G. Andrianov, and Y. T. Struchkov, J.C.S. Chem. Comm., 1974, 150.
3. D.H.R. Barton, R. B. Boar, and D. A. Widdowson, J. Chem. Soc. (C), 1970, 1213.
4. A. R. Battersby, A. K. Bhatnagar, P. Hackett, C. W. Thornber, and J. Staunton, Chem. Comm., 1968, 1214.
5. S. M. Kupchan, C.-K. Kim, and K. Miyano, submitted for publication.
6. All new compounds were characterized by concordant analytical and spectral data. The structural formulas containing asymmetric atoms refer to racemic compounds.
7. Treatment of a N-ethoxycarbonylnorproerythrinadienol similar to 2a with methyl fluorosulfonate led to the corresponding aporphine in 0.9% yield.⁸
8. T. Kametani, K. Takahashi, K. Ogasawara, and K. Fukumoto, Chem. Pharm. Bull., 1973, 21, 662.
9. S. M. Kupchan and C.-K. Kim, J. Am. Chem. Soc., 1975, 97, 5623.
10. The melting point (as the perchlorate salt) and ir, uv, nmr, and mass spectra were in good agreement with those reported for laurifonine.
11. S. M. Kupchan, V. Kameswaran, J. T. Lynn, D. K. Williams, and A. J. Liepa, J. Am. Chem. Soc., 1975, 97, 5622.

Received, 28th November, 1975