HETEROCYCLES, Vol. 60, No. 3, 2003, pp. 615 - 622
Received, 30th October, 2002, Accepted, 22nd January, 2003, Published online, 31st January, 2003

ON THE SYNTHESIS OF TWO DIMETHOXY-1,3,4,5-TETRAHYDROPYRROLO[4,3,2-*de*]QUINOLINE REGIOISOMERS

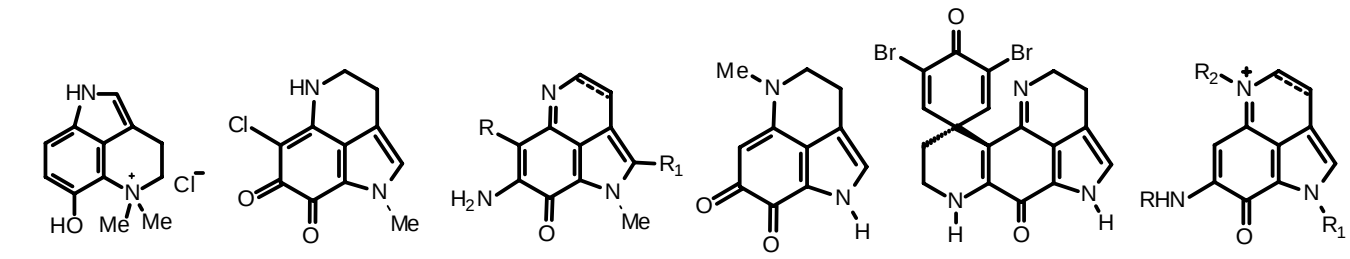
Sarah Chackal, Fabienne Dudouit, Raymond Houssin, and Jean-Pierre Hénichart*

Albert Lespagnol Institute of Pharmaceutical Chemistry, EA 2692, University of Lille 2, BP 83, 59006 Lille, France; E-mail: henicha@phare.univ-lille2.fr

Abstract – Many marine alkaloids are biologically active products and possess the 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline core as a common feature. This is a report of the synthesis of two of the title molecules with confirmation of their structure.

Over the past thirty years, chemists interested in natural marine products have successfully discovered a large number of new targeting compounds. The tricyclic 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline ring system is a structural element common to the poison dehydrobufotenine[1] and to several groups of marine alkaloids such as batzellines,[2] isobatzellines,[3] damirones,[4] discorhabdins[5-7] and makaluvamines[8-10] (Chart 1), which possess potentially useful biological activities including cytotoxicity and topoisomerase II inhibition.[11,12]

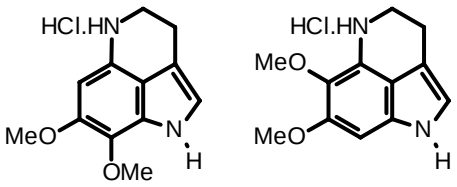
Chart 1



In our search for new antitumour polycyclic heteroaromatic compounds, we focused on the preparation of regioisomers (**1**) and (**2**), as synthons, possessing the 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline core (Chart 2). The methoxy groups, present in the structures, are potential precursors of *o*-catechol readily

oxidizable into *o*-quinone or quinonimine, known as inducers of reactive oxygen species by classical metabolic pathways.

Chart 2

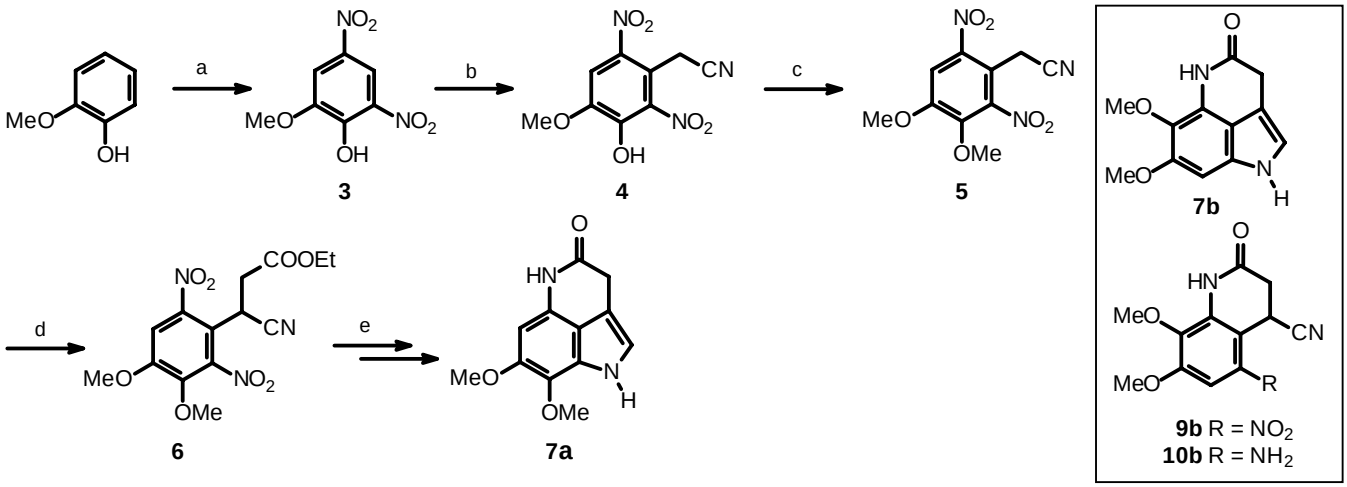


1 **2**

Compound (**1**) may be obtained from **7a** (Scheme 1), a key intermediate in the synthesis of makaluvamine D and discorhabdin C. Although **7a** was obtained[13] *via* vicarious nucleophilic substitution (VNS) on 4,6-dinitroguaiacol (**3**), no evidence was provided concerning the cyclisation pathway leading to **7a** (or to its isomer **7b**)**.**

This paper gives proof as to the structural characterization of tetrahydropyrrolo[4,3,2-*de*]quinoline (**7a**) and its isolated intermediates following the strategy previously mentioned,[13] along with the synthesis of the pyrrolo[4,3,2-*de*]quinoline (**2**).

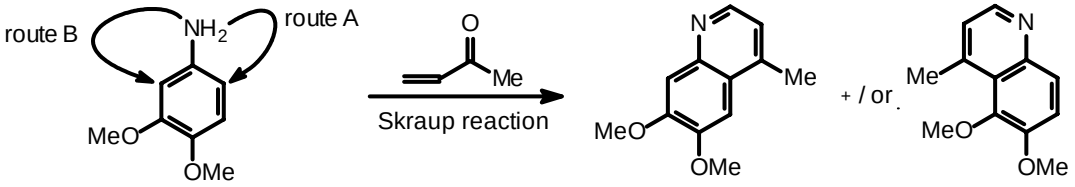
Scheme 1[†]



[†] Reagents and conditions: (a) HNO_3, AcOH, -5°C, 12 h, 42% (b) phenoxyacetonitrile, *t*-BuOK, DMF, 0°C, 40 min, 70% (c) $(MeO)_2SO_2$, $NaHCO_3$, acetone, reflux, 9 h, 80% (d) ethyl bromoacetate, K_2CO_3, KI, acetonitrile, rt, 5 h, 82% (e) $PdCl_2$/Fe or 10% Pd/C, H_2, EtOH, AcOH, 30°C, 4 days, 48%.

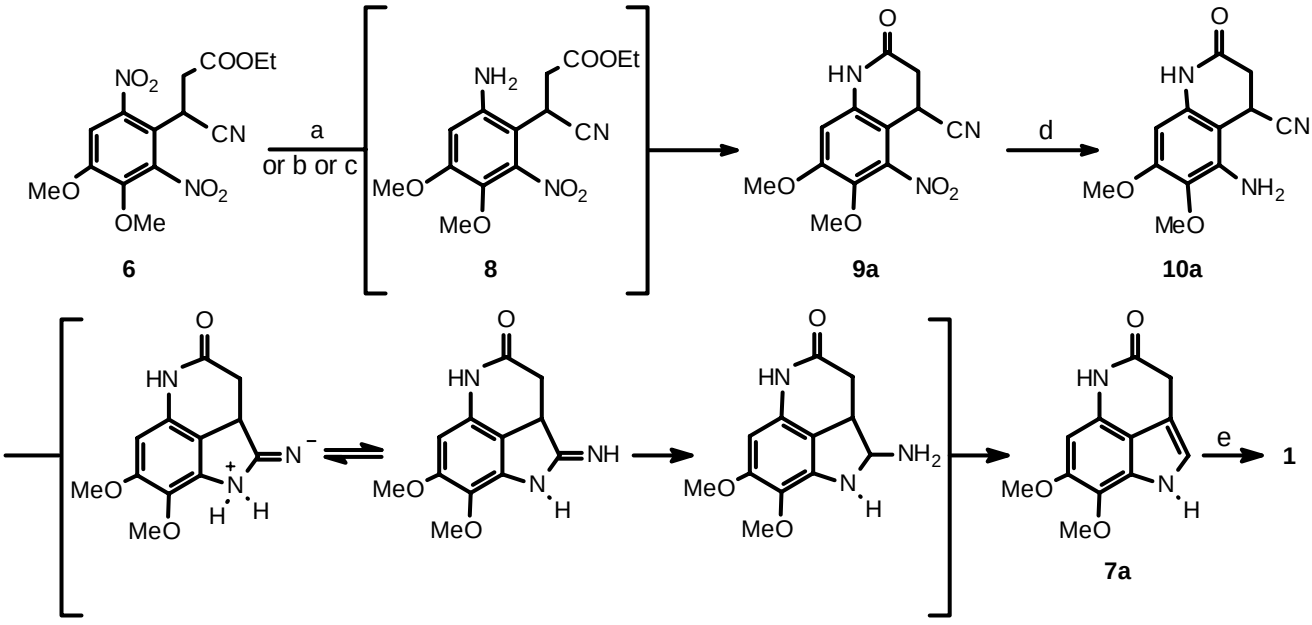
As regards compound (**1**), we decided to exclude the strategy which consists in building its quinoline moiety before creating the third condensed pyrrole cycle: Skraup quinoline reaction between 4-aminoveratrole and 3-buten-2-one (Scheme 2) should theoretically lead to two isomers, i.e. 6,7-dimethoxy- (route A) and 5,6-dimethoxy- (route B) -4-methylquinolines.

Scheme 2



We adapted Makosza's report[13] on the synthesis of the precursor (**7a**) in a multigram scale which however lacks structural identification: the double cyclisation step (Scheme 1) of the penta-substituted aromatic compound (**6**) should allow for the formation of pyrroloquinoline (**7b**) beside the expected pyrroloquinoline (**7a**). As stated,[13] starting from guaiacol, consecutive electrophilic dinitration (compound (**3**)), vicarious nucleophilic substitution with phenoxyacetonitrile (compound (**4**)), *O*-methylation of phenolic hydroxy (compound (**5**)) and nucleophilic substitution of the benzylic carbon with ethyl bromoacetate led to dinitroester (**6**). A study of the reduction-cyclisation step on **6** enabled us to identify the intermediates whose structure depends on the reaction temperature (Scheme 3). Hydrogenation of **6** ($PdCl_2$/Fe or 10% Pd/C) at 0°C for 7 h selectively reduced the less sterically hindered nitro group to give non-isolated 4-aminoveratrole (**8**) whose *in situ* cyclisation gave 5-nitroquinolin-2-one (**9a**).

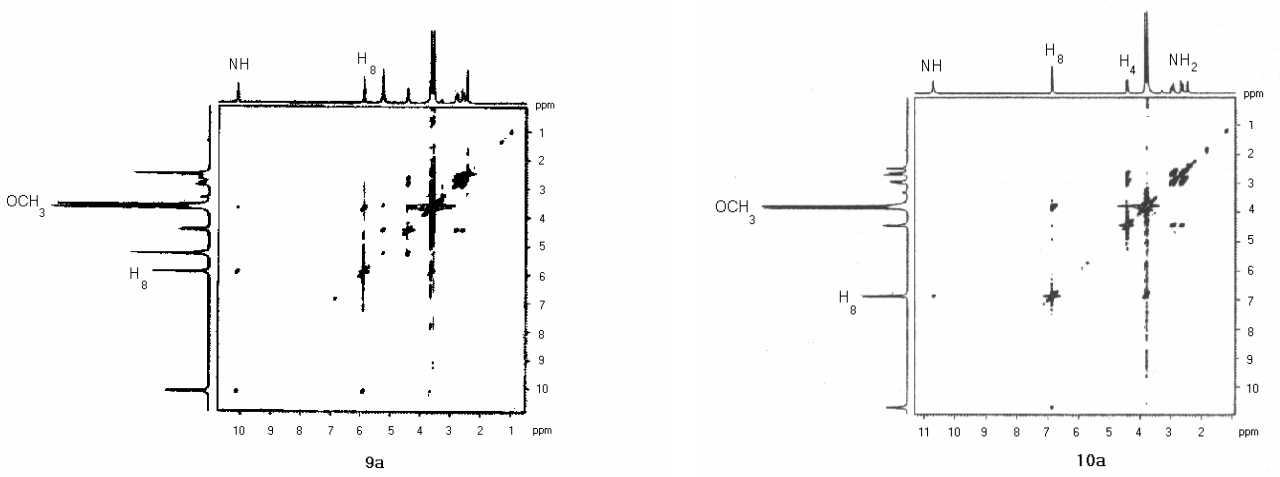
Scheme 3[†]



[†] Reagents and conditions: (a) when $PdCl_2$/Fe, H_2, EtOH, AcOH, 0°C, 7 h, 88% of **9a** (b) when $PdCl_2$/Fe, H_2, EtOH, AcOH, 30°C, 100 h, 48% of **7a** (c) when $PdCl_2$/Fe, H_2, EtOH, AcOH, 30°C, 7 h, 88% of **10a** (d) $PdCl_2$/Fe, H_2, EtOH, AcOH, 0°C, 14 h, 95% (e) BH_3-Me_2S/THF, 20°C, 5 h, 80%.

The regioselectivity of the reduction of **6** into quinolinone (**9a**) was demonstrated by 2D ROESY NMR (Figure 1) where a spatial correlation was observed between H_8 and NH, H_8 and OCH_3, excluding quinolinone (**9b**) (Scheme 1). Reduction of both nitro groups and subsequent cyclisation into 4-aminoquinolin-2-one (**10a**) was achieved when hydrogenation was carried out at 30°C or when quinolinone (**9a**) was allowed to react at 0°C for 14 h. The 2D ROESY NMR spectrum (Figure 1) highlighted respective interactions between H_8 and NH, H_8 and OCH_3, H_4 and NH_2, corresponding to quinolinone (**10a**) and excluding structure (**10b**). Finally, cyclisation of ester (**6**) into 7,8-dimethoxy-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinolin-2-one (**7a**) occurred, under the same conditions, at 10°C < T ≤30°C for 100 h, according to the mechanism proposed (Scheme 3). The last reduction of the lactam function of **7a** into light-unstable pyrroloquinoline (**1**) was found effective with borane-methyl sulfide complex/THF at room temperature for 5 h (80% of crude oil).

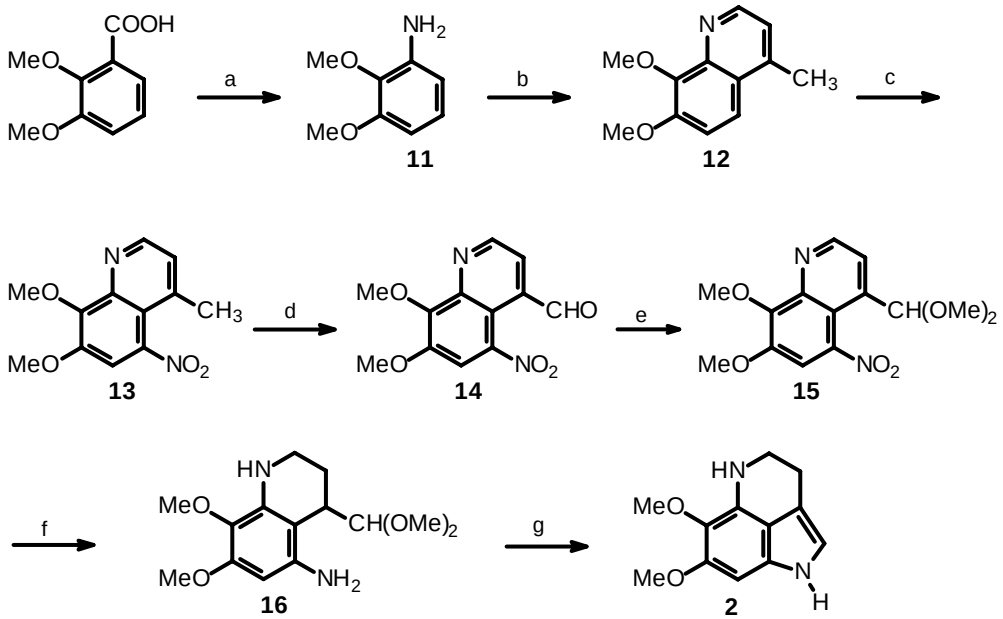
Figure 1: 2D ROESY NMR spectra of 9a and 10a (DMSO-d_6)



Due to the formation of pyrroloquinoline (**1**) only in the sequence described in Scheme 3, we planned (Scheme 4) the synthesis of its isomer (**2**) using 2,3-dimethoxyaniline (**11**) readily obtained[14] from the Curtius rearrangement of 2,3-dimethoxybenzoic acid. The strategy was prompted by Joule's work[15] on the preparation of **1**. In this case, the Skraup reaction with 3-buten-2-one leads unambiguously to the single product 7,8-dimethoxy-4-methylquinoline (**12**), whose mononitration (65% yield) regioselectively proceeded at -40°C to give the 5-nitro derivative (**13**) as ascertained by 2D ROESY NMR (the reaction at 0°C led to 5,6-dinitration). Oxidation with a mild and selective reagent[16] for α- or γ- methyl groups of heteroaromatic bases (I_2/t-BuI/$FeCl_2$/TFA/DMSO) led to 4-formylquinoline (**14**). After ketalization of the aldehyde giving **15**, the simultaneous reduction of the nitro group and of heterocyclic moiety was found effective with a large excess of $NaBH_4$ and $NiCl_2$ (67% yield). Subsequent cyclisation of

tetrahydroquinoline (**16**) following deprotection of the carbonyl (HCl/THF) gave pyrroloquinoline (**2**) in 64% yield.

Scheme 4[†]



[†] Reagents and conditions: (a) i: DPPA, EtOH, Et_3N, THF, 60°C, 1 h 30, ii: KOH, EtOH, reflux, 4 h (b) 3-buten-2-one, $FeCl_3$, AcOH, reflux, 1 h 30 min (c) fuming HNO_3, -40°C, 1 h (d) I_2, $FeCl_2$, *t*-BuI, TFA, DMSO, 80°C, 1 h (e) 37% HCl, MeOH, reflux, 24 h (f) $NaBH_4$, $NiCl_2$, MeOH, rt, 30 min (g) 1N HCl, THF, 40°C, 1 h.

This is the description of the synthesis of two isomeric tetrahydro[4,3,2-*de*]quinolines using pathways dependent on their structural characteristics, and their assigned structure.

EXPERIMENTAL

General. Melting points were determined with a capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 300 MHz. Chemical shifts are reported in ppm downfield from TMS. Coupling constants are given in Hertz. Elemental analyses were performed by the Service Central d'Analyse-Département Analyse Elémentaire, CNRS, F-69390 Vernaison.

4-Cyano-6,7-dimethoxy-5-nitro-1,2,3,4-tetrahydroquinolin-2-one (9a) - Yield 88%; mp 208-209°C (EtOAc) (lit.,[13] yield 48%; mp 210-212°C (*i*-PrOH)); *Rf* = 0.59; ^{1}H NMR (DMSO-d_6) 2.64 (d, 1H, J_{gem} = 16.5), 2.86 (dd, 1H, J_{gem} = 16.5, J_{aa} = 6.5), 3.60 (s, 3H), 3.70 (s, 3H), 4.46 (d, 1H, J_{aa} = 6.5), 5.94 (s, 1H), 10.14 (s, 1H).

5-Amino-4-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroquinolin-2-one (10a) - $PdCl_2$/Fe (0.3 g from 0.33 g of $PdCl_2$ and 1.5 g of Fe) was added to a solution of ester (**6**)[13] (1 g, 9.2 mmol) in EtOH 95% (25 mL) and AcOH (2 mL). The suspension was stirred under hydrogen for 7 h at 30°C. The catalyst was filtered off, the filtrate was evaporated to yield 616 mg (88%) of amine (**10a**): mp 207°C (EtOAc); *Rf* = 0.52 (EtOAc); IR (KBr) 3360, 2260, 1680, 1630 cm^{-1}; ^1H NMR (DMSO-d_6) 2.69 (d, 1H, J_{gem} = 16.5), 3.00 (dd, 1H, J_{gem} = 16.5, J_{aa} = 6.5), 3.81 (s, 3H), 3.88 (s, 3H), 4.47 (d, 1H, J_{aa} = 6.5), 5.31 (br s, 2H), 6.90 (s, 1H), 10.73 (s, 1H); Anal. Calcd for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 16.99. Found: C, 58.01; H, 5.54; N, 17.21.

7,8-Dimethoxy-4-methylquinoline (12) - Aniline (**11**)[14] (11.1 g, 72.5 mmol) was added to a solution of $FeCl_3$ (20.6 g, 76.17 mmol) in glacial AcOH (150 mL) heated to reflux; then 3-methylbuten-2-one (6.33 mL, 6.17 mmol) was added dropwise. The mixture was refluxed for 1 h 30 min. After cooling to rt, the reaction mixture was diluted with water and made alkaline with K_2CO_3. The organic layer was then extracted with EtOAc, and the extract was washed with saturated aqueous NaCl, dried over $MgSO_4$, and concentrated. After removal of the solvent, the crude oily product was subjected to column chromatography (silica gel; EtOAc/Heptane 7:3 → EtOAc). Evaporation of the solvents yielded 10.3 g (70%) of quinoline (**12**) as a green oil: *Rf* = 0.15 (EtOAc/Heptane 7:3); IR (KBr) 1611 cm^{-1}; ^1H NMR ($CDCl_3$) 2.64 (d, 3H, J_4 = 0.8), 4.02 (s, 3H), 4.10 (s, 3H), 7.09 (dd, 1H, J_3 = 4.2, J_4 = 0.8), 7.33 (d, 1H, J_o = 9.1), 7.71 (d, 1H, J_o = 9.5), 8.75 (d, 1H, J_3 = 4.2); Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.57; H, 6.62; N, 6.71.

7,8-Dimethoxy-4-methyl-5-nitroquinoline (13) - Quinoline (**12**) (10.2 g, 50.2 mmol) was added in portions to fuming HNO_3 (41.7 mL, 1.05 mol) cooled to -40°C. The mixture was stirred for 1 h at -40°C. The reaction mixture was then poured onto ice and neutralized with 50% aqueous NaOH with the temperature maintained below -10°C. The organic layer was extracted with EtOAc, and the extract was washed with water, 10% aqueous K_2CO_3, saturated aqueous NaCl, dried over $MgSO_4$, and concentrated to give the nitro derivative (**13**) as a yellow powder (8.1 g, 65%): mp 89°C (cyclohexane); *Rf* = 0.42 (EtOAc/Heptane 7:3); IR (KBr) 1609, 1518, 1352 cm^{-1}; ^1H NMR ($CDCl_3$) 2.52 (s, 3H), 4.04 (s, 3H), 4.17 (s, 3H), 7.25 (d, 1H, J_3 = 4.1), 7.60 (s, 1H), 8.85 (d, 1H, J_3 = 4.4); Anal. Calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.28. Found: C, 58.33; H, 5.02; N, 11.02.

4-Formyl-7,8-dimethoxy-5-nitroquinoline (14) - TFA (0.38 mL, 5.04 mmol), *t*-BuI (0.1 mL, 0.88 mmol), I_2 (1.03 g, 4.07 mmol) and $FeCl_2$ (0.03 g, 0.24 mmol) were added to nitroquinoline (**13**) (1 g, 4.03 mmol) in DMSO (12 mL) and the mixture was heated at 80°C for 1 h. After column chromatography (silica gel; EtOAc/Heptane 2:8→ EtOAc/Heptane 4:6), the solvents were removed *in vacuo* and the resulting crude product was dissolved in CH_2Cl_2, and the organic phase was washed successively with 20% aqueous $Na_2S_2O_3$, 10% aqueous K_2CO_3, saturated aqueous NaCl, dried over

$MgSO_4$, and concentrated to give aldehyde (**14**) as a yellow powder (550 mg, 52%): mp 151°C (EtOH); *Rf* = 0.33 (EtOAc/Heptane 7:3); IR (KBr) 1705, 1607, 1519, 1370 cm^{-1}; ^1H NMR ($CDCl_3$) 4.11 (s, 3H), 4.27 (s, 3H), 7.77 (d, 1H, J_3 = 4.4), 8.14 (s, 1H), 9.20 (d, 1H, J_3 = 4.1), 10.17 (s, 1H); Anal. Calcd for $C_{12}H_{10}N_2O_5$: C, 54.97; H, 3.84; N, 10.68. Found: C, 55.21; H, 3.63; N, 10.76.

7,8-Dimethoxy-4-dimethoxymethyl-5-nitroquinoline (15) - 37% HCl (0.26 mL, 8.58 mmol) was added to a solution of aldehyde (**14**) (1.5 g, 5.72 mmol) in MeOH (30 mL) and the reaction mixture was refluxed for 24 h. After neutralization with 10% aqueous K_2CO_3, the solvent was removed *in vacuo*. The residual aqueous layer was extracted with EtOAc and the organic layer was washed with saturated aqueous NaCl, dried over $MgSO_4$, and concentrated. The crude product was subjected to column chromatography (silica gel; EtOAc/Heptane 1:1). Evaporation of the solvents yielded 1.07 g (61%) of acetal **15** as a yellow powder: mp 88°C (cyclohexane); *Rf* = 0.41 (EtOAc/Heptane 7:3); IR (KBr) 1615, 1530, 1349 cm^{-1}; ^1H NMR ($CDCl_3$) 3.31 (s, 6H), 4.07 (s, 3H), 4.20 (s, 3H), 5.70 (s, 1H), 7.74 (dd, 1H, J_3 = 4.3, J_4 = 1.2), 7.89 (s, 1H), 9.02 (d, 1H, J_3 = 4.3); Anal. Calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.28. Found: C, 57.82; H, 5.12; N, 10.96.

5-Amino-7,8-dimethoxy-4-dimethoxymethyl-1,2,3,4-tetrahydroquinoline (16) - Anhydrous $NiCl_2$ (3.03 g, 23.37 mmol) and portionwise $NaBH_4$ (0.88 g, 23.37 mmol) were added to a solution of ketal (**15**) (1.2 g, 3.90 mmol) in MeOH (20 mL). The reaction mixture was stirred for 30 min at rt, quenched with H_2O, and extracted with EtOAc. The organic extract was washed with saturated aqueous NaCl, dried over $MgSO_4$, and concentrated. The crude oily product was subjected to column chromatography (silica gel; EtOAc/Heptane 1:1). Evaporation of the solvents yielded 736 mg (67%) of **15** as a purple oil: *Rf* = 0.30 (EtOAc/Heptane 7:3); IR (KBr) 3421, 3354cm^{-1}; ^1H NMR ($CDCl_3$) 1.54-1.66 (m, 1H), 2.06-2.11 (m, 1H), 3.13-3.17 (m, 1H), 3.30-3.36 (m, 2H), 3.35 (s, 3H), 3.40 (s, 3H), 3.73 (s, 3H), 3.79 (s, 3H), 4.04 (br s, 2H), 4.45 (d, 1H, *J* = 8.5), 4.50 (br s, 1H), 5.65 (s, 1H); Anal. Calcd for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.46; H, 8.52; N, 12.50.

6,7-Dimethoxy-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline hydrochloride (2) - Ketal (**15**) (0.78 g, 2.76 mmol) was reacted with 1N aqueous HCl (15 mL) in THF (10 mL) at 40°C for 1 h. The reaction mixture was made basic with 10% aqueous K_2CO_3, and extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl, dried over $MgSO_4$, and concentrated. Evaporation of the solvent gave a white powder which was dissolved in methanol before methanol saturated with HCl was added, to yield **2** as a white solid (386 mg, 64%): mp > 250°C (MeOH/Et_2O); *Rf* = 0.34 (EtOAc/Heptane 7:3); IR (KBr) 3350, 3330, 1619 cm^{-1}; ^1H NMR (DMSO-d_6) 2.80 (t, 2H, *J* = 5.4), 3.27 (t, 2H, *J* = 5.4), 3.60 (s, 3H), 3.73 (s, 3H), 5.42 (br s, 2H), 6.14 (s, 1H), 6.62 (s, 1H), 10.17 (s, 1H); MS (EI) *m/z* 218 (M^+, 88), 203 (100), 188 (20), 160 (27), 131 (18), 69 (35); Anal. Calcd for $C_{12}H_{14}N_2O_2$.HCl (0.25H_2O): C, 55.81; H, 5.62; N, 10.85; Cl, 13.75. Found: C, 55.99; H, 5.93; N, 10.76; Cl, 13.63.

REFERENCES

1. F. Märki, A. V. Robertson, and B. Witkop, *J. Am. Chem. Soc.*, 1961, **83**, 3341.
2. S. Sakemi, H. H. Sun, C. W. Jefford, and G. Bernardinelli, *Tetrahedron Lett.,* 1989, **30**, 2517.
3. H. H. Sun, S. Sakemi, N. Burrres, and P. McCarthy, *J. Org. Chem.*, 1990, **55**, 4964.
4. D. B. Stierle, and D. J. Faulkner, *J. Nat. Prod.*, 1991, **54**, 1134.
5. N. B. Perry, J. W. Blunt, J. D. McCombs, and M. H. G. Munro, *J. Org. Chem.*, 1986, **51**, 5476.
6. N. B. Perry, J. W. Blunt, and M. H. G. Munro, *Tetrahedron*, 1988, **44**, 1727.
7. N. B. Perry, J. W. Blunt, M. H. G. Munro, T. Higa, and R. Sakai, *J. Org. Chem.*, 1988, **53**, 4127.
8. E. V. Sadanandan, S. K. Pillai, M. V. Lakshmikantham, A. D. Billimoria, J. S. Culpepper, and M. P. Cava, *J. Org. Chem.*, 1995, **60**, 1800.
9. D. C. Radisky, E. S. Radisky, L. R. Barrows, B. R. Copp, R. A. Kramer, and C. M. Ireland, *J. Am. Chem. Soc.,* 1993, **115**, 1632.
10. T. Izawa, S. Nishiyama, and S. Yamamura, *Tetrahedron*, 1994, **50**, 13593.
11. L. R. Barrows, D. C. Radisky, B. R. Copp, D. S. Swaffar, R. A. Kramer, R. L. Warters, and C. M. Ireland, *Anti-Cancer Drug Design*, 1993, **8**, 333.
12. Q. Ding, K. Chichak, and J. W. Lown, *Curr. Med. Chem.*, 1999, **6**, 1.
13. M. Makosza, J. Stalewski, and O. S. Maslennikova, *Synthesis*, 1997, **10**, 1131.
14. J. D. White, K. M. Yager, and T. Yakura, *J. Am. Chem. Soc.*, 1994, **116**, 1831.
15. D. Roberts, J. A. Joule, M. A. Bros, and M. Alvarez, *J. Org. Chem.*, 1997, **62**, 568.
16. E. Vismara, F. Fontana, and F. Minisci, *Gazz. Chim. Ital.*, 1987, **117**, 135.