Oxidation Reactions of Some Indolocarbazoles

Stuart W. McCombie and Susan F. Vice*

Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, New Jersey 07033-0539

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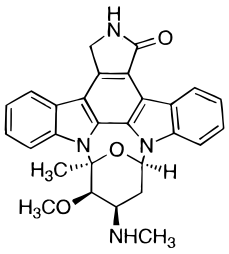
Introduction

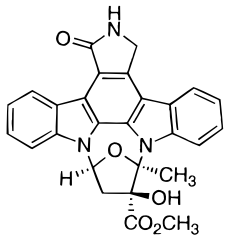
Interest in designing antagonists of protein kinase C (PKC) for disease states such as psoriasis, hypertension, cancer, and HIV-infection has resulted in numerous reports in both the patent and open literature over the past several years.[1−3]

Furthermore, attempts to synthesize the naturally occurring, potent PKC inhibitor staurosporine **(1)**[4] generated a flurry of activity[5] from a number of researchers throughout the 1980's but did not culminate in its total synthesis. A conceptually more succinct approach to this indolocarbazole-containing natural product has recently been completed by Danishefsky and co-workers.[6]

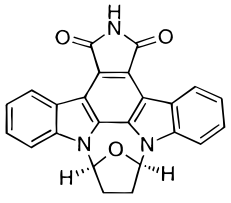
The PKC program in our laboratories[1f,g] focused on designing and synthesizing compounds related to staurosporine (**1**) and K-252a (**2**), another naturally occurring,



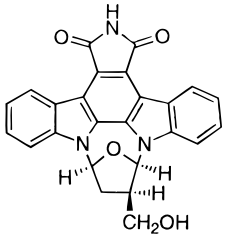
Staurosporine **1**



K-252a **2**



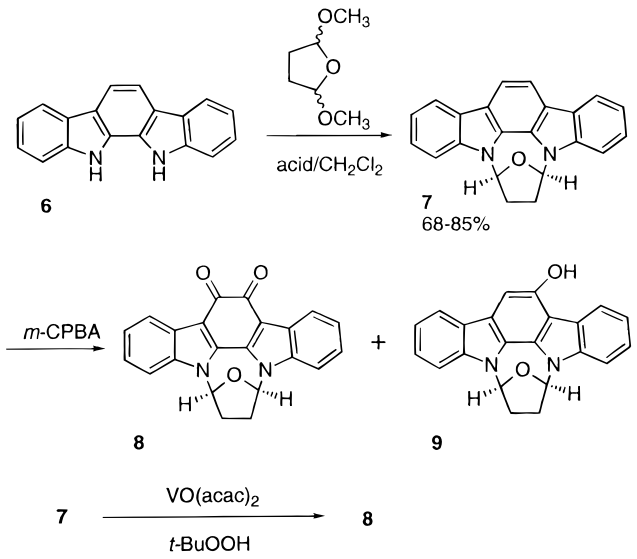
SCH 46440 **3**



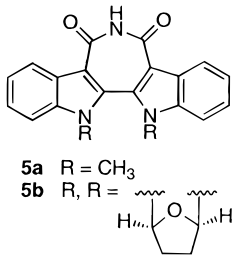
SCH 47112 **4**

indolocarbazole-containing PKC inhibitor. Part of our effort in this area has led to the preparation of a series of imide-containing, potent inhibitors of PKC, which lack the C-methyl present in the naturally occurring products. Two examples (i.e., **3** and **4**) from this series are illustrated above.

Scheme 1



We wished to determine if the ring size and proximity of the biindolyl system to the imide portion was necessary for maintaining potency, and thus imides of structure **5** were proposed for construction. The preparation of these targets allowed us to explore and study some novel oxidation reactions of indolocarbazole derivatives, and our observations are the subject of this paper.



5a R = CH_3
5b R, R =

Results and Discussion

Concurrently, we had devised an efficient method of producing **7**, a cyclocondensation product of 2,5-dimethoxytetrahydrofuran and indolocarbazole (**6**).[1f] Treatment of **7** with 4 equiv of *m*-CPBA in CH_2Cl_2 gave the purple dione **8** in 32% yield, a second, rather air-sensitive component which was assigned the phenol-like structure **9**, plus several other minor components, which were not characterized (Scheme 1).

Although this oxidation procedure gave us sufficient quantitities of dione **8** for the preparation of simple (mono) oxime and hydrazone derivatives, we sought a more preparatively useful method to complete the synthesis of our desired imide.

tert-Butyl hydroperoxide in the presence of $VO(acac)_2$ is known to convert phenanthrene to the corresponding 9,10-dione in 91% yield.[7] Reaction of the electron rich

* To whom correspondence should be addressed. Phone: (908) 298-3462. FAX: (908) 298-7152. E-mail: susan.vice@spcorp.com.

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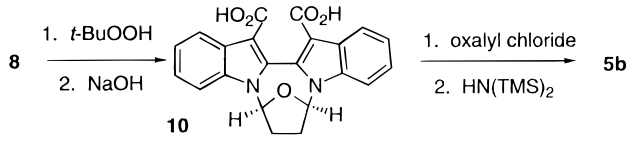
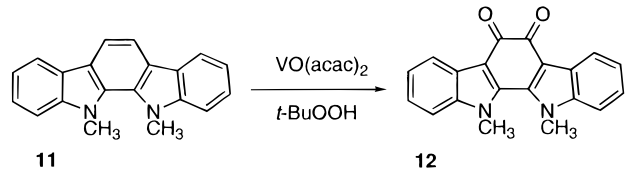
Scheme 2



Scheme 3



parent **6** (0.1 M in PhCl/room temperature or reflux/10 equiv 90 or 70% aqueous *tert*-butyl hydroperoxide/1−8 mol % $VO(acac)_2$) gave high molecular weight material that was difficult to characterize and was clearly not the simple, highly symmetrical desired oxidation product. However, application of this oxidizing system to the indolocarbazole derivative **7** gave a 76−86% yield of the desired dione **8**. No other oxidation products were detected during the course of the reaction (TLC analysis).

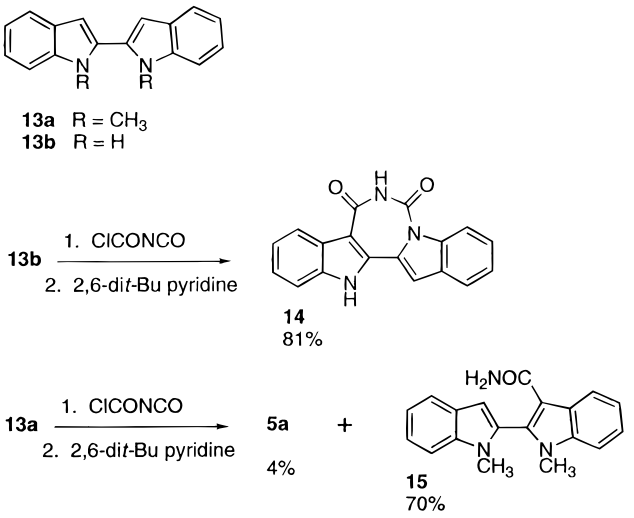
In an effort to generate other potentially useful, reactive intermediates related to **8**, other oxidizing systems were screened. For example, **6** and **7** gave complex mixtures of products when treated with dimethyldioxirane, whereas both **6** and **7** were resistant to oxidation with OsO_4/NMO and were recovered unchanged. In a related system[8] in which the sugar portion contains a C−C double bond, OsO_4 attacked only the olefinic double bond, underscoring the difference in these systems between a true olefinic double bond and a "double bond" contained within an electron rich aromatic system.

The preparation of our desired imide **5b** is described in Scheme 2. Although dione **8** was resistant to further oxidation with peracids, cleavage to the dicarboxylic acid **10** was achieved efficiently in the presence of basic *tert*-butyl hydroperoxide. Diacid chloride formation using a standard method followed by treatment with $HN(TMS)_2$ gave the imide **5b** directly.

Reaction of *N*,*N*-dimethylindolocarbazole (**11**)[9] with the $VO(acac)_2$/*tert*-butyl hydroperoxide system as described above produced only high molecular weight material that could not be characterized by standard methods. After some experimentation, dione **12** was produced in 48% yield by stirring a dichloromethane solution of **11** at room temperature in the presence of the aforementioned oxidizing system (Scheme 3).

Oxidative cleavage of the dione **12** using conditions described for the tetrahydrofuranyl case led to a complex mixture of products that could not be converted to the desired imide. Imide **5a** was prepared for biological evaluation by reaction of **13a**[10] with *N*-chlorocarbonyl isocyanate, in 4% yield. Although the 2,2′-indole dimer **13b**[10] reacted efficiently with *N*-chlorocarbonyl isocyanate to give the urea **14** via sequential C−C and N−C bond-forming processes, the *N*,*N*-dimethyl derivative **13a** gave amide **15** as the major product, after hydrolytic work up, and only a small amount of the desired imide **5a** (Scheme 4).

Scheme 4



Imides **5** were not significantly active in our primary PKC screen, relative to SCH 47112 and SCH 46440. However, the information gleaned from this study will allow us to not only investigate further the reactivity of the indolocarbazole nucleus and its derivatives but also to probe the structure−activity relationships of this interesting class of compounds.

Experimental Section

8,11-Epoxy-8,9,11-tetrahydrodiindolo[1,2,3-*fg*:3′,2′,1′-kl]-[1,6]benzodiazocine (7). To a mixture of indolocarbazole[11] (5.00 g, 19.5 mmol), CH_2Cl_2 (98 mL), and 2,5-dimethoxytetrahydrofuran (12 mL) was added camphorsulfonic acid (1.00 g) in a single portion. The resulting solution was stirred at room temperature for 12−24 h. After approximately 30 min, a precipitate was noted. At the end of the reaction time, the precipitate was collected by suction filtration, washed with cold 3:2 CH_2Cl_2:hexane (2 × 25 mL), and dried under high vacuum at room temperature to give **7** (4.61 g, 73% yield) as a cream-colored solid. This reaction was carried out several times on various scales (0.2−20 g), and yields were in the range of 68−85%: mp 280−283 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.11−2.22 (m, 2 H), 2.70−2.84 (m, 2 H), 7.01−7.08 (m, 2 H), 7.33−7.43 (m, 2 H), 7.50−7.61 (m, 4 H), 8.02 (s, 2 H) 8.25 (d, J = 6 Hz, 2 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 30.73, 87.58, 109.52, 112.17, 119.46, 119.68, 120.33, 123.97, 124.60, 124.87, 137.20; IR (KBr DRIFT) ν 3046, 2997, 1651, 1564, 1445; MS (CI) m/z (relative intensity) 324 (34), 325 (100).

6,7,8,9-Tetrahydro-6,9-epoxydiindolo[1,2,3-*fg*:3′,2′,1′-*kl*]-[1,6]benzodiazocine-15,16-dione (8).[12] To a solution of indolocarbazole derivative **7** (0.325 g, 1.00 mmol) and CH_2Cl_2 (40 mL) was added, portionwise, 80−85% *m*-CPBA (0.8 g, 4 equiv). The resulting solution was stirred for 1 h at room temperature, applied directly to a column of silica gel, and eluted with,

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(12) Compounds **5**, **8**, and **12** formed stable solvates with water, DMF, and DMSO and were difficult to obtain in the free form. Attempts to generate accurate C, H, N analyses failed, perhaps because of this solvation phenomenon.

successively, 5:1 CH_2Cl_2:hexanes; CH_2Cl_2; 1−10% Et_2O:CH_2Cl_2 gradient. The fractions containing product (R_f = 0.4 in 10% Et_2O:CH_2Cl_2; green component) were evaporated, and the resulting solid residue was crystallized by evaporation from 1:1 Et_2O:CH_2Cl_2 to a low volume and then filtration to give **8** (0.114g; 32% yield) as a green powder: mp > 350 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.37−2.56 (m, integration obscured by DMSO-d_6), 2.67−2.88 (m, 2 H), 7.04−7.20 (m, 2 H), 7.28−7.44 (m, 2 H), 7.72−7.89 (m, 2 H), 7.93−8.07 (m, 2 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 34.23, 88.77, 111.62, 111.84, 120.66, 124.45, 124.71, 125.64, 135.01, 135.96, 175.94; IR (KBr DRIFT) ν 3058, 2946, 1636, 1448; MS (CI) m/z (relative intensity) 354 (6), 355 (100), 356 (25); HRMS calcd (for MH^+) 355.1083, found 355.1071.

6,7,8,9-Tetrahydro-6,9-epoxydiindolo[1,2,3-*fg*:3′,2′,1′-*kl*]-[1,6]benzodiazocine-15,16-dione (8). Indolocarbazole derivative **7** (1.00 g, 3.09 mmol), chlorobenzene (20 mL), $VO(acac)_2$ (41 mg, 5 mol %), and *tert*-butyl hydroperoxide (70% aqueous, 3.40 mL) were mixed together and heated at reflux for 3 h. The reaction mixture was cooled, diluted with CH_2Cl_2 (750 mL), and filtered through a pad of Celite. Evaporation of the solvents gave dione **8** (941 mg, 86%).

7,8,9,10-Tetrahydro-7,10-epoxydiindolo[1,2-*a*:2′,1′,-c][1,4]-diazocine-1,16-dicarboxylic Acid (10). To a solution of dione **8** (303 mg; 0.86 mmol) and DMF (44 mL) was added *tert*-butyl hydroperoxide (0.38 mL of a 70% aqueous solution) and then 10% NaOH (w/v NaOH/H_2O; 1.32 mL). After the solution was stirred for 1 h at room temperature, ice (50 g) and H_2O (100 mL) were added and the pH was adjusted to 5[13] with 5% aqueous $NaHSO_3$ (∼23 mL). A precipitate was noted, and the reaction flask was cooled in an ice bath for 1 h. The resulting diacid (240 mg) was collected by suction filtration. The aqueous layer was extracted with $CHCl_3$ or CH_2Cl_2 (3 × 75 mL), washed with brine, and dried over $MgSO_4$. The solution was filtered, evaporated, and pumped to give a solid which was combined with the above precipitate to give the diacid **10** (260 mg; 78%) as a yellow solid: mp 155−158 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.41 (bs, 2 H), 1.87−2.14 (bm, 2 H), 6.96 (bs, 2 H), 7.15 (t, 2 H), 7.27 (t, 2 H), 7.70 (d, 2 H), 8.07 (d, 2 H), 12.30 (bs, 2 H, exchanges with D_2O); IR (KBr DRIFT) ν 2992, 2876, 1676; MS (FAB) m/z (relative intensity) 389 (51), 388 (57), 371 (70), 345 (100); HRMS calcd (for MH^+) 388.1059, found 388.1069.

5,7-Ethano-5*H*,7*H*,12*H*-6-oxa-4b,7a,13-triazadiindeno-[1,2,3-*ef*:1′,2′,3′-*kl*]heptalene-12,14(13*H*)-dione (5b).[12] To a cooled (10 °C) mixture of diacid **10** (135.8 mg, 0.35 mmol), CH_2Cl_2 (10 mL; passed through basic alumina before use), and DMF (0.003 mL) was added oxalyl chloride (0.063 mL), dropwise. The cooling bath was removed, the resulting solution was stirred for 2 h, volatile materials were removed in vacuo, and CH_2Cl_2 (3.0 mL) was added. The resulting solution was cooled to 5 °C, and $HN(TMS)_2$ (0.13 mL) was added dropwise. After being stirred at room temperature for 18 h, the solution was poured into ice and the mixture was allowed to warm to room temperature. The resulting precipitate was collected, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), washed with brine, dried over $MgSO_4$, filtered, and evaporated to give a yellow solid which was identical (TLC (9:1 CH_2Cl_2:MeOH) and ^{1}H NMR) with the precipitate collected from the water layer. The solids were combined, adsorbed onto Celite, and chromatographed on silica gel, eluting with 50:1 CH_2Cl_2:MeOH. Evaporation of solvent gave **5b** (68 mg; 52%) as a yellow solid: mp (with decompostion) 364 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.36−2.38 (bm, 2 H), 2.67−2.73 (bm, 2 H), 7.28 (bs, 2 H), 7.44 (t, 2 H), 7.53 (t, 2 H), 7.92 (d, 2 H), 8.36 (d, 2 H), no evidence for NH in this solvent system; ^{13}C NMR (75 MHz, DMSO-d_6) δ 32.62, 88.65, 106.50, 111.04, 122.02, 123.94, 125.98, 127.34, 129.70, 135.16, 156.07; IR (KBr DRIFT) ν 3363, 3058, 2936, 1706, 1676; MS (EI) m/z (relative intensity) 371 (78), 370 (32), 369 (18).

11,12-Dihydro-11,12-dimethylindolo[2,3-*a*]carbazole-5,6-dione (12).[12] *N*,*N*-Dimethylindolocarbazole (**11**) (356.7 mg; 1.26 mmol), CH_2Cl_2 (12 mL), and $VO(acac)_2$ (16.6 mg; 5 mol %) were mixed together, and *tert*-butyl hydroperoxide (70% aqueous; 1.32 mL) was added dropwise. After being stirred for 3.5 h, the mixture was diluted with CH_2Cl_2 (15 mL) and filtered. The collected solid (202.0 mg) was washed sequentially with H_2O (2 × 15 mL) and toluene (2 × 10 mL) and air dried with suction for several hours. The organic layer from above was diluted with CH_2Cl_2 (75 mL), washed with saturated aqueous $NaHSO_3$ (50 mL) brine (25 mL), dried over $MgSO_4$, filtered, and concentrated to a 3 mL volume. This extract was applied to a column of silica gel (20 g) and eluted to give, after evaporation of the fractions, dione **12** (53.4 mg). This sample was identical (TLC: 30:1 CH_2Cl_2:EtOAc; ^{1}H NMR) to the solid collected above. Dione **12**, a purple solid (yield: 48−52% over several runs), was very insoluble in common organic solvents and sparingly soluble in DMSO and acetone: mp > 310 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 4.41 (s, 6 H), 7.49 (m, 4 H), 7.78 (d, 2 H), 8.29 (d, 2 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 36.13, 112.39, 113.19, 120.28, 124.53, 124.59, 125.81, 139.11, 140.23, 176.38; IR (KBr DRIFT) ν 3050, 2953, 1632, 1449; MS (CI) m/z (relative intensity) 331 (46), 315 (95), 314 (55), 146 (100); HRMS calcd (for MH^+) 315.1134, found 315.1155.

5,6-Dihydro-5,6-dimethyl-11*H*-azepino[4,3-*b*:5,6-*b*′]diindole-11,13(12*H*)-dione (5a). The dimer **13a** (447.4 mg, 1.72 mmol) was dissolved in CH_3CN (90 mL) and was cooled in an ice bath. *N*-Chlorocarbonyl isocyanate (0.17 mL) was added dropwise, and the resulting solution was stirred at room temperature for 1 h 20 min at which time 2,6- di-*tert*-butyl pyridine (0.48 mL) was added. After the mixture was stirred at room temperature for 4 days, the observed precipitate was collected by suction filtration, washed with Et_2O (2 × 1 mL), and dried at high vacuum for 24 h to give **5a** as a solid (25.4 mg, 4%): mp 321−324 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.98 (s, 6 H), 7.37 (m, 2 H), 7.50 (m, 2 H), 7.74 (d, 2 H), 8.19 (d, 2H), 10.52 (s, 1H, exchanges with D_2O); IR (KBr DRIFT) ν 3164, 3046, 2975, 1657, 1622; MS (EI) m/z (relative intensity) 329 (100), 330 (23).

The CH_3CN portion was assayed for **5a** by TLC (50:1 CH_2Cl_2:MeOH) but only the initial addition product could be detected (R_f = 0.21). This solution was successively heated at reflux for 2 h; a second portion of 2,6- di-*tert*-butylpyridine (0.48 mL) was added, and the resulting solution was heated at reflux for 1 h. TLC analysis after each of these operations did not detect the presence of **5a**. The reaction solution was cooled, diluted with CH_2Cl_2 (150 mL), washed with 10% HCl (50 mL) and brine (50 mL), and dried over $MgSO_4$. Filtration and evaporation of the solvents gave crude **15** as a dark oil, which was further purified by column chromatography (silica gel; 50:1 CH_2Cl_2:MeOH as the eluant). Evaporation of the appropriate fractions gave **15** as a tan solid (365 mg, 70%): mp 224.5−226 °C.

Acknowledgment. We would like to thank our Library Information Services and our Physical-Analytical Department for their support.

Supporting Information Available: ^{1}H NMR spectra of compounds **7**, **5a,b**, **10**, and **12**; ^{13}C NMR spectra of compounds **7** and **8**; IR spectra of **8** and **12** (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(13) Lowering the pH to 4 or below causes relatively rapid decarboxylation and generates a mixture of mono- and didecarboxylated products.