A Model for the Biogenesis of the Spirobenzylisoquinoline Alkaloids[1]

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Abstract: Reduction of 2,3-dimethoxy-10,11-dibenzyloxy-13-methylprotoberberine iodide (**22**) with lithium aluminum hydride in ether gave 2,3-dimethoxy-10,11-dibenzyloxy-13-methyl-7,8-dihydroprotoberberine (**24**). N-Methylation followed by hydrolysis with 48% aqueous hydrobromic acid then afforded 2,3-dimethoxy-10,11-dihydroxy-13-methyl-7,8-dihydroprotoberberine methobromide (**26**). When **26** was heated in base, rearrangement occurred to the quinone methide **28**. Tautomerization of **28** to spiro[1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline-1,2′-1′-methylene-5′,6′-dihydroxyindane] (**29**) took place when DMSO was added.

In the course of his systematic investigation of the isoquinoline alkaloids, Manske reported in 1940 the isolation, from *Corydalis ochotensis* Turcz. (Fumariaceae), of two related alkaloids, ochotensine and ochotensimine.[2] These were not at that time fully characterized, but in 1964 McLean and coworkers presented the correct structure for ochotensimine,[3,4] and two years later an X-ray analysis of ochotensine methiodide conclusively established the structure and absolute configuration of ochotensine to be as in expression **1**, and hence that of ochotensimine to be as in **2**.[5] Since that time a number of nonbiogenetic syntheses of ochotensimine and related systems have been carried out.[6-10]

Very recently, the structures of five additional alkaloids also possessing a spirobenzylisoquinoline nucleus have been reported.[11-13]

At the start of our investigations, no biogenetic hypothesis had been advanced to account for the presence of spirobenzylisoquinolines in nature. An initial clue to the identity of their precursors was adumbrated, however, by consideration of Manske's original isolation work. Also present in *C. ochotensis*, along with ochotensine (**1**) and **2** were three other alkaloids of established structures, namely protopine (**3**), cryptocavine (**4**), and aurotensine (**5**).[2] Since **3** and **4** are clearly derivable from protoberberines, and aurotensine is itself a protoberberine, this ring system immediately became a likely candidate as a precursor for the spirobenzylisoquinolines.

Extending these speculations further, the protoberberine precursor should, by analogy with ochotensine (**1**) and ochotensimine (**2**), have its oxygen substituents present at positions 2, 3, 9, and 10, and should also bear methyl groups at N-7 and C-13. Finally, the ring C exocyclic methylene in the spirobenzylisoquinolines **1** and **2** could be present as an endocyclic C-13(14) double bond in the protoberberine precursor. Inclusion of all these features into the protoberberine system led to the formulation of the dihydroprotoberberine salt **6** as a hypothetical progenitor for alkaloids **1** and **2**.

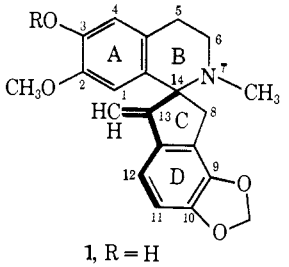
At first glance, the dihydroprotoberberine salt **6** appears to be at best only tangentially related to the spirobenzylisoquinolines. But it was considered that the phenolic groups at C-9 and 10, coupled with the quaternary nitrogen at position 7, could be the functionalities through which species **6** could rearrange to the spirobenzylisoquinoline **9**. In a basic medium, the diphenolic salt **6** could undergo cleavage to the quinonoid intermediate **7** which by the electrocyclic process indicated could form the spirane **8**. A tautomeric shift would then yield the diphenol **9** which may easily be converted in the plant to ochotensimine (**2**).

In order to test *in vitro* the above hypothesis, the synthesis of the C-9,10 substituted protoberberine **6** was first considered. Perusal of the known methods of preparation for protoberberines, however, quickly revealed that C-10,11 substituted protoberberines are much more readily prepared than their C-9,10 analogs. It was decided, therefore, to synthesize instead the diphenolic dihydroprotoberberine salt **26** which, as will be seen later, lends itself equally well to the purposes of this investigation.

The preparation of species **26** in the laboratory involved initially the synthesis of the dibenzyloxyprotoberberine salt **22**, and the details of this work will now be discussed.

Alkylation of the methyl ester of 3,4-dimethoxyphenylacetic acid with methyl iodide using sodium amide as the base gave a single product which crystallized on standing, namely methyl 2-(3′,4′-dimethoxyphenyl)propionate (**10**). Hydrolysis of this ester with 48% hydrobromic acid in acetic anhydride afforded a glaze which did not crystallize, but exhibited physical properties identical with those reported by Bougault for the desired 2-(3′,4′-dihydroxyphenyl)propionic acid (**11**).[14]

(1) For a preliminary communication see M. Shamma and C. D. Jones, *J. Amer. Chem. Soc.*, **91**, 4009 (1969).
(2) R. H. F. Manske, *Can. J. Res. B*, **18**, 75 (1940).
(3) S. McLean and M.-S. Lin, *Tetrahedron Lett.*, 3819 (1964).
(4) S. McLean, M.-S. Lin, and R. H. F. Manske, *Can. J. Chem.*, **44**, 2449 (1966).
(5) S. McLean, M.-S. Lin, A. C. Macdonald, and J. Trotter, *Tetrahedron Lett.*, 185 (1966).
(6) S. McLean, M.-S. Lin, and J. Whelan, *ibid.*, 2425 (1968).
(7) B. A. Beckett and R. B. Kelly, *J. Heterocycl. Chem.*, **5**, 685 (1968).
(8) B. A. Beckett and R. B. Kelly, *Can. J. Chem.*, **47**, 250 (1969).
(9) H. Irie, T. Kishimoto, and S. Uyeo, *J. Chem. Soc. C*, 3051 (1968).
(10) T. Kametani, S. Takano, and S. Hibino, *J. Pharm. Soc. Jap.*, **88**, 1123 (1968).
(11) R. H. F. Manske, *Can. J. Res. Sect. B*, **16**, 438 (1938).
(12) J. K. Saunders, R. A. Bell, C.-Y. Chem, and D. B. MacLean, with R. H. F. Manske, *Can. J. Chem.*, **46**, 2873 (1968).
(13) R. H. F. Manske, R. Rodrigo, D. B. MacLean, D. E. F. Gracey, and J. K. Saunders, *ibid.*, **47**, 3585 (1969); and R. H. F. Manske, R. G. A. Rodrigo, D. B. MacLean, D. E. F. Gracey, and J. K. Saunders, *ibid.*, **47**, 3589 (1969).
(14) M. Bougault, *Ann. Chim. (Paris)*, **25**, 564 (1902).



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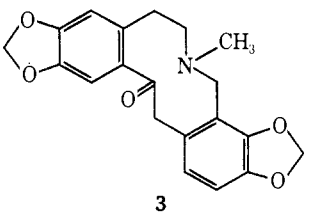

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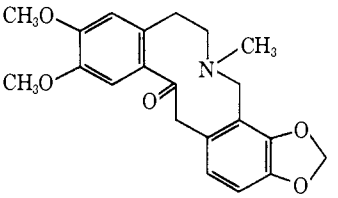

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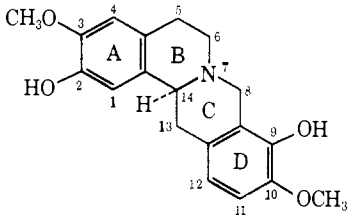

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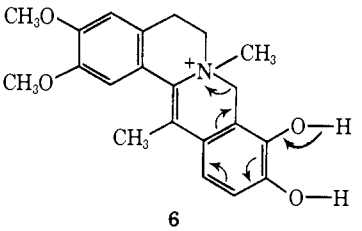

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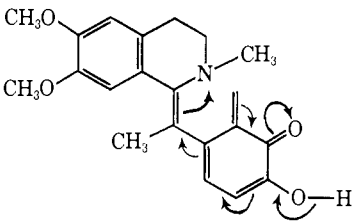

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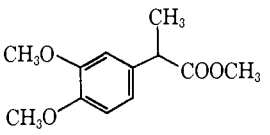

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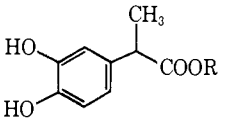
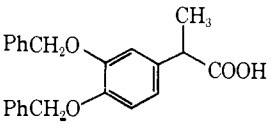


11, R = H
12, R = CH_3



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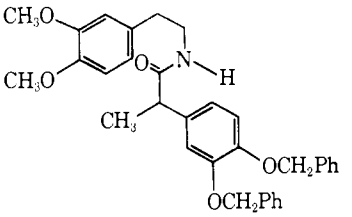

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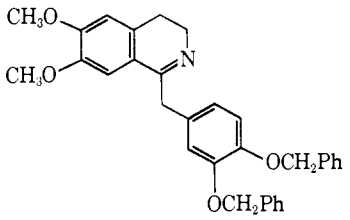

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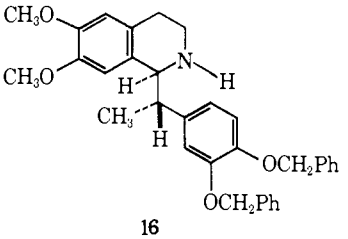

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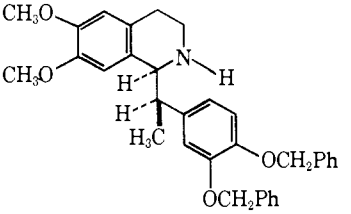

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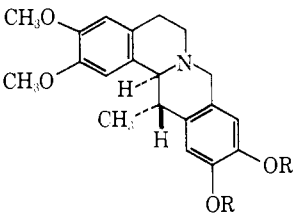
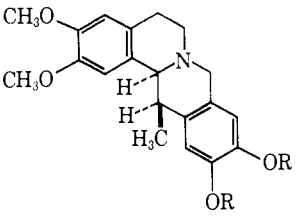
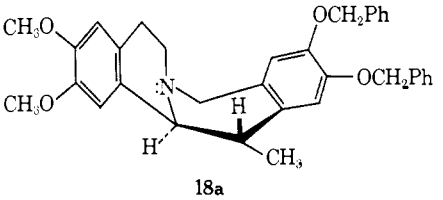


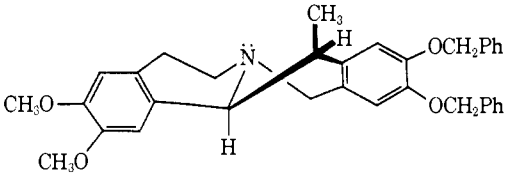
18, R = CH_2Ph
20, R = H



19, R = CH_2Ph
21, R = H



18a



19a

Bearing in mind the difficulties in handling such an easily oxidizable and water soluble diphenolic acid, it was decided to esterify the crude product without purification. The glaze was, therefore, refluxed in methanolic hydrogen chloride and the product distilled *in vacuo*. The colorless ester **12** thus obtained crystallized on standing.

Protection of the two phenolic groups as dibenzyl ethers was the next step in the synthesis. Working under a nitrogen atmosphere, the methyl ester **12** was refluxed with 2 equiv of potassium carbonate and an excess of benzyl chloride. The crude ester product mixture was saponified, and acidification provided the required propionic acid derivative **13**.

The acid chloride derived from the acid **13** was dissolved in chloroform, and added dropwise to homoveratrylamine in the presence of sodium carbonate. The amide **14** was thus readily obtained in

crystalline form and in high yield. Bischler–Napieralski cyclization of **14** gave rise to the imine **15**, and the reduction of this product to a secondary amine was studied under a variety of different experimental conditions.

Reduction of **15** with zinc in acetic acid gave a mixture of diastereoisomeric secondary amines **16** and **17** in a 55:45 ratio, based on the nmr integrals of the C-methyl doublets which appeared at δ 1.39 and 0.91, respectively. When the reduction was carried out with lithium aluminum hydride in ether at room temperature, the ratio of products changed to 60:40, and with sodium borohydride in ethanol at room temperature it reached 80:20. In all of these instances, the isomer **16** with the C-methyl signal at δ 1.39 was the predominant species.

The different mixtures of isomers obtained above reacted readily with formalin to provide mixtures of the C-13-methyltetrahydroprotoberberines **18** and **19**. Such mixtures could be separated by preparative tlc, and each of the two components could be crystallized from methanol.

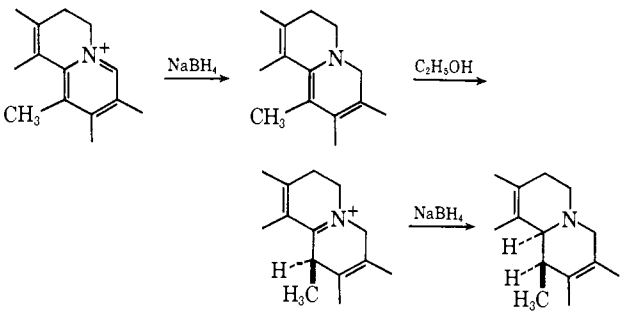
The tetracyclic base **18**, R_f 0.25 in ether, exhibited a C-methyl doublet at δ 1.39 (J = 7.0 Hz). This value together with the very fast pseudo-first-order rate of methiodide formation at which it quaternized (218×10^{-4} sec^{-1}), allowed the assignment of a *cis* B/C ring junction, and provided proof of the *trans* relationship for the C-13 and C-14 hydrogens as indicated in **18** or in conformational expression **18a**.[15]

The minor product **19**, R_f 0.85 in ether, showed a C-13 methyl group relatively upfield at δ 0.91 (J = 7.0 Hz). The very slow rate of N-methylation for this isomer (3.9×10^{-4} sec^{-1}), together with the upfield position of the C-13 methyl signal in the nmr spectrum permitted the stereochemical assignment shown in conformational expression **19a** for this molecule.[15]

It was then found that reduction of the imine **15** with sodium borohydride in ethanol at 0° gave the benzylisoquinoline isomer **16** in an almost pure state and in high yield. Carrying out a Mannich cyclization on this material with formalin gave essentially a single compound as an oil which crystallized on trituration with methanol. The product was the *cis* B/C fused tetrahydroprotoberberine **18**. The preferential formation of the benzylisoquinoline **16** from the imine **15** may be predicted on the basis of Cram's rule.[16]

Heating the tetrahydroprotoberberine **18** with excess mercuric acetate provided a yellow solution of the desired quaternary protoberberine salt **22** as the acetate, from which the less soluble iodide salt could be precipitated by addition of potassium iodide. The uv spectrum of the iodide salt **22** exhibited a maximum at 308 mμ, indicating the ring D substituents to be at C-10 and C-11 rather than at C-9 and C-10.[17]

Reduction by sodium borohydride in ethanol at 0° reverted the salt **22** to the tetrahydroprotoberberine stage, but only the *trans* B/C isomer **19** (or **19a**) was produced. Such a stereochemical result must be due to attack of hydride from the less-hindered side of the intermediate immonium ion as indicated below.



Each of the tetrahydroprotoberberines **18** and **19** could be debenzylated cleanly by refluxing in hydrobromic acid and ethanol. The two corresponding diphenols **20** and **21** were each obtained in 70% yield. The *cis* B/C fused isomer **20** showed a methyl doublet at δ 1.37, J = 7.0 Hz, while the B/C *trans* diastereoisomer[18] exhibited a methyl doublet relatively upfield at δ 0.89, J = 7.0 Hz.

Debenzylation was also performed on the quaternary protoberberine iodide **22**. The resulting 2,3-dimethoxy-10,11-dihydroxy-13-methylprotoberberine bromide **23**, gave a uv spectrum with a maximum at 312 mμ, pointing to a 10,11-substitution pattern.[17] Subsequent reduction of this material with sodium borohydride in ethanol at 0° provided only one of the two possible tetrahydroprotoberberine isomers, namely species **21**.

The next stage was the transformation of the protoberberine **22** into the required diphenolic salt **26**. Working under a dry nitrogen atmosphere, lithium aluminum hydride in ether reduction of the salt **22** produced the unstable dihydroprotoberberine base **24** in 80% yield. Rapid N-methylation was carried out by refluxing with methyl iodide in acetonitrile for 12 hr, while oxygen was rigorously excluded from the reaction mixture. Evaporation of the solvent and trituration with methanol gave the desired 2,3-dimethoxy-10,11-dibenzyloxy-13-methyl-7,8-dihydroprotoberberine methiodide (**25**) in 78% yield. Examination of the nmr spectrum of product **25** confirmed that N-methylation of **24** had occurred exclusive of any C-13 methylation. The C-methyl singlet was at δ 2.26 and the N-methyl singlet appeared further downfield at δ 3.16.

The final step in the preparation of the diphenolic dihydroprotoberberine salt **26** involved selective debenzylation of **25** without concomitant cleavage of the ring A methoxyls or fission of the benzylic N-7 to C-8 bond. This operation was carried out successfully by refluxing **25** in hydrobromic acid and ethanol, so that the desired 2,3-dimethoxy-10,11-dihydroxy-13-methyl-7,8-dihydroprotoberberine methobromide **26** was obtained as pale yellow prisms in 92% yield. The product was stable in air, but sensitive to light.

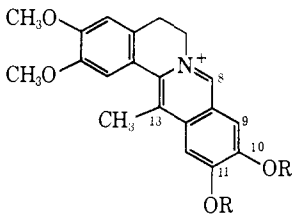
The anion of **26** was next generated in ethanol by addition of 1 equiv of sodium hydroxide solution. The yellow solution was carefully protected from oxygen, and refluxed for 12 hr. Considerable fading of the yellow color indicated that the reaction had progressed beyond the anion stage, and this was confirmed when addition of hydrogen bromide failed to regenerate the starting material.

(15) M. Shamma, C. D. Jones, and J. A. Weiss, *Tetrahedron*, **25**, 4347 (1969).

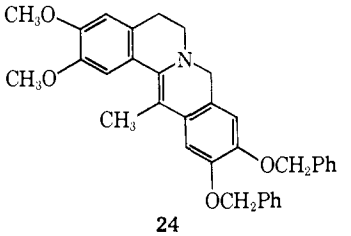
(16) D. J. Cram and F. A. A. Elhafez, *J. Amer. Chem. Soc.*, 74, 5828 (1952).

(17) M. Shamma, M. J. Hillman, and C. D. Jones, *Chem. Rev.*, **69**, 779 (1969).

(18) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 1034.



22, R = CH_2Ph
23, R = H



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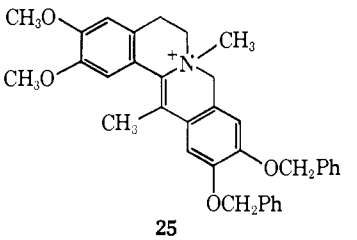

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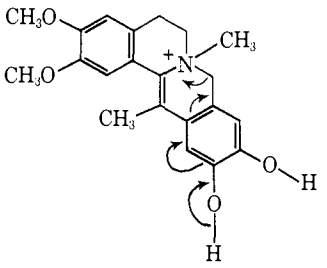

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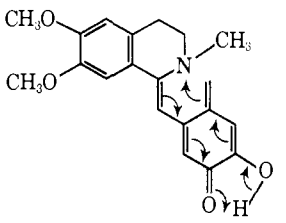

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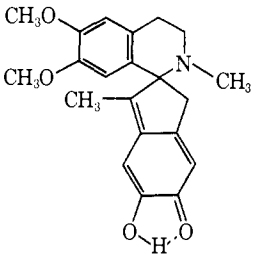

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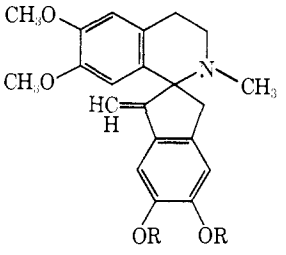
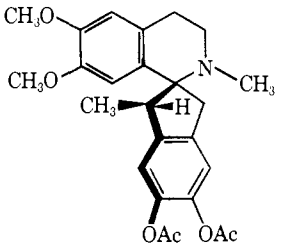


29, R = H
32, R = Ac



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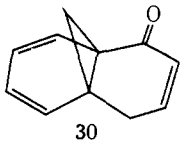
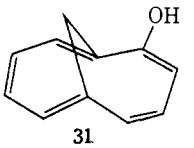


30

DMSO
C_6H_6



31

The resulting acidic solution was evaporated to a brown oily residue which was dissolved in water. Basification with sodium bicarbonate and extraction with chloroform provided a yellow oil which was analyzed spectroscopically. It was immediately apparent that the desired diphenolic spirobenzylisoquinoline **29** had not been obtained since the nmr spectrum exhibited no protons in the vinylic region. Rather, the oil appeared to be the quinone methide **28** with a C-methyl singlet at δ 1.91, an N-methyl singlet at δ 2.12, two methoxyl singlets at δ 3.62 and 3.82, and four quinonoidal protons at δ 6.00, 6.40, 6.54, and 6.70. The ir spectrum had peaks at 6.15, 6.25, and 6.32 μ due to the C=O and C=C groups, while the uv spectrum showed a maximum at 320 mμ indicative of a highly conjugated species such as **28**. The quinone methide **28** had thus been formed from the methobromide salt **26** *via* the transient intermediate **27** by the electronic shifts indicated. One factor militating in favor of the formation of the quinone methide **28** over the diphenol **29** is the stabilizing intramolecular hydrogen bonding present in the former species.

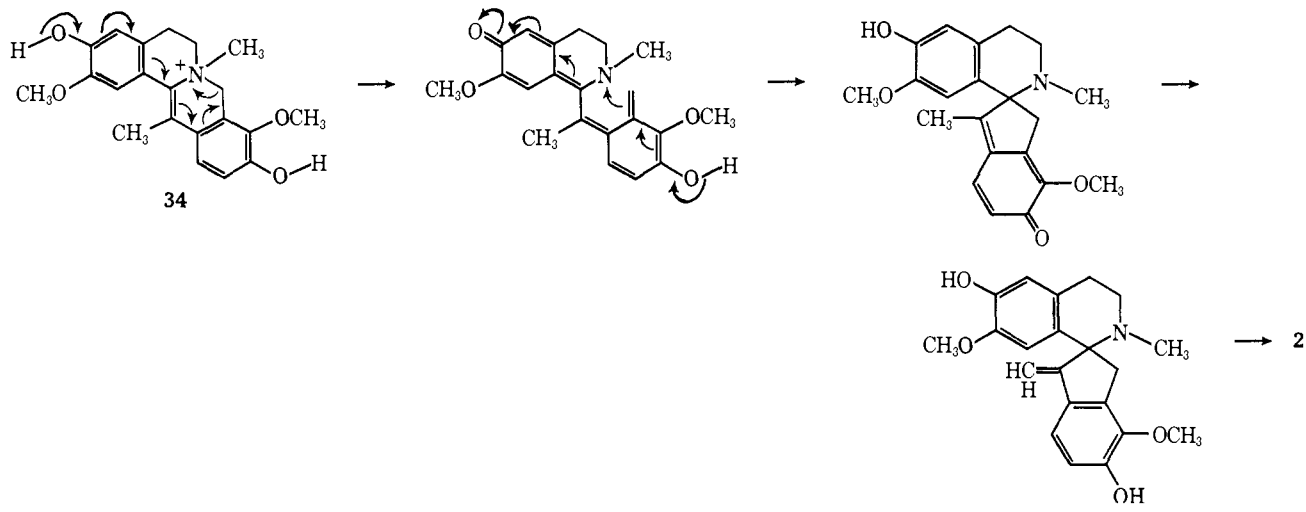
When the quinone methide **28**, which had been formed in the excellent yield of 92% from the salt **26**, was dissolved in DMSO, a virtually quantitative enolization to the desired diphenolic spirobenzylisoquinoline **29** occurred. The nmr spectrum of **29** showed an upfield N-methyl singlet at δ 2.02, no C-methyl absorption, and two O-methyl functions as singlets at δ 3.45 and 3.70. Most importantly, there were also two one-proton singlets in the vinylic region at δ 4.60 and 5.36, attributable to the exocyclic methylene group. Noteworthy also is the fact that a sample of the DMSO solution showed a molecular ion at *m/e* 353, correct for the expected formula of $C_{21}H_{23}O_4N$.

The enolization of **28** to **29** could be accomplished with dry DMF or N,N-dimethylacetamide, as well as with DMSO. Such solvents are capable of forming strong hydrogen bonds through their oxygen atoms, but are not efficient suppliers of protons. In polar solvents which are also good protons donors, *e.g.*, ethanol and acetic acid, the diphenol **29** reverted quantitatively back to the quinone methide **28**. It should be noted in passing that a similar equilibrium involving DMSO has been reported by Vogel and coworkers.[19] The ketone **30**, although greatly favored in benzene solution, is 97% enolized in DMSO to afford the phenol **31**.

Attempts to prepare a pure sample of the diphenol **29** free of DMSO were unsuccessful The oil was sensitive to oxygen and tended to revert to its quinone methide form. However, acetylation of crude **29** produced the diacetate derivative **32** in 65% yield, based on the quinone methide **28**.

The diacetate **32** was obtained as a very pale yellow oil. Its nmr spectrum showed an upfield N-methyl singlet at δ 2.10, as well as six acetoxy protons as a singlet at δ 2.28. Magnetically nonequivalent C-8 methylene protons were evident as two broad singlets at δ 3.11 and 3.34, and two methoxyl singlets were situated at δ 3.62 and 3.80. The exocyclic methylene protons were present as singlets at δ 4.97 and 5.63 with a J value of $\sim$0 Hz. The four aromatic protons appeared as singlets between δ 6.24 and 7.29.

(19) E. Vogel, W. Schrock, and W. A. Boll, *Angew. Chem., Int. Ed. Engl.*, **5**, 732 (1966).



34

Catalytic reduction of the exocyclic double bond in the spirobenzylisoquinoline **32** gave rise to the dihydrodiacetate derivative **33**. The most salient feature in the nmr spectrum of the latter compound was a C-methyl doublet at δ 0.95 (J = 6.5 Hz). This value compares favorably with the corresponding doublet in dihydroochotensimine which appears at δ 0.95 (J = 7.2 Hz).[4]

The stereochemistry at C-13 in the dihydro derivative **33** was deduced from consideration of the pseudo-first-order rates of quaternization in acetonitrile solution.[20] The unreduced diacetate **32** was found to N-methylate with methyl iodide at a rate of 6.6×10^{-4} sec^{-1} at 25°. The observed rate of 20.4×10^{-4} sec^{-1} for **33** constitutes more than a threefold increase over that of **32**, so that the tertiary nitrogen atom in the reduced diacetate must be sterically less hindered than in the parent olefin diacetate. This is true only if the C-methyl group is pointing away from the nitrogen as shown in expression **33**. Such a configuration for the dihydro derivative would also be predicted on mechanistic ground, since the catalyst would approach from the less-hindered side, *i.e.*, the nitrogen side, during the reduction of the olefin **32**.

The mechanism presented here for the transformation **26** → **27** → **28** is further supported by the fact that refluxing the undebenzylated salt **25** for 24 hr in ethanol with 1 equiv of sodium hydroxide yielded no rearranged product whatsoever. The presence of phenolic groups is, therefore, a requirement for the rearrangement to occur.

Even though the diphenolic salt **26** has now been rearranged to a spirobenzylisoquinoline, there is no certainty that its diphenolic analog **6** is indeed the precursor of ochotensimine (**2**) in the plant. Rather, the dihydroprotoberberine salt **34** could, at least theoretically, act equally well as a progenitor for ochotensimine by the route indicated. We are, therefore, presently testing this hypothesis *in vitro* by synthesizing **35**, and attempting to rearrange it in base to **36**. The important point here is that the skeleton present in species **6**, **26**, **34**, or **35**, should be viewed as a highly conjugated system, where hydroxyl substituents at different positions may have the same overall effect on the course of the rearrangement reaction.

(20) M. Shamma and J. M. Richey, *J. Amer. Chem. Soc.*, **85**, 2507 (1963).

Experimental Section

Standard Experimental Procedures. Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind. Melting points are uncorrected.

Infrared spectra were recorded on a Perkin-Elmer 257 spectrophotometer. Ultraviolet spectra were measured on a Coleman Hitachi 124 instrument. The nmr data were obtained using a Varian A-60A spectrometer. Except where specified otherwise, deuteriochloroform was the solvent and TMS was employed as an internal reference. Mass spectra were obtained on an A.E.I.-MS-902 spectrometer.

Rates of methiodide formation were obtained on 3 mg of sample in 10 ml of acetonitrile at 25° by measuring the change of solution resistance with respect to time. The apparatus and procedure for this technique have been reported earlier.[20] All tlc was on Merck Silica Gel-254 plates.

Methyl 2-(3′,4′-Dimethoxyphenyl)propionate (10). A 2-l., three-necked flask was fitted with an ammonia inlet, a Dry Ice condenser, a dropping funnel, and a magnetic stirrer. Liquid ammonia (800 ml) was condensed and then a slurry of sodium amide was prepared from 22.79 g (0.991 mol) of sodium and 300 mg (0.005 mol) of $Fe(NO_3)_3 \cdot 6H_2O$ according to Fieser.[18]

Methyl (3′,4′-dimethoxyphenyl)acetate (207.25 g, 0.986 mol) in anhydrous ether (100 ml) was added with stirring. After 10 min, 140.0 g (0.985 mol) of methyl iodide in 100 ml of dry ether was added dropwise and stirring was continued for 3 hr. Anhydrous ammonium chloride (20 g) was then added and the reaction mixture evaporated to a yellow residue. The oily material was taken up in 500 ml of ether and 100 ml of water, and the ether separated, dried, and evaporated. The yellow oil which remained was vacuum distilled, bp 126–128° (0.2 mm), and provided 203 g (92%) of white needles: mp 47–48°; nmr δ 1.43 (d, 3, J = 7.5 Hz, CCH_3), 3.69 (s, 3, $COOCH_3$), 3.78, 3.82 (s, 6, $ArOCH_3$), 3.64 (q, 1, J = 7.5 Hz, $MeCH$), 6.82–6.90 (m, 3, ArH).

Methyl 2-(3′,4′-Dihydroxyphenyl)propionate (12). A solution of 40.0 g (0.178 mol) of methyl 2-(3′,4′-dimethoxyphenyl)propionate (**10**) in 200 ml of 48% aqueous HBr was deoxygenated and 100 ml of acetic anhydride was cautiously added through the condenser. The mixture was heated for 12 hr in a 140° oil bath with passage of a slow stream of nitrogen. The mixture was cooled and the solvent evaporated to provide a brown glaze of crude 2-(3′,4′-dihydroxyphenyl)propionic acid (**11**).

The glaze was dissolved in methanol, treated with dry HCl, and refluxed for 12 hr. The usual work-up gave a yellow oil which on vacuum distillation provided 31.4 g (90% overall) of colorless product, bp 157–160° (0.2 mm). The liquid became crystalline on standing: mp 102–103°; ir ($CHCl_3$) 5.78 μ (ester C=O); nmr (DMSO-d_6 + $CDCl_3$ with TMS as internal standard) δ 1.41 (d, 3, J = 7.5 Hz, CCH_3), 3.60 (q, 1, J = 7.5 Hz, $MeCH$), 3.63 (s, 3, $COOCH_3$), 6.5–6.9 (m, 3, ArH), 7.6–9.2 (m, 2, OH).

2-(3′,4′-Dibenzyloxyphenyl)propionic Acid (13). A suspension of 31.4 g (0.160 mol) of methyl 2-(3′,4′-dihydroxylphenyl)propionate (**12**) in 300 ml of absolute ethanol was mixed with 50.5 g (0.400 mol) of benzyl chloride and the mixture degassed with nitrogen. Potassium carbonate (45.5 g, 0.330 mol) was added and the mixture refluxed with stirring for 12 hr. The solution was cooled, filtered, and the solvent evaporated. The ether layer was washed with

dilute NaOH and then dried to yield crude methyl 2-(3′,4′-dibenzyloxyphenyl)propionate. This ester was immediately saponified by refluxing for 3 hr with 22.4 g (0.400 mol) of KOH in 200 ml of methanol. The solvent was evaporated and the residue dissolved in water, washed with ether, and acidified with 10% aqueous HCl. A clear, colorless oil which precipitated was extracted into chloroform, dried, and the solvent evaporated. Vacuum drying of the residue yielded white crystals, mp 96–98°, in a yield of 57.4 g (99% overall), recrystallized from methanol. *Anal.* Calcd for $C_{23}H_{22}O_4$: C, 76.22; H, 6.12. Found: C, 76.31; H, 6.22.

N-(3,4-Dimethoxyphenylethyl)-2-(3′,4′-dibenzyloxyphenyl)propionamide (14). A suspension of 25.0 g (0.069 mol) of dry 2-(3′,4′-dibenzyloxyphenyl)propionic acid (**13**) in 150 ml of anhydrous ether was stirred overnight with 1 drop of pyridine and 8.85 g (0.075 mol) of $SOCl_2$. The solvent was evaporated to give 2-(3′,4′-dibenzyloxyphenyl)propionyl chloride as an oily, cream-colored solid. This acid chloride was dissolved in 100 ml of chloroform and added dropwise to a chilled mixture of 12.5 g (0.069 mol) of 3,4-dimethoxyphenylethylamine, 100 ml of chloroform, 10.6 g (0.10 mol) of Na_2CO_3, and 50 ml of water. Stirring was continued for 1 hr. The chloroform layer upon work-up gave a crude, oily amide which crystallized readily on trituration with ether. After one recrystallization from methanol, white crystals were obtained in a yield of 33.5 g (92%), mp 115–116°. *Anal.* Calcd for $C_{33}H_{35}O_5N$: C, 75.40; H, 6.71. Found: C, 75.50; H, 6.77.

1-(α-Methyl-3′,4′-dibenzyloxybenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline (15). The above amide **14** (20.0 g, 0.0382 mol), 13.5 g (0.088 mol, 8 ml) of $POCl_3$, and 100 ml of dry toluene were refluxed for 1 hr. The solvent was evaporated and the residue dissolved in methanol. The yellow solution was poured into excess cold water. After washing with ether, the aqueous layer was treated with ice and basified with concentrated ammonium hydroxide. Following saturation with NaCl, the aqueous phase was extracted with ether. Drying (anhydrous K_2CO_3) and evaporation of the ether gave the desired imine **15** in a yield of 18.9 g (97%). This yellow product was immediately subjected to further transformations: nmr δ 1.50 (d, 3, J = 7.0 Hz, CCH_3), 3.57, 3.82, (s, 6, ArOCH_3), 4.18 (q, 1, J = 7.0 Hz, Me-CH), 5.10 (s, 4, OCH_2Ph), 6.6–7.5 (m, 15, ArH); ir ($CHCl_3$) 6.13 μ (imine C=N).

erythro-**1-(α-Methyl-3′,4′-dibenzyloxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (16).** The above imine **15** (18.9 g, 0.0373 mol) in 200 ml of absolute ethanol was chilled to 0°. Sodium borohydride (1.41 g, 0.0373 mol) was added in small portions with stirring, and the stirring continued for 3 hr. Concentrated HCl was added. When a pH of 4 had been reached, the ethanol was evaporated and the residue dissolved in water and chloroform. Ice was added and the mixture was basified with ammonium hydroxide. The chloroform was separated, washed with water, dried, and evaporated to yield 18.8 g (99%) of the desired secondary amine as a pale yellow oil. An isomeric purity of at least 95% was indicated by nmr spectroscopy: nmr δ 1.36 (d, 3, J = 7.0 Hz, CCH_3), 1.97 (m, 1, NH), 3.76 (s, 6, ArOCH_3), 4.08 (d, 1, J = 5 Hz, NCHAr), 4.97, 5.05 (s, 4, OCH_2Ph), 6.4–7.4 (m, 15, ArH); mass spectrum (70 eV) m/e (relative intensity) 509 (4) (M^+) for $C_{33}H_{35}O_4N$, 418 (1), 385 (5), 327 (2), 294 (23), 278 (4), 248 (4), 233 (2), 221 (4), 205 (3), 192 (100), 91 (39).

2,3-Dimethoxy-10,11-dibenzyloxy-13α-methyl-14αH-tetrahydroprotoberberine (18). A mixture of 38.0 g (0.075 mol) of **16**, 0.5 g of sodium bicarbonate, and 50 ml of methanol was heated to boiling. Formalin (100 ml) was added and the mixture treated with 100 ml of water, whereupon a viscous oil separated. The entire reaction mixture was transferred to a separatory funnel with the aid of chloroform. After saturation with NaCl the chloroform was separated and the aqueous phase was extracted further with chloroform. The combined extracts were added to 10 ml of concentrated HCl at 0°. The mixture was stirred for 1 hr, poured into 200 ml of water, basified by ammonium hydroxide, and the chloroform separated. Drying, filtration, and evaporation gave a yellow oily residue.

The above procedure was repeated twice using the yellow oil in place of **16** to ensure conversion of starting material to the tetrahydroprotoberberine. The oil obtained in this manner crystallized from methanol to give 23.4 g (60%) of **18** as white powder: mp 130°, R_f 0.25 in ether; nmr δ 1.39 (d, 3, J = 7.0 Hz, CCH_3), 2.6–3.1 (m, 5, CHMe + CH_2CH_2), 3.4–4.2 (m, 3, NCH_2Ar + NCHAr), 3.74, 3.76 (s, 6, ArOCH_3), 5.02 (s, 4, OCH_2Ph), 6.50, 6.54, 6.64, 6.70 (s, 4, ArH), 7.0–7.4 (m, 10, Ph–). The pseudo-first-order rate of methiodide formation was 218 × 10^{-4} sec^{-1} at 25° in acetonitrile.[20] *Anal.* Calcd for $C_{34}H_{35}O_4N$: C, 78.28; H, 6.76. Found: C, 78.15; H, 6.77.

2,3-Dimethoxy-10,11-dibenzyloxy-13-methylprotoberberine Iodide (22). A solution of 10.0 g (19.2 mmol) of the tetrahydroprotoberberine **18** in 200 ml of 20% aqueous acetic acid was treated with 24 g (74 mmol) of mercuric acetate, and the mixture heated on a steam bath for 8 hr. After cooling to 60° and filtering off the solid, the yellow filtrate was saturated with H_2S, and filtered while still hot through Filter-cel. The resulting yellow solution was cooled until slightly cloudy, then treated dropwise with excess 20% KI solution. Yellow crystals appeared and these were collected and washed with cold water. The desired protoberberine iodide **22** was obtained as yellow needles, mp 145° dec, 12.2 g (99%). A sample was recrystallized from chloroform: nmr (DMSO-d_6 with TMS as internal reference), δ 2.95 (s, 3, CCH_3), 2.9–3.3 (m, 2, ArCH_2CH_2), 3.88, 3.92 (s, 6, ArOCH_3) 4.5–4.9 (m, 2, N^+CH_2), 5.38, 5.57 (s, 4, OCH_2Ph), 7.1–7.9 (m, 15, ArH); uv max (95% C_2H_5OH) 218 mμ (log ε 4.57), 265 (4.28), 288 (4.41), 308 (4.34), 340 sh (4.08), 370 (3.67). *Anal.* Calcd for $C_{34}H_{32}O_4NI$: C, 63.26; H, 5.00. Found: C, 62.63; H, 4.95.

2,3-Dimethoxy-10,11-dibenzyloxy-13β-methyl-14αH-tetrahydroprotoberberine (19). A suspension of 500 mg (0.775 mmol) of 2,3-dimethoxy-10,11-dibenzyloxy-13-methylprotoberberine iodide (**22**) in 50 ml of absolute ethanol was chilled to 0°, and treated with small portions of sodium borohydride, 500 mg. The mixture was stirred for 1 day. The ethanol was evaporated, the residue was taken up in chloroform and water, and the organic layer separated. After the usual work-up, 388 mg (96%) of the desired product was obtained which was found to be a single isomer, R_f 0.85 (ether) on tlc. The product crystallized from ethanol to give 360 mg of white prisms: mp 132°; nmr δ 0.91 (d, 3, J = 7.0 Hz, CCH_3), 2.2–3.3 (m, 5, CHMe + CH_2CH_2), 3.4–4.1 (m, 3, C-8 methylene + C-14 H), 3.82 (s, 6, ArOCH_3), 5.12 (s, 4, OCH_2Ph), 6.60 (1), 6.67 (2), 6.78 (1), (s, 4, ArH), 7.2–7.5 (m, 10, Ph–); M^+ m/e 531 for $C_{34}H_{35}O_4N$. The rate of methiodide formation was 3.9 × 10^{-4} sec^{-1}.[20]

2,3-Dimethoxy-10,11-dihydroxy-13α-methyl-14αH-tetrahydroprotoberberine (20). A suspension of 400 mg (0.769 mmol) of **18** was refluxed for 6 hr with 6 ml of 48% aqueous HBr and 6 ml of absolute ethanol. The solvent was evaporated and the residue dissolved in water. After basification with sodium bicarbonate, the aqueous phase was continuously extracted with ether for 4 hr. Work-up of the ether layer gave a yellow oil which crystallized from methanol to yield 185 mg (70%) of white crystals. This material (R_f 0.3 in ether) had mp 160–162°: nmr δ 1.37 (d, 3, J = 7.0 Hz, CCH_3), 2.6–3.1 (m, 5, CHMe + CH_2CH_2), 3.2–4.2 (m, 3, C-8 methylene + C-14 H), 3.70 (s, 6, ArOCH_3), 6.36, 6.57, 6.60, 6.70 (s, 4, ArH), 6.0–7.2 (m, 2, OH); uv max (95% C_2H_5OH) 225 (sh) mμ (log ε 4.12), 287 (3.84); mass spectrum (70 eV) m/e 341 (33) (M^+) for $C_{20}H_{23}O_4N$, 326 (10), 192 (100), 150 (29).

2,3-Dimethoxy-10,11-dihydroxy-13β-methyl-14αH-tetrahydroprotoberberine (21). Prepared from **19** in the same manner as above. White crystals, 183 mg (70%), were isolated. This material (**21**) had mp 197° and an R_f in ether of 0.5. The mass spectrum was identical with that of the C-13-α-methyl diastereoisomer except for negligible intensity differences: nmr δ 0.89 (d, 3, J = 7.0 Hz, CCH_3), 2.4–3.5 (m, 5, CHMe + CH_2CH_2), 3.5–4.1 (m, 3, C-8 methylene + C-14 H), 3.86 (s, 6, ArOCH_3), 6.56, 6.63, 6.69, 6.74 (s, 4, ArH), 7.0–8.0 (m, 2, OH); uv max (95% C_2H_5OH) 225 (sh) mμ (log ε 3.92), 287 (3.76).

2,3-Dimethoxy-10,11-dihydroxy-13-methylprotoberberine Bromide (23). A suspension of 2.4 g (3.72 mmol) of 2,3-dimethoxy-10,11-dibenzyloxy-13-methylprotoberberine iodide (**22**) was refluxed for 6 hr under nitrogen with a mixture of 75 ml of ethanol and 75 ml of 48% aqueous HBr. The solvent was evaporated and water added. The yellow crystals which appeared on scratching were filtered and washed with water to give 1.64 g (95%) of product. This material consisted of yellow needles: mp 290–295° dec; nmr (DMSO-d_6 with DMSO peak at δ 2.50), δ 2.68 (s, 3, CCH_3), 2.8–3.2 (m, 2, C-5 methylene H), 3.82 (s, 6, ArOCH_3), 4.2–4.8 (m, 2, C-6 methylene H), 7.03, 7.24, 7.34, 7.40 (s, 4, ArH); uv max (95% C_2H_5OH) 220 (sh) mμ (log ε 4.69), 289 (4.86), 312 (4.89), 375 (4.50).

Reduction of 2,3-Dimethoxy-10,11-dihydroxy-13-methylprotoberberine Bromide (23) with Sodium Borohydride. A suspension of 500 mg (1.20 mmol) of **23** in 25 ml of ethanol was chilled to 0°. Sodium borohydride (190 mg, 5.0 mmol) was added and stirring was continued for 12 hr in a nitrogen atmosphere. The ethanol was evaporated and the residue was dissolved in 10% HCl. After basification with $NaHCO_3$, the aqueous phase was continuously extracted with ether. The ether layer gave a yellow residue which was a singlet spot on tlc (R_f 0.5 in ether). Crystallization from methanol gave 347 mg (95%) of white crystals. The ir, uv, and

nmr spectra of this material were identical in all respects with the data given earlier for **21** prepared by the debenzylation of **19**. Additionally, a mixture melting point with authentic **21** melted at 197° (no depression).

2,3-Dimethoxy-10,11-dibenzyloxy-13-methyl-7,8-dihydroprotoberberine (24). A slurry of 2.0 g (53 mmol) of $LiAlH_4$ in 150 ml of anhydrous ether was deoxygenated and chilled to 0°. There was added 5.0 g (7.8 mmol) of powdered 2,3-dimethoxy-10,11-dibenzyloxy-13-methylprotoberberine iodide (**22**) in small portions and the mixture was stirred for 0.5 hr with continued cooling and passage of N_2. Saturated aqueous sodium sulfate and then water were added. The mixture stirred with 2 g of anhydrous Na_2SO_4 for a few minutes. The flask was sealed under nitrogen and transferred to a dry nitrogen atmosphere in a glove bag. The ether was filtered off and the residual salts were washed with dry ether. Anhydrous potassium carbonate was added, and the yellow solution was filtered. Evaporation of the ether and drying *in vacuo* gave the dihydroprotoberberine as a light yellow foam: 1.3 g (80%); nmr δ 2.25 (s, 3, CCH_3), 3.84 (s, 6, $ArOCH_3$), 4.05 (s, 2, C-8 methylene *H*), 5.08, 5.11 (s, 4, OCH_2Ph), 6.69, 6.64, 6.84, 7.05 (s, 4, Ar*H*), 7.0–7.4 (m, 10, Ph); the pseudo-first-order rate of methiodide formation was 5×10^{-4} sec^{-1} at 25° in acetonitrile.[20] The compound was unstable.

2,3-Dimethoxy-10,11-dibenzyloxy-13-methyl-7,8-dihydroprotoberberine Methiodide (25). The dihydroberberine free base **24** (3.2 g, 6.2 mmol) was dissolved in 25 ml of dry, purified acetonitrile and refluxed with 5 ml of methyl iodide for 12 hr, in a nitrogen atmosphere. The mixture was cooled and the solvent evaporated. Upon trituration with methanol, pale yellow crystals formed which amounted to 3.10 g (78%): mp 165–170° dec; nmr δ 2.26 (s, 3, CCH_3), 3.16 (s, 3, NCH_3), 3.89, 3.92 (s, 6, $ArOCH_3$), 5.22 (s, 4, OCH_2Ph), 5.28 (AB, 2, ics = 60 Hz, J = 15 Hz, C-8 methylene *H*), 6.93, 7.00, 7.05, 7.40 (s, 4, Ar*H*), 7.1–7.6 (m, 10, Ph–); uv max (95% C_2H_5OH) 240 mμ (sh) (log ε 4.42), 290 sh (4.11), 330 (4.47). *Anal.* Calcd for $C_{35}H_{36}O_4NI$: C, 63.54; H, 5.49. Found: C, 63.47; H, 5.56.

2,3-Dimethoxy-10,11-dihydroxy-13-methyl-7,8-dihydroprotoberberine Methobromide (26). A mixture of 1.90 g (2.87 mmol) of the methiodide salt **25**, 10 ml of 48% aqueous HBr, and 10 ml of ethanol was refluxed under nitrogen for 6 hr, the flask being protected from light by an aluminum foil.

The reaction mixture was evaporated to dryness. The foam was washed with absolute ether, then dried. Warming the resulting residue with a little ethanol gave white crystals which amounted to 1.14 g (92%): mp 235° dec; nmr (DMSO-d_6 with DMSO at δ 2.50) δ 2.26 (s, 3, CCH_3), 2.94 (s, 3, NCH_3), 3.82 (s, 6, $ArOCH_3$), 4.85 (AB, 2, ics = 28 Hz, J = 14 Hz, C-8 methylene *H*), 6.81 (1), 6.97 (1), 7.06 (2) (s, 4, Ar*H*); uv max (95% C_2H_5OH) 232 mμ (log ε 4.18), 330 (4.20). *Anal.* Calcd for $C_{21}H_{24}O_4NBr$: C, 58.07; H, 5.57. Found: C, 57.84; H, 5.66.

Rearrangement of 2,3-Dimethoxy-10,11-dihydroxy-13-methyl-7,8-dihydroprotoberberine Methobromide (26) to the Quinone Methide 28. The methobromide salt **26** (400 mg, 0.92 mmol) was suspended in 50 ml of absolute ethanol and degassed thoroughly with N_2. Passage of a slow stream of N_2 was continued throughout the following procedure until after the addition of HCl.

Through the condenser was added 0.92 mmol (1.2 ml of 0.77 *N*) of NaOH. The mixture was refluxed for 12 hr. After cooling and acidification by addition of 10% HCl, a pale brown solution was obtained which was fairly stable to air. The ethanol and water were evaporated to dryness to give a pale brown foam. This residue was dissolved in water and chloroform, deoxygenated, basified with sodium bicarbonate, and extracted further with chloroform. The combined organic extracts were dried and filtered under N_2 to give a yellow solution. On evaporation to dryness, 300 mg (92%) of the quinone methide **28** was obtained. Although this yellow oil was somewhat unstable to oxygen, the following data could be obtained on a freshly prepared sample: ir ($CHCl_3$) 6.15, 6.25, 6.32 μ (C=O + C=C); nmr δ 1.91 (s, 3, CCH_3), 2.12 (s, 3, NCH_3), 3.62, 3.82 (s, 6, $ArOCH_3$), 6.00, 6.40, 6.54, 6.70 (s, 4, Ar*H* + quinonoid *H*); uv max (95% C_2H_5OH) 210 mμ (log ε 4.27), 273 (3.75), 292 (3.58), 320 (3.85).

Enolization of the Quinone Methide 28 to Spiro[1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline-1,2′-1′-methylene-5′,6′-dihydroxyindan] (29). The yellow, oily quinone methide **28** (100 mg, 0.284 mmol) was dissolved in 10 ml of dry, deoxygenated chloroform, and 2 drops of DMSO-d_6 added. Evaporation of the chloroform gave a light brown solution of the diphenol **29** in residual DMSO-d_6: nmr (DMSO-d_6 with DMSO at δ 2.50) δ 2.02 (s, 3, NCH_3), 3.33 (AB, 2, ics = 39 Hz, J = 19 Hz, C-8 methylene *H*), 3.45, 3.70 (s, 6, $ArOCH_3$), 4.60, 5.36 (s, 2, vinylic *H*), 6.16, 6.54, 6.61, 6.92 (s, 4, Ar*H*), 5.9–7.2 (m, 2, *OH*); mass spectrum M^+ at *m/e* 353 for $C_{21}H_{23}O_4N$.

Spiro[1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline-1,2′-1′-methylene-5′,6′-diacetoxyindan] (32). The quinone methide **28** (100 mg, 0.284 mmol) was converted to the diphenol **29** by treatment with a few drops of DMSO in 20 ml of chloroform. The solution was stirred and treated at 0° with 110 mg (0.10 ml, 1.40 mmol) of acetyl chloride and 146 mg (0.20 ml, 1.45 mmol) of triethylamine. After 2 hr, the solvent was evaporated, and the residue dissolved in water and chloroform. The organic phase was separated, washed with 2% sodium carbonate, dried, filtered, and evaporated to yield 110 mg of a crude tan oil. This material was purified by preparative tlc using ether as solvent. Elution of the major band (R_f 0.7–0.8) gave 80 mg (65%) of the desired diacetate derivative of **29** as a pale yellow oil: nmr δ 2.10 (s, 3, NCH_3), 2.28 (s, 6, $CH_3C{=}O$), 2.7–2.9 (m, 4, CH_2CH_2), 3.11, 3.34 (s, C-8 methylene *H*), 3.62, 3.80 (s, 6, $ArOCH_3$), 4.97, 5.63 (s, 2, vinylic H), 6.24, 6.50, 7.02, 7.29 (s, 4, Ar*H*); uv max (95% C_2H_5OH) 255 mμ (log ε 4.06), 292 (3.80), 310 (3.72); ir ($CHCl_3$) 5.67 μ (ester C=O); mass spectrum (70 eV) *m/e* 437 (95) (M^+ for $C_{25}H_{27}O_6N$), 422 (7), 394 (33), 393 (33), 379 (7), 352 (100), 205 (33); the rate of methiodide formation was 6.6×10^{-4} sec^{-1} at 25°.[20]

Spiro[1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline-1,2′-1′-methyl-5′,6′-diacetoxyindan] (33). The above diacetate **32** (20 mg, 0.046 mmol) was dissolved in 5 ml of MeOH containing 20 mg of 5% Pd on C. The mixture was hydrogenated at room temperature for 12 hr. Work-up gave the reduced compound **33**. After drying *in vacuo*, the product was obtained as 20 mg (99%) of a white foam: ir ($CHCl_3$) 5.67 μ (ester C=O); nmr δ 0.95 (d, 3, J = 6.5 Hz, $CHCH_3$), 2.25 (s, 6, $CH_3C{=}O$), 2.49 (s, 3, NCH_3), 3.43, 3.80 (s, 6, $ArOCH_3$), 6.11, 6.59, 6.81, 7.11 (s, 4, Ar*H*); uv max (95% C_2H_5OH) 280 mμ (log ε 3.85); mass spectrum (70 eV) *m/e* 439 (100), 424 (22), 410 (55), 396 (45), 367 (22), 354 (45), 205 (22); high resolution mass measurement M^+ calcd for $C_{25}H_{29}O_6N$: *m/e* 439.1993; found *m/e* 439.1965; the rate of methiodide formation was 20.4×10^{-4} sec^{-1} at 25°.[20]

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