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SYNTHESIS OF ISODECARINE

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Abstract - The cyclization of 3-bromo-6-methoxy-2-(naphtho[2,3-*d*][1,3]dioxol-5-ylaminomethyl)phenol (**2**) using tributyltinhydride under radical-mediated conditions was accompanied by spontaneous oxidation and afforded directly isodecarine (2-methoxy[1,3]benzodioxolo[5,6-*c*]phenanthridin-1-ol, (**3**). 2-Methoxy-6-(naphtho[2,3-*d*][1,3]dioxol-5-ylaminomethyl)-phenol (**4**) was isolated as a side product. Isodecarine was also prepared by the catalytic debenzylation of 7-benzyloxy-8-methoxy-2,3-methylendioxybenzo-[*c*]phenanthridine (**5**). This compound was efficiently converted to 7-benzyloxy-8-methoxy-5-methyl-2,3-methylenedioxybenzo[*c*]phenanthridinium trifluoromethanesulfonate (**6**) in high yield and with a short reaction time.

INTRODUCTION

Benzo[*c*]phenanthridines are widely explored biologically active alkaloids.[1] Some have been intensively studied mainly because of their antitumor activity.[2,3] From this point of view, one of the most promising compounds is 7-hydroxy-8-methoxy-5-methyl-2,3-methylenedioxybenzo[*c*]phenanthridinium hydrogen-sulphate designated NK109 which exhibits significant anticancer activity *in vitro*, [4] especially against drug-resistant human tumor cell lines.[5] It was also found to be a very active inhibitor of Topo II.[6-9] As described previously, the hydroxyl group in position 7 is essential for the antitumor activity.[10]

The synthesis of benzo[*c*]phenanthridines is based on a cyclization of appropriate naphtho[2,3-*d*][1,3]dioxol-5-ylamines *via* a radical [11,12] or benzyne mechanism.[11, 13] In both cases, the hydroxyl group

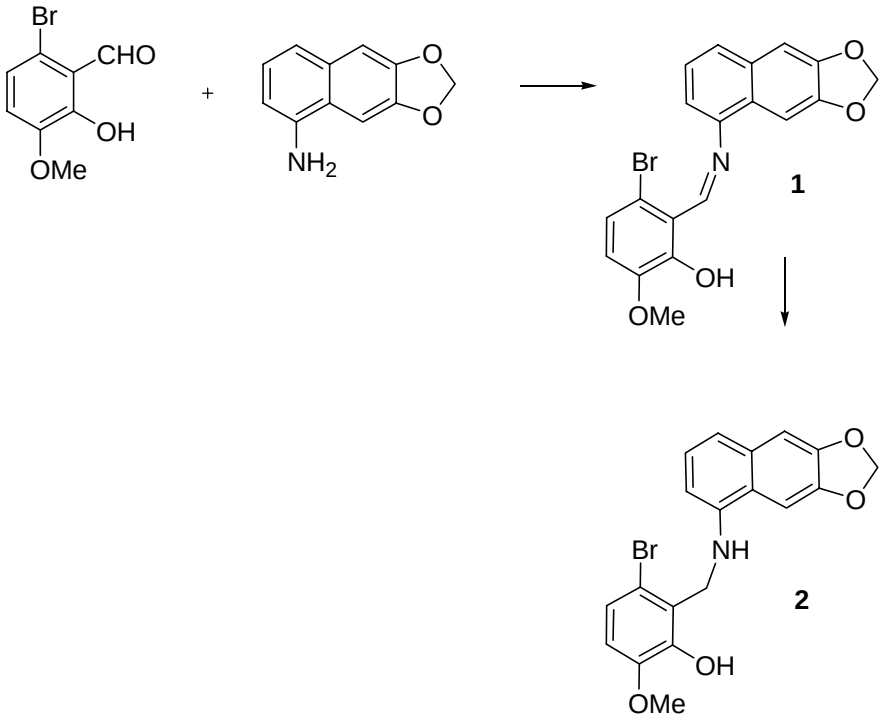
is protected by methylation or benzylation. Here, we report the radical cyclization of unprotected 3-bromo-6-methoxy-2-(naphtho[2,3-*d*][1,3]dioxol-5-ylaminomethyl)phenol **(2)** leading to isodecarine **(3)**, that has not been synthesized before. The only preparation reported is based on the thermolysis of chelerythrine.[14] Isodecarine has also been isolated from the root bark of *Zanthoxylum integrifoliolum*.[15] This paper is the only to describe the biological activity of isodecarine. The authors successfully tested this compound for cytotoxic activity against P-388 or HT-29 cell lines *in vitro*.

The efficient synthesis of isodecarine we developed renders this substance available for advanced biological screening.

RESULTS AND DISCUSSION

The starting phenol **1** was prepared by the reaction of naphtho[2,3-*d*][1,3]dioxol-5-ylamine with 6-bromo-2-hydroxy-3-methoxybenzaldehyde (Scheme 1), which are both commercially available. The reaction was completed in high yield by heating in EtOH. Since compound **1** is of low solubility in organic solvents, subsequent reduction with sodium borohydride was carried out in suspension in DMF. The reduction quantitatively yielded appropriate phenol **2** (Scheme 1).

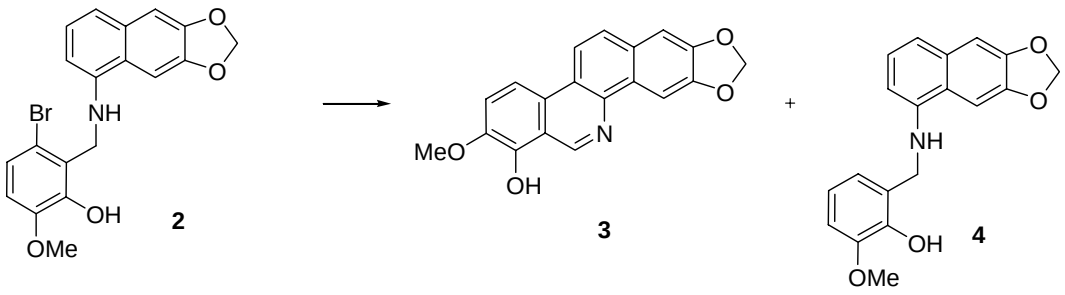
Scheme 1



Although compound **2** has been already described,[16] its direct cyclization to phenanthridine derivative has not been reported. However, radical cyclization of similar compounds[11,12] with a protected hydroxyl

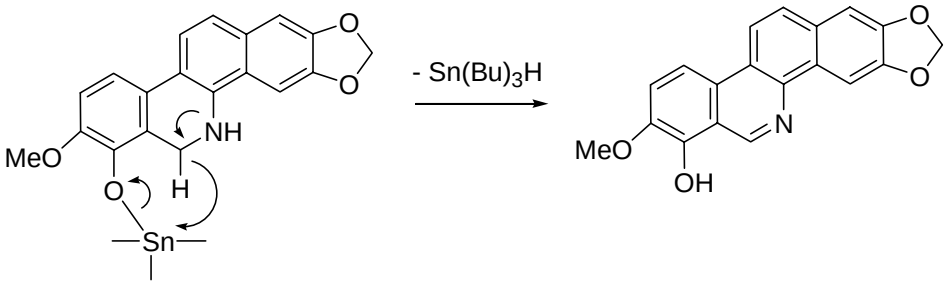
group has been published. We were interested in the possibility of direct synthesis of isodecarine (**3)** from the unprotected phenol **2** using tributyltinhydride and AIBN. The cyclization was carried out in dry toluene under argon and yielded the desired derivative **3** in a yield of 49%. Simultaneously, 2-methoxy-6-(naphtho[2,3-*d*][1,3]dioxol-5-ylaminomethyl)phenol **(4)** was isolated as a side product in a yield of 20%. The compound **4** and its *O*-alkyl derivatives have not been described before.

Scheme 2



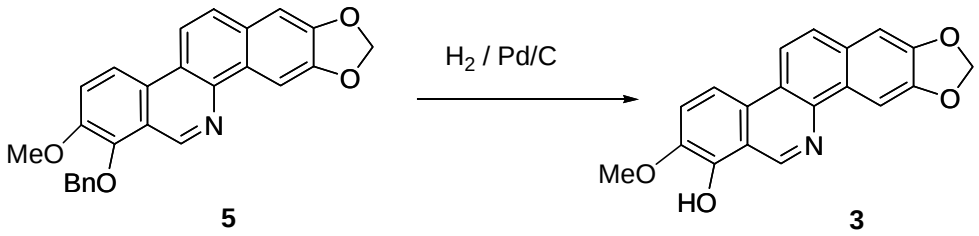
It is necessary to point out that compound **3** was formed without the use of oxidizing agent. For the preparation of similar phenanthridine alkaloids, manganese dioxide is necessary for the aromatization. [11, 12] We hypothesize, that spontaneous oxidation is caused by binding of tributyltin moiety to hydroxyl oxygen with subsequent releasing of tributyltinhydride (Scheme 3). The resonance energy is probably the driving force of this oxidation.

Scheme 3



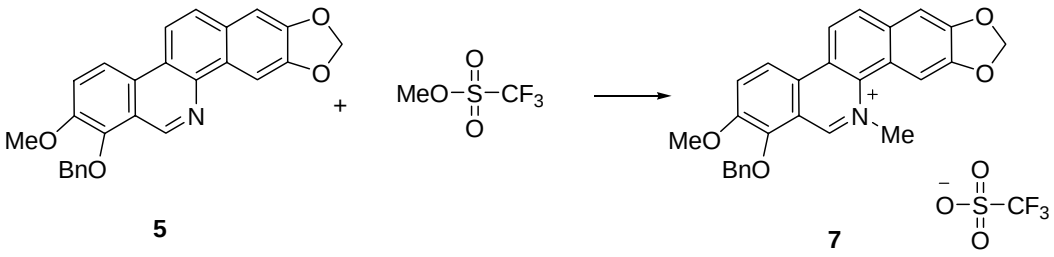
Alternatively, isodecarine (**3)** was prepared by debenzylation of the derivative **5**, which had been prepared according to the literature (Scheme 4).[11] However, this reaction procedure is longer because of the need to protect and deprotect the hydroxyl group during the synthesis.

Scheme 4



When we successfully synthesized isodecarine **(3)**, we were interested in its direct *N*-methylation leading to the derivative NK109. Unfortunately, we were not able to find conditions for the selective methylation of the nitrogen as it is known e.g. for hydroxyquinolines[17,18] or hydroxyisoquinolines.[19] Thus, the methylation of the benzylated derivative **5** was necessary to use. In a literature the methylation of benzylated phenanthridine **5** with methyltriflate was reported as unsuccessful, because of partial debenzylation of the starting compound.[11] The methylation with nitrobenzenesulfonate for 35 h was described instead. We have found out that it is possible to easily prepare quaternary ammonium salt **7** by the reaction with methyltriflate in strictly anhydrous solution. The reaction was completed after three hours in a yield of 96% (Scheme 5).

Scheme 5



In conclusion, we have developed the efficient synthesis of isodecarin by the direct radical cyclization of phenol **2** without the need of hydroxyl group protection and subsequent oxidation. This makes the synthetical route three steps shorter in comparison to ones described for similar phenanthridine alkaloids.

EXPERIMENTAL

Melting points were determined on a Boetius stage and are uncorrected. Infrared spectra were measured in KBr discs and scanned on an ATI Unicam Genesis FTIR instrument and values are described in cm^{-1}. NMR spectra were measured in solutions in DMSO-d_6 on a Bruker Avance 300 spectrometer (300 MHz) with TMS as internal standard; the chemical shifts are reported in ppm, interaction constants in Hz. Mass

spectrometric experiments were performed using an LCQ ion trap mass spectrometer (Finnigan MAT, San Jose, CA, USA).

3-Bromo-6-methoxy-2-(naphtho[2,3-*d*][1,3]dioxol-5-yliminomethyl)phenol (1)

Naphtho[2,3-*d*][1,3]dioxol-5-ylamine (1.20 g, 6.41 mmol) was dissolved in hot EtOH (70 mL) and the solution was mixed with 6-bromo-2-hydroxy-3-methoxybenzaldehyde (1.48 g, 6.41 mmol) dissolved in EtOH (20 mL). The mixture was refluxed for 15 min and then cooled in an ice bath. The precipitated solid was filtered, washed with EtOH and dried. Yield: 2.22 g (87%), mp 215-217 °C (EtOH – $CHCl_3$); ^{1}H-NMR, (DMSO-d_6): 3.84 (s, 3H, CH_3), 6,18 (s, 2H, CH_2), 7.10 (d, J = 8.7 Hz, 1H), 7.19 (d, J = 8.7 Hz, 1H), 7.34-7.45 (m, 4H), 7.75 (d, J = 7.8 Hz, 1H), 9.10 (s, 1H), 14.78 (s, 1H); ^{13}C-NMR, (DMSO-d_6): 55.9, 98.1, 101.5, 103.9, 113.7, 115.1, 116.2, 116.4, 122.3, 124.4, 124.7, 126.6, 130.9, 147.4, 147.9, 148.2, 148.4, 153.4, 163.2; MS (APCI, *m/z*): 400.0 a 402.0 $[M+H]^+$; 318.0 and 400.0 $[M-H]^-$; IR: 3443, 3002, 2835, 1599, 1464, 1248, 1038, 798. *Anal*. Calcd for $C_{19}H_{14}BrNO_4$: C, 57.02; H, 3.53; N, 3.50%. Found C, 56.95; H, 3.54; N, 3.42%.

3-Bromo-6-methoxy-2-(naphtho[2,3-*d*][1,3]dioxol-5-ylaminomethyl)phenol (2)

Compound **1** (2.0 g, 5.0 mmol) was suspended in DMF (30 mL) and treated with $NaBH_4$ (190 mg, 5.0 mmol) at rt. After 1 h, the formed solution was slowly added to a stirred mixture of acetic acid (0.5 mL) and water (200 mL) cooled in an ice-bath. The precipitated solid was filtered, washed carefully with water and dried. Yield: 2.0 g (99 %). mp 118-121 °C; ^{1}H-NMR, (DMSO-d_6): 3.80 (s, 3H, CH_3), 4.43 (bs, 2H, CH_2), 5.71 (bs, 1H, NH), 6.07 (s, 2H, CH2), 6.63 (d, J = 7.5 Hz, 1H), 6.86 (d, J = 9.0 Hz, 1H), 6.98-7.05 (m, 2H), 7.11 (d, J = 7.5 Hz, 1H), 7.16 (s, 1H), 7.62 (s, 1H), 9.36 (s, 1H); ^{13}C-NMR, (DMSO-d_6): 42.7, 55.9, 98.6, 100.8, 103.4, 103.9, 112.1, 115.7, 119.1, 122.2, 124.3, 124.9, 129.7, 130.9, 143.4, 146.3, 146.5, 146.7, 147.1; MS (APCI, *m/z*): 402.0 and 404.0 $[M+H]^+$; 400.3 and 402.3 $[M-H]^-$; IR 3430, 2900, 1617, 1535, 1468, 1244, 1040, 791. *Anal*. Calcd for $C_{19}H_{16}BrNO_4$: C, 56.73; H, 4.01; N, 3.48%. Found C, 56.78; H, 4.04; N, 3.67%.

2-Methoxy-6-(naphtho[2,3-*d*][1,3]dioxol-5-ylaminomethyl)phenol (4) and 7-Hydroxy-8-methoxy-2,3-methylenedioxybenzo[*c*]phenanthridine (3)

The solution of compound **2** (700 mg, 1.74 mmol) and *n*Bu_3SnH (1 g, 3.48 mmol) in toluene (50 mL) was heated to 90 °C under argon atmosphere. AIBN (428 mg, 2.61 mmol) was then added and the reaction mixture was maintained at 110 °C for 90 min. After cooling the solvent was evaporated and the residue was purified by column chromatography (silica gel, toluene – MeOH 100/0.5 v/v). Yield: 115 mg (20%) of **4** (the first fraction) and 274 mg (49 %) of compound **3** (the second fraction).

Compound **4**

mp 115-118 °C (EtOH-water); ^{1}H-NMR, (DMSO-d_6): 3.80 (s, 3H, CH_3), 4.40 (d, J = 6.0 Hz, 2H, CH_2), 6.09 (s, 2H, CH_2), 6.25 (d, J = 6.9 Hz, 1H), 6.42 (t, J = 6.0 Hz, 1H, NH), 6.65 (t, J = 7.8 Hz, 1H), 6.77-6.82 (m, 2H), 6.92 (d, J = 7.8 Hz, 1H), 6.98 (d, J = 7.8 Hz, 1H), 7.15 (s, 1H), 7.65 (s, 1H), 8.71 (s, 1H); ^{13}C-NMR, (DMSO-d_6): 41.2, 55.7, 98.4, 100.8, 102.9, 103.9, 109.9, 115.1, 118.4, 118.8, 119.5, 124.9, 126.2, 130.9, 142.4, 142.6, 146.2, 146.7, 147.1; MS (APCI, *m/z*): 324.1 $[M+H]^+$; 322.3 $[M-H]^-$; IR 3431, 2900, 1619, 1531, 1475, 1250, 1043, 781. *Anal*. Calcd for $C_{19}H_{17}NO_4$: C, 70.58; H, 5.30; N, 4.33%. Found C, 70.60; H, 5.24; N, 4.20%.

7-Hydroxy-8-methoxy-2,3-methylenedioxybenzo[*c*]phenanthridine (3)

10% Pd/C (50 mg) was added to a solution of compound **5** [11] (140 mg, 0.342 mmol) in THF (15 mL). The mixture was hydrogenated under normal pressure for 18 h (the reaction was checked by TLC). The catalyst was then filtered off and the solution evaporated to dryness. The residue was dissolved in a warm mixture of EtOH (16 mL) and THF (4 mL) and after evaporation of solvents to 10 mL, the mixture was left to crystallize at 2 °C. The solid was filtered off, washed with EtOH and dried. Yield: 78.2 mg (72 %), mp 265-268 °C (lit., [15] 225-227°C); ^{1}H-NMR, (DMSO-d_6): 4.00 (s, 3H, CH_3), 6.22 (s, 2H, CH_2), 7.50 (s, 1H), 7.73 (d, J = 9.0 Hz, 1H), 7.95 (d, J = 9.0 Hz, 1H), 8.26 (d, J = 8.7 Hz, 1H), 8.51-8.54 (m, 2H), 9.67 (s, 1H), 9.98 (bs, 1H); ^{13}C-NMR, (DMSO-d_6): 56.8, 100.9, 101.4, 104.5, 113.1, 117.3, 118.6, 118.9, 119.7, 126.8, 147.0, 128.2, 129.3, 138.8, 142.7, 144.1, 146.5, 147.8, 148.0; MS (APCI, *m/z*): 320.2 $[M+H]^+$; 318.3 $[M-H]^-$; IR spectra: 3435, 2903, 1624, 1582, 1465, 1286, 1251, 1040, 871. *Anal*. Calcd for $C_{19}H_{13}NO_4$: C, 71.47; H, 4.10; N, 4.39%. Found C, 71.27; H, 4.32; N, 4.34%.

7-Benzyloxy-8-methoxy-5-methyl-2,3-methylenedioxybenzo[*c*]phenanthridinium trifluoromethanesulfonate (7)

Compound **5** [11] (450 mg, 1.1 mmol) was suspended in dry toluene (9 mL) and methyl triflate (360 mg, 2.2 mmol) was added. The reaction mixture was stirred in a sealed vial at 90 °C for 3 h. After cooling to rt, the precipitated solid was filtered off, washed with toluene (2 x 5 mL) and dried.

Yield: 606 mg (96 %), mp 214-215 °C; ^{1}H-NMR, (DMSO-d_6): 4.12 (s, 3H), 4.94 (s, 3H), 5.43 (s, 2H), 6.34 (s, 2H), 7.33-7.44 (m, 4H), 7.62 (d, J = 7.2 Hz, 2H), 7.71 (s, 1H), 8.22-8.25 (m, 2H), 8.71-8.76 (m, 2H), 9.90 (s, 1H); MS (APCI, *m/z*): 424.3 $[M]^+$; IR 3070, 1605, 1543, 1486, 1271, 1156, 1031, 637. *Anal*. Calcd for $C_{28}H_{22}F_3NO_7S$: C, 58.64; H, 3.87; N, 2.44%. Found C, 58.48; H, 3.77; N, 2.46%.

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