timates $k_2/k_{-1} \sim 0.4$ for CO and $k_2/k_{-1} \sim 1$ for O_2. In this regard, as in the cooperativity of ligation, the behavior of CO and of O_2 in Hb is comparable, differing markedly from that of NO.

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Registry No. FePP(1-MeIm)(NO), 76759-31-4; FePP(NO), 54854-55-6; FePP(1-MeIm), 70085-59-5; FePP(1-MeIm)$_2$, 78261-95-7; FePP(2-MeIm), 70085-59-5.

Total Synthesis of (±)-14-Epicorynoline, (±)-Corynoline, and (±)-6-Oxocorynoline

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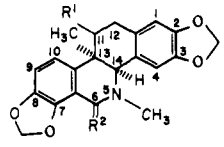
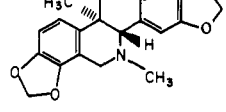
Received June 7, 1982

Abstract: The condensation of piperonylidenemethylamine (**15**) with 3,4-(methylenedioxy)-7-methylhomophthalic anhydride (**14**) has been utilized as the key step in a total synthesis of the naturally occurring hexahydrobenzo[*c*]phenanthridine alkaloids (±)-corynoline (**1**), (±)-6-oxocorynoline (**2**), and (±)-14-epicorynoline (**3**). The production of each of the desired diastereomers **16** and **17** was maximized under certain specified reaction conditions. An unusual fragmentation reaction was discovered during the conversion of the diazo ketone **20** to the substituted 1(2*H*)-isoquinolone **22** under acidic conditions. Two conformers of the tetracyclic intermediate **30** were detected at room temperature by 470-MHz ^{1}H NMR spectroscopy. The identity of (+)-isocorynoline with (+)-14-epicorynoline was also demonstrated.

(±)-Corynoline,[1] (+)-corynoline (**1**),[2] 6-oxocorynoline (**2**),[3] and



1, R^1 = ◄ OH; R_2 = H_2
2, R^1 = ◄ OH; R_2 = O
9, R^1 = ıılı OH; R_2 = H_2



3, R = ◄ OH
4, R = ~ OAc
5, R = ◄ OAc
6, R = ıılı OAc
31, R = ıılı OH
32, R = ıılı OSO_2CH_3
34, R = H

(+)-14-epicorynoline (**3**)[1,4] are benzophenanthridine alkaloids that have been isolated from *Corydalis incisa*. The structure **1** of (±)-corynoline was proposed in 1963 after contemplation of the results of chemical degradation studies, spectroscopic evidence, and biosynthetic considerations.[5] This structure assignment was later confirmed by an X-ray analysis of the *p*-bromobenzoate.[6] The absolute configuration of (+)-corynoline (**1**) was established by chemical correlation with (+)-14-epicorynoline (**3**),[2,7] the absolute configuration of which was proven by X-ray analysis of the bromoacetate.[8] At the outset of the present study the structural identities of (+)-isocorynoline and (+)-acetylisocorynoline appeared to be the subject of some confusion. In fact, (+)-acetylisocorynoline had appeared in the literature as three different structures, **4**,[9] **5**,[3] and **6**.[10]

Considerable effort has already been directed toward the total synthesis of the naturally occurring BC cis-fused hexahydrobenzo[*c*]phenanthridine alkaloids. The first synthesis of (±)-chelidonine (**7**) was executed by using the intramolecular Diels–Alder reaction of an *o*-quinodimethane derived from a benzocyclobutene.[11] More recently, the photocyclization of enamides was exploited during a total synthesis of (±)-corynoline (**1**), (±)-12-hydroxycorynoline (**8**), and (±)-11-epicorynoline (**9**).[12] Significant work has also been done on the chemical transformation of certain 13-methylprotoberberine alkaloids to analogues of the naturally occurring *cis*-13-methylbenzophenanthridines.[13] Other analogues of corynoline (**1**) have been prepared from homophthalimide derivatives.[14] However, very little work has been reported on the total synthesis of the naturally occurring BC trans-fused alkaloid 14-epicorynoline (**3**). We recently reported a total synthesis of (±)-chelidonine (**7**) that was based on the

(1) Tani, C.; Takao, N. *Yakugaku Zasshi* **1962**, *82*, 594.
(2) Takao, N.; Kamigauchi, M.; Iwasa, K. *Tetrahedron* **1979**, *1977*.
(3) Nonaka, G.; Nishioka, I. *Chem. Pharm. Bull.* **1975**, *23*, 521.
(4) Kametani, T.; Ihara, M.; Honda, T. *Phytochemistry* **1971**, *10*, 1881.
(5) Takao, N. *Chem. Pharm. Bull.* **1963**, *11*, 1306, 1312.
(6) Kametani, T.; Honda, T.; Ihara, M.; Shimanouchi, H.; Sasada, Y. *Tetrahedron Lett.* **1972**, 3729.
(7) Takao, N.; Bersch, H.-W.; Takao, S. *Chem. Pharm. Bull.* **1973**, *21*, 1096.
(8) Takao, N.; Kamigauchi, M.; Iwasa, K.; Tomita, K.; Fujiwara, T.; Wakahara, A. *Tetrahedron Lett.* **1974**, 805.
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(10) Shamma, M.; Moniot, J. L. "Isoquinoline Alkaloids Research, 1972–1977"; Plenum Press: New York, 1978; p 271.
(11) Oppolzer, W.; Keller, K. *J. Am. Chem. Soc.* **1971**, *93*, 3836. An improved version of this synthesis was recently communicated: Oppolzer, W. *Heterocycles* **1980**, *14*, 1615.
(12) Ninomiya, I.; Yamamoto, O.; Naito, T. *J. Chem. Soc., Perkin Trans. I* **1980**, 212.
(13) Onda, M.; Yuasa, K.; Okada, J.; Kataoka, K.; Abe, K. *Chem. Pharm. Bull.* **1973**, *21*, 1333. Onda, M.; Yuasa, K.; Okada, J. *Ibid.* **1974**, *22*, 2365. Onda, M.; Harigaya, Y.; Horie, J. *Heterocycles* **1977**, *8*, 89. Onda, M.; Yamaguchi, H., Harigaya, Y. *Chem. Pharm. Bull.* **1980**, *28*, 866.
(14) Iida, H.; Endo, I.; Narimiya, M.; Kikuchi, T. *Heterocycles* **1980**, *14*, 1325.

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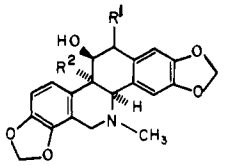
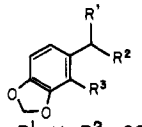
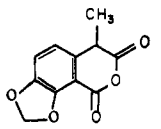


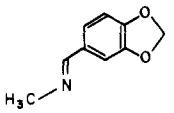
7, R^1 = H; R^2 = H
8, R^1 = OH; R^2 = CH_3



10, R^1 = H; R^2 = COOH; R^3 = COOH
11, R^1 = CH_3; R^2 = COOH; R^3 = COOH
12, R^1 = H; R^2 = CN; R^3 = COOEt
13, R^1 = CH_3; R^2 = CN; R^3 = COOEt



14

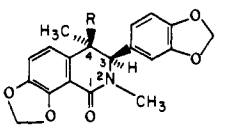


15

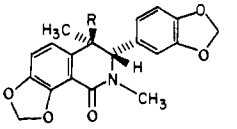
condensation of piperonylidenemethylamine (**15**) with a substituted homophthalic anhydride derived by cyclodehydration of compound **10**.[15] The purpose of the present investigation was to probe the extension of this methodology to the preparation of both cis-fused and trans-fused natural products of the 13-methylbenzophenanthridine series.[16] At the beginning it was not obvious whether or not the key condensation reaction could be extended to the 7-methylhomophthalic anhydride derivative **14**, which was desired to make the quaternary carbons present in the isoquinolones **16** and **17**. Provided the reaction would occur, another unknown was the stereochemical outcome.

The first task was preparation of the required anhydride **14**. Since we had already made the homophthalic acid **10**,[15] it was initially converted to its trianion by using 3 equiv of lithium diisopropylamide as the base in a mixture of tetrahydrofuran and hexamethylphosphoramide. Methylation of this trianion with methyl iodide afforded the desired compound **11** in 42% yield after an acidic workup. Cyclodehydration of the diacid **11** in refluxing acetyl chloride provided the required anhydride **14**. The moderate yield in the conversion of **10** to **11** led to the investigation of an alternative pathway. The known cyano ester **12**[15] gave a red monoanion with lithium diisopropylamide at −78 °C, which on alkylation with methyl iodide gave compound **13** in 71% yield. Alkaline hydrolysis of **13** then yielded the intermediate **11**.

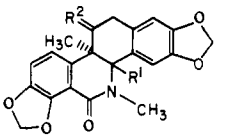
Condensation of the anhydride **14** with piperonylidenemethylamine **15** in methanol at room temperature led to a mixture of diastereomeric isoquinolones **16** and **17**, which could be readily separated as a consequence of the much lower solubility of the sodium salt of **16** in 20% aqueous sodium hydroxide compared with that of the salt of **17**. The relative configuration assignments in **16** and **17** were tentatively made on the basis of the ^{1}H NMR spectra. In both isomers the 3,4-(methylenedioxy)phenyl substituents are assumed to exist predominantly in the pseudoaxial



16, R = COOH
18, R = $COOCH_3$
20, R = $COCHN_2$



17, R = COOH
19, R = $COOCH_3$
29, R = $COCHN_2$
35, R = CH_2COOH



21, R^1 = H; R^2 = O
30, R^1 = H; R^2 = O
33, R^1 = H; R^2 = H, OH

orientation in order to avoid a nonbonded interaction with the *N*-methyl group.[17] This is analogous to the effect of A strain in cyclohexenes.[18] One would expect the C-4 methyl group in the diastereomer **17** to appear at higher field than that of isomer **16** because of the shielding effect of the vicinal *cis*-(methylenedioxy)phenyl substituent.[19] Accordingly, the diastereomer that displayed the signal for the *C*-methyl group at δ 1.37 in its NMR spectrum was assigned structure **17**, while the isomer showing the *C*-methyl signal at δ 1.77 was given structure **16**. In addition, the C-3 methine proton in **16** appeared at δ 4.60, upfield relative to that of **17**, which resonated at δ 4.92. In six-membered rings, equatorial protons are shielded slightly more by vicinal cis axial methyl groups than by vicinal trans equatorial methyl groups.[20] Finally, the signal for the methoxycarbonyl protons of the methyl ester **18** of acid **16** appears at δ 3.47 whereas the corresponding signal of the diastereomeric ester **19** appears at δ 3.67. The methoxycarbonyl protons of the equatorial ester group of **18** may experience the shielding effect of the aromatic (methylenedioxy)phenyl substituent, whereas those of the axial ester group of **19** may not.[21] These arguments are of a tentative nature, but it was decided nevertheless at this point to proceed with the knowledge that the stereochemistry of the two diastereomers **16** and **17** could ultimately be unambiguously assigned by conversion of these intermediates to natural products of known structure.

Considerable effort was directed toward investigation of the effect of varying reaction conditions on the stereochemical outcome of the condensation of the imine **15** and the anhydride **14**. In agreement with the previous study on 3,4-(methylenedioxy)-homophthalic anhydride unsubstituted at C-7,[15] it was found that nonpolar solvents maximize production of the diastereomer **17**

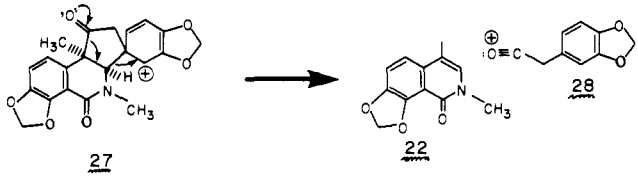
(15) Cushman, M.; Choong, T.-C.; Valko, J. T.; Koleck, M. P. *J. Org. Chem.* **1980**, *45*, 5067.
(16) This work has been outlined in two prior communications: Cushman, M.; Abbaspour, A.; Gupta, Y. P. *Heterocycles* **1982**, *19*, 1431. Cushman, M.; Gupta, Y. P. *Heterocycles* **1982**, *19*, 1587.
(17) Cushman, M.; Gentry, J.; Dekow, F. W. *J. Org. Chem.* **1977**, *42*, 1111.
(18) Johnson, F. *Chem. Rev.* **1968**, *68*, 375.
(19) Similar shielding effects have been documented in aryl-substituted pyrrolidines: Rueppel, M. L.; Rapoport, H. *J. Am. Chem. Soc.* **1971**, *93*, 7021.
(20) Segre, A.; Musher, J. I. *J. Am. Chem. Soc.* **1967**, *89*, 706.
(21) Similar arguments were previously advanced in order to explain the relative configuration assignments in related piperidinones: Cushman, M.; Castagnoli, N., Jr. *J. Org. Chem.* **1973**, *38*, 440.

Table I. Effect of Reaction Conditions on the Stereochemical Outcome of the Condensation of 3,4-(Methylenedioxy)-7-methylhomophthalic Anhydride (**14**) and Piperonylidenemethylamine (**15**)[a]

solvent	temp, °C[b]	% 16[c]	% 17
MeOH	23	45	55
MeOH	65	43	57
CH_3CN	82	42	58
CF_3COOH	23	40	60
CH_3CN	23	40	60
neat[d]	23	40	60
DMF	23	39	61
MeOH	−65	38	62
Me_2SO	23	32	68
AcOH	118	25	75
$CHCl_3$	23	23	77
$CHCl_3$	61	20	80
xylene	23	10	90
benzene	23	8	92

[a] The combined yields of the diastereomers are essentially quantitative. [b] In all cases, except the neat reaction, the reaction time was 1 h. [c] Estimated from NMR integrations. [d] The neat reaction was performed by shaking the two solids in a wiggle-bug ball mill for 1 min.

Scheme I



27 22 28

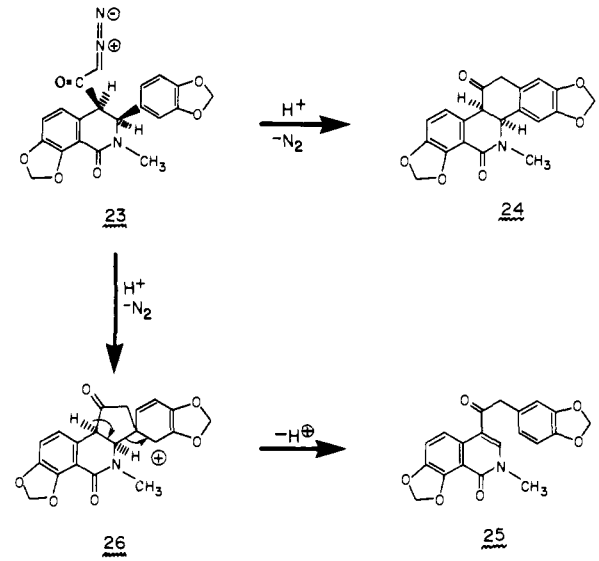
in which the (methylenedioxy)phenyl substituent and the carbonyl group are trans (Table I). Although the other diastereomer **16** consistently proved to be the minor isomer formed under a wide variety of reaction conditions, it was formed in largest amounts in more polar solvents. We presently have no convincing rationale for this effect.

Treatment of the acid chloride of **16** with diazomethane gave the diazo ketone **20**, which on brief exposure to trifluoroacetic acid yielded a mixture from which the desired tetracyclic ketone **21** could be isolated in 37% yield.[22] The other major product in the reaction mixture was the isoquinolone **22** (Scheme I), which was isolated in 27% yield. In connection with the formation of compound **22**, it should be mentioned that the related diazo ketone **23** (Scheme II) had previously been converted to products **24** (19% yield) and **25** (22% yield) during a synthesis of chelidonine (**7**).[15] The conversion of **23** to **25** was rationalized as proceeding through a spirocyclic cation (**26**) in a reaction which bears some resemblance to the Hayashi rearrangement.[23] Since this type of reaction should be effectively blocked by the *C*-methyl group present in **20**, there was reason to expect that the conversion of **20** to **21** would occur in higher yield than previously experienced in the transformation of **23** to **24**. Although the conversion of **20** to **21** did prove to be more efficient, evidently a major competing reaction was the fragmentation of the analogous spirocyclic cation **27** as shown in Scheme I.

The synthesis of (±)-corynoline (**1**) was completed by lithium aluminum hydride reduction of the tetracyclic keto amide **21**. (±)-6-Oxocorynoline (**2**) was also prepared by sodium borohydride reduction of the same intermediate **21**.

Attention was then focused on total synthesis of the BC trans-fused 13-methylbenzophenanthridine (±)-14-epicorynoline (**3**). The required diastereomer **17** was obtained in 89% yield when the condensation of **14** and **15** was performed in benzene. The acid chloride of **17** was converted to the diazo ketone **29** as before with diazomethane. Treatment of the diazo ketone **29** with trifluoroacetic acid afforded the ketone **30**.

Scheme II



23 24 26 25

Two conformations of the tetracyclic ketone **30** were detected by 470-MHz ^1H NMR spectroscopy at room temperature in either Me_2SO-d_6 or $CDCl_3$ solvent. The coalescence temperature T_c in Me_2SO-d_6 proved to be approximately 80 °C. The ratio of the two conformers at room temperature was 6:4. Examination of Dreiding models reveals that a severe nonbonded interaction exists between the *N*-methyl group and the C-4 hydrogen atom in compound **30**. The two conformers evident at room temperature may exist with the *N*-methyl group either slightly above or below the plane of the A ring. The abnormally high fields of the signals for the two *N*-methyl groups (δ 2.631 and 2.625) of these conformers indicate that they do exist near the plane of the A ring.

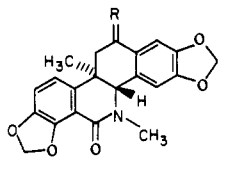
Reduction of intermediate **30** with lithium aluminum hydride in refluxing dioxane provided compound **31**. Comparison of the 470-MHz ^1H NMR spectrum of our synthetic compound **31** with that of authentic (+)-isocorynoline revealed that (+)-isocorynoline *is not* (+)-**31**.[24] This result also proves that structure **6** is incorrect for (+)-acetylisocorynoline.

Several unsuccessful attempts were made to convert compound **31** to (±)-14-epicorynoline (**3**). Treatment of **31** with triphenylphosphine, diethyl azodicarboxylate, and formic acid in tetrahydrofuran[25] gave back the starting material even when the mixture was heated at reflux. Attempts to displace the mesylate group of **32** with various oxygen-containing nucleophiles including potassium nitrite in dimethyl sulfoxide or dimethylformamide, tetra-*n*-butylammonium formate in acetone, potassium acetate in hexamethylphosphoramide, and potassium hydroxide in ethanol all resulted in the formation of mixtures containing the starting material and the alcohol **31**. Efforts to introduce a double bond between C-11 and C-12 by dehydration of compounds **31** and **33** or by dehydrogenation of **34** were unrewarded. Treatment of the amino alcohol **31** with thionyl chloride alone or in the presence of pyridine resulted in reisolation of the starting material, while subjection of the corresponding lactam **33** to these conditions gave a complex mixture of products. Attempted dehydrogenation of **34** with dichlorodicyanobenzoquinone in chloroform likewise resulted in the formation of an obstinate mixture of products from which nothing could be isolated even after repeated thin-layer chromatography. This route was eventually abandoned in favor of an alternative strategy starting from the diazo ketone **29**.

The intermediate **29** was subjected to silver oxide in refluxing methanol to afford an ester which was hydrolyzed in ethanolic potassium hydroxide, giving the acid **35** in 83% overall yield.

(22) Beames, D. J.; Mander, L. N. *Aust. J. Chem.* **1974**, *27*, 1257.
(23) Hayashi, M. *J. Chem. Soc.* **1927**, 2516. Hayashi, M. *Ibid.* **1930**, 1513, 1520, 1524. Newman, M. *Acc. Chem. Res.* **1972**, *5*, 354.
(24) We are grateful to Dr. G. Nonaka, Kyushu University, for a sample of (+)-isocorynoline.
(25) Bose, A. K.; Lal, B.; Hofmann, W. A., III; Manhas, M. S. *Tetrahedron Lett.* **1973**, 1619.

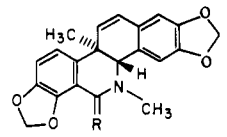
Treatment of **35** with a mixture prepared by adding phosphorus pentoxide to methanesulfonic acid gave the Friedel–Crafts product **36**.[26] Sodium borohydride reduction of the ketone **36** afforded



36, R = O

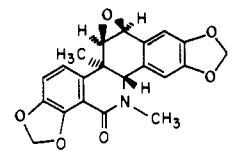
37, R = —H, ····OH

38, R = ····H, —OH



39, R = O

40, R = H_2



41

a mixture of alcohols **37** and **38** from which the major diastereomer could be isolated in 83% yield. The major isomer is assumed to have structure **37** since the borohydride is expected to approach the ketone predominantly from the side of the ring which is opposite that of the axial methyl group.[27] The minor diastereomer **38** was also isolated in 5% yield. The alcohol **37** was dehydrated by using *p*-toluenesulfonic acid in refluxing benzene to give product **39**. Attempted conversion of either **39** or its reduction product **40** to (±)-14-epicorynoline (**3**) using hydroboration–oxidation led to intractable mixtures. However, compound **39** could be cleanly converted to the epoxide **41**. The steric hindrance created by the axial methyl group of intermediate **39** causes the peracid to attack the double bond from the β side. Lithium aluminum hydride reduction of the epoxide **41** then gave (±)-14-epicorynoline (**3**). The 470-MHz ^{1}H NMR spectrum of our synthetic material was identical with the spectra of both (+)-isocorynoline and (+)-14-epicorynoline.[28] This work constitutes the first total synthesis of (±)-14-epicorynoline, and it also establishes the identity of (+)-14-epicorynoline with (+)-isocorynoline.

Experimental Section

All reactions were performed under a nitrogen atmosphere. Melting points were determined on a Thomas-Hoover Unimelt or on a Meltemp apparatus and are uncorrected. NMR spectra were recorded on a Varian EM-360 60-MHz spectrometer or on an FT-80 80-MHz spectrometer in $CDCl_3$ solvent, except where noted. The high-resolution 470-MHz NMR spectra were obtained by using a Nicolet NTC-470 spectrometer and the data accumulated by using 32K free induction decays. Chemical shifts are reported in parts per million relative to Me_4Si as internal standard. IR spectra were recorded on a Beckman IR-33 spectrophotometer. Preparative thin-layer chromatography (TLC) was performed on Merck silica gel 60 F-254. Microanalyses were performed by the Purdue Microanalytical Laboratory. The mass spectra were determined on a Finnegan 4000 spectrometer using an ionization potential of 70 eV. The chemical ionization mass spectra (CIMS) were obtained by using isobutane as the reagent gas. Organic extracts were dried by using $MgSO_4$.

α-Methyl(2-carboxy-3,4-(methylenedioxy)phenyl)acetic Acid (11). Method A. An oven-dried, round-bottomed flask (100 mL) was purged with nitrogen and capped with a septum. A solution of diisopropylamine (2.505 g, 24.8 mmol) in dry THF (10 mL) was injected, and the solution was cooled to 0 °C during 15 min. A solution of *n*-butyllithium in hexane (2.4 M, 11.66 mL, 27.98 mmol) was added dropwise by syringe to the stirred solution. After 1 h, a solution of the diacid **10**[15] (1.792 g, 7.99 mmol) in THF (16 mL) and HMPA (6 mL) was added dropwise during 30 min. After the mixture was stirred for an additional 1 h, a solution of methyl iodide (5.68 g, 40.0 mmol) in THF (10 mL) was added dropwise. The reaction mixture was then stirred for 2 h before the solid was filtered and washed with Et_2O and $CHCl_3$. The solid was dissolved in water (20 mL). The solution was washed with $CHCl_3$, cooled to 0 °C, acidified with concentrated HCl, and extracted with $CHCl_3$. The organic extract was diluted with hexane and cooled to −10 °C overnight. The solid was filtered, washed with cold water, and dried to afford the product **11**: 0.80 g, 42%; mp 172–173 °C; IR (KBr) 3300–2460, 1700, 1660 cm^{-1}; NMR (60 MHz, $CDCl_3$–Me_2SO_4-d_6, 1:4) δ 6.90 (s, 2 H), 6.10 (s, 2 H), 4.36 (q, 1 H, J = 7 Hz), 1.41 (d, 3 H, J = 7 Hz). Anal. ($C_{11}H_{10}O_6$) C, H.

Method B. A mixture of the phenylacetonitrile **13** (4.381 g, 17.72 mmol), KOH (3.16 g), and water (14 mL) was heated at reflux for 3 h. The solution was cooled and acidified with concentrated HCl. The precipitate was filtered, washed with water, dried, and crystallized from Me_2CO–hexane to yield the solid diacid **11**: 3.091 g, 73%.

3,4-(Methylenedioxy)-7-methylhomophthalic Anhydride (14). A mixture of diacid **11** (1.78 g, 7.47 mmol) and acetyl chloride (7 mL) was heated at reflux for 6 h. After the mixture was allowed to stand at −10 °C overnight, the solid anhydride **14** was filtered: 1.50 g, 91%; mp 137–138 °C; IR (KBr) 1780, 1735, 1620, 1440, 1260, 1025, 980 cm^{-1}; NMR (60 MHz, $CDCl_3$–Me_2SO-d_6, 1:3) δ 7.22 (d, 1 H, J = 8 Hz), 6.94 (d, 1 H, J = 8 Hz), 6.28 (s, 2 H), 4.11 (q, 1 H, J = 8 Hz), 1.63 (d, 3 H, J = 8 Hz). Anal. ($C_{11}H_8O_5$) C, H.

α-Methyl(2-(ethoxycarbonyl)-3,4-(methylenedioxy)phenyl)acetonitrile (13). An oven-dried, round-bottomed flask (100 mL) was purged with nitrogen and then capped with a septum. A solution of diisopropylamine (3.28 g, 32.41 mmol) in THF (10 mL) and HMPA (2 mL) was injected and the solution cooled to −78 °C during 30 min. A solution of *n*-butyllithium in hexane (2.4 M, 12.5 mL, 30 mmol) was added dropwise to the stirred solution. After 40 min, a solution of the benzylcyanide **12**[15] (5.825 g, 25.0 mmol) was added dropwise during 20 min. The red reaction mixture was stirred for 40 min. A solution of methyl iodide (7.10 g, 50.0 mmol) in THF (10 mL) was added. After 5 min at −78 °C, the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was poured into cold 10% aqueous HCl (100 mL) and extracted with $CHCl_3$ (4 × 30 mL). The organic layers were combined, washed with water, and dried, and the solvent was evaporated. The residue was dissolved in benzene and applied to a silica gel column (80 g, 60–200 mesh), which had been packed by using hexane. Elution of the column with benzene–petroleum ether (1:1) furnished the product **13**. The analytical sample was crystallized from benzene–petroleum ether: 4.381 g, 71%; mp 61–62 °C; IR ($CHCl_3$) 2115, 1700 cm^{-1}; NMR (60 MHz) δ 7.23 (d, 1 H, J = 8 Hz), 6.97 (d, 1 H, J = 8 Hz), 6.13 (s, 2 H), 4.82 (q, 1 H, J = 7 Hz), 4.47 (q, 2 H, J = 7 Hz), 1.73 (d, 3 H, J = 7 Hz), 1.47 (t, 3 H, J = 7 Hz); mass spectrum, m/e (relative intensity) 247 (M^+, 69), 219 (41), 218 (73), 202 (74), 201 (100), 200 (32), 191 (22), 190 (22), 174 (19), 173 (48), 172 (32), 162 (15). Anal. ($C_{13}H_{13}NO_4$) C, H, N.

***N*-Methyl-*r*-3-(3,4-(methylenedioxy)phenyl)-*c*-4-carboxy-*t*-4-methyl-7,8-(methylenedioxy)-3,4-dihydro-1(2*H*)-isoquinolone (16).** A solution of piperonylidenemethylamine (**15**, 2.10 g, 12.87 mmol) in MeOH (20 mL) was added dropwise to a stirred suspension of the anhydride **14** (2.58 g, 11.72 mmol) in MeOH (20 mL). After the mixture was stirred for 1 h, the solvent was evaporated and 20% aqueous NaOH (20 mL) was added to the residue. The white precipitate was filtered and washed with 20% aqueous NaOH (4 mL). The precipitate was then added to 15% aqueous NaOH (20 mL) and the solid dissolved by adding water (50 mL). The solution was acidified by dropwise addition of concentrated HCl. The solid was filtered, washed with cold water, and dried. Recrystallization from acetone gave analytically pure **16**: 1.29 g, 29%; mp 238–240 °C; IR ($CHCl_3$) 3380–2800, 1720, 1705, 1632, 1590 cm^{-1}; NMR (60 MHz, $CDCl_3$–Me_2SO-d_6, 3:1) δ 9.66 (br s, 1 H) 7.27 (d, 1 H, J = 8 Hz), 6.90 (d, 1 H, J = 8 Hz), 6.67 (m, 3 H), 6.13 (m, 2 H), 5.77 (s, 2 H), 4.60 (s, 1 H), 3.03 (s, 3 H), 1.77 (s, 3 H); mass spectrum, m/e (relative intensity) 383 (M^+, 5), 339 (10), 337 (26), 325 (21), 220 (31), 192 (37), 176 (45), 164 (74), 163 (68), 162 (67), 148 (53), 147 (100), 135 (16), 121 (21), 104 (16), 91 (18), 78 (31). Anal. ($C_{20}H_{17}NO_7$) C, H, N.

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(28) We are indebted to Dr. N. Takao, Kobe Women's College of Pharmacy, for a sample of (+)-14-epicorynoline.

***N*-Methyl-*r*-3-(3,4-(methylenedioxy)phenyl)-*t*-4-carboxy-*c*-4-methyl-7,8-(methylenedioxy)-3,4-dihydro-1(2*H*)-isoquinolone (17). Method A.** The alkaline filtrate from above was cooled on an ice bath and acidified with concentrated HCl. The light yellow solid was filtered, washed with water, and dried. Crystallization from $CHCl_3$–petroleum ether yielded the pure product **17**: 2.97 g, 66%; mp 165–167 °C; IR 3460–2800, 1702, 1692, 1622, 1583 cm^{-1}; NMR (60 MHz, $CDCl_3$–Me_2SO-d_6, 3:1) δ 9.33 (br s, 1 H), 7.38–6.33 (m, 3 H), 6.95 (d, 1 H, *J* = 8 Hz), 6.72 (d, 1 H, *J* = 8 Hz), 6.20 (s, 2 H), 5.93 (s, 2 H), 4.92 (s, 1 H), 3.00 (s, 3 H), 1.37 (s, 3 H); mass spectrum, *m/e* (relative intensity) 383 (M^+, 5), 339 (21), 338 (30), 337 (100), 336 (39), 325 (34), 324 (20), 308 (18), 220 (21), 217 (21), 216 (21), 192 (36), 176 (37), 164 (88), 163 (33), 162 (36), 148 (49), 147 (38). Anal. ($C_{20}H_{17}NO_7$) C, H, N.

Method B. A solution of piperonylidenemethylamine (**15**, 2.76 g, 16.91 mmol) in benzene (10 mL) was added dropwise to a suspension of the anhydride **14** (3.70 g, 16.80 mmol) in benzene (30 mL) at room temperature. After the mixture was stirred for 1.5 h, the solvent was evaporated and the residue crystallized from $CHCl_3$–petroleum ether to give the product **17**: 5.75 g, 89%.

***N*-Methyl-*r*-3-(3,4-(methylenedioxy)phenyl)-*c*-4-(methoxycarbonyl)-*t*-4-methyl-7,8-(methylenedioxy)-3,4-dihydro-1(2*H*)-isoquinolone (18).** The acid **16** (0.04 g, 0.1 mmol) was added to an excess of diazomethane in Et_2O–EtOH (0.5 mL) at −10 °C. The reaction mixture was allowed to stand at 0 °C for 2 h before the precipitate was filtered, washed with Et_2O, and dried to yield the ester (0.03 g). A second crop (0.008 g) was obtained by evaporation of the filtrate and recrystallization of the residue from EtOH. The analytical sample was recrystallized from EtOH–Et_2O: 0.037 g, 93%; mp 185–186 °C; IR ($CHCl_3$) 1733, 1715, 1632, 1590 cm^{-1}; NMR (60 MHz) δ 6.93–6.50 (m, 5 H), 6.23 (m, 2 H), 5.97 (m, 2 H), 4.45 (s, 1 H), 3.47 (s, 3 H), 3.03 (s, 3 H), 1.72 (s, 3 H); mass spectrum, *m/e* (relative intensity) 397 (M^+, 16), 235 (13), 234 (100), 206 (28), 191 (58). Anal. ($C_{21}H_{19}NO_7$) C, H, N.

***N*-Methyl-*r*-3-(3,4-(methylenedioxy)phenyl-*t*-4-(methoxycarbonyl)-*c*-4-methyl-7,8-(methylenedioxy)-3,4-dihydro-1(2*H*)-isoquinolone (19).** The acid **17** (0.08 g, 0.2 mmol) was added to a solution of excess diazomethane in Et_2O–EtOH (1 mL) at −10 °C. The reaction mixture was allowed to stand at 0 °C for 2 h. The solvent was evaporated and the residue crystallized from $CHCl_3$–petroleum ether to yield the ester **19**: 0.07 g, 88%; mp 110–112 °C; IR ($CHCl_3$) 1715, 1630, 1590 cm^{-1}; NMR (60 MHz) δ 7.10–6.37 (m, 3 H), 6.98 (d, 1 H, *J* = 8 Hz), 6.72 (d, 1 H, *J* = 8 Hz), 6.25 (s, 2 H), 5.97 (s, 2 H), 4.90 (s, 1 H), 3.67 (s, 3 H), 3.03 (s, 3 H), 1.33 (s, 3 H); mass spectrum, *m/e* (relative intensity) 397 (M^+, 5), 234 (24), 206 (12), 191 (21), 162 (5), 149 (6), 105 (6), 91 (9), 87 (14), 85 (79), 83 (100), 66 (18). Anal. ($C_{21}H_{19}NO_7$) C, H, N.

***N*-Methyl-*r*-3-(3,4-(methylenedioxy)phenyl)-*c*-4-(diazoacetyl)-*t*-4-methyl-7,8-(methylenedioxy)-3,4-dihydro-1(2*H*)-isoquinoline (20).** Thionyl chloride (2 mL) was added to the acid **16** (1.0 g, 2.61 mmol) and the mixture stirred for 12 h at room temperature. The thionyl chloride was evaporated. Benzene (4 mL) was added to the residue and then evaporated. The residue was then dissolved in benzene (40 mL) and added dropwise to a solution of excess diazomethane in alcohol-free Et_2O at −10 °C. The reaction mixture was stirred at room temperature for 2 h. The light yellow precipitate was filtered and recrystallized from MeOH to afford the pure diazo ketone **20**: 0.845 g, 79%; mp 180 °C dec; IR ($CHCl_3$) 2880, 2078, 1635 cm^{-1}; NMR (60 MHz) δ 7.03–6.55 (m, 5 H), 6.27 (m, 2 H), 5.98 (m, 2 H), 4.67 (s, 1 H), 4.33 (s, 1 H), 3.02 (s, 3 H), 1.68 (s, 3 H); mass spectrum, *m/e* (relative intensity) 379 (M^+ − 28, 81), 217 (75), 216 (97), 188 (100), 162 (50).

***cis*-*N*-Methyl-2,3-(methylenedioxy)-6,11-dioxo-7,8-(methylenedioxy)-10b-methyl-4b,5,6,10b,11,12-hexahydrobenzo[*c*]phenanthridine (21).** The diazo ketone **20** (70 mg, 0.17 mmol) was added to trifluoroacetic acid (1 mL) at 0 °C. After 10 min the trifluoroacetic acid was evaporated at room temperature. Preparative TLC (Et_2O–benzene–EtOAc, 5:5:2) furnished the pure product **21**: 24 mg, 37%; mp 220–221 °C; IR ($CHCl_3$) 1743, 1702, 1632, 1590 cm^{-1}; NMR (60 MHz) δ 6.77 (d, 1 H, *J* = 8 Hz), 6.70 (s, 1 H), 6.60 (s, 1 H), 6.53 (d, 1 H, *J* = 8 Hz), 6.13 (m, 2 H), 5.98 (s, 2 H), 4.57 (s, 1 H), 3.67 (s, 2 H), 3.37 (s, 3 H), 1.53 (s, 3 H); mass spectrum, *m/e* (relative intensity) 379 (M^+, 37), 322 (8), 217 (4), 216 (100), 188 (33), 160 (12). Anal. ($C_{21}H_{17}NO_6$) C, H, N.

***N*-4-Dimethyl-1,2-dihydro-7,8-(methylenedioxy)isoquinoline (22).** The preparative TLC from the above experiment also gave compound **22**. The analytical sample was prepared by recrystallization from $CHCl_3$–petroleum ether: 10 mg, 27%; mp 179–180 °C; IR ($CHCl_3$) 1650, 1622, 1606, 1465 cm^{-1}; NMR (60 MHz) δ 7.28 (d, 1 H, *J* = 9 Hz), 7.03 (d, 1 H, *J* = 9 Hz), 6.73 (br s, 1 H), 6.23 (s, 2 H), 3.50 (s, 3 H), 2.20 (s, 3 H); mass spectrum, *m/e* (relative intensity) 217 (M^+, 100). Anal. ($C_{12}H_{11}NO_3$) C, H, N.

(±)-Corynoline (1). A mixture of compound **21** (15 mg, 0.038 mmol) and $LiAlH_4$ (25 mg) in THF (10 mL) was heated at reflux for 17 h. The reaction mixture was cooled to 0 °C and decomposed by addition of water (0.3 mL), 15% aqueous NaOH (0.3 mL), and finally water (0.3 mL). The mixture was stirred for 15 min and then filtered. The aluminates were washed with $CHCl_3$, and the combined organic layers were dried and evaporated. Preparative TLC of the residue gave pure corynoline (**1**). The analytical sample was recrystallized from methanol: 10 mg, 72%; mp 216–217 °C (lit.[1] mp 216–217 °C); NMR (470 MHz) δ 6.93 (d, 1 H, *J* = 8.3 Hz), 6.81 (d, 1 H, *J* = 8.3 Hz), 6.68 (s, 1 H), 6.65 (s, 1 H), 6.00 (d, 1 H, *J* = 1.5 Hz), 5.97 (d, 1 H, *J* = 1.5 Hz), 5.96 (s, 2 H), 4.05 (d, 1 H, *J* = 15.4 Hz), 3.96 (m, 1 H), 3.46 (d, 1 H, *J* = 15.4 Hz), 3.32 (br s, 1 H), 3.16 (d, 1 H, *J* = 17.9 Hz), 3.10 (d of d, 1 H, *J* = 17.9, 4.5 Hz), 2.22 (s, 3 H), 1.58 (br s, 1 H), 1.15 (s, 3 H); mass spectrum, *m/e* (relative intensity) 367 (M^+, 69), 349 (100), 334 (30), 318 (27), 202 (21), 190 (19), 176 (13), 162 (15).

(±)-6-Oxocorynoline (2). A mixture of compound **21** (7 mg, 0.018 mmol) and $NaBH_4$ (30 mg) in methanol (4 mL) was heated at reflux for 1 h. The reaction mixture was then cooled to room temperature, diluted with water (8 mL), and allowed to stand for 30 min before it was filtered. The precipitate was washed with cold water and dried to yield pure 6-oxocorynoline: 6 mg, 87%; mp 310–312 °C; IR ($CHCl_3$) 2895, 1640, 1590, 1470, 1450, 1410, 1360, 1165, 1020, 910 cm^{-1}; NMR (470 MHz) δ 7.51 (d, 1 H, *J* = 8.2 Hz), 6.74 (d, 1 H, *J* = 8.2 Hz), 6.60 (s, 1 H), 6.40 (s, 1 H), 6.06 (d, 1 H, *J* = 1.2 Hz), 5.91 (d, 1 H, *J* = 1.3 Hz), 5.85 (d, 1 H, *J* = 1.4 Hz), 5.83 (d, 1 H, *J* = 1.3 Hz), 4.15 (d of d, 1 H, *J* = 10.6, 6.6 Hz), 4.08 (s, 1 H), 3.45 (s, 3 H), 3.04 (d, 1 H, *J* = 10 Hz), 3.02 (d, 1 H, *J* = 7 Hz), 1.51 (s, 3 H); mass spectrum, *m/e* (relative intensity 381 (M^+, 100), 364 (21), 363 (84), 218 (53), 205 (21), 176 (21), 175 (32), 148 (21).

***N*-Methyl-*r*-3-(3,4-(methylenedioxy)phenyl)-*t*-4-(diazoacetyl)-*c*-4-methyl-7,8-(methylenedioxy)-3,4-dihydro-1(2*H*)-isoquinolone (29).** Thionyl chloride (3 mL) was added to the acid **17** (1.646 g, 4.29 mmol), and the mixture was stirred for 12 h at room temperature. The thionyl chloride was evaporated, and benzene (4 mL) was added to the residue. The benzene was then evaporated. The residue was dissolved in benzene (50 mL), and the solution was added dropwise to a solution of excess diazomethane in alcohol-free Et_2O (150 mL) at −10 °C. The reaction mixture was stirred at room temperature for 2 h. The precipitate was filtered and recrystallized from MeOH to afford the pure diazo ketone **29**: 1.20 g, 69%; mp 166 °C dec; IR ($CHCl_3$) 2880, 2085, 1630 cm^{-1}; NMR (470 MHz) δ 6.88 (d, 1 H, *J* = 7.9 Hz), 6.64 (m, 2 H), 6.52 (d, 1 H, *J* = 8.0 Hz), 6.33 (s, 1 H), 6.22 (d, 1 H, *J* = 1.2 Hz), 6.21 (d, 1 H, *J* = 1.1 Hz), 5.88 (d, 1 H, *J* = 1.3 Hz), 5.86 (d, 1 H, *J* = 1.4 Hz), 4.96 (s, 1 H), 4.69 (s, 1 H), 2.95 (s, 3 H), 1.22 (s, 3 H); mass spectrum, *m/e* (relative intensity) 379 (M^+ − 28, 64), 338 (30), 234 (46), 191 (46), 188 (61), 164 (61), 162 (43); CIMS, *m/e* (relative intensity) 408 (M^+ + 1, 11), 380 (10), 338 (19), 93 (100). Anal. ($C_{21}H_{17}N_3O_6$) C, H, N.

***trans*-*N*-Methyl-2,3-(methylenedioxy)-6,11-dioxo-7,8-(methylenedioxy)-10b-methyl-4b,5,6,10b,11,12-hexahydrobenzo[*c*]phenanthridine (30).** The diazo ketone **29** (0.926 g, 2.27 mmol) was added to trifluoroacetic acid (4.5 mL) at 0 °C. After 1 min the trifluoroacetic acid was evaporated at room temperature. Crystallization of the residue from MeOH gave the pure product **30**: 0.363 g, 42%; mp 285–286 °C; IR (KBr) 1735, 1625, 1590 cm^{-1}; NMR (470 MHz, Me_2SO-d_6, 28 °C) δ 7.12–6.75 (m, 4 H), 6.13–6.02 (m, 4 H), 4.92 and 4.89 (two s, 1 H, 6:4), 3.82 and 3.81 (two d, 1 H, ratio 6:4, *J* = 21.6, 21.7 Hz), 3.27 and 3.26 (two d, 1 H, 6:4, *J* = 21.6, 21.7 Hz), 2.631 and 2.625 (two s, 3 H, 6:4), 1.23 and 1.18 (two s, 3 H, 6:4); NMR (470 MHz, Me_2SO-d_6, 80 °C) δ 7.00–6.79 (m, 4 H), 6.14 (s, 1 H), 6.12 (s, 1 H), 6.07 (s, 1 H), 6.05 (s, 1 H), 4.91 (s, 1 H), 3.82 (d, 1 H, *J* = 21.5 Hz), 3.30 (d, 1 H, *J* = 21.6 Hz), 2.68 (s, 3 H), 1.25 (s, 3 H); mass spectrum, *m/e* (relative intensity) 379 (M^+, 33), 322 (11), 216 (100), 188 (84), 160 (26). Anal. ($C_{21}H_{17}NO_6$) C, H, N.

(±)-13-Epicorynoline (31). A mixture of the keto lactam **30** (0.14 g, 0.37 mmol) and $LiAlH_4$ (0.28 g) in dioxane (20 mL) was heated at reflux for 16 h. The reaction mixture was cooled to 0 °C and decomposed by addition of water (2 mL), 15% aqueous NaOH (2 mL), and finally water (2 mL). The aluminates were filtered and washed with $CHCl_3$. The combined organic layers were dried and evaporated. Crystallization of the residue from MeOH gave the pure product **31**: 0.12 g, 88%; mp 238–240 °C; IR ($CHCl_3$), 3360–3260, 2905, 2840, 2748, 1460, 1440, 1400, 1335, 1298, 1125, 1105, 1087, 1010, 905 cm^{-1}; NMR (470 MHz) δ 6.93 (s, 1 H), 6.78 (s, 2 H), 6.57 (s, 1 H), 5.98 (s, 2 H), 5.92 (s, 1 H), 5.89 (s, 1 H), 4.29 (d, 1 H, *J* = 16.5 Hz), 4.25 (d of d, 1 H, *J* = 8, 8 Hz), 3.36 (d, 1 H, *J* = 16.5 Hz), 3.10 (s, 1 H), 2.89 (d of d, 1 H, *J* = 15.2, 7.6 Hz), 2.82 (d of d, 1 H, *J* = 14.6, 9.8 Hz), 2.24 (s, 3 H), 1.10 (s, 3 H); mass spectrum, *m/e* (relative intensity) 367 (M^+, 18), 205 (16), 204 (100), 189 (19), 175 (12), 164 (7), 163 (6), 162 (8).

13-Epicorynolinyl Methanesulfonate (32). A solution of the amino alcohol **31** (42 mg, 0.11 mmol) and methanesulfonyl chloride (20 mg, 0.17 mmol) in pyridine (1 mL) was allowed to stand at room temperature for 12 h. The solution was diluted with cold water, and the precipitate was filtered, washed with water, and crystallized from MeOH to give the pure mesylate **32**: 44 mg, 88%; mp 204–206 °C; IR ($CHCl_3$) 2890, 2820, 2755, 1710, 1590, 1463, 1440, 1400, 1335, 1310, 1300, 1142, 930, 900 cm^{-1}; NMR (80 MHz) δ 6.90 (s, 1 H), 6.77 (s, 2 H), 6.55 (s, 1 H), 5.93 (s, 2 H), 4.91 (d of d, 1 H, J = 8, 8 Hz), 4.26 (d, 1 H, J = 17 Hz), 3.34 (d, 1 H, J = 17 Hz), 3.15 (m, 3 H), 2.54 (s, 3 H), 2.20 (s, 3 H), 1.23 (s, 3 H); mass spectrum, m/e (relative intensity) 349 (M^+ – 96, 72), 187 (37), 186 (100). Anal. ($C_{22}H_{23}NO_7S$) C, H, N.

6-Oxo-13-Epicorynoline (33). A mixture of compound **30** (74 mg, 0.20 mmol) and sodium borohydride (0.1 g) in MeOH (5 mL) was heated at reflux for 1 h. The solution was concentrated and diluted with water. The precipitate was filtered, washed with water, and crystallized from MeOH to afford the product **33**: 60 mg, 79%; mp 262–263 °C; IR ($CHCl_3$) 3410, 2870, 1635, 1598, 1445, 1350, 1290 cm^{-1}; NMR (80 MHz) δ 6.90–6.72 (m, 4 H), 6.08 (s, 2 H), 6.02 (s, 2 H), 4.51 (m, 2 H), 3.23–2.75 (m, 2 H), 2.87 (s, 3 H), 1.41 (br s, 1 H), 1.08 (s, 3 H); mass spectrum, m/e (relative intensity) 381 (M^+, 79), 219 (13), 218 (100), 191 (10), 190 (69), 161 (10), 85 (10), 83 (15).

***trans*-*N*-Methyl-2,3-(methylenedioxy)-7,8-(methylenedioxy)-10b-methyl-4b,5,6,10b,11,12-hexahydrobenzo[*c*]phenanthridine (34).** A mixture of the mesylate **32** (20 mg, 0.04 mmol) and $LiAlH_4$ (0.04 g) in dioxane (8 mL) was heated at reflux for 19 h. The reaction mixture was decomposed by the dropwise addition of water (0.5 mL), 15% aqueous NaOH (0.5 mL), and again water (0.5 mL). The solid was filtered and washed with $CHCl_3$. The combined organic layers were dried, and the solvent was evaporated to yield the product **34**, which was recrystallized from $CHCl_3$–hexane: 14 mg, 89%; mp 232–234 °C; IR ($CHCl_3$) 2900, 1595, 1450, 1345, 1305 cm^{-1}; NMR δ 6.94 (s, 1 H), 6.79 (s, 1 H), 6.78 (s, 1 H), 6.58 (s, 1 H), 5.98 (s, 2 H), 5.93 (d, 1 H, J = 1.4 Hz), 5.89 (d, 1 H, J = 1.4 Hz), 4.28 (d, 1 H, J = 1.4 Hz), 5.89 (d, 1 H, J = 1.4 Hz), 4.28 (d, 1 H, J = 16.6 Hz), 3.69 (s, 1 H), 3.36 (d, 1 H, J = 16.6 Hz), 3.25–2.80 (m, 2 H), 2.24 (s, 3 H), 1.25 (m, 2 H), 1.11 (s, 3 H).

***N*-Methyl-*r*-3-(3,4-(methylenedioxy)phenyl)-*t*-4-(carboxymethyl)-*c*-4-methyl-3,4-dihydro-1(2*H*)-isoquinolone (35).** A suspension of the diazo ketone **29** (0.940 g, 2.3 mmol) and Ag_2O (0.5 g) in MeOH (180 mL) was heated at reflux for 2 h. The brown mixture was filtered (Celite) and the filtrate evaporated. The brown residue was treated with KOH (0.3 g) in 95% EtOH (20 mL) and the mixture heated at reflux for 4 h. The solvent was evaporated. Water was added to the residue, and the solution was acidified with concentrated HCl. The mixture was extracted with $CHCl_3$. The organic phase was then extracted with 5% aqueous $NaHCO_3$. The aqueous phase was acidified with concentrated HCl and extracted with $CHCl_3$. The organic phase was washed with saturated aqueous NaCl and dried. The solvent was evaporated and the residue purified by column chromatography on silica gel ($CHCl_3$–hexane–MeOH, 49:49:2 as eluent) to afford pale yellow crystals: 0.759 g, 83%; mp 132–134 °C; IR ($CHCl_3$) 3450–2850, 1720, 1690, 1625, 1580 cm^{-1}; NMR (60 MHz) δ 6.85–6.32 (m, 5 H), 6.23 (s, 2 H), 5.97 (s, 2 H), 4.65 (s, 1 H), 3.05 (s, 3 H), 2.95 (d, 1 H, J = 14 Hz), 2.55 (d, 1 H, J = 14 Hz), 1.25 (s, 3 H); CIMS, m/e (relative intensity) 398 (M^+ + 1, 4), 382 (12), 381 (20), 380 (100), 189 (18), 164 (57).

***trans*-*N*-Methyl-2,3-(methylenedioxy)-6,12-dioxo-7,8-(methylenedioxy)-10b-methyl-4b,5,6,10b,11,12-hexahydrobenzo[*c*]phenanthridine (36).** A solution prepared by adding P_2O_5 (2.5 g) to methanesulfonic acid (25 g, 98%) was warmed to 45 °C. The acid **35** (250 mg, 0.63 mmol) was added and the mixture stirred for 30 min, during which it changed from pale yellow to dark brown. The reaction mixture was poured into ice–water and extracted with $CHCl_3$. The organic phase was washed with 5% aqueous NaOH and with water. The organic solution was dried and evaporated. The residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH, 99:1 as eluent) to yield a pale yellow solid. The analytical sample was recrystallized from MeOH: 200 mg, 84%; mp 265–267 °C; IR ($CHCl_3$) 2900, 1660, 1630, 1450, 1360 cm^{-1}; NMR (470 MHz) δ 7.46 (s, 1 H), 6.69 (d, 1 H, J = 8.0 Hz), 6.84 (s, 1 H), 6.62 (d, 1 H, J = 8.0 Hz), 6.20 (d, 1 H, J = 1.2 Hz), 6.08 (d, 1 H, J = 1.2 Hz), 6.07 (s, 2 H), 5.21 (s, 1 H), 3.13 (d, 1 H, J = 14.7 Hz), 3.08 (s, 3 H), 2.64 (d, 1 H, J = 14.7 Hz), 1.11 (s, 3 H); CIMS, m/e (relative intensity) 380 (M^+ + 1, 100). Anal. ($C_{21}H_{17}NO_6$) C, H, N.

***N*-Methyl-2,3-(methylenedioxy)-6-oxo-7,8-(methylenedioxy)-10b-methyl-12α-hydroxy-4bβ,5,6,10bα,11,12-hexahydrobenzo[*c*]phenanthridine (37).** A suspension of compound **36** (200 mg, 0.53 mmol) and $NaBH_4$ (200 mg, 5 mmol) in isopropyl alcohol (180 mL) was stirred at room temperature for 16 h. The sovlent was evaporated, and water was added to the residue. The mixture was acidified with concentrated HCl. The crystalline solid was filtered. The analytical sample was recrystallized from MeOH: 167 mg, 83%; mp 250–252 °C; IR (KBr) 3400, 2940, 1620 cm^{-1}; NMR (80 MHz) δ 6.96–6.74 (m, 4 H), 6.18 (d, 1 H, J = 1.3 Hz), 6.07 (d, 1 H, J = 1.3 Hz), 5.99 (s, 2 H), 4.94 (m, 1 H), 4.73 (s, 1 H), 3.17 (s, 3 H), 2.32–1.91 (m, 2 H), 1.09 (s, 3 H). Anal. ($C_{21}H_{19}NO_6$) C, H, N.

***N*-Methyl-2,3-(methylenedioxy)-6-oxo-7,8-(methylenedioxy)-10b-methyl-12β-hydroxy-4bβ,5,6,10bα,11,12-hexahydrobenzo[*c*]phenanthridine (38).** The aqueous filtrate from above was extracted with $CHCl_3$. The extract was dried and evaporated. The residue was crystallized from MeOH to yield compound **38**: 11 mg, 5%; mp 246–248 °C; IR ($CHCl_3$) 3600–3000, 1640, 1470 cm^{-1}; NMR (80 MHz) δ 6.86 (d, 1 H, J = 8.0 Hz), 6.84 (s, 1 H), 6.81 (d, 1 H, J = 8.0 Hz), 6.58 (s, 1 H), 6.07 (d, 1 H, J = 1.2 Hz), 5.94 (d, 1 H, J = 1.2 Hz), 5.86 (s, 2 H), 4.67 (br s, 1 H), 4.05 (s, 1 H), 3.36 (s, 3 H), 2.72 (d of d, 1 H, J = 15.0, 3.9 Hz), 2.20 (d of d, 1 H, J = 15.0, 3.9 Hz), 1.83 (br s, 1 H), 1.37 (s, 3 H); CIMS, m/e (relative intensity) 382 (M^+ + 1, 100).

***trans*-*N*-Methyl-2,3-(methylenedioxy)-6-oxo-7,8-(methylenedioxy)-10b-methyl-4b,5,6,10b-tetrahydrobenzo[*c*]phenanthridine (39).** A solution of the alcohol **37** (115 mg, 0.3 mmol) and *p*-toluenesulfonic acid (45 mg) in benzene (100 mL) was heated at reflux for 16 h. The solution was extracted with 5% aqueous $NaHCO_3$, washed with water, and dried, and the solvent was evaporated. The residue was purified by column chromatography on silica gel ($CHCl_3$–MeOH, 20:1 as eluent) to give the product **39** as a white solid. The analytical sample was prepared by recrystallization from MeOH: 104 mg, 95%; mp 251–253 °C; IR ($CHCl_3$) 2960, 1630, 1440, 1020 cm^{-1}; NMR (470 MHz) δ 6.94 (s, 1 H), 6.88 (s, 2 H), 6.64 (s, 1 H), 6.37 (d, 1 H, J = 17.0 Hz), 6.36 (d, 1 H, J = 17.0 Hz), 6.16 (d, 1 H, J = 1.2 Hz), 6.06 (d, 1 H, J = 1.2 Hz), 5.97 (d, 1 H, J = 1.4Hz), 5.96 (d, 1 H, J = 1.4 Hz), 5.01 (s, 1 H), 3.31 (s, 3 H), 1.00 (s, 3 H); CIMS, m/e (relative intensity) 364 (M^+ + 1, 100). Anal. ($C_{21}H_{17}NO_5$) C, H, N.

***trans*-*N*-Methyl-2,3-(methylenedioxy)-7,8-(methylenedioxy)-10b-methyl-4b-5,6,10b-tetrahydrobenzo[*c*]phenanthridine (40).** A mixture of the lactam **39** (40 mg, 0.11 mmol) and $LiAlH_4$ (80 mg, 2 mmol) in THF (4 mL) was heated at reflux for 4 h. The reaction mixture was decomposed by addition of water (0.1 mL), 15% aqueous NaOH (0.1 mL), and water (0.3 mL) at 0 °C. The solid was filtered and washed with $CHCl_3$. The combined organic layers were dried and evaporated. Column chromatography of the residue on silica gel ($CHCl_3$ as eluent) afforded the product **40** as a pale yellow crystalline solid: 36 mg, 94%; mp 154–156 °C; IR ($CHCl_3$) 2840, 1450, 1240, 1020 cm^{-1}; NMR (80 MHz) δ 7.13 (s, 1 H), 6.93 (d, 1 H, J = 8.3 Hz), 6.77 (d, 1 H, J = 8.3 Hz), 6.64 (s, 1 H), 6.29 (s, 2 H), 5.69 (s, 4 H), 4.25 (d, 1 H, J = 16 Hz), 4.15 (s, 1 H), 4.02 (d, 1 H, J = 16.2 Hz), 2.62 (s, 3 H), 1.16 (s, 3 H); CIMS, m/e (relative intensity) 350 (M^+ + 1, 100).

***N*-Methyl-2,3-(methylenedioxy)-6-oxo-7,8-(methylenedioxy)-10bα-methyl-11,12-epoxy-4bβ,5,6,10b,11α,12α-hexahydrobenzo[*c*]phenanthridine (41).** A solution of *m*-chloroperbenzoic acid (38 mg, 0.22 mmol) in CH_2Cl_2 (2 mL) was added dropwise to a solution of compound **39** (40 mg, 0.11 mmol) in CH_2Cl_2 (7 mL). After being stirred for 1 h at room temperature, the reaction mixture was washed with 10% aqueous KI, 10% aqueous $Na_2S_2O_3$, 10% aqueous Na_2CO_3, and water. The solvent was evaporated, and the solid residue was purified by chromatography on neutral alumina (grade III, 10 g, benzene–$CHCl_3$, 2:1 as eluent) to give the epoxide **41**: 32 mg, 77%; mp 204–206 °C; IR ($CHCl_3$) 2980, 1640, 1455, 1030 cm^{-1}; NMR (80 MHz) δ 7.10–6.84 (m, 4 H), 6.19 (d, 1 H, J = 1.3 Hz), 6.04 (d, 1 H, J = 1.3 Hz), 6.01 (s, 2 H), 4.84 (s, 1 H), 3.98 (s, 2 H), 3.20 (s, 3 H), 1.00 (s, 3 H); CIMS, m/e (relative intensity) 380 (M^+ + 1, 20), 140 (100).

(±)-14-Epicorynoline (3). A mixture of the epoxide **41** (30 mg, 0.08 mmol) and $LiAlH_4$ (40 mg, 1 mmol) was heated at reflux for 4 h. The reaction mixture was decomposed by the addition of water (0.05 mL), 15% aqueous NaOH (0.05 mL), and water (0.15 mL) at 0 °C. The solid was filtered and washed with $CHCl_3$. The combined filtrates were dried and evaporated. The yellow residue was purified by column chromatography on neutral alumina (grade III, 10 g, benzene–EtOAc, 95:5 as eluent) to yield (±)-14-epicorynoline (**3**). The analytical sample was prepared by recrystallization from MeOH: 24 mg, 83%; mp 174–176 °C; IR ($CHCl_3$) 3400, 2860, 1450, 1435, 1020 cm^{-1}; NMR (470 MHz) δ 7.17 (s, 1 H), 6.88 (d, 1 H, J = 8.2 Hz), 6.76 (d, 1 H, J = 8.2 Hz), 6.61 (s, 1 H), 5.97 (s, 2 H), 5.92 (d, 1 H, J = 1.5 Hz), 5.90 (d, 1 H, J = 1.5 Hz), 4.50 (s, 1 H), 4.32 (d, 1 H, J = 5.0 Hz), 4.26 (d, 1 H, J = 17.0 Hz), 3.95 (d, 1 H, J = 17.0 Hz), 3.21 (d of d, 1 H, J = 18.3 and 5.0 Hz), 2.82 (d, 1 H, J = 18.3 Hz), 2.48 (s, 3 H), 1.10 (s, 3 H); CIMS, m/e (relative intensity) 368 (M^+ + 1, 100).

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Registry No. (±)-**1**, 68035-45-0; (±)-**2**, 82950-95-6; (±)-**3**, 83607-67-4; **10**, 66303-84-2; (±)-**11**, 82929-73-5; (±)-**13**, 83607-71-0; (±)-**14**, 82929-74-6; **15**, 63254-33-1; (±)-**16**, 82929-75-7; (±)-**17**, 83607-68-5; (±)-**18**, 85083-21-2; (±)-**19**, 85083-22-3; (±)-**20**, 82929-76-8; (±)-**21**, 82929-77-9; **22**, 85083-23-4; (±)-**29**, 83607-69-6; (±)-**30**, 83607-63-0; (±)-**31**, 83607-66-3; (±)-**32**, 85083-24-5; (±)-**33**, 85083-25-6; (±)-**34**, 85083-26-7; (±)-**35**, 83607-70-9; (±)-**36**, 83607-64-1; (±)-**37**, 83632-43-3; (±)-**38**, 83632-42-2; (±)-**39**, 83607-65-2; (±)-**40**, 85096-81-7; (±)-**41**, 85083-27-8.

Studies on the Catalyzed Interconversions of Vitamin A Derivatives

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Abstract: The kinetics of the I_2-catalyzed isomerization of the retinal isomers were studied. The all-trans isomer formed 13-*cis*-retinal rapidly with a rate constant of 1.9×10^{-4} s^{-1}. The reverse reaction occurred with a rate constant of 4.5×10^{-4} s^{-1}. The 11-cis isomer was first converted to *all-trans*-retinal with a rate constant of 3.1×10^{-4} s^{-1}, although the 13-cis isomer was also rapidly formed. The 9-cis isomer was isomerized to the 9-cis,13-cis isomer before the other isomers were generated and the 13-cis isomer was converted to its all-trans congener prior to the formation of the other isomers. Similar results appear to occur when other methods of catalysis are used. This isomerization about the C_{13}–C_{14} double bond appears to be a kinetically favored event, eliminating the possibility that 11-cis might be a kinetic product formed from the all-trans isomer. At equilibrium, only 0.1% of 11-*cis*-retinal is found. Equilibration of *all-trans*-retinol palmitate also generated very little of the 11-cis isomer (≤0.2%) 11-*cis*-retinol palmitate at equilibrium. The implications of these results for an 11-*cis*-retinal regeneration mechanism in the eye are discussed.

The stereoisomers of vitamin A aldehyde figure importantly both in visual transduction in animals and in energy production in certain bacteria. In animals, the photoisomerization of 11-*cis*-retinal to *all-trans*-retinal, both bound as protonated Schiff's bases to opsin, is the initial step in visual transduction.[1] In separate steps, the thermal resynthesis of 11-*cis*-retinal must occur for scotopic vision to proceed. In *Halobacterium halobium* the photoisomerization of the protonated Schiff's bases of *all-trans*- and 13-*cis*-retinal, bound to bacteriorhodopsin, leads to the translocation of protons across the bacterial membrane.[2]

Since the photochemical and thermal interconversions of certain stereoisomers of vitamin A aldehyde are of such great importance in biological processes, it is of some importance to gain a clear picture of the equilibrium positions of the various isomers and their rates of interconversion. As far as we are aware there are no data in the literature concerning the kinetics of retinoid interconversions and the data on the equilibrium positions seemed to depend on the method used to establish the equilibrium.[3-5] In this paper we report a study on the iodine-catalyzed equilibration and the rates of interconversion of the vitamin A aldehyde stereoisomers. In addition, we determined the equilibrium position of the retinol palmitates, the major storage form of vitamin A in the eye.[6,7]

Materials and Methods

11-*cis*-, 9-*cis*-, and 13-*cis*-retinal were generous gifts of Dr. William E. Scott of Hoffmann-La Roche Inc. *all-trans*-Retinal and *all-trans*-retinol palmitate were products of Sigma Laboratories, Inc. [15-^{3}H]-*all-trans*-Retinal of specific activity 70 μCi/μmol was synthesized by oxidizing 15-^{3}H]retinol (New England Nuclear) with freshly prepared MnO_2 by the published procedure.[8] The retinol palmitates were prepared from the desired retinol isomer and palmitoyl chloride by the published procedure.[9] The trifluoroacetic acid was a product of Aldrich Chemical Co. Chloroform and iodine were products of the Fisher Chemical Co. The chloroform was distilled before use. HPLC-grade *n*-heptane, *n*-hexane, and diethyl ether were products of Burdick and Jackson Laboratories.

High-pressure liquid chromatographic (HPLC) separations of the retinal isomers were accomplished by using a 5 μm particle size 25 cm size Hibar-II, LiChrosorb silica column (Merck, Inc.) with 10–12% ether/hexane as an eluent at a flow rate of 0.7–0.8 mL/min. A Waters Model M-6000A HPLC pump was used with either a Model 440 UV detector, containing a 365-nm filter, or a Model 480 variable-wavelength detector. The retinol palmitates were separated on the same system by using 0.5% ether/hexane as an eluent with a flow rate of 0.7 mL/min. The amounts of isomers formed in quantities >1% were measured from the areas of the peaks after correcting for the relative extinction coefficients.[10,11]

The equilibration studies were carried out as follows: The position of equilibrium was determined by using the 9-*cis*-, 11-*cis*-, 13-*cis*-, and *all-trans*-retinal isomers or the corresponding retinol palmitates in *n*-heptane with I_2 as a catalyst (0.79 μmol/mL I_2, 0.24 μmol/mL retinal or retinol palmitate at 50 °C). All manipulations were done under a red safety light, and the I_2 solutions were treated in aluminum foil wrapped extraction tubes capped under N_2. At various times a small aliquot, approximately 0.5 mL, was washed with an equal volume of a saturated sodium thiosulfite solution. The heptane layer was removed and dried over anhydrous sodium sulfate, and a standard aliquot was injected into the HPLC. The same equilibrium was reached from all four isomers.

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