Tetrahedron Letters No. 47, pp 4521 - 4524.

0040-4039/79/1115-4521$02.00/0

A BIOGENETICALLY PATTERNED CONVERSION OF PALMATINE INTO POLYCARPINE

Natesan Murugesan and Maurice Shamma*

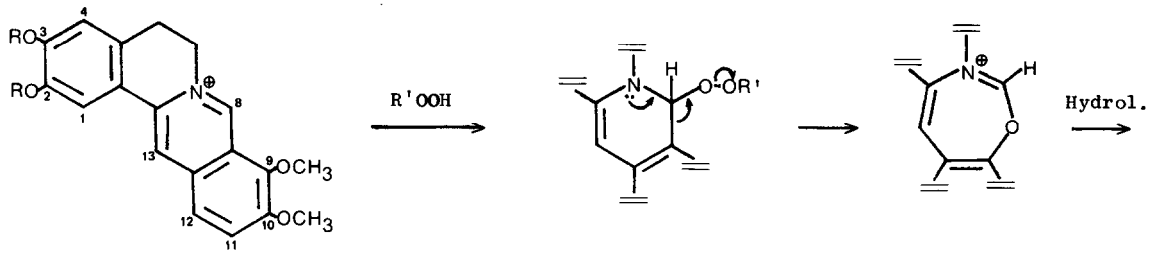
Department of Chemistry, The Pennsylvania State University,

University Park, Pennsylvania 16802

Oxidation of palmatine (1) choride with m-chloroperbenzoic acid in methylene chloride in the presence of sodium bicarbonate at near -78° C yields polycarpine (2). A new biogenetic route to the aporphines is proposed which does not involve phenolic oxidative coupling, and proceeds through the intermediacy of protoberberinium salts.

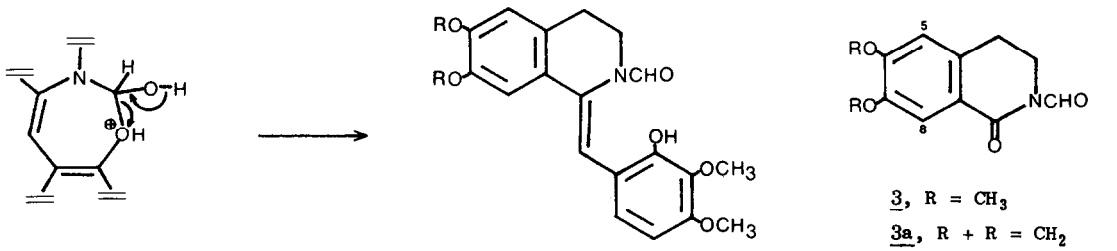
Within the nexus of known naturally occurring benzylisoquinolines, the alkaloid polycarpine (2) found in Enantia polycarpa Engl. et Diels (Annonaceae) can be singled out because of its unusual structural features which include an N-formyl enamide as well as three oxygenated substituents in the bottom ring. Following its structural elucidation, it was adumbrated that polycarpine is the result of formaldehyde attack on a 3,4-dihydrobenzylisoquinoline.[1]

It appeared to us, however, that polycarpine (2) must be derived biogenetically from the protoberberinium salt palmatine (1) through hydroperoxide attack at the C-8 iminium site, followed by rearrangement and hydrolysis as denoted below; especially since palmatine is known to accompany polycarpine in the plant.[2]



1, R = CH_3

1a, R + R = CH_2



2, R = CH_3

2a, R + R = CH_2

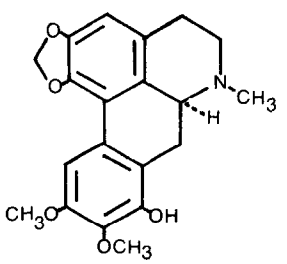
3, R = CH_3

3a, R + R = CH_2

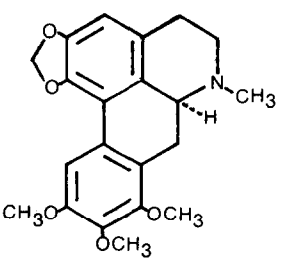
Efforts to achieve such a transformation in vitro in preparative yields were, therefore, initiated. Treatment of readily available berberine (1a) chloride with m-chloroperbenzoic acid in HOAc, HMPT, or CH_2Cl_2; H_2O_2 at different pH's; and peracetic acid in HOAc, HMPT, or CH_2Cl_2; all at varying temperatures, were to no avail. Finally, the use of m-chloroperbenzoic acid in CH_2Cl_2 in the presence of solid sodium bicarbonate at near -78° C led to a 20% yield of the required oily benzylisoquinoline enamide 2a, $C_{20}H_{19}NO_6$; $\nu_{max}^{CHCl_3}$ 1610, 1660 and 3500 cm^{-1}; λ_{max}^{EtOH} 220, 292 and 332 nm (log ε 4.59, 4.21 and 4.19); δ ($CDCl_3$) 2.83 (2H, t, J = 6 Hz, $ArCH_2$), 3.83 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.93 (2H, t, J = 6 Hz, CH_2N), 5.92 (2H, s, OCH_2O), 6.15 (1H, s, OH), 6.53, 6.80 and 7.23 (3 x 1H, 3s, ArH or =CH), 6.38 (1H, d, J = 9 Hz, ArH), 6.95 (1H, d, J = 9 Hz, ArH), and 8.07 (1H, s, NCHO); m/e 369 (M^+, base), 354, 352, 341, 340, 326, 324, 308, 296, 294, 181, 176 and 151; together with a 15% yield of N-formylnoroxyhydrastinine (3a), $C_{11}H_9NO_4$, mp 159-160° C (EtOH); $\nu_{max}^{CHCl_3}$ 1675 and 1705 cm^{-1}; δ ($CDCl_3$) 2.91 (2H, t, J = 6 Hz, $ArCH_2$), 3.95 (2H, t, J = 6 Hz, CH_2N), 6.03 (2H, s, OCH_2O), 6.68 (1H, s, H-5), 7.51 (1H, s, H-8), and 9.56 (1H, s, NCHO); m/e 219 (M^+, base), 191, 190, 172, 163, 162 and 134.

Oxidation of palmatine (1) chloride under identical conditions led to a 40% yield of colorless crystals of 2, mp 179-180° C (MeOH), spectrally identical with polycarpine (Lit.[1] mp 178-180° C from MeOH). In this instance, the accompanying imide was 3, N-formylcorydaldine, $C_{12}N_{13}NO_4$, mp 134-137° C (decomp.) (MeOH); $\nu_{max}^{CHCl_3}$ 1675 and 1705 cm^{-1}; δ ($CDCl_3$) 2.95 (2H, t, J = 6 Hz, $ArCH_2$), 3.93 (6H, s, 2 x OCH_3), 3.96 (2H, t, J = 6 Hz, CH_2N), 6.68 (1H, s, H-5), 7.58 (1H, s, H-8), and 9.60 (1H, s, NCHO); m/e 235 (M^+, base), 207, 179 and 178; isolated in 8% yield.

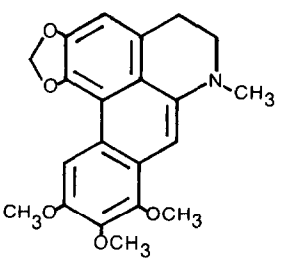
An intriguing possibility is that benzylisoquinoline enamides may not be the ultimate capstone of a long biogenetic process originating with tyrosine and proceeding through the intermediacy of reticuline and protoberberinium salts. Thus, enamide 2a could conceivably undergo facile geometric isomerization about the central double bond succeeded by electrocyclization to provide an aporphinoid. Aporphine bases which could ultimately result from such a process would be leucoxine (4),[3] ocopodine (5),[3,4] and dehydroocopodine (6),[5] found mainly within the genus Ocotea (Lauraceae).



4

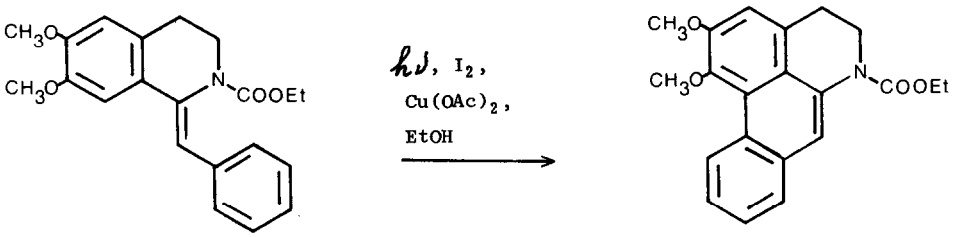


5



6

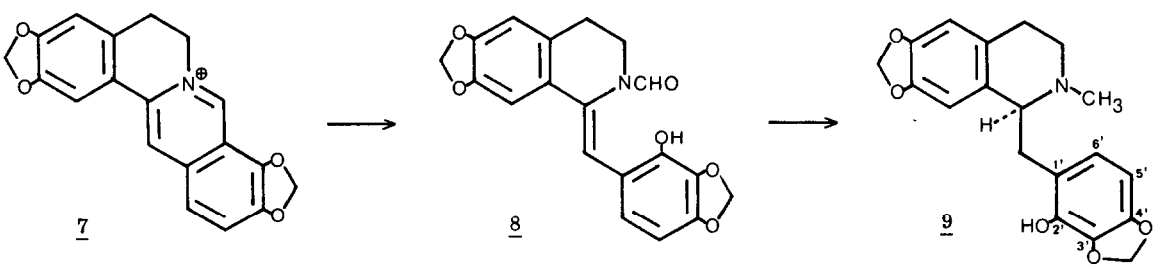
Noteworthy in this context is the fact that the photocyclization of non-phenolic benzylisoquinoline enamides and enurethans to aporphinoids is a well established transformation:[6]



It should be cautioned, however, that this new route for aporphine biogenesis, whose importance lies in that it does not require phenolic oxidative coupling, is hypothetical and must await support by in vivo studies with appropriately labeled precursors before it can be accepted.

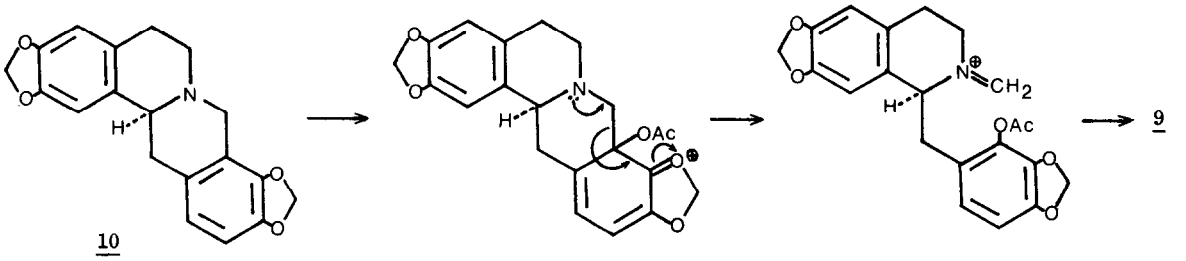
A benzylisoquinoline alkaloid structurally related to polycarpine (2) is (-)-ledecorine (9), obtained from Corydalis ledebouriana K. et K. (Fumariaceae), which incorporates three oxygenated substituents in the bottom ring.[7,8] The balance of probability is that this base is derived either from hydroperoxide type oxidation of the protoberberinium alkaloid coptisine (7) to afford enamide 8 with subsequent formyl hydrolysis, stereospecific reduction, and N-methylation (Path A); or alternatively from a retro-Mannich condensation of a protoberberine quinol acetate[9] derived from (-)-tetrahydrocoptisine (10) (Path B).[10]

Path A



7 8 9

Path B

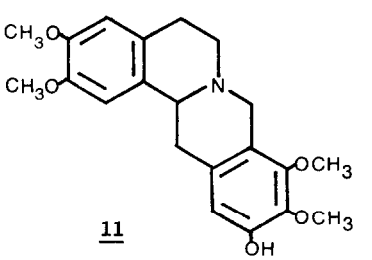


10 9

Acknowledgments:- This research was supported by grant NS15437 awarded by the National Institute of Neurological and Communicative Disorders and Stroke, PHS, DHEW. The authors are grateful to Professors Jack L. Beal, Michael P. Cava and Paul L. Schiff, Jr., for alkaloidal samples.

References and Notes

1. A. Jössang, M. Leboeuf, A. Cavé, M. Damak and C. Riche, C.R. Acad. Sci., Ser. C, 284, 467 (1977).
2. A parallel oxidation is known to occur in the benzophenanthridine series: H. Ishii, T. Ishikawa, S.-T. Lu and I.-S. Chen, Tetrahedron Lett., 1203 (1976).
3. V. Vecchieti, C. Casagrande and G. Ferrari, Farmaco ed. Sci., 32, 767 (1977).
4. M.P. Cava, Y. Watanabe, K. Bessho and M.J. Mitchell, Tetrahedron Lett., 2437 (1968).
5. M.P. Cava and A. Venkateswarlu, Tetrahedron, 27, 2639 (1971).
6. M.P. Cava, M.J. Mitchell, S.C. Havlicek, A. Lindert and R.J. Spangler, J. Org. Chem., 35, 175 (1970). N.C. Yang, A. Shani and G.R. Lenz, J. Am. Chem. Soc., 88, 5369 (1969). See also S.M. Kupchan, J.L. Moniot, R.M. Kanojia and J.B. O'Brien, J. Org. Chem., 36, 2413 (1971).
7. I.A. Israilov, M.S. Yunusov and S.Yu. Yunusov, Khim. Prir. Soedin., 537 (1978); Chem. Nat. Compds., 465 (1979).
8. The S absolute configuration indicated here for (-)-ledecorine (9) is the reverse of that assigned in Ref. 7 above. It is known that N-methyltetrahydrobenzylisoquinolines incorporating a phenolic function in ring C at C-2' and belonging to the S configuration are levorotatory: J. Kunitomo, K. Morimoto, K. Yamamoto, Y. Yoshikawa, K. Azuma and K. Fujitani, Chem. Pharm. Bull. (Tokyo), 19, 2197 (1971).
9. H. Hara, M. Hosaka, O. Hoshino and B. Umezawa, Tetrahedron Lett., 3809 (1978).
10. There is a definite possibility that, in the future, protoberberine alkaloids will be recognized which bear a trioxygenated ring D, with one of the three substituents, most likely in the form of a phenol, located at C-12. Such protoberberines can arise in nature from intramolecular cyclization of 2',3',4'- or 2',4',5'-substituted N-formyl benzylisoquinoline enamides or the corresponding N-methylidenetetrahydrobenzylisoquinolinium salts formed through routes parallel to paths A or B above. A plausible candidate for such a protoberberine would be stepharotine whose assigned structure 11 placing the phenolic function at C-11 has been challenged: W. Augstein and C.K. Bradsher, J. Org. Chem., 34, 1349 (1969). For other syntheses of compound 11 see M. Tomita, M. Kozuka, H. Ohyabu and K. Fujitani, J. Pharm. Soc. Japan, 90, 82 (1970); and S. Ishiwata and K. Itakura, Chem. Pharm. Bull. (Tokyo), 18, 896 (1970).



11

(Received in USA 20 August 1979)