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# THE BIOSYNTHESIS OF THE ALKALOIDS OF *CORYDALIS MEIFOLIA* WALL.

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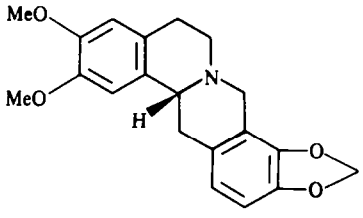
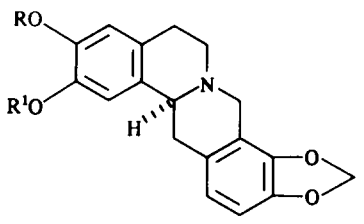
**Abstract**—Tracer experiments show that corlumine, cavidine and yenhusomine are stereospecifically biosynthesized from (*R*)-(−)-reticuline.

*Corydalis meifolia* Wall. (Papaveraceae), a perennial herb, grows at an altitude of 12,000–15,000 ft in the Himalayan region.[1] The extract of the plant is used by the natives in the treatment of various ailments.[2] The leaves and stems of the plant have been extensively investigated for their alkaloidal constituents[3] and the alkaloids isolated are: tetrahydroprotoberberines, (+)-sinactine (**1**), stylopine (**2**), cheilanthifoline (**3**), (+)-cavidine (**4**), apocavidine (**5**) and dehydrocavidine (**6**); spirobenzylisoquinolines, yenhusomine (**11**) and yenhusomidine (**7**); phthalideisoquinoline, corlumine (**12**); benzophenanthridine, dihydrosanguinarine (**8**) and protopine (**9**). (+)-Cavidine, protopine, corlumine, yenhusomine and dehydrocavidine exhibited spasmolytic activity.[3] Ochotensine, an alkaloid that occurs in many *Corydalis* species stimulates isolated muscles of rabbit uterus and induces a fall in blood pressure in anaesthetized cats.[4]

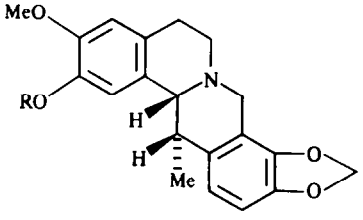
Biogenetically, all the alkaloids isolated so far, from *C. meifolia* could be derived in nature from suitably substituted 1-benzyltetrahydroisoquinoline precursors. Tracer experiments have shown that the



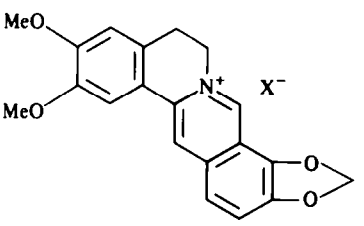
**1**



**2** R = R₁ = −CH₂−
**3** R = Me, R¹ = H



**4** R = Me
**5** R = H



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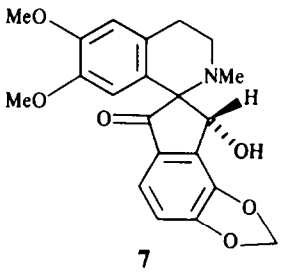

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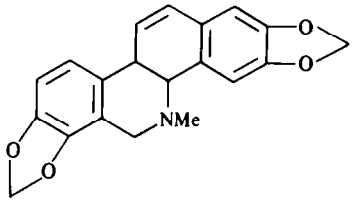


**8**

phthalideisoquinoline alkaloids such as hydrastine and narcotine are specifically derived in nature from the 1-benzylisoquinoline (+)-reticuline.[5] (*S*)-Scoulerine,[5] isocorypalmine[6] and canadine[6] were also shown to be the precursors of narcotine. Further the conversion of scoulerine into narcotine involves removal of a 13-pro-*s*-hydrogen atom.[7] It has been proved firmly that 13-methyltetrahydroprotoberberine such as corydaline and the spirobenzylisoquinoline alkaloid, ochotensine and benzophenanthridine alkaloid sanguinarine are all structural variants of the 1-benzylisoquinoline skeleton[8] and reticuline is the precursor of corydaline alkaloids. Further (*S*)-scoulerine is shown to be specifically incorporated into sanguinarine.

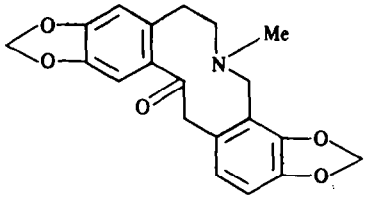
The biosyntheses of phthalideisoquinoline alkaloid, corlumine (12), 13-methyltetrahydroprotoberberine alkaloid, (+)-cavidine (4) and spirobenzylisoquinoline alkaloid, yenhusomine (11) have not been studied. We now report the results of tracer experiments that have been carried out on these alkaloids.

Initial feeding of (L)-[U-$^{14}$C]tyrosine (experiment 1) to young cut branches of *Cocculus laurifolius* DC. (Menispermaceae) plant demonstrated that the plants were actively biosynthesizing cavidine (4), yenhusomine (11) and corlumine (12).

Feeding of tyrosine in parallel with labelled (±)-norreticuline (13) (experiment 2) and (±)-reticuline (14) (experiment 3) demonstrated that 13 and 14 were efficient precursors of 4, 11 and 12.

Feeding of labelled protosinomenine (15) (experiment 4), nororientaline (16) (experiment 5) and norlaudanidine (17) (experiment 6) established that 15–17 were very poorly metabolized by the plant to form cavidine (4), yenhusomine (11) and corlumine (12).

The regiospecificity of $^{14}$C-label in the biosynthetic cavidine (4) derived from the feeding of (±)-N-[$^{14}CH_3$]reticuline (experiment 7) was established as follows. Labelled cavidine (4) was oxidized with $I_2$/alcohol to afford dehydrocavidine (6) with essentially the same molar activity as the parent base. Compound 6 was then treated with phenylmagnesium bromide to give 8-phenyldihydrocavidine (27) with



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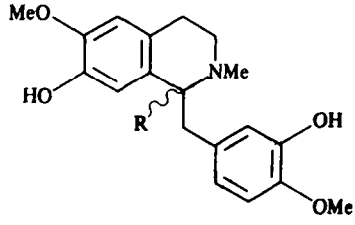
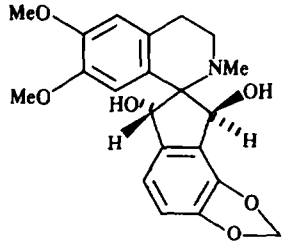
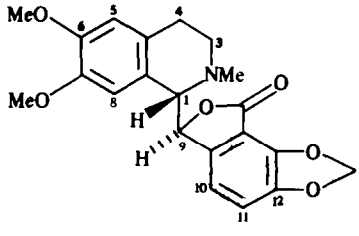


**10a** R = —— H
**10b** R = ıılı H



11



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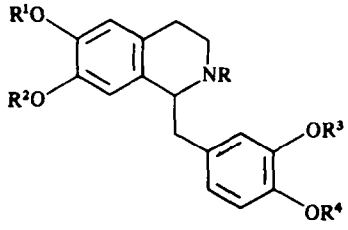


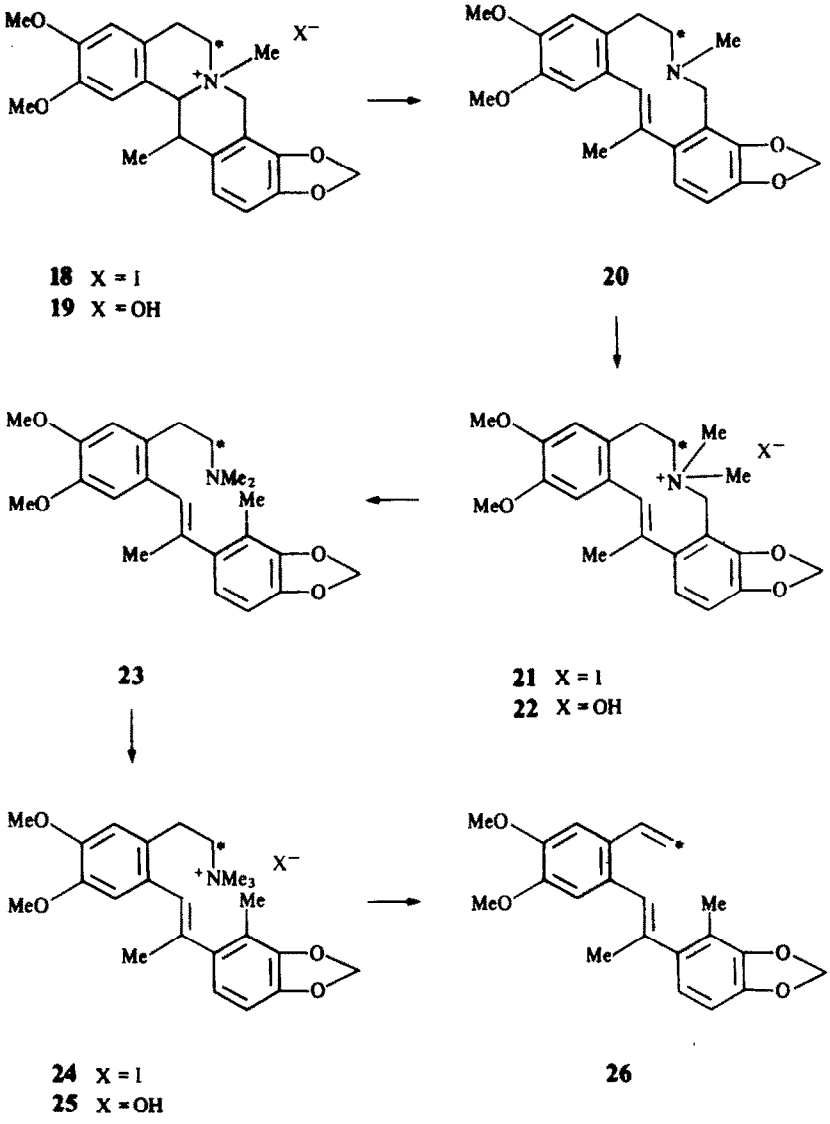
**13** R = $R^2$ = $R^3$ = H; $R^1$ = $R^4$ = Me
**14** R = $R^1$ = $R^4$ = Me; $R^2$ = $R^3$ = H
**15** R = $R^2$ = $R^4$ = Me; $R^1$ = $R^3$ = H
**16** R = $R^2$ = $R^4$ = H; $R^1$ = $R^3$ = Me
**17** R = $R^3$ = H; $R^1$ = $R^2$ = $R^4$ = Me

essentially no loss of activity. Kuhn–Roth oxidation of **27** in the usual way furnished radioactive benzoic acid (96% activity of original).

Feeding of (±)-[1-$^{3}$H,3-$^{14}$C]norreticuline (**13**) (experiment 8) gave labelled cavidine (**4**), yenhusomine (**11**) and corlumine (**12**). The $^{14}C/^{3}H$ ratio in the precursor was 1 : 9, whereas in **4**, **11** and **12**, it was 1 : 7.8, 1 : 2 and 1 : 8, respectively. The results thus established that the H atom at the asymmetric centre $C_{13a}$ in **4** and **12** remain untouched during the biotransformation of **13** into **4** and **12** whereas it is lost during the biotransformation into **11**. The results were thus in agreement with the suggested biogenetic pathway for yenhusomine (**11**).

The regiospecificity of the label in the biosynthetic cavidine derived from (±)-[1-$^{3}$H, 3-$^{14}$C]norreticuline (experiment 8) was demonstrated as follows. Labelled **4** was converted into its methiodide (**18**) and then into its methohydroxide form (**19**) with essentially no loss of radioactivity. Hofmann degradation of **19** yielded the methine-I (**20**) which had essentially the same radioactivity as that of the parent base. Compound **20** was treated with MeI to afford methine methiodide (**21**) which was passed through amberlite IR-410 anion exchange resin to give the corresponding methohydroxide (**22**). Treatment of **22** with Raney Ni gave the methine-II (**23**) with essentially the same molar radioactivity as the parent base. Radioactive **23** was converted first into its corresponding methiodide (**24**) and then into the methohydroxide (**25**). Hofmann degradation of **25** afforded methine-III (**26**) with essentially no loss of radioactivity. Ozonolysis of **26** furnished radioactive formaldehyde (dimedone derivative, 90% activity of original).

The regiospecificity of the $^{14}$C label in the biosynthetic corlumine (**12**) derived from the feeding of (±)-[1-$^{3}$H, 3-$^{14}$C]norreticuline (experiment 8) was demonstrated as follows. Reductive cleavage of the biosynthetic corlumine (**12**) with Zn/HCl gave radioactive O-methylcorypalline (**28**) with essentially the same molar activity. Compound **28** was converted into its methiodide **29** and then to the corresponding




**18** X = I
**19** X = OH

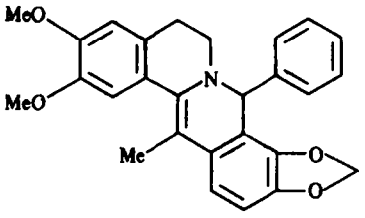
**20**

**21** X = I
**22** X = OH

**23**

**24** X = I
**25** X = OH

**26**



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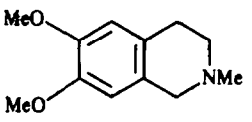

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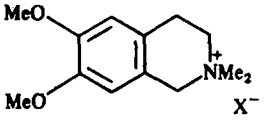
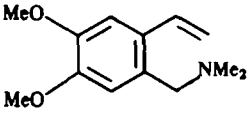


29 X = I
30 X = OH



31

methohydroxide (30). Hofmann degradation of 30 gave radioactive methine (31) with essentially the same molar activity as that of the parent base. Ozonolysis of 31 afforded labelled formaldehyde (dimedone derivative, 98% of original activity).

Feeding of (±)-[1-$^3$H, 4'-O-$^{14}CH_3$]norreticuline (13) (experiment 9) gave labelled cavidine (4), yenhusomine (11) and corlumine (12). Biosynthetic cavidine (4) derived from (±)-[1-$^3$H, 4'-O-$^{14}CH_3$]norreticuline (experiment 9) was heated with HCl. The liberated radioactive formaldehyde was trapped as formaldehyde-dimethone (98% of original activity). Similarly the methylenedioxy groups of the biosynthetic corlumine (12) and yenhusomine (11) derived from (±)-[1-$^3$H, 4'-O-$^{14}CH_3$]norreticuline (13) feeding, were cleaved to furnish formaldehyde-dimethone (96 and 97% activity of original, respectively).

Parallel feedings of (*S*)-(+)- and (*R*)-(−)-reticulines demonstrated that the (*R*)-(−)-enantiomer was incorporated more efficiently than the (*S*)-(+)-enantiomer.

(*R*)-Reticuline does exist in the plant and it is specifically incorporated into (+)-cavidine (4), yenhusomine (11) and corlumine (12), hence, reticuline is a true precursor of these alkaloids.

## EXPERIMENTAL

For general directions (spectroscopy details and counting method) see Ref. 9.

*Syntheses of precursors.* The racemates of norlaudanosoline derivatives (13–17),[9–12] (*S*)- and (*R*)-reticulines[13] were prepared as described earlier.

*Labelling of precursors.* Specifically labelled 1-benzyltetrahydroisoquinoline precursors were prepared by base-catalysed tritiation. Nonspecifically labelled protosinomenine was prepared by acid-catalysed tritiation. (±)-[3-$^{14}$C]Norreticuline (13), (±)-[N-$^{14}CH_3$]reticuline (14), (±)-[4'-O-$^{14}CH_3$]norreticuline (13) and (±)-[1-$^3$H]norreticuline (13) were prepared by the procedure described earlier.

*Feeding experiments.* The labelled precursors were dissolved in $H_2O$ (1 ml) containing tartaric acid (5 mg). Freshly cut young branches of *Cocculus laurifolius* DC. (Menispermaceae) plant were dipped into the soln of the precursor. When uptake of the precursor was complete, $H_2O$ was added for washing the precursor. The twigs were then dipped in $H_2O$ and kept alive for 6–7 days to metabolize the precursor.

### *Isolation of alkaloids*

*Cavidine* (4). Young cut branches and leaves (typically 600 g wet wt) of *C. laurifolius* were macerated in EtOH (250 ml) with radioinactive 4 (100 mg) and left overnight. The EtOH was then decanted and the plant material was percolated with EtOH (4 × 200 ml). The combined ethanolic percolate was

Table 1. Tracer experiments on *C. laurifolius*

| Expt No. | Precursor fed | Percentage incorporation into (+)-Cavidine (4) | Corlumine (12) | Yenhusomine (11) |
|---|---|---|---|---|
| 1 | (L)-[U-$^{14}$C]Tyrosine | 0.017 | 0.02 | 0.03 |
| 2 | (±)-[3-$^{14}$C]Norreticuline (13) | 0.16 | 0.25 | 0.13 |
| 3 | (±)-[2',6',8-$^3H_3$]Reticuline (14) | 0.22 | 0.65 | 0.70 |
| 4 | (±)-[Aryl-$^3$H]Protosinomenine (15) | 0.002 | 0.001 | 0.001 |
| 5 | (±)-[5',8-$^3H_2$]Nororientaline (16) | 0.001 | 0.002 | 0.001 |
| 6 | (±)-[2',6'-$^3H_2$]Norlaudanidine (17) | 0.007 | 0.001 | 0.003 |
| 7 | (±)-N-[$^{14}CH_3$]Reticuline (14) | 0.62 | 0.35 | 0.485 |
| 8 | (±)-[1-$^3$H, 3-$^{14}$C]Norreticuline (13) ($^{14}$C/$^3$H ratio 1:9.1) | 0.5 ($^{14}$C) (1:8) | 0.4 ($^{14}$C) (1:7.8) | 0.3 ($^{14}$C) (1:2.1) |
| 9 | (±)-[1-$^3$H, 4'-O-$^{14}CH_3$]Norreticuline (13) ($^{14}$C/$^3$H ratio 1:13.2) | 0.7 ($^{14}$C) (1:12) | 0.3 ($^{14}$C) (1:11.4) | 0.4 ($^{14}$C) (1:1.8) |
| 10 | (*S*)-(+)-[2',6',8-$^3H_3$]Reticuline | 0.03 | 0.07 | 0.12 |
| 11 | (*R*)-(−)-[2',6',8-$^3H_3$]Reticuline | 0.21 | 0.15 | 0.42 |

concentrated *in vacuo* to afford a greenish viscous mass which was extracted with 5% HCl (4 × 20 ml). The acidic extract was defatted with n-hexane (4 × 15 ml) and basified with $Na_2CO_3$. The liberated bases were extracted with $CHCl_3$ (4 × 25 ml), washed with water, dried and the solvent removed. The crude base (130 mg), so obtained, was purified by preparative TLC (plates: silica gel, solvent: $CHCl_3$–MeOH, 99.5:0.5). The desired band was cut and eluted with $CHCl_3$–MeOH (80:20) to give cavidine (**4**) (70 mg), m.p. 144–145° (lit.[14] 145°). The radiochemical purity of the base was checked by the dilution method.

*Corlumine* (**12**). Young cut branches (typically 120 g wet wt) of *C. laurifolius* were macerated in EtOH (250 ml) with **12** (90 mg). The plant material was worked up as above to give $CHCl_3$ soluble crude base (120 mg) which was subjected to preparative TLC (plates: silica gel, solvent: $CHCl_3$–MeOH, 97:3) to afford **12** (60 mg), m.p. 155° (lit.[15] m.p. 155°).

*Yenhusomine* (**11**). Young cut branches (typically 110 g wet wt) of *C. laurifolius* were macerated in EtOH (300 ml) with **11** (90 mg). The plant material was worked up in the usual way to give chloroform soluble crude base (100 mg) which was subjected to preparative TLC (plates: silica gel, solvent: $CHCl_3$–MeOH, 94:6) to furnish **11** (55 mg), m.p. 125–126° (lit.[16] m.p. 126°).

*Degradations*

(1) *Biosynthetic cavidine* (**4**) *derived from* (±)-[1-$^3$H, 4'-O-$^{14}CH_3$]*norreticuline*. A soln of labelled **4** (180 mg) (molar activity $5.48 \times 10^3$ disint $min^{-1}$ $mmol^{-1}$) and dimedone (405 mg) in conc HCl (7.2 ml) was heated in a sealed tube at 120° for 18 hr. The mixture was then cooled, diluted with $H_2O$ (50 ml) and extracted with ether. The ether extract was washed with 5% $NaHCO_3$ aq and then with $H_2O$, dried ($Na_2SO_4$) and evaporated. The residue was purified over silica gel column. Elution with $C_6H_6$–$CHCl_3$ (3:1) afforded pure formaldehyde-dimethone, crystallized from MeOH–$Et_2O$ to constant activity, m.p. 186–188° (lit.[17] m.p. 188°) (molar activity $5.37 \times 10^3$ disint $min^{-1}$ $mmol^{-1}$) (98% of original activity).

(2) *Biosynthetic corlumine* (**12**) *derived from* (±)-[1-$^3$H, 4'-O-$^{14}CH_3$]*norreticuline*. Radioactive **12** (190 mg) (molar activity $2.3 \times 10^4$ disint $min^{-1}$ $mmol^{-1}$) was cleaved as described above to furnish formaldehyde-dimethone (molar activity $2.20 \times 10^4$ disint $min^{-1}$ $mmol^{-1}$) (96% of original activity).

(3) *Biosynthetic yenhusomine* (**11**) *derived from* (±)-[1-$^3$H, 4'-O-$^{14}CH_3$]*norreticuline*. Labelled **11** (molar activity $1.90 \times 10^4$ disint $min^{-1}$ $mmol^{-1}$) was treated with conc HCl as described earlier to afford radioactive formaldehyde-dimethone ($1.84 \times 10^4$ disint $min^{-1}$ $mmol^{-1}$) (97% of original activity).

(4) *Biosynthetic cavidine* (**4**) *derived from* N-[$^{14}CH_3$]*reticuline*. Labelled **4** (155 mg) (molar activity $3.58 \times 10^3$ disint $min^{-1}$ $mmol^{-1}$) in EtOH (4.5 ml) was refluxed with $I_2$ (160 mg) to furnish *dehydrocavidine* **6** (145 mg) (molar activity $3.52 \times 10^3$ disint $min^{-1}$ $mmol^{-1}$), m.p. 248–250° (MeOH) (lit.[3] m.p. 248–252°). The preceding radioactive **6** was treated with phenylmagnesium bromide to give 8-*phenyldihydrocavidine* **27**, m.p. 154–156° (molar activity $3.48 \times 10^3$ disint $min^{-1}$ $mmol^{-1}$). MS: *m/e* 427 ($M^+$). (Found: C, 75.86; H, 5.82; N, 3.26. Calc for $C_{27}H_{25}NO_4$: C, 75.88; H, 5.85; N, 3.28%.)

Kuhn–Roth oxidation of **27** in the usual way afforded radioactive benzoic acid (molar activity $3.43 \times 10^3$ disint $min^{-1}$ $mmol^{-1}$) (96% of original activity).

(5) *Biosynthetic cavidine* (**4**) *derived from* [3-$^{14}$C]*norreticuline*. Radioactive **4** (500 mg) (molar activity $1.58 \times 10^3$ disint $min^{-1}$ $mmol^{-1}$) in MeOH (10 ml) was refluxed with MeI (6 ml) for 24 hr to give the *cavidine methiodide* **18** (650 mg) (molar activity $1.60 \times 10^3$ disint $min^{-1}$ $mmol^{-1}$), m.p. 195° (MeOH); $\lambda_{max}$(MeOH): 208 and 290 nm; $\nu_{max}$(KBr): 1610, 1510, 1460, 1250 and 1055 $cm^{-1}$; NMR ($CDCl_3$ + DMSO-$d_6$): $\delta$ 0.91 (d, 3H, CH—C$\underline{H}_3$, J = 7 Hz), 3.33 (N—C$\underline{H}_3$), 3.84 (s, 6H, 2 × OC$\underline{H}_3$) and 6.0 (s, 2H, O—C$\underline{H}_2$—O); MS: *m/e* 353 ($M^+$). (Found: C, 53.01; H, 5.00; N, 2.80. Calc for $C_{22}H_{25}NO_4I$: C, 53.33; H, 5.05; N, 2.83%.)

A soln of the preceding radioactive **18** in MeOH was passed through a column of freshly generated IR-410 anion exchange resin ($OH^-$ form) to furnish the corresponding labelled *methohydroxide* (**19**). Radioactive **19** was refluxed with KOH (14 g in 10 ml $H_2O$) for 4 hr to afford the labelled *cavidine methine-I* (**20**) (380 mg), purified by preparative TLC (plates: silica gel, solvent: $CHCl_3$–MeOH, 98:2). Pure biosynthetic **20** was crystallized from MeOH–$C_6H_6$, m.p. 156–158° (molar activity $1.57 \times 10^3$ disint $min^{-1}$ $mmol^{-1}$); $\lambda_{max}$(MeOH): 325, 288 and 206 nm; $\nu_{max}$(KBr): 3300, 1580, 1440, 1240 and 1100 $cm^{-1}$; NMR ($CDCl_3$): $\delta$ 1.8 (s, 3H, —C=C—C$\underline{H}_3$), 2.18 (N—C$\underline{H}_3$), 3.86 and 3.88 (2 × OC$\underline{H}_3$) and 5.90 (s, 2H, O—C$\underline{H}_2$—O); MS: *m/e* 367 ($M^+$). (Found: C, 71.90; H, 6.72; N, 3.75. Calc for $C_{22}H_{25}NO_4$: C, 71.93; H, 6.81; N, 3.81%.)

The foregoing methine-I (**20**) in MeOH (10 ml) was refluxed with MeI (5 ml) for 8 hr to furnish the *cavidine methylmethine methiodide* **21** (420 mg) (molar activity $1.52 \times 10^3$ disint $min^{-1}$ $mmol^{-1}$), m.p. 201–202° (MeOH): $\nu_{max}$(KBr): 2910, 1630, 1600, 1510, 1460 and 1220 $cm^{-1}$; NMR ($CDCl_3$ + DMSO-$d_6$): $\delta$ 1.90 (s, 3H, —C=C—C$\underline{H}_3$), 3.08 (N—$CH_3$), 3.55 (N—C$\underline{H}_3$), 3.79 (s, 6H, 2 × OC$\underline{H}_3$) and 6.07 (s, 2H, O—C$\underline{H}_2$—O); MS: *m/e* 367 ($M^+ - 142$). (Found: C, 54.20; H, 5.48; N, 2.74. Calc for $C_{23}H_{28}NO_4I$: C, 54.22; H, 5.50; N, 2.75%.)

The corresponding methohydroxide **22** was prepared by passing a soln of **21** in MeOH through a column of freshly generated amberlite IR-410 anion exchange resin ($OH^-$ form).

The foregoing labelled **22** in NaOH aq (50%, 15 ml) was treated with Raney Ni (3 g) and refluxed for 2.5 hr. Worked up in the usual manner to afford the *cavidine methine-II* **23** (280 mg) (molar activity $1.55 \times 10^3$ disint $min^{-1}$ $mmol^{-1}$), m.p. 102–103° ($CHCl_3$–MeOH); $\lambda_{max}$(MeOH): 290, 260 and 204 nm; $\nu_{max}$(KBr): 2950, 1600, 1510, 1460 and 1240 $cm^{-1}$; NMR($CDCl_3$): $\delta$ 1.92 (s, 3H, C$\underline{H}_3$—Ar), 2.21 (s, 9H, 2 × N—C$\underline{H}_3$ and —C(H)=C—C$\underline{H}_3$), 3.81 (s, 6H, 2 × OC$\underline{H}_3$) and 5.88 (s, 2H, O—C$\underline{H}_2$—O); MS: *m/e* 383 ($M^+$). (Found: C, 72.00; H, 7.44; N, 3.83. Calc for $C_{23}H_{29}NO_4$: C, 72.06; H, 7.57; N, 3.65%.)

The preceding labelled **23** in MeOH was refluxed with MeI (3 ml) for 6 hr to afford radioactive *cavidine methine-II methiodide* **24** (300 mg) (molar activity $1.50 \times 10^3$ disint $min^{-1}$ $mmol^{-1}$), m.p. 138–140° (MeOH); $\lambda_{max}$(MeOH): 290, 268 and 202 nm; $\nu_{max}$(KBr): 3450, 1620, 1515, 1465 and 1220 $cm^{-1}$; NMR($CDCl_3$ + DMSO-$d_6$): $\delta$ 1.9 (s, 3H, C$\underline{H}_3$—Ar), 2.15 (s, 3H, —C(H)=C—C$\underline{H}_3$), 3.3 (s, 9H, 3 × N—C$\underline{H}_3$), 3.74 (OC$\underline{H}_3$) and 3.86 (OC$\underline{H}_3$) and 5.86 (s, 2H, O—C$\underline{H}_2$—O); MS: *m/e* 383 ($M^+ - 142$). (Found: C, 54.82; H, 6.06; N, 2.64. Calc for $C_{24}H_{32}NO_4I$: C, 54.85; H, 6.09; N, 2.66%.)

The foregoing labelled **24** was then converted into the corresponding *methohydroxide* **25** in the usual manner. Radioactive **25** was refluxed with KOH (6.8 g in 9.5 ml $H_2O$) for 4 hr to afford the *cavidine methine-III* **26**, m.p. 232–235° ($CHCl_3$–MeOH) (120 mg) (molar activity $1.44 \times 10^3$ disint $min^{-1}$ $mmol^{-1}$); $\lambda_{max}$(MeOH): 290, 270 (s) and 202 nm; $\nu_{max}$(KBr): 2910, 1600, 1560, 1500, 1460 and 1240 $cm^{-1}$; NMR($CDCl_3$): $\delta$ 1.85 (s, 3H, C$\underline{H}_3$—Ar), 2.17 (s, 3H, —C(H)=C—C$\underline{H}_3$), 3.81 (OC$\underline{H}_3$) and 3.83 (OC$\underline{H}_3$), and 5.86 (s, 2H, O—C$\underline{H}_2$—O); MS: *m/e* 338 ($M^+$). (Found: C, 74.50; H, 6.49. Calc for $C_{21}H_{22}O_4$: C, 74.55; H, 6.51%.)

Ozonized $O_2$ was passed through a soln of labelled **26** (100 mg) in EtOAc (9 ml) at −70° for 20 min. The solvent from the resulting mixture was removed under reduced pressure. To the residue, $H_2O$ (40 ml), Zn dust (430 mg) and $AgNO_3$ (17.5 mg) were added and the mixture refluxed for 20 min. The HCHO thus generated was distilled into a soln of dimedone (400 mg) in EtOH aq (100 ml). After 1 hr the soln was concentrated to 5 ml and left for 12 hr. The ppt was chromatographed over a column of $SiO_2$. Elution with $CHCl_3$ gave radioactive

formaldehyde-dimethone, m.p. 187–188° (lit.[17] 188°) (molar activity $1.42 \times 10^3$ disint $min^{-1}$ $mmol^{-1}$) (90% of original activity).

(6) *Biosynthetic corlumine* (**12**) *derived from* [3-$^{14}$C]*norreticuline*. Labelled **12** (250 mg) (molar activity $5.70 \times 10^3$ disint $min^{-1}$ $mmol^{-1}$) in 50% HCl was refluxed with Zn metal for 8 hr. The mixture was basified with $Na_2CO_3$ and then extracted with $CHCl_3$. The combined $CHCl_3$ layer was washed with $H_2O$, dried ($Na_2SO_4$) and solvent removed *in vacuo* to afford a residue which was purified by PLC (plates: silica gel; solvent: benzene–EtOAc, 1:3) to give pure radioactive *2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline* (**28**, m.p. 81–82° (lit.[18] m.p. 83–84°) (molar activity $5.62 \times 10^3$ disint $min^{-1}$ $mmol^{-1}$).

Compound **20** was refluxed with MeI to furnish the *2,2-dimethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline iodide* (**29**, m.p. 230–232° (dec) (lit.[19] m.p. 233–234° (dec)) (molar activity $5.65 \times 10^3$ disint $min^{-1}$ $mmol^{-1}$).

The methiodide **29** was converted into the corresponding methohydroxide **30** by passing through a column of freshly generated amberlite IR-410 anion exchange resin.

Radioactive **30** was pyrolyzed to give 4,5-dimethoxy-2-vinylbenzyldimethylamine (**31**) as an oil which solidified after being kept at 2° for several days, m.p. 26–28° (lit.[19] m.p. 27–28.5°) (molar activity $5.60 \times 10^3$ disint $min^{-1}$ $mmol^{-1}$).

Ozonolysis of the preceding labelled **31** was carried out as described earlier to furnish radioactive *formaldehyde-dimethone*, m.p. 187–188° (lit.[17] m.p. 188°) (molar activity $5.58 \times 10^3$ disint $min^{-1}$ $mmol^{-1}$) (98% of original activity).

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