Tetrahedron Vol. 34, pp. 1435–1439
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0040-4020/78/0501-1435/$02.00/0

A TOTAL SYNTHESIS OF CORYDALINE

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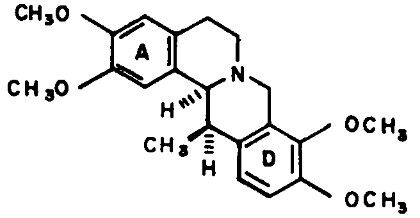
(*Received in the USA* 11 *October* 1977; *Received in the UK for publication* 16 *December* 1977)

Abstract—A total synthesis of (±)-corydaline **1** is described in which the condensation of 3,4-dihydro-6,7-dimethoxyisoquinoline **10** with 3,4-dimethoxyhomophthalic anhydride **9** is utilized as the convergent step. A new procedure for the preparation of **9** is also described. The Beckmann rearrangement of an α-ketooxime **4** with phosphorus pentachloride in chloroform is shown to afford the 3-chloro-1-(2*H*)isoquinolone **5** by a fragmentation-recombination type mechanism.

Corydaline **1** is an alkaloid which was discovered in 1826 by Wackenroder during his investigation of the tubers of *Corydalis tuberosa*,[1] a herb which is native to Central Europe.[2] Corydaline has since been isolated from many species of *Corydalis* in yields ranging from 0.01 to 2.0%.[3-11] After a century of intensive study by many workers[5,6,12-16] a correct structural formula was proposed[17,18] and confirmed by total syntheses of (±)-corydaline[19] and oxydehydrocorydaline.[20] The total synthesis of (±)-corydaline by Späth and Kruta[19] involved a complicated isolation procedure and proceeded from papaverine in only *ca.* 0.04% yield. During our work on the total synthesis of (±)-corydaline it was reported that the photocyclization of enamides[21,22] had been modified to allow another synthesis of the alkaloid,[23] and several partial syntheses from palmatine[24,25] and thalictricavine[25] have been devised. One difficulty posed by total synthesis of (±)-corydaline has been to establish the *cis* relationship of the methine protons at C-13 and C-14.[27,28] Also the 9,10-dimethoxy substitution pattern of ring D presents a challenge since it is not readily accessible by Mannich cyclization of an appropriately substituted benzylisoquinoline.



Our approach to the total synthesis of (±)-corydaline is based on the recently discovered reaction of homophthalic anhydrides with 3,4-dihydroisoquinolines,[29,30] and Haimova *et al.* have also pointed out the possible use of this reaction to prepare protoberberine alkaloids such as corydaline and cavidine.[30] We therefore initially required large quantities of 3,4-dimethoxyhomophthalic anhydride **9**. Although a synthesis of **9** was reported by Haworth, Koepfli and Perkin in 1926,[31] the experimental procedure is cumbersome and either low yields or no yields were reported for individual steps. We attempted to repeat their work and found that the reactions which they reported without yields either proceed poorly or fail completely. Our synthesis of **9** (Chart 1) closely parallels the work of Perkin *et al.*[31] but it should be noted that the following modifications were made in order to improve on the poor yields resulting from their methods. Substitution of hot polyphosphoric acid[32] for concentrated sulfuric acid raised the yield from 27% to 72% in the conversion of **2** to the indanone **3**. A solution of the indanone **3**, concentrated hydrochloric acid, and isoamylnitrite in ethanol was then saturated with HCl and the desired isonitrosoketone **4** was obtained in 74% yield. We have also found trifluoroacetic anhydride in acetonitrile to be superior to either *p*-toluenesulfonyl chloride in sodium hydroxide or phosphorus pentachloride (*vide infra*) in effecting the Beckmann fragmentation of **4** to the nitrile **6**. The previous workers[31] also indicated that the hydrolysis product of the nitrile **6** (i.e. **7**) must be converted to the corresponding anhydride, presumably in order to facilitate isolation of a crystalline product. We have found that this unnecessarily adds two steps to the sequence, since **7** can be crystallized directly from a mixture of benzene and hexane in 92% yield. Finally, Perkin *et al.* reported that they were unable to obtain a crystalline sample of 3,4-dimethoxyhomophthalic acid **8** from the reductive debromination of **7** using a large amount of sodium amalgum, whereas we have isolated the crystalline homophthalic acid **8** in high yield by hydrogenolysis of **7** over palladium on charcoal in ethanolic potassium hydroxide. In summary, we have been able to isolate and characterize every intermediate in Chart 1 in yields far surpassing those obtained by the previously reported methods.[31]

Treatment of the oxime **4** with 3.6 equivalents of phosphorus pentachloride in chloroform for 30 min at room temperature afforded a 41% yield of the Beckmann fragmentation product **6**. When the reaction was allowed to proceed for 16 hr in an attempt to increase the yield of **6**, a high melting solid was isolated instead in 76% yield. The intensities of the isotope peaks at $M^+ + 4(26)$ and $M^+ + 2(100)$ relative to the molecular ion M^+ (79) in the mass spectrum clearly indicated the presence of one chlorine and one bromine atom, while the NMR spectrum of the compound dissolved in trifluoroacetic acid displayed two low field singlets at δ 8.24 and 7.90 in addition to the signals for the methoxyl protons at 4.45 and 4.20. These data as well as the IR spectrum are consistent with the isoquinoline **5**. Compound **5** could conceivably arise from a classical Beckmann rear-

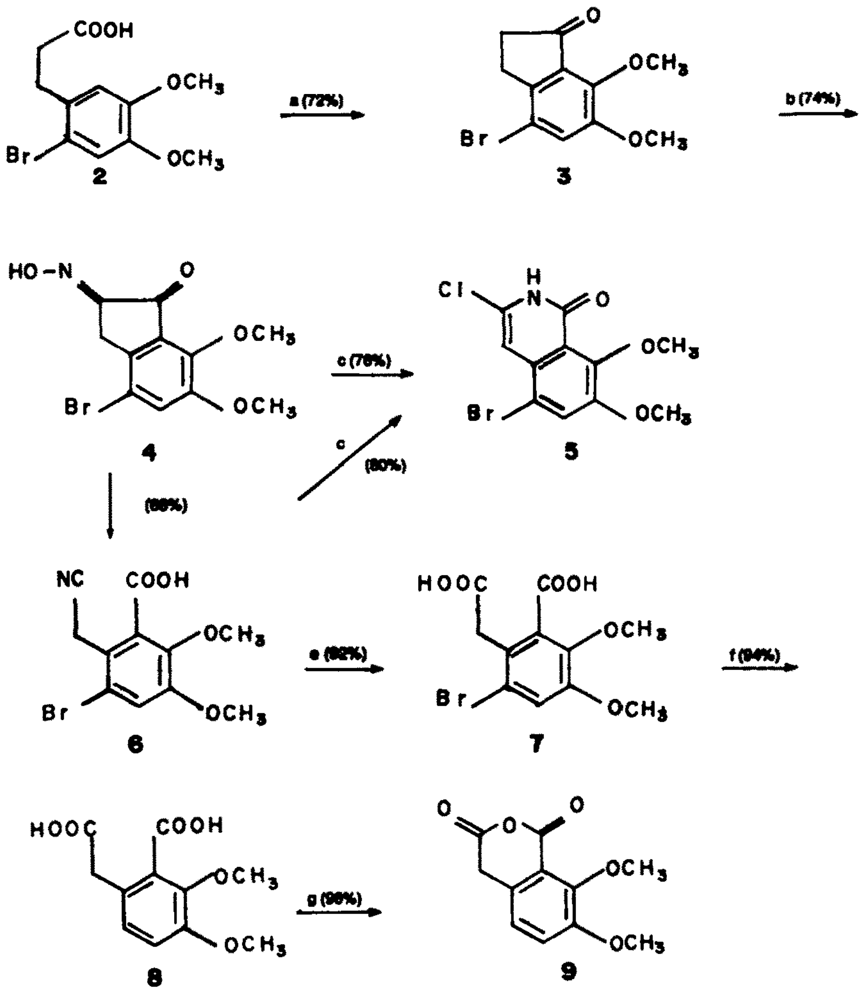


Chart 1.

a, PPA, steam bath (30 min); b, isoamyl nitrite, ethanolic HCl, 5–10° (30 min), then 45° (15 min); c, PCl_5, $CHCl_3$, 23° (16 h); d, $(CF_3CO)_2O$, CH_3CN, 23° (48 h); e, 15% aq KOH, reflux (4 h); f, H_2, 5% Pd/C, ethanolic KOH, 23° (4 h); g, AcCl, reflux (2 h).

rangement.[34,35] However, relatively recently it has been established that in certain cases the "normal" Beckmann rearrangement product may be formed by a Ritter type recombination reaction of the cation and the nitrile initially formed by a fragmentation process.[36–40] These arguments in conjunction with the observation that *o*-cyanomethylbenzoyl chlorides are converted to 3-chloro-1-isoquinolones in the presence of HCl[41,42] lead us to suggest that the pathway outlined in Chart 2 is the most likely possibility. Also in agreement with this mechanism is the observation that resubjection of the previously isolated *o*-carboxyphenyl-acetonitrile **6** to the reaction conditions for 16 hr led cleanly to the isoquinolone **5**. Thus the low yield of the Beckmann fragmentation

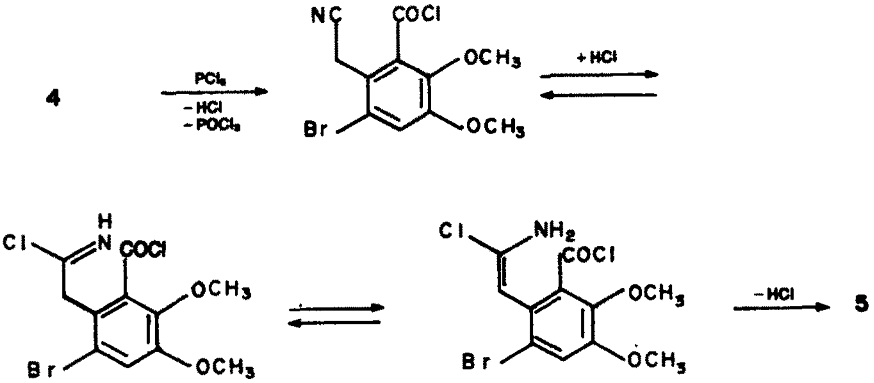


Chart 2.

product obtained with phosphorus pentachloride is explained by a novel fragmentation-recombination reaction.

Condensation of 3,4 - dihydro - 6,7 - dimethoxyisoquinoline 10[43] with anhydride 9 proceeded exothermally in chloroform to a 3:1 diastereomeric mixture of *trans*- and *cis*-2,3,9,10-tetramethoxy-8-oxo-13-carboxytetrahydroprotoberberines, respectively, which on heating in acetic acid was converted to the thermodynamically more stable *cis* isomer 11 ($J_{AB} = 4$ Hz, Chart 3).[29] These as well as our previous results[29] on the stereochemical outcome of the condensation are in contrast to those of Haimova *et al.*, who report that the condensation of 10 with 4,5-dimethoxyhomophthalic anhydride in dichloroethane and one equivalent of triethylamine at room temperature proceeds directly to *cis* - 2,3,10,11 - tetramethoxy - 8 - oxo - 13 - carboxytetrahydroprotoberberine, although their assignment of the relative configuration was actually made on the corresponding methyl ester.[30] The driving force for the epimerization is probably relief of the nonbonded interaction between the pseudoequatorial carboxyl group and C-1 of aromatic ring *A* which is present in the *trans* diastereomer. The NMR spectrum of the corresponding methyl ester 12, prepared with diazomethane, displayed the anticipated[29] high field singlet (δ 3.33) assigned to the pseudoaxial methoxycarbonyl protons which are shielded by the aromatic rings. Reduction of 12 with lithium aluminum hydride afforded the amino alcohol 13, which on treatment with methanesulfonyl chloride in pyridine under carefully controlled conditions gave a crystalline mesylate 14 in high yield. (±)-Corydaline was then obtained by sodium borohydride reduction of 14 in refluxing ethanol. The NMR spectrum of our synthetic (±)-corydaline displayed the C-13 methyl doublet at δ 0.97, the C-8 methylene AB quartet with doublets at 4.19 and 3.49 (J = 16 Hz), and the C-14 methine doublet at 3.68 (J = 3 Hz) which have been reported for the natural product.[27,28] The Bohlmann bands which appeared in the IR spectrum at 2785 and 2735 cm^{-1} are also consistent with the *trans* quinolizidine conformation of corydaline.

EXPERIMENTAL

All reactions were performed under a nitrogen atmosphere unless otherwise noted and solvents were removed on a rotary evaporator under reduced pressure. M.Ps were taken on a Thomas Hoover Unimelt or a Meltemp apparatus and are uncorrected. NMR spectra were recorded on a Varian EM-360 60 MHz instrument or Jeol PFT-100 spectrometer, and except where noted, in $CDCl_3$ solvent. Chemical shifts are reported in ppm relative to TMS as internal standard. IR spectra were recorded on a Beckman IR-33 spectrophotometer. Mass spectra were determined on a Dupont 21-492B double-focusing spectrometer using an ion source temperature of 200–280°, an ionization potential of 70 eV, and an ionizing current of 100 μA. Microanalyses were performed by Dr. C. S. Yeh and associates of Purdue University.

4-Bromo-6,7-dimethoxy-1-indanone 3. 3 - (2 - Bromo - 4,5 - dimethoxyphenyl) - propionic acid (2, 38.60 g, 0.134 mol) was added to warm polyphosphoric acid (386 g) and the mixture heated and stirred on a steam bath for 25 min. The deep red

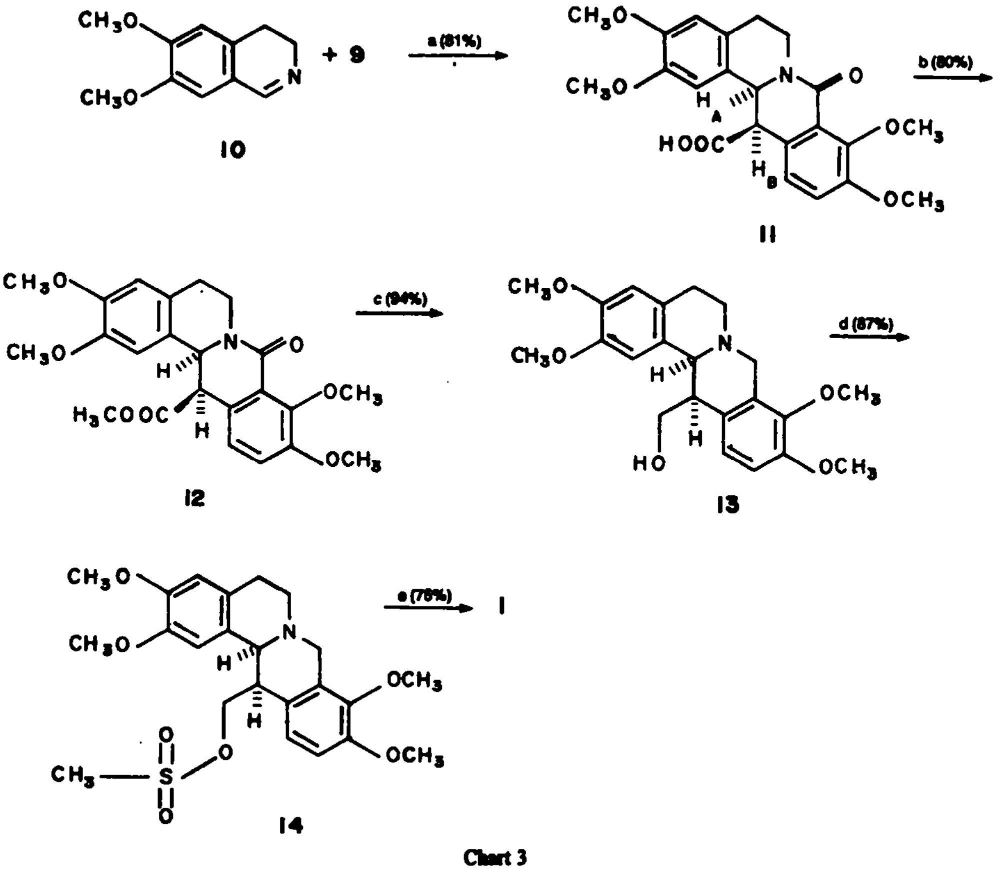


Chart 3

a, (1) $CHCl_3$, room temperature (30 min), (2) AcOH, reflux (24 h); b, CH_2N_2, Et_2O–EtOH, 0° (2 h); c, $LiAlH_4$, THF–Et_2O (3:1), reflux (16 h); d, MsCl, pyridine, 35° (4 h); e, $NaBH_4$, EtOH, reflux (48 h).

reaction mixture was poured onto ice water (1.5 l) and the aq phase extracted with $CHCl_3$ (2 × 300 ml, then 2 × 150 ml). The combined organic extracts were washed with H_2O (300 ml), 10% aq $NaHCO_3$ (300 ml), 5% of aq $NaHCO_3$ (300 ml), and finally H_2O (300 ml). The $CHCl_3$ solution was then dried ($MgSO_4$) and evaporated. The brown, oily residue was triturated with CH_3OH and the crystalline product (26.00g, 72%) isolated by filtration: m.p. 118–120° (lit.[31] m.p. 120–121°). IR (KBr) 2965, 1705, 1245 cm^{-1}; NMR δ 7.37 (s, 1H), 4.02 (s, 3H), 3.93 (s, 3H), 2.85 (m, 4H).

2 - *Isonitroso* - 4 - *bromo* - 6,7 - *dimethoxy* - 1 - *indanone* 4. The indanone 3 (63.61 g, 0.235 mol) was added to a solution of freshly distilled isoamyl nitrite (40 ml, 0.297 mol) in EtOH (180 ml). The mixture was cooled to 5° and concd. HCl (11.8 ml) added dropwise while maintaining the temp. at 5–10°. The mixture was then saturated with HCl while maintaining the temp. below 10°. After 30 min an exothermic reaction occurred and the temp. increased to 45°. The temp. was kept at 45° for 15 min, after which the mixture solidified. EtOH (100 ml) was then added and the suspension was stirred at 45° for 45 min, after which H_2O (200 ml) was added. The solid was filtered and washed with H_2O (600 ml). Recrystallization from 95% EtOH (3 l) yielded the product as a yellow powder (52.00 g, 74%): m.p. 228–230° dec (lit.[31] m.p. 236°); IR (KBr) 3200, 2925, 1730, 1650, 1260 cm^{-1}; NMR ($CDCl_3$-pyridine-d_5, 1:1) δ 15.10 (bs, 1H), 7.38 (s, 1H), 4.07 (s, 3H), 3.83 (s, 3H), 3.71 (s, 2H).

3 - *Chloro* - 5 - *bromo* - 7,8 - *dimethoxy* - 1 - (2*H*) *isoquinolone* (5). (A) To a solution of the isonitrosoketone 4 (0.5 g, 1.66 mmol) in $CHCl_3$ (2.5 ml) was added PCl_5 (1.25 g, 6.01 mmol). The reaction mixture was stirred at room temp. for 16 h, during which a yellow precipitate formed. Water (7.5 ml) was added and the product filtered and recrystallized from $CHCl_3$, yielding a colorless solid (0.40 g, 76%): m.p. 255–257°; IR (KBr) 3330, 3160, 1670, 1580, 1280 cm^{-1}; NMR (CF_3COOH) δ 8.25 (s, 1H), 7.90 (s, 1H), 4.45 (s, 3H), 4.20 (s, 3H); mass spectrum *m/e* (rel intensity) 321 (26, $M^+ + 4$), 319 (100, $M^+ + 2$), 317 (79), 306 (21), 304 (76), 302 (69), 292 (21), 290 (81), 288 (70), 240 (30), 238 (29), 197 (16), 195 (46).

Anal. Calc. for $C_{11}H_9NO_3ClBr$: C, 41.47; H, 2.85; N, 4.40; Cl, 11.13; Br, 25.08. Found: C, 41.57; H, 3.06; N, 4.68; Cl, 10.97; Br, 25.28%.

(B) To a suspension of 6 (200 mg, 0.666 mmol) in $CHCl_3$ (2 ml) was added PCl_5 (0.75 g, 3.6 mmol). After the mixture was stirred at room temp. for 16 h, water (2 ml) was added and the $CHCl_3$ was evaporated. The product was filtered, washed with water (5 ml) and dried, yielding the crude product (201 mg, 95%). The analytical sample was recrystallized from $CHCl_3$ (10 ml), yielding a colorless solid (169 mg, 80%): m.p. 250–252°. The NMR and IR spectra were identical with those of the previously isolated material.

2 - *Carboxy* - 3,4 - *dimethoxy* - 6 - *bromophenylacetonitrile* 6. (A) To a solution of the isonitrosoketone 4 (1.00 g, 3.32 mmol) in $CHCl_3$ (5 ml) was added PCl_5 (2.5 g, 12.02 mmol). An exothermic reaction proceeded and the mixture was stirred at room temp. for 30 min. The reaction mixture was decomposed by addition of water (10 ml). The organic layer was separated, dried ($MgSO_4$), and evaporated, yielding an oil which crystallized from water as a colorless, solid hydrate. The solid was heated at 85° (0.1 mm) over P_2O_5 for 12 h, yielding the dehydrated product (0.41 g, 41%): m.p. 132–134° (lit. m.p. of monohydrate[31] 98–100°); IR (KBr) 2980, 2260, 1730, 1220 cm^{-1}; NMR δ 7.18 (s, 1H), 3.95 (s, 5H), 3.88 (s, 3H); mass spectrum *m/e* rel. intensity 301 (98, $M^+ + 2$), 299 (M^+, 100), 286 (78), 284 (93), 282 (73), 281 (74), 272 (28), 270 (28), 268 (58), 266 (57), 259 (28), 257 (32), 240 (63), 238 (64).

(B) The ketoxime 5 (0.5 g, 1.66 mmol) was stirred in polyphosphoric acid (26 g) for 8 h at room temp. before addition of ice (20 g). The mixture was stirred for 30 min and then extracted with $CHCl_3$ (2 × 50 ml). The $CHCl_3$ layer was dried ($MgSO_4$) and evaporated, leaving a glass (0.39 g). Crystallization from water yielded the product (0.05 g, 10%), which was identical with the previously isolated solid.

(C) The isonitrosoketone 4 (9.0 g, 0.03 mol) in CH_3CN (108 ml) was treated with trifluoracetic anhydride (19 g, 0.09 mol). The mixture was allowed to stir for 48 h at room temp. Evaporation of the solvent left a brown oil which dissolved in $CHCl_3$ (100 ml). The solution was extracted with 15% NaOH. The aqueous extract was acidified by addition of conc. HCl and allowed to stand at room temp. overnight. The precipitate was filtered and recrystallized from water (250 ml) to yield the product (6.1 g, 68%). It was identical with the previously isolated solid.

3,4 - *Dimethoxy* - 6 - *bromohomophthalic acid* 7. The nitrile 6 (18.00 g, 0.06 mol) was heated in 15% aq KOH (216 ml) at reflux for 4 h. The solution was cooled and acidified with concd HCl to pH 1. The solution was then saturated with NaCl and extracted with Et_2O (2 × 100 ml). The combined Et_2O layers were dried ($MgSO_4$) and evaporated to yield an oil (18.86 g). The oil was dissolved in benzene (150 ml) and hexane was added until crystallization of colorless needles (17.66 g, 92%) began: m.p. 171–172° (lit.[31] m.p. 166–167°); IR (KBr) 3300–2500, 1710, 1260 cm^{-1}; NMR ($CDCl_3$-pyridine-d_5, 5:1) δ 15.75 (s, 2H, exchangeable with D_2O), 7.20 (s, 1H), 4.00 (s, 2H), 3.95 (s, 3H), 3.80 (s, 3H).

3,4-*Dimethoxyhomophthalic acid* 8. The diacid 7 (16.00 g, 0.05 mol) was dissolved in a solution of KOH (5.6 g, 0.1 mol) in EtOH (400 ml), and 5% Pd/C (3.2 g) was then added. The mixture was then hydrogenated at 50 psia for 4 h. H_2O (100 ml) was then added and the mixture filtered through celite. The filtrate was acidified with conc. HCl, saturated with NaCl, and extracted with Et_2O (2 × 200 ml). The combined Et_2O extracts were dried ($MgSO_4$) and evaporated to give a white powder. The analytical sample (11.27 g, 94%) was recrystallized from benzene–hexane: m.p. 114–115°; IR (KBr) 3300–2500, 1700, 1260 cm^{-1}: NMR δ 10.90 (s, 2H, exchangeable with D_2O), 7.00 (s, 2H), 3.95 (s, 3H), 3.70 (s, 5H).

3,4-*Dimethoxyhomophthalic anhydride* 9. The homophthalic acid 8 (5.84 g, 24 mmol) was heated in refluxing AcCl (100 ml) for 2 h. The solution was concentrated to a volume of 5 ml and Et_2O (60 ml) was added. The colorless plates (5.13 g, 96%) were filtered: m.p. 116–117° (lit.[31] m.p. 104–105°); IR (KBr) 2960, 1790, 1750, 1255 cm^{-1}; NMR δ 7.27 (d, 1H, J = 9 Hz), 7.02 (d, 1H, J = 9 Hz), 4.00 (s, 2H), 3.97 (s, 3H), 3.92 (s, 3H).

cis - 2,3,9,10 - *Tetramethoxy* - 8 - *oxo* - 13 - *carboxytetrahydroprotoberberine* 11. A solution of 3,4-dimethoxyhomophthalic anhydride (9, 2.00 g, 9.00 mmol) in $CHCl_3$ (8 ml) was added to a stirred solution of 3,4-dihydro-6,7-dimethoxyisoquinoline (1.72 g, 9. mmol) in $CHCl_3$ (3 ml). A vigorous exothermic reaction occurred as the mixture was stirred at room temperature for 30 min. Evaporation of the solvent left a yellow powder (3.72 g, m.p. 202–210°) which crystallized from CH_3CN (280 ml) in colorless plates. The solid contained an equivalent of CH_3CN which was removed by heating at 100° (0.1 mm) overnight. The solid (3.34 g, 90%, m.p. 217–220°) was a 3:1 mixture of *trans*:*cis* diastereomers as judged by NMR integrations. The solid was heated at reflux in AcOH (50 ml) for 24 h and the AcOH then evaporated. The oily residue was dissolved in CH_3CN (270 ml). The product (3.01 g, 81%) crystallized in colorless plates: m.p. 233–235° dec; IR (KBr) 3300–2700, 2920, 1725, 1640, 1250 cm^{-1}; NMR ($CDCl_3$-pyridine-d_5) δ 10.20 (b, 1H, exchangeable with D_2O), 7.22 (d, J = 8 Hz, 1H), 7.02 (d, J = 8 Hz, 1H), 6.85 (s, 1H), 6.65 (s, 1H), 5.12 (d, J = 4 Hz, 1H), 4.90 (m, 1H), 4.10 (s, 3H), 3.92 (s, 3H), 3.88 (s, 3H), 3.85 (s, 3H), 3.00 (m, 4H); mass spectrum *m/e* (rel intensity) 413 (M^+, 10), 369 (12), 236 (6), 222 (12), 192 (100), 178 (18).

Anal. Calc. for $C_{22}H_{23}NO_7$: C, 63.92; H, 5.61; N, 3.39. Found: C, 63.84; H, 5.90; N, 3.13%.

cis - 2,3,9,10 - *Tetramethoxy* - 8 - *oxo* - 13 - *methoxycarbonyltetrahydroprotoberberine* 12. The *cis* acid 11 (2.91 g, 7.04 mmol) was slowly added to a solution of diazomethane (*ca.* 3 g) in Et_2O–EtOH at 0°. After 2 h at 0° the excess diazomethane was decomposed by addition of AcOH. The solvent was evaporated and the oily residue crystallized on trituration with Et_2O. The solid (2.91 g) was then recrystallized from EtOAc–hexane (1:1) to yield analytically pure material (2.42 g, 80%): m.p. 152–154°; IR (KBr) 2910, 1735, 1645, 1255 cm^{-1}; NMR ($CDCl_3$-pyridine-d_5, 10:1) δ 7.03 (s, 2H), 6.73 (s, 1H), 6.65 (s, 1H), 5.05 (d, J = 4 Hz, 1H), 5.00 (m, 1H), 4.03 (s, 3H), 3.87 (s, 9H), 3.33 (s, 3H), 2.93 (m, 4H); mass spectrum *m/e* (rel intensity) 427 (M^+, 16), 237 (13), 236 (100), 208 (16), 193 (16).

Anal. Calc. for $C_{23}H_{25}NO_7$: C, 64.63; H, 5.90; N, 3.28. Found: C, 64.69; H, 6.05; N, 3.16%.

cis - 2,3,9,10 - *Tetramethoxy* - 13 - *hydroxymethyltetrahydro*-

protoberberine 13. $LiAlH_4$ (0.693 g, 18.7 mmol) was added to a solution of the *cis* ester 12 (2.00 g, 4.68 mmol) in THF (150 ml) and Et_2O (50 ml). The mixture was heated at reflux for 16 h. The mixture was cooled and the excess hydride decomposed by addition of H_2O (0.7 ml), 15% aq NaOH (0.7 ml), and finally H_2O (2.1 ml). The aluminates were filtered and washed with THF (100 ml). The combined filtrates were dried ($MgSO_4$) and evaporated to yield a solid (1.70 g, 94%), m.p. 202–204°. The analytical sample was recrystallized from 50% aq EtOH: m.p. 201–203° dec; IR (KBr) 3400, 2920, 2740, 1250 cm^{-1}; NMR δ 7.10 (d, J = 8 Hz, 1H), 6.93 (d, J = 8 Hz, 1H), 6.63 (s, 2H), 5.70 (b, 1H, exchangeable with D_2O), 4.30 (d, J = 14 Hz, 1H), 3.93 (s, 12H), 3.80–2.40 (m, 9H); mass spectrum *m/e* (rel intensity) 385 (M^+, 100), 368 (11), 354 (24), 220 (16), 194 (22), 192 (18), 190 (11), 179 (11), 177 (8), 165 (17).

Anal. Calc. for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.48; H, 7.13; N, 3.35%.

cis - 2,3,9,10 - *Tetramethoxy* - 13 - *methanesulfonylmethyltetrahydroprotoberberine* 14. Methanesulfonyl chloride (200 μl) was added to a solution of the *cis* alcohol 13 (0.50 g, 1.30 mmol) in pyridine (5 ml). The solution was stirred at 35° for 4 h and then poured into H_2O (50 ml). The aqueous phase was extracted with $CHCl_3$ (3 × 50 ml). The $CHCl_3$ was evaporated and the last traces of pyridine were removed from the oil residue at 23° (0.1 mm). Trituration of the oil with EtOH then gave a crystalline product (0.52 g, 95%): m.p. 114–115° dec; IR (KBr) 2925, 2740, 1250 cm^{-1}; NMR δ 7.15 (d, J = 9 Hz, 1H); 6.85 (d, J = 9 Hz, 1H), 6.80 (s, 1H), 6.63 (s, 1H), 4.25 (m, 2H), 3.95 (s, 12H), 3.90–2.40 (m, 8H), 2.65 (s, 3H).

(±)-*Corydaline* 1. $NaBH_4$ (350 mg, 9.7 mmol) was added to a stirred suspension of the mesylate 14 (0.52 g, 1.12 mmol) in 95% EtOH (50 ml). The mixture was heated at reflux for 48 h and then poured into H_2O (50 ml). The aqueous phase was extracted with $CHCl_3$ (3 × 50 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated to yield the crude product (0.43 g) as a solid, m.p. 133–136°. Recrystallization from 50% aq MeOH (40 ml) gave pure (±)-corydaline (0.31 g, 75%): m.p. 133–134° (lit.[44] m.p. 135°); IR (KBr) 2955, 2785, 2735, 1245 cm^{-1}; NMR δ 6.92 (s, 2H), 6.73 (s, 1H), 6.65 (s, 1H), 4.27 (d, J = 16 Hz, 1H), 3.93 (s, 12H), 3.68 (d, J = 3 Hz, 1H), 3.49 (d, J = 16 Hz, 1H), 3.43–2.30 (m, 5H, 0.97) (d, J = 7 Hz, 3H); mass spectrum *m/e* (rel intensity) 369 (M^+, 74), 344 (12), 179 (16), 178 (100), 163 (19).

Anal. Calc. for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.74; H, 7.65; N, 3.76%.

Acknowledgement—This investigation was supported by Grant 1 RO1 CA19204-2, awarded by the National Cancer Institute, Dhew.

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