BIOMIMETIC SYNTHESIS OF THE DIBENZAZONINE ALKALOID LAURIFONINE

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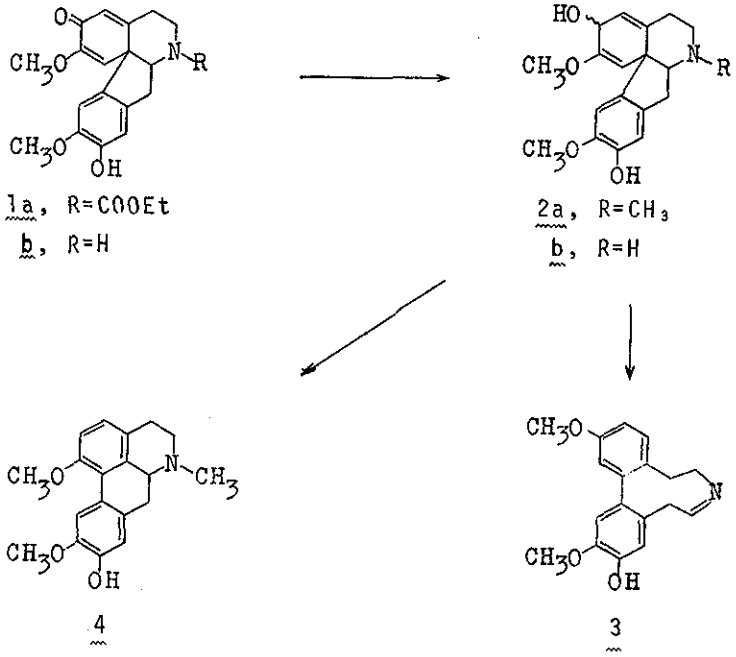
A facile and efficient biomimetic synthesis of laurifonine (9a) is described. Reduction of (±)-O-methylflavinantine (5a) with sodium borohydride yielded a mixture of the epimeric dienols 6a, in 83% yield. Treatment of the dienol mixture with boron trifluoride-etherate followed by hydrogenation over platinum in methanol gave laurifonine (9a, 81%). When a mixture of (±)-proerythrinadienols (2a) was subjected to acid-catalyzed rearrangement, the (±)-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 dibenzazonine 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 dibenzazonine alkaloid precursors, (±)-N-ethoxycarbonylnorproerythrinadienone (1a)[5] was treated with $LiAlH_4$ in THF under reflux for 16 hr, and a mixture of the epimeric dienols (2a) was obtained. This mixture could be separated by preparative t&c to give (±)-proerythrinadienol I[6] (60%, mp 167.5-169°



1a, R=COOEt
b, R=H

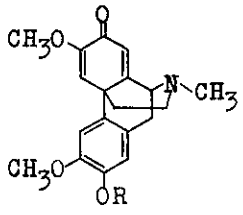
2a, R=CH3
b, R=H

4

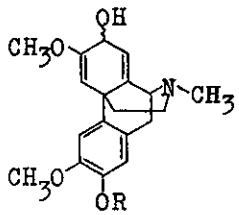
3

(MeOH-Et_2O); uv λ_{max}^{EtOH} (log ε) 291 (3.74), 235 (sh, 3.94) nm; ir $\lambda_{max}^{CHCl_3}$ 2.82, 6.04 μ; nmr ($CDCl_3$) δ 6.80 and 6.30 (s, s, 2H, Ar<u>H</u>), 5.84 (d, J=3 Hz, 1H, olefinic <u>H</u>), 4.64 (s, 1H, olefinic <u>H</u>), 4.72 (d, <u>J</u>=3 Hz, 1H, >C<u>H</u>-OH), 3.79 and 3.50 (s, s, 6H, 2-OC<u>H</u>$_3$), 2.33 (s, 3H, N-C<u>H</u>$_3$); mass spectrum <u>m/e</u> (%) 329 (10, M^+), 312 (100), 311 (83), 296 (46), 281 (21)) and (±)-proerythrinadienol II (14%; mp 169.5-171° (MeOH-Et_2O); uv λ_{max}^{EtOH} (log ε) 291 (3.72), 235 (sh, 3.94) nm; ir $\lambda_{max}^{CHCl_3}$ 2.82, 6.04 μ; nmr ($CDCl_3$) δ 6.81 and 6.50 (s, s, 2H, Ar<u>H</u>), 5.88 (d, <u>J</u>=4 Hz, 1H, olefinic <u>H</u>), 4.68 (s, 1H, olefinic <u>H</u>), 4.66 (d, <u>J</u>=4 Hz, 1H, >C<u>H</u>-OH), 3.80 and 3.48 (s, s, 6H, 2-OC<u>H</u>$_3$), 2.33 (s, 3H, N-C<u>H</u>$_3$); mass spectrum <u>m/e</u> (%) 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 (±)-proerythrinadienols I and II (<u>2a</u>) gave, in 85% yield, (±)-1,10-dimethoxy-9-hydroxyaporphine (<u>4</u>) 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-Et_2O); uv λ_{max}^{EtOH} (log ε) 316 (4.18), 307 (4.19), 279 (4.04), 269 (sh, 3.92), 233.5 (4.59) nm; ir $\lambda_{max}^{CHCl_3}$ 2.82 μ; nmr ($CDCl_3$) δ 7.89 (s, 1H, C-11 <u>H</u>), 6.98 (d, <u>J</u>=8.6 Hz, 1H, C-2 <u>H</u> or C-3 <u>H</u>), 6.88 (d, <u>J</u>=8.6 Hz, 1H, C-2 <u>H</u> or C-3 <u>H</u>), 6.80 (s, 1H, C-8 <u>H</u>), 3.90 and 3.86 (s, s, 6H, 2-OC<u>H</u>$_3$), 2.54 (s, 3H, N-C<u>H</u>$_3$); mass spectrum <u>m/e</u> (%) 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 (±)-proerythrinadienols (<u>2a</u>) favors the aporphine route (<u>2a</u> → <u>4</u>) instead of the dibenzazonine route (<u>2a</u> → <u>3</u>). 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]

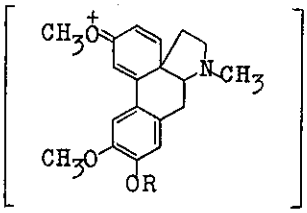
To evaluate the alternative route (<u>via</u> morphinandienone) (±)-<u>O</u>-methylflavinantine (<u>5a</u>)[9] was reduced with $NaBH_4$ in methanol



5a, R=CH_3
b, R=H



6a, R=CH_3
b, R=H



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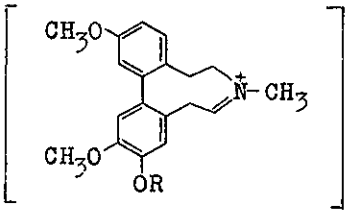

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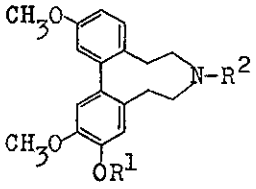
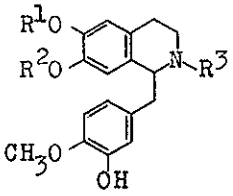
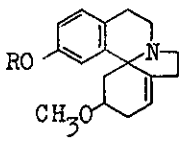


9a, $R^1=R^2=CH_3$
b, $R^1=H$, $R^2=CH_3$
c, $R^1=CH_3$, $R^2=H$
d, $R^1=R^2=H$



10a, $R^1=R^3=H$, $R^2=CH_3$
b, $R^1=R^3=CH_3$, $R^2=H$



11a, R=H
b, R=CH_3

to yield the epimeric dienols (6a) in 83% yield. These were also separable by preparative t&c, i.e., (±)-O-methylflavinantinol I as a crystalline material (mp 161-162.5° (MeOH-Et_2O); ir $\lambda_{max}^{CHCl_3}$ 2.73, 2.80, 6.04 μ; uv λ_{max}^{EtOH} (log ε) 285 (3.68), 232 (sh, 3.96) nm; nmr ($CDCl_3$) 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, >CH-OH), 3.87, 3.85, and 3.73 (all s, 9H, 3-OCH_3), 2.45 (s, 3H, N-CH_3); mass spectrum m/e (%) 343 (54, M^+), 328 (39), 326 (47), 325 (100), 310 (36)), and (±)-O-methylflavinantinol II as an oil (ir $\lambda_{max}^{CHCl_3}$ 2.73, 2.80, 6.04 μ; uv λ_{max}^{EtOH} (log ε) 285 (3.68), 232 (sh, 3.98) nm; nmr ($CDCl_3$) 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, >CH-OH), 3.87, 3.84, and 3.74 (all s, 9H, 3-OCH_3), 2.46 (s, 3H, N-CH_3); mass spectrum m/e (%) 343 (29, M^+), 328 (20), 326 (37), 325 (100), 310 (36)). Treatment of the mixture of (±)-O-methylflavinantinols (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 dibenzazonine 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 dibenzazonine alkaloids which occur in plants of the family Menispermaceae may arise by a pathway similar to route B, whereas the dibenzazonines 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.

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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]

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10. The melting point (as the perchlorate salt) and ir, uv, nmr, and mass spectra were in good agreement with those reported for laurifonine.

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Received, 28th November, 1975