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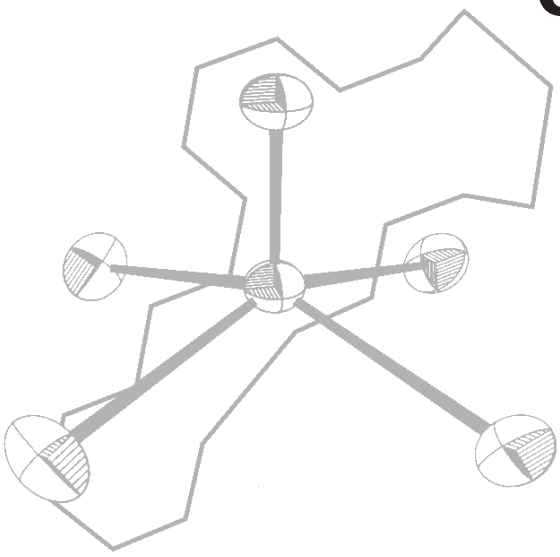

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Synthesis of (±)-Cathaformine*

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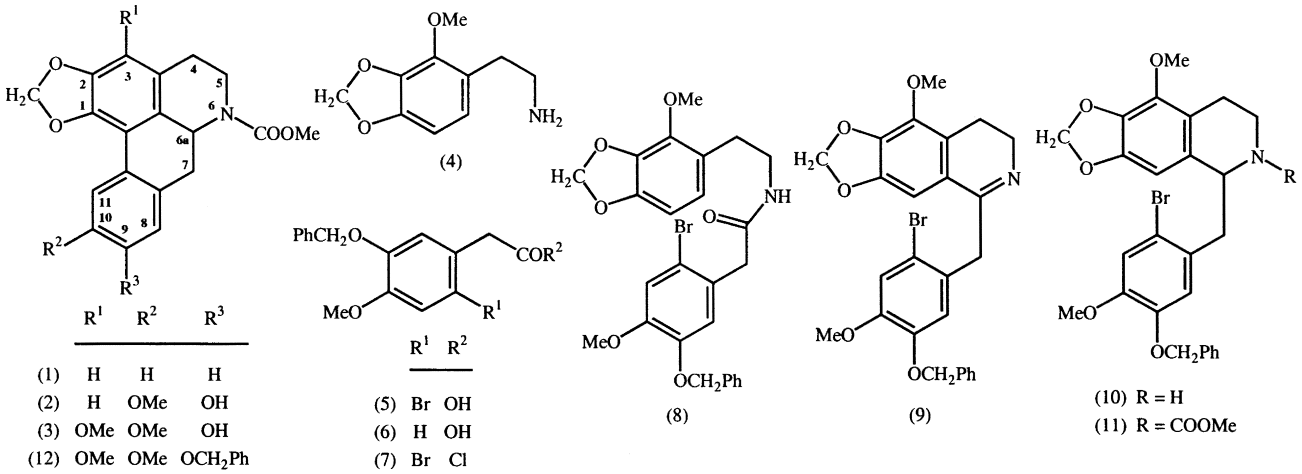
The structure previously assigned to the *N*-(methoxycarbonyl)aporphine alkaloid (+)-cathaformine has been confirmed by a total synthesis of the racemic substance in which the key step involved formation of ring C by a radical-initiated cyclization.

Keywords. Alkaloid; aporphine; isoquinoline; synthesis.

At present, only three aporphine alkaloids with an *N*-(methoxycarbonyl) group are found to occur in Nature. These are (–)-romucosine (1) found in *Rollinia mucosa* (Annonaceae),[1] and (+)-cathafoline (2) and (+)-cathaformine (3) found in *Cassytha filiformis* (Lauraceae).[2] Although extensive spectroscopic analysis was employed in the structural elucidation of these alkaloids, the correctness of these structures has not been confirmed by a total synthesis. In view of our interest in the synthesis of isoquinoline alkaloids, we have completed a total synthesis of (±)-cathaformine and now report the details of the synthesis in this communication.

The strategy employed in the present synthesis was based on the construction of ring C of (±)-cathaformine by a radical-initiated cyclization first described by Castedo *et al*.[3] For this purpose, the required starting materials were the ethylamine (4)[4] and the bromo acetic acid (5). Thus bromination of acid (6) readily afforded acid (5) the acid chloride (7) of which was reacted with amine (4) to afford amide (8). Amide (8) was converted into dihydroisoquinoline (9) by a Bischler–Napieralski reaction. Reduction of (9) with sodium borohydride gave (10) which was treated with methyl chloroformate to give carbamate (11). Carbamate (11) exhibited the phenomenon of hindered rotation around the amide bond as expected of acylated 1-benzyltetrahydroisoquinolines.[4] Thus, the two aromatic protons on the benzyl substituent gave rise to four distinct singlets at δ 6.56, 6.50, 6.32 and 6.18 with a total integration of two protons while the CH_3 protons of the methoxycarbonyl group gave rise to two distinct singlets at δ 3.84 and 3.30 with a total integration of three protons. Treatment of carbamate (11) with tributyltin hydride and azobis(isobutyronitrile) afforded aporphine (12) in 17.3% yield. The structure of aporphine (12) was supported by ^{1}H n.m.r. data in which the two protons of the methylenedioxy group gave rise to an AB quartet with a coupling constant of 1.46 Hz characteristic of aporphine alkaloids bearing a methylenedioxy group on positions 1 and 2.[4] In addition, the two protons of the benzyloxy group were found to be non-equivalent. These gave rise to an AB quartet with a coupling constant of 12.27 Hz. In view of the distance of the benzyloxy group from the A/D ring junction, such non-



	R^1	R^2	R^3
(1)	H	H	H
(2)	H	OMe	OH
(3)	OMe	OMe	OH
(12)	OMe	OMe	OCH_2Ph

	R^1	R^2
(5)	Br	OH
(6)	H	OH
(7)	Br	Cl

* Dedicated to Professor W. C. Taylor, on the occasion of the 70th anniversary of his birthday, for his contributions to the advancement of organic chemistry in developing countries.

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equivalence of these protons is rather unexpected. Finally, the benzyl protecting group was removed by catalytic hydrogenolysis at 35–40 psi to afford (±)-cathaformine, the ^{1}H and ^{13}C n.m.r. spectral data of which were identical in all respects with those of natural (+)-cathaformine.

Experimental

Melting points were determined on a Stuart MP-2 apparatus and are uncorrected. Ultraviolet spectra were recorded on methanol solutions with a Hitachi U-3300 spectrophotometer. Infrared spectra were recorded on Nujol mulls with a Nicolet Impact 400 spectrophotometer. ^{1}H and ^{13}C magnetic resonance spectra were recorded on (D)chloroform solutions at 60 MHz with a Varian EM360A spectrometer or at 400 MHz for ^{1}H and 100 MHz for ^{13}C with a Varian Inova 400 MHz spectrometer. Tetramethylsilane was used as the internal standard. Mass spectra were run on a Hewlett Packard 5989B spectrometer. Elemental microanalyses were performed with a Perkin–Elmer 2400 elemental analyser.

5-Benzyloxy-2-bromo-4-methoxyphenylacetic Acid (5)

Bromine (32.4 g) was cautiously added to a solution of 3-benzyloxy-4-methoxyphenylacetic acid (50 g) and anhydrous sodium acetate (50 g) in acetic acid (500 ml) and the mixture was stirred for 1 h at room temperature. Water (2 litres) was then added and the yellow precipitate was filtered off and recrystallized from ethanol to give colourless crystals (44 g, 68.2%), m.p. 146–147° (lit.[5] 145°). ^{1}H n.m.r. (60 MHz) δ 7.47–7.13, m, 5×Ph H; 7.03, s, ArH; 6.80, s, ArH; 5.05, s, CH_2; 3.83, s, OCH_3; 3.70, s, CH_2.

*2-(5-Benzyloxy-2-bromo-4-methoxyphenyl)-*N*-(2-methoxy-3,4-methylenedioxyphenethyl)acetamide (8)*

A mixture of acid (5) (27 g) and thionyl chloride (25 g) in chloroform (210 ml) was refluxed for 1 h, then the solvent and excess thionyl chloride were removed under vacuum. The resulting crude acid chloride (7) was dissolved in chloroform (120 ml) and added portionwise to a mixture of 2-(2-methoxy-3,4-methylenedioxyphenyl)ethylamine (4) (14 g) in chloroform (125 ml) and 5% $NaHCO_3$ (190 ml) under ice cooling. The mixture was stirred at room temperature for 5 h. Water (350 ml) and chloroform (210 ml) were added and the chloroform layer was washed with 3 M HCl (2×175 ml), water (350 ml), 5% $NaHCO_3$ (350 ml), water and brine, then dried. Removal of the solvent gave a pale brown solid which was recrystallized from ethanol to give the *amide* (8) as colourless prisms (32.0 g, 84.6%), m.p. 141–142° (Found: C, 59.2; H, 4.7; N, 2.8. $C_{26}H_{26}BrNO_6$ requires C, 59.1; H, 5.0; N, 2.6%). λ_{max} 228sh, 284 nm; log ϵ 3.98, 3.40. ν_{max} 3325 (NH), 1652 (C=O), 1602, 1541, 1260, 1213, 1164, 1032, 978, 797, 751, 722 cm^{-1}. ^{1}H n.m.r. (60 MHz) δ 7.46–7.10, m, 5×Ph H; 6.96, s, ArH; 6.73, s, ArH; 6.33, s, 2×ArH; 5.80, s, OCH_2O; 5.40, br s, NH; 5.00, s, $PhCH_2$; 3.83, s, OCH_3; 3.80, s, OCH_3; 3.46, s, CH_2; 3.28, t, *J* 6 Hz, CH_2N; 2.58, t, *J* 6 Hz, CH_2. Mass spectrum *m/z* 529 (M^+, 1%), 527 (M^+, 1%), 448 (37), 270 (32), 199 (12), 178 (89), 129 (12), 91 (100), 57 (44).

1-(5-Benzyloxy-2-bromo-4-methoxybenzyl)-5-methoxy-6,7-methylenedioxy-3,4-dihydroisoquinoline (9)

A solution of the amide (8) (8 g) and phosphorus oxychloride (16 g) in benzene (100 ml) was refluxed for 3 h, and the excess reagent and solvent were removed under vacuum. The resulting red residue was shaken with chloroform (240 ml) and dilute ammonia (100 ml). The chloroform layer was washed with water (100 ml), brine, then dried. Removal of the solvent gave a brown viscous residue which crystallized from ethanol to give the *dihydroisoquinoline* (9) as pale brown prisms (4.85 g, 62.9%), m.p. 157–158° (Found: C, 61.3 ; H, 4.6 ; N, 2.9. $C_{26}H_{24}BrNO_5$ requires C, 61.2; H, 4.7; N, 2.7%). λ_{max} 237sh, 283, 322 nm; log ϵ 4.01, 3.67, 3.57. ν_{max} 1664, 1589, 1274, 1223, 1210, 1152, 1086, 1069, 1053, 1023, 961 cm^{-1}. ^{1}H n.m.r. (60 MHz) δ 7.43–7.13, s, 5×Ph H; 7.00, s, ArH; 6.70, s, ArH; 6.56, s, ArH; 5.86, s, OCH_2O, 4.98, s, $PhCH_2$; 3.94, s, OCH_3 and CH_2; 3.80, s, OCH_3; 3.51, t, *J* 6 Hz, CH_2N; 2.59, t, *J* 6 Hz, CH_2.

1-(5-Benzyloxy-2-bromo-4-methoxybenzyl)-5-methoxy-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (10)

Sodium borohydride (0.5 g) was added portionwise to a stirred solution of the dihydroisoquinoline (9) (4.8 g) in ethanol (100 ml) and the mixture was refluxed for 1 h. The mixture was then shaken with water (100 ml) and chloroform (100 ml). The chloroform layer was washed with brine, then dried. Removal of the solvent gave a white solid which was recrystallized from ethanol to give the *tetrahydroisoquinoline* (10) as colourless prisms (4.27 g, 89.3%), m.p. 154–155° (Found: C, 61.1; H, 4.9; N, 2.9. $C_{26}H_{26}BrNO_5$ requires C, 61.0; H, 5.1; N, 2.7%). λ_{max} 228sh, 287 nm; log ϵ 3.99, 3.40. ν_{max} 3319 (NH), 1602, 1572, 1506, 1321, 1312, 1257, 1213, 1163, 1131, 1101, 1069, 1044, 983, 934, 915, 878, 844, 801, 785, 762, 746, 699, 635 cm^{-1}. ^{1}H n.m.r. (60 MHz) δ 7.50–7.13, m, 5×Ph H; 7.03, s, ArH; 6.71, s, ArH; 6.51, s, ArH; 5.83, s, OCH_2O; 5.11, s, $PhCH_2$; 4.30–4.00, m, H 1; 3.96, s, OCH_3; 3.85, s, OCH_3; 3.65–2.43, m, 3×CH_2; 2.06, br s, NH. Mass spectrum *m/z* 206 (100), 190 (18), 118 (7), 91 (48).

Methyl 1-(5-Benzyloxy-2-bromo-4-methoxybenzyl)-5-methoxy-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (11)

Methyl chloroformate (4.70 g) was added portionwise to a stirred mixture of the tetrahydroisoquinoline (10) (4.27 g) in chloroform (25 ml) and sodium hydrogen carbonate (4.16 g) at 0–5°. Stirring was continued at room temperature for 3 h. Water (60 ml) and chloroform (60 ml) were added and the chloroform layer was washed with brine, then dried. Removal of the solvent gave a viscous residue (4.78 g) which was passed through a column of alumina (125 g) packed in benzene. Elution with benzene followed by crystallization from ethanol gave the *carbamate* (11) as pale yellow prisms (1.54 g, 32.4%), m.p. 187–188° (Found: C, 58.8; H, 4.8; N, 2.6. $C_{28}H_{28}BrNO_7$ requires C, 59.0; H, 5.0; N, 2.5%). λ_{max} 229sh, 286 nm; log ϵ 4.03, 3.42. ν_{max} 1686 (C=O), 1625, 1601, 1510, 1497, 1325, 1311, 1261, 1215, 1204, 1163, 1117, 1085, 1066, 1049, 1042, 1024, 988, 976, 960, 945, 914, 885, 873, 872, 867, 850, 803, 767, 752, 743, 731, 698 cm^{-1}. ^{1}H n.m.r. (60 MHz) δ 7.56–7.10, s, 5×Ph H; 7.00, s, ArH; 6.56, 6.50, 6.32, 6.18, 4s, 2×ArH of both conformers; 5.82, s, OCH_2O; 5.36–5.03, m, H 1; 5.00, s, $PhCH_2$; 3.97, s, OCH_3; 3.83, s, OCH_3; 3.84, 3.30, 2s, $COOCH_3$ of both conformers; 3.76–2.30, m, 3×CH_2. Mass spectrum *m/z* 264 (100), 204 (6), 178 (3), 91 (20).

Methyl 9-Benzyloxy-3,10-dimethoxy-1,2-methylenedioxy-noraporphine-6-carboxylate (12)

A solution of azobis(isobutyronitrile) (2.32 g) and tributyltin hydride (9.11 g) in toluene (159 ml) was added dropwise over 3.5 h to a refluxing solution of the carbamate (11) (9.11 g) in toluene (232 ml) under nitrogen. The resulting mixture was then refluxed for 24 h. The solvent was removed under vacuum and the residue was dissolved in acetonitrile (100 ml) and washed with hexane (3×500 ml), then dried. Removal of the solvent under vacuum gave a brown residue which crystallized from ethanol to give the *noraporphine* (12) as pale brown prisms (1.35 g, 17.3%), m.p. 204–205° (Found: C. 68.5; H, 5.3; N, 3.0. $C_{28}H_{27}NO_7$ requires C, 68.7; H, 5.6; N, 2.9%). λ_{max} 233sh, 284, 304, 315 nm; log ϵ 4.08, 3.88, 3.90, 3.87. ν_{max} 1710 (C=O), 1605, 1517, 1280, 1249, 1215, 1203, 1120, 1054, 1026, 998, 983, 962, 940, 917, 868, 773, 756, 745, 722 cm^{-1}. ^{1}H n.m.r. (400 MHz) δ 7.68, s, H 11; 7.47–7.26, m, 5×Ph H; 6.80, s, H 8; 6.08, d *J* 1.46 Hz, 1H, OCH_2O; 5.93, d *J* 1.46 Hz, 1H, OCH_2O; 5.19, d, *J* 12.27 Hz, 1H, $PhCH_2$; 5.14, d, *J* 12.27 Hz, 1H, $PhCH_2$; 4.80, m, H 6a; 4.40, m, H 5α; 4.00, s, C 3–OCH_3; 3.93, s, C 10–OCH_3; 3.76, s, $NCOOCH_3$; 2.90, m, 2H, H 5β and H 7α; 2.79, m, 2H, H 7β and H 4α; 2.46, m, H 4β. Mass spectrum *m/z* 489 (M^+, 21%), 460 (5), 398 (100), 367 (31), 311 (28), 296 (24), 250 (15), 221 (13), 152 (18), 115 (17), 91 (67).

(±)-*Cathaformine (3)*

A solution of the noraporphine (11) (331 mg) in ethanol (170 ml) was hydrogenolysed in the presence of 10% Pd/C (334 mg) at 35–40 psi for 8 h. The catalyst was filtered off and the solvent removed under vacuum to give a viscous residue which crystallized from ethanol to give (±)-cathaformine as pale brown prisms (131 mg, 48.6%), m.p. 241–242°

(Found: C, 63.0; H, 5.1, N, 3.7. $C_{21}H_{21}NO_7$ requires C, 63.2; H, 5.3; N, 3.5%). λ_{max} 236sh, 284, 304, 314 nm; log ϵ 4.03, 3.86, 3.89, 3.87. ν_{max} 3408 (OH), 1683 (C=O), 1631, 1615, 1584, 1513, 1331, 1289, 1264, 1248, 1226, 1217, 1200, 1166, 1130, 1119, 1097, 1051, 1000, 981, 977, 962, 935, 924, 870, 799, 773 cm^{-1}. ^1H n.m.r. (400 MHz) δ 7.61, s, H 11; 6.82, s, H 8; 6.09, d, *J* 1.46 Hz, 1H, OCH_2O; 5.94, d, *J* 1.46 Hz, 1H, OCH_2O; 4.78, m, H 6a; 4.41, m, H 5α; 4.00, s, C 3–OCH_3; 3.93, s, C 10–OCH_3; 3.75, s, $NCOOCH_3$; 2.90, m, 2H, H 5β and H 7α; 2.80, m, 2H, H 7β and H 4α; 2.47, m, H 4β. ^{13}C n.m.r. (100 MHz) δ 155.8, s, $NCOOCH_3$; 145.4, s; 144.7, s; 143.4, s; 139.1, s; 135.4, s; 128.9, s; 126.0, s; 122.9, s; 120.5, s; 114.6, d; 111.2, d; 100.8, t, OCH_2O; 59.9, q, C 3–OCH_3; 56.3, q, C 10–OCH_3; 52.8, q, $NCOOCH_3$; 52.0, d, C 6a; 38.9, t, C 4; 34.1, t, C 7; 24.0, t, C 5. Mass spectrum *m/z* 399 (M^+, 64%), 367 (80), 311 (100), 264 (14), 209 (8), 171 (11), 129 (19), 97 (21).

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