# New Alkaloids and Related Artifacts from *Cyclea peltata*[1a,b]

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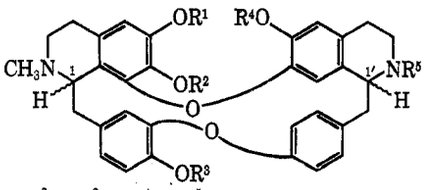
Five new bisbenzylisoquinoline alkaloids, cycleapeltine (**11**), cycleadrine (**5**), cycleacurine (**19**), cycleanorine (**8**), and cycleahomine chloride (**14**), have been isolated from *Cyclea peltata* Diels and their structures determined. Three related artifacts have also been isolated and the structures **16**, **26**, and **31** advanced on the basis of spectroscopic and chemical evidence.

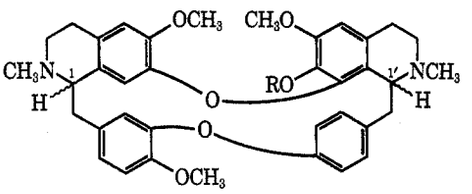
The bisbenzylisoquinoline alkaloid *dl*-tetrandrine was found to have a significant inhibitory activity against the Walker intramuscular carcinosarcoma 256 in rats, over a wide dosage range.[2] Subsequent studies revealed that the dextrorotatory enantiomer, tetrandrine (**1**), was equally active. Tetrandrine has undergone extensive preclinical toxicological studies and has been selected for clinical trial. The promising biological activity prompted the procurement by the National Cancer Institute of a large collection of roots of *Cyclea peltata* Diels,[3-5] for the isolation of kilogram quantities of tetrandrine. In view of the *in vivo* tumor-inhibitory activity of related alkaloids[2,6] as well, it was deemed of interest to examine the mother liquors of the large-scale extraction of tetrandrine as a potentially unique source of new alkaloid tumor inhibitors. We report here the isolation and structural elucidation of cycleapeltine (**11**), cycleadrine (**5**), cycleacurine (**19**), cycleanorine (**8**), and cycleahomine chloride (**14**), five new bisbenzyltetrahydroisoquinoline alkaloids from *Cyclea peltata*. In addition, three related artifacts have been isolated and structures **16**, **26**, and **31** advanced.

The extraction of 6000 lb of *Cyclea peltata* was carried out by a procedure modified only slightly from our initial laboratory work.[3,5] The bulk of tetrandrine (**1**) and the other major alkaloid, fangchinoline (**2**), were retained and the extraction mother liquors containing the water-soluble, methanol-soluble, and glycol-soluble alkaloids were sent to us for investigation.

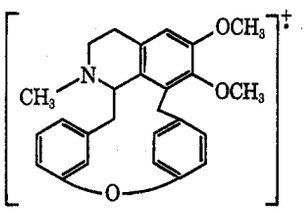
Acid extraction of an aliquot of the methanol-soluble alkaloids gave fraction D, which after column chromatography on alumina and fractional recrystallization eventually yielded large amounts of **1** and much smaller amounts of another crystalline alkaloid, cycleapeltine, $C_{37}H_{40}N_2O_6$ [mp 232–234°; $[\alpha]D$ − 106° ($CHCl_3$)]. The nmr spectrum of cycleapeltine exhibited two *N*-methyl signals at $\tau$ 7.47 and 7.53 and three *O*-methyl signals at 6.07, 6.27, and 6.71. Its mass spectrum indicated a fragmentation pattern characteristic of a "head to head" bisbenzyltetrahydroisoquinoline alkaloid with two diphenyl ether link-



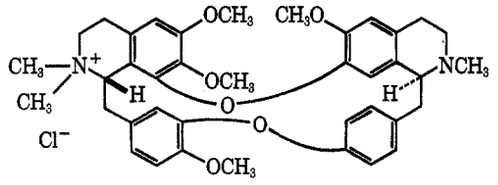
**1**, $R^1 = R^2 = R^3 = R^4 = R^5 = CH_3$ (1-*S*, 1′-*S*)
**2**, $R^1 = R^3 = R^4 = R^5 = CH_3$; $R^2 = H$ (1-*S*, 1′-*S*)
**3**, $R^1 = R^2 = R^3 = R^4 = R^5 = CH_3$ (1-*R*, 1′-*S*)
**4**, $R^1 = R^2 = R^4 = R^5 = CH_3$; $R^3 = H$ (1-*R*, 1′-*S*)
**5**, $R^1 = R^3 = R^4 = R^5 = CH_3$; $R^2 = H$
**6**, $R^1 = R^2 = R^3 = R^5 = CH_3$; $R^4 = H$
**7**, $R^2 = R^3 = R^4 = R^5 = CH_3$; $R^1 = H$
**8**, $R^1 = R^2 = R^3 = R^4 = CH_3$; $R^5 = H$ (1-*S*, 1′-*S*)
**9**, $R^1 = R^2 = R^3 = R^4 = CH_3$; $R^5 = COOCH_3$ (1-*S*, 1′-*S*)



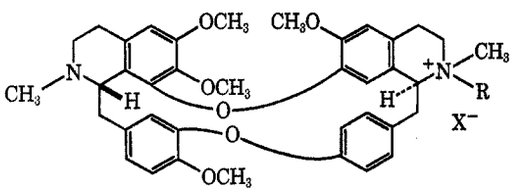
**10**, R = H (1-*R*, 1′-*R*)
**11**, R = H (1-*S*, 1′-*S*)
**12**, R = $CH_3$ (1-*S*, 1′-*S*)



**13**



**14**



**15**, R = $CH_3$; X = I
**16**, R = $CH_2Cl$; X = Cl

(1) (a) Tumor Inhibitors. LXXIX. Part LXXVIII: S. M. Kupchan, V. Kameswaran, and J. W. A. Findlay, *J. Org. Chem.*, **38**, 405 (1973). (b) This investigation was supported by grants from the National Cancer Institute (CA-11718 and CA-12059) and a contract with the Division of Cancer Treatment, National Cancer Institute (NIH 71-2099). (c) National Institutes of Health Postdoctoral Fellow, 1971–1972.

(2) (a) S. M. Kupchan, 7th Pan American Congress of Pharmacy and Biochemistry, Buenos Aires, Argentina, Dec 1966; *Chem. Eng. News*, **44**, 64 (1966). (b) J. L. Hartwell and B. J. Abbott, *Advan. Pharm. Chemother.*, **7**, 117 (1969).

(3) S. M. Kupchan, N. Yokoyama, and B. S. Thyagarajan, *J. Pharm. Sci.*, **50**, 164 (1961).

(4) The *Cyclea peltata* roots (6000 lb) were collected in India in January 1967 by Meer Corp.

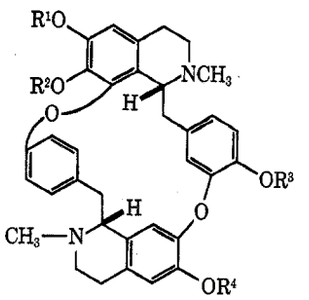
(5) The large-scale extraction and fractionation was carried out by Dr. J. A. Ellard, Monsanto Research Corp., Dayton, Ohio, under a contract with Drug Research and Development, Division of Cancer Treatment, National Cancer Institute. We thank Dr. Harry B. Wood, Jr., NCI, for making the mother liquors available to us.

(6) (a) S. M. Kupchan, T.-H. Yang, G. S. Vasilikiotis, M. H. Barnes, and M. L. King, *J. Org. Chem.*, **34**, 3884 (1969); (b) S. M. Kupchan and A. J. Liepa, *Chem. Commun.*, 599 (1971).

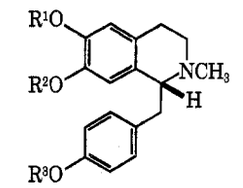
ages.[7] All of these data are in accord with those reported for limacusine (**10**) except that the optical rotation is of the opposite sign,[8] suggesting that cycleapeltine (**11**) is the antipode of **10**. Accordingly, treatment of **11** with methanolic diazomethane yielded a product identical with the known *O*-methylrepandine (**12**).[9]

Acid extraction (with subsequent neutralization to pH 7.0–7.5) of an aliquot of the glycol-soluble alkaloids (fraction A) gave fraction E, which after column chromatography on alumina yielded more **1** and a slightly more polar oil. Thin layer chromatography of this oil on alumina yielded **2** and an optically inactive isomeric alkaloid, cycleadrine, isolated as its bishydriodide salt (mp 223–224°). Treatment of this salt with aqueous ammonia liberated the free base, $C_{37}H_{40}N_2O_6$, mp 160–162°. The nmr spectrum of cycleadrine exhibited two *N*-methyl signals at $\tau$ 7.57 and 7.75 and three *O*-methyl signals at 6.12, 6.12, and 6.27. Its mass spectrum indicated a fragmentation pattern characteristic of a "head to head" bisbenzyltetrahydroisoquinoline alkaloid with two diphenyl ether linkages. The base-induced bathochromic uv shift suggested a phenolic functionality. Treatment of the free base with methanolic diazomethane yielded a product identical with isotetrandrine (**3**),[9a,b,10] apart from its optical inactivity. Of the four possible de-*O*-methylisotetrandrine isomers, only berbamine (**4**) is known and the reported data[10] excluded it from further consideration. Distinction between the remaining three isomers, **5**, **6**, and **7**, could be made by examination of the spectra data. The mass spectral rearrangement[7] ion **13** is of value. As the observed ion **13** was at *m/e* 417 (11%), structure **6** could be excluded, since the C:D ring isoquinoline nucleus that was lost during the rearrangement would have had to contain a methoxyl group. The choice between structures **5** and **7** was based on the nmr chemical shift of the high-field methoxyl signal. A methoxyl group at the 7 position usually appears near $\tau$ 6.80.[9] As the highest field methoxyl signal in cycleadrine is only at $\tau$ 6.27, cycleadrine could be assigned structure **5** in the form of a mixture of two antipodal diastereomers of **2**.

Basification to pH 12 of the acid extract of fraction A gave fraction F, which after separation on an anionic ion exchange column and subsequent tlc on alumina yielded a third alkaloid, cycleacurine, isolated as its bishydrobromide salt, mp 293–296°. Treatment of this salt with aqueous sodium bicarbonate liberated the amorphous free base, $C_{35}H_{36}N_2O_6$, mp 205–208°, $[\alpha]D$ – 202° ($CH_3OH$). The nmr spectrum (DMSO-$d_6$) of cycleacurine exhibited two *N*-methyl signals at $\tau$ 7.52 and 7.82 and a single *O*-methyl signal at 6.25. Its mass spectrum indicated a fragmentation pattern characteristic of a "head to tail" bisbenzyltetrahydroisoquinoline alkaliod with two diphenyl ether linkages.[11] The solubility properties as well as a base-induced bathochromic uv shift suggested the presence of



**17**, $R^1 = R^2 = R^3 = R^4 = CH_3$
**18**, $R^1 = R^2 = R^3 = H$; $R^4 = CH_3$
**19**, $R^2 = R^3 = R^4 = H$; $R^1 = CH_3$
**20**, $R^2 = R^3 = R^4 = CH_2CH_3$; $R^1 = CH_3$



**21**, $R^1 = CH_2CH_3$; $R^2 = R^3 = H$
**22**, $R^1 = CH_3$; $R^2 = R^3 = CH_2CH_3$
**23**, $R^2 = CH_3$; $R^1 = R^3 = H$
**24**, $R^3 = CH_3$; $R^1 = R^2 = H$

several phenolic functionalities. Treatment of the free base with methanolic diazomethane yielded a product which was shown to be the antipode of the known di-*O*-methyl-*d*-curine, **17**.[12]

To locate the methoxyl position in cycleacurine, it was necessary to identify the phenol groups. For this purpose, tri-*O*-ethylcycleacurine was prepared by treatment of the free base with methanolic diazoethane. The methoxyl chemical shift in this derivative was at $\tau$ 6.15, suggesting that it occupied one of the C-6 positions.[9a] Cycleacurine would then have either structure **18** or **19**. The choice of structure **19** was based on the structures of the products of sodium–liquid ammonia cleavage of the triethyl derivative. The course of sodium–liquid ammonia reductive cleavage of curine derivatives is well established.[13] Treatment of tri-*O*-ethylcycleacurine with sodium in liquid ammonia yielded only two major products, as expected. The phenolic product contained an *O*-ethyl group and could therefore be assigned structure **21**. The nonphenolic product was then expected to have structure **22**. That the nonphenolic product was **22** and not **23** or **24** followed from its spectral data. The mass spectral base peak corresponding to loss of the benzyl group was at *m/e* 220, indicating that the isoquinoline nucleus contained the methoxy group and only one ethoxyl group. The methoxyl chemical shift in the nonphenolic product was at $\tau$ 6.16, clearly indicative of the C-6 location.[9] The nonphenolic cleavage product could then be assigned structure **22** and cycleacurine structure **19**.

The methanol eluate from ion exchange chromatography of fraction F was passed through a column of ion exchange resin (chloride form) and then chromatographed on a column of neutral alumina.

Cycleanorine (**8**), the least abundant of the compounds studied, was isolated from the later column fractions by preparative tlc and subsequent crystal-

(7) J. Baldas, I. R. C. Bick, T. Ibuka, R. S. Kapil, and Q. N. Porter, *J. Chem. Soc., Perkin Trans. 1*, 592 (1972).
(8) M. Tomita and H. Furukawa, *Tetrahedron Lett.*, 4293 (1966).
(9) (a) I. R. C. Bick, J. Harley-Mason, N. Sheppard, and M. J. Vernengo, *J. Chem. Soc.*, 1896 (1961); (b) M. Tomita, K. Fujitani, A. Kato, H. Furukawa, Y. Aoyagi, M. Kitano, and T. Ibuka, *Tetrahedron Lett.*, 857 (1966); (c) I. R. C. Bick, E. S. Ewen, and A. R. Todd, *J. Chem. Soc.*, 695 (1953).
(10) I. R. C. Bick, P. S. Clezy, and W. D. Crow, *Aust. J. Chem.*, **9**, 111 (1956).
(11) J. Baldas, I. R. C. Bick, T. Ibuka, R. S. Kapil, and Q. N. Porter, *J. Chem. Soc., Perkin Trans. 1*, 599 (1972).
(12) L. J. Haynes, E. J. Herbert, and J. R. Plimmer, *J. Chem. Soc. C*, 615 (1966).
(13) I. R. C. Bick and P. S. Clezy, *J. Chem. Soc.*, 3893 (1953).

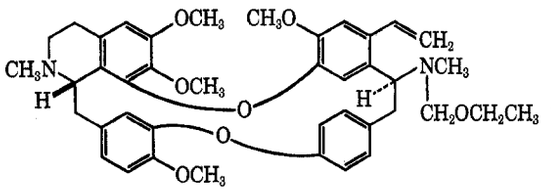
lization, mp 171–172°, $[\alpha]D$ +308° ($CHCl_3$). The molecular formula $C_{37}H_{40}N_2O_6$ was advanced on the basis of elemental analysis and high-resolution mass spectrometry. The nmr spectrum showed signals corresponding to one *N*-methyl ($\tau$ 7.67) and four *O*-methyl groups ($\tau$ 6.12, 6.30, 6.67, and 6.78). The close similarity of the aromatic region of the spectrum to that of tetrandrine (**1**) suggested that cycleanorine (**8**) might be a *N*-demethyl analog of **1**. This was confirmed by reductive N-methylation of **8** with formaldehyde and sodium borohydride,[14] which afforded **1** in fair yield. The assignment of position of the *N*-methyl group in **8** follows from the presence of an ion at *m/e* 431 in the mass spectrum, which can be attributed to an ion of structure **13**.[7]

The structure of cycleanorine (**8**) was confirmed by synthesis from tetrandrine (**1**), through the intermediacy of the monocarbamate **9** which on alkaline hydrolysis gave **8**.[15]

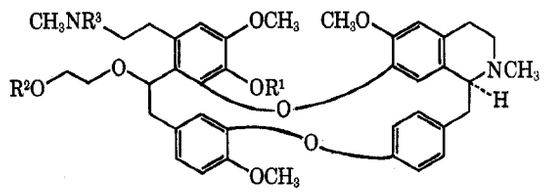
Cycleahomine chloride (**14**) was also isolated by preparative tlc of the later column fractions and purified by crystallization, mp 190–194°, $[\alpha]D$ +103° ($CHCl_3$). The empirical formula $C_{38}H_{45}N_2O_6Cl$ was advanced on the basis of elemental analysis. The nmr spectrum showed signals corresponding to one free *N*-methyl ($\tau$ 7.63), two quaternary *N*-methyl ($\tau$ 6.46 and 6.70), and four *O*-methyl ($\tau$ 6.06, 6.28, 6.62, and 6.70) groups. The pattern of the ten aromatic proton resonances was again almost superimposable on the spectrum of tetrandrine (**1**), suggesting that cycleahomine was one of the two possible monomethyl quaternary salts of tetrandrine. This was confirmed by conversion of cycleahomine chloride (**14**) to tetrandrine bismethiodide[16] by treatment with an excess of methyl iodide.

Monomethylation of tetrandrine with 1 equiv of methyl iodide did not give cycleahomine iodide but the isomeric compound **15**, which could be distinguished from the natural product on the basis of its nmr spectrum. In accord with the selective monocarbamation of tetrandrine noted above, quaternization of the 6,7-dioxygenated isoquinoline nitrogen of tetrandrine was evidently favored.

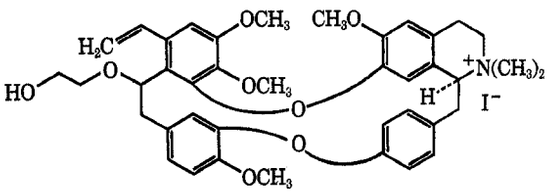
The compound **16**, present in large amounts in the earlier column fractions, was purified by preparative tlc on alumina and subsequent crystallization from acetone, mp 213–217°, $[\alpha]D$ + 156° ($CHCl_3$), and the empirical formula $C_{39}H_{44}N_2O_6Cl_2$ assigned on the basis of elemental analysis. In the nmr spectrum signals corresponding to one free *N*-methyl ($\tau$ 7.63), one quaternized *N*-methyl ($\tau$ 6.70), and four *O*-methyl groups were apparent, together with a multiplet at $\tau$ 5.4 (2 H) which could not be immediately assigned. Treatment with potassium *tert*-butoxide and 1-propanethiol in dimethylacetamide at room temperature converted **16** to cycleanorine (**8**) in good yield, indicating that **16** was a derivative of tetrandrine (**1**) quaternized on the nitrogen of the 6,7-dioxygenated isoquinoline moiety. That the quaternizing substituent was in fact a chloromethyl group could be inferred from the empirical formula of **16**. In refluxing ethanolic sodium ethoxide **16** smoothly underwent Hofmann elimination to yield the unstable styrene **25**. The nmr spectrum of **25** showed, in addition to the ABX pattern typtical of a styrene grouping [dd (1 H), $\tau$ 2.12, $J_{trans}$ = 18, $J_{cis}$ = 11 Hz; d (1 H), $\tau$ 4.48, $J_{trans}$ = 18 Hz; d (1 H), $\tau$ 4.82, $J_{cis}$ = 11 Hz], an AB quartet at $\tau$ 5.66 ($\Delta\nu$ 25 Hz, $J$ = 9 Hz) which can be attributed to the system $-NCH_2O-$ and a triplet ($\tau$ 8.73, $J$ = 6 Hz) corresponding to the $OCH_2CH_3$ system. From the



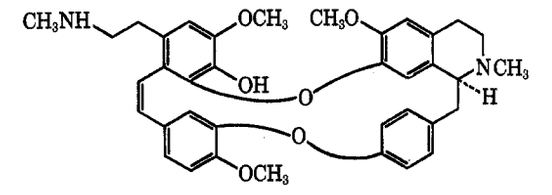
**25**



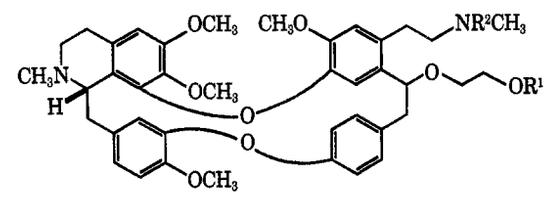
**26**, $R^1 = R^2 = R^3 = H$
**27**, $R^1 = R^2 = R^3 = COCH_3$
**28**, $R^1 = R^2 = H$; $R^3 = CH_3$



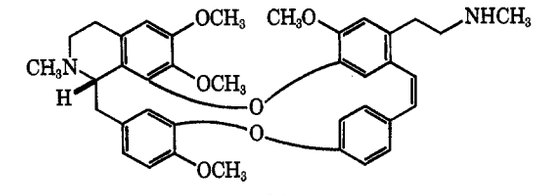
**29**



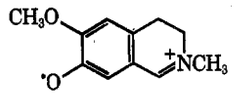
**30**



**31**, $R^1 = R^2 = H$
**32**, $R^1 = R^2 = COCH_3$
**33**, $R^1 = H$; $R^2 = CH_3$



**34**



**35**

(14) M. Tomita, K. Fujitani, Y. Masaki, and Y. Okamoto, *Chem. Pharm. Bull.*, **16**, 70 (1968).
(15) M.-M. Abdel-Monem and P. S. Portoghese, *J. Med. Chem.*, **15**, 208 (1972).
(16) C.-K. Chuang, C.-Y. Hsing, Y.-S. Kao, and K.-J. Chang, *Chem. Ber.*, **72**, 519 (1939).

nmr and the mass spectrum ($M^+$ at *m/e* 680), it is apparent that the chlorine of the chloromethyl group is replaced by ethoxide under the conditions used for the elimination.

In view of the fact that tetrandrine (**1**) was the principal component of the alkaloidal extract of *Cyclea peltata* and of the large quantity of dichloromethane used in the extraction, it is perhaps not surprising that significant quantities of **16** were isolated. Methylene halides are known to react with tertiary amines to give quaternary ammonium salts[17] and a number of alkaloids[18] have been shown to give chloromethyl chlorides under conditions similar to those of the extraction procedure used in this instance. Indeed, tetrandrine (**1**) was found to react very slowly with dichloromethane at room temperature to afford **16**.

The compound **26** was purified from the appropriate column fractions by succcessive crystallizations from benzene and ethanol, mp 177–179°, $[\alpha]D$ −237° ($CHCl_3$). The molecular formula $C_{39}H_{46}N_2O_8$ was advanced on the basis of elemental analysis and confirmed by high-resolution mass spectrometry. The uv spectrum showed a maximum at 284 nm ($\epsilon$ 12,100) and a bathochromic shift indicative of a phenolic chromophore was observed upon addition of sodium hydroxide. The nmr spectrum showed signals corresponding to two free *N*-methyl groups ($\tau$ 7.64 and 7.74), three *O*-methyl [$\tau$ 6.14 (6 H) and 6.27 (3 H)] groups, and ten aromatic protons.

On treatment with acetic anhydride in pyridine **26** afforded a noncrystalline triacetyl derivative **27**, the ir spectrum of which showed bands corresponding to a phenolic acetate (5.70 $\mu$), an aliphatic acetate (5.78 $\mu$), and an acetamide (6.12 $\mu$) group. Reductive methylation yielded a single *N*-methyl derivative **28**, indicating the presence of a secondary amino group in **26**. Permethylation of **26** with methyl iodide in methanol containing sodium carbonate yielded the corresponding bismethiodide, which did not exhibit a base shift in the uv, indicating that the free phenolic hydroxyl had been methylated. This compound smoothly underwent Hofmann elimination with methanolic sodium methoxide to yield the product **29**, the nmr of which showed signals corresponding to two quaternary *N*-methyl groups [$\tau$ 6.80 (6 H)] and four *O*-methyl groups ($\tau$ 6.07, 6.18, 6.50, and 6.65) together with two one-proton doublets at 4.37 ($J$ = 17 Hz) and 4.63 ($J$ = 10 Hz) which could be attributed to a styrene group. The styrene structure of **29** suggested the presence of the system $ArCH_2CH_2NHCH_3$ in **26**. On heating with aqueous hydrochloric acid **26** afforded as the major product the stilbene **30**, high-resolution mass spectrometry of which indicated a molecular formula $C_{37}H_{40}N_2O_6$.

Since **16** had previously been shown to be an artifact formed during the isolation procedure, the facile loss of a $C_2H_6O_2$ unit from **26** on treatment with aqueous acid suggested that **26** might be regarded as having arisen from a monophenolic bisbenzyltetrahydroisoquinoline alkaloid through formal addition of glycol with concomitant opening of an isoquinoline ring. Since fangchinoline (**2**) is the only monophenolic bisbenzyltetrahydroisoquinoline alkaloid which has been isolated from *Cyclea peltata*[3] in significant amounts, it is the most probable precursor for formation of such an artifact. The presence of an ion in the high-resolution mass spectrum of **26** corresponding to the fragment **35** favors the structure **26** rather than that in which the 6,7-dioxygenated tetrahydroisoquinoline ring is opened.

A second artifact **31** isolated from the column fraction preceding that containing **26** was purified as its crystalline bisoxalate, which was decomposed with ammonium hydroxide to give the free base, mp 161–163°, $[\alpha]D$ +174° ($CHCl_3$). The molecular formula $C_{40}H_{48}N_2O_8$ was advanced on the basis of elemental analysis of the bisoxalate and supported by high-resolution mass spectrometry of the free base. The absence of a bathochromic shift in the uv spectrum [$\lambda_{max}^{EtOH}$ 283 nm ($\epsilon$ 6780)] indicated that the compound was nonphenolic. In the nmr spectrum signals corresponding to two *N*-methyl groups ($\tau$ 7.36 and 7.42), four *O*-methyl ($\tau$ 6.11, 6.32, 6.60, and 6.82) groups, and ten aromatic protons were in evidence. With acetic anhydride in pyridine **31** yielded a noncrystalline diacetyl derivative **32**, which showed bands at 5.78 and 6.12 $\mu$ in the ir, corresponding to an aliphatic acetate and an acetamide group. The presence of a secondary amino function was again confirmed by reductive methylation, which gave the *N*-methyl derivative **33**. Treatment of **31** with aqueous acid gave a crystalline product **34**, the high-resolution mass spectrum of which suggested a molecular formula $C_{38}H_{42}N_2O_6$ (*i.e.*, a loss of $C_2H_6O_2$ from **31**). That **31** might be the *O*-methyl derivative of **26** was refuted by the dissimilarity of their respective permethylation products. However, the similarity of the aromatic region of the nmr spectrum of **31** to that of tetrandrine and the absence of an ion (*m/e* 191) in the mass spectrum of **31** corresponding to the fragment **35** suggests that the compound has the structure shown, and may have been formed by formal glycol addition and ring opening of tetrandrine (**1**).

In view of the isolation of significant amounts of the artifact **16** in the extracts, it is conceivable that this is an intermediate in the formation of the glycol adduct **31**, the latter being formed through direct substitution of the quaternary nitrogen. This course is favored over the intermediacy of the corresponding stilbene which might arise by Hofmann elimination *in situ*, since Hofmann elimination has been shown to give the styrene **25**. The formation of **26** from fangchinoline (**2**) might be expected to parallel that of **31** from tetrandrine (**1**).

## Experimental Section

Melting points were determined on a Mettler FP2 melting point apparatus. Values of $[\alpha]D$ were obtained on a Perkin-Elmer PE141 polarimeter and are approximated to the nearest degree. Ultraviolet spectra were determined on a Coleman EPS-3T recording spectrophotometer and infrared spectra on a Perkin-Elmer PE257 recording spectrophotometer. Nmr spectra were determined on a Varian HA-100 spectrometer in $CDCl_3$ (except where otherwise noted) using tetramethylsilane as the internal standard. Routine mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6E spectrometer and high-resolu- mass spectra on a AEI MS-902 mass spectrometer. Microanalyses were carried out by Spang Microanalytical Laboratory, Ann Arbor, Mich. Commercially prepared tlc plates (E. M.

(17) (a) D. A. Wright and C. A. Wulff, *J. Org. Chem.*, **35**, 4252 (1970); (b) H. Bohme, M. Hilp, L. Koch, and E. Ritter, *Chem. Ber.*, **104**, 2018 (1971).

(18) R. Besselievre, N. Langlois, and P. Potier, *Bull. Soc. Chim. Fr.*, 1477 (1972).

Reagents) were used exclusively. For preparative tlc either aluminum oxide (type T, 1.5 × 200 × 200 mm) or silica gel (F-254, 2 × 200 × 200 mm) plates were used. Analytical tlc was carried out using silica gel (F-254, 0.25 mm) plates eluted with $NEt_3$–MeOH–$CHCl_3$ (5:10:85). Organic solutions were routinely dried with magnesium sulfate and evaporated to dryness on a rotary evaporator *in vacuo*.

**Large-Scale Extraction of *Cyclea peltata*.**[5]—The ground roots of *C. peltata* were extracted with isopropyl alcohol, the extract was filtered, and the filtrate was extracted first with heptane–toluene and then 0.5 *N* HCl. The acidic solution was adjusted to pH 8.6 with $NH_4OH$ and extracted with $CH_2Cl_2$ and the organic layer was evaporated to a residue which was then partitioned between benzene and aqueous glycol (fraction A). On standing, fangchinoline (**2**) precipitated from the benzene layer and was removed by filtration. The filtrate was evaporated to a residue which was extracted successively with heptane (fraction B) and methanol (fraction C).

**Isolation of Cycleapeltine (11).**—An aliquot (2 l.) of fraction C was evaporated to a thick syrup, dissolved in $CHCl_3$, and reevaporated. This residue was redissolved in $CHCl_3$ (2 l.) and shaken with 5% aqueous citric acid (2 l.). The aqueous phase was separated, shaken with $CHCl_3$ (2 l.), and allowed to stand for 12 hr. After separation and decantation from a large amount of tar, the aqueous phase was basified with ammonium hydroxide and extracted with $CHCl_3$ (2 × 500 ml). The $CHCl_3$ extract was evaporated to yield fraction D. This was applied to an alumina column (2 kg, Woelm, basic, activity I) and eluted with $CHCl_3$ until the eluent showed only traces of tetrandrine (**1**). The combined $CHCl_3$ eluents were evaporated to a residue which was dissolved in acetone and boiled, and hexane was added until crystals began to separate. After 24 hr the crystals were filtered and washed briefly with acetone–hexane (1:2). The solid, approximately 20 g, was stirred with EtOAc–$CHCl_3$–MeOH (6:3:1, 200 ml) with a gradual increase in the temperature until the mass of fine needles had dissolved and only a heavy crystalline residue of plates remained. These were filtered, crystallized from EtOAc, and recrystallized from EtOH–$CHCl_3$ to give 1.30 g of cycleapeltine (**11**): mp 232–234°; $[\alpha]^{25}D$ −106° (*c* 1.0, $CHCl_3$); nmr $\tau$ 7.47, 7.53 (2 s, 6 H, $2NCH_3$), 6.07, 6.27, 6.71 (3 s, 9 H, 3 $OCH_3$); mass spectrum *m/e* (rel intensity) 608 (52), 381 (67), 367 (33), 191.5 (22), 191 (100); uv $\lambda_{max}^{95\%\ EtOH}$ 282 nm ($\epsilon$ 5200).

*Anal.* Calcd for $C_{37}H_{40}N_2O_6$: C, 73.00; H, 6.57; N, 4.61. Found: C, 72.89; H, 6.66; N, 4.63.

**Isolation of Cycleadrine (5).**—An aliquot (2 l.) of fraction A was extracted with $CHCl_3$ (4 × 500 ml). The combined $CHCl_3$ extracts were washed with 5% aqueous sodium chloride (1.5 l.) and evaporated to a viscous syrup. The syrup obtained in the above manner from 10 l. of fraction A was dissolved in $CHCl_3$ (2 l.) and shaken with 5% aqueous citric acid (2 l.). The aqueous phase was separated, filtered, adjusted to pH 4.0–4.5 by gradual addition of ammonium hydroxide, and extracted with $CHCl_3$ (2 × 1 l.). The aqueous phase was then adjusted to pH 7.0–7.5 by further addition of ammonium hydroxide and again extracted with $CHCl_3$ (2 × 1 l.). This $CHCl_3$ extract was evaporated to yield approximately 8.0 g of a dark brown foamy residue, fraction E.

Thirty grams of fraction E were dissolved in a small amount of $CHCl_3$ and applied to an alumina column (1.4 kg, Woelm, basic, activity I) and eluted with $CHCl_3$ until the eluent showed only traces of tetrandrine (**1**). The column solvent was then changed to 1% MeOH–$CHCl_3$ and elution continued until only traces of fangchinoline (**2**) were seen in the eluate. The combined 1% MeOH–$CHCl_3$ fractions were then evaporated to a residue (1.6 g). This residue was separated by preparative tlc on alumina using chloroform as the eluent. The faster moving major component ($R_f$ ~0.5) was recovered and evaporated to a residue. This residue was dissolved in MeOH (5 ml) and hydroiodic acid (0.8 g, 47% aqueous) was added, followed by addition of EtOAc (10 ml). The mixture was warmed gently on a water bath for 10 min and then stirred at ambient temperatures under nitrogen for 24 hr. The solid was filtered, washed briefly with 5% MeOH–EtOAc, and recrystallized from aqueous EtOH to yield 0.8 g of cycleadrine bishydriodide, mp 223–224°, $[\alpha]^{25}D$ 0° (*c* 1.0, $H_2O$).

*Anal.* Calcd for $C_{37}H_{40}N_2O_6 \cdot 2HI$: C, 51.40; H, 4.90; N, 3.24; I, 29.36. Found: C, 51.19; H, 5.21; N, 3.19; I, 29.08.

Cycleadrine bishydriodide (0.8 g) was dissolved in ammonium hydroxide (10 ml) and extracted with ether (4 × 10 ml). The combined ether extracts were washed with water (2 × 10 ml), dried ($Na_2SO_4$), and evaporated to a white residue which was recrystallized from acetone–hexane to give 0.5 g of cycleadrine (**5**): mp 160–162°; $[\alpha]^{25}D$ 0° (*c* 1.0, $CHCl_3$); nmr $\tau$ 7.57, 7.75 (2 s, 6 H, 2 $NCH_3$), 6.12, 6.12, 6.27 (3 s, 9 H, 3 $OCH_3$); mass spectrum *m/e* (rel intensity) 608 (64), 417 (11), 381 (80), 367 (32), 191.5 (25), 191 (100); uv $\lambda_{max}^{95\%\ EtOH}$ 282 nm ($\epsilon$ 6400).

*Anal.* Calcd for $C_{37}H_{40}N_2O_6$: C, 73.00; H, 6.57; N, 4.61. Found: C, 72.97; H, 6.54; N, 4.58.

**Isolation of Cycleacurine (19).**—The pH 7.0–7.5 aqueous layer from the cycleadrine (**5**) isolation was made strongly basic by further addition of ammonium hydroxide and extracted with $CHCl_3$ (2 × 1 l.). The $CHCl_3$ extract was evaporated to yield approximately 80 g of a dark brown residue, fraction F. A portion of fraction F (20 g) was dissolved in MeOH (100 ml) and added to a 250-g ion exchange column (Dowex I-X8; $^-OH$ form, prepared by stirring the ion exchange resin first in 3% hydrochloric acid and then in 5% aqueous potassium hydroxide and washing with MeOH). The MeOH solution was passed slowly through the column and elution was continued with MeOH until the eluate was colorless. Evaporation of the methanol eluate yielded a residue (17 g), fraction G. Then the column was eluted with 5% HOAc–MeOH until the eluate was colorless. The acid eluate was evaporated to a residue (2.2 g), dissolved in water (20 ml), basified with ammonium hydroxide, and extracted with $CHCl_3$ (2 × 50 ml). The $CHCl_3$ extract was evaporated to a residue, subjected to preparative tlc, and eluted with MeOH–$Et_3N$–$CHCl_3$ (10:15:75). The major component ($R_f$ ~0.5) was recovered and dissolved in MeOH (5 ml), and hydrobromic acid (1.0 g, 48% aqueous) was added followed by addition of EtOAc (10 ml). The mixture was warmed gently on a water bath for 10 min and then stirred at ambient temperatures under nitrogen for 24 hr. The solid was filtered, washed briefly with 5% MeOH–EtOAc, and recrystallized from aqueous EtOH to yield 0.25 g of cycleacurine bishydrobromide as its monohydrate, mp 293–296°.

*Anal.* Calcd for $C_{35}H_{36}N_2O_6 \cdot 2HBr \cdot H_2O$: C, 55.28; H, 5.30; N, 3.68. Found: C, 55.57; H, 5.39; N, 3.78.

Cycleacurine bishydrobromide (0.25 g) was added to 10% aqueous sodium bicarbonate (10 ml) and stirred at ambient temperatures for 24 hr. The solid was filtered, washed with water, and recrystallized from acetonitrile to yield 0.18 g of cycleacurine as its bishydrate: mp 205–208°; $[\alpha]^{25}D$ −202° (*c* 1.0, $CH_3OH$); nmr (DMSO-$d_6$) $\tau$ 7.52, 7.82 (2 s, 6 H, 2 $NCH_3$), 6.25 (s, 3 H, $OCH_3$); mass spectrum *m/e* (rel intensity) 580 (52), 298 (100), 297 (54), 283 (29); uv $\lambda_{max}^{95\%\ EtOH}$ 284 nm ($\epsilon$ 6750).

*Anal.* Calcd for $C_{35}H_{36}N_2O_6 \cdot 2H_2O$: C, 68.40; H, 6.57; N, 4.83. Found: C, 68.30; H, 6.50; N, 4.55.

**Fractionation of the Basic Alkaloids.**—Fraction G (17 g) in MeOH (100 ml) was slowly passed through a column of Dowex I-X8 ion exchange resin ($Cl^-$ form, 250 g), and the eluate was evaporated to a residue and column chromatographed on alumina (Merck neutral grade I, 410 g). Column fractions eluted with $CHCl_3$, 1–3% MeOH–$CHCl_3$, 3% MeOH–$CHCl_3$, 5% MeOH–$CHCl_3$, and 10% MeOH–$CHCl_3$ were combined to give fractions H, J, K, L, and M, respectively.

**Isolation of 16.**—Fraction H was evaporated to give a brown residue, essentially homogeneous by tlc, purification of which by preparative tlc on alumina, using 5% MeOH–$CHCl_3$ as eluent, afforded a colorless solid (0.7 g) which was crystallized from acetone to yield fine colorless needles: mp 213–217° dec; $[\alpha]^{25}D$ +156° (*c* 0.41, $CHCl_3$); uv $\lambda_{max}^{EtOH}$ 283 nm ($\epsilon$ 7600); ir $\lambda_{max}^{CHCl_3}$ 3.42, 3.54, 6.25, 6.34, 6.66 $\mu$; nmr $\tau$ 2.3–4.2 (10 H, ArH), 5.40 (m, 2 H, $-CH_2Cl$), 6.06 (br s, 6 H, 2 $OCH_3$), 6.25 (2 s, 6 H, 2 $OCH_3$), 6.70 (s, 3 H, $NCH_3$), 7.63 (s, 3 H, $NCH_3$).

*Anal.* Calcd for $C_{39}H_{44}N_2O_6Cl_2 \cdot 3^1/_2H_2O$: C, 61.00; H, 6.64; N, 3.65; Cl, 9.24. Found: C, 60.99; H, 6.05; N, 3.65; Cl, 8.93.

**Isolation of 31.**—Fraction K gave a brown residue (2.2 g) on evaporation which proved to be a mixture by tlc. Preparative tlc on alumina using 10% MeOH–$CHCl_3$ as eluent afforded the major component (0.5 g) essentially homogeneous by tlc. Treatment with aqueous oxalic acid and crystallization of the product from aqueous MeOH yielded **31** as its bisoxalate (200 mg), mp 207–209° dec.

*Anal.* Calcd for $C_{40}H_{48}N_2O_8 \cdot 2H_2C_2O_4 \cdot 2H_2O$: C, 58.66; H, 6.22; N, 3.11. Found: C, 58.68; H, 6.27; N, 3.12.

Treatment of the oxalate (100 mg) with ammonium hydroxide solution, extraction with $CHCl_3$, and evaporation of the organic extract gave the free base **31** (74 mg), which was crystallized from

methyl ethyl ketone as colorless needles: mp 161–163°; $[\alpha]^{25}D$ +174° (*c* 1.00, $CHCl_3$); uv $\lambda_{max}^{EtOH}$ 283 nm (ε 6780); ir $\lambda_{max}^{CHCl_3}$ 3.41, 6.26, 6.33, 6.67, 8.90 μ; nmr τ 2.6–3.9 (8 H, ArH), 4.28 (s, 1 H, ArH), 4.95 (d, 1 H, *J* = 9 Hz, ArH), 6.11, 6.32, 6.60, 6.82 (4 s, 12 H, 4 $OCH_3$), 7.36, 7.42 (2 s, 6 H, 2 $NCH_3$); mass spectrum *m/e* (rel intensity) 684 (100), 622 (30), 198 (25). Mass calcd for $C_{40}H_{48}N_2O_8$, 684.3408; found, 684.3349.

**Isolation of 26.**—Fraction L was evaporated to dryness to give a brown residue (1.5 g) which was redissolved in benzene (100 ml) and on standing afforded **26** as pale yellow needles (150 mg), mp 151–153°.

*Anal.* Calcd for $C_{39}H_{46}N_2O_8 \cdot 2C_6H_6$: C, 74.00; H, 7.03; N, 3.39. Found: C, 74.33; H, 7.24; N, 3.40.

Recrystallization from EtOH gave **26** as colorless needles free of solvent: mp 176–178°; $[\alpha]^{25}D$ −237° (*c* 1.00, $CHCl_3$); uv $\lambda_{max}^{EtOH}$ 284 nm (ε 12,100), shifted to 305 nm on addition of NaOH; ir $\lambda_{max}^{KBr}$ 2.94, 3.10, 3.43, 6.25, 6.36, 6.70 μ; nmr τ 2.7–4.0 (10 H, ArH), 6.14 (s, 6 H, 2 $OCH_3$), 6.27 (s, 3 H, $OCH_3$), 7.64, 7.74 (2 s, 6 H, 2 $NCH_3$); mass spectrum *m/e* (rel intensity) 670 (88), 608 (65), 381 (70), 191.5 (25), 191 (100). Mass calcd for $C_{39}H_{46}N_2O_8$, 670.3251; found, 670.3249. Mass calcd for $C_{11}H_{13}NO_2$, 191.0945; found, 191.091.

*Anal.* Calcd for $C_{39}H_{46}N_2O_8$: C, 69.83; H, 6.91; N, 4.18. Found: C, 69.90; H, 6.90; N, 4.11.

**Isolation of Cycleanorine (8).**—On evaporation fraction M yielded a brown gum (2.0 g), which was shown by tlc to be a complex mixture. Preparative tlc on silica gel using $NEt_3$–MeOH–$CHCl_3$ (5:10:85) as eluent gave two major bands. The upper band was rechromatographed on alumina using 5% MeOH–$CHCl_3$ as eluent to give a tlc-homogeneous oil (10 mg) which yielded cycleahomine chloride (**14**, 5 mg) on crystallization from MeOH. The lower band was also purified by preparative tlc on alumina, using 10% MeOH–$CHCl_3$ as eluent, to give a colorless residue (20 mg) which afforded cycleanorine (**8**, 10 mg) as colorless needles from aqueous ethanol: mp 170–172°; $[\alpha]^{25}D$ +308° (*c* 0.52, $CHCl_3$); uv $\lambda_{max}^{EtOH}$ 282 nm (ε 10,200); ir $\lambda_{max}^{CHCl_3}$ 3.42, 6.25, 6.33, 6.77 μ; nmr τ 2.6–3.1 (10 H, ArH), 6.12, 6.30, 6.67, 6.78 (4 s, 12 H, 4 $OCH_3$), 7.67 (s, 3 H, $NCH_3$); mass spectrum *m/e* (rel intensity) 608 (55), 431 (18), 381 (80), 191 (100).

*Anal.* Calcd for $C_{37}H_{40}N_2O_6$: C, 73.00; H, 6.62; N, 4.60. Found: C, 72.89; H, 6.64; N, 4.61.

**Isolation of Cycleahomine Chloride (14).**—The benzene mother liquors from the crystallization of **26** above were chromatographed on preparative alumina tlc plates using 5% MeOH–$CHCl_3$ to afford two major bands. Extraction of the higher $R_f$ band gave **26** (100 mg). Extraction of the lower $R_f$ band gave a yellow gum (35 mg) which gave cycleahomine chloride (**14**) as colorless prisms (12 mg) on crystallization from $CH_2Cl_2$–EtOAc: mp 190–194°; $[\alpha]^{25}D$ +103° (*c* 0.15, $CHCl_3$); $\lambda_{max}^{EtOH}$ 284 nm (ε 12,000); ir $\lambda_{max}^{CHCl_3}$ 3.34, 3.41, 6.24, 6.32, 6.65 μ; nmr τ 2.6–4.0 (10 H, ArH), 5.5 (m, 1 H, $ArCHN^+$), 6.06, 6.28, 6.62 (3 s, 9 H, 3 $OCH_3$), 6.70 (br s, 6 H, $OCH_3$, $^+NCH_3$), 6.46 (br s, 3 H, $^+NCH_3$), 7.63 (s, 3 H, $NCH_3$).

*Anal.* Calcd for $C_{39}H_{45}N_2O_6Cl$: C, 69.60; H, 6.75; N, 4.20. Found: C, 69.18; H, 6.80; N, 4.31.

**O-Methylation of Cycleapeltine (11) to *O*-Methylrepandine (12).**—A solution of **11** (50 mg) in $CH_3OH$ (5 ml) was treated with an excess of ethereal diazomethane at 0–5° for 4 days. Evaporation of the solution and preparative tlc of the residue on alumina with $CHCl_3$ as the eluent yielded **12** (46 mg),[9] crystallized from acetone–hexane: mp 208–210°; $[\alpha]^{25}D$ −71° (*c* 0.48, $CHCl_3$); nmr τ 7.43, 7.47 (2 s, 6 H, 2 $NCH_3$), 6.05, 6.28, 6.58, 6.97 (4 s, 12 H, 4 $OCH_3$); mass spectrum *m/e* (rel intensity) 622 (52), 431 (5), 395 (55), 381 (25), 198.5 (25), 198 (100), 175 (34), 174 (20).

**O-Methylation of Cycleadrine (5) to Isotetrandrine (3).**—Treatment of **5** (40 mg) in the above manner yielded **3** (40 mg): mp 180–182°; $[\alpha]^{25}D$ 0° (*c* 1.0, $CHCl_3$); nmr τ 7.41, 7.71 (2 s, 6 H, 2 $NCH_3$), 6.08, 6.24, 6.38, 6.88 (4 s, 12 H, 4 $OCH_3$); mass spectrum *m/e* (rel intensity) 622 (56), 431 (6), 395 (58), 381 (26), 198.5 (28), 198 (100), 175 (40), 174 (29); identical (melting point, nmr, mass spectrum) with an authentic sample.[9a,b]

**O-Methylation of Cycleacurine (19) to Di-*O*-methyl-*l*-curine (17).**—Treatment of **19** (30 mg) in the above manner yielded **17** (18 mg): mp 117–119°; $[\alpha]^{25}D$ −265° (*c* 1.0, $CHCl_3$); nmr τ 7.46, 7.67 (2s , 6 H, 2 $NCH_3$), 6.12, 6.14, 6.28, 6.31 (4 s, 12 H, 4 $OCH_3$); mass spectrum *m/e* (rel intensity) 622 (48), 312 (100); identical in melting point, nmr, and mass spectrum with authentic di-*O*-methyl-*d*-curine,[9a,12] but with opposite $[\alpha]D$.

**O-Ethylation of Cycleacurine (19) to Tri-*O*-ethylcycleacurine (20).**—Treatment of **19** (270 mg) in the above manner but with diazoethane yielded **20** (210 mg) which was subjected to degradative studies without further purification: nmr τ 7.35, 7.58 (2 s, 6 H, 2 $NCH_3$), 6.16 (s, 3 H, $OCH_3$), 8.46, 8.65, 8.69 (3 t, 9 H, *J* = 7 Hz, 3 $OCH_3CH_3$); mass spectrum *m/e* (rel intensity) 664 (100), 340 (76), 326 (87). Mass calcd for $C_{41}H_{48}N_2O_6$, 664.351; found, 664.356.

**Sodium–Liquid Ammonia Cleavage of Tri-*O*-ethylcycleacurine (20).**—Tri-*O*-ethylcycleacurine (100 mg) was dissolved in benzene–toluene (2:1, 12 ml). Liquid ammonia (80 ml) was added, followed by sodium metal (0.3 g). The mixture was stirred for 1 hr and then allowed to warm up to ambient temperature overnight. The residue was dissolved in water (10 ml) and extracted with ether (6 × 10 ml). The combined ether layers were dried ($Na_2SO_4$), evaporated to a residue, applied to two 200 × 200 × 1.5 mm alumina plates, and eluted with $CHCl_3$. Aside from a small residue, only two components were apparent: the nonpolar (nonphenolic) product and the polar (phenolic) product. These were recovered.

The nonphenolic product **22** resisted crystallization and was characterized as a pale yellow oil: nmr τ 3.11 (AB quartet, Δν 23 Hz, 4 H, *J* = 8 Hz, para-disubstituted benzene), 3.45, 3.94 (2 s, 2 H, 1,2,4,5-tetrasubstituted benzene), 5.99, 6.20, (2 q, 4 H, *J* = 6.5 Hz, 2 $OCH_2CH_3$), 6.16 (s, 3 H, $OCH_3$), 7.44 (s, 3 H, $NCH_3$), 8.54, 8.60 (2 t, 6 H, *J* = 6.5 Hz, 2 $OCH_2CH_3$); mass spectrum *m/e* (rel intensity) 355 (<0.1), 220 (100), all other peaks less than 5; mass spectrum (chemical ionization, $Ar/H_2O$) *m/e* (rel intensity) 356 (56), 221 (100). Mass calcd for $C_{22}H_{29}NO_3 + H^+$, 356.225; found, 356.223.

The phenolic product, **21**, also failed to crystallize and was similarly characterized as a pale yellow oil: nmr τ 3.27 (AB quartet, Δν 29 Hz, 4 H, *J* = 8 Hz, para-disubstituted benzene), 3.47, 3.57 (2 s, 2 H, 1,2,4,5-tetrasubstituted benzene), 4.79 (br s, 2 H, ArOH), 5.93 (q, 2 H, *J* = 6.5 Hz, $OCH_2CH_3$), 7.51 (s, 3 H, $NCH_3$), 8.52 (t, 3 H, *J* = 6.5 Hz, $OCH_2CH_3$); mass spectrum *m/e* (rel intensity) 313 (<0.1), 206 (100), all other peaks less than 5; mass spectrum (chemical ionization, $Ar/H_2O$) *m/e* (rel intensity) 314 (62), 207 (100). Mass calcd for $C_{19}H_{23}NO_3 + H^+$, 314.175; found, 314.176.

**N-Methylation of Cycleanorine (8).**—To a cooled solution of cycleanorine (20 mg) in MeOH (0.5 ml), aqueous formaldehyde (37%, 0.2 ml) was added and the solution was stirred at 5° for 0.5 hr. Sodium borohydride (50 mg) was added cautiously over a further 0.5 hr, the solution was allowed to come to room temperature, and water (2 ml) was added. Extraction of the solution with $CHCl_3$ (10 ml) and evaporation of the solvent gave a crystalline residue which was subjected to preparative tlc on alumina using $CHCl_3$ as eluent. Extraction of the major band followed by crystallization from acetone–hexane afforded tetrandrine (**1**, 10 mg) as colorless needles, identical (tlc, mixture melting point, ir) with an authentic sample.

**Demethylation of Tetrandrine (1).**—To a solution of tetrandrine (3 g) in dry dimethoxyethane (125 ml) an excess of methyl chloroformate (6 ml) was added and the mixture was left at room temperature for 12 hr. The solution was neutralized by addition of $NH_4OH$ and evaporated to dryness and the residue was subjected to preparative tlc on silica gel using 8% MeOH–$CHCl_3$ as eluent. Extraction of the major band gave the crude monocarbamate **9**, which was crystallized from $CH_2Cl_2$–EtOH as colorless needles (0.81 g), mp 219–220°.

*Anal.* Calcd for $C_{39}H_{42}N_2O_8$: C, 70.25; H, 6.35; N, 4.20. Found: C, 70.06; H, 6.49; N, 4.22.

The carbamate **9** (0.5 g) was dissolved in a solution of KOH in glycol (10%, 10 ml) and heated at 185° for 1 hr. The cooled solution was made acidic with aqueous HCl, basified after 5 min with $NH_4OH$, and extracted with $CHCl_3$ (2 × 10 ml). Evaporation of the organic extract followed by preparative tlc of the residue on alumina with 2% MeOH–$CHCl_3$ as eluent and subsequent crystallization from EtOH afforded cycleanorine (**8**) as colorless needles (250 mg), mp 170–172°, identical (tlc, mixture melting point, ir) with an authentic sample.

**Tetrandrine Bismethiodide.**—Cycleahomine chloride (5 mg) in MeOH (0.2 ml) was treated with methyl iodide (0.1 ml) at room temperature for 15 hr. Evaporation of the solvent and crystallization of the residue from MeOH afforded tetrandrine bismethiodide, mp 264–268° (lit.[16] mp 265–269°), identical (tlc, mixture melting point, ir, $[\alpha]D$) with an authentic sample.

**Tetrandrine Monomethiodide (15).**—Tetrandrine (50 mg) in MeOH (2 ml) was treated with methyl iodide (5 μl) and the solu-

tion was allowed to stand at room temperature for 12 hr. Evaporation of the solvent, preparative tlc of the residue on alumina with 5% MeOH–$CHCl_3$ as eluent, and subsequent crystallization from wet $CH_2Cl_2$–EtOAc afforded the monomethiodide **15** as colorless needles (10 mg): mp 208–211° dec; $[\alpha]^{25}D$ +163° (*c* 0.50, $CHCl_3$); uv $\lambda_{max}^{EtOH}$ 281 nm (ε 12,500); ir $\lambda_{max}^{CHCl_3}$ 3.42, 6.26, 6.34, 6.68 μ; nmr τ 2.1–4.8 (10 H, ArH), 6.09 (br s, 6 H, $^+NCH_3$, $OCH_3$), 6.26, 6.59, 6.74 (3 s, 9 H, 3 $OCH_3$), 6.52 (br s, 3 H, $^+NCH_3$), 7.66 (s, 3 H, $NCH_3$).

*Anal.* Calcd for $C_{39}H_{45}N_2O_6I \cdot H_2O$: C, 59.85; H, 6.05; N, 3.58. Found: C, 60.08; H, 6.05; N, 3.59.

**Dealkylation of 16.**—To a solution of KO-*t*-Bu (1.1 g) and 1-propanethiol (1.1 g) in dimethyl acetamide (15 ml) was added **16** (0.5 g) and the mixture was stirred at room temperature for 18 hr. The mixture was poured into 2% aqueous HCl (25 ml), the solution was washed with ether (2 × 25 ml), and the washings were discarded. After heating at 80° for 5 min the solution was neutralized with $NH_4OH$ and extracted with ether (2 × 25 ml) and the ether extract was evaporated to give a yellow oil (420 mg) which was subjected to preparative tlc on silica gel eluted with 15% MeOH–$CHCl_3$. The major band ($R_f$ 0.1–0.2) afforded cycleanorine (**8**, 248 mg) as colorless needles from aqueous EtOH: mp 170–172°; $[\alpha]^{25}D$ +311° (*c* 0.62, $CHCl_3$); identical (tlc, mixture melting point, ir, nmr) with an authentic sample.

**Hofmann Degradation of 16.**—A solution of **16** (100 mg) in 4% ethanolic NaOEt (10 ml) (prepared *in situ* by dissolving 100 mg of Na in 10 ml of EtOH) was heated at reflux for 1 hr, water (10 ml) was added, and the solution was extracted with $CHCl_3$ (2 × 20 ml). Evaporation of the solvent afforded a colorless glass (70 mg), homogeneous by tlc, which quickly decomposed on standing: nmr τ 2.12 (dd, 1 H, $J_1$ = 18, $J_2$ = 11 Hz, ArCH=), 2.6–3.8 (10 H, ArH), 4.48 (d, 1 H, $J$ = 18 Hz, $=CH_2$–), 4.82 (d, 1 H, $J$ = 11 Hz, $=CH_2$–), 5.54 (d, 1 H, $J$ = 9 Hz, $NCH_2O$), 5.79 (d, 1 H, $J$ = 9 Hz, $NCH_2O$), 6.09, 6.24, 6.58, 6.68 (4 s, 12 H, 4 $OCH_3$), 7.38, 7.70 (2 s, 6 H, 2 $NCH_3$), 8.73 (t, 3 H, $J$ = 6 Hz, $-CH_2CH_3$); mass spectrum *m/e* (rel intensity) 680 (3), 634 (100), 619 (60), 497 (58).

**Preparation of 16.**—Tetrandrine (1 g) in $CH_2Cl_2$ (100 ml) was allowed to stand for 6 days, the solvent was evaporated, and the residue was subjected to preparative tlc on alumina, using 10% MeOH–$CHCl_3$ as eluent, to afford two bands. The higher $R_f$ band gave starting material (0.71 g) and the lower afforded **16** which was crystallized as colorless needles (12 mg) from EtOAc–isopropyl alcohol and was found to be identical (tlc, mixture melting point, ir) with **16** isolated above.

**Acetylation of 26.**—To **26** (20 mg) in pyridine (0.5 ml) was added acetic anhydride (0.2 ml) and the solution was allowed to stand at room temperature for 15 hr. Water (1 ml) was added and the mixture was extracted with $CHCl_3$ (2 × 5 ml). Evaporation of the organic extract afforded the triacetate **27** as a colorless glass (16 mg): ir $\lambda_{max}^{KBr}$ 3.43, 5.70, 5.78, 6.12, 6.23, 6.35, 8.17 μ; nmr τ 2.5–4.0 (10 H, ArH), 6.11 (s, 3 H, $OCH_3$), 6.30 (s, 6 H, 2 $OCH_3$), 6.94 (s, 3 H, $NCH_3Ac$), 7.68 (s, 3 H, $NCH_3$), 7.89 (s, 3 H, $OCH_3$), 7.94 (s, 6 H, 2 $COCH_3$); mass spectrum *m/e* (rel intensity) 796 (30), 423 (25), 121 (100).

**N-Methylation of 26.**—This was carried out using the procedure described in the methylation of cycleanorine (**8**) above, to afford **28** as colorless needles from aqueous EtOH: mp 199–201°; $[\alpha]^{25}D$ −207° (*c* 1.00, $CHCl_3$); ir $\lambda_{max}^{KBr}$ 2.95 (br), 3.43, 6.25, 6.34, 6.67 μ; nmr τ 2.5–2.9 (10 H, ArH), 6.10 (s, 6 H, 2 $OCH_3$), 6.23 (s, 3 H, $OCH_3$), 7.66 (br s, 9 H, 3 $NCH_3$); mass spectrum *m/e* (rel intensity) 684 (100), 622 (30).

*Anal.* Calcd for $C_{40}H_{48}N_2O_8$: C, 70.09; H, 7.18; N, 3.96. Found: C, 70.15; H, 7.07; N, 4.08.

**Permethylation of 26.**—To a solution of **26** (140 mg) in refluxing MeOH (10 ml) were added anhydrous $K_2CO_3$ (100 mg) and methyl iodide (0.5 ml) and the solution was allowed to cool to room temperature. A further 0.5 ml of methyl iodide was added and the solution was allowed to stand for 18 hr. Evaporation of the solvent and trituration of the residue with water afforded the crude methiodide (160 mg) which was crystallized from MeOH as colorless prisms (142 mg): mp 260° dec; uv $\lambda_{max}^{EtOH}$ 280 nm (ε 14,700); ir $\lambda_{max}^{KBr}$ 3.45, 6.26, 6.35, 6.70 μ; nmr (DMSO-$d_6$) τ 2.9–4.3 (10 H, ArH), 6.24, 6.32, 6.62, 6.76 (4 s, 12 H, 4 $OCH_3$), 6.74 (s, 15 H, 5 $^+NCH_3$).

*Anal.* Calcd for $C_{44}H_{58}N_2O_8I_2 \cdot 2H_2O$: C, 51.00; H, 6.01; N, 2.71. Found: C, 50.63; H, 5.88; N, 2.74.

**Hofmann Degradation of Permethylated 26.**—The procedure used was essentially that employed in the degradation of **16** above. Permethylated **26** (112 mg) afforded upon reflux with 2.5% methanolic NaOMe for 18 hr a mixture of products (66 mg) from which the styrene **29** was crystallized from MeOH as colorless prisms (46 mg): mp 202–204°; uv $\lambda_{max}^{EtOH}$ 263 nm (ε 16,200) and 292 (8310); ir $\lambda_{max}^{KBr}$ 3.44, 6.22, 6.33, 6.68 μ; nmr ($CDCl_3$–$CD_3CO_2D$) τ 2.5–3.4 (12 H, ArH, $ArCHCH_2$), 4.37 (d, 1 H, $J$ = 17 Hz, $ArCHCH_2$), 4.63 (d, 1 H, $J$ = 10 Hz, $ArCHCH_2$), 6.07, 6.18, 6.50, 6.65 (4 s, 12 H, 4 $OCH_3$), 6.80 [br s, 6 H, $^+N(CH_3)_2$].

*Anal.* Calcd for $C_{40}H_{46}NO_8I \cdot H_2O$: C, 59.15; H, 5.92; N, 1.72. Found: C, 59.36; H, 5.97; N, 1.87.

**Acid Degradation of 26.**—A solution of **26** (104 mg) in 10% aqueous HCl (2 ml) was heated at steam bath temperature for 3 hr, and the cooled solution was made alkaline with $NH_4OH$ and extracted with $CHCl_3$ (2 × 5 ml). Evaporation of the organic solvent and preparative tlc of the residue on alumina using 20% MeOH–$CHCl_3$ as eluent gave the stilbene **30** (35 mg), which was crystallized from MeOH as colorless prisms: mp 167–171°; uv $\lambda_{max}^{EtOH}$ 281 nm (ε 2800); ir $\lambda_{max}^{KBr}$ 3.43, 6.26, 8.95, 11.80 μ; nmr τ 2.5–3.9 (12 H, 10 ArH, 2 =CH–), 6.06, 6.20, 7.12 (3 s, 9 H, 3 $OCH_3$), 7.48, 7.70 (2 s, 6 H, 2 $NCH_3$); mass spectrum *m/e* (rel intensity) 608 (100), 191 (35). Mass calcd for $C_{37}H_{40}N_2O_6$, 608.289; found, 608.288.

*Anal.* Calcd for $C_{37}H_{40}N_2O_6 \cdot {}^1/_2MeOH$: C, 72.10; H, 6.74; N, 4.49. Found: C, 71.74; H, 7.06; N, 4.70.

**Acetylation of 31.**—This was carried out in an identical manner with that of **26** above, and **31** (20 mg) yielded the diacetate **32** (12 mg) as a colorless glass: ir $\lambda_{max}^{KBr}$ 3.60, 5.80, 6.05, 8.95 μ; nmr τ 2.6–4.0 (8 H, ArH), 4.9 (m, 2 H, ArH), 6.11, 6.34, 6.55, 6.76 (4 s, 12 H, 4 $OCH_3$), 7.78, 7.88 (2 s, 6 H, 2 $NCH_3$), 8.06, 8.08 (2 s, 6 H, 2 $COCH_3$); mass spectrum *m/e* (rel intensity) 768 (100).

**N-Methylation of 31.**—This was carried out using the procedure described in the methylation of cycleanorine (**8**) above. Thus the bisoxalate of **31** (400 mg) yielded **33** (291 mg) as colorless needles from EtOH: mp 170–171°; $[\alpha]^{25}D$ +180° (*c* 1.00, $CHCl_3$); uv $\lambda_{max}^{EtOH}$ 282 nm (ε 8000); ir $\lambda_{max}^{KBr}$ 3.42, 6.33, 7.87, 8.91 μ; nmr τ 2.6–3.8 (8 H, ArH), 4.14 (s, 1 H, ArH), 4.86 (d, 1 H, $J$ = 8.5 Hz, ArH), 6.05, 6.19, 6.55, 6.72 (4 s, 12 H, 4 $OCH_3$), 7.30 (s, 3 H, $NCH_3$), 7.60 [s, 6 H, $N(CH_3)_2$]; mass spectrum *m/e* (rel intensity) 698 (100), 636 (48).

*Anal.* Calcd for $C_{41}H_{50}N_2O_8$: C, 70.46; H, 7.21; N, 4.01. Found: C, 70.22; H, 7.19; N, 4.06.

**Permethylation of 31.**—This was carried out in a similar manner to the permethylation of **26** above. Compound **31** (50 mg) afforded the corresponding bismethiodide (40 mg), which crystallized from MeOH as colorless prisms: mp 225–227° dec; uv $\lambda_{max}^{EtOH}$ 281 nm (ε 2460); ir $\lambda_{max}^{KBr}$ 3.43, 6.27, 6.34, 8.98 μ; nmr (DMSO-$d_6$) τ 1.80 (s, 1 H, ArH), 2.33 (m, 1 H, ArH), 5.80 (m, 1 H, ArH), 3.0–3.7 (5 H, ArH), 4.12 (m, 1 H, ArH), 5.10 (m, 1 H, ArH), 6.12, 6.16, 6.48, 6.65 (4 s, 12 H, 4 $OCH_3$), 6.60 (s, 15 H, 5 $NCH_3^+$).

*Anal.* Calcd for $C_{44}H_{58}N_2O_8I_2 \cdot 2H_2O$: C, 51.00; H, 6.01; N, 2.71. Found: C 51.30; H, 5.93; N, 2.74.

**Acid Degradation of 31.**—The bisoxalate of **31** (50 mg) in 15% aqueous HCl (2 ml) was heated at steam bath temperature for 0.5 hr. The solution was allowed to cool, made alkaline with $NH_4OH$, and extracted with ether. Evaporation of the solvent and preparative tlc of the residue on alumina, using 10% MeOH–$CHCl_3$ as eluent, afforded the stilbene **34**, which was crystallized from MeOH as colorless needles (26 mg): mp 125–127°; uv $\lambda_{max}^{EtOH}$ 290 nm (ε 1750), 325 (1590); ir $\lambda_{max}^{KBr}$ 3.60, 6.18, 13.85 μ; nmr τ 2.6–3.6 (9 H, ArH), 2.98 (s, 1 H, ArH), 6.08, 6.73 (2 s, 6 H, 2 $OCH_3$), 6.19 (s, 6 H, 2 $OCH_3$), 7.40, 7.46 (2 s, 6 H, 2 $NCH_3$); mass spectrum *m/e* (rel intensity) 622 (100), 174 (10).

**Registry No.**—**1**, 518-34-3; **3**, 477-57-6; **5**, 38769-07-2; **5** 2HI, 38906-65-9; **8**, 38769-08-3; **9**, 38849-79-5; **11**, 38849-80-8; **12**, 4021-17-4; **14**, 38849-82-0; **15**, 38849-83-1; **16**, 38769-09-4; **17**, 1812-55-1; **19**, 38849-84-2; **19** 2HBr, 38769-11-8; **20**, 38769-12-9; **21**, 38769-13-0; **22**, 6681-71-6; **26**, 38769-15-2; **26** methiodide, 38849-85-3; **27**, 38769-16-3; **28**, 38769-17-4; **29**, 38769-18-5; **30**, 38769-19-6; **31**, 38769-20-9; **31** dioxalate, 38769-21-0; **31** dimethiodide, 38769-22-1; **32**, 38769-23-2; **33**, 38769-24-3; **34**, 38849-86-4.