Journal of Natural Products
Vol. 49, No. 3, pp. 373-385, May-Jun 1986

PHOTO-OXIDATIVE CLEAVAGE: AN ALTERNATIVE METHOD FOR DEGRADING BISBENZYLISOQUINOLINE ALKALOIDS

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ABSTRACT.—A photo-oxidative cleavage reaction observed for the benzylisoquinoline alkaloid (±)-laudanosine (**1**) has been applied to the degradation of bisbenzylisoquinoline alkaloids. This reaction involves the cleavage of rings AB and CD from rings E and F in these systems, and in the case of isotetrandrine (**9**), for example, yields 3-(4′-formylphenoxy)-4-methoxybenzaldehyde (**13**) and, after further reaction ($NaBH_4$ reduction and thermal dehydration), the amino-lactam 3′,4′-dihydro-6′-methoxy-7′-[1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-(isoquinolin-8-yl)oxy]-2′-methyl-1′(2*H*)-isoquinolinone (**14**). This general reaction sequence has also been applied to berbamine, phaeanthine, nortenuipine, tenuipine, obaberine, aromoline diacetate, nemuarine, micranthine, apateline, *N*-methyltelobine, and cycleanine, or derivatives of some of these alkaloids. The reaction sequence affords an alternative degradative procedure useful for structural elucidation or structural confirmation purposes. Further reductions of some of the nitrogen-containing reaction products are described.

The usual methods employed for degrading bisbenzylisoquinoline alkaloids in the course of structural determination have involved either oxidative cleavage of the "isoquinoline" portions from the lower benzylic moieties or reductive cleavage of the diphenyl ether linkages. Both methods suffer from certain disadvantages: direct oxidation with manganese dioxide (1,2) or potassium permanganate (3-5), while successful in some instances, usually involves difficulties in isolating the nitrogen-containing fragment. Hofmann degradation followed by ozonolysis has been widely used, but it suffers from a lack of regiospecificity in methine-base formation (6). Reductive methods, by which the diphenyl ether linkages are cleaved, have been the most successful in general, a major advantage being that they give two *N*-containing fragments with the chiral centers intact. However, difficulties arise with alkaloids containing a dibenzo-*p*-dioxin nucleus (7,8) or a methylene-dioxy group (6): the former is incompletely cleaved, and the latter affords a competing reaction that drastically reduces the yield and renders the results ambiguous.

The ready benzylic cleavage of these bases on electron impact (9) led us to investigate the possibility of a photo-induced analogue of this process. During the course of this investigation, a new photo-oxidative cleavage reaction was found (10), the results of which are now described in full in this paper. This work is complemented by the later discovery of a related ground-state oxidative cleavage process involving cerium (IV) (11).

RESULTS AND DISCUSSION

In a series of preliminary experiments designed to select suitable conditions for the oxidative cleavage, a MeOH solution of (±)-laudanosine (**1**) was subjected to uv irradiation through Pyrex in the presence of oxygen. Veratraldehyde (**5**) was obtained in good yield, together with approximately equal quantities of the lactam **2** (plus **3**) and the corresponding carbinolamine **4** (iminium salt form), isolated as its $NaBH_4$ reduction product **6** (Scheme 1). Variations in the reaction conditions, including the use of methylene blue as sensitiser, afforded the same products but in variable yields (7,10,12).

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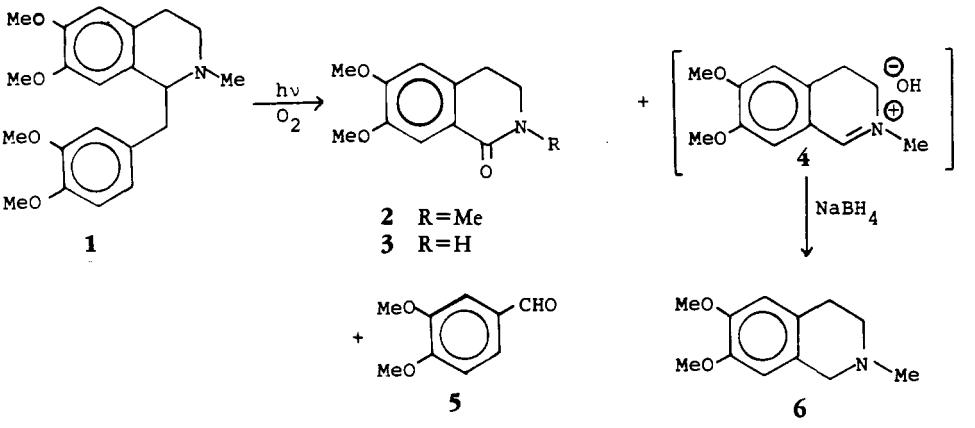
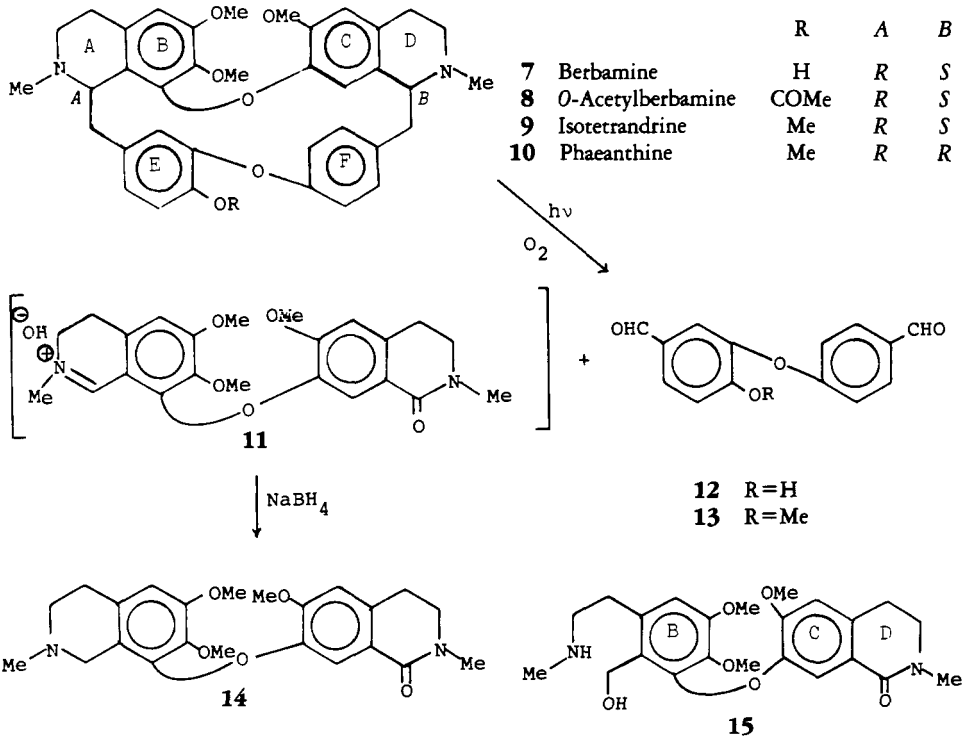


SCHEME 1

Similar reaction conditions were then applied to a series of bisbenzylisoquinoline alkaloids[3] of known structure. Isotetrandrine (**9**) gave two major products in fair yield: the dialdehyde **13** and a highly polar substance with the properties of a carbinolaminolactam. This material, which is represented with some degree of probability as **11**, was not isolated as such, but as its borohydride reduction product, the aminolactam **14**; the open-chain product **15** was also formed, but it readily dehydrated to give **14** (Scheme 2, Table 1). Evidence for the structure of the latter compound was obtained by Birch reduction, which afforded **6** in nearly quantitative yield. A mixture of products resulting from rings C and D was also formed, from which no pure substance could be obtained;



		R	A	B
7	Berbamine	H	*R*	*S*
8	*O*-Acetylberbamine	COMe	*R*	*S*
9	Isotetrandrine	Me	*R*	*S*
10	Phaeanthine	Me	*R*	*R*

SCHEME 2

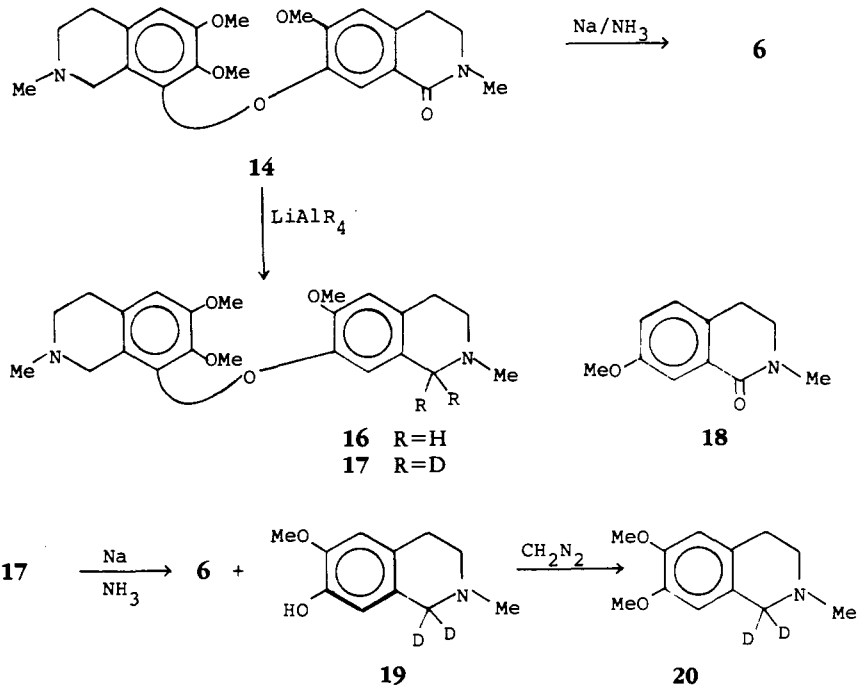
[3]For two detailed recent reviews on the bisbenzyisoquinoline alkaloids, see Guha *et al.* (13) and Schiff (14).

TABLE 1. Photo-oxidative Cleavage of Some Bisbenzylisoquinoline Alkaloids and Derivatives

Starting Material	Concentration (in MeOH)	Irradiation Time (h)	Unchanged Material (%)	Upper Half (%)	Lower Half (%)
Berbamine (**7**)	1.65×10^{-3}mol/300ml	7	35	**14** 15	**12** 35
O-Acetylberbamine (**8**)	1.43×10^{-3}mol/300ml	10.25	8 as (**7**)	**14** 15	**12** 29.5
Isotetrandrine (**9**)	1.61×10^{-3}mol/200ml	15	—	**15** 31.6; **14**	**12** 30.6
Phaeanthine (**10**)	1.61×10^{-3}mol/250ml	16	—	**14** 28	**13** 29.4
Nortenuipine (**21**)	8.05×10^{-4}mol/300ml	8	—	—	**24** 29.6
O-Acetylnortenuipine (**22**)	1.50×10^{-3}mol/250 ml	13.5	—	**29** 8.4	**24** 12.5
Tenuipine (**23**)	4.71×10^{-4}mol/300 ml	6	—	**14** 21.4	**24** 35
Obaberine (**25**)	8.05×10^{-4}mol/250ml	15	—	**14** 27.8	**13** 19.6
O,O-Diacetylaromoline (**27**)	1.47×10^{-3}mol/250ml	13.5	—	**29** 17	**12** 11.2
Nemuarine (**30**)	6.58×10^{-4}mol/300ml	24	7.5	**32** 3.6; **34** 12.9	**12** 18.4
O-Methylnemuarine (**31**)	4.82×10^{-4}mol/300ml	7	—	**32** 3.6; **34** 18.4	**13** 24.3
O,N-Dimethylmicranthine (**36**)	1.13×10^{-3}mol/250ml	18	23	**42** 11	**13** 20
N-Methyltelobine (**38**) (*O,N*-Dimethylapateline)	5.55×10^{-3}mol/200ml	14	3	**42** 10; **43** 8	**13** 7
Cycleanine (**44**)	6.34×10^{-4}mol/250ml	10	10	**46** 29	—

from analogy with the reaction of **2** with sodium and liquid NH_3, the principal product of which is **18**, it is possible that the above-mentioned mixture contained some demethoxylated material.

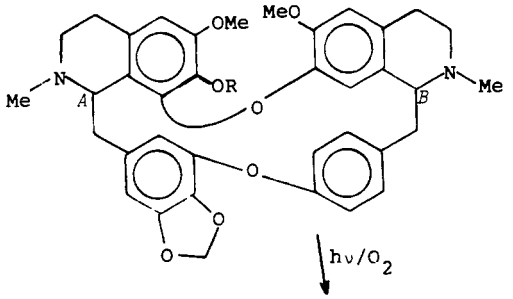
When the lactam group in **14** was reduced with $LiAlH_4$, a diamine (**16**) was obtained with two extra benzylic protons, whose ^{1}H-nmr signals could readily be identified by comparison with the spectrum of the analogous compound **17** formed by $LiAlD_4$ reduction of **14**. This deuterated product on Birch reduction gave **6** and an aminophenol (**19**) which could be methylated to yield the substance **20**, identical with **6** except that the benzylic protons adjacent to the amino group had been replaced by deuterium (Scheme 3). The position of the lactam group is thus fixed in the initial nitrogen-containing photolysis product as that shown in **11**.



SCHEME 3

On oxidative photolysis of phaeanthine (**10**), a diastereomer of isotetrandrine (**9**), the same products were obtained in comparable yield under the same conditions, from which it appears that the course of the reaction is not appreciably influenced by stereochemistry (Table 1).

Oxidative photolysis of berbamine (**7**), an analogue of isotetrandrine (**9**) with a phenolic group replacing one of the methoxyls, yielded the corresponding products **12** and **14**, although the yield of the latter was halved as compared with that from **9**. The same two products were obtained in similar yield on photolysis of *O*-acetylberbamine (**8**). The presence of a methylenedioxy group also lowers the yield of the nitrogen-containing photolysis product, although not as severely as an hydroxyl. In the case of tenuipine (**23**), the same carbinolamino-lactam **11** was obtained as before, together with the dialdehyde **24** analogous to **13**, but with a methylenedioxy group instead of a methoxyl (Scheme 4). Nortenuipine (**21**) has both an hydroxyl and a methylenedioxy group, and in this case, no nitrogen-containing product at all could be isolated; however, *O*-acetylnortenuipine (**22**) gave a low yield of the carbinolamino-lactam **28**, from which the amino-lactam **29** could be obtained by borohydride reduction (Scheme 4). The structure of this product, the first to be isolated from the nitrogen-containing portion of this alkaloid, proved identical with the corresponding product from the *O,O*-diacetyl derivative **27** of aromoline, an alkaloid whose structure has been rigorously established (15) by degradation and by spectroscopy; the structures of tenuipine (**23**) and nortenuipine (**21**), which previously rested on spectroscopic evidence only, are thus also confirmed (6,16).

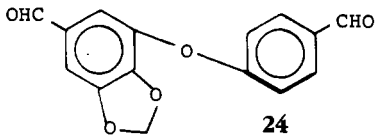


		R	A	B
21	Nortenuipine	H	*R*	*R*
22	*O*-Acetylnortenuipine	COMe	*R*	*R*
23	Tenuipine	Me	*R*	*R*

11/28 +

NaBH4

14/29

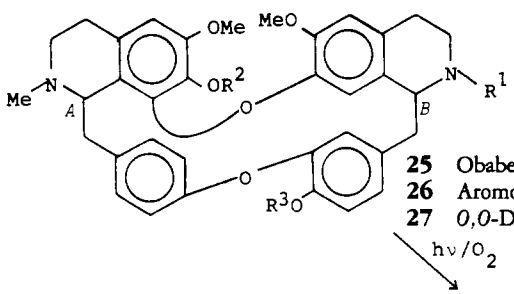


24

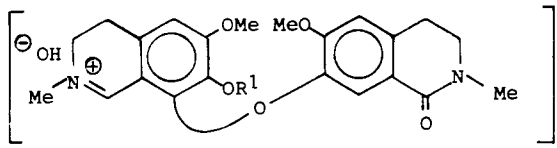
SCHEME 4

Obaberine (**25**) is structurally different from phaeanthine and isotetrandrine, with an alternative arrangement of the oxy substituents in rings E and F which results in a different shape of the molecule. Nevertheless, on oxidative photolysis, obaberine gave the same products **13** and **11**, the latter being isolated as the $NaBH_4$ reduction product **14** as before. It is evident that the oxidation levels in rings A and D, carbinolamine and lactam, respectively, are a function of the substitution patterns in rings B and C. Aromoline (**26**), which has two phenolic groups, may be photo-oxidised satisfactorily if the hydroxyls are first acetylated: thus, diacetylaromoline (**27**) gave **12** and **29** in reasonable yields (Scheme 5).

Nemuarine (**30**) has a unique structure with a 5-6′ ether link between the isoquinoline residues (17). Oxidative photolysis proceeded normally except that a small

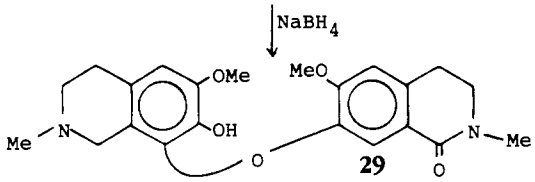


		R^1	R^2	R^3	*A*	*B*
25	Obaberine	Me	Me	Me	*S*	*R*
26	Aromoline	Me	H	H	*S*	*R*
27	*O,O*-Diacetylaromoline	Me	COMe	COMe	*S*	*R*



12/13

28 R^1=H or Ac



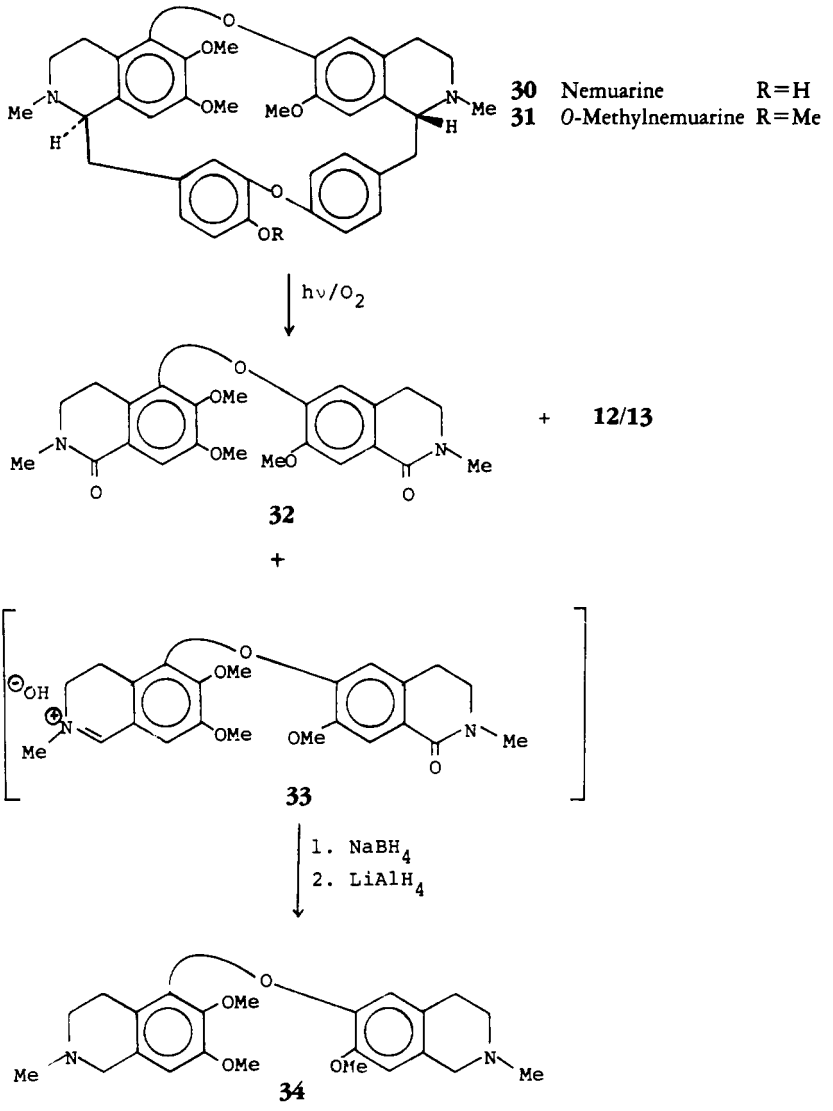
29

SCHEME 5

amount of a dilactam (**32**) was obtained in addition to a carbinolamino-lactam (**33**) and the dialdehyde **12**; *O*-methylnemuarine (**31**) behaved similarly to yield **13, 32,** and **33**. The latter compound was reduced first with borohydride, then with $LiAlH_4$ to give the diamine **34**, isomeric with **16** but differing from it in its spectroscopic properties (Scheme 6).

The diastereomeric alkaloids micranthine (**35**) (18) and apateline (**37**) (19) have a dibenzodioxin nucleus, which occasions difficulties in the standard Birch reduction method of degradation. The *O,N*-dimethyl derivatives of these bases, **36** and **38**, respectively, each gave on oxidative photolysis the dialdehyde **13** and the carbinolamino-lactam **40** in low yield (Scheme 7). The latter was reduced with $NaBH_4$ to the aminolactam **42** which was then further reduced with $LiAlH_4$ to the diamine **41**. In the experiment on *O,N*-dimethylapateline (*N*-methyltelobine, **38**) carried out under the same conditions as those described above, a small yield of the aminolactam **43** was obtained in addition to **42** and **13**; evidently, *N*-demethylation had taken place to some extent during the oxidative photolysis.

In order to locate the *N*-methyl groups in alkaloids of the micranthine and apateline series, and to clarify the relationship between these bases, methylated derivatives were prepared corresponding to **36** and **38** in which the protons of the *N*-methyl groups R^1 were partially substituted by deuterium. On oxidative photolysis of *O,N*-dimethylapateline (*N*-methyltelobine) labeled in this way (**39**), an aminolactam (cf. **42**) was obtained which was deuterated in the same position as that obtained from the analogue of **36** that had been labeled by the same procedure (18): thus, micranthine and apateline have the same structure in the upper parts of their molecules. The ^{1}H-nmr spectra of both **42** and its labeled analogue showed one aromatic proton singlet resonating at much lower field than the other two. This signal can be attributed to a proton that lies in the deshielding zone of the amide carbonyl and must thus be located at the 8′ position; the carbonyl itself must be at position 1′ in ring D, as in the case of the above-

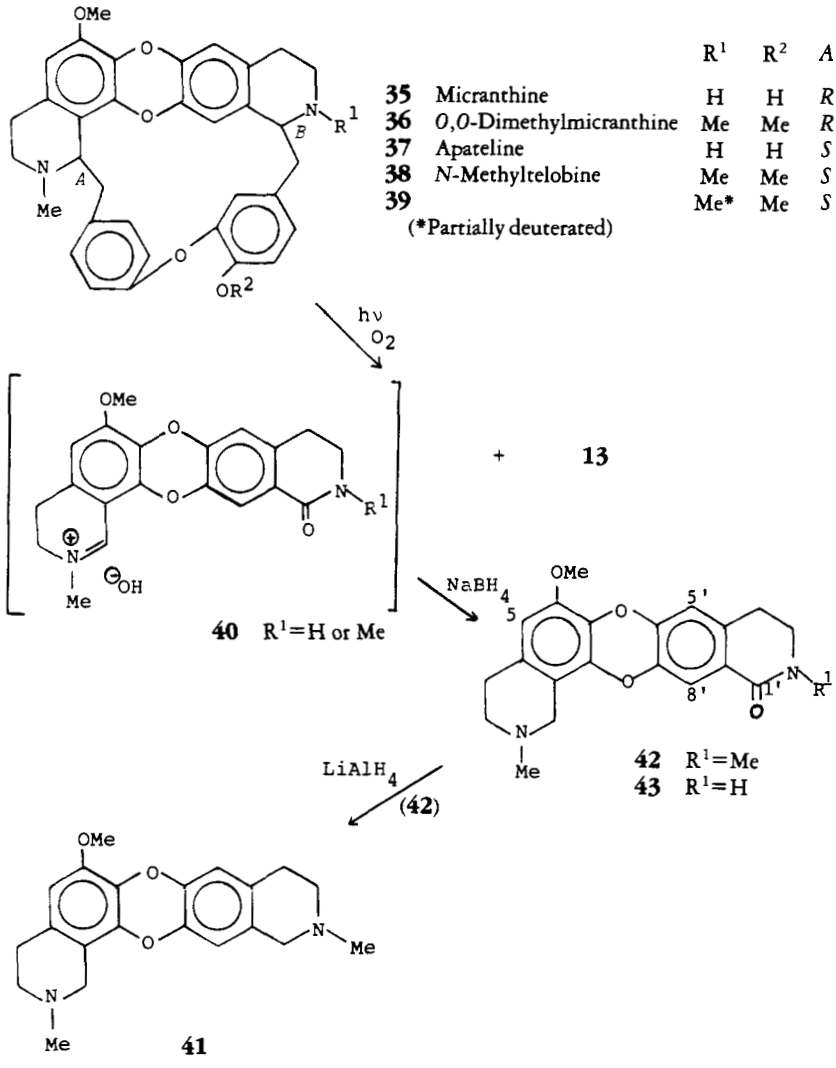


SCHEME 6

mentioned aminolactams **2** and **29**. Furthermore, the signal due to the partially deuterated *N*-methyl group in the labeled aminolactam (cf. **42**) is likewise shifted downfield to a considerable extent: this *N*-methyl group must be adjacent to the carbonyl, at position 2′ of ring D. This location was confirmed by the fact that the aminolactam **43** showed no *N*-methylamide signal.

Cycleanine (**44**) has a symmetrical structure of the head-to-tail type; on oxidative photolysis it gave one product only, the carbinol-amino-aldehyde **45** (Scheme 8). This substance was reduced to the corresponding aminoalcohol **46**, which was characterized by conversion to the acetylated and quaternized derivative **48**. No lactam-type product of oxidative photolysis could be detected, in harmony with the substitution pattern of **44** and with the products of photolysis of the head-to-head, tail-to-tail type alkaloids.

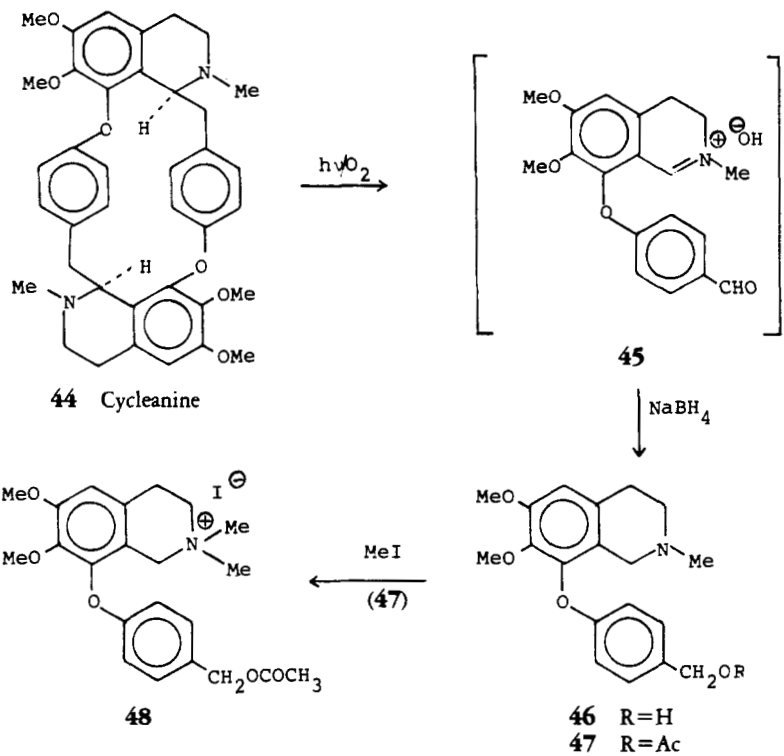
Another type of biscoclaurine alkaloid which is not amenable to degradation by the Birch reduction is that with a diphenyl link, such as phlebicine (**49**). On oxidative photolysis of its *O,O*-dimethyl derivative followed by borohydride reduction, the products obtained were **14** and a known diphenyldiol, thus establishing directly the princi-



SCHEME 7

pal features of the structure (20). The presence of a hindered phenolic group that cannot be alkylated, as in thalibrunine (**50**), also interferes with the Birch reduction of diphenylether links. On oxidative photolysis of **50** followed by reduction with zinc and acid, the diamine **51**, a methoxyl derivative of **16**, was isolated, and its structure was proved by synthesis (21). The structure of the lower half of thalibrunine was revised later on the basis of further degradative studies (5).

The mechanism of the photo-oxidative cleavage of laudanosine and the bisbenzylisoquinoline alkaloids has been examined in some detail (12,22), and the results will be presented in other papers. Uncertainties still remain, although singlet oxygen does not appear to be involved, and the availability of the lone pair of electrons on each nitrogen is necessary for the reaction to proceed. It is possible that more than one mechanism is operative. Further, although the iminium salt forms of the carbinolamines are represented in this paper as giving rise to the respective tetrahydroisoquinoline moieties on subsequent reduction, studies on a simple model system suggest the situation may be more complicated than this.



44 Cycleanine

45

46 R=H
47 R=Ac

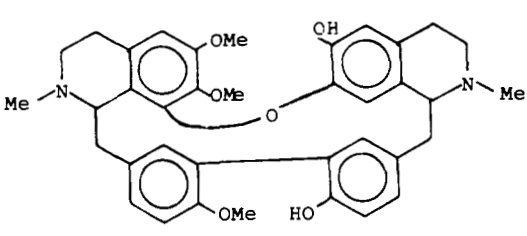
48

SCHEME 8

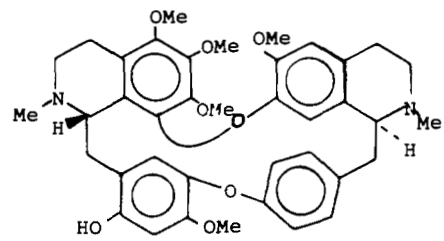
The oxidation level obtained in the tetrahydroisoquinolyl moieties does seem to be influenced largely by the oxygenation pattern in the aromatic ring components. Ether substitution capable of stabilizing the salt form, when both *ortho* and *para* to this functionality, hinders further oxidation to the lactam, inasmuch as this is believed to proceed via the carbinolamine derivative of the salt. However, exceptions do exist as with the nitrogen-containing cleavage product from thalibrunine (21). While further studies are necessary to fully clarify the mechanisms involved, the usefulness of the photo-oxidative cleavage as a degradative method is established.

EXPERIMENTAL

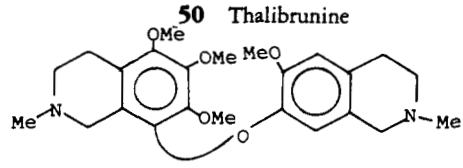
GENERAL EXPERIMENTAL PROCEDURES.—Melting points were determined on a Yanagimoto Seisakusho Micro-Melting Point apparatus and are uncorrected. Tlc and preparative tlc were carried out on



49 Phlebicine



50 Thalibrunine



51

Merck silica gel GF_{254}. Ir spectra were determined on a Perkin-Elmer Spectrometer Model 221. Absorption bands are described as strong (s), medium (m), or weak (w) in intensity. Frequencies are in cm^{-1}. Nmr spectra were recorded with a JEOL Model JNM-4H-100 Spectrometer at 100 MHz in $CDCl_3$ unless otherwise specified, with TMS as internal standard. Chemical shifts are given in δ values, and coupling constants in Hz. Peaks are described as singlet (s), doublet (d), triplet (t), quartet (q), or multiplet (m).

Microanalyses were determined by the CSIRO Microanalytical Laboratories, Melbourne. Owing to the small quantities of many of the bisbenzylisoquinoline alkaloids available, microanalysis was not feasible in certain instances. Hrms was used where possible in such cases to determine molecular formulae. These spectra were run on an AEI MS 902 or VG MM 70 70F instrument at 70 eV with a source temperature of 150° or 200°, by the direct insertion technique. Low-resolution ms was run on an EAI Quad 300, employing an inlet temperature of 250° and an electron beam energy of 70 eV. Intensities are given in parentheses as percentages of base peak intensity.

GENERAL IRRADIATION PROCEDURE.—Irradiation was conducted at room temperature (25°) in a water-cooled immersion-type photochemical reactor provided with a Hanovia 450 Watt medium pressure mercury arc lamp with glass filter sleeves. The solution was stirred magnetically during the entire irradiation. The photolyses were monitored by tlc. To remove any carbonyl-containing material, the AR MeOH and $CHCl_3$ used in the photolyses and for separation of products were freshly distilled over $NaBH_4$.

PREPARATION OF COMPOUNDS FOR PHOTOLYSIS.—*Laudanosine* (**1**).—(±)-Laudanosine was prepared by Mirza's method (23) and used in the racemic form.

O,O-*Diacetylaromoline* (**27**).—To a solution of aromoline (2 g, 3.4×10^{-3} mol) in pyridine (30 ml) under reflux, Ac_2O (4 ml, 4×10^{-2} mol) was added dropwise. When the addition was complete, the solution was refluxed for 6 h, then cooled to room temperature and neutralized with a 10% solution of NH_4OH. The mixture was extracted with $CHCl_3$, and the extract was washed twice with H_2O, then evaporated to dryness. The residue was purified by preparative tlc with $CHCl_3$-MeOH (9:1) as solvent. The major fraction gave *O,O*-diacetylaromoline (1.9 g, 83%) as a colorless solid, mp 140-145°; ^{1}H nmr 1.38 (s, $COCH_3$), 2.26 (s, $COCH_3$), 2.52 (s, NCH_3), 2.63 (s, NCH_3), 2.50-3.53 (m, 14H), 3.65 (s, OCH_3), 3.72 (s, OCH_3), 5.53 (s, H-8), 6.20-.50 (m, 9ArH); ms *m/z* 678 (M^+). Found: 678.2966. Calcd. for $C_{40}H_{42}N_2O_8$: 678.2938. Calcd. for $C_{40}H_{42}N_2O_8$⅓ $CHCl_3$: C, 67.4; H, 5.94, N, 3.89. Found: C, 67.69; H, 5.93; N, 3.72%.

O-*Acetylnortenuipine* (**22**).—This compound was prepared by the same procedure as for *O,O*-diacetylaromoline in 95% yield, mp 160-165°; ^{1}H nmr 1.60 (s, $COCH_3$), 2.37 (s, NCH_3), 2.59 (s, NCH_3), 3.43 (s, OCH_3), 3.72 (s, OCH_3), 2.60-3.80 (m, 14H), 5.94-7.40 (m, ArH+O-CH_2-O); ms *m/z* 664 (M^+). Found: 664.2810. Calcd. for $C_{39}H_{40}N_2O_8$: 664.2781. Calcd. for $C_{39}H_{40}N_2O_8$½ $CHCl_3$: C, 68.42; H, 5.91; N, 4.09. Found: C, 68.34; H, 5.93; N, 4.02%.

PHOTOLYSIS OF LAUDANOSINE.—*Preparation of* **2, 3, 5** *and* **6**.—Laudanosine (217 mg, 6.45×10^{-4} mol) in MeOH (200 ml) was irradiated through Pyrex in the presence of oxygen for 3 h. The solution was concentrated, and the residue was subjected to preparative tlc with $CHCl_3$-MeOH (96:4) as solvent. The following fractions were isolated:

Fraction 1 (Rf=0.9) gave 3,4-dimethoxybenzaldehyde (**5**) as a colorless solid (65 mg, 66.5%) which was redissolved in Et_2O and washed once with H_2O. The Et_2O layer was dried over Na_2SO_4 and evaporated to a yellow oil which crystallized to give pale yellow needles, mp 41-43° [lit. (24) 43-44.5°]; ^{1}H nmr 3.95 (s, OCH_3), 3.99 (s, OCH_3), 6.99 and 7.47 (ABq, J_{AB}=8.5, H-5+H-6), 9.85 (s, CHO); ms *m/z* 166 (M^+).

Fraction 2 (Rf=0.75) gave a pale yellow solid (59 mg, 45.1%) which after recrystallization from EtOAc formed colorless needles of 3,4-dihydro-6,7-dimethoxy-2-methyl-1(2*H*)-isoquinolinone (**2**), mp 123-125°, alone or on admixture with an authentic sample (25); ir ($CHCl_3$) ν max 1644 (s, C=O); ^{1}H nmr 2.94 (t, *J*=7, 2H-4), 3.14 (s, NCH_3), 3.55 (t, *J*=7, 2H-3), 3.93 (s, 2×OCH_3), 6.64 (s, H-5), 7.61 (s, H-8); ms *m/z* 221 (M^+).

Fraction 3 (Rf=0.6) gave a pale yellow solid (16 mg), 12%) which was recrystallized from EtOAc to give 3,4-dihydro-6,7-dimethoxy-1(2*H*)-isoquinolinone (**3**), mp 170-172° [lit. (26,27) 172-173°]; ir (nujol) ν max 3200 (br, N-H), 1630 (s, C=O); ^{1}H nmr 2.92 (t, *J*=7, 2H-4), 3.58 (t, *J*=7, 2H-3), 3.94 (s, 2×OCH_3), 6.68 (s, H-5), 6.70 (br, NH), 7.58 (s, H-8); ms *m/z* 207 (100, M^+). Found: 207.0892. Calcd. for $C_{11}H_{13}NO_3$: 207.0895.

Fraction 4 (Rf=0.4) gave unchanged laudanosine (18 mg, 8.3%).

Fraction 5 (Rf=0.3) was obtained in an amount too small for further study.

Fraction 6 (base line) was left in contact with silica gel and 75% aqueous MeOH (30 ml), and the slurry was stirred with $NaBH_4$ (ca. 150 mg) for 12 h. More H_2O (20 ml) was added, and the mixture was

warmed on a water bath for 20 min, cooled to room temperature, then $CHCl_3$ (30 ml) was added. The mixture was stirred and filtered, and the silica gel was washed thoroughly with more $CHCl_3$. The $CHCl_3$ layer in the filtrate was separated, washed once with H_2O, and evaporated to give a colorless solid (52 mg, 42%). Recrystallization from Me_2CO-light petroleum gave 6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**6**), mp 83-84° [lit. (28) 83-84°]; ^1H nmr 2.46 (s, NCH_3), 2.60-2.90 (m, 2H-3+2H-4), 3.52 (s, 2H-1), 3.86 (s, $2\times OCH_3$), 6.52 (s, 1ArH), 6.61 (s, 1ArH); ms *m/z* 207 (M^+). Calcd. for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.24; H, 8.15; N, 6.60%.

PHOTOLYSIS OF BISBENZYLISOQUINOLINE ALKALOIDS.—*Photolysis of Isotetrandrine. Preparation of* **13, 15,** *and* **14**.—Isotetrandrine (**9**, 1.0 g, 1.61×10^{-3} mol) in MeOH (200 ml) was irradiated through Pyrex in the presence of oxygen until all the starting material had reacted (15 h). The solution was concentrated to 10 ml and subjected to preparative tlc with $CHCl_3$-MeOH (92:8) as solvent. Two major fractions were isolated:

Fraction 1 (Rf=0.85) gave a pale yellow solid (125 mg, 30.6%) which was recrystallized from light petroleum to give 3-(4′-formylphenoxy)-4-methoxybenzaldehyde (**13**) as colorless needles, mp 77-79°, alone or in admixture with an authentic sample (29,30); ^1H nmr 3.90 (s, OCH_3), 6.95-7.82 (m, 7ArH), 9.86 (s, CHO), 9.90 (s, CHO).

Fraction 2 (base line) was left in contact with silica gel and treated with 75% aqueous MeOH and a little concentrated NH_4OH. $NaBH_4$ (ca. 1 g) was added with stirring, and the slurry was stirred at room temperature overnight. More H_2O (50 ml) was added, the mixture was boiled on a water bath for 25 min, then cooled to room temperature, and $CHCl_3$ (50 ml) was added. The mixture was stirred and filtered, then the $CHCl_3$ layer was separated and evaporated to dryness. The residue was subjected to preparative tlc with $CHCl_3$-MeOH (92:8) as solvent. The fraction with Rf=0.4 gave the lactam aminoalcohol **15** (201 mg, 31.6%); ^1H nmr 2.46 (s, 2-NCH_3), 2.70-3.00 (m, $3\times CH_2$), 3.07 (s, 2′-NCH_3), 3.40-3.54 (m, CH_2), 3.58 (s, CH_2-O), 3.64 (s, OCH_3), 3.81 (s, OCH_3), 3.94 (s, OCH_3), 5.70 (br, OH), 6.55 (s, H-5), 6.72 (s, H-5′), 7.00 (br, NH), 7.21 (s, H-8′).

Upon recrystallization from aqueous alcohol, **15** was all converted to 3′,4′-dihydro-6′-methoxy-7′-[1,2,3,4-tetrahydro-6, 7-dimethoxy-2-methyl-(isoquinolin-8-yl)oxy]-2′-methyl-1′(2H)-isoquinolinone (**14**),[4] mp 128-130° (d); ir ($CHCl_3$) ν max 1645 (s, C=O); ^1H nmr 2.37 (s, 2-NCH_3), 2.60-3.00 (m, $3\times CH_2$), 3.05 (s, 2′-NCH_3), 3.44 (s, 2, H-1), 3.40-3.60 (m, 2H-3′), 3.66 (s, 7-OCH_3), 3.83 (s, 6′-OCH_3), 3.98 (s, 6-OCH_3), 6.54 (s, H-5), 6.71 (s, H-5′), 7.18 (s, H-8′); ms *m/z* 413 (100), $(M+1)^+$, 412 (81, M^+), 397 (65.5), 206 (39.5). Found: 412.1985. Calcd. for $C_{23}H_{28}N_2O_5$: 412.1997.

Reduction of the material from fraction 2 in the absence of NH_4OH gave the amino-lactam **14** directly.

Photolysis of other Bisbenzylisoquinoline Alkaloids and Derivatives.—Results from the photo-oxidation of these substances performed under similar conditions to those used for isotetrandrine are shown in Table 1. The isolation procedure for the *N*-containing upper halves was essentially the same as that for the photolysate from isotetrandrine, but with NH_4OH being omitted. In the case of nemuarine (**30**) and of *O*-methylnemuarine (**31**), the *N*-containing upper-half product **34** was isolated after further reduction with $LiAlH_4$.

PHYSICAL AND SPECTROSCOPIC DATA OF PRODUCTS IN TABLE 1 NOT PREVIOUSLY DESCRIBED.—*3-(4′-Formylphenoxy)-4,5-methylenedioxybenzaldehyde* (**24**).—mp 70.5-71.5° (H_2O/EtOH); Rf ($CHCl_3$-MeOH, 92:8)=0.8; ir ($CHCl_3$) ν max 3022 (w), 2920 (w), 2843 (w), 2794 (w), 2735 (w), 1692 (s), 1598 (s), 1500 (s), 1435 (s), 1378 (m), 1301 (s), 1232 (m), 1160 (s); ^1H nmr 6.08 (s, OCH_2O), 7.10 (d, J=8, H-2′+H-6′), 7.25 (s, H-2+H-6), 7.85 (d, J=8, H-3′+H-5′), 9.75 (s, CHO), 9.91 (s, CHO); ms *m/z* 270 (100, M^+), 269 (61), 256 (13.4), 86 (13.5), 84 (19). Found: 270.0526. Calcd. for $C_{15}H_{10}O_5$: 270.0526. Calcd. for $C_{15}H_{10}O_5$ ¼ H_2O: C, 65.57; H, 3.85. Found: C, 65.47; H, 4.02%.

3-(4′-Formylphenoxy)-4-hydroxybenzaldehyde (**12**),—mp 135-136° (H_2O/EtOH), Rf ($CHCl_3$-MeOH, 92:8)=0.7; ir ($CHCl_3$) ν max 3024 (w), 2967 (w), 2922 (w), 2830 (w), 2732 (w), 1694 (s), 1598 (s), 1440 (m), 1380 (m), 1310 (s), 1234 (m), 1162 (s); ^1H nmr 6.92-7.95 (m, 7ArH); 9.81 (s, CHO), 9.91 (s, CHO); ms *m/z* 242 (100, M^+), 241 (73), 213 (13), 120 (17). Found: 242.0573. Calcd. for $C_{14}H_{10}O_4$: 242.0578.

3′,4′-Dihydro-6′-methoxy-7′-{1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methyl-(isoquinolin-8-yl)oxy}-2′-methyl-1′(2H)-isoquinolinone (**29**).—mp 125-129° (d); Rf ($CHCl_3$-MeOH, 3:1)=0.6; ir (nujol) ν max 3300-3400 (br, OH), 1630 (s, C=O); ^1H nmr 2.37 (s, 2-NCH_3), 2.70 (m, 2H-4), 2.90 (m, 2H-4′+2H-3), 3.05 (s, 2′-NCH_3), 3.45 (s, 2H-1), 3.50 (m, 2H-3′), 3.82 (s, 6′-OCH_3), 3.98 (s, 6-OCH_3); 5.05 (br, OH), 6.49 (s, H-5), 6.71 (s, H-5′), 7.22 (s, H-8′); ms *m/z* 398 (M^+, 100), 397 (99), 384 (20), 383 (80), 367 (13), 355 (21), 354 (12), 340 (21), 329 (16), 324 (12), 301 (16), 291 (10), 283 (12), 245 (13), 237

[4]Primes are used for protons associated with rings C and D.

(11), 208 (26), 207 (55), 199 (16), 192 (70), 191 (22), 190 (23), 178 (10), 177 (13), 176 (11), 164 (12), 161 (23), 147 (21), 136 (13). Found: 398.1829. Calcd. for $C_{22}H_{26}N_2O_5$: 398.1811.

3',4'-Dihydro-7'-methoxy-6'-{3,4-dihydro-6,7-dimethoxy-2-methyl-1{(2H)-isoquinolon-5-yl)oxy}-2'-methyl-1'(2H)-isoquinolinone (**32**).—mp 67°; Rf ($CHCl_3$-MeOH, 9:1)=0.9; ^{1}H nmr 2.65-2.8 (m, CH_2), 3.09 (2×NCH_3), 3.4-3.6 (m, 2×CH_2), 3.7-3.9 (m, CH_2), 3.81 (OCH_3), 3.92 (OCH_3), 3.98 (OCH_3), 6.18 (s, 1H), 7.59 (s, 1H), 7.68 (s, 1H); ms *m/z* 426 (100, M^+), 424 (11), 383 (8), 352 (7), 220 (5), 219 (12), 213 (8). Found: 426.1788. Calcd. for $C_{23}H_{26}N_2O_6$: 426.1789. Compound **32** was difficult to obtain pure.

1',2',3',4'-Tetrahydro-7'methoxy-6'-{1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-(isoquinolin-5-yl)oxy}-2'-methyl-isoquinoline (**34**).—This compound was prepared from **33** by initial extraction from the silica gel and reduction with $NaBH_4$, followed by further reduction of the organic residue obtained after work up with $LiAlH_4$; the general procedure for this latter reduction was as described later for the preparation of **16**. Compound **34** was difficult to purify; Rf ($CHCl_3$-MeOH, saturated with NH_3, 7:1)=0.6; ^{1}H nmr 2.42 (s, NCH_3), 2.62 (s, NCH_3), 2.4-2.7 (m, 4×CH_2), 3.52 (m, 2×CH_2), 3.72 (s, OCH_3), 3.83 (s, OCH_3), 3.90 (s, OCH_3), 6.21 (s, ArH), 6.49 (s, ArH), 6.6 (s, ArH); ms *m/z* 399 (23), 398 (100, M^+), 397 (88), 383 (9), 367 (10), 206 (13), 198 (15), 178 (17), 177 (14), 176 (18). Found: 398.2173. Calcd. for $C_{23}H_{30}N_2O_4$: 398.2205.

6,7-Dimethoxy-2-methyl-8-(4'-hydroxymethylphenoxy)-1,2,3,4-tetrahydroisoquinoline (**46**).—mp 41-3° (d); Rf ($CHCl_3$-MeOH, 92:8)=0.5; ir ($CHCl_3$) ν max 3586 (m), 3360 (br), 2998 (m), 2936 (s), 2838 (w), 2794 (w), 1610 (s), 1580 (m), 1550 (s), 1460 (s), 1420 (m), 1355 (m), 1270 (m), 1232 (m), 1166 (m), 1120 (s), 1068 (m), 1013 (w); ^{1}H nmr 2.33 (s, NCH_3), 2.65 (m, 2H-4), 2.90 (m, 2H-3), 3.38 (s, 2H-1), 3.67 (s, OCH_3), 3.85 (s, OCH_3), 3.95 (br, OH), 4.51 (s, 2 benzylic H), 6.59 (s, H-5), 6.78 and 6.17 (AA'BB' q, J=8, 4ArH). Found: 329.1589 (M^+). Calcd. for $C_{19}H_{23}NO_4$: 329.1626.

1,2,3,4,3',4'-Hexahydro-6-methoxy-2,2'-dimethyl-p-dioxino{2,3-g: 5,6-h'}di-isoquinolin-1'(2H)-one (**42**).—mp 199-205°;[5] Rf($CHCl_3$-MeOH, 92:8)=0.4; ir ($CHCl_3$) ν max 1649 (s, C=O); ^{1}H nmr 2.48 (s, 2-NCH_3), 2.60-3.00 (m, 2H-3+2H-4+2H-4'), 3.14 (s, 2'-NCH_3), 3.40 (m, 2H-1+2H-3'), 3.80 (s, OCH_3), 6.30 (s, ArH), 6.70 (s, ArH), 7.58 (s, ArH); ms *m/z* 366 (M^+), 365 (47), 352 (26), 351 (21), 324 (22), 323 (100), 309 (26), 266 (13), 154 (12), 149 (13), 86 (24), 57 (13). Found: 366.1555. Calcd. for $C_{21}H_{22}N_2O_4$: 366.1579.

1,2,3,4,3'4'-Hexahydro-6-methoxy-2-methyl-p-dioxino{2,3-g: 5,6-h'}di-isoquinolin-1'(2H)-one (**43**). —mp 260-270° (MeOH), Rf ($CHCl_3$-MeOH, 92:8)=0.3; ir (KBr) ν max 3425 (w, N-H), 1665 (s, C=O); ^{1}H nmr (CD_3OD) 2.50 (s, NCH_3) 2.65-3.00 (m, 2H-3+2H-4+2H-4'), 3.38 (m, 2H-3'), 3.52 (s, 2H-1), 3.86 (s, OCH_3), 6.49 (s, ArH), 6.80 (s, H-5), 7.48 (s, ArH); ms *m/z* 352 (M^+). Calcd. for $C_{20}H_{20}N_2O_4.CH_3OH$: C, 65.61; H, 6.29; N, 7.29. Found: C, 66.01; H, 5.97.

MISCELLANEOUS REACTIONS.—*Sodium-Liquid NH_3 Reduction of* **14**.—A solution of **14** (23 mg, 5.58×10^{-5} mol) in a mixture of C_6H_6 (80 ml) and toluene (20 ml) was added to liquid NH_3 (300 ml). The mixture was stirred and sodium (ca. 200 mg) was added portionwise until a blue coloration persisted. Stirring was continued for 2 h, then NH_4Cl (500 mg) was added, and the solution was stirred until all the NH_3 had evaporated. Water (100 ml), then 5% NaOH solution (20 ml) were added and the C_6H_6 layer was separated, washed with H_2O, and evaporated to dryness. The residue was subjected to preparative tlc to give colorless needles of **6** (12 mg, 96%), identified by comparison of its mp and ^{1}H-nmr spectrum with those of an authentic sample (28).

The aqueous solution from the reaction mixture was neutralized with dilute HCl and extracted with $CHCl_3$. The $CHCl_3$ extract was evaporated to give a yellow oil which, after treatment with CH_2N_2, gave no **6** but a mixture of several components which were not further investigated.

Sodium-Liquid NH_3 Reduction of **2**.—A solution of **2** (160 mg, 7.24×10^{-4} mol) in C_6H_6-toluene (80-20 ml) was treated with liquid NH_3 and sodium in a manner similar to that for **14** above. Purification of the product by preparative tlc gave 3,4-dihydro-7-methoxy-2-methyl-1(2*H*)-isoquinolinone (**18**) as a pale yellow oil (132 mg, 95%); ir ($CHCl_3$) ν max 2937 (m), 2840 (w), 1642 (s), 1606 (s), 1570 (m), 1495 (s), 1430 (m), 1335 (m), 1280 (s), 1220 (w), 1140 (w), 1060 (w), 1030 (m), 776 (m); ^{1}H nmr 2.90 (t, J=7, 2H-4), 3.12 (s, NCH_3), 3.52 (t, J=7, 2H-3), 3.82 (s, OCH_3), 6.93 (dd, J=8 and 2, H-6), 7.05 (d, J=8, H-5), 7.59 (d, J=2, H-8); ms *m/z* 191 (M^+).

Reduction of **14** *with $LiAlH_4$*.—$LiAlH_4$ (15 mg, 3.95×10^{-4} mol) was stirred with sodium-dried THF (10 ml) under reflux. A solution of **14** (60 mg, 1.45×10^{-4} mol) in dry THF (20 ml) was added dropwise. After the addition was complete, the reaction mixture was refluxed with stirring for 3 h. EtOAc (2 ml) was then added and the solution was evaporated to dryness. The residue was redissolved in $CHCl_3$ (50 ml) and dilute HCl (50 ml). The acid layer was separated and basified with 10% NH_4OH, then extracted with

[5]Originally quoted in error as 99-105°, Bick *et al.* (18).

$CHCl_3$. Evaporation of the solvent gave a pale yellow solid which was purified by preparative tlc to give **16** (50 mg, 88%), mp 50-55° (d); ir ($CHCl_3$) ν max 2935 (m), 2830 (w), 2780 (w), 1630 (m), 1603 (s), 1498 (s), 1440 (w), 1410 (w), 1300 (w), 1268 (s), 1126 (s), 1050 (w), 1000 (w), 752 (m); ^{1}H nmr 2.38 (s, 2×NCH_3), 2.61 (m, 2H-4+2H-4′), 2.85 (m, 2H-3+2H-3′), 3.32 (s, 2H-1′), 3.42 (s, 2H-1), 3.68 (s, 7-OCH_3), 3.83 (s, 6′-OCH_3), 3.92 (s, 6-OCH_3), 6.17 (s, H-8′), 6.54 (s, H-5), 6.68 (s, H-5′); and ms *m/z* 398 (97, M^+), 397 (100), 367 (60), 206 (81). Found: 398.2203. Calcd. for $C_{23}H_{30}N_2O_4$: 398.2205.

When lithium aluminium deuteride was used instead of $LiAlH_4$, **17** was obtained in 90% yield; the ^{1}H-nmr spectrum was identical with that of **16** except for the absence of a peak at δ 3.32.

Sodium-Liquid NH_3 Reduction of **17**.—A solution of **17** (50 mg, 1.25×10^{-4} mol) in a mixture of C_6H_6-toluene (1:1, 100 ml) was stirred with liquid NH_3 (100 ml). Sodium (200 mg, 8.7×10^{-3} mol) was added portionwise until a blue coloration persisted. The solution was stirred for a further 2 h, then NH_4Cl (500 mg) was added, and the solution was stirred until all the NH_3 had evaporated. The residue was evaporated and redissolved in $CHCl_3$ and a little H_2O. The $CHCl_3$ layer was extracted with a 10% solution of NaOH, then evaporated to give crude **6**. The aqueous extract was neutralized with dilute HCl and extracted with $CHCl_3$ to give crude **19**. Purification of both products by preparative tlc gave **6** (25 mg, 96%) and **19** (18 mg, 74%). ^{1}H-nmr spectrum of **19**: 2.45 (s, NCH_3), 2.60-2.90 (m, 2H-3+2H-4), 3.85 (s, OCH_3); 6.58 (br s, 2ArH).

A solution of **19** (18 mg) in MeOH (5 ml) was treated twice with excess CH_2N_2. Evaporation of the solvent gave a yellow oil which was redissolved in $CHCl_3$ and extracted with dilute HCl. The acidic extract was neutralized with 10% NH_4OH, then extracted twice with $CHCl_3$. Evaporation of the $CHCl_3$ gave **20** as a pale yellow solid (18 mg, 98%) whose ^{1}H-nmr spectrum was identical with that of **6** except for the absence of a peak at δ 3.52.

Reduction of the Amino-lactam **42** *with $LiAlH_4$*.—$LiAlH_4$ (1.6 g) and the amino-lactam **42** (350 mg, 9.56×10^{-4} mol) were stirred in dry THF (50 ml) for 12 h. EtOAc (5 ml) was then added, and the solution was evaporated to dryness. The residue was partitioned between $CHCl_3$ (200 ml) and 5% aqueous HCl (200 ml), then filtered. The filtrate was neutralized with 10% NH_4OH and the $CHCl_3$ layer was separated, washed with H_2O, dried (Na_2SO_4), then evaporated to give a pale yellow solid which was subjected to preparative tlc with $CHCl_3$-MeOH (85:15) as solvent to yield 1,1′,2,2′,3,3′,4,4′-octahydro-6-methoxy-2,2′-dimethyl-p-dioxino [2,3-g: 5,6-h′]-di-isoquinoline (**41**) (227.5 mg, 68%); Rf=0.4; mp 135-145° (MeOH); ^{1}H nmr 2.41 (s, 2′-NCH_3), 2.47 (s, 2-NCH_3), 2.50-2.90 (m, 2H-3+2H-4+2H-3′+2H-4′); 3.42 (s, 2H-1′), 3.46 (s, 2H-1), 3.83 (s, OCH_3), 6.30 (s, H-8), 6.50 (s, H-5′), 6.69 (s, H-5). Ms *m/z* 352 (M^+).

6,7-Dimethoxy-2-methyl-8-(4′-acetoxymethylphenoxy)-1,2,3,4-tetrahydroisoquinoline (**47**).—Ac_2O (2 ml) was added dropwise to a solution of **46** (176 mg, 0.534 mmol) in pyridine (5 ml). The solution was stirred at room temperature for 24 h. Cold H_2O (5 ml) was added, then the mixture was made alkaline with concentrated NH_4OH and extracted with $CHCl_3$ (2×10 ml). The $CHCl_3$ extract was dried (Na_2SO_4), then evaporated to dryness and the residue was purified by preparative tlc ($CHCl_3$-4% MeOH). The acetate **47** (Rf=0.40) was isolated as a yellow oil (134 mg, 68%); ir (liquid film) ν max 1735 (s, ester C=O); ^{1}H nmr 2.0 (s, $COCH_3$), 2.40 (s, NCH_3), 2.65 (t, J=5, 2H-4), 2.93 (t, J=5, 2H-3), 3.40 (s, 2H-1), 3.70 (s, OCH_3), 3.86 (s, OCH_3), 5.04 (s, 2 benzylic H), 6.62 (s, H-5), 6.85 and 7.27 (AA′BB′ q, J=8, H-2′+H-3′+H-5′+H-6′). This compound was further characterized as its methiodide salt **48**.

6,7-Dimethoxy-2,2-dimethyl-8-(4′-acetoxymethylphenoxy)-1,2,3,4-tetrahydroisoquinolinium Iodide (**48**).—An excess of methyl iodide (2 ml) was added to a solution of **47** (96 mg, 0.258 mmol) in dry MeOH (10 ml). The mixture was refluxed for 2 h, then evaporated to dryness. The methiodide **48** was obtained as a pale yellow solid (86 mg, 65%) on crystallization from C_6H_6, mp 184-186°; ir (nujol) ν max 1735 (s, C=O), 1240 (s, OAc); ^{1}H nmr 2.05 (s, $COCH_3$), 3.25 (t, J=5, 2H-4), 3.45 (s, $N(CH_3)_2$), 3.64 (s, OCH_3), 3.88 (s, OCH_3), 4.22 (t, J=5, 2H-3), 4.46 (s, 2H-1), 5.00 (s, 2 benzylic H), 6.75 (s, H-5), 6.85 and 7.25 (AA′BB′ q, J_{AB}=8, H-2′+H-3′+H-5′+H-6′). Calcd. for $C_{22}H_{22}INO_5$: C, 51.47, H, 5.50, N, 2.72. Found: C, 51.13; H, 5.40; N, 2.61%.

ACKNOWLEDGMENTS

The award of Colombo Plan Scholarships to two of us (L.v.T. and P.W.) is gratefully acknowledged, together with a grant in support of this work from the Australian Research Grants Committee. We also thank Drs. J.K. MacLeod and Professor R.N. Warrener (ANU, Canberra) and Dr. C.P. Whittle (CSIRO, Canberra) for mass spectra.

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Received 8 May 1985