REACTION OF 1-BENZYLINDOLE-2,3-DICARBOXYLIC ANHYDRIDE WITH 3-BROMO-4-LITHIOPYRIDINE: FORMAL SYNTHESIS OF ELLIPTICINE

Yasuyoshi Miki,* Yoshitaka Tada, and Ko-ichi Matsushita

Faculty of Pharmaceutical Sciences, Kinki University, 3-4-1, Kowakae, Higashi-Osaka 577-8502, Japan

Abstract - Reaction of 1-benzylindole-2,3-dicarboxylic anhydride with 3-bromo-4-lithiopyridine gave 2-(3-bromoisonicotinoyl)indole-3-carboxylic acid as the sole product. The indole-3-carboxylic acid could be converted to 6-benzylellipticine quinone in five steps.

Ellipticine quinone is an important intermediate in synthesis of ellipticine, which has potent antitumor activity[1] and outstanding syntheses of ellipticine quinone have been reported by Snieckus[2] and Joule.[3] Recently, we showed that 1-benzylindole-2,3-dicarboxylic anhydride (**1**) was a useful synthon in the synthesis of natural products, murrayaquinone-A[4] and ellipticine,[5] 2-acylindoles,[6] and cyclopent[3,4-*b*]-indol-3-ones.[7] In this paper we report the efficacy of **1** and its application to the synthesis of ellipticine quinone.

Reaction of 1-benzylindole-2,3-dicarboxylic anhydride (**1**)[6] with 3-bromo-4-lithiopyridine[8] (2.5 equiv), which was synthesized by the method of Gribble,[9] in tetrahydofuran at -78°C, gave 1-benzyl-2-(3-bromoisonicotinoyl)indole-3-carboxylic acid (**2**) in 15% yield. (Table 1, run 1) Next, we treated **1** with 3-bromo-4-lithiopyridine (2.0 equiv), which was prepared by the method of Effenberger,[10] at -96°C to afford **2** in 25% yield. (run 2) Finally, we were able to obtain **2** in 42% yield by treatment of **1** with 1.2 equiv of 3-bromo-4-lithiopyridine. (run 3) In these reaction conditions, 1-benzyl-3-(3-bromo-isonicotinoyl)indole-2-carboxylic acid (**3**), an isomeric product of **2**, was not produced.[6] These results are shown in Table 1.

Scheme 1

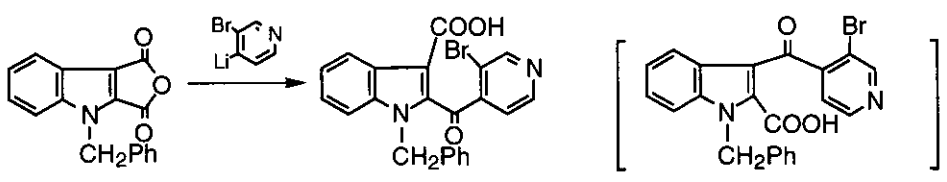


Table 1

Run	3-Bromo-4-lithiopyridine	Temp	Yield(%)
1	2.5 eq	-78°C	15
2	2.0 eq	-96°C	25
3	1.2 eq	-96°C	42

1-Benzyl-2-(3-bromoisonicotinoyl)indole-3-carboxylic acid (**2**) was converted to the corresponding amide (**4**) by treatment with oxalyl chloride, followed by diethylamine. The ketone (**4**) was led to an alcohol (**5**) by reduction with sodium borohydride. The alcohol (**5**) was treated with *t*-butyllithium (2.5 equiv) in tetrahydofuran to give a mixture of 6-benzylellipticine quinone (**6**)[11] and a debrominated alcohol (**7**) in 40% and 19% yields, respectively. (Table 2, run 1) Several efforts were made to isolate the quinone (**6**), but the results attained under various conditions were less than satisfactory. (entries 2-4) These results are shown in Table 2.

Scheme 2

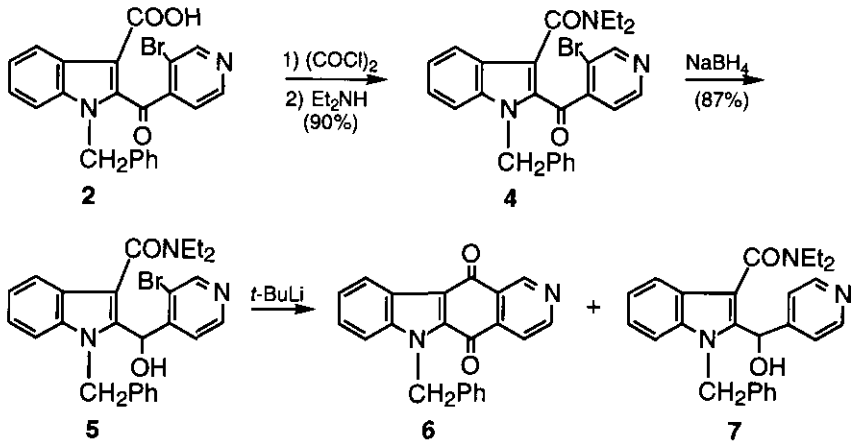
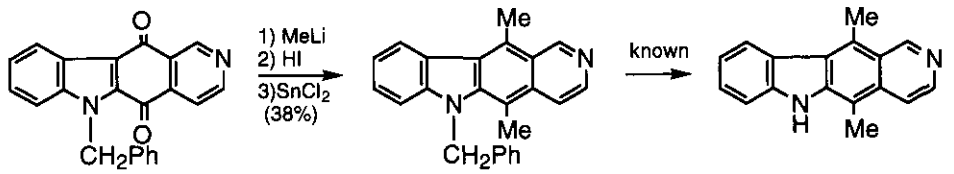


Table 2

Run	*t*-BuLi	Solvent	Condition	Yield (%) 6	7	5
1	2.4 eq	THF	-78°C, 1 h	40	19	–
2	2.4 eq	THF	-90°C, 17 h	26	58	–
3	2.4 eq	Et_2O	-78°C, 1 h	10	33	36
4	4.8 eq	Et_2O	-78°C, 1 h	23	54	–

6-Benzylellipticine (**8**) was obtained in 38% yield by treatment of the quinone (**6**) with methyllithium, then hydriodic acid, followed by tin(II) chloride.[2,11] The 6-benzyl derivative (**8**) has already been converted to ellipticine by Murakami.[12]

Scheme 3



6 8

EXPERIMENTAL

Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. The ^{1}H-NMR spectra were determined on a JEOL JNM-GSX 270 spectrometer using tetramethylsilane as an internal standard. The IR spectra were recorded with a JASCO FT/IR-7000 spectrophotometer. The high MS were recorded on a JOEL JMS-HX100 spectrometer. Column chromatography was performed on E. Merck silica gel 60 (70-230 mesh or 230-400 mesh). Tetrahydrofuran (THF) was distilled from sodium and benzophenone prior to use.

1-Benzyl-2-(3-bromoisonicotinoyl)indole-3-carboxylic Acid (2)

A solution of 1-benzylindole-2,3-dicarboxylic anhydride (**1**)[6](693 mg, 2.5 mmol) in THF (10 mL) was added to a solution of 3-bromo-4-lithiopyridine [prepared from 3-bromopyridine (0.29 mL, 3.0 mmol), diisopropylamine (0.46 mL, 3.3 mmol), and *n*-butyllithium (1.92 mL of a 1.56 M *n*-hexane solution, 3 mmol) in THF (10 mL) at -96°C] at -96°C and the mixture was stirred for 1 h. Saturated NH_4Cl solution was added to the reaction mixture and the mixture was concentrated. The residue was purified by column chromatography (CH_2Cl_2 : MeOH = 50 : 1) to give 1-benzyl-2-(3-bromoisonicotinoyl)indole-3-carboxylic acid (**2**) (453 mg, 42%) as a pale yellow solid: mp 260-262°C (acetone). IR (Nujol) ν: 1678 cm^{-1}; ^{1}H-NMR (d_6-DMSO) δ: 5.60 (2H, s, C*H*$_2$Ph), 7.10-7.45 (8H, m, aromatic protons), 7.69 (1H, br d, *J* = 9 Hz, H-7), 8.07 (1H, br d, *J* = 8 Hz, H-4), 8.53 (1H, d, *J* = 5 Hz, H-6'), 8.82 (1H, s, H-2'); HRMS *m/z* (M^+) calcd for $C_{22}H_{15}N_2O_3Br$: 434.0266. Found: 434.0251.

1-Benzyl-3-*N*,*N*-diethylcarbamoyl-2-indolyl 3-Bromo-4-pyridyl Ketone (4)

A mixture of 1-benzyl-2-(3-bromoisonicotinoyl)indole-3-carboxylic acid (**2**) (261 mg, 0.6 mmol) and oxalyl chloride (0.52 mL, 6.0 mmol) in CH_2Cl_2 (1 mL) was stirred for 2 h at rt and evaporated off. To a solution of the residue in CH_2Cl_2 (3 mL) was added triethylamine (0.25 mL, 1.8 mmol) and diethylamine (0.19 mL, 1.8 mL) and the mixture was stirred for 10 min under ice-cooling. Water was added to the reaction mixture and the mixture was extracted with ether. The combined extracts were washed with water and dried over Na_2SO_4, then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane : AcOEt = 5 : 1) to give 1-benzyl-3-*N*,*N*-diethylcarbamoyl-2-indolyl 3-bromo-4-pyridyl ketone (**4**) (266 mg, 90%) as a yellow oil: IR (Neat) ν: 1738, 1636 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 0.84 (3H, t, *J* = 7 Hz, CH_2CH_3), 0.98 (3H, t, *J* = 7 Hz, CH_2CH_3), 3.09-3.24 (4H,

m, CH_2CH_3), 5.86 (2H, s, CH_2Ph), 7.12-7.58 (10H, m, aromatic protons), 8.56 (1H, d, J = 5 Hz, H-6'), 8.71 (1H, s, H-2').

1-(1-Benzyl-3-*N*,*N*-diethylcarbamoyl-2-indolyl)-1-(3-bromo-4-pyridyl)methanol (5)

To a solution of 1-benzyl-3-*N*,*N*-diethylcarbamoyl-2-indolyl 3-bromo-4-pyridyl ketone (**4**) (147 mg, 0.3 mmol) in MeOH (5 mL) was added sodium borohydride (57 mg, 1.5 mmol) and the mixture was stirred for 10 min under ice-cooling. Water was added to the reaction mixture and the mixture was extracted with CH_2Cl_2. The combined extracts were washed with water and dried over Na_2SO_4, then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane : AcOEt = 5 : 1) to yield (1-benzyl-3-*N*,*N*-diethylcarbamoyl-2-indolyl)(3-bromo-4-pyridyl)methanol (**5**) (130 mg, 87%) (2.25 g, 74%), mp 73-75°C (*n*-hexane) as white crystals. IR (Nujol) ν: 3358, 1650 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 0.54 (3H, br s, CH_2CH_3), 1.11 (3H, m, J = 7 Hz, CH_2CH_3), 3.00-3.66 (4H, m, CH_2CH_3), 5.47-6.17 (4H, m, *CHOH* and CH_2Ph), 7.13-7.41 (9H, m, aromatic protons), 7.88 (1H, br s, aromatic proton), 8.51 (1H, s, H-2'), 8.54 (1H, br s, aromatic proton). *Anal.* Calcd for $C_{26}H_{26}N_3O_2Br$: C, 63.42; H, 5.32; N, 8.53. Found: C, 63.52; H, 5.50; N, 8.43.

6-Benzylellipticine Quinone (6) and (1-Benzyl-3-*N*,*N*-diethylcarbamoyl-2-indolyl)(4-pyridyl)methanol (7)

To a solution (1-benzyl-3-*N*,*N*-diethylcarbamoyl-2-indolyl)(3-bromo-4-pyridyl)methanol (**5**)(1.48 g, 3.0 mmol) in THF (75 mL) at -78 °C under argon was added *t*-butyllithium (4.2 mL of a 1.7 M pentane solution, 7.2 mmol) and the mixture was stirred at -78 °C for 1 h, then at rt overnight. The reaction mixture was acidified with 10% hydrochloric acid and the mixture was extracted with CH_2Cl_2. The combined extracts were washed with water and dried over Na_2SO_4. The solvent was evaporated off to afford a residue, which was purified by column chromatography (CH_2Cl_2 : AcOEt = 10 : 1) to give 6-benzylellipticine quinone(**6**) (401 mg, 40%) and (1-benzyl-3-*N*,*N*-diethylcarbamoyl-2-indolyl)(4-pyridyl)-methanol (**7**) (234 mg, 19%).

6; mp 267-268°C (from EtOH) [lit.,[2] 268°C]. IR (Nujol) ν: 1658 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 5.99 (2H, s, CH_2Ph), 7.15-7.53 (8H, m, aromatic protons), 7.93 (1H, d, J = 5 Hz, H-4), 8.48-8.58 (1H, m, H-10), 9.02 (1H, d, J = 5 Hz, H-3), 9.46 (1H, s, H-1). HRMS *m/z*: (M^+) calcd for $C_{22}H_{14}N_2O_2$: 338.1055. Found: 338.1030.

7; IR (neat) ν: 3216, 1600 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 0.67 (3H, br s, CH_2CH_3), 1.02 (3H, br s, CH_2CH_3), 3.10-3.56 (4H, m, CH_2CH_3), 5.40-6.51 (4H, m, CH_2Ph and *CHOH*), 7.01-7.46 (11H, m, aromatic protons), 8.35-8.40 (2H, m, H-2' and H-6'). HRMS *m/z*: (M^+) calcd for $C_{26}H_{27}N_3O_2$: 413.2103. Found: 413.2073.

6-Benzylellipticine

To a suspension of 6-benzylellipticine quinone (**6**)(51 mg, 0.15 mmol) in THF (6 mL) at rt under argon was added methyllithium (0.57 mL of a 1.14 M ether solution, 0.65 mmol) and the mixture was stirred 30 min, then a solution of 47% hydriodic acid (0.9 mL) in MeOH (2.25 mL) was added and the mixture was

stirred for 40 min. The reaction mixture was concentrated and acetic acid was added to the mixture to afford precipitates which were filtered by suction. A suspension of the precipitates, $SnCl_2$ (203 mg, 0.9 mmol), concentrated hydrochloric acid (0.9 mL) in acetic acid (4.5 mL) and THF (4.5 mL) was refluxed for 4.5 h. The reaction mixture was made alkaline with saturated aqueous $NaHCO_3$ solution and extracted with $CHCl_3$. The extracts were washed with water, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (CH_2Cl_2 : MeOH = 200 : 1) to yield 6-benzylellipticine (19 mg, 38%), mp 240-244°C (from benzene) (lit.,[2] 239-240°C, lit.,[12] 243-246°C). ^{1}H-NMR ($CDCl_3$) δ: 2.84 (3H, s, 5-C*H*$_3$), 3.32 (3H, s, 11-C*H*$_3$), 5.77 (2H, s, C*H*$_2$Ph), 7.16-7.54 (8H, m, aromatic protons), 7.86 (1H, d, J = 6 Hz, H-4), 8.42 (1H, d, J = 8 Hz, H-10), 8.49 (1H, d, J = 6 Hz, H-3), 9.73 (1H, s, H-1). HRMS *m/z*: (M^+) calcd for $C_{24}H_{20}N_2$: 336.1626. Found: 336.1614.

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13. The ketone (**4**) was treated with $LiN(TMS)_2$ in THF at -78°C, but **4** was recovered.
14. Treatment of the alcohol (**5**) with *s*-butyllithium gave the ellipticine quinone (**6**) in 10% yield.

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