# Aryne Formation from 2-Bromolaudanosine. Fate of the 5,6,12,12a-Tetrahydrodibenzo[*b*,*g*]indolizinium Ion and an Alternative Synthesis of Glaucine

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A synthesis of 2-bromolaudanosine (**10**) is described. The aryne formed from **10** and amide ion in ammonia yields the corresponding 5,6,12,12a-tetrahydrodibenzo[*b*,*g*]indolizinium ion (**13**) by intramolecular capture, and 2-aminolaudanosine (**11**) by external addition of amide ion. Compound **13** is converted *in situ* to 5,6-dimethoxy-2-(4,5-dimethoxy-2-vinylphenyl)-1-methylindoline (**14**) and 5,6-dimethoxy-2-(4,5-dimethoxy-2-ethylphenyl)-1-methylindole (**15**). Compound **11** provides an alternative source of glaucine (**12**).

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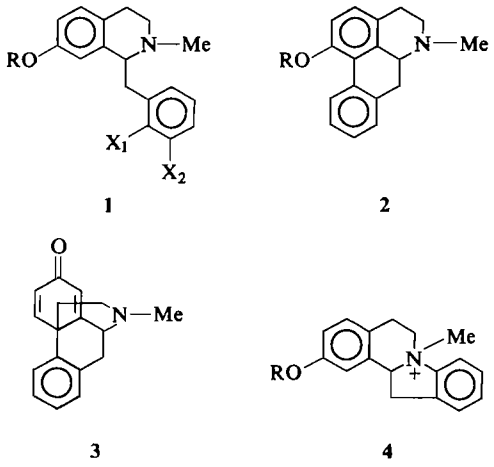
On décrit une synthèse de la bromo-2 laudanosine (**10**). L'aryne, qui se forme par réaction de **10** avec l'ion amidure dans l'ammoniac, conduit à l'ion correspondant tétrahydro-5,6,12,12a dibenzo[*b*,*g*] indolizinium (**13**) par capture intramoléculaire et à l'amino-2 laudanosine (**11**) par addition externe de l'ion amidure. On transforme *in situ* le composé **13** en diméthoxy-5,6 (diméthoxy-4,5 vinyl-2 phényl)-2 méthyl-1 indoline (**14**) et en diméthoxy-5,6 (diméthoxy-4,5 éthyl-2 phényl)-2 méthyl-1 indole (**15**). Le composé **11** s'avère une source de rechange pour la glaucine (**12**).

[Traduit par le journal]

The use of appropriately substituted 1-(2- or 3-halogenobenzyl)-1,2,3,4-tetrahydroisoquinolines (**1**) as sources of arynes for synthesis of modified 1-benzyl-1,2,3,4-tetrahydroisoquinoline alkaloids such as aporphines (**2**), morphinandienones (**3**), and 5,6,12,12a-tetrahydrodibenzo-[*b*,*g*]indolizinium salts (**4**)(Scheme 1) has attracted considerable attention in recent years.[1] Thus, cine-substitution via an aryne ($X_1$ = H, $X_2$ = Br → $X_1$ = $NH_2$, $X_2$ = H), coupled with Pschorr cyclization, has been used in synthesis of the aporphine alkaloid laureline (1), whilst direct aporphine formation from a phenolic precursor (R = H) has been achieved in a synthesis of domesticine (2). The possibility of aporphine and morphinandienone formation occurring from such a phenolic precursor (R = H) has also been explored, without success under the conditions initially employed (1*b*), but successfully at higher mole ratios (between 8 and 10 to 1) of sodamide or potassamide to halogenocompound (3, 4). Parallel routes have been used to synthesize 5,6,12,12a-tetrahydrodibenzo[*b*,*g*]-indolizinium salts, both via the corresponding tetrahydroindolizines (5, 6) and directly (4, 7).




SCHEME I

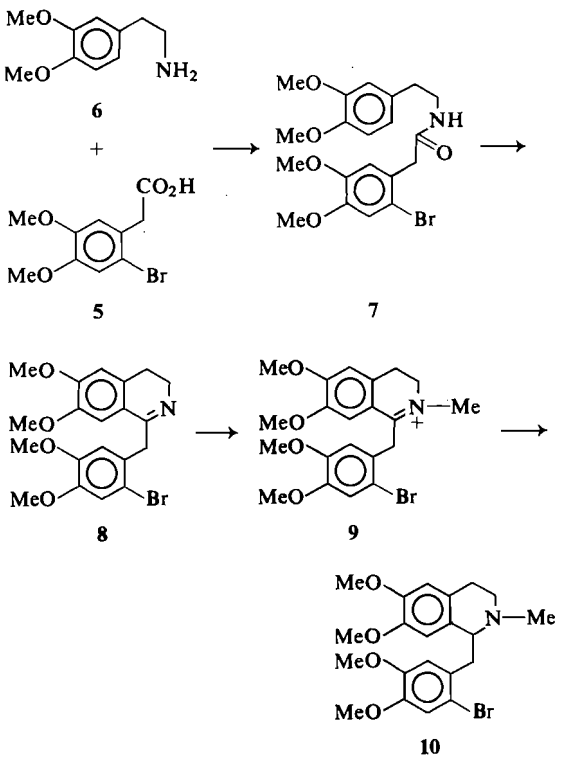
An aryne route has also been used for indoline synthesis associated with *Erythrina* alkaloid studies (8).

The formation and demise of 5,6,12,12a-tetrahydrodibenzo[*b*,*g*]indolizinium ions in potassamide-ammonia is important in leading to by-products in such aporphine syntheses (1). Direct evidence for formation of such ions under these conditions was provided in due course by Kametani *et al.* (7) using a 7-hydroxyisoquinoline

[1]Other substituents are omitted for simplicity in formulae **1–4**.

precursor, the cation produced being presumably stabilized by deprotonation of the phenolic group and regenerated during work-up; no Hofmann elimination was observed. Similar results have been reported by Kessar *et al.* (4). These workers also obtained indications of Hofmann elimination (1) when using a 6-hydroxyisoquinoline precursor although this case was complicated by accompanying dehydrogenation. The original problem of the behavior of non-phenolic 5,6,12,-12a-tetrahydrodibenzo[*b*,*g*]indolizinium ions in potassamide–ammonia is considered in the present communication.

The tetramethoxy series shown (Scheme 2) was chosen for examination. Bromination of 3,4-dimethoxyphenylacetic acid gave the bromo-acid **5** which was treated with thionyl (or oxalyl) chloride, followed by the amine **6**, to give the amide **7**. After cyclization of **7** with phosphoryl chloride in benzene, isolation of the product **8** as the iminium chloride **8***a* was most conveniently effected by treatment of the reaction mixture with anhydrous methanol. Treatment of **8** with methyl iodide gave **9** which was reduced with sodium borohydride to 2-bromolaudanosine (**10**), identical with material prepared by brominating a sample of (±)-laudanosine.




SCHEME 2

Aryne reactions of **10** were carried out both with potassamide and with sodamide in liquid ammonia and the products were isolated chromatographically. In order of elution, these were **A** ($C_{21}H_{25}NO_4$), **B** ($C_{21}H_{25}NO_4$), and **C** ($C_{21}H_{28}N_2O_4$).

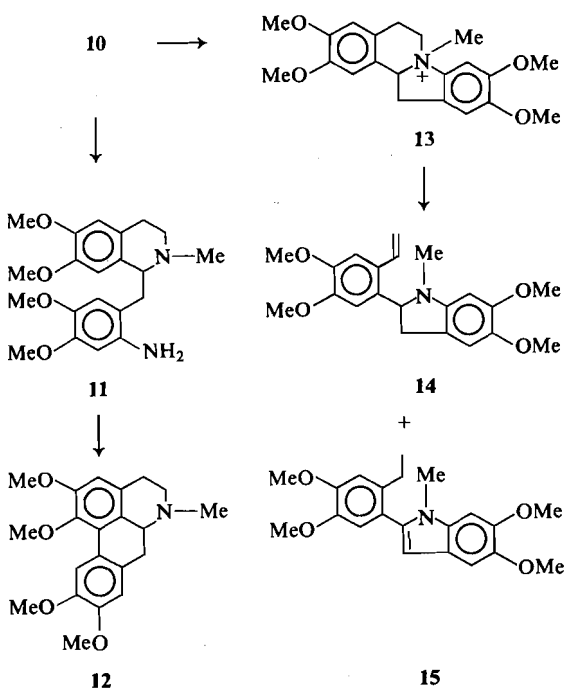
Compound **C** was recognized as the diamine **11** by melting point and i.r. spectral correlations and by known conversion to (±)-glaucine, **12**, (Scheme 3) which was characterized as the methiodide (9). External addition of amide ion to the aryne had thus occurred preferentially at the carbon atom remote from the methoxy-groups as expected (1); interestingly, 4-amino-veratrole had been previously identified as the main product from reaction of 4-bromoveratrole with potassamide in ammonia.[2]

Compound **B** proved to be the indoline **14**, identity being confirmed by comparison with an authentic sample prepared from **13** by conventional Hofmann elimination (10). The mass spectrum of **14** shows the $M-2$ fragment characteristically associated with indolines (dihydroindoles) which can undergo loss of hydrogen to give the corresponding indoles (6, 8). Contrary to earlier report, **14** forms a methiodide (10).

Compound **A**, the most interesting product, was identified as the indole **15**. This formulation is supported by the n.m.r. spectrum, which established *inter alia* the presence of an ethyl group, mass spectrum, and instantaneous positive Ehrlich reaction. Formation of **15** from **13** under analogous conditions was confirmed in a separate experiment.

It is clear that intramolecular addition of the tertiary nitrogen atom to the aryne will compete with other possible internal or external nucleophilic additions in these reactions. The likely fate of the resulting tetrahydrodibenzoindolizinium ion (unless otherwise stabilized) is Hofmann elimination to give the corresponding indoline.[3] The isomeric indole presumably arises from isomerization of the indoline, or of its conjugate base followed by reprotonation, under the reaction conditions though these mechanisms have yet to be distinguished experimentally. There is

[2]M. S. Gibson and G. W. Prenton. Unpublished results.
[3]Available data on the (impure) laureline by-product are consistent with this view.




SCHEME 3

no direct evidence for alternative Hofmann elimination to give a nine-membered ring, but we subscribe to the view that any such process might pass unnoticed owing to protonation and recyclization to the indolizinium ion, *e.g.* during workup (4). Some phenolic indolizinium ions survive potassamide–ammonia treatment (*i.e.* do not undergo Hofmann elimination), as noted above (4, 7).

The indolizinium salt **13** was required during this work, necessitating a reexamination of the reaction of 2-bromotetrahydropapaverine with sodamide in ammonia. This has been reported to yield the desired 5,6,12,12a-tetrahydrodibenzo[*b*,*g*]indolizine together with its product of oxidation, the 5,6-dihydrodibenzo[*b*,*g*]indolizine (6). We were not able to isolate the former compound satisfactorily using the published procedure and have found it expedient to collect the two products together, concentrate the former, and quaternize with methyl iodide to give the indolizinium salt **13**. The relative ease of oxidation of the tetrahydro- to the dihydroindolizines (cf. oxidation of indolines to indoles) is presumably a cause of difficultly reproducible yields in these reactions and *ipso facto* of discrepancies in yields reported in syntheses of 5,6,12,12a - tetrahydrodibenzo[*b*,*g*]indolizinium alkaloids (5, 6).

## Experimental

Proton magnetic resonance spectra were recorded on a Varian A-60 spectrometer using tetramethylsilane as internal standard. Mass spectra were determined with an AEI-MS30 double-beam double-focusing mass spectrometer.

Liquid ammonia was distilled from potassium chips prior to use.

*2-Bromo-4,5-dimethoxyphenylacetic Acid, 5*

The published method (11) was modified as follows. A solution of bromine (4.2 g) in glacial acetic acid (25 ml) was added dropwise to a stirred solution of 3,4-dimethoxyphenylacetic acid (5.0 g) in acetic acid (20 ml) with external cooling in ice water. The resulting slurry was heated at 60 °C for 20 min and then poured into ice water with stirring. The precipitate was filtered off and washed with aqueous sodium bisulfite solution and water. Crystallization from aqueous ethanol (50%) gave the bromo-acid **5** as needles (5.0 g, 71%), m.p. 117–118 °C (lit. (11) m.p. 113–114 °C).

*N-(3,4-Dimethoxyphenethyl)-2-bromo-4,5-dimethoxyphenylacetamide, 7*

2-Bromo-4,5-dimethoxyphenylacetic acid **5** (5.0 g) was converted to the acid chloride by reaction with $SOCl_2$ (6.5 ml) in dry benzene (20 ml). After removal of excess $SOCl_2$ and benzene *in vacuo*, the acid chloride was dissolved in ether (25 ml) and added during 15 min to a stirred solution of 3,4-dimethoxyphenethylamine **6** (4.3 ml) in ether (70 ml) and 40% (w/v) aqueous NaOH solution (4 ml). The resulting mixture was poured into water (250 ml) with stirring and the p*H* was adjusted to 8–9. The precipitate was filtered off, washed with water, and dried. Crystallization from benzene–ethanol gave the *amide* **7** as needles (6.7 g, 84%), m.p. 161–162 °C.

Anal. Calcd. for $C_{20}H_{24}BrNO_5$: C, 54.80; H, 5.52; N, 3.20 Found: C, 54.86; H, 5.43; N, 3.14.

*1-(2-Bromo-4,5-dimethoxybenzyl)-3,4-dihydro-6,7-dimethoxyisoquinolinium Chloride, 8a*

A solution of **7** (5.0 g) in dry benzene (11 ml) and freshly distilled $POCl_3$ (7.5 ml) was heated under reflux (steam bath) for 3.5 h under dry nitrogen. Excess $POCl_3$ was destroyed by dropwise addition of anhydrous methanol (35 ml) to the cooled solution until the vigorous reaction subsided, when more methanol (15 ml) was added to ensure completion. After 1 h, the mixture was poured into ether (400 ml) and, after chilling, the precipitate was filtered off, washed with ether, and dried. Crystallization from ether–methanol gave the *iminium chloride* **8a** (4.8 g, 92%) as a hemi-solvate, m.p. 232–234 °C; i.r. (KBr) 1655 $cm^{-1}$ ($\rangle C{=}\overset{+}{N}-$). Alternative attempts at crystallization resulted in yellowing of the sample.

Anal. Calcd. for $C_{20}H_{23}BrClNO_4 \cdot \frac{1}{2}CH_3OH$: C, 52.07; H, 5.32; N, 2.96. Found: C, 51.76; H, 5.10; N, 3.07.

*1-(2-Bromo-4,5-dimethoxybenzyl)-3,4-dihydro-2-methyl-6,7-dimethoxyisoquinolinium Iodide, 9*

The iminium chloride **8a** (2.5 g) was shaken with ammonium hydroxide (25 ml, *d* 0.88), water (10 ml), and benzene (100 ml) until the solid disappeared. The benzene layer was separated, washed with water, dried ($K_2CO_3$), and evaporated. The residual base was dissolved in

methanol (5 ml) and methyl iodide (7 ml) was added. After 48 h, the crystalline *iminium iodide* **9** (3.0 g, 97%) was filtered off. Crystallization from acetonitrile gave pale yellow orthorhombic crystals, m.p. 246–247 °C (dec.); i.r. (KBr) 1630 $cm^{-1}$ ($\backslash C{=}\overset{+}{N}-$).

Anal. Calcd. for $C_{21}H_{25}BrINO_4$: C, 44.86; H, 4.48; N, 2.49. Found: C, 44.67; H, 4.41; N, 2.45.

*1-(2-Bromo-4,5-dimethoxybenzyl)-1,2,3,4-tetrahydro-2-methyl-6,7-dimethoxyisoquinoline [(±)-2-Bromolaudanosine], 10*

To a stirred suspension of the iminium iodide **9** (2.5 g) in methanol (125 ml) and water (15 ml) was added $NaBH_4$ (2 g) in very small portions. The yellow color slowly faded. The solution was then stirred for 6 h at room temperature followed by 30 min at reflux. Solvents were evaporated and the residue was treated with water, made basic (NaOH), and extracted with ether. The ether extract was washed, dried ($K_2CO_3$), and evaporated to give (±)-2-bromolaudanosine **10** (1.5 g, 77%), which crystallized from ethanol as needles, m.p. 122–124 °C identical with a sample (m.p. 123–124 °C) prepared by Dr. G. W. Prenton by brominating (±)-laudanosine.

Anal. Calcd. for $C_{21}H_{26}BrNO_4$: C, 57.80; H, 5.96; Br, 18.18; N, 3.18. Found: C, 57.8; H, 6.1; Br, 18.2; N, 3.3.

*Aryne Reaction of 2-Bromolaudanosine, (a), with Potassamide, (b), with Sodamide in Ammonia*

(*a*) A solution of (±)-2-bromolaudanosine **10** (4.5 g) in anhydrous tetrahydrofuran (35 ml) was added slowly to a stirred solution of potassamide, prepared from potassium (14 g), in liquid ammonia (300 ml). The resulting reddish-brown mixture was stirred in refluxing ammonia for 6 h and ammonium chloride (35 g) was then added in portions. Ammonia was allowed to evaporate overnight under a stream of nitrogen and the residue was then treated with water (80 ml) and extracted with benzene (total; 800 ml). The benzene extract was washed with water, dried ($K_2CO_3$), and evaporated to give a dark brown oil which contained at least five components (t.l.c.).

The oil was chromatographed on neutral alumina using benzene as eluant. One component concentrated in the first eluates (totalling 900 ml). Evaporation *in vacuo* gave a pale yellow oil which was dissolved in ethanol (5 ml) and kept overnight to give colorless crystals (0.4 g, 11%) of *5,6-dimethoxy-2-(4,5-dimethoxy-2-ethylphenyl)-1-methylindole*, **15**, m.p. 132–133 °C; n.m.r. ($CDCl_3$) δ 7.11 (s, 1H, aromatic proton), 6.86 (s, 2H, aromatic protons), 6.79 (s, 1H, aromatic proton), 6.32 (s, 1H, aromatic proton), 3.96 (s, 3H, OMe), 3.91 (s, 6H, OMe), 3.82 (s, 3H, OMe), 3.46 (s, 3H, NMe), 2.49 (q, $J$ = 8.0 Hz, 2H, $CH_2CH_3$), and 1.09 (t, $J$ = 8.0 Hz, 3H, $CH_2CH_3$); mass spectrum *m/e* 355 ($M^+$), 340 ($M - CH_3$), 190 ($C_{11}H_{12}NO_2$), 177.5 ($M^{2+}$), and 165 ($C_{10}H_{13}O_2$); u.v. $\lambda_{max}$ (methanol) 304 (log ε 4.03) and 220 nm (4.36). Compound **15** gave an immediate violet coloration when treated with a cold solution of *p*-dimethylaminobenzaldehyde in ethanol and HCl (Ehrlich's reagent), and did not form a methiodide when treated with methyl iodide.

Anal. Calcd. for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 71.24; H, 7.37; N, 3.74.

Further elution with benzene–ether (9:1) gave eluates (totalling 700 ml) which were evaporated *in vacuo* to yield a pale yellow oil which crystallized slowly after addition of a few drops of methanol. Recrystallization from methanol gave colorless aggregates (0.1 g, 2.7%) of 5,6-dimethoxy-2-(4,5-dimethoxy-2-vinylphenyl)-1-methylindoline, **14**, m.p. 125–127 °C, identical with a sample prepared as described below; mass spectrum *m/e* 355 ($M^+$), 353 ($M - 2$), 340 ($M - CH_3$), 338, 324, 312, 310, 201, 192 ($C_{11}H_{14}NO_2$), 180, 177.5 ($M^{2+}$), 177, 165, 162, 161, 146 and 136; u.v. $\lambda_{max}$ (methanol) 306 (log ε 3.85) and 258 nm (4.20).

Elution was continued, increasing the proportion of ether in the eluting mixture to benzene–ether (2:1). Evaporation of these eluates *in vacuo* gave a yellow oil which crystallized slowly from methanol (20 ml) to give colorless needles (1.35 g, 35%), m.p. 142–144 °C, of 1-(2-amino-4,5-dimethoxybenzyl)-1,2,3,4-tetrahydro-2-methyl-6,7-dimethoxyisoquinoline, **11**, identical (mixture m.p., t.l.c., i.r. spectrum) with a sample from a previous experiment.

From a previous similar experiment using 2-bromolaudanosine (2.0 g), compound **11** was isolated according to an earlier procedure (9). The product was decolorized (charcoal) and crystallized three times from methanol to give colorless needles (0.3 g, 18%) of **11**, m.p. 144 °C (lit. (9) m.p. 144–145 °C); the i.r. spectrum corresponded with published data.

(*b*) A solution of 2-bromolaudanosine (4.0 g) in anhydrous tetrahydrofuran (35 ml) was added slowly to a stirred solution of sodamide, prepared from sodium (15 g), in liquid ammonia (375 ml). The brown mixture was stirred for 5 h and ammonium chloride (50 g) was then added in portions. The mixture was then worked up as in the foregoing experiment to give a brown oil which contained, as above, at least five components (t.l.c.).

Chromatography (Florisil–benzene) gave, from the first eluates, a pale yellow oil which crystallized slowly after addition of a few drops of ethanol to give the indole **15** (0.08 g, 2.5%), m.p. 132–133 °C, identical with the foregoing sample (mixture m.p., i.r. and u.v. spectra, t.l.c., and Ehrlich reaction).

Further elution (benzene–ether) gave a pale yellow oil which crystallized, as above, from methanol to give the indoline **14** (0.8 g, 25%), m.p. 125–127 °C, identical with a sample prepared as described below.

Next eluted was a small amount of unidentified reddish material, followed (ether as eluant) by **11** (0.3 g, 8%), m.p. 143–145 °C, identical with the foregoing sample (mixture m.p., t.l.c., i.r. spectrum).

*1,2,9,10-Tetramethoxyaporphine [(±)-Glaucine], 12*

Compound **11** was converted to glaucine **12** as described by Kametani and Noguchi (9) and was characterized as the methiodide (2–3% overall), m.p. 216 °C (lit. (9) m.p. 218–220 °C); mass spectrum *m/e* 370 ($M^+$), 369 ($M - 1$), 355 ($M - CH_3$), 354, 340, 324, 312, 165, 152, 142 ($CH_3I$), 128 (HI), and 127 (I). The u.v. spectrum was identical with that reported.

*1-(2-Bromo-4,5-dimethoxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline [(±)-2-Bromotetrahydropapaverine]*

Sodium borohydride (1.6 g) was added in small portions to a stirred solution of the iminium chloride **8***a* (2.0 g) in methanol (50 ml) and water (7 ml). After 8 h at room temperature followed by 1 h at reflux, solvents were evaporated *in vacuo* and the solid residue was

treated with water, made basic (NaOH), and the mixture was extracted with ether. The ether solution was washed, dried ($K_2CO_3$), and evaporated to give 2-bromotetrahydropapaverine as plates (1.7 g, 89%), m.p. 112 °C (lit. (12) m.p. 111 °C). Infrared and n.m.r. data corresponded with those reported.

*Aryne Reaction of 2-Bromotetrahydropapaverine: 5,6-Dihydro-2,3,9,10-tetramethoxydibenzo[b,g]indolizine and 5,6,12,12a-Tetrahydro-2,3,9,10-tetramethoxy-7-methyldibenzo[b,g]indolizinium Iodide*

(*a*) The published procedure (6) was first followed, but from the complex mixture only the dihydroindolizine (2–5%), m.p. 200–202 °C, could be isolated; none of the desired iodide was obtained when the mixture was treated with methyl iodide.

From a similar experiment with 2-bromotetrahydropapaverine (5.0 g), the crude product was chromatographed on Florisil using benzene and benzene–ether as eluants to give an oil; this was treated with methyl iodide (15 ml) in benzene (5 ml) to give the desired iodide which crystallized from acetonitrile as colorless needles (0.6 g, 10.5%), m.p. 243–245 °C (dec.), identical with the product from the following procedure.

(*b*) A solution of 2-bromotetrahydropapaverine (5.0 g) in dry tetrahydrofuran (45 ml) was added slowly to a stirred solution of potassamide, prepared from potassium (14 g) in liquid ammonia (500 ml). After 5 h, ammonium chloride (35 g) was added and the reaction products were isolated using benzene as in the cases described above. The brown oil thus obtained was chromatographed on Florisil using benzene and benzene–ether (6:1) as eluants and the 5,6-dihydro- and 5,6,12,12a-tetrahydroindolizines were collected together (volume eluted, 900 ml). Evaporation *in vacuo* and crystallization of the pale yellow residue from ethanol gave the 5,6-dihydroindolizine as colorless scales (0.92 g, 23%), m.p. 201–202 °C (lit. (6) m.p. 202–204 °C); the mass spectrum corresponded with that reported. The ethanolic mother liquor was evaporated *in vacuo* and the residue was treated with methyl iodide (15 ml) in benzene (7 ml). The 5,6,12,12*a*-tetrahydroindolizinium iodide, **13**, crystallized from acetonitrile as needles (1.4 g, 25%), m.p. 243–245 °C (dec.) (lit. (6) m.p. 243–245 °C (dec.)); identity was confirmed by mass spectral correlation.

*Formation of 5,6-Dimethoxy-2-(4,5-dimethoxy-2-ethylphenyl)-1-methylindole, **15** from the 5,6,12,12a-Tetrahydroindolizinium Iodide, **13***

Compound **13** (0.5 g) was added to a stirred solution of potassamide, prepared from potassium (2 g), in liquid ammonia (100 ml) and dry tetrahydrofuran (5 ml). After 5.5 h, ammonium chloride (10 g) was added and the mixture was worked up in the normal way to give a brown oil. Thin layer chromatography showed the presence of at least four components, resembling those obtained (with the exception of **11**) from reaction of 2-bromolaudanosine and potassamide under similar conditions. The oil was chromatographed on Florisil using benzene and benzene–ether as eluants. Fractions containing **15** (t.l.c.) were collected and evaporated. Addition of a few drops of ethanol to the pale yellow oil led to the slow crystallization of the indole **15** (20 mg, 5.5%), m.p. 132–133 °C, identical (mixture m.p., t.l.c., and mass spectrum) with the foregoing sample.

*5,6-Dimethoxy-2-(4,5-dimethoxy-2-vinylphenyl)-1-methylindoline and -1,1-dimethylindolinium Iodide*

The published procedure (10) was modified as follows. Potassium hydroxide (6.0 g) was added to a boiling solution of **13** (0.25 g) in water (21 ml) and the mixture was refluxed for 6 h, cooled, and extracted with ether. The ether solution was washed, dried ($K_2CO_3$), and evaporated *in vacuo* to give a pale yellow oil which crystallized slowly after addition of a few drops of methanol. Recrystallization from methanol gave the indoline **14** (0.16 g, 87%), m.p. 126–127.5 °C (lit. (10) m.p. 125–126 °C). The indoline produced a violet coloration slowly when heated with Ehrlich's reagent, presumably as a result of conversion to an indole derivative. Identity of the various samples of **14** was established by mixture m.p., t.l.c., and spectral correlations.

Methyl iodide (2.5 ml) was added to a solution of **14** (0.1 g) in benzene (0.75 ml). After 28h at *ca.* 40 °C, the crystalline deposit was collected and crystallized from acetonitrile to give *5,6-dimethoxy-2-(4,5-dimethoxy-2-vinylphenyl)-1,1-dimethylindolinium iodide* as colorless needles (0.13 g, 93%), m.p. 214–215 °C; the mass spectrum showed *m/e* 369 ($M^+ - 1$), 355 ($M^+ - CH_3$), 354, 353, 340, 338, and 326.

Anal. Calcd. for $C_{22}H_{28}INO_4$: C, 53.13; H, 5.67; N, 2.82. Found: C, 53.48; H, 5.57; N, 3.01.

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