Syntheses of (±)-2,3-Dimethoxyberbine, (±)-Norcoralydine, and (±)-Demethoxycarbonyldihydrogambirtannine

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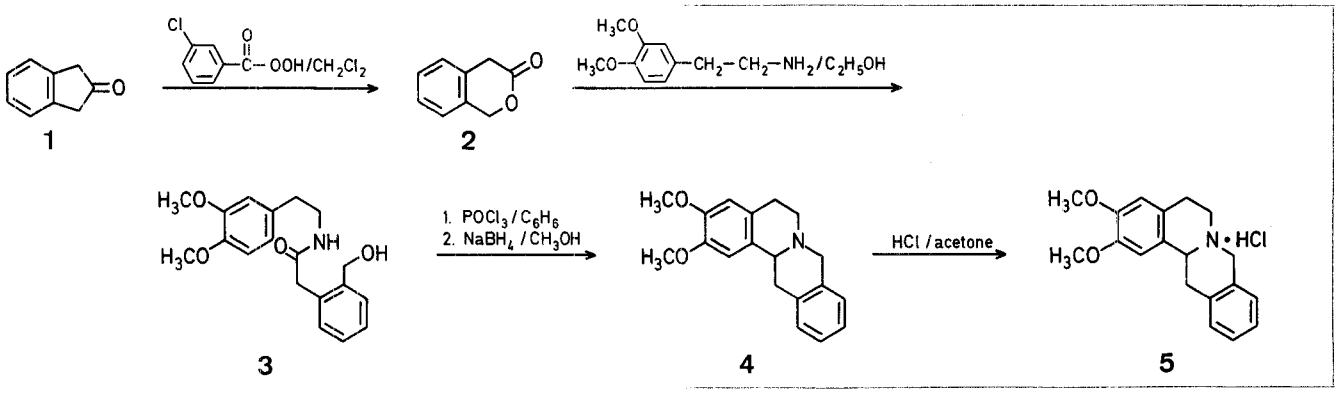
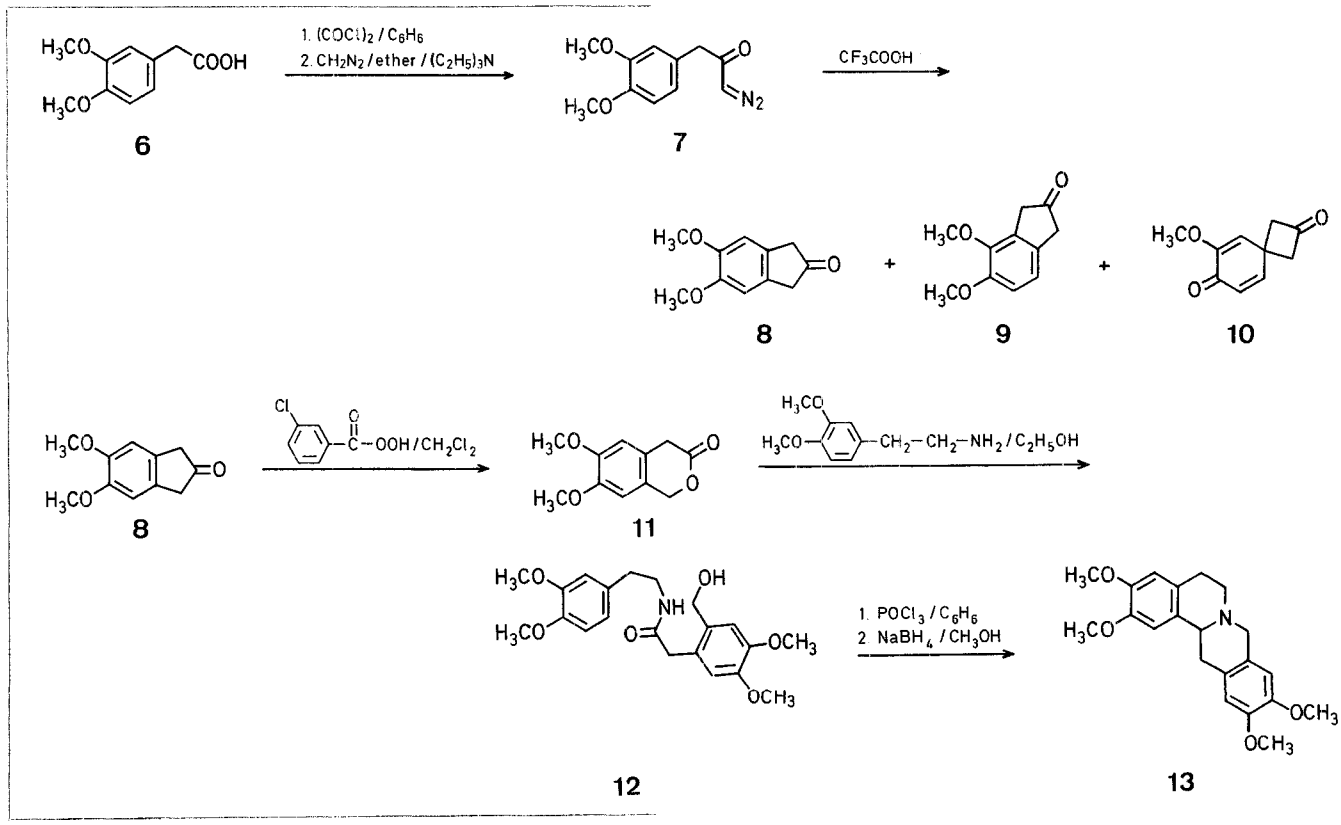
The Baeyer-Villiger oxidation of 1-indanone and its derivatives has been utilised for the synthesis of coumarins[1]. The present communication deals with the synthesis of some naturally occurring tetrahydroprotoberberine and indole alkaloids using 3-isochromanone and its derivative. The key synthons have been prepared from the appropriate 2-indanones **(1, 8)** by Baeyer-Villiger oxidation of the latter with *m*-chloroperbenzoic acid. The substituted 2-indanone **8** was, however, synthesised from the suitably substituted phenylacetic acid derivative **6** by diazoketone cyclisation.

For the synthesis of (±)-2,3-dimethoxyberbine **(4)**, the substituted hydroxyamide **3** was required. This was prepared by condensing 2-(3,4-dimethoxyphenyl)-ethylamine with 3-isochromanone **(2)** in refluxing alcohol. The lactone **2** was, however, obtained directly by Baeyer-Villiger oxidation of 2-indanone **(1)** with *m*-chloroperbenzoic acid in dry dichloromethane at 0°C. The desired alkaloid **4** was then synthesised from the hydroxyamide **3** by Bischler-Napieralski condensation with phosphoryl chloride in dry benzene followed by sodium borohydride reduction. However, the alkaloid itself is an oil and so was converted to its crystalline hydrochloride derivative **(5)** in 30% overall yield. Its structure was confirmed from spectral data, microanalyses, and by comparison with an authentic sample[2].

Synthesis of (±)-norcoralydine **(13)** was also achieved following the same reaction sequence. 3,4-Dimethoxyphenyl acetic acid **(6)** was converted to the diazoketone **7** following the standard procedure[3]. The diazoketone thus obtained was then cyclised to its 2-indanone derivative **8** by treatment with trifluoroacetic acid at −20°C. The resulting ketone was oxidised with *m*-chloroperbenzoic acid in dry dichloromethane to the key synthon, 6,7-dimethoxy-3-isochromanone **(11)**. The structure of the lactone was confirmed from its spectral data and microanalyses. In addition to **8**, two minor components





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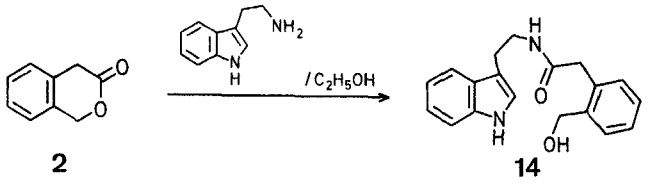
were isolated whose structures were assigned as **9** and **10**. The lactone **11** was subsequently condensed with 2-(3,4-dimethoxyphenyl)-ethylamine in boiling alcohol and the resulting hydroxyamide **12** was cyclised as before. The imine so obtained was reduced and the resulting product on fractionation gave the desired base, (±)-norcoralydine **(13)**, identical with an authentic sample[4] in overall 40% yield.

This reaction was extended to the synthesis of indole alkaloids. 3-Isochromanone **(2)** was treated with tryptamine in refluxing alcohol when the hydroxyamide **(14)** generated was converted to the desired base, (±)-demethoxycarbonyldihydrogambirtannine[5] **(15)** by Bischler-Napieralski reaction followed by the reduction of the imine salt in 30% overall yield. The structure of the free base was confirmed by comparison with an authentic sample[6]. The synthesis of alloyohimbine and related compounds have been achieved by the same approach.



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The new and simple route thus developed for the syntheses of the tetrahydroprotoberberine alkaloids and the yohimbinoid skeleton with the desired chirality offers an additional method for the synthesis of yohimbinoid alkaloids, studies on which are underway.

The melting points were recorded in a Kofler block and are uncorrected. The U.V. spectra (in 95% aldehyde-free ethanol) were recorded with a Varian-634 spectrophotometer, I.R. spectra with a Beckman IR 20 spectrometer and ^{1}H-N.M.R. spectra with a 80 MHz Varian CFT-20 spectrometer, using TMS as internal standard.

3-Isochromanone (2):

2-Indanone (**1**; 5.5 g, 40 mmol) is dissolved in dry dichloromethane (10 ml) and thoroughly cooled in ice. The ice-cold solution is added to a cooled solution of *m*-chloroperbenzoic acid (8.6 g, 50 mmol) in dry dichloromethane (50 ml) and the reaction flask is stoppered. The flask is vigorously shaken and allowed to stand at room temperature for 10 min with occasional swirling, and finally is kept at 0°C for 10 days. The precipitated *m*-chlorobenzoic acid is filtered off, washed with dichloromethane, and the combined dichloromethane layers are washed with 1% sodium hydrogen carbonate solution, water, and dried with sodium sulphate. On removal of the solvent a crude solid is obtained which is crystallised from methanol to give **2**; yield: 5.54 g (90%); m.p. 79–80°C (Lit.[7] m.p. 82–83°C).

$C_9H_8O_2$	calc.	C 72.97	H 5.42	
(148.0)	found	72.91	5.38	

I.R. (KBr): ν = 1740 cm^{-1} (s).

^{1}H-N.M.R. ($CDCl_3$): δ = 3.85 (s, 2H); 5.38 (s, 2H); 7.1–7.3 ppm (m, 4H).

***N*-[2-(3,4-Dimethoxyphenyl)-ethyl]-2-(hydroxymethyl)-phenylacetamide (3):**

A mixture of 2-(3,4-dimethoxyphenyl)-ethylamine (0.53 g, 3 mmol) and **2** (0.44 g, 3 mmol) dissolved in ethanol (15 ml) is refluxed for 20 h. The alcohol is evaporated and the gummy residue is purified by column chromatography on silica gel. From the fraction eluted with benzene/ethyl acetate (1:1), the desired hydroxyamide **3** is obtained; yield: 0.750 g (77%), m.p. 98–99°C. T.L.C. [benzene/ethyl acetate (1:1)]: single spot at R_f = 0.42.

$C_{19}H_{23}NO_4$	calc.	C 69.30	H 6.99	N 4.26
(329.0)	found	69.38	6.85	4.20

I.R. (KBr): ν = 3300–3320 (br); 1650 cm^{-1} (s).

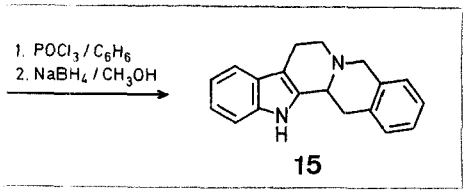
U.V. (ethanol): λ_{max} = 209 (logε = 4.28); 280 nm (3.44).

^{1}H-N.M.R. ($CDCl_3$): δ = 2.00 (br s, 1H); 2.66 (t, 2H, J = 6.8 Hz); 3.36 (m, 2H); 3.54 (s, 2H); 3.77 (s, 3H); 3.82 (s, 3H); 4.55 (br s, 2H, D_2O exchangeable); 6.30 (ill-resolved triplet, 1H, D_2O-exchangeable); 6.58 (m, 3H, Ring A); 7.22 ppm (m, 4H, Ring D).

M.S.: m/e = 329 ($M^{\cdot+}$).

(±)-2,3-Dimethoxyberbine (4):

The hydroxyamide **3** (0.500 g, 1.5 mmol) is dissolved in dry benzene (5 ml) and the solution is stirred magnetically under nitrogen. To it a solution of phosphoryl chloride (1.4 ml, 16 mmol, freshly distilled) in dry benzene (5 ml) is added in one portion and the mixture is heated under reflux with a continuous flow of nitrogen for 1.5 h. The reaction mixture is then cooled under nitrogen; excess phosphoryl chloride and benzene are evaporated under vacuum. The residue dissolved in methanol (Merck; 10 ml) is cooled to 0°C at which temperature sodium borohydride (1.5 g) is added in small portions during a period of 1 h and solution is kept overnight. Excess borohydride is decomposed by ice-cold water and the mixture is extracted with chloroform,



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washed with water and dried with sodium sulphate. On removal of the chloroform, a yellowish gum is obtained which, on chromatography on neutral alumina, affords pure (±)-2,3-dimethoxyberbine **(4)** on eluting with benzene/ethyl acetate (4:1); yield: 40%. The free base is converted to its hydrochloride derivative **5** with hydrochloric acid in acetone and the compound so obtained is crystallised from methanol to afford **5**; yield: 153.5 mg (30%); m.p. 250–252°C (dec) (Lit.[2], m.p. 250–252°C).

I.R. (KBr): ν = 2950 (m); 1600 (s); 1520 (s); 1440 cm^{-1} (m).

U.V. (ethanol): λ_{max} = 211 (logε = 4.30); 285 nm (3.45).

^{1}H-N.M.R. (DMSO-d_6): δ = 3.68 (s, 3H); 3.70 (s, 3H); 4.42 (s, 1H); 6.72, 6.92 (2s, 2H, ring A); 7.11 ppm (m, 4H, Ring D).

3,4-Dimethoxyphenylmethyl Diazomethyl Ketone (7):

3,4-Dimethoxyphenylacetic acid (**6**; 1.95 g, 10 mmol) is converted to the diazoketone by the conventional method[3]. The reaction product on chromatography over neutral alumina gives the desired diazoketone **7** on elution with 50% petroleum ether/ether mixture; yield: 1.65 g (75%).

$C_{11}H_{12}N_2O_3$	calc.	C 60.00	H 5.45	N 12.75
(220.0)	found	60.12	5.40	12.68

I.R. (KBr): ν = 2105 (s), 1625 cm^{-1} (s).

^{1}H-N.M.R. ($CDCl_3$): δ = 3.53 (s, 2H); 3.81 (s, 6H); 5.10 (s, 1H); 6.75 ppm (m, 3H).

5,6-Dimethoxy-2-indanone (8):

To a well-stirred and cooled (−20°C) solution of trifluoroacetic acid (99.9%, 10 ml), a solution of diazoketone **7** (0.1 g, 0.45 mmol) in dry dichloromethane (2 ml) is added dropwise under an atmosphere of nitrogen over a period of 15 min. The whole solution subsequently is stirred for another 5 min and excess trifluoroacetic acid is removed under vacuo. The resulting residue on chromatography over silica gel affords a white crystalline compound with benzene as eluent; yield: 0.06 g (69%); m.p. 120°C (dec). [T.L.C. (petroleum ether (60–80°C)/benzene (1:1): R_f = 0.51]. The compound is crystallised from benzene/petroleum ether (60–80°C) mixture.

$C_{11}H_{12}O_3$	calc.	C 68.75	H 6.25	
(192.0)	found	68.71	6.20	

I.R. (KBr): ν = 1750 cm^{-1} (s).

^{1}H-N.M.R. ($CDCl_3$): δ = 3.44 (s, 4H); 3.82 (s, 6H); 6.76 ppm (s, 2H).

Preparative T.L.C. of the residual gummy mass after column chromatography in benzene/ethyl acetate (2:1) mixture over silica gel affords

two other minor semi-solid components. The structures of these compounds **9** and **10**, were assigned on the basis of their spectral data.

9; yield: 0.005 g (6%); $R_f = 0.45$.

I.R. (neat): $\nu = 1745$ cm^{-1} (s).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 3.42$ (s, 2H); 3.57 (s, 2H); 3.77 (s, 6H); 6.5–6.7 ppm (m, 2H).

10; yield: 0.003 g (4%); $R_f = 0.23$.

I.R. (neat): $\nu = 1785$ (s), 1660 cm^{-1} (m).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.07$ (s, 2H); 2.56 (s, 2H); 3.79 (s, 3H); 6.57 (s, 1H); 6.69 (d, 1H, $J = 7.5$ Hz); 7.30 ppm (d, 1H, $J = 7.5$ Hz).

6,7-Dimethoxy-3-isochromanone (11):

5,6-Dimethoxy-2-indanone (**8**; 0.5 g, 2.6 mmol) is subjected to Baeyer-Villiger oxidation with *m*-chloroperbenzoic acid. The product after usual work up on chromatography over silica gel gives the desired 6,7-dimethoxy-3-isochromanone **(11)** on elution with benzene/ethyl acetate (1:1) mixture; yield: 0.347 g (64%). The compound is crystallised from methanol (shining needles); m.p. 106–107 °C (Lit.[8], m.p. 108–109.5 °C).

$C_{11}H_{12}O_4$	calc.	C 63.46	H 5.76
(208.0)	found	63.48	5.72

I.R. (KBr): $\nu = 1735$ cm^{-1} (s).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 3.54$ (s, 2H); 3.79 (s, 6H); 5.16 (s, 2H); 6.62, 6.64 ppm (2s, 2H).

***N*-[2-(3,4-Dimethoxyphenyl)-ethyl]-(4,5-dimethoxy-2-hydroxymethyl)-phenylacetamide (12):**

2-(3,4-Dimethoxyphenyl)-ethylamine (0.325 g, 1.8 mmol) is condensed with **11** (0.350 g, 1.7 mmol) in boiling ethanol following the above procedure for 17 h. After completion of the reaction, as monitored by T.L.C., excess alcohol was distilled off. The residue is dissolved in acetone and triturated with ether whereupon a solid separates. It is filtered off and crystallised from acetone/ether mixture to afford the desired hydroxyamide **(12)**; yield: 500 mg (74%); m.p. 118–120 °C; T.L.C. [benzene/ethyl acetate (1:1)]: $R_f = 0.53$.

$C_{21}H_{27}NO_6$	calc.	C 64.78	H 6.94	N 3.59
(389.0)	found	64.71	6.89	3.60

I.R. (KBr): $\nu = 3280$ (m); 3100 (br); 1625 cm^{-1} (m).

U.V. (ethanol): $\lambda_{max} = 210$ ($\log\varepsilon = 5.45$); 232 (5.15); 280 nm (4.70).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.60$ (t, 2H, $J = 6.8$ Hz), 2.77 (s, 1H, D_2O-exchangeable), 3.2–3.5 (m, 4H, $-COCH_2$ and $-NHCH_2$), 3.73 (s, 6H); 3.75 (s, 3H); 3.78 (s, 3H); 4.43 (s, 2H); 6.18 (ill resolved triplet, 1H, D_2O-exchangeable), 6.5–6.8 ppm (m, 5H, Rings A and D).

M.S.: $m/e = 389$ ($M^{\cdot+}$).

(±)-Norcoralydine (13):

The hydroxyamide **12** (0.400 g, 1 mmol) is allowed to react with phosphoryl chloride (1 ml, 10 mmol) in dry benzene (6 ml) under nitrogen following the procedure above. After the removal of excess phosphoryl chloride and benzene, the imine salt is reduced with sodium borohydride (1 g) and usual work up as above gives a gummy mass. The latter is chromatographed over silica gel to afford (±)-norcoralydine **(13)** on elution with ethyl acetate; yield: 140 mg (40%); m.p. 153–155 °C (Lit.[4], m.p. 157–158 °C).

$C_{21}H_{25}NO_4$	calc.	C 70.98	H 7.04	N 3.94
(355.0)	found	70.92	6.95	3.90

I.R. (KBr): $\nu = 2900$ (m); 2840 (s); 1600 (s); 1500 (m); 1480 cm^{-1} (m).

U.V. (ethanol): $\lambda_{max} = 212$ ($\log\varepsilon = 4.34$), 285 nm (3.84).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 3.76$ (s, 6H); 3.79 (s, 6H); 6.5–6.6 ppm (m, 4H, Rings A and D).

M.S.: $m/e = 355$ ($M^{\cdot+}$).

***N*-[2-(3-Indolyl)-ethyl]-2-(hydroxymethyl)-phenylacetamide (14):**

A mixture of tryptamine (0.6 g, 7.50 mmol) and **2** (0.6 g, 7.50 mmol) is refluxed in ethanol (20 ml) for 20 h. The residue so obtained, after removal of ethanol, is chromatographed on neutral alumina and the fraction eluted with benzene/ethyl acetate (1:1) mixture affords the hydroxyamide **14**; yield: 1 g (83%), m.p. 159–160 °C. The hydroxyamide **14** is crystallised from acetone/petroleum ether. T.L.C. [benzene/ethyl acetate (1:1)]: $R_f = 0.47$.

$C_{19}H_{20}N_2O_2$	calc.	C 74.02	H 6.49	N 9.09
(308.0)	found	73.90	6.42	8.95

I.R. (KBr): $\nu = 3380$ (br); 3240 (m); 3080 (m); 1620 cm^{-1} (s).

U.V. (ethanol): $\lambda_{max} = 291$ ($\log\varepsilon = 3.84$); 281 (3.90); 273 (3.88); 222 nm (4.66).

^{1}H-N.M.R. (DMSO-d_6): $\delta = 2.7$–3.2 (m, 4H, partially merged with H_2O of DMSO-d_6); 3.42 (s, 2H); 4.48 (d, 2H, $J = 5.1$ Hz; collapses to s on shaking with D_2O); 5.14 (t, 2H, $J = 5.1$ Hz, disappears with D_2O); 6.9–7.1 (m, 9H); 8.07 (t, 1H, $J = 5.0$ Hz, D_2O-exchangeable); 10.67 ppm (s, 1H, vanishes with D_2O).

M.S.: $m/e = 308$ ($M^{\cdot+}$).

(±)-Demethoxycarbonyldihydrogambirtannine (15):

Hydroxyamide **14** (0.523 g, 1.7 mmol) is refluxed with phosphoryl chloride (1.6 ml, 1.7 mmol) in dry benzene (10 ml) under an atmosphere of nitrogen for 1.5 h as before. After the reaction is complete, the imine salt is reduced with sodium borohydride (1.2 g) and on usual work up as above a semi-solid mass is obtained. The latter is purified by chromatography over neutral alumina. The fraction eluted with ethyl acetate affords (±)-demethoxycarbonyldihydrogambirtannine **(15)** as pale yellow needles; yield: 0.13 g (30%); m.p. 192–194 °C (Lit.[6], m.p. 192–195 °C). T.L.C. [benzene/ethyl acetate (1:1)]: $R_f = 0.51$, single spot.

$C_{19}H_{18}N_2$	calc.	C 83.21	H 6.57	N 10.22
(274.0)	found	83.15	6.50	10.18

I.R. (KBr): $\nu = 3440$ (s); 2920 (m); 1580 (s); 1490 (m); 1445 cm^{-1} (m).

U.V. (ethanol): $\lambda_{max} = 291$ ($\log\varepsilon = 3.80$); 282 (3.82); 273 (3.89); 225 nm (4.59).

U.V. (NaOH/H_2O): $\lambda_{max} = 291$ ($\log\varepsilon = 3.76$); 283 (3.87); 272 (3.85); 226 nm (4.56).

U.V. (50% $HClO_4$): $\lambda_{max} = 217$ ($\log\varepsilon = 4.51$); 271 nm (3.93).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.5$–3.4 (m, 6H); 3.6–4.1 (m, 3H); 7.0–7.5 (m, 8H); 7.77 ppm (s, 1H, D_2O-exchangeable).

The authors wish to express their thanks to Dr. B. C. Das, Institut de Chimie des Substances Naturelles, France, to Professor F. Bohlmann, Institut für Organische Chemie der Technischen Universität Berlin for recording mass spectra. Sincere thanks are also accorded to Dr. P. C. Das, CCRAS, Calcutta for providing 2-(3,4-dimethoxyphenyl)-ethylamine and to UGC, New Delhi for providing financial assistance to one of the authors (S. G.).

Received: April 22, 1981

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