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SYNTHESIS OF 5*H*-BENZO[*b*]CARBAZOLE-6,11-DIONES FROM BENZOYLINDOLECARBOXYLIC ACIDS

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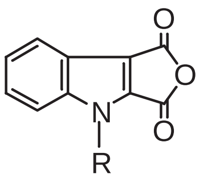
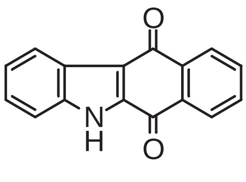
Abstract – Treatment of 1-benzyl-3-(4-methoxybenzoyl)indole-2-carboxylic acid with phosphorus pentachloride gave the corresponding acid chloride, which was treated with titanium(IV) chloride to afford 9-methoxy-5*H*-benzo[*b*]carbazole-6,11-dione. In a similar manner, 1-benzenesulfonyl-2-(4-methoxybenzoyl)indole-3-carboxylic acid provided 9-methoxy-5*H*-benzo[*b*]carbazole-6,11-dione. However, 1-benzyl-3-(4-methoxybenzyl)indole-2-carboxylic acid could be converted to 8-methoxy-5*H*-benzo[*b*]carbazole-6,11-dione.

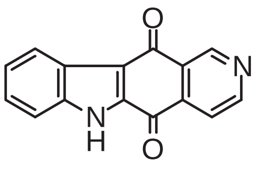
5*H*-Benzo[*b*]carbazole quinones and their aza analogues (ellipticine quinones) show versatile biological activities and are candidates for treatment of human cancers.[1-3] Snieckus[4] and Kelly[5] reported an elegant synthesis of the quinones by reaction of directed *ortho*-litiated aromatic amides with indole-3-carbaldehyde. Useful syntheses of the 5*H*-benzo[*b*]carbazole-6,11-quinones were reported by several groups, but the methods have a limitation of the substituents on the benzene ring.[1,3,4,6] We showed that 1-benzylindole-2,3-dicarboxylic anhydride (**1a**) was a useful synthon in the synthesis of murrayaquinone-A,[8] ellipticine,[9] and ellipticine quinone.[10] Recently, we reported that reaction of indole-2,3-dicarboxylic anhydride (**1**) with anisoles provided 1-benzyl-3-(4-methoxybenzoyl)indole-2-carboxylic acids and 1-benzenesulfonyl-2-(4-methoxybenzoyl)indole-3-carboxylic acids.[11] In this paper we report a synthesis of 5*H*-benzo[*b*]carbazole-6,11-quinones from 1-benzyl-3-(4-methoxybenzoyl)indole-2-carboxylic acid and 1-benzenesulfonyl-2-(4-methoxybenzoyl)indole-3- carboxylic acid.



1a: CH_2Ph, **1b**: SO_2Ph



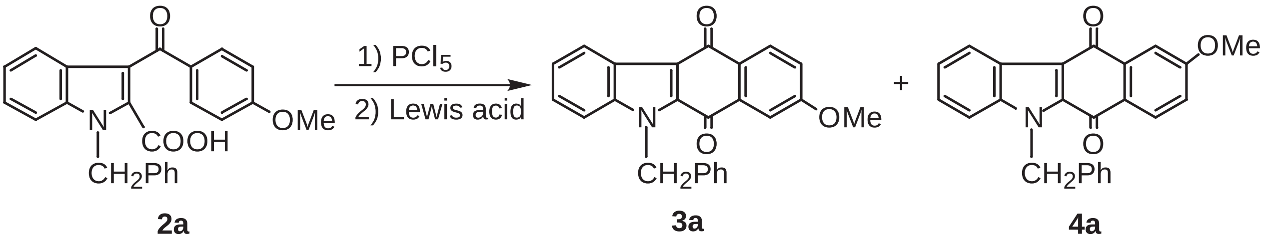
5*H*-benzo[*b*]carbazole-6,11-quinone



ellipticine quinone

Treatment of 1-benzyl-3-(4-methoxybenzoyl)indole-2-carboxylic acid (**2a**)[11] with phosphorus pentachloride, followed by aluminum chloride gave a mixture of 8-methoxy- (**3a**) and 9-methoxy-5*H*-benzo[*b*]carbazole-6,11-diones (**4a**) (**3a** : **4a** = about 2 : 3). (Entries 1, 2) When 2.0 equivalents of aluminium chloride were used, the quinone (**4a**) was isolated in 34% yield as a major product and the quinone (**3a**) in 8% yield as a minor product (**3a** : **4a** = about 1 : 4). (Entry 3) Next, we treated the corresponding acid chloride of **2a** with titanium(IV) chloride as a Lewis acid to provide **4a** as the sole or a major product. (Entries 4, 5) In a similar manner, the carboxylic acid (**5a**), which was prepared from the reaction of **1a** with 4-methoxyphenylmagnesium bromide in 89% yield, provided **4a** as a major product. (Entry 6) (Scheme 1, 2) These results are shown in Table 1.

Scheme 1



Scheme 2

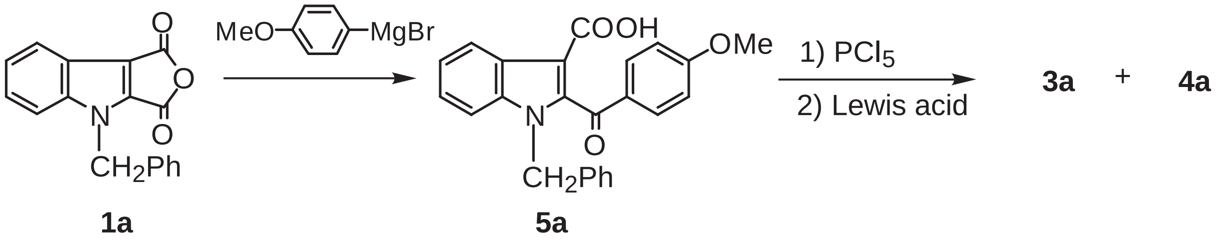
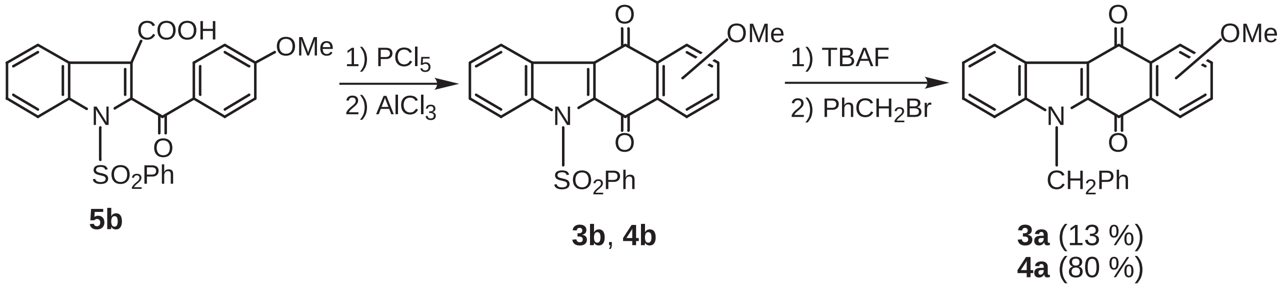


Table 1

Entry	Substrate	Lewis acid	Time	Yield (%)		
				3a	**4a**	Total
1	**2a**	$AlCl_3$ (0.5 eq)	2.5 h	21	29	50
2	**2a**	$AlCl_3$ (1.2 eq)	1.5 h	24	37	61
3	**2a**	$AlCl_3$ (2.0 eq)	6 h	8	34	42
4	**2a**	$TiCl_4$ (0.5 eq)	7 h	-	34	34
5	**2a**	$TiCl_4$ (1.2 eq)	4 h	-	45	45
6	**2a**	$TiCl_4$ (2.0 eq)	6 h	4	35	39
7	**5a**	$TiCl_4$ (1.2 eq)	4 h	4	53	57

In a similar manner, treatment of the corresponding acid chloride of 1-benzenesulfonyl-2-(4-methoxybenzoyl)indole-3-carboxylic acid (**5b**)[11] with aluminum chloride gave a mixture of 8-methoxy- (**3b**) and 9-methoxy-5*H*-benzo[*b*]carbazole-6,11-diones (**4b**) in 49% yield as an inseparable mixture. The mixture of the two quinone (**3b**) and (**4b**) was treated with tetrabutylammonium fluoride,[13] then benzyl bromide in the presence of potassium carbonate to provide a separable mixture of 8-methoxy- (**3a**) and 9-methoxy-5*H*-benzo[*b*]carbazole-6,11-diones (**4a**) in 13% and 80% yields, respectively. (Scheme 3)

Scheme 3



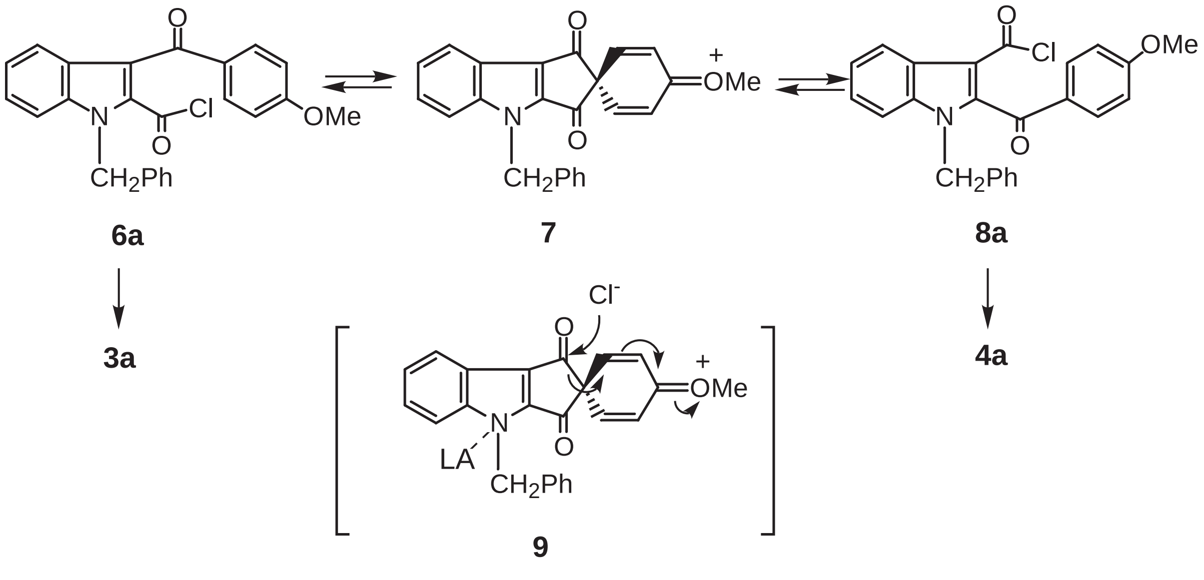
5b

3b, **4b**

3a (13 %)
4a (80 %)

A plausible mechanism of the formation of the quinone (**4a**) as a major product from the carboxylic acid (**2a**) is as follows: **2a** was converted to the acid chloride (**6a**), which gave a spiro derivative (**7**) by treatment of the Lewis acid as known as the Hayashi rearrangement.[14-16] **8a** was obtained by attack of a chloride anion toward the intermediate (**9**) because the carbonyl group of the 3-psition of **9**, which was produced by coordination of an indole nitrogen of **7** with an excess of Lewis acid, is more reactive toward a nucleophile than that of the 2-position. The carboxylic acids (**5a**) and (**5b**) also gave the quinones *via* a similar intermediate (**7**) because a similar ratio of the two quinones was isolated. (Scheme 4)

Scheme 4



6a

7

8a

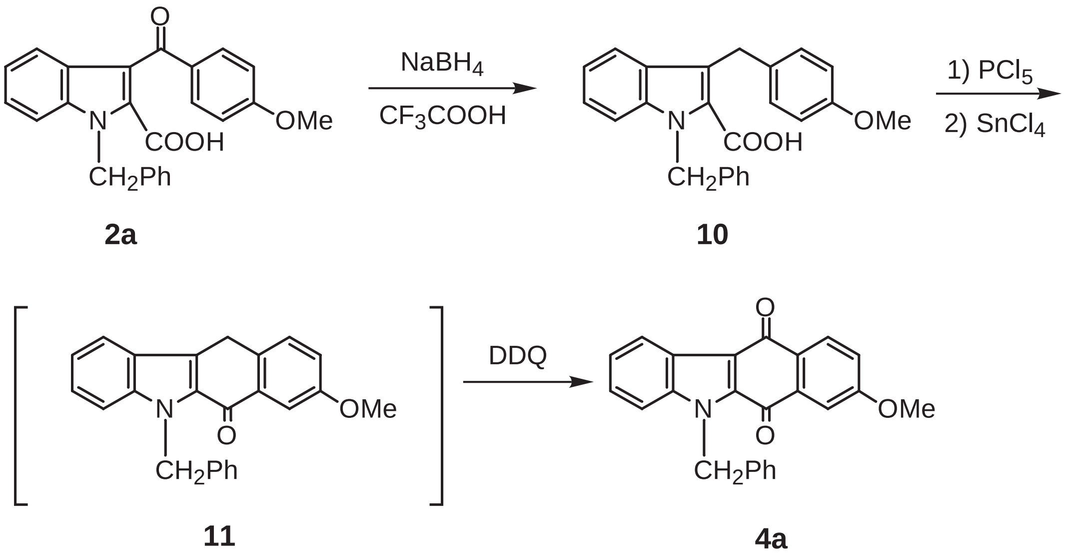
3a

4a

9

In order to avoid the formation of the isomeric quinone by the Hayashi rearrangement, we examined the reactivity of the corresponding benzyl derivative (**10**). Reduction of **2a** with sodium borohydride[17] in the presence of trifluoroacetic acid gave the benzyl derivative (**10**) in 90% yield. Treatment of **10** with phosphorus pentachloride, followed by tin(IV) chloride and DDQ gave 8-methoxy-5*H*-benzo[*b*]carbazole-6,11-dione (**4a**) in 76% yield. (Scheme 5)

Scheme 5



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). THF was distilled from sodium and benzophenone prior to use.

5-Benzyl-8-methoxy-5*H*-benzo[*b*]carbazole-6,11-dione (3a) and 5-Benzyl-9-methoxy-5*H*-benzo[*b*]carbazole-6,11-dione (4a)

From 1-Benzyl-3-(4-methoxybenzoyl)indole-2-carboxylic Acid (2a)

A mixture of 1-benzyl-3-(4-methoxybenzoyl)indole-2-carboxylic acid (**2a**)[11] (96 mg, 0.25 mmol) and phosphorus pentachloride (104 mg, 0.50 mmol) in 1,2-dichloroethane (5 mL) was refluxed for 30 min. After cooling the solution, aluminum chloride or titanium(IV) chloride (1 M dichloromethane solution) was added to the reaction mixture. The mixture was refluxed for 1.5-7 h, neutralized with 5% sodium hydrogen carbonate aqueous solution, and extracted with $CHCl_3$. The extracts were washed with water, dried over Na_2SO_4, and concentrated under reduced pressure to afford a residue, which was purified by preparative thin-layer chromatography on silica gel (*n*-hexane : $CHCl_3$ = 1 : 1) to give 5-benzyl-8-methoxy-5*H*-benzo[*b*]carbazole-6,11-dione (**3a**) (19 mg, 21%) as an orange solid and 5-benzyl-9-methoxy-5*H*-benzo[*b*]carbazole-6,11-dione (**4a**) (27 mg, 29%) as a yellow solid.

3a; mp 183-185°C (AcOEt). IR (Nujol) ν: 1659, 1643 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.93 (3H, s, OCH_3), 5.98 (2H, s, CH_2), 7.14-7.46 (9H, m, aromatic protons), 7.59 (1H, d, *J* = 3 Hz, H-7), 8.15 (1H, d, *J* = 8.5 Hz, H-10), 8.45-8.51 (1H, m, H-1). *Anal.* Calcd for $C_{24}H_{17}NO_3$: C, 78.46; H, 4.66; N, 3.81. Found: C, 78.46; H, 4.59; N, 3.82.

4a; mp 203-205°C (AcOEt). IR (Nujol) ν: 1651 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.93 (3H, s, OCH_3), 5.98 (2H, s, CH_2), 7.11 (1H, dd, *J* = 8.5, 3 Hz, H-8), 7.15-7.47 (9H, m, aromatic protons), 7.68 (1H, d, *J* = 3 Hz, H-10), 8.07 (1H, d, *J* = 8.5 Hz, H-7), 8.43-8.49 (1H, m, H-1). *Anal.* Calcd for $C_{24}H_{17}NO_3$: C, 78.46; H, 4.66; N, 3.81. Found: C, 78.55; H, 4.65; N, 3.76.

From 1-Benzenesulfonyl-2-(4-methoxybenzoyl)indole-3-carboxylic Acid (5b)

A mixture of 1-benzenesulfonyl-2-(4-methoxybenzoyl)indole-3-carboxylic acid (**5b**)[11] (218 mg, 0. 5 mmol) and phosphorus pentachloride (208 mg, 1.0 mmol) in 1,2-dichloroethane (10 mL) was refluxed for 30 min. After cooling the solution, aluminum chloride (80 mg, 0.6 mmol) was added to the solution and the mixture was refluxed for 5 h. The reaction mixture was quenched with water, extracted with $CHCl_3$: MeOH (10 : 1). The extracts were washed with water, dried over Na_2SO_4, and concentrated under reduced pressure to afford a residue, which was purified by column chromatography on silica gel (*n*-hexane : AcOEt = 5 : 1) to give an inseparable mixture of 5-benzenesulfonyl-8-methoxy-5*H*-benzo[*b*]carbazole-6,11-dione and 5-benzenesulfonyl-9-methoxy-5*H*-benzo[*b*]carbazole-6,11-dione (103 mg, 49%).

A suspension of the mixture of the two quinones (84 mg, 0.2 mmol) and tetrabutylammonium fluoride (0.2 mL of a 1 M THF solution) in THF (1 mL) was stirred for 30 min. The reaction mixture was diluted with water and the precipitates were collected by filtration to afford an orange solid (43 mg). The suspension of the orange solid (20 mg, 0.07 mmol), potassium carbonate (19 mg, 0.14 mmol), and benzyl bromide (17 μL, 0.14 mmol) in acetonitrile (1 mL) was refluxed for 1.5 h. The reaction mixture was diluted with water and extracted with $CHCl_3$: MeOH (10 : 1). The extracts were washed with water, dried over Na_2SO_4, and concentrated under reduced pressure to afford a residue, which was purified by preparative thin-layer chromatography on silica gel (benzene) to give **3a** (3 mg, 13%) and **4a** (21 mg, 80%).

1-Benzyl-2-(4-methoxybenzoyl)indole-3-carboxylic Acid (5a)

To a solution of 1-benzylindole-2,3-dicarboxylic anhydride (**1a**)[12] (831 mg, 3 mmol) in THF (18 mL) was added 4-methoxyphenylmagnesium bromide (12 mL of 0.5 M THF solution, 6 mmol) at -78°C under argon and the mixture was stirred for 30 min. 10% HCl solution was added to the reaction mixture and the mixture was extracted with $CHCl_3$: MeOH (10 : 1). The combined extracts were washed with water and dried over Na_2SO_4, then concentrated under reduced pressure to give a solid. The solid was mixed well with *n*-hexane and collected by filtration to afford 1-benzyl-2-(4-methoxybenzoyl)indole-3-carboxylic acid (**5a**) (1.03 g, 89%) as a white solid, mp 261-263°C (MeOH-acetone). IR (Nujol) ν: 1657 cm^{-1};

^{1}H-NMR (DMSO-d_6) δ: 3.84 (3H, s, OCH_3), 5.32 (2H, s, CH_2), 6.95-8.16 (13H, m, aromatic protons). *Anal.* Calcd for $C_{24}H_{19}NO_4$: C, 74.79; H, 4.97; N, 3.64. Found: C, 74.77; H, 5.04; N, 3.52.

1-Benzyl-3-(4-methoxybenzyl)indole-2-carboxylic Acid (10)

Sodium borohydride (2.70 g, 71 mmol) was added to trifluoroacetic acid (60 mL, 760 mmol) at 0°C under Ar over 30 min. A solution of 1-benzyl-2-(4-methoxybenzoyl)indole-3-carboxylic acid (**2a**) (1.50 g, 3.9 mmol) in dichloromethane (60 mL) was added to the mixture and the reaction mixture was stirred overnight at rt. The mixture was diluted with water and extracted with dichloromethane. 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 ($CHCl_3$: MeOH = 50 : 1) to give 1-benzyl-3-(4-methoxybenzyl)indole-2-carboxylic acid (**10**) (1.30 g, 90%) as a white solid : mp 194-196°C (AcOEt-*n*-hexane). IR (Nujol) ν: 1667 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.74 (3H, s, OCH_3), 4.52 (2H, s, CH_2), 5.80 (2H, s, CH_2), 6.76-6.81 (2H, m, aromatic protons), 7.00-7.33 (10H, m, aromatic protons), 7.66 (1H, br d, J = 8 Hz, H-4). *Anal.* Calcd for $C_{24}H_{21}NO_3$: C, 77.61; H, 5.70; N, 3.77. Found: C, 77.55; H, 5.71; N, 3.65.

8-Methoxy-5*H*-benzo[*b*]carbazole-6,11-dione (4a)

A mixture of 1-benzyl-2-(4-methoxybenzyl)indole-3-carboxylic acid (**10**) (223 mg, 0.6 mmol) and phosphorus pentachloride (250 mg, 1.2 mmol) in dichloromethane (12 mL) was stirred for 30 min at rt. To the solution was added tin(IV) chloride (0.72 mL of a 1 M dichloromethane solution, 0.72 mmol) and the reaction mixture was stirred for 30 min at –20°C. DDQ (272 mg, 1.2 mmol) was added to the mixture and the reaction mixture was stirred for 1 h at –20°C. Water was added to the reaction mixture and the mixture was extracted with dichloromethane, washed with water, and dried over Na_2SO_4. The extracts were concentrated under reduced pressure to afford a residue, which was purified by column chromatography (*n*-hexane : $CHCl_3$ = 1 : 1) to give 8-methoxy-5*H*-benzo[*b*]carbazole-6,11-dione (**4a**) (167 mg, 76%).

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