2 H). These signals are due to the para, meta, and ortho protons, respectively, of a phenyl ring, as confirmed by the spin decoupling experiments in Figure 2. The extraordinary high field position of these phenyl protons, which requires their placement in the porphyrin ring current, and the presence of all the protons due to protoporphyrin IX in the NMR spectrum uniquely identify the green porphyrin as *N*-phenylprotoporphyrin IX (dimethyl ester). Very similar, if simpler, spectra are obtained if the pigment is first resolved into two fractions. The NMR spectra of the two fractions, however, indicate that each fraction consists of two very similar isomeric structures. The four possible isomers of *N*-phenylprotoporphyrin thus appear to be formed, the isomers with the *N*-phenyl substituent on two of the nonequivalent nitrogen atoms being resolved from those with the substituent on the other two nitrogens. Studies in progress have established that the green porphyrin mixture is a major product of the phenylhydrazine–hemoglobin interaction.

The globin envelope does not play an essential role in arylation of heme by phenylhydrazine. In effect, a similar mixture of *N*-phenylprotoporphyrin IX isomers is produced in moderate yield when hemin is allowed to react with phenylhydrazine·HCl.[9] The reaction does not take place under anaerobic conditions. This reaction not only excludes a mechanistic role for the protein in heme arylation, it also confirms the structure of the green porphyrin and provides the first synthetic route to *N*-arylporphyrins. The scope of the synthetic procedure is under investigation.

Benzene, nitrogen, hydrogen peroxide, and superoxide are known products of the aerobic reaction of phenylhydrazine with hemoglobin.[3,10] Phenyl radicals generated by the heterolysis of phenyldiazene are presumed as intermediates in benzene formation.[11] The reaction of phenyl radicals with prosthetic heme thus offers an attractive mechanism for the biological formation of *N*-phenylheme, although the details of the interaction and its role in hemoglobin precipitation and cell lysis remain to be elucidated.[12] The only precedent for this process is our recent finding that the prosthetic heme of cytochrome P-450 is *N*-alkylated during catalytic turnover of olefinic and acetylenic substrates.[14] The involvement of the heme nitrogens in the interactions of both hemoglobin and cytochrome P-450 suggests a possible general role for such reactions in abnormal heme catabolism.

Acknowledgment. This research was supported by NIH Grants GM-25515, P50 AM-18520, and RR-00719. P.R.O.M. is a Fellow of the Alfred P. Sloan Foundation (1978–1982).

(8) Porphyrin ring NMR assignments: 9.90–10.25 (4 H, meso), 7.60–8.40 (2 H, $CH{=}CH_2$), 5.90–6.50 (4 H, $CH{=}CH_2$), 3.95–4.40 (4 H, $ArCH_2$) 3.25–3.70 (18 H, CH_3), and 2.70–3.30 ppm (4 H, CH_2CO_2).

(9) Hemin chloride (20 mg) and disodium EDTA (10 mg), dissolved in 2 mL of NaOH (0.1 N) and diluted to 10 mL with H_2O, were brought to pH 8 with phosphate buffer (1 N) before phenylhydrazine·HCl (50 mg) was added. After 1 h, the mixture was acidified (1 N HCl), and the precipitated solid was put through the same workup as the hemoglobin pigment.[5]

(10) (a) Rostorfer, H. H.; Cormier, M. J. *Arch. Biochem. Biophys.* **1957**, *71*, 235–249. (b) Goldberg, B.; Stern, A.; Peisach, J. *J. Biol. Chem.* **1976**, *251*, 3045–3051. (c) Cohen, G.; Hochstein, P. *Biochemistry* **1964**, *3*, 895–900. (d) Goldberg, B.; Stern, A. *J. Biol. Chem.* **1975**, *250*, 2401–2403.

(11) (a) Huang, P. C.; Kosower, E. M. *J. Am. Chem. Soc.* **1968**, *90*, 2367–2376. (b) Nicholson, J.; Cohen, S. G. *Ibid.* **1966**, *88*, 2247–2251.

(12) Oxyhemoglobin is converted to methemoglobin by reducing agents like phenylhydrazine[13a] and superoxide,[13b] a product of phenylhydrazine autoxidation.[10b] Methemoglobin in turn reverts to oxyhemoglobin on reaction with superoxide.[13b] The oxidation state of the heme during the arylation reaction is therefore uncertain at this time. An in-depth examination of the reaction mechanism is under way.

(13) (a) Castro, C. E.; Wade, R. S.; Belser, N. D. *Biochemistry* **1978**, *17*, 225–231. (b) Winterbourne, C. C.; McGrath, B. M.; Carrell, R. W. *Biochem. J.* **1976**, *155*, 493–502.

(14) (a) Ortiz de Montellano, P. R.; Kunze, K. L.; Mico, B. A. *Mol. Pharmacol.* **1980**, *18*, 602–605. (b) Ortiz de Montellano, P. R.; Beilan, H. A.; Kunze, K. L.; Mico, B. A. *J. Biol. Chem.* **1981**, *256*, 4395–4399. (c) Ortiz de Montellano, P. R.; Beilan, H. A.; Kunze, K. L. *Ibid.* **1981**, *256*, 6708–6713. (d) Ortiz de Montellano, P. R.; Kunze, K. L. *Ibid.* **1980**, *255*, 5578–5585.

Structure Revision of 37 Lycoctonine-Related Diterpenoid Alkaloids

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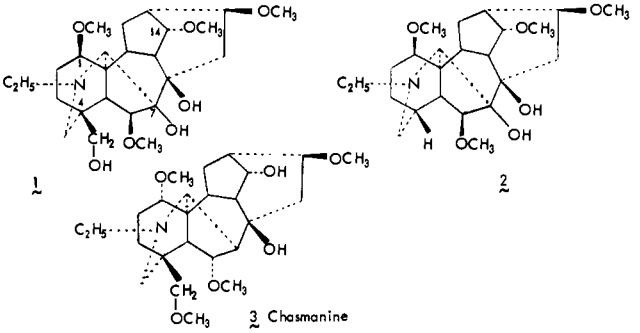
Received June 29, 1981

The structure of the key C_{19}-diterpenoid alkaloid, lycoctonine, was established as **1** in 1956 by an X-ray analysis of the hydroiodide salt of 4-de(oxymethylene)lycoctonine (**2**).[1] Since then



the structures of most of the lycoctonine-type alkaloids[2] have been assigned on the basis of chemical and/or spectral correlation with lycoctonine.[3] In 1976, we revised[4] the configuration of the C-(1)-methoxyl group of chasmanine (**3**) from β to α on the basis of X-ray analysis and mentioned that the reported[5] chemical correlation between browniine and chasmanine is in error. This statement assumed that the structure of browniine was correct, since its structure had been assigned[6] on the basis of direct chemical correlation with lycoctonine. Recently, we learned that X-ray analysis of two rearrangement products of a lycoctonine derivative has indicated a configuration of the C(1)-methoxyl group in these two compounds opposite to that reported in the original X-ray analysis of compound **2**.[7] This development has prompted us to submit a preliminary report of our own investigation of this problem.

Methylation of delsoline (**4**) with methyl iodide and sodium hydride in a sealed tube at reflux temperature afforded mainly the known alkaloid delphatine (**5**).[8,9] Because the α configuration of the C(1)-hydroxyl in delsoline is well established by chemical[10]

(1) M. Przybylska and L. Marion, *Can. J. Chem.*, **34**, 185 (1956); **37**, 1843 (1959).

(2) These alkaloids possess the skeleton of lycoctonine in which the C(7) position is always oxygenated by hydroxyl or methoxyl or methylenedioxyl groups.

(3) S. W. Pelletier and N. V. Mody *Alkaloids (N.Y.)*, **17**, 1–103 (1979).

(4) S. W. Pelletier, W. H. DeCamp, and Z. Djarmati, *J. Chem. Soc., Chem. Commun.* 253 (1976).

(5) O. E. Edwards, L. Fonzes, and L. Marion, *Can. J. Chem.*, **44**, 583 (1966).

(6) M. H. Benn, M. A. M. Cameron, and O. E. Edwards, *Can. J. Chem.*, **41**, 477 (1963).

(7) O. E. Edwards, personal communication to S. W. Pelletier, 23 March 1981, O. E. Edwards, *Can. J. Chem.*, in press; M. Cygler, M. Przybylska, and O. E. Edwards, *Acta Crystallogr.* in press.

(8) M. S. Yunusov and S. Yu. Yunusov, *Khim. Prir. Soedin.*, **6**, 334 (1970).

(9) S. W. Pelletier, R. S. Sawhney, H. K. Desai, and N. V. Mody, *J. Nat. Prod.*, **43**, 395 (1980).

(10) F. Sparatore, R. Greenhalgh, and L. Marion, *Tetrahedron*, **4**, 157 (1958).

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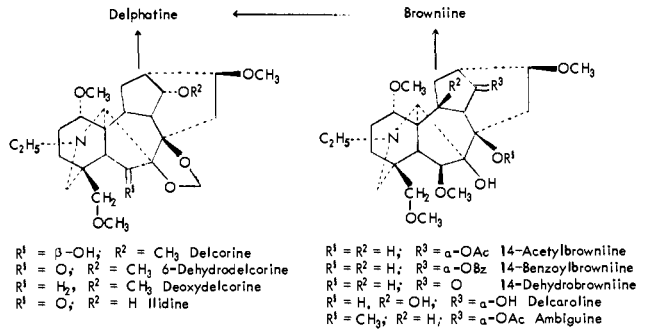
Scheme I

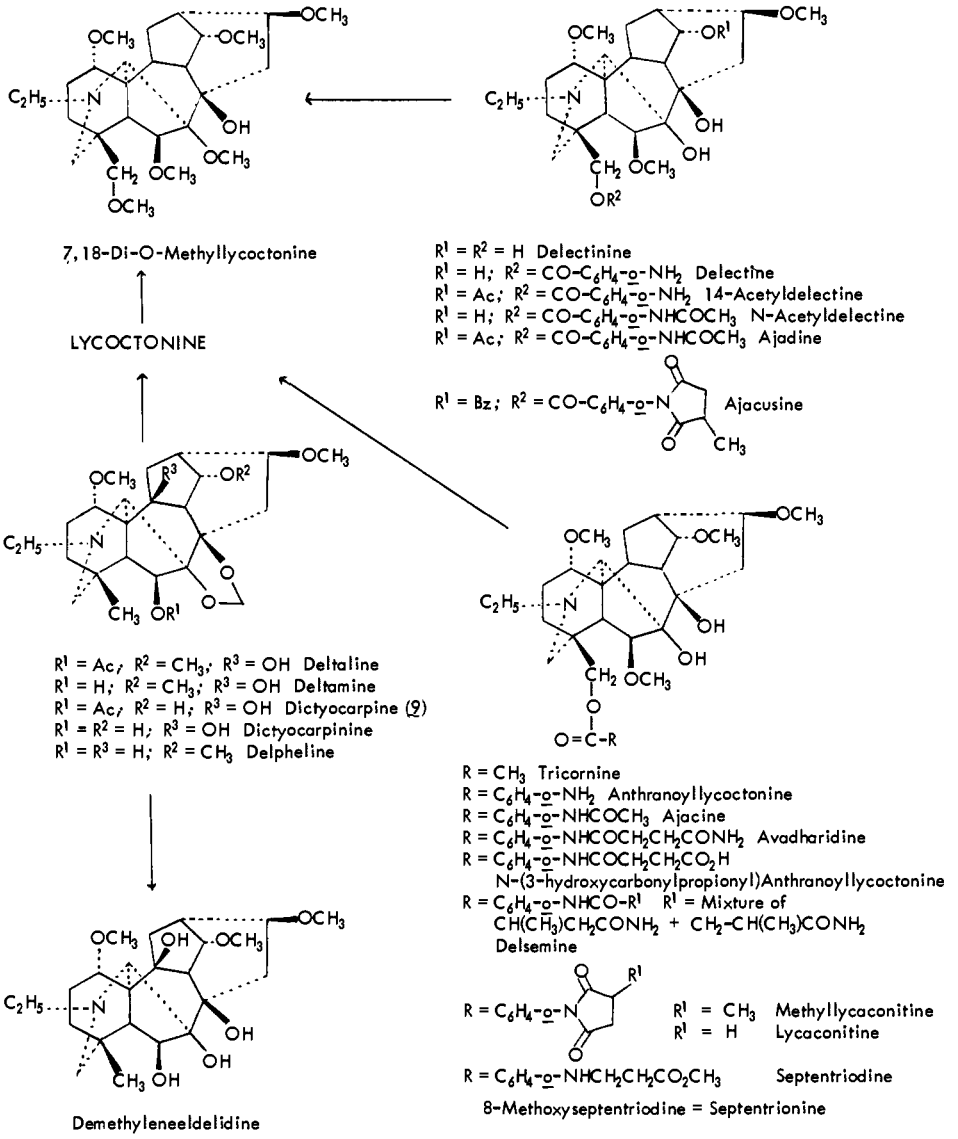


perchlorate ($R = 0.081$).[13] We have also confirmed the revised structue of another key alkaloid,, dictyocarpine (**9**), by X-ray analysis ($R = 0.105$).[13]

In view of the above results, the configuration of the C(1)-methoxy group in 37 C_{19}-diterpenoid alkaloids which have been chemically related with lycoctonine, browniine, or delphatine must be also revised from β to α. Schemes I and II present the corrected structures and correlation diagrams for all the lycoctonine-related alkaloids.[14]

In 1977, Sakai Shinma, and Okamoto reported[15,16] the structure determintion of a new alkaloid, gigactonine (**8**). Methylation of gigactonine gave delsoline (**4**) and a dimethylated product which showed the same mass spectrum as that of a sample of delphatine (**5**) prepared from lycoctonine. Howevr, these investigators

Scheme II



and spectral data,[11] *delphatine must also have a C(1)-α-methoxyl group.* We have also transformed lycoctonine[9] and browniine to delphatine by methylation with methyl iodide and sodium hydride. *Therefore, the structures of lycoctonine and browniine must be revised to* **6** and **7**, *respectively.*[12] The revised structure for browniine (**7**) was confirmed by the X-ray analysis of browniine

claimed that the IR and ^{1}H NMR spectra of the dimethylated product were different from those of delphatine (**5**). In the full report of this work,[16] the ^{1}H NMR spectral data given for the

(11) S. W. Pelletier, N. V. Mody, R. S. Sawhney, and J. Bhattacharyya, *Heterocycles*, **7**, 327 (1977).

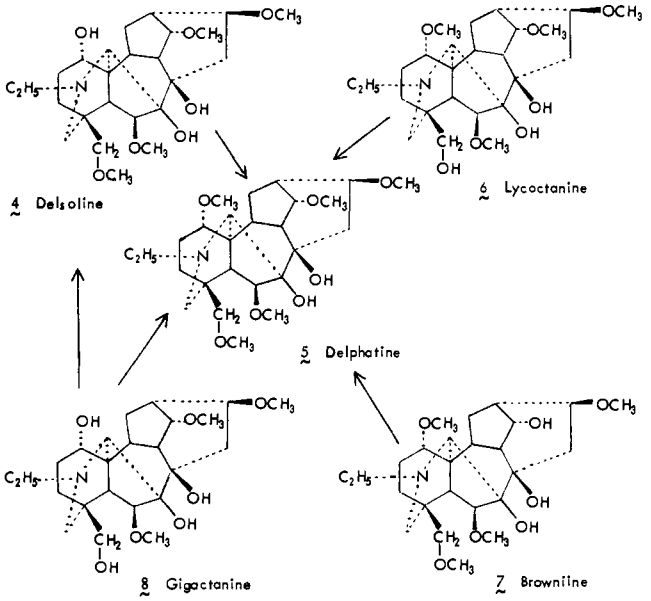
(12) The stereochemistry shown for the C(14) group in these alkaloids is with reference to the cyclopentane ring.

(13) A detailed X-ray analysis of browniine perchlorate and dictyocarpine will be published later.

(14) Owing to the limited space available here, complete references and correlation diagrams pertaining to these lycoctonine–related alkaloids will be published along with the X-ray analysis results.

(15) S. Sakai, N. Shinma, and T. Okamoto, *Heterocycles*, **8**, 207 (1977).

(16) S. Sakai, N. Shinma, S. Hasegawa, and T. Okamoto, *Yakugaku Zasshi*, **98** (10), 1376 (1978).



dimethylated product of gigactonine and that given for delphatine, prepared from lycoctonine, are so similar that the minor differences in their chemical shifts could result from solvent effects. On the basis of our results, it seems likely that the dimethlated product prepared from gigactonine and the sample of delphatine prepared from lycoctonine are identical.

Of interest is the fact that there is not a single, naturally occurring C_{19}-diterpenoid alkaloid which bears a C(1)-β-OCH_3 group.[17]

(17) The configuration of the C(1)-methoxyl group must be also revised from β to α in delbiterine (16-demethyldelphatine) and in elatine (7,8-methylenedioxy)methyllycaconitine.

Total Synthesis of (+)-Compactin (ML-236B)

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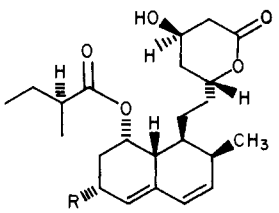
Compactin[1] (**1**) and ML-236B are identical fungal metabolites isolated from strains of *Penicillium brevicompactum* and *Penicillium citrinum*, respectively. Compactin has been shown to be a potent competitive inhibitor[2] of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase), the rate-controlling enzyme in cholesterol biosynthesis.

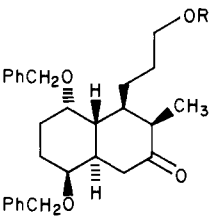


1, R = H
2, R = CH_3

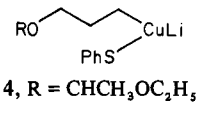
(1) Brown, A. G.; Smale, T. C.; King, T. J.; Hasenkamp, R.; Thompson, R. H. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1165.
(2) Endo, A.; Kuroda, M.; Tanzawa, K. *FEBS Lett.* **1976**, *72*, 323.

The apparent efficacy of **1** as a therapeutic agent for the treatment of hypercholesterolemia in humans and the enhanced activity of mevinolin, **2**, in in vitro animal models precipitated our interest to devise general synthetic methodologies for the preparation of this important family of substituted hexahydronaphthalene lactones. Herein, we report the first synthesis of (+)-compactin.

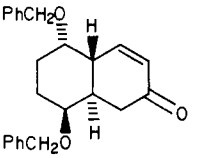
Central to our synthetic plan is the development of a viable route to **3**. This key intermediate not only possesses strategically situated oxygen functionalities for the eventual elaboration of the *transoid* conjugated diene but also allows the construction of the highly sensitive β-hydroxy lactone of **1** during the final stages of the synthetic sequence. We projected that **3** might be prepared by the combination of conjugate addition of the functionalized mixed cuprate **4**[3,4] to the enone **5**[5] and trapping of the resulting kinetic enolate with a suitable electrophile. In turn, **5** may be derived from the readily available *trans*-dione (**6**).[6]



3, R = $CHCH_3OC_2H_5$

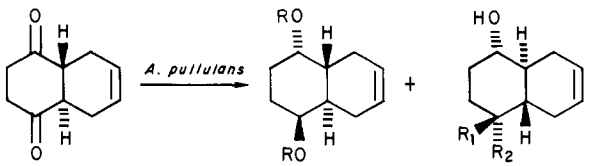


4, R = $CHCH_3OC_2H_5$



5

Since chemical reduction of **6** with diisobutylaluminum hydride afforded a statistical mixture of racemic diastereomers, we decided to effect the reduction of **6** into **7** by using microbial methods. Although microbiological conversion of **6** to **7** had been reported,[7] the yield of this transformation was very low. On the other hand, exposure of **6** to *Aureobasidium pullulans* NRRL Y-12610[8] afforded **7**, in 33% yield, accompanied by **8** (22%) and (±)-**9** (45%). The optical purities of **7** and **8** were confirmed by their oxidation with Jones reagent to give (−)-**6** and (+)-**6**, respectively. The inherent symmetry element (C_2 axis) in this chiral intermediate, **7**, and its ready accessibility via microbial methods markedly facilitated the ensuing transformations. Treatment of



(±)-**6**

7, R = H
10, R = CH_2Ph

8, R_1 = OH; R_2 = H
9, R_1 = H; R_2 = OH

7 with 2 equiv of NaH in Me_2SO at 25 °C, followed by the addition of $C_6H_5CH_2Cl$[9] gave **10** (99%) as an oil, which upon reaction with phenylselenenyl bromide (HOAc/KOAc, 25 °C, 1 h) furnished **11**. Saponification of **11** [1.2 equiv of KOH/CH_3OH–ether (4:1), 25 °C, 2 h] afforded **12** (89%), which was oxidized to the corresponding selenoxide (H_2O_2/THF, 25 °C, 2.5 h). The latter undergoes smooth elimination on heating at 55 °C for 2 h to give the allylic alcohol **13**, which without isolation was subjected to Jones oxidation to give **5** (71% from **10**).

(3) Eaton, P. E.; Cooper, G. F.; Johnson, R. C.; Mueller, R. H. *J. Org. Chem.* **1972**, *37*, 1947.
(4) Posner, G. H.; Brunelle, D. J.; Sinoway, L. *Synthesis* **1974**, 662.
(5) Crossley, N. S. *Tetrahedron Lett.* **1971**, 3327.
(6) Van Tamelen, E. E.; Shamma, M.; Burgstahler, A. W.; Wolinsky, J.; Tamm, R.; Aldrich, P. E. *J. Am. Chem. Soc.* **1969**, *91*, 7315. Ireland, R. E.; Marshall, J. A. *J. Org. Chem.* **1962**, *27*, 1620.
(7) Aklin, W.; Prelog, V.; Schenker, F.; Serdarevic, B.; Walter, P. *Helv. Chim. Acta* **1965**, *48*, 1725.
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(9) Iwashige, T.; Saeki, H. *Chem. Pharm. Bull.* **1967**, *15*, 1803.

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