REDUCTION AND CARBOXYLATION OF 1-CHLOROMETHYL-6,7-DIMETHOXY-3,4-DIHYDROISOQUINOLINIUM SALTS. AN EASY ENTRY TO 1-HYDROXYMETHYL-1,2,3,4-TETRAHYDROISOQUINOLINE ALKALOIDS

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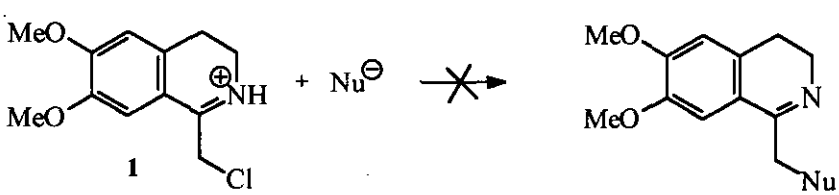
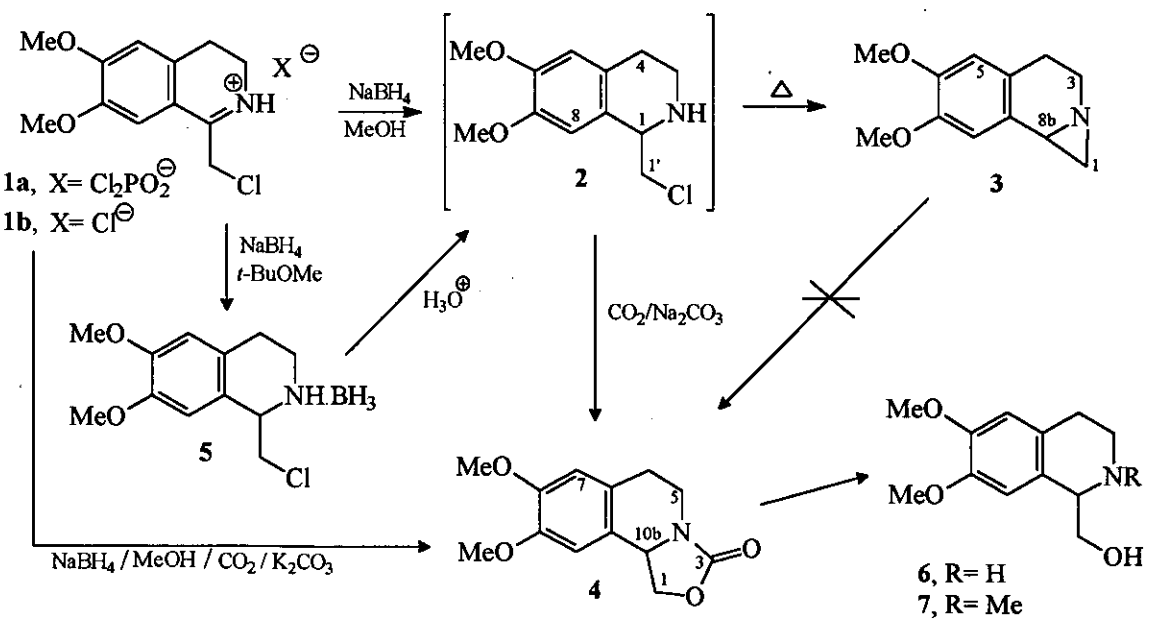
Abstract- At 25°C, the $NaBH_4$/MeOH reduction of the title isoquinolinium salts gave the aziridine exclusively. At a low temperature (0°C) in the presence of CO_2/K_2CO_3, the 2-oxazolidinone was obtained in almost quantitative yield. Controlled hydrolysis of the borane complex derived from the isoquinolinium salts also gave the cyclic carbamate. (±)-Calycotomine and its *N*-Me derivative were obtained in high yields.

Certain isoquinoline alkaloids share a structural feature: a hydroxymethyl group at position 1 of the heterocyclic nucleus.[1] They include from simple isoquinolines found in *Fabaceae* and *Cactaceae* to complex antitumor agents such as quinocarcin from *Streptomyces* cultures[2] and ecteinascidins from caribian tunicates.[3] Most of their syntheses introduce the substituent before the heterocycle is formed *via* the Bischler-Napieralski or Pictet-Spengler reaction.[4] This latter approach requires a methoxyl or a hydroxyl group at *para* position of the cyclization site,[5] while the Bischler-Napieralski ring closure is preferred for non-phenolic substrates. However, low yields and inconsistent results have been reported for the cyclization of *O*-substituted derivatives of *N*-(3,4-dimethoxy-β-phenylethyl)glycolamide.[6] Moreover, attempts at converting the 1-chloromethylisoquinolinium (**1**) to the corresponding 1-hydroxymethyl and 1-acetoxymethyl derivatives by reaction with silver hydroxide and NaOAc, respectively, failed.[6b]



One reason for this failure is the ease of dimerization to the corresponding pentacyclic pyrazino[2,1-*a*:5,4-*a'*]diisoquinoline derivative.[7] We presumed that the reactivity of the free base of **1** could be diminished by reduction of the C=N double bond to prevent dimerization. We herewith report that, following reduction of **1**, the reactivity of 1-chloromethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**2**) can be shifted from the formation of the aziridine (**3**) to carbonate fixing to give the 2-oxazolidinone (**4**) in high yield.

When **1a,b** were reduced under the usual conditions ($NaBH_4$, MeOH, 25 °C), the 1-chloromethyltetrahydroisoquinoline (**2**) could not be obtained, but the aziridine (**3**)[6c] was produced in high yield. At a low temperature (0°C), the reduction product (**2**) was observed in the ^1H nmr spectrum of the reaction, but readily cyclized and hindered isolation. In order to avoid the cyclization, **1** was reduced in *t*-butyl methyl ether and the borane-complex (**5**) was isolated in a 95% yield. Hydrolysis of the borane[8] and substitution of the halogen was attempted in aqueous acetone/HCl at 25 °C. Neutralization of the reaction mixture with Na_2CO_3 gave **3** and a minor component was characterized as the oxazolidinone (**4**)[9] (6:1 ratio).



This result was interpreted in terms of carboxylation of the amine (**2**) to the carbamate, followed by displacement of the chlorine atom, a process that competes with the aziridine formation.[10] Consequently, the hydrolysis of **5** was carried out under a positive pressure (1.5 atm) of CO_2 in the presence of a large excess of Na_2CO_3 at low temperature throughout to obtain 82% of **4**. Hydrolysis

of the borane was assumed to take place before the carboxylation, so we returned to the $NaBH_4$ reduction of **1b** in a CO_2/K_2CO_3 saturated MeOH solution at 0°C for 24 h, giving rise to oxazolidinone (**4**) in 95% yield. Hydrolysis or $LiAlH_4$ reduction of **4** gave the isoquinoline alkaloid (±)-calycotomine (**6**)[5b] or its *N*-methyl derivative (**7**)[5d] in more than 70% yield from homoveratrylamine. In conclusion, this work opens a new access to 2-oxazolidinones *via* reduction/carboxylation of an α-chloroimine.

EXPERIMENTAL

General. All mp values are uncorrected. EIms were measured at 70 eV on a HP-5988A instrument. Silica gel 60 F_{254} was used for preparative tlc. ^1H and ^{13}C nmr spectra were recorded on a Bruker WP-200 SY spectrometer. Proton chemical shifts are referred to residual chloroform (δ 7.24 ppm) and carbon chemical shifts to the solvent ($^{13}CDCl_3$ = 77 ppm). ^1H and ^{13}C nmr signals were assigned from 2D COSY and DEPT experiments.

1-Chloromethyl-6,7-dimethoxy-3,4-dihydroisoquinoline hydrogen dichlorophosphate (1a): A CH_3CN (20 ml) solution of $POCl_3$ (20 g, 130 mmol) was dropwise added to a CH_3CN (200 ml) solution of *N*-(3,4-dimethoxy-β-phenylethyl)chloroacetamide[11] (23.2 g, 90 mmol) and the mixture was refluxed for 3 h. The volume of the reaction mixture was reduced *in vacuo* to 50 ml and toluene (50 ml) was added until the dichlorophosphate separated (32 g, 95%) as an orange crystalline solid. mp 152-153°C (1:1, acetonitrile-toluene). ^1H Nmr ($CDCl_3$) (δ, ppm): 7.13 (s, 1H, H-8), 6.74 (s, 1H, H-5), 4.83 (s, 2H, CH_2Cl), 3.76 and 3.69 (two s, 3H each, 2xOCH_3), 3.69 (t, 2H, J=8.2 Hz, H-3,3'), 2.91 (t, 2H, J=8.2 Hz, H-4,4'). ^{13}C Nmr ($CDCl_3$ + CD_3OD) (δ, ppm): 170.6 (C-1), 157.2 (C-6), 148.5 (C-7), 134.5 (C-4a), 115.0 (C-8a), 111.6, 111.0 (C-5, C-8), 56.4, 56.2 (2xOCH_3), 41.0 (C-3), 38.7 (C-1'), 24.5 (C-4). Anal. Calcd for $C_{12}H_{15}NO_4Cl_3P$: C, 38.48; H, 4.04; N, 3.74. Found: C, 38.11; H, 4.16; N, 3.61.

1-Chloromethyl-6,7-dimethoxy-3,4-dihydroisoquinoline hydrogen chloride (1b): To a solution of the dichlorophosphate (**1a**) (10 g, 26 mmol) in MeOH (sat. with HCl, 75 ml), ether (200 ml) was added to give pale yellow crystals of the salt (**1b**) (5.8 g, 86%). mp 201-202°C [lit.,[6b] mp 209-210°C (decomp.)].

(±)-6,7-Dimethoxy-1,3,4,8b-tetrahydroazirino[2,1-*a*]isoquinoline (3): To a MeOH (75 ml) stirred suspension of **1a** (1 g, 2.7 mmol), $NaBH_4$ (1 g, 26 mmol) was added in small portions over a period of 30 min at 25°C. After stirring for 2 h, the solvent was removed and the residue was extracted with

CH_2Cl_2. The organic layer was washed with water, dried over Na_2SO_4 and concentrated *in vacuo* to give **3** as an oil (521 mg, 94%) that crystallized on standing. mp 102-103°C (lit.,[6c] mp 96-97°C).

(±)-1-Chloromethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-borane (5): Solid $NaBH_4$ (182 mg, 4.8 mmol) was added portionwise to a stirred suspension of **1b** (1 g, 3.6 mmol) in *t*-butyl methyl ether (120 ml). After 12 h the reaction mixture was filtered and the solid residue was extracted with *t*-butyl methyl ether (3 x 15 ml) and $CHCl_3$ (3 x 15 ml). The combined organic solutions were dried over Na_2SO_4 and concentrated to afford the amine-borane complex (**5**) (880 mg, 95%) as a white crystalline solid. mp 142-143°C. ^{1}H Nmr ($CDCl_3$) (δ, ppm): 6.58 (s, 1H, H-8), 6.51 (s, 1H, H-5), 4.39 (dd, 1H, J = 11.9 and 2.5 Hz, CHCl), 4.34-4.22 (m, 2H, H-1 and NH), 3.86 (dd, 1H, J = 11.9 and 5.3 Hz, CHCl), 3.83 and 3.82 (two s, 3H each, 2xOCH_3), 3.49-3.31 (m, 1H, H-3), 3.15-2.70 (m, 3H, H-3', H-4,4'). ^{13}C Nmr ($CDCl_3$) (δ, ppm): 148.7, 148.3 (C-6, C-7), 126.0, 122.1 (C-4a, C-8a), 111.2, 108.8 (C-5, C-8), 62.2 (C-1), 56.0, 55.8 (2xOCH_3), 47.4 (C-1'), 47.1 (C-3), 25.8 (C-4). EIms m/*z* (%): 257, 256, 255, 254 (M^+), 206 (9), 192 (100). Ir (ν, cm^{-1}) (KBr): 2400-2280 (B-H). Anal. Calcd for $C_{12}H_{19}NO_2BCl$: C, 56.44; H, 7.51; N, 5.49. Found: C, 56.06; H, 7.37; N, 5.45.

(±)-8,9-Dimethoxy-3-oxo-1,5,6,10b-tetrahydro-3*H*-oxazolo[4,3-*a*]isoquinoline (4):

From 5: A mixture of amine-borane complex (**5**) (200 mg, 0.78 mmol) and acetone (40 ml) was treated with 1N HCl (40 ml). After stirring for 15 min at 25°C the reaction was made alkaline with 5% aqueous Na_2CO_3 and extracted with $CHCl_3$. ^{1}H Nmr spectrum of the crude product showed a major component identified as **3**, and a minor component **4**, that was separated by preparative tlc (silica gel; 12:1 $CHCl_3$-MeOH) as an oil that crystallized on standing (30 mg, 15%). In a second experiment, the reaction was carried out at 0°C, under a positive pressure of CO_2 (1.5 atm). After 15 min, a large excess of solid sodium carbonate was added, and stirring was continued at this temperature for 24 h. Work-up as above, afforded the oxazolidinone (**4**) in a 82% yield. mp 99-100°C. ^{1}H Nmr ($CDCl_3$) (δ, ppm): 6.59 (s, 1H, H-10), 6.41 (s, 1H, H-7), 4.93 (dd, 1H, J = 8.0 and 7.5 Hz, H-1), 4.74 (dd, 1H, J = 8.0 and 8.4 Hz, H-1'), 4.13 (dd, 1H, J = 7.5 and 8.4 Hz, H-10b), 4.06 (ddd, 1H, J = 12.0, 5.0 and 1.0 Hz, H-5), 3.83 and 3.82 (two s, 3H each, 2xOCH_3), 3.17 (ddd, 1H, J = 12.0, 12.0 and 4.0 Hz, H-5'), 2.98 (ddd, 1H, J = 16.0, 12.0 and 5.0 Hz, H-6), 2.62 (ddd, 1H, J = 16.0, 4.0 and 1.0 Hz, H-6'). ^{13}C Nmr ($CDCl_3$) (δ, ppm): 157.5 (C-3), 148.5, 148.4 (C-8, C-9), 126.2, 125.9 (C-6a, C-10a), 112.0, 107.4 (C-7, C-10), 69.4 (C-1), 56.1, 55.9 (2xOCH_3), 54.1 (C-10b), 38.8 (C-5), 27.0 (C-6). EIms m/*z*(%): 249 (M^+, 100), 248 (M^+-1, 70), 234 (19), 218 (24), 191 (45), 176 (35). Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.28; H, 5.90; N, 5.38.

From **1b**: To a cooled (0 °C) and stirred suspension of K_2CO_3 (4 g, 29 mmol) in MeOH (100 ml) was added **1b** (1 g, 3.6 mmol) followed by $NaBH_4$ (1 g, 26 mmol). The reaction mixture was stirred for 24 h under a positive pressure of CO_2 (1.5 atm) while the temperature was kept below 5 °C. The reaction mixture was filtered, the separated solid was washed with MeOH (3 x 15 ml) and the methanolic extracts were concentrated to dryness. The residue was suspended in H_2O (100 ml) and extracted with $CHCl_3$ (3 x 50 ml). The extracts were dried (Na_2SO_4) and the solvent was removed to afford 850 mg (95%) of pure **4** (tlc, ^1H nmr).

(±)-Calycotomine (6): A solution of oxazolidinone (**4**) (76 mg, 0.3 mmol) in 10% ethanolic sodium hydroxide (15 ml) was refluxed for 6 h. After the evaporation of solvent, H_2O (15 ml) was added and the mixture was extracted with $CHCl_3$ (4 x 15 ml). The organic layer was dried over Na_2SO_4 and concentrated to afford **6** as a white solid that was recrystallized from benzene (61 mg, 90%). mp 134-135°C (lit.,[5b] mp 134°C).

(±)-*N*-Methylcalycotomine (7): To a stirred solution of $LiAlH_4$ (70 mg, 1.8 mmol) in THF (20 ml) a solution of oxazolidinone (**4**) (100 mg, 0.4 mmol) in THF (10 ml) was added under nitrogen atmosphere. After being refluxed for 1 h, the mixture was cooled to 20°C, and H_2O (0.1 ml), 10% NaOH (0.1 ml) and H_2O (0.1 ml) were sequentially added. The inorganic salts were removed by filtration, the solid was washed with $CHCl_3$ (3 x 10 ml) and the combined filtrates were dried over Na_2SO_4 and evaporated to afford (±)-*N*-methylcalycotomine (**7**) as colorless oil (62 mg, 65%). The ^1H nmr data are in agreement with those reported[5d, 12] for both (*R*)-**7** and (*S*)-**7**.

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