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# PALLADIUM CATALYZED INSERTION OF CARBON MONOXIDE INTO BENZYL-TETRAHYDROISOQUINOLINES

## A NEW SYNTHESIS OF BERBINE ALKALOIDS[1]

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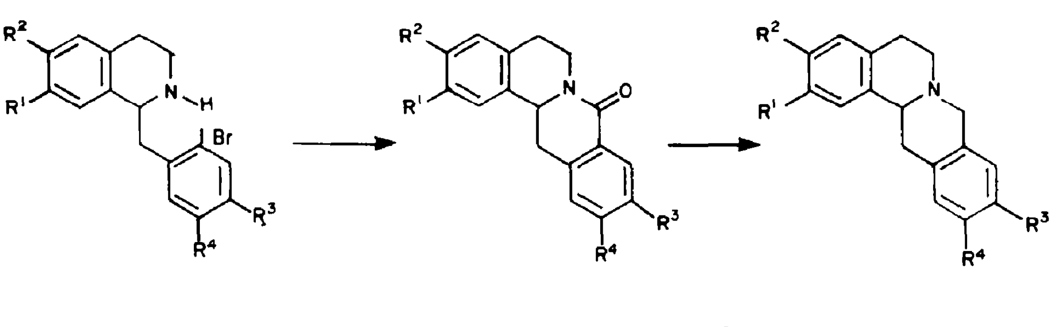
**Abstract**—A new total synthesis of the berbine alkaloid ring system has been achieved. Palladium catalyzed insertion of carbon monoxide into the 1 - (2 - bromobenzyl) - substituted - 1,2,3,4 - tetrahydroisoquinolines (**1a–d**) by the use of catalytic amounts of palladium diacetate and triphenylphosphine in the presence of tri-n-butylamine afforded the berbin-8-ones (**2a–d**) which, on reduction with lithium aluminium hydride gave the berbines (±)-berbine **3a**, (±)-2,3-dimethoxyberbine **3b**, (±)-xylopinine **3c** and (±)-pseudoepitetrahydroberbine **3d**.

The synthesis of the tetracyclic berbine ring system has been achieved in a variety of ways.[3–8] Naturally occurring and modified berbine derivatives have shown hypotensive activity[9–11] and the recent use of tetrahydropalmatine as an antipsychotic drug[12–14] has increased interest in this class of compounds. Owing chiefly to the interesting biological activity[15] in this class of compounds we have recently concentrated mainly on the problem of berbine synthesis and some successful syntheses have been reported from our laboratory.[16–22]

Recently, palladium-catalyzed carbonylation has been recognised as a useful route to the benzolactams.[23] We became interested in this reaction as the key precursors to the desired berbines, the 1 - (2 - bromobenzyl) - substituted - 1,2,3,4 - tetrahydroisoquinolines **1a–d** were easily accessible and could be carbonylated to give the berbin-8-ones **2a–d**. The berbines **3a–d** were easily prepared by the lithium aluminium hydride reduction of the berbinones **2a–d** thus providing a convenient total synthesis of alkaloids, (±)-berbine **3a**, (±)-2,3-dimethoxyberbine **3b**, (±)-xylopinine **3c** and (±)-pseudoepitetrahydroberbine **3d** (Chart 1).



$R^1 = R^2 = R^3 = R^4 = H$ (1a) → (2a) → (3a)
$R^1 = R^2 = OCH$; $R^3 = R^4 = H$ (1b) → (2b) → (3b)
$R^1 = R^2 = R^3 = R^4 = OCH_3$ (1c) → (2c) → (3c)
$R^1 = R^2 = OCH_3$; $R^3 = R^4 =$ (1d) → (2d) → (3d)
$OCH_2O$

Chart 1.

The 1 - (2 - bromobenzyl) - substituted - 1,2,3,4 - tetrahydroisoquinolines **1a–d** used in the present work were prepared by standard procedures involving the Schotten–Baumann condensation[24] of the β-phenethylamines with the brominated phenylacetic acids, the Bischler–Napieralski cyclization of the product followed by sodium borohydride reduction[25] of the resulting dihydroisoquinoline intermediates.

The carbonylation was carried out by heating the 1 - (2 - bromobenzyl) - 1,2,3,4 - tetrahydroisoquinolines **1a–d** with catalytic amounts of palladium diacetate (4–6 mole%) and triphenylphosphine (6 mole%) in presence of tri-n-butylamine under a carbon monoxide atmosphere at 95–100° for 30–140 h. The resulting bergin-8-ones **2a–d** were reduced to the desired berbines **3a–d** by lithium aluminium hydride in refluxing tetrahydrofuran.

### EXPERIMENTAL

M.ps were determined on a Toshniwal apparatus and are uncorrected. The NMR spectra were recorded on a Varian A-6 60 MHz or a WCB-WH-90 MHz spectrometer. Chemical shifts are reported in ppm relative to TMS as internal standard. IR spectra were recorded on IR-S or Perkin–Elmer 337 spectrophotometers. All solutions were dried over anhydrous sodium sulphate.

5,6,13,13a - *Tetrahydro* - 8H - *dibenzo* - [a,g]*quinolizin* - 8 - *one* **2a**

1 - (2 - Bromobenzyl) - 1,2,3,4 - tetrahydroisoquinoline (150 mg) was heated with palladium diacetate (4 mole%) and triphenylphosphine (6 mole%) under a carbon monoxide atmosphere in the presence of tri-n-butylamine (2.2 g) for 30 h at 100° (bath temperature). The mixture was cooled, extracted with $CHCl_3$ and

the extract was washed with dilute HCl, water and dried. Removal of the solvent *in vacuo* gave after recrystallization from $Et_2O$–$CH_2Cl_2$ the berbin-8-one **2a** (60 mg, 43.0%) as dull yellow prisms, m.p. 168–170°; IR (KBr) 1640 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 8.28–8.08 (1H, m, C-9H), 7.58–7.16 (7H, m, other aromatic protons), 5.13–4.75 (2H, m, C-13a H and 6-H), 3.18–2.86 (5H, m, other methylene protons). Calc. for $C_{17}H_{15}NO$: C, 81.9; H, 6.06; N, 5.62. Found: C, 81.7; H, 6.00; N, 5.84%.

### 5,6,13,13a - *Tetrahydro* - 8H - *dibenzo* - [a,g] *quinolizine* (±)-*berbine* **3a**

To a solution of the berbin-8-one **2a** (115 mg) in anhydrous tetrahydrofuran (6 ml) was added lithium aluminium hydride (350 mg) in portions while the solution was kept at 0° under constant stirring. The mixture was refluxed for 10 h. After cooling, the excess hydride was decomposed by dropwise addition of water and the mixture was poured into water. The aqueous solution was extracted with $CH_2Cl_2$ and dried. Removal of the solvent *in vacuo* afforded the berbine **3a** (70 mg, 50.6%), m.p. 84° (lit[26] m.p. 83–85°). **3a** was identical in all respects with an authentic sample prepared following the method of Margni *et al.*[26]

### 5,6,13,13a - *Tetrahydro* - 2,3 - *dimethoxy* - 8H - *dibenzo*[a,g] *quinolizin* - 8 - *one* **2b**

1 - (2 - bromobenzyl) - 1,2,3,4 - tetrahydro - 6,7 - dimethoxyisoquinoline prepared from homoveratrylamine and 2-bromophenyl-acetic acid was reacted as described for compound **2a** to give 2,3-dimethoxyberbin-8-one **2b** (40%), m.p. 140–141° (lit.[27] m.p. 141–142°); IR ($CHCl_3$) 1645 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 8.20 (1H, m, 9-H), 6.75 (1H, s, 1- or 4-H), 6.70 (1H, s, 4- or 1-H), 5.17–4.69 (2H, m, 13a and 6-H), 3.90 (6H, s, $OCH_3 \times 2$). Calc. for $C_{19}H_{19}NO$: C, 82.83; H, 6.82; N, 5.05. Found: C, 82.1; H, 6.71; N, 5.00%.

### 5,6,13,13a - *Tetrahydro* - 2,3 - *dimethoxy* - 8H - *dibenzo*[a,g] *quinolizine* **3b**

By the procedure given for compound **3a**, the berbin-8-one **2b** was reduced to give the 2,3-dimethoxyberbine (52%) as a clear oil. UV $\lambda_{max}^{CH_3OH}$ 286, 281, 272 nm; IR (KBr) 2840–2750 (Bohlmann bands) $cm^{-1}$; NMR (DMSO-$d_6$) $\delta$ 3.69 (3H, s, $OCH_3$), 3.72 (3H, s, $OCH_3$), 3.85 (1H, distorted t, J = 3 Hz; 13a-H), 6.60 (1H, s, ArH), 6.80 (1H, s, ArH), 7.05 (4H, s, 4×ArH). Calc. for $C_{19}H_{21}NO_2$: C, 77.2; H, 7.11; N, 4.74. Found: C, 77.4; H, 7.16; N, 4.58%.

### 5,6,13,13a - *Tetrahydro* - 2,3,10,11 - *tetramethoxy* - 8H - *dibenzo[a,g]quinolizin* - 8 - *one* **2c**

1 - (2 - Bromo - 4,5 - dimethoxybenzyl) - 1,2,3,4 - tetrahydro - 6,7 - dimethoxyisoquinoline (105 mg) was heated with palladium diacetate (4 mole%) and triphenylphosphine (6 mole%) in presence of tri-n-butylamine (600 mg) at 100° under a carbon monoxide atmosphere for 72 h. Work up as above gave 2,3,10,11 - tetramethoxyberbin - 8 - one **2c** (60 mg, 53%), m.p. 191° (lit[28] m.p. 190–192°; lit[29] m.p. 188–189°); IR ($CHCl_3$) 1650, 1610, 1600, 1515 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 7.60 (1H, s, 9-H), 6.75 (3H, s, 1-, 4- and 12-H), 5.20–4.70 (2H, m, 6- and 13a-H), 3.93 (9H) and 3.91 (3H) (each s, $OCH_3 \times 4$). Calc. for $C_{21}H_{23}NO_5$: C, 68.2; H, 6.30; N, 3.81. Found: C, 67.9; H, 6.40; N, 3.82%.

### 5,6,13,13a - *Tetrahydro* - 2,3,10,11 - *tetramethoxy* - 8H - *dibenzo*[a,g] *quinolizine*: (±)-*xylopinine* **3c**

The berbin-8-one **2c** was reduced with lithium aluminium hydride as above to give the 2,3,10,11-tetramethoxyberbine **3c** (49%), m.p. 157° (lit[30] m.p. 157–158°); IR (KBr) 1610, 1515 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 6.60 (s, 1H), 6.55 (s, 1H), 6.52 (s, 1H), 6.47 (s, 1H), 3.82 (s, 3H), 3.80 (s, 9H), 2.9–3.9 (m, 9H). Calc. for $C_{21}H_{25}NO_4$: C, 70.9; H, 7.04; N, 3.94. Found: C, 70.7; H, 7.00; N, 3.78%.

### 5,6,13,13a - *Tetrahydro* - 2,3 - *dimethoxy* - 8H - *dibenzo* - [a][1,3] - *benzodioxolo*[5,6-g] *quinolizin* - 8 - *one* **2d**

1 - (4,5 - Methylenedioxy - 2 - bromobenzyl) - 1,2,3,4 - tetrahydro - 6,7 - dimethoxyisoquinoline (100 mg) was heated with palladium diacetate (4 mole%) and triphenylphosphine (6 mole%) in the presence of tri-n-butylamine (1.86 g) under a carbon monoxide atmosphere at 95° for 30 h. Work up as for the compound **2a** after recrystallization from EtOAc–$Et_2O$ gave (3d) (40 mg, 50%), m.p. 175–176°; NMR ($CDCl_3$) $\delta$ 7.60 (s, 1H), 6.70 (br, s, 3H), 5.95 (s, 2H), 4.65–5.09 (m, 2H), 3.90 (s, 6H), 2.50–3.10 (m, 5H). Calc. for $C_{21}H_{23}NO_5$: C, 68.2; H, 6.28; N, 3.80. Found: C, 67.8; N, 6.40; N, 3.80%.

### 5,6,13,13a - *Tetrahydro* - 2,3 - *dimethoxy* - 8H - *dibenzo* - [a][1, 3] - *benzodioxolo*[5,6-g]*quinolizine* **3d**: (±)-*pseudoepitetrahydroberbine*

The berbin-8-one **2d** was reduced with lithium aluminium hydride as above to give 2,3 - dimethoxy - 10,11 - methylenedioxy - berbine **3d** (71%); m.p. 155–156°; IR (KBr) 1620, 1540, 1510 $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 6.75 (s, 1H), 6.64 (s, 2H), 6.55 (s, 1H), 5.90 (s, 2H), 3.88 (s, 3H), 3.85 (s, 3H), 2.5–3.75 (m, 9H). Calc. for $C_{20}H_{21}NO_4$: C, 70.7; H, 6.24; N, 4.13. Found: C, 70.6; H, 6.42; N, 3.9%.

The hydrochloride had m.p. 263–265°; IR (KBr) 1620, 1530, 1505 $cm^{-1}$.

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