Monatshefte für Chemie 135, 1289–1295 (2004)
DOI 10.1007/s00706-004-0204-8

Monatshefte für Chemie
Chemical Monthly
Printed in Austria

A Convenient Synthesis of 1-Benzyl-1,2,3,4-tetrahydroisoquinolines by Combined *Strecker/Bruylants* Reaction

Eberhard Reimann* and **Christian Ettmayr**

Department Pharmazie – Zentrum für Pharmaforschung, Ludwig-Maximilians-Universität München, D-81377 München, Germany

Received March 8, 2004; accepted March 29, 2004
Published online June 24, 2004

Summary. *Strecker* reaction of iodophenethylamines with phenylacetaldehydes afforded the corresponding α-aminonitriles, which on treatment with *i*-propyl magnesium chloride underwent a *Bruylants* reaction to give the title compounds. Their structures were deduced by NMR and by an independent preparation starting from papaverine. The educts were easily available by standard procedures.

Keywords. Alkaloids; Cyclizations; Hydrogenation; Iodination; Iodine–magnesium exchange reaction.

Introduction

The structure of many alkaloids exhibiting significant physiological activities is based on substituted 1,2,3,4-tetrahydroisoquinolines. The most important ones in this field are the 1-benzyl derivatives, which are known to be central key precursors in the biosynthesis of a variety of alkaloids, *e.g.* aporphines, bisbenzylisoquinolines, cularine and erythrina alkaloids, protoberberines, and morphine [1, 2]. On the other hand substituted tetrahydroisoquinolines have been found to exhibit a broad spectrum of biological activities [3] and furthermore being relevant to pathogenesis of *Parkinson*'s disease [4–6]. Finally 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid should be mentioned representing an interesting constrained analogue of phenylalanine and being used for the construction of conformationally restricted analogues of biological active peptides [7, 8]. In this regard tetrahydroisoquinolines also have received increasing attention from the viewpoint of medicinal chemistry.

In this connection we envisioned the combined *Strecker/Bruylants* reactions previously established for our synthesis of erythrinanes [9] to be a general and efficient approach to 1-substituted 1,2,3,4-tetrahydro-isoquinolines **IV** mentioned

* Corresponding author. E-mail: ebrei@cup.uni-muenchen.de

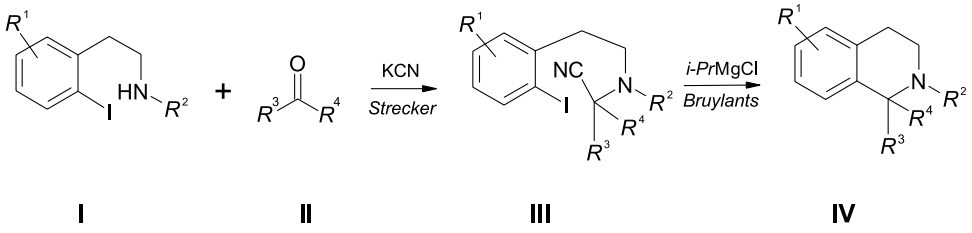
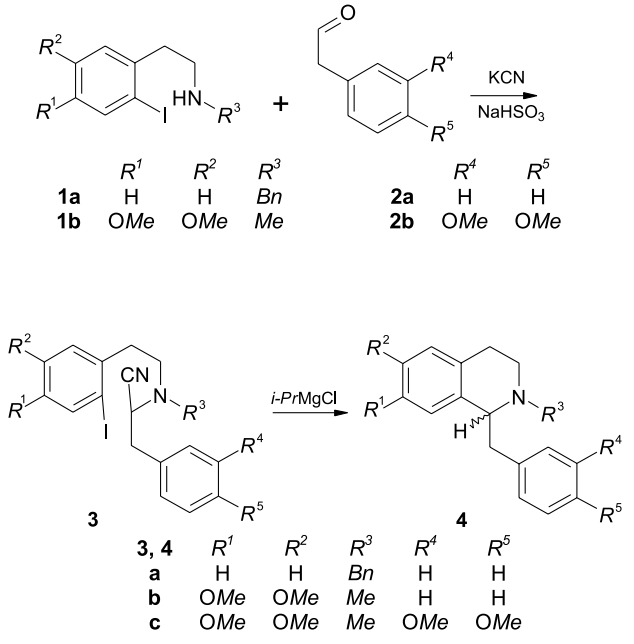


Fig. 1. General route to 1-substituted 1,2,3,4-tetrahydroisoquinolines

above starting from iodinated phenethylamines **I** and appropriate carbonyl compounds **II** *via* the α-aminonitriles **III** according to Fig. 1. Herein we wish to report a further example of this strategy by synthesizing the title compounds.

Results and Discussion

The synthesis route is depicted in Scheme 1. Thus, the iodophenethylamines **1** were reacted with the phenylacetaldehydes **2** affording the α-aminonitriles **3**. The yields obtained were satisfactory (70–89%) when the initial *Strecker* reaction was performed in the presence of sodium hydrogen sulfite according to Ref. [10]. In contrast to the aminonitriles recently prepared [9] the products **3** contained remarkable amounts of impurities, which had to be removed by FC or crystallization (Experimental). Finally, the nitriles **3** were treated with *i*-propyl magnesium chloride in *THF* providing the 1-benzyltetrahydoisoquinolines **4**, among others the alkaloid (±)-laudanosine (**4c**).

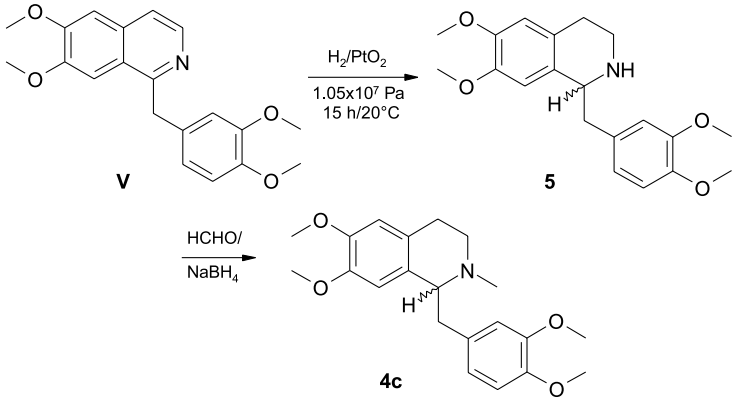


	R^1	R^2	R^3
1a	H	H	*Bn*
1b	O*Me*	O*Me*	*Me*

	R^4	R^5
2a	H	H
2b	O*Me*	O*Me*

3, 4	R^1	R^2	R^3	R^4	R^5
a	H	H	*Bn*	H	H
b	O*Me*	O*Me*	*Me*	H	H
c	O*Me*	O*Me*	*Me*	O*Me*	O*Me*

Scheme 1

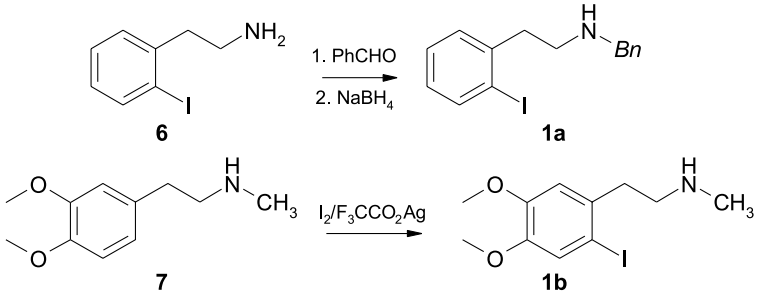


Scheme 2

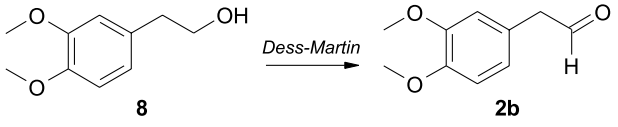
The lower yields obtained in comparison to the erythrinanes (41–66 *vs.* 71–78% [9]) may be attributed to the sensitivity of the products towards light and air as indicated by an intensive fluorescence, which could be observed after thin layer chromatography on silica gel. The structures of **4** were easily deduced from NMR spectroscopy and additionally by an independent synthesis of **4c**. Thus, papaverine **V** was catalytically hydrogenated affording *rac*-norlaudanosine **5** which in turn was *N*-methylated to give the target product **4c** (Scheme 2).

The educts **1** were prepared according to known procedures starting from 2-iodophenethylamine (**6**) and *N*-methylhomoveratrylamine (**7**) [9, 11, 12] (Scheme 3); the dimethoxyphenylacetaldehyde **2b**, not described until now, was nearly quantitatively obtained by oxidation of the corresponding phenylethanol **8** with the *Dess-Martin* reagent [13–15] (Scheme 4).

In summary we have shown the combined *Strecker/Bruylants* reactions to be a convenient two-step route for the preparation of synthetically valuable 1-benzyl-



Scheme 3



Scheme 4

1,2,3,4-tetrahydroisoquinolines starting from easily available phenethyl derivatives. This method suggests to be a useful, general approach to a wide range of similar 1-substituted targets and should be an alternative route to overcome limitations arising from the classical constructions of tetrahydroisoquinoline derivatives, *e.g*. *Bischler-Napieralski*, *Pictet-Spengler*, and *Pomeranz-Fritsch* reaction [16]. Further work is currently undertaken in our laboratory to explore the scope and limitation of the route presented herein.

Experimental

Melting points are measured with a *Reichert* hot-stage microscope and are uncorrected. IR: Perkin Elmer FT-IR Paragon 1000 and Jasco FT-IR 410. NMR: Jeol GSX 400 and Jeol GSX 500 (^{1}H: 400 and 500 MHz, ^{13}C: 100 and 125 MHz, $CDCl_3$, *TMS* as internal reference); MS (70 eV): Hewlett Packard MS-Engine. Elemental analyses: Heraeus CHN-Rapid and Elementar Vario EL; the results were in good agreement with the calculated values. Thin layer chromatography (TLC): Al sheets Kieselgel 60 F_{254} (Merck) and Al sheets Aluminiumoxid F_{254} (Fluka), each thickness of layer 0.2 mm. Flash chromatography (FC): ICN-Sili Tech 32–63, 60 A and Aluminiumoxid Typ 507 C neutral 0.05–0.15 mm. Compound **6** was prepared according to Ref. [9]; 90% phenylacetaldehyde (**2a**), *N*-methylhomoveratrylamine (**7**), and 2-(3,4-dimethoxyphenyl)ethanol (**8**) are commercial products.

Benzyl-[2-(2-iodophenyl)ethyl]amine (**1a**)

A mixture of 835 mg of **6** and 369 mg of benzaldehyde (each 3.38 mmol) in 20 cm^3 of dry toluene was refluxed with H_2O separation by a *Dean-Stark* trap for 2 h. After removing the solvent *in vacuo* the residue was dissolved in 20 cm^3 of *Me*OH and 278 mg (7.32 mmol) of $NaBH_4$ were added under ice-cooling. The mixture was refluxed for 1 h, the solvent was evaporated *in vacuo* and then 50 cm^3 of H_2O were added to the residue. After extracting with 3×50 cm^3 of Et_2O and drying the extracts (Na_2SO_4) the solvent was removed *in vacuo* and the residue was purified by FC (silica gel; CH_2Cl_2:*Me*OH:25% NH_3 = 100:3:0.5). Yield 1.08 g (85%) colourless oil; TLC (eluent see FC): $R_f = 0.46$; MS (CI): m/z (%) = 366 ($M^{+\bullet} + 29$, 3), 338 ($M^{+\bullet} + 1$, 100), 210 (12), 120 (94), 91 (43); ^{1}H and ^{13}C spectra were identical with those reported in Ref. [11].

[2-(2-Iodo-4,5-dimethoxyphenyl)ethyl]methylamine (**1b**, $C_{11}H_{16}INO_2$)

To a solution of 1.0 g (5.13 mmol) of **7** in 25 cm^3 of dry CH_2Cl_2 was added 2.39 g of F_3CCO_2Ag and 2.74 g of I_2 (each 10.8 mmol) at −5°C under vehement stirring. After 20 min the yellow solid was filtered off and washed with 25 cm^3 of CH_2Cl_2. The filtrate was washed with 3×50 cm^3 of a 3:1 mixture of saturated $Na_2S_2O_3$ and saturated Na_2CO_3, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was purified by FC (silica gel; CH_2Cl_2:*Me*OH:25% NH_3 = 100:1:1). Yield 1.19 g (72%) colourless oil; TLC (eluent see FC): $R_f = 0.35$; MS (CI): m/z (%) = 322 ($M^{+\bullet} + 1$, 100), 278 (3), 194 (27); ^{1}H NMR: $\delta = 7.21$ and 6.76 (2s, 2arom H), 3.85 and 3.84 (2s, 2OCH_3), 2.89–2.83 and 2.82–2.76 (2m, aryl-CH_2 and N-CH_2), 2.48 (s, N-CH_3). 2.19 (s, NH) ppm; ^{13}C NMR: δ = 149.28, 147.96, 135.07, 121.74, 112.55, 88.06, 56.13, 55.91, 52.10, 40.62, 36.48 ppm.

(3,4-Dimethoxyphenyl)acetaldehyde (**2b**)

Preparation according to Ref. [17], but starting from 2-(3,4-dimethoxyphenyl)ethanol (**8**) and without purifying by FC: **8** 911 mg (5.0 mmol), *Dess-Martin* reagent [14, 15] 2.54 g (6.0 mmol), 20 cm^3 CH_2Cl_2. Yield 891 mg (99%) light yellow oil; TLC (CH_2Cl_2:*Me*OH = 100:1): $R_f = 0.41$; IR (film):

$\bar{\nu} = 1722$ (C=O) cm^{-1}; MS (CI): m/z (%) = 181 ($M^{+\bullet} + 1$, 100), 167 (10), 151 (7); ^{1}H NMR: $\delta = 9.73$ (t, $J = 2.3$ Hz, CHO), 6.87 (d, $J = 8.2$ Hz, 1arom H), 6.77 (dd, $J = 8.2$, 2.0 Hz, 1arom H), 6.71 (d, $J = 2.0$ Hz, 1arom H), 3.88 (s, $2OCH_3$), 3.63 (d, $J = 2.3$ Hz, CH_2) ppm; ^{13}C NMR: $\delta = 199.45$, 149.20, 148.30, 124.01, 121.74, 112.49, 111.50, 55.81, 55.77, 50.02 ppm.

General Procedure for the Synthesis of α-Aminonitriles **3**

To a solution of the aldehyde **2** and $NaHSO_3$ (each 1 molquiv) in a mixture of 1 cm^3 of H_2O and 3 cm^3 of *Me*OH was added 1 molquiv amine **1** and 1.02 molquiv KCN and the mixture was heated under reflux for 1 h. After cooling to ambient temperature the mixture was diluted with H_2O and Et_2O (each 15 cm^3), rendered alkaline with saturated Na_2CO_3, and extracted with 3×15 cm^3 of Et_2O. The combined ether extracts were washed with 20 cm^3 of brine, dried (Na_2SO_4), and evaporated *in vacuo*. The residue (**3a** and **3c**) was purified by FC (silica gel; eluent see TLC), that of **3b** was crystallized from Et_2O.

2-{Benzyl-[2-(2-iodophenyl)ethyl]amino}-3-phenylpropionitrile (**3a**, $C_{24}H_{23}IN_2$)

90% **2a** 122 mg (0.92 mmol), $NaHSO_3$ 96 mg (0.92 mmol), **1a** 310 mg (0.92 mmol), KCN 61 mg (0.94 mmol), H_2O 1 cm^3, *Me*OH 3 cm^3; yield 300 mg (70%) colourless oil; TLC (*n*-hexane:*Et*OAc = 9:1): $R_f = 0.45$; IR (film): $\bar{\nu} = 2223$ (C≡N) cm^{-1}; MS (CI): m/z (%) = 440 ($M^{+\bullet} + 1 - HCN$, 100), 314 (16), 222 (24), 91 (14); ^{1}H NMR (500 MHz): $\delta = 7.80$ (dd, $J = 7.8$, 1.2 Hz, 1arom H), 7.30–7.21, 7.20–7.14, and 7.11–7.06 (3m, 7, 2, and 3arom H), 6.91 (dt, $J = 7.8$, 1.6 Hz, 1arom H), 4.14 and 3.56 (2d, each $J = 13.5$ Hz, N-CH_2-aryl), 3.81 (t, $J = 7.8$ Hz, CH), 3.09–2.85 (m, 5H), 2.77–2.70 (m, 1H) ppm; ^{13}C NMR (100 MHz): $\delta = 141.87$, 139.54, 137.20, 135.77, 130.25, 129.24 (2C), 128.63 (2C), 128.60 (2C), 128.50 (2C), 128.39, 128.28, 127.56, 127.20, 117.45, 100.44, 56.40, 56.06, 51.50, 39.11, 38.03 ppm.

2-{[2-(2-Iodo-4,5-dimethoxyphenyl)ethyl]methylamino}-3-phenylpropionitrile (**3b**, $C_{20}H_{23}IN_2O_2$)

90% **2a** 172 mg (1.29 mmol), $NaHSO_3$ 135 mg (1.29 mmol), **1b** 415 mg (1.29 mmol), KCN 85 mg (1.31 mmol), H_2O 1 cm^3, *Me*OH 3 cm^3; yield 517 mg (89%) colourless crystals; mp 123°C (Et_2O); TLC (*Et*OAc): $R_f = 0.65$; IR (KBr): $\bar{\nu} = 2221$ (C≡N) cm^{-1}; MS (CI): m/z (%) = 424 ($M^{+\bullet} + 1 -$ HCN, 100), 298 (18), 206 (6), 146 (17); ^{1}H NMR (400 MHz): $\delta = 7.34–7.23$ (m, 5arom H), 7.20 and 6.70 (2s, 2arom H), 3.84 and 3.83 (2s, $2OCH_3$), 3.79 (t, $J = 7.7$ Hz, CH), 3.08–2.96 (m, 2H), 2.91–2.74 (m, 3H), 2.68–2.56 (m, 1H), 2.50 (s, N-CH_3) ppm; ^{13}C NMR (100 MHz): $\delta = 149.36$, 148.15, 135.94, 134.38, 129.11 (2C), 128.68 (2C), 127.29, 121.67, 116.92, 112.57, 88.10, 59.83, 56.15, 55.95, 55.36, 38.74, 38.59, 38.15 ppm.

3-(3,4-Dimethoxyphenyl)-2-{[2-(2-iodo-4,5-dimethoxyphenyl)ethyl]methylamino}propionitrile (**3c**, $C_{22}H_{27}IN_2O_4$)

2b 245 mg (1.36 mmol), $NaHSO_3$ 141 mg (1.36 mmol), **1b** 430 mg (1.34 mmol), KCN 88 mg (1.34 mmol), H_2O 1 cm^3, *Me*OH 3 cm^3; yield 519 mg (76%) colourless oil; TLC (CH_2Cl_2:*Me*OH = 100:3): $R_f = 0.56$; IR (film): $\bar{\nu} = 2222$ (C≡N) cm^{-1}; MS (CI): m/z (%) = 484 ($M^{+\bullet} + 1 - HCN$, 100), 358 (18), 206 (28); ^{1}H NMR (500 MHz): $\delta = 7.20$ (s, 1arom H), 6.82–6.78 (m, 3arom H), 6.72 (s, 1arom H), 3.88 and 3.87 (2s, $2OCH_3$), 3.84 (s, $2OCH_3$), 3.76 (dd, $J = 8.9$, 6.4 Hz, CH), 3.03–2.92 and 2.90–2.76 (2m, 2 and 3H), 2.65–2.58 (m, 1H), 2.50 (s, N-CH_3) ppm; ^{13}C NMR (125 MHz): $\delta = 149.42$, 149.01, 148.32, 148.21, 134.32, 128.36, 121.71, 121.34, 117.02, 112.59, 112.30, 111.35, 88.13, 60.14, 56.17, 55.98, 55.95, 55.90, 55.41, 38.79, 38.63, 37.85 ppm.

*General Procedure for the Synthesis of Tetrahydroisoquinolines **4** by Intramolecular Bruylants Reaction*

To a solution of 1 molquiv aminonitrile **3** in cm^3 of dry *THF* was added a solution of 1.05 molquiv 2 *M* *i-Pr*MgCl in the same solvent at −50°C under N_2. After stirring at −50°C for an additional h the mixture was slowly warmed up to ambient temperature during 3–4 h and then refluxed under N_2 at 60°C for 3 h. The cold mixture was poured into 30 cm^3 of H_2O, rendered alkaline with an aqueous solution of Na_2CO_3, and extracted with 3×30 cm^3 of Et_2O. The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by FC (eluents were the same as used for TLC).

1,2-Dibenzyl-1,2,3,4-tetrahydroisoquinoline (**4a**, $C_{23}H_{23}N$)

3a 195 mg (0.42 mmol), 2 *M* *i-Pr*MgCl 0.22 cm^3 (0.44 mmol), *THF* 5 cm^3; yield 53 mg (41%) pale yellow oil; TLC (*n*-hexane:*Et*O*Ac* = 9:1): $R_f = 0.54$; MS (CI): m/z (%) = 314 ($M^{+\bullet} + 1$, 100), 222 (87); ^{1}H NMR (400 MHz): $\delta = 7.30$–7.06 (m, 13arom H), 6.86 (d, $J = 7.4$ Hz, 1arom H), 3.90 (dd, $J = 5.5$, 8.2 Hz, CH), 3.75 and 3.71 (2d, each $J = 13.7$ Hz, N-CH_2-aryl), 3.37 (ddd, $J = 13.2$, 10.8, 4.9 Hz, 1H), 3.15 (dd, $J = 8.2$, 13.9 Hz, 1H), 3.00 (ddd, $J = 16.8$, 10.8, 6.0 Hz, 1H), 2.90 (dd, $J = 13.9$, 5.5 Hz, 1H), 2.90–2.84 (m, 1H), 2.57 (ddd, $J = 16.8$, 4.9, 2.5 Hz, 1H) ppm; ^{13}C NMR (100 MHz): $\delta = 140.13$, 139.40, 138.05, 134.55, 129.71 (2C), 128.96, 128.61 (2C), 128.26, 128.04 (2C), 127.90 (2C), 126.67, 126.05, 125.82, 125.46, 62.65, 57.83, 42.96, 42.39, 24.34 ppm.

1-Benzyl-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**4b**)

3b 150 mg (0.33 mmol), 2 *M* *i-Pr*MgCl 0.18 cm^3 (0.36 mmol), *THF* 5 cm^3; yield 65 mg (66%) pale yellow oil; TLC (CH_2Cl_2:*Me*OH:NH_3 25% = 100:3:0.5): $R_f = 0.30$; MS (CI): m/z (%) = 298 ($M^{+\bullet} + 1$, 53), 206 (100); the ^{1}H NMR spectrum is in accordance with that reported in Ref. [18]; ^{13}C NMR (100 MHz): $\delta = 147.33$, 146.28, 139.95, 129.90 (2C), 129.00, 128.19, 126.00 (2C), 125.65, 111.19, 111.06, 64.90, 55.77, 55.43, 46.71, 42.59, 41.20, 25.41 ppm.

1-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (rac-laudanosine, **4c**)

A. According to the General Procedure (see above): **3c** 260 mg (0.51 mmol), 2 *M* *i-Pr*MgCl 0.27 cm^3 (0.54 mmol), *THF* 5 cm^3; yield 101 mg (55%) colourless crystals; mp 117°C (*Et*OH, Ref. [19] 117–119°C); TLC (CH_2Cl_2:*Me*OH:NH_3 25% = 100:8: 0.5): $R_f = 0.35$; MS (CI): m/z (%) = 358 ($M^{+\bullet} + 1$, 100), 206 (67); ^{1}H and ^{13}C spectra were in line with those reported in Ref. [19].

B. From norlaudanosine (5) (see below) according to Ref. [20]: To a solution of the crude product **5** (0.27 mmol) in 3 cm^3 of *Me*OH was added 0.6 cm^3 of 37% formaldehyde. The mixture was stirred at ambient temperature for 1 h, then 90 mg (2.4 mmol) of $NaBH_4$ were slowly added and stirring was continued for 18 h at the same temperature. Further work up was accomplished following Ref. [20]. Yield 86 mg (89%); the analytical data were completely in line with those obtained under A.

1-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (rac-norlaudanosine, **5**)

To a solution of 102 mg (0.3 mmol) of papaverine (**V**) in 5 cm^3 of acetic acid *p.a.* was added 15 mg of *Adams* catalyst (PtO_2–H_2O) and the mixture was hydrogenated for 15 h at ambient temperature and 1.05×10^7 Pa initial pressure of H_2. The catalyst was centrifuged off, and after diluting with 5 cm^3 of H_2O the solution was rendered alkaline with saturated Na_2CO_3 and extracted with 4×5 cm^3 of $CHCl_3$. The combined extracts were dried (Na_2SO_4) and the solvent was removed *in vacuo*. Yield 94 mg (91%)

nearly colourless oil; TLC ($CHCl_3$:*Me*OH:NH_3 25% = 16:1:0.3): $R_f = 0.40$ (**V**: $R_f = 0.68$); MS (CI): m/z (%) = 344 ($M^{+\bullet} + 1$, 63), 192 (100); the ^1H spectrum was in line with that reported in Ref. [19].

References

[1] Schuette HR (1996) Progress in Botany **57**: 114
[2] Phillipson JD, Roberts MF, Zenk MH (eds) (1985) The Chemistry and Biology of Isoquinoline Alkaloids. Springer-Verlag, Berlin Heidelberg New York Tokyo
[3] Monsees A, Laschat S, Kotila S, Fox T, Würthwein EU (1997) Liebigs Ann/Recueil 533 and further lit. cited herein
[4] Yamakawa T, Ohta S (1997) Biochem Biophys Res Commun **236**: 676
[5] Okuda K, Kotake Y, Ohta S (2003) Bioorg Med Chem Letters **13**: 2853
[6] Shinohara T, Takeda A, Toda J, Terasawa N, Sano T (1997) Heterocycles **46**: 555
[7] Kotha S, Sreenivasachary N (2001) Eur J Org Chem **17**: 3375
[8] Mash EA, Williams LJ, Pfeiffer SS (1997) Tetrahedron Lett **38**: 6977; see also: Spengler J, Schedel H, Sieler J, Quaedflieg PJLM, Broxterman QB, Duchateau ALL, Burger K (2001) Synthesis 1513 and further lit. cited herein
[9] Reimann E, Ettmayr C (2004) Monatsh Chem (in press)
[10] Ha HJ, Ahn YG, Lee GS (1999) Tetrahedron Asymm **10**: 2327
[11] Wolfe JP, Rennels RA, Buchwald SL (1996) Tetrahedron **52**: 7525
[12] Kobayashi S, Kihara M, Matsumoto H (1978) Yakugaku Zasshi **96**: 863; CA (1978) **89**: 197764n
[13] Dess DB, Martin JC (1983) J Org Chem **48**: 4156
[14] Dess DB, Martin JC (1991) J Am Chem Soc **113**: 7277
[15] Ireland RE, Liu L (1993) J Org Chem **58**: 2899
[16] Reimann E (1980) Chinoline und Isochinoline. In: Korte F (ed) Methodicum Chimicum, vol 4. Georg Thieme Verlag, Stuttgart New York, p 261 and further lit. cited herein
[17] Kraus GA, Melekhov A (1999) J Org Chem **64**: 1720
[18] Gottlieb L, Meyers AI (1990) J Org Chem **55**: 5659
[19] Sinohara T, Takeda A, Toda J, Sano T (1998) Heterocycles **48**: 981
[20] Coppola GM (1991) J Heterocyclic Chem **28**: 1772