Dihydropyridines in synthesis and biosynthesis. V.[1,2] Synthesis of pyridocarbazole alkaloids: olivacine and (±)-guatambuine

JAMES P. KUTNEY, MASAKI NODA, NORMAN G. LEWIS, BEATRICE MONTEIRO, DANUTA MOSTOWICZ, AND BRIAN R. WORTH

Department of Chemistry, University of British Columbia, 2036 Main Mall, University Campus, Vancouver, B.C., Canada V6T 1Y6

Received March 15, 1982

JAMES P. KUTNEY, MASAKI NODA, NORMAN G. LEWIS, BEATRICE MONTEIRO, DANUTA MOSTOWICZ, and BRIAN R. WORTH. Can. J. Chem. **60**, 2426 (1982).

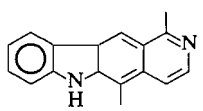
A synthetic route to the pyridocarbazole alkaloids, olivacine and guatambuine is described. The crucial step in the synthesis utilizes tricarbonylchromium(0) complexes of a suitable dihydropyridine system and illustrates the application of such complexes for the preparation of such alkaloids.

JAMES P. KUTNEY, MASAKI NODA, NORMAN G. LEWIS, BEATRICE MONTEIRO, DANUTA MOSTOWICZ et BRIAN R. WORTH. Can. J. Chem. **60**, 2426 (1982).

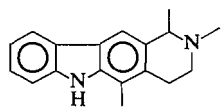
On décrit une voie d'accès aux alcaloides pyridocarbazole, olivacine et guatambuine. L'étape fondamentale de la synthèse utilise les complexes tricarbonylchrome(0) d'un système dihydropyridine convenable et illustre l'application de ces complexes à la préparation de tels alcaloides.

[Traduit par le journal]

The pyridocarbazole alkaloids, including olivacine (**1**) and guatambuine (**2**), have received considerable interest due to their promising antitumor activity (3–5). The total synthesis of representatives of this family of alkaloids has been the subject of numerous studies (6–21). Several of the synthetic approaches reported employed cyclization of pyridyl-substituted indoles to generate the linear pyridocarbazole skeleton. However, the yields obtained have generally been low.



1



2

Our interest in the stabilization and use of very reactive dihydropyridine systems led us to investigate the utility of tricarbonylchromium(0) complexes (e.g. **8**) in the synthesis of natural products (22, 23). Here we envisaged the complex **8** to provide a nucleophilic center at the indole-3 position, for appropriate substitution employing a one-carbon electrophile, and subsequent cyclization to the pyridocarbazole skeleton utilizing the masked enamine (dihydropyridine) unit (Scheme 1).

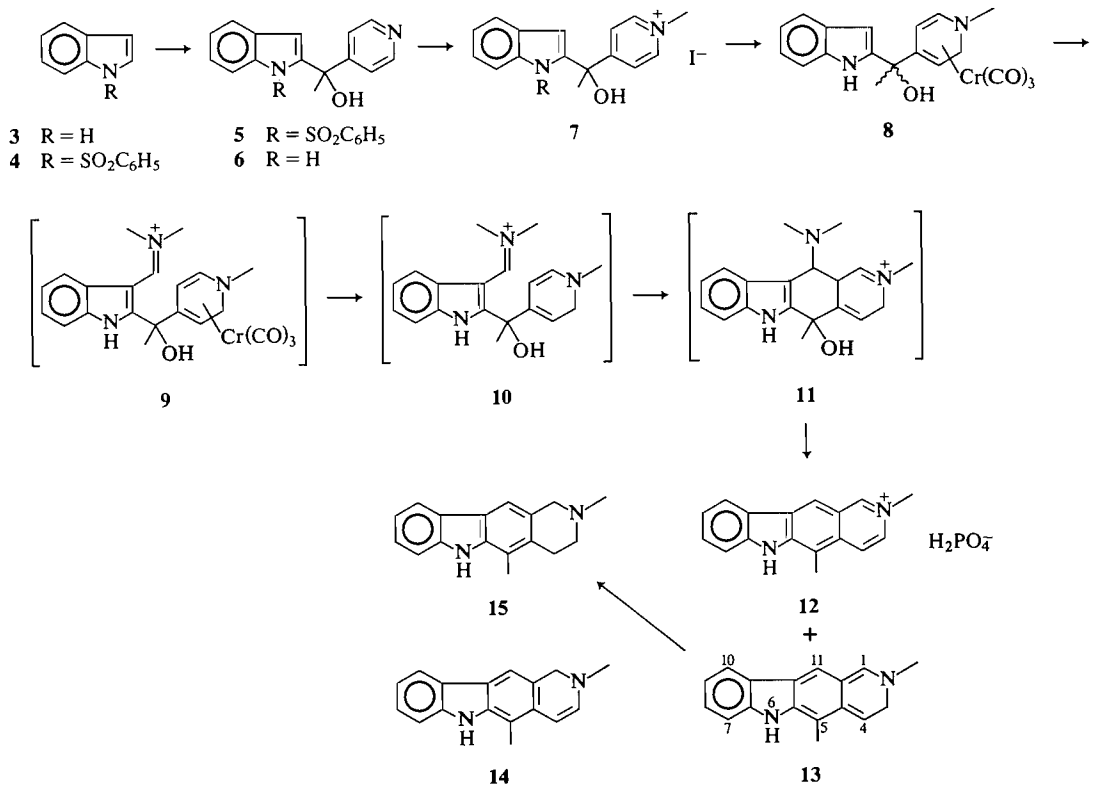
Condensation of 1-benzenesulphonylindole (**4**), readily derived from indole (**3**), with 4-acetylpyridine gave **5** which was readily hydrolyzed to **6** (19, 24). Iodomethylation of **6** provided the corresponding pyridinium salt **7** in high yield. Reduction of **7** with sodium borohydride and protection of the resulting dihydropyridine, in the usual manner (22), afforded the tricarbonylchromium(0) complex **8** as red crystals in 56% overall yield. High resolution ^{1}Hmr revealed two sets of resonances, indicating the product as a mixture of two diastereoisomers in the ratio of 2:1 (see Experimental). As expected, in the major isomer the methyl group (δ 1.44) on the chiral center is in the more stable configuration, that is, on the opposite side of the bulky tricarbonylchromium group. These methyl protons (δ 1.88) of the other epimer being affected significantly by the deshielding property of the tricarbonylchromium group resonated as substantially lower field.

Reaction of complex **8** with the Vilsmeier reagent, prepared from DMF and $POCl_3$, formed an intermediate which on direct treatment with pyridine afforded a mixture of yellow products **12** and **13** in high yield. Considerable efforts were expended in attempting to separate this mixture by various chromatographic methods. Eventually a portion was separated by careful silica gel column chromatography to give sufficient material for characterization of the two compounds. The less polar minor compound was assigned the structure **13** based on its spectral properties (C4-H, broad doublet at δ 8.22, J = 8 Hz; C1-H, singlet at δ 9.14). Clearly structure **14** must possess two doublets for the corresponding C3- and C4-vinyl protons. The major product **12** was isolated as the phosphate salt. Formation of **12** from **8** can be rationalized according to Scheme 1 (viz. **8** → **9** → **10** → **11**). The

[1]For Part IV, see ref. 1.

[2]For a preliminary report of this work see ref. 2.

0008-4042/82/192426-05$01.00/0



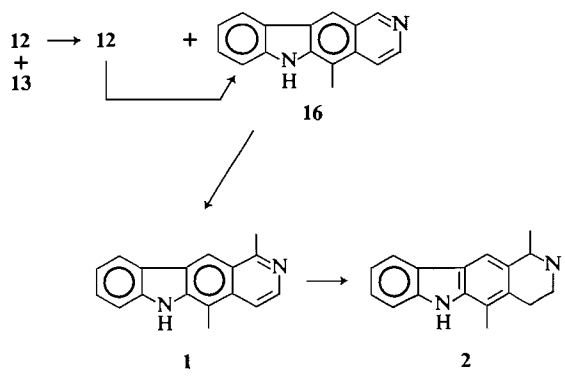
SCHEME 1

reduction product **13**, also isolated in this mixture, can be rationalized via a reductive process involving the dihydropyridine system generated from the complex **8**. However, direct evidence for this process is lacking. Reduction of the mixture **12** and **13** with sodium borohydride resulted in a single product 1-desmethylguatambuine (**15**) (89% yield from **8**). Similar reduction of a small sample of pure **13** also gave **15** as the product, thus supporting the structural assignment for **13**.

With the pyridocarbazole skeleton constructed (compounds **12** and **13**), subsequent elaboration of these intermediates to complete the syntheses of olivacine (**1**) and (±)-guatambuine (**2**) was achieved as shown in Scheme 2. Dehydrogenation of the mixture of **12** and **13** using Pd/C at 300°C afforded a mixture of unconverted **12** and the pyridine derivative **16**. The latter was easily separated from **12** which was also readily demethylated to **16** using triphenylphosphine in DMF or HMPA.

Reaction of **16** with methyllithium in dry THF and subsequent oxidation of the dihydropyridine intermediate with iodine provided olivacine (**1**) in 54% yield. Iodomethylation of **1** followed by reduction with sodium borohydride afforded (±)-guatambuine (**2**). Further confirmation of **1** and **2** was established by thin layer chromatography comparison with authentic samples.

These studies have provided a further demonstration of the utility of chromium tricarbonyl complexing in the stabilization of highly reactive dihydropyridine systems. This reactive dienamine generated *in situ* at an appropriate stage in the synthesis affords an interesting and efficient preparation of pyridocarbazole alkaloids.



SCHEME 2

Experimental

Melting points were determined on a Kofler block and are uncorrected. Ultraviolet (uv) spectra were recorded on a Cary 15 spectrophotometer in methanol solution. The wavelengths of absorption maxima are reported in nanometers (nm) with log ε in parentheses. Infrared (ir) spectra were measured on a Perkin–Elmer model 710 or 457 spectrophotometer as KBr disc. The absorption maxima are reported in wavenumbers (cm^{-1}), calibrated with respect to the absorption band of polystyrene at 1601 cm^{-1}. Proton magnetic resonance (^{1}Hmr) spectra were recorded on either a Varian HA- or XL-100 or a 270 MHz spectrometer with TMS as internal standard. The integrated peak areas, signal multiplicities, and proton assignments are given in parentheses. Low resolution mass spectra (ms) were determined on either an AEI MS-902 or an Atlas CH-4B spectrometer. High resolution mass spectra were measured on an AEI MS-902 instrument. Microanalyses were carried out by Mr. P. Borda of the Microanalytical Laboratory, University of British Columbia. Column chromatography utilized Merck silica gel 60 (70–230 mesh). Preparative and thin layer chromatography utilized Merck silica gel GF_{254}. As a matter of routine, all reagents and solvents were recrystallized or distilled before use.

1-Benzenesulfonylindole (4)

Potassium hydride (54 g, 22.1% (0.29 mol)) was added to a solution of anhydrous THF (150 mL) and HMPA (40 mL) at 0°C. To this mixture was added indole (23.4 g (0.2 mol)) in anhydrous THF (50 mL) over 30 min under nitrogen, which was then warmed to room temperature for 1 h. The mixture was cooled to 0°C and benzenesulfonyl chloride (41 g (0.23 mol)) was added dropwise. The mixture was stirred at room temperature for 20 h and poured into water and extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4) and concentrated. The precipitate was filtered to give **4** (35.5 g, 68%). Recrystallization of the product from CH_2Cl_2–hexane gave colourless needles, mp 78°C (lit. (23) mp 77.5–79°C).

1-(1-Benzenesulfonyl indole-2-yl)-1-(4-pyridyl)-ethanol (5)

tert-Butyllithium (40 mL (1.85 *M*), 75 mmol) was added dropwise to benzenesulfonylindole (**4**) (12.8 g, 50 mmol) in dry THF (270 mL) under nitrogen at 0°C. The reaction mixture was stirred at room temperature for 2 h, cooled to 0°C, and 4-acetylpyridine (13 mL, 118 mmol) was added dropwise. The resulting yellowish suspension was stirred overnight at room temperature and poured into water (200 mL) and extracted with CH_2Cl_2. The organic extracts were washed with water, dried (Na_2SO_4), and evaporated to give colourless crystals. The crystals were filtered and washed with acetone to give **5** (8.5 g, 48%). From the mother liquor crude **5** (2.5 g) was obtained. Recrystallization from acetone–$CHCl_3$ gave pure **5** (2.0 g, 17%), total yield 65%, mp 228–229°C (from $CHCl_3$) (lit. (23) mp. 229–230°C).

Indole-2-yl-1-(4-pyridyl)-ethanol (6)

The alcohol **5** (3 g, 7.96 mmol) was added to a 2 *M* methanol sodium hydroxide solution (500 mL) and heated for 4 h, cooled, and extracted with ether (600 mL). The organic extract was evaporated and recrystallized from $CHCl_3$ to give **6** (1.36 g, 72%), mp 218–221°C (lit. (23) mp 221°C); ir ν_{max}: 3400, 3290, 1600; uv λ_{max}: 283 (3.86), 274 (3.92), 256 (3.95), 253 (3.92), 211 (4.53); ^{1}Hmr (DMSO-d_6) δ: 1.88 (3H, s), 6.18 (1H, s, OH), 6.31 (1H, d, J = 2 Hz, C3′-H), 7.40–6.80 (4H, m, ArH), 7.46 (2H, d, J = 6 Hz, C3-H, C5-H), 8.49 (2H, d, J = 6 Hz, C2-H, C6-H), 10.92 (1H, s, N*H*); ms *m/e*: 238 (M^+), 220, 205, 160. High resolution mass determination, calcd. for $C_{15}H_{14}N_2O$: 238.1106; found: 238.1123. *Anal.* calcd. for $C_{15}H_{14}N_2O$: C 75.63, H 5.88, N 11.76; found: C 75.55, H 5.70, N 11.95.

Indole-2-yl-1-(4-pyridylmethiodide)-ethanol (7)

The alcohol **6** (390 mg) was added to a solution of ethyl acetate (30 mL) and CH_3I (2 mL). The suspension was heated at 50°C for 5 h. The resulting precipitate was removed by suction filtration to afford an amorphous powder **7** (554 mg, 89%), ir ν_{max}: 3285, 1640; uv λ_{max}: 287 (3.63), 277 (3.85), 262 (4.06), 257 (4.07), 217 (4.70); ^{1}Hmr (DMSO-d_6) δ: 1.98 (3H, s), 4.26 (3H, s, N—CH_3), 6.44 (1H, s, C3′-H), 6.72 (1H, s, O*H*), 7.56–6.82 (4H, m, ArH), 8.17 (2H, d, J = 6.8 Hz, C3-H, C5-H), 8.93 (2H, d, J = 6.8 Hz, C2-H, C6-H).

The complexes 8

$NaBH_4$ (5%) in ether (40 mL) and 2 *N* NaOH (15 mL) was added to the pyridinium salt **7** (570 mg, 1.5 mmol) in MeOH (15 mL) under nitrogen at 0°C. The two phase system was stirred vigorously for 50 min at 0°C. The aqueous layer was removed, and then the ether layer was washed briefly with 2 *N* NaOH (5 mL) and dried with anhydrous Na_2SO_4, K_2CO_3, and a small amount of KOH for 1 h at 0°C. The dried ether solution was added under nitrogen to a solution of trisacetonitriletricarbonyl chromium (1.5 equiv.) in dry ether at 0°C and the mixture was stirred for 3 h. The resulting red solution was filtered through previously degassed Florisil (20 g) with degassed dichloromethane under a nitrogen atmosphere to afford **8** as a mixture of diastereomers in the ratio of 2:1. Recrystallization of the red mixture with ether and petroleum ether (30–60°C) under nitrogen gave red needles (390 mg, 56%, mp 65–67°C (dec.)), which contained one mole equiv. of ether (by ^{1}Hmr spectroscopy and microanalysis), ir ν_{max}: 1941, 1866, 1821 cm^{-1}; uv (Et_2O)λ_{max}: 400 (3.61), 289 (3.87), 281 (3.93), 266 (3.96), 219 (4.53); ^{1}Hmr (C_6C_6) δ: 1.14 (6H, t, J = 7 Hz, methyl of ether) 1.30 (3H × 1/3, N—C*H*$_3$), 1.34 (3H × 2/3, N—C*H*$_3$), 1.44 (3H × 2/3, C*H*$_3$), 1.88 (3H × 1/3, C*H*$_3$), 1.99 (1H × 1/3, C6-H, bd, J = 10 Hz), 2.09 (1H × 2/3, C6-H, bd, J = 10 Hz), 2.56 (1H × 1/3, C6-H, bd, J = 10 Hz), 2.68 (1H × 2/3, C6-H, bd, J = 10 Hz), 2.62 (1H, OH, bs), 3.15 (1H, C5-H, bs), 3.31 (4H, q, J = 7 Hz, methylene of ether), 4.34 (1H × 1/3, C2-H, bd, J = 5 Hz), 4.45 (1H × 2/3, C2-H, bd, J = 5 Hz), 5.61 (1H × 1/3, C3-H, dd, J = 5 Hz, J = 2 Hz), 5.84 (1H × 2/3, C3-H, dd, J = 5 Hz, J = 2 Hz), 6.14 (1H × 2/3, C3′-H, d, J = 2 Hz), 6.38 (1H × 1/3, C3′-H, d, J = 2 Hz), 7.25–7.35 (3H, C5′,6′,7′-H, m), 7.64–7.78 (1H, C4′-H, m), 8.28–8.56 (N*H*, bs); ms *m/e*: 390 (M^+), 376, 372, 362, 334, 320, 306, 288, 237 (100%). High resolution molecular weight determination, calcd. for $C_{19}H_{18}N_2O_4Cr$: 390.0701; found: 390.0704. *Anal.* calcd. for $C_{19}H_{18}N_2O_4Cr.C_4H_{10}O$: C 59.48, H 6.03, N 6.03; found: C 59.50, H 6.13, N 5.93.

Formation of 12 and 13

Vilsmeier reagent prepared from DMF (0.4 mL, 5.1 mmol), $POCl_3$ (0.24 mL, 2.6 mmol), and CH_2Cl_2 (0.32 mL) was added dropwise to a CH_2Cl_2 (5 mL) solution of the complex **8** (948 mg, 2.4 mmol) at −5°C under nitrogen. The mixture was stirred at 0°C for 2 h and then at room temperature for 20 min. After evaporation of the solvent, the residues were dissolved in pyridine (30 mL), and heated at 50–55°C for 5 h. Pyridine was removed and the resulting residue was purified by silica gel (30 g) column chromatography with CH_2Cl_2–MeOH (10:1) as eluant to afford a yellow mixture of **12** and **13** (727 mg, 91%, in ratio of ca. 7:3 by ^{1}Hmr spectroscopy). This mixture was not readily resolved by various chromatographic methods. Eventually a portion (200 mg) was applied on a silica-gel column (30 g) and eluted carefully with CH_2Cl_2–MeOH (10:1). The less polar fractions contained mainly **13** which on recrystallization from ethyl acetate – MeOH gave **13** as yellow needles (40 mg), mp 312–315°C (dec.); ir ν_{max}: 3127, 1660, 1620, 1604, 1595; uv λ_{max}: 378 (4.05), 312 (4.02), 304 (3.97), 282 (4.34), 235 (4.10); ^{1}Hmr (DMSO-d_6) δ: 2.55 (3H, s, C*H*$_3$), 3.73 (3H, s, —NC*H*$_3$), 4.02 (2H, C2-H, bt, J = 8 Hz), 7.2–7.8 (4H, C7, 10 – H, m), 8.22 (1H,

C4-H, d, J = 8 Hz), 8.5 (1H, C11-H, s), 9.14 (1H, C1-H, s), 12.22 (1H, bs, N*H*); ms *m/e*: 250 (M^+ +2), 249 (M^+ + 1, 100%), 248 (M^+), 247, 246, 232, 231, 207, 206, 204. High resolution molecular weight determination, calcd. for $C_{17}H_{16}N_2$: 248.1315; found: 248.1299. More polar fractions containing **12** were combined and concentrated to give the product as yellow needles (140 mg) (from EtOAc–MeOH), mp 297–300°C (dec.); ir ν_{max}: 3150, 1643, 1625, 1610, 1582; uv λ_{max}: 234 (4.59), 245 (4.51), 280 (4.56), 298 (4.88), 350 (3.89); ^{1}Hmr (DMSO-d_6) δ: 2.94 (3H, s), 4.46 (3H, s), 7.39 (1H, t, J = 7.5 Hz, C9-H), 7.7–7.8 (2H, m, C 7 & 8 – H), 8.4–8.6 (3H, m, C3 & 4-H, C10-H), 9.11 (1H, s, C11-H), 9.93 (1H, s, C1-H), 12.32 (1H, N*H*). *Anal.* calcd. for $C_{17}H_{15}N_2.H_2PO_4.H_2O$: C 56.36, H 5.29, N 7.73; found: C 56.76, H 5.07, N 7.59.

*Dehydrogenation of a mixture of **12** and **13***

A mixture of **12** and **13** (0.2 g) was mixed with 20% Pd/C (0.2 g) and heated under nitrogen at 300–320°C for 30 min. The black solid was extracted with hot MeOH and the solvent evaporated. The residues were separated by silica gel column chromatography with CH_2Cl_2–MeOH as eluant. Elution with CH_2Cl_2–MeOH (10:1) afforded **16** (19 mg, 9.5% from complex **8**) as colourless prisms, mp 270–276°C (dec.) (CH_2Cl_2–pet. ether) (lit. (16) mp 290–292°C (dec.)); ir ν_{max}: 3120, 1632, 1618, 1595; uv λ_{max}: 222 (4.41), 236 (4.30), 263 (4.60), 272 (4.73), 282 (4.84), 293 (4.85), 325 (3.74); ^{1}Hmr ($CDCl_3$) δ: 2.82 (3H, s), 7.90 (1H, d, J = 6 Hz, C4-H), 8.26 (1H, d, J = 7 Hz, C11-H), 8.54 (1H, d, J = 6 Hz, C3-H), 8.59 (s, C11-H), 9.44 (s, C1-H), 8.2–8.3 (1H, bs, N*H*); ms *m/e*: 232 (M^+ 100%), 231, 229, 204, 203. High resolution molecular weight determination, calcd. for $C_{16}H_{12}N_2$: 232.1001; found: 232.0992. *Anal.* calcd. for $C_{16}H_{12}N_2$: C 82.73, H 5.21, N 12.06; found: C 82.40, H 5.11, N 12.31.

Elution with CH_2Cl_2–MeOH (5:1) provided unreacted **12** (130 mg).

*Demethylation of **12***

The salt **12** (50 mg) and triphenylphosphine (46 mg, 0.176 mmol) were dissolved in DMF (5 mL) and refluxed under nitrogen for 86 h. After evaporation of solvent, the mixture was separated by silica gel column chromatography to give **16** (18 mg, 54%) and unreacted **12** (23 mg, 46%).

Alternatively, **12** (50 mg) and triphenyl phosphine (46 mg) were dissolved in HMPA (2 mL) and heated under nitrogen at 185–190°C for 5 h. The solvent was removed under reduced pressure and the residue separated by silica gel column chromatography to give the crude product **16** which was suspended in water and then extracted with ether. Evaporation of the ether extracts gave pure **16** (15 mg, 45%).

*N-Methyl-5-methyl-1,2,3,4-tetrahydro-6H-pyrido[4,3-b]carbazole (**15**)*

$NaBH_4$ (excess) was added to a MeOH solution (1 mL) of the mixture of **12** and **13** (10 mg) at 0°C and stirred for 1 h. After evaporation of solvent the residue was taken up in water and extracted with CH_2Cl_2. Concentration of the organic extracts gave **15** (7.5 mg, 89% from complex **8**), mp 205–207°C (from ether); ir ν_{max}: 3320, 1613; uv λ_{max}: 232 (4.62), 238 (4.71), 248 (4.56), 259 (4.40), 287 (4.11), 297 (4.32), 326 (3.66), 340 (3.53); ^{1}Hmr (DMSO-d_6) δ: 2.52 (3H, s), 2.69 (2H, bs, C3-H), 2.89 (2H, bs, C3-H), 3.17 (1H, s, C1-H), 3.41 (1H, s, C1-H), 3.65 (3H, bs, N—C*H*$_3$), 7.09 (1H, t, J = 7.5 Hz, C9-H), 7.33 (1H, t, J = 7.5 Hz, C8-H), 7.44 (1H, d, J = 8.5 Hz, C7-H), 7.60 (1H, s, C11-H), 7.98 (1H, d, J = 8.5 Hz, C10-H), 10.90 (1H, bs, N*H*); ms *m/e*: 250 (M^+), 249 (100%), 233, 207, 191. High resolution molecular weight determination, calcd. for $C_{17}H_{18}N_2$: 250.1471; found: 250.1449. *Anal.* calcd. for $C_{17}H_{18}N_2$: C 80.92, H 7.19, N 11.10; found: C 81.28, H 7.17, N 11.19.

Reduction of **13** (5 mg) with $NaBH_4$ (8 mg) under similar conditions also resulted in a single product **15** (3 mg) with physical properties identical to those above.

*1-Methyl-5-methyl-6H-pyrido[4,3-b]carbazole, olivacine (**1**)*

CH_3Li solution (1 M, 0.75 mL) was added to a solution of **16** (35 mg) in dry THF (2 mL) at 0°C under nitrogen. The mixture was stirred at room temperature for 30 min and then refluxed for another 1 h. MeOH was added to quench excess CH_3Li and then I_2 (38 mg) was added. After stirring of the mixture for 30 min, the solvent was removed and the residue triturated with water. The product was collected and purified by silica gel column chromatography to give **1** (20 mg, 54%) as yellow prisms (from ether), mp 303–306°C (dec.) (lit. (5) mp 318–326°C (dec.)); ir ν_{max}: 3120, 1635, 1615, 1600; uv λ_{max}: 218 (4.39), 235 (4.31), 265 (4.49), 273 (4.63), 283 (4.78), 289 (4.77), 303 (4.17), 324 (3.55); ^{1}Hmr ($CDCl_3$) δ: 2.82 (3H, s), 3.13 (3H, s), 7.79 (1H, C4-H, d, J = 6 Hz), 8.28 (1H, C10-H, d, J = 7 Hz), 8.3–8.2 (1H, bs, N*H*), 8.42 (1H, C3-H, d, J = 6 Hz), 8.78 (1H, s, C11-H); ms *m/e*: 247, 246 (M^+ 100%), 245, 231, 217, 204. High resolution molecular weight determination, calcd. for $C_{17}H_{14}N_2$: 246.1158; found: 246.1156. *Anal.* calcd. for $C_{17}H_{14}N_2.2/3\ H_2O$: C 79.07, H 5.94, N 10.85; found: C 79.38, H 6.20, N 10.13.

*1-Methyl-5-methyl-N-methyl-1,2,3,4-tetrahydropyrido[4,3-b]carbazole, (+)-gutambuine (**2**)*

Olivacine (**1**, 22 mg) and CH_3I (excess) in MeOH (2 mL) were heated at 50°C for 5 h and then evaporated to dryness. The residue was dissolved in MeOH (3 mL) and $NaBH_4$ (excess) was added at 0°C and stirred for 1 h. After removal of solvent, the residue was quenched with water and extracted with CH_2Cl_2. The combined organic extract was purified by preparative tlc to give **2** (9 mg, 40%) as colourless needles, mp 247–250°C (from ether) (lit. (9) mp 249–252°C); ir ν_{max}: 3120, 1616; uv λ_{max}: 216 (4.26), 232 (4.34), 277 (4.42), 247 (4.30), 258 (4.16), 285 (3.86), 296 (4.06), 325 (3.50), 348 (3.42); ^{1}Hmr ($CDCl_3$) δ: 1.56 (3H, d, J = 6 Hz), 2.40 (3H, s), 2.54 (3H, s), 3.88 (1H, q, C1-H), 7.74 (1H, s, C11-H), 8.05 (1H, d, J = 8 Hz, C10-H), 7.80 (1H, bs, NH); ms *m/e*: 264 (M^+), 263, 249 (100%), 247. High resolution molecular weight determination, calcd. for $C_{18}H_{20}N_2$: 264.1628; found: 264.1617. *Anal.* calcd. for $C_{18}H_{20}N_2$: C 81.78, H 7.63, N 10.60; found: C81.25, H 7.52, N 10.96.

Acknowledgements

Financial aid from the Natural Sciences and Engineering Research Council of Canada is gratefully acknowledged. We are grateful to Dr. Lewis S. L. Choi for helpful discussions and assistance.

1. J. P. KUTNEY, Y. KARTON, N. KAWAMURA, and B. R. WORTH. Can. J. Chem. **60**, 1269 (1982).
2. J. P. KUTNEY, M. NODA, N. G. LEWIS, B. MONTEIRO, D. MOSTOWICZ, and B. R. WORTH. Heterocycles, **16**, 1469 (1981).
3. A. AHOND, A. CAVE, T. A. CONNORS, L. K. DALTON, N. DAT-XUONG, M. HAYAT, F. LE GOFFIC, A. GOUYETTE, M. M. JANOT, C. KAN-FAN, G. MATHE, J. LE MEN, J. MIET, J. POISSON, P. POTIER, and T. SEVENET. Biomedicine, **21**, 101 (1974).
4. E. M. ACTA, O. P. CREWS, L. GOODMAN, and C. W. MOSHER. J. Med. Chem. **9**, 237 (1966).
5. N. DAT-XUONG, C. GOSS, C. PAOLETTI, and J. B. LE PECQ. C. R. Acad. Sci. **277**, 2289 (1973).
6. J. SCHMUTZ and H. WITTWER. Helv. Chim. Acta, **43**, 793 (1960).
7. M. SAINSBURY. Synthesis, 437 (1977).

8. D. S. GRIERSON and J. P. KUTNEY. Heterocycles, **3**, 171 (1975).
9. T. KAMETANI, Y. ICHIKAWA, T. SUZUKI, and K. FUKUMOTO. Heterocycles, **3**, 401 (1975); J. Chem. Soc. Perkin Trans. I, 2102 (1975).
10. R. BESSELIEVRE and H. P. HUSSON. Tetrahedron Lett. **22**, 1873 (1976).
11. F. A. HOCHSTEIN, G. A. IACOBUCCI, and R. B. WOODWARD. J. Am. Chem. Soc. **81**, 4434 (1959).
12. P. A. CRANWELL and J. E. SAXTON. J. Chem. Soc. 3482 (1966).
13. T. R. GOVINDACHARI, S. RAJAPPA, and V. SUDARSANAM. Indian J. Chem. **1**, 247 (1963).
14. R. N. STILLWELL. Ph.D. Thesis, Harvard University, 1964.
15. L. K. DALTON, S. DEMERAC, B. C. ELMES, J. W. LODER, J. M. SWAN, and T. TEITEI. Aust. J. Chem. **20**, 2715 (1967).
16. K. N. KILMINSTER and M. SAINSBURY. J. Chem. Soc. Perkin Trans. I, 2264 (1972).
17. A. AHOND, F. LE GOFFIC, and A. GOUYETTE. Tetrahedron, **29**, 3357 (1973).
18. N. M. HASAN and A. P. KOZIKOWSKI. J. Org. Chem. **42**, 2039 (1977).
19. R. BESSELIEVRE, C. THAL, H. P. HUSSON, and P. POTIER. J. Chem. Soc. Chem. Commun. **90** (1975).
20. S. J. MARTINEZ and J. A. JOULE. J. Chem. Soc. Chem. Commun. 818 (1976).
21. T. NAITO, N. IIDA, and I. NINOMIYA. J. Chem. Soc. Chem. Commun. 44 (1981).
22. J. P. KUTNEY, R. A. BADGER, W. R. CULLEN, R. GREENHOUSE, M. NODA, V. E. RIDAURA-SANZ, Y. H. SO, A. ZANAROTTI, and B. R. WORTH. Can. J. Chem. **57**, 300 (1979).
23. J. P. KUTNEY, T. C. W. MAK, D. MOSTOWICZ, J. TROTTER, and B. R. WORTH. Heterocycles, **12**, 1517 (1979).
24. H. F. RUSSELL and R. J. SUNDBERG. J. Org. Chem. **38**, 3324 (1973).