pH 1, then extracted twice with diethyl ether. After drying and concentration, the crude oil (3.4 g) was dissolved in 40 mL of CH_2Cl_2, cooled at 10 °C, and treated with 40 mL of an 0.3 M diazomethane/CH_2Cl_2 solution. After a further 15 min at rt, concentration and fast chromatography (20 min, 50 parts of silica gel, hexane/AcOEt (7/3)) gave 1 g of pure ester sulfinate. These esters gave by decomposition on silica gel the starting sulfone. By HPLC, we observed four peaks A, B, C, D. The preparative HPLC on a 100-mg scale allowed us to separate each of them in a pure state. Only B and D crystallized. ^{1}H NMR (250 MHz): A δ 1.31 (s, Me *gem*); 1.37 (s, Me *gem*); 1.49 (s, *t*-Bu); 1.50 (s, *t*-Bu); 1.7–1.9 (m, H_1, H_3); 3.67 (s, CH_3OS); 4.13 (dd, J = 1, 11 Hz); 5 (d, CHCO); 5.2 (AB, CH_2O); 6.9–7.4 (m, Ar); B δ 1.31 (s, Me *gem*); 1.35 (s, Me *gem*); 1.50 (s, *t*-Bu); 1.50 (s, *t*-Bu); 1.7–1.9 (m, H_1, H_3); 3.68 (s, CH_3OS); 4.29 (dd, J = 2.6, 11.5); 4.77 (d, CHCO); 5.07 (AB, CH_2O); 6.9–7.4 (m, Ar); C δ 1.23 (s, Me *gem*); 1.34 (s, Me *gem*); 1.41 (s, *t*-Bu); 1.49 (s, *t*-Bu); 1.9–2.2 (m, H_1, H_3); 3.80 (s, CH_3OS); 4.13 (dd, J = 1, 10.5); 5 (d, CHCO); 5.07 (AB, CH_2O); 6.9–7.4 (m, Ar); D δ 1.26 (s, Me *gem*); 1.33 (s, Me *gem*); 1.42 (s, *t*-Bu); 1.51 (s, *t*-Bu); 1.9–2.3 (m, H_1, H_3); 3.84 (s, CH_3OS); 4.19 (dd, J = 2.6, 11); 4.69 (d, CHCO); 5.08 (AB, CH_2O); 6.9–7.4 (m, Ar). CIMS (NH_3): m/z 640 ($M + NH_4^+$), 623 ($M + H^+$), 567, 542, 487, 349, 223, 183 for each of the four. IR: 1720–1735 (CO), 1312–1339 cm^{-1} (SO_2) for each of the four.

***tert*-Butyl 2-(*tert*-Butylthio)-3-hydroxynonanoate (12).** To a stirred solution of 5 mL of diisopropylamine (36 mmol) in 40 mL of dry THF was added at –60 °C 20 mL of a 1.6 M solution of *n*-BuLi in hexane (32 mmol). After 45 min at –60 °C was added a solution of 5.2 g of sulfide **6f** (25 mmol) in dry THF (40 mL). After 30 min at –30 °C, 4.2 g of commercial *n*-heptanal (31 mmol) in 20 mL of dry THF was added and the reaction mixture was allowed to warm to rt. The reaction medium was poured in 200 mL of saturated NaH_2PO_4 and extracted with isopropyl ether. After drying and evaporation of the organic phase, the crude alcohol was chromatographed on silica gel (hexane/AcOEt (9/1) as eluent) to afford 7.16 g (88%) of a mixture of isomers. Mp: 36 °C. ^{1}H NMR (250 MHz): δ 0.88 (t, CH_3); 1.17–1.75 (m, CH_2): 1.36 (s, *t*-Bu); 1.49 (s, *t*-Bu); 3.04 (s, OH); 3.08 (d, J = 8 Hz, CHS); 3.20 (d, J = 6, CHS); 3.67 (m, CHO); 3.76 (m, CHO). IR: 3598 (OH); 1718 (CO); 1368 cm^{-1} (Me).

***tert*-Butyl 2-[(*tert*-Butylsulfonyl)oxy]-3-hydroxynonanoate (13).** To a stirred solution of 0.5 g of sulfide **12** (16 mmol) in 2 mL of CH_2Cl_2 was added at 20 °C a solution f 0.88 g of commercial *m*-CPBA (4 mmol) in 13 mL of CH_2Cl_2. The white suspension was stirred 2 h at rt and poured in aqueous $NaHCO_3$ solution (0.4 g in 50 mL of water) and extracted with CH_2Cl_2 (3 × 25 mL). After drying and evaporation, the crude oil was chromatographed on silica gel to afford 0.37 g (67%) of a white solid. Mp: 58.5 °C. ^{1}H NMR (250 MHz): δ 0.88 (t, CH_3); 1.29–1.52 (m, CH_2); 1.46 (s, *t*-Bu); 1.49 (s, *t*-Bu); 3.70 (OH); 3.99 (d, J = 10 Hz, CHS); 4.39 (m, CHO). IR: 3550 (OH); 1728 (CO); 1369 (Me); 1298, 1109 cm^{-1} (SO_2).

tert*-Butyl 2-[(*tert*-Butylsulfonyl)oxy]-2-nonenoate (14).** To a stirred solution of 0.5 g of alcohol **13** (1.4 mmol) and 0.15 mL of methanesulfonyl chloride (1.94 mmol) in 5 mL of CH_2Cl_2 was added at 0 °C 0.4 mL of triethylamine (2.9 mmol). After 60 h at rt, the reaction medium was poured in saturated aqueous KH_2PO_4 solution and extracted with CH_2Cl_2. After drying and evaporation, the crude oil was chromatographed on silica gel (hexane/AcOEt (9/1)) to afford 0.18 g (38%) of a mixture of isomers and a large quantity of deconjugated sulfonyl product **16**. By careful chromatography on silica gel with hexane/isopropyl ether as eluent, the **14*Z and **14*E*** isomers were purely obtained. ^{1}H NMR (250 MHz): *Z* δ 0.89 (t, CH_3); 1.29 (m, CH_2); 1.41 (s, *t*-Bu); 1.53 (s, *t*-Bu); 2.75 (allylic CH_2); 7.37 (t, vinylic H); *E* δ 0.89 (t, CH_3); 1.29 (m, CH_2); 1.41 (s, *t*-Bu); 1.53 (s, *t*-Bu); 2.39 (allylic CH_2); 6.92 (t, vinylic H). ^{13}C NMR (75 MHz): *z* δ 14, 22.4, 23.7, 27.9–31.5, 62, 83.1, 132.5, 159.8, 162.3 (dt, $^1J_{C-H}$ = 6.5 Hz); *Z* δ 14.1, 22.4, 23.9, 27.9–31.5, 61.5, 83.7, 134.2, 153.2, 162.1 (dt, $^3J_{C-H}$ = 11 Hz); IR: 3550 (OH); 1728 (CO); 1369 (Me); 1298, 1109 cm^{-1} (SO_2).

tert*-Butyl 2-Nonenoate (15).** As for reduction of **5b** in PTC system. **14*Z gave **15*E*** in 25% yield. **14*E*** gave **15*Z*** in 16% yield (60–80% yield of deconjugated sulfonyl product **16**). ^{1}H NMR (250 MHz): *Z* δ 0.88 (t, CH_3); 1.2–1.45 (m, CH_2); 1.49 (s, *t*-Bu); 2.6 (m, allylic CH_2); 5.66 (dt, J = 1.5, 11 Hz, H α CO); 6.11 (dt, J = 7.5, 11 Hz, H β CO); *E* δ 0.88 (t, CH_3); 1.2–1.50 (m, CH_2); 1.48 (s, *t*-Bu); 2.16 (m, allylic CH_2); 5.74 (dt, J = 1.5, 15.5 Hz, H α CO); 6.86 (dt, J = 7, 15.5 Hz, H β CO). IR: *Z* 1708 (CO); 1639 (double bond *Z*), 1369 cm^{-1} (Me); *E* 1706 (CO); 1642 (double bond *E*), 1369 cm^{-1} (Me).

***tert*-Butyl 2-[(*tert*-Butylsulfonyl)oxy]-3-nonenoate (16).** Isolated from the above reduction. ^{1}H NMR (250 MHz): δ 0.88 (t, CH_3); 1.2–1.40 (m, CH_2); 1.45 (s, *t*-Bu); 1.50 (s, *t*-Bu); 2.14 (m, allylic CH_2); 4.55 (d, J = 9 Hz); 5.57 (dd, J = 9, 16 Hz); 5.81 (dt, J = 6, 16 Hz).

Acknowledgment. We thank Dr. D. Rowlands for giving a British touch to this manuscript.

Supplementary Material Available: ^{1}H NMR spectra of compounds **6a**, **6f**, **3c**, **4f**, **4c**, **7a**, **5b**, **9a**, **10a** (*Z* and *E*), **12–14**, **15** (*Z* and *E*), and **16** (17 pages). This material is contained in many 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.

A Novel Entry to 4,7-Indoloquinones via the Fremy's Salt Oxidative Degradation of 4-Formyl-7-hydroxyindoles

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Received May 20, 1991

A novel synthetic approach toward 4-formyl-7-hydroxyindoles and 4,7-indoloquinones is described. Basically, two major operations need to be carried out, namely: (1) ozonization of the appropriately protected 4-amino-5-hydroxyindenes leading eventually to 4-formyl-7-hydroxyindoles and (2) Fremy's salt promoted oxidative degradation of the later compounds to the desired 4,7-indoloquinones. A formal synthesis of PDE I and PDE II has been achieved.

A common building block to mitosenes[1] and many naturally occurring quinones[2] such as isobatzellins,[3] kinamycins,[4] discorhabdin,[5] murrayaquinones,[6] etc. is the indoloquinone unit shown (Figure 1).

0022-3263/92/1957-0589$03.00/0

Table I. ^{1}H NMR (ppm) and ^{13}C NMR (ppm) of 6-Oxo-6*H*,7*H*,8*H*-indeno[4,5-*d*]oxazoles 2

2a		2b		2c	
^{1}H NMR	^{13}C NMR	^{1}H NMR	^{13}C NMR	^{1}H NMR	^{13}C NMR
7.12 (s, 1 H)	204.29	7.16 (s, 1 H)	205.14	7.13 (s, 1 H)	207.71
4.00 (s, 3 H)	164.01	4.00 (s, 3 H)	164.49	3.99 (s, 3 H)	164.42
3.70 (dt, 1 H, J = 7.0 and 2.9 Hz)	144.44	3.28 (t, 2 H, J = 5.5 Hz)	144.66	3.56 (dd, 1 H, J = 18.0 and 8.0 Hz)	144.74
	144.27	2.77 (t, 2 H, J = 5.5 Hz)	144.17		144.32
3.02 (dd, 1 H, J = 9.0 and 7.0 Hz)	138.84	2.68 (s, 3 H)	139.88	2.81 (dd, 1 H, J = 18.0 and 3.4 Hz)	139.23
			139.28		138.26
	133.31		134.23		133.39
2.82 (s, 3 H)	99.60		100.23	2.73 (m, 1 H)	100.50
2.31 (dd, 1 H, J = 9.0 and 2.9 Hz)	55.61		55.93	2.67 (s, 3 H)	55.95
	44.97		35.98	1.33 (d, 3 H, J = 7.2 Hz)	41.83
1.54 (d, 3 H, J = 7.0 Hz)	30.38		22.16		31.23
	20.32		14.05		16.11
	13.79				14.07

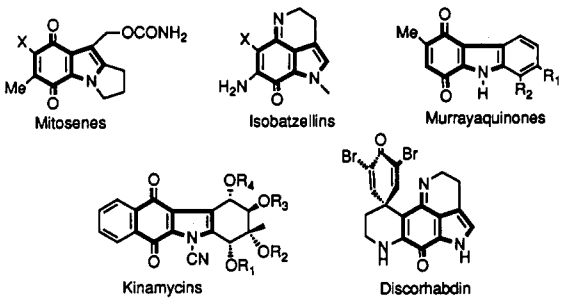

Figure 1.

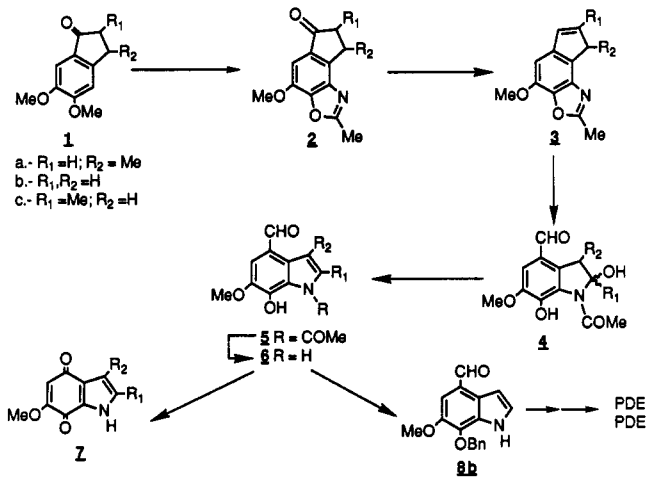

Figure 2.

Prompted by the recent activity on the synthesis of indoloquinones,[7] we would like to report herein that our recently developed oxidative degradation approach (ODA)[8] works well for the purpose of acquiring the above indoloquinone skeleton. In addition, the methodology described below allows for the synthesis of 4-formyl-7-hydroxyindoles, a type of compound of recent interest due to the valuable properties shown by 3′,5′-cAMP phosphodiesterase inhibitors PDE-I and PDE-II.[9]

Our first part of the plan (Figure 2) called for reaching the indole skeleton.[10] After some failures with the ozonolysis of several partially protected 4-amino-5-hydroxyindenes, the fully protected benzoxazole derivatives **3** were employed. The key benzoxazoles **3** were straightforwardly derived from the easily available indanones **1** through

(1) Mitosene semiquinones appear to be the species responsible for the mitomycins' capacity to alkylate and cross-link double helical DNA. See: Egberston, M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1987**, *109*, 2204. Simple mitosenes have useful antibiotic properties. For the synthesis of mitosenes and related compounds, see: Wender, P. A.; Cooper, C. B. *Tetrahedron Lett.* **1987**, *28*, 6125. Fukuyama, T.; Yang, L. *Tetrahedron Lett.* **1986**, *27*, 6299. Shaw, K. J.; Luly, J. R.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 4515. Rebek, S. H.; Shue, Y.-K.; Gehret, J.-C.; Zimmerman, S. *J. Org. Chem.* **1984**, *49*, 5164. Luly, J. R.; Rapoport, H. *J. Am. Chem. Soc.* **1983**, *105*, 2859. Luly, J. R.; Rapoport, H. *J. Org. Chem.* **1982**, *47*, 2404 and references cited therein.

(2) Thomson, R. H. *Naturally occurring quinones III: recent advances*; Chapman and Hall: London, 1987. Thomson, R. H. *Naturally occurring quinones*; Academic Press: New York, 1971. *The chemistry of the quinonoid compounds*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons: New York, 1988.

(3) Sakemi, S.; Sun, H. H.; Jefford, C. W.; Bernardinelli, G. *Tetrahedron Lett.* **1989**, *30*, 1989.

(4) Ito, S.; Matsuya, T.; Omura, S.; Otani, M.; Nakayawa, A.; Iwai, Y.; Othani, T.; Hata, T. *J. Antibiot.* **1970**, *23*, 315. Hata, T.; Omura, S.; Iwai, Y.; Nakagawa, A.; Otani, M. *J. Antibiot.* **1971**, *24*, 353. Omura, S.; Nakagawa, A.; Yamada, H.; Hata, T.; Furusakai, A.; Watanabe, T. *Chem. Pharm. Bull.* **1973**, *21*, 931. Ishiki, K.; Sama, T.; Naganawa, H.; Matsuda, N.; Hattori, S.; Hamada, M.; Takeuchi, T.; Oosono, M.; Ishizuka, M. *J. Antibiot.* **1989**, *42*, 467.

(5) Perry, N. B.; Blunt, J. W.; McCombs, J. D.; Munro, M. H. G. *J. Org. Chem.* **1986**, *51*, 5476. Kobayashi, J.; Cheng, J.; Ishibashi, M.; Nakamura, H.; Ohizumi, Y.; Hirate, Y.; Sasaki, T.; Lu, H.; Clardy, J. *Tetrahedron Lett.* **1987**, *28*, 4939. Perry, N. B.; Blunt, J. W.; Munro, M. H. G. *Tetrahedron* **1988**, *44*, 1727. Perry, N. B.; Blunt, J. W.; Munro, M. H. G.; Higa, T.; Sakai, R. *J. Org. Chem.* **1988**, *53*, 4127.

(6) Wu, T.-S.; Ohta, T.; Furukawa, H. *Heterocycles* **1983**, *20*, 1267. Furukawa, H.; Wu, T.-S.; Ohta, T. *Chem. Pharm. Bull.* **1985**, *33*, 4132. Furukawa, H.; Yogo, M.; Ito, C. *Chem. Pharm. Bull.* **1985**, *33*, 1320.

(7) For the synthesis of *N*-cyanoindolyl-4,7-quinones, see: Dmitrenko, G. I.; Nielsen, K. E.; Steingart, C.; Ming, N. S.; Wilson, J. W.; Weeratunga, G. *Tetrahedron Lett.* **1990**, *31*, 3681. Weeratunga, G.; Prasad, G. K. B.; Dilley, J.; Taylor, N. J.; Dmitrenko, G. I. *Tetrahedron Lett.* **1990**, *31*, 5713. For the synthesis of mitosenes, see: ref 1 and Roth, R. H.; Remers, W. A.; Weiss, M. J. *J. Org. Chem.* **1966**, *31*, 1012. Allen, G. R., Jr.; Poletto, J. F.; Weiss, M. J. *J. Am. Chem. Soc.* **1964**, *86*, 3877. Allen, G. R., Jr.; Poletto, J. F.; Weiss, M. J. *J. Am. Chem. Soc.* **1964**, *86*, 3878. Remers, W. A.; Weiss, M. J. *J. Am. Chem. Soc.* **1966**, *88*, 804. For the synthesis of benzo[*f*]indole-4,9-diones, see: Maruyama, K.; Osuka, A.; Nakagawa, K.; Nabeshima, T.; Tabushi, K. *Synthesis* **1989**, 628. For the synthesis of dihydroindolopirroloquinones, see: Maruyama, K.; Nagai, N.; Naruta, Y. *Chem. Lett.* **1987**, 97. Naruta, Y.; Nagai, N.; Arita, Y.; Maruyama, K. *J. Org. Chem.* **1987**, *52*, 3956. The first reported syntheses of indoloquinones are due to: Blackhall, A.; Thomson, R. H.; *J. Chem. Soc.* **1954**, 3916. Clifford, B.; Nixon, P.; Salt, C.; Tomlinson, M. *J. Chem. Soc.* **1961**, 3516.

(8) Saá, J. M.; Llobera, A.; García-Raso, A.; Costa, A.; Deyá, P. M. *J. Org. Chem.* **1988**, *53*, 4263. Saá, J. M.; Llobera, A. *Tetrahedron Lett.* **1987**, *28*, 5045. Saá, J. M.; Llobera, A. Deyá, P. M. *Chem. Lett.* **1987**, 771. See also: Saá, J. M.; Capó, M.; Marti, C.; García-Raso, A. *J. Org. Chem.* **1990**, *55*, 288.

(9) For recent syntheses of these compounds, see: Kemoto, N.; Enomoto, Y.; Tanaka, Y.; Nitanai, K.; Umezawa, H. *Agric. Biol. Chem.* **1979**, *43*, 559. Kemoto, N.; Enomoto, Y.; Miyagaki, M.; Tanaka, Y.; Nitanai, K.; Umezawa, H. *Agric. Biol. Chem.* **1979**, *43*, 555. Bolton, R. E.; Moody, C. J.; Rees, C. W.; Tojo, G. *J. Chem. Soc., Chem. Commun.* **1985**, 1775. Rawal, V. H.; Cava, M. P. *J. Am. Chem. Soc.* **1986**, *108*, 2110. Boger, D. L.; Coleman, R. S. *J. Org. Chem.* **1986**, *51*, 3250. Carter, P.; Fitzjhon, S.; Magnus, P. *J. Chem. Soc., Chem. Commun.* **1986**, 1162. Carter, P.; Fitzjhon, S.; Magnus, P. *J. Am. Chem. Soc.* **1987**, *109*, 2711. Boger, D. L.; Coleman, R. S. *J. Am. Chem. Soc.* **1987**, *109*, 2717.

(10) A closely related strategy (ozonolysis of appropriately substituted 1,4-dihydronaphthalenes or substituted aniline derivatives) has been previously applied for the synthesis of 4-substituted indoles. See: Maehr, H.; Smallheer, J. *J. Am. Chem. Soc.* **1985**, *107*, 2943. Danishefsky, S. J.; Phillips, G. B. *Tetrahedron Lett.* **1984**, *25*, 3159. See also: Plieninger, H.; Suhr, K. *Chem. Ber.* **1956**, *89*, 270. Plieninger, H.; Meyer, E.; Nassirian, F. S.; Weidmann, E. *Liebigs Ann. Chem.* **1976**, 1475. Plieninger, H.; Lehnert, W., *Chem. Ber.* **1967**, *100*, 2427. Plieninger, H.; Lehnert, W.; Mangold, D., *Chem. Ber.* **1967**, *100*, 2421. Pleininger, H.; Schmalz, D. *Chem. Ber.* **1976**, *109*, 2140.

Table II. ^1H NMR (ppm) and ^{13}C NMR (ppm) of Indeno[4,5-*d*]oxazoles 3

3a		3b		3c	
^1H NMR	^{13}C NMR	^1H NMR	^{13}C NMR	^1H NMR	^{13}C NMR
6.86 (s, 1 H)	163.30	6.92 (s, 1 H)	163.23	6.73 (s, 1 H)	163.60
6.76 (dd, 1 H, J = 5.4 and 1.5 Hz)	142.92	6.89 (dt, 1 H, J = 5.4 and 1.8 Hz)	143.01	6.44 (q, 1 H, J = 1.5 Hz)	145.37
	140.59		141.67		143.28
6.49 (dd, 1 H, J = 5.4 and 1.5 Hz)	140.36	6.58 (dt, 1 H, J = 5.4 and 1.8 Hz)	138.26		143.08
	137.98		137.92		138.46
4.01 (s, 3 H)	130.59	4.02 (s, 3 H)	132.94	3.97 (s, 3 H)	126.80
3.78 (broad q, 1 H, J = 7.5 Hz)	129.42	3.59 (t, 2 H, J = 1.8 Hz)	131.41	3.43 (s, 2 H)	126.66
	103.28		125.12		124.73
2.65 (s, 3 H)	100.50	2.65 (s, 3 H)	100.35	2.60 (s, 3 H)	100.07
1.48 (d, 3 H, J = 7.5 Hz)	55.74		55.70	2.15 (d, 3 H, J = 1.5 Hz)	56.24
	43.37		35.91		39.83
	15.05		13.80		16.39
	13.81				14.26

Table III. ^1H NMR (ppm) and ^{13}C NMR (ppm) of 4,7-Indoloquinones 7

7a		7b		7c	
^1H NMR[a]	^{13}C NMR[b]	^1H NMR[a]	^{13}C NMR[c]	^1H NMR[b]	^{13}C NMR[b]
6.74 (s, 1 H)	183.02	7.05 (d, 1 H, J = 2.5 Hz)	183.46	6.16 (q, 1 H, J = 0.6 Hz)	182.96
	170.03		171.11		166.73
5.57 (s, 1 H)	160.08	6.60 (d, 1 H, J = 2.5 Hz)	160.18	5.66 (s, 1 H)	159.78
3.72 (s, 3 H)	132.12		129.55	3.74 (s, 3 H)	138.42
2.20 (s, 3 H)	125.63	5.73 (s, 1 H)	127.83	2.23 (d, 3 H, J = 0.6 Hz)	128.17
	122.95	3.83 (s, 3 H)	127.66		121.70
	110.10		107.54		106.28
	106.45		107.27		105.77
	56.30		56.70		56.17
	11.91				12.51

[a] $CDCl_3$ + CD_3OD. [b] DMSO-d_6. [c] CD_3OD + DMSO-d_6.

regioselective demethylation (NaCN/DMSO),[11] followed by orthonitration ($NaNO_2/HNO_3$), reduction ($SnCl_2/HCl$), and protection (AcOH/Δ) of the resulting *o*-aminophenol, thereby providing **2** which on further reduction ($NaBH_4$) and dehydration (AcOH/Δ) led to **3**. Ozonolysis (O_3/MeOH/CH_2Cl_2, −78 °C; Me_2S) of the resulting oxazole **3** yielded the expected crude dialdehydes (containing varying amounts of monoketal derivatives) in moderate to good yield. The crude mixture, without further purification, yielded 1-acetyl-2-hydroxyindolines **4** (except for the case of **3c** which directly provided **5c**) on treatment with aqueous acid at room temperature. Dehydration of **4** provided 1-acetyl-4-formyl-7-hydroxyindoles **5** as crystalline materials having a strong tendency to undergo deacylation (even during chromatography on silica gel) to the, not unexpectedly, unstable hydroxy indoles **6**. Actually, **5c** and **6c** could not be obtained as analytically pure compounds due to their lability toward hydrolysis and oxidation.

In agreement with previous findings,[12] the only observable products of the Fremy's salt promoted oxidative degradation of 4-formyl-7-hydroxyindoles **6** were the desired orange-red 4,7-indoloquinones **7**. This is remarkable in view of the Ishii's peri effect which predicts the formation of increasing amounts of the ortho oxidation product for closely related cases.[13] In our view the aldehyde might undergo easy hydration to release peri strain, the resulting hydrate being the actual educt suffering Fremy's salt oxidation. On the other hand, N-acetyl derivatives **5a** and **5b** were found to be almost inert toward oxidation by Fremy's salt under otherwise identical conditions, thereby proving the strong dependence of Fremy's salt oxidation on the substrate's redox potential.[12]

It is worth noting that **5b** could be easily converted into **8b**, a key intermediate in the Rees et al. synthesis of PDE-I and PDE-II.[9] Our synthetic material was found to be identical to that of Rees et al.[14] In our view, this novel route toward 4-substituted indoles,[15] being a flexible one, might be of use for the synthesis of analogues of PDE I and PDE II.

In summary, 4,7-indoloquinones can be easily prepared by a novel route which involves ozonolysis of the oxazole derivative of 4-amino-5-hydroxyindenes, followed by direct Fremy's salt oxidative degradation of the key 4-formyl-7-hydroxyindoles. The latter reaction appears to be a valuable alternative to the classic two-step approach (—CHO → —OH → =O) involving a Dakin reaction[16] followed by oxidation.

In principle, this plan could also be applicable for the construction of quinolinoquinones and other higher homologues.

Experimental Section

General Methods. All melting points are uncorrected and were taken on a capillary melting point apparatus. Proton NMR spectra were obtained on a Varian FT-80A or a Bruker WP 200SY spectrometer in $CDCl_3$ with Me_4Si as internal standard, unless otherwise noted. Electron-impact mass spectra were recorded on a Hewlett-Packard 5988A GC/MS operating at 70-eV ionizing energy. Infrared spectra were recorded on a Hitachi 260-10 infrared spectrophotometer. Elemental analyses were obtained at the Servei de Microanalisi del CSIC (Barcelona). High-resolution mass spectra (HRMS) were obtained with a Kratos MS-50 (Santiago de Compostela) and VG Micromass ZAB-2F (La La-

(11) McCarthy, J. R.; Moore, J. L.; Cregge, R. J. *Tetrahedron Lett.* **1978**, *19*, 5183.
(12) Saá, J. M.; Morey, J.; Rubido, C. *J. Org. Chem.* **1986**, *51*, 4471.
(13) Ishii, H.; Hanaoka, T.; Asaka, T.; Harada, Y.; Ikeda, N. *Tetrahedron* **1976**, *32*, 2693.
(14) We warmly thank Prof. C. W. Rees for kindly providing us with a sample of authentic **8b**.
(15) See, inter allia: Clark, R. D.; Repke, D. B. *Heterocycles* **1984**, *22*, 195. Kozikowski, A. *Heterocycles* **1981**, *16*, 267. Moyer, M. P.; Shiurba, J. F.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 5106. Harrington, P. J.; Hegedus, L. S. *J. Org. Chem.* **1984**, *49*, 2657.
(16) Hassall, C. H. *Org. React. (New York)* **1957**, *9*, 73.

guna, Tenerife). Column chromatographies were performed on silica gel Merck (Kieselgel 40). Dimethoxyindanones **1a** and **1c** were prepared according to literature procedures.[17] Compound **1b** was used as received from Aldrich.

The standard workup procedure employed throughout involved extraction of the aqueous solution with three to five 25-mL portions of CH_2Cl_2 or Et_2O, drying over anhydrous sodium sulfate, and evaporation in vacuo. The residue was usually flash chromatographed on silica gel prior to bulb-to-bulb distillation or crystallization.

Synthesis of 6-Oxoindenooxazoles 2. 4-Methoxy-2,8-dimethyl-6-oxo-6*H*,7*H*,8*H*-indeno[4,5-*d*]oxazole (2a). A solution of dimethoxy indanone **1a** (12.67 g, 0.061 mol) and sodium cyanide (17.0 g, 0.34 mol) in 120 mL of DMSO was heated with continuous stirring at 100 °C during 16 h. The standard workup provided 8.73 g (74%) of **5-hydroxy-6-methoxy-3-methyl-1-indanone** as a white solid, mp 102–104 °C (prisms/CH_2Cl_2). IR (KBr): 3600–3000, 1680, 1590, 1505, 1330, 1310, 1280, 1220, 1050, 875 cm^{-1}. ^1H NMR: 7.17 (s, 1 H), 6.98 (s, 1 H), 3.92 (s, 3 H), 3.34 (dt, 1 H, J = 7.0 and 3.1 Hz), 3.01 (dd, 1 H, J = 8.6 and 7.0 Hz), 2.22 (dd, 1 H, J = 8.6 and 3.1 Hz), 1.35 (d, 3 H, J = 7.0 Hz) ppm. ^{13}C NMR: 205.13, 155.67, 152.93, 147.06, 127.89, 109.72, 103.56, 55.40, 44.83, 31.77, 20.61 ppm. EIMS: m/e 192 (M^+, 59), 178 (11), 177 (100), 149 (30), 91 (12), 77 (14). Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.75; H, 6.25. Found: C, 68.61; H, 6.20. To an ether solution of this compound (0.60 g, 3.12 mmol) was added 1.4 mL of HNO_3 (saturated with $NaNO_2$) dropwise. The mixture was stirred at room temperature for an additional 2 h. The precipitated crude nitro compound was filtered and purified by crystallization in acetic acid, thereby resulting in 0.54 g (73%) of **5-hydroxy-6-methoxy-3-methyl-4-nitro-1-indanone** as a yellow solid, mp 142–144 °C (prisms/AcOH). IR (KBr): 3200, 1700, 1605, 1590, 1540, 1345, 1310, 1270, 1130, 1105 cm^{-1}. ^1H NMR: 11.28 (s, 1 H), 7.40 (s, 1 H), 4.05 (dt, 1 H, J = 6.9 and 1.7 Hz), 3.99 (s, 3 H), 2.98 (dd, 1 H, J = 19.1 and 6.8 Hz), 2.34 (dd, 1 H, J = 19.1 and 1.7 Hz), 1.29 (d, 3 H, J = 6.8 Hz) ppm. ^{13}C NMR: 203.00, 152.23, 150.28, 149.01, 128.60, 109.60, 56.78, 44.80, 33.45, 21.73 ppm. EIMS: m/e 237 (M^+, 30), 223 (11), 192 (13), 150 (13), 149 (100), 85 (15), 84 (11), 83 (13), 73 (12), 71 (25), 69 (18). Anal. Calcd for $C_{11}H_{11}NO_5$: C, 55.70; H, 4.64; N, 5.91. Found: C, 55.74; H, 4.60; N, 5.88.

The crude nitro compound (0.20 g, 0.89 mmol) was reduced by treatment with a cooled (0 °C) solution of 3 mL of concentrated HCl and 1.4 g (6.2 mmol) of $SnCl_2{\cdot}2H_2O$. The resulting mixture was stirred at room temperature for 16 h. The standard workup procedure provided 0.14 g (80%) of **4-amino-5-hydroxy-6-methoxy-3-methyl-1-indanone** as white plates, mp 155–157 °C (CH_2Cl_2). IR (KBr): 3400, 3320, 3300–2900, 1680, 1610, 1575, 1470, 1340, 1080, 830, 750 cm^{-1}. ^1H NMR: 6.78 (s, 1 H), 3.89 (s, 3 H), 3.38 (dt, 1 H, J = 6.9 and 1.9 Hz), 2.93 (dd, 1 H, J = 8.6 and 6.9 Hz), 2.23 (dd, 1 H, J = 8.6 and 1.9 Hz), 1.36 (d, 3 H, J = 6.9 Hz) ppm. ^{13}C NMR: 205.48, 146.96, 140.38, 138.27, 130.42, 128.24, 95.15, 56.14, 45.86, 30.27, 19.95 ppm. EIMS: m/e 207 (M^+, 60), 193 (12), 192 (100), 149 (10), 86 (37), 84 (61). Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.77; H, 6.28; N, 6.76. Found: C, 63.73; H, 6.27; N, 6.78.

A solution of the above amino indanone (0.53 g, 2.56 mmol) in 20 mL of glacial acetic acid was gently refluxed with stirring during 15 h. The usual workup yielded 0.46 g (78%) of **2a** as white needles, mp 96–98 °C (CH_2Cl_2). IR (KBr): 2980, 1700, 1630, 1610, 1490, 1225, 1190, 1150, 1090, 830 cm^{-1}. EIMS: m/e 231 (M^+, 44), 217 (13), 216 (100), 188 (11). Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.53; H, 5.63; N, 6.06. Found: C, 67.39; H, 5.58; N, 6.00.

4-Methoxy-2-methyl-6-oxo-6*H*,7*H*,8*H*-indeno[4,5-*d*]oxazole 2b was prepared as shown above for **2a**. Thus, demethylation of commercial 5,6-dimethoxy-1-indanone (**1b**, 1 g, 5.20 mmol) yielded 0.75 g (81 %) of **5-hydroxy-6-methoxy-1-indanone** as white prisms, mp 148–150 °C (CH_2Cl_2). IR (KBr): 3100–2700, 1655, 1570, 1295, 1270, 1205, 1140 cm^{-1}. ^1H NMR: 7.17 (s, 1 H), 6.94 (s, 1 H), 3.91 (s, 3 H), 3.01 (t, 2 H, J = 5.7 Hz), 2.64 (t, 2 H, J = 5.7 Hz) ppm. ^{13}C NMR ($CDCl_3$–acetone-d_6): 204.69, 152.56, 150.13, 146.95, 128.69, 110.87, 103.63, 55.33, 35.75, 24.58 ppm. EIMS: m/e 178 (M^+, 100), 163 (42), 150 (23), 135 (68), 107 (41), 77 (25). Anal. Calcd for $C_{10}H_{10}O_3$: C, 67.41; H, 5.62. Found: C, 67.74; H, 5.58.

This compound (0.60 g, 3.37 mmol) on nitration yielded 0.55 g (73%) of **5-hydroxy-6-methoxy-4-nitro-1-indanone** as yellow needles, mp 190–192 °C (AcOH). IR(KBr): 3150, 1690, 1590, 1535, 1255, 1225, 1120, 1030 cm^{-1}. ^1H NMR ($CDCl_3$–MeOD): 7.44 (s, 1 H), 3.99 (s, 3 H), 3.46 (t, 2 H, J = 5.4 Hz), 2.72 (t, 2 H, J = 5.4 Hz) ppm. ^{13}C NMR (DMSO-d_6): 203.52, 149.75, 148.07, 142.66, 128.25, 128.12, 107.42, 57.02, 35.58, 23.93 ppm. EIMS: m/e 223 (M^+, 100), 205 (45), 188 (46), 162 (40), 160 (44), 106 (43), 77 (83). Anal. Calcd for $C_{10}H_9NO_5$: C, 53.81; H, 4.03; N, 6.28. Found: C, 53.54; H, 4.01; N, 6.12.

The nitro compound (0.20 g, 0.89 mmol) furnished 0.15 g (89%) of **4-amino-5-hydroxy-6-methoxy-1-indanone** as white plates, mp 168–170 °C (CH_2Cl_2). IR (KBr): 3460, 3380, 1670, 1625, 1475, 1350, 1200, 1090 cm^{-1}. ^1H NMR ($CDCl_3$–MeOD): 6.80 (s, 1 H), 3.90 (s, 3 H), 2.90 (m, 2 H), 2.66 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$–DMSO-d_6): 205.23, 147.20, 137.88, 135.42, 130.94, 127.73, 94.46, 55.42, 35.46, 21.59 ppm. EIMS: m/e 193 (M^+, 100), 178 (37), 150 (23), 136 (16), 122 (15), 81 (15), 69 (24).

The amino compound (0.15 g, 0.78 mmol) on treatment with acetic acid gave 0.12 g (70%) of **2b** as white needles, mp 182–184 °C (CH_2Cl_2). IR (KBr): 2960, 1700, 1500, 1440, 1330, 1200, 1160, 1100 cm^{-1}. EIMS: m/e 217 (M^+, 100), 189 (36), 174 (19), 146 (30), 118 (13), 77 (25). Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.36; H, 5.07; N, 6.45. Found: C, 66.34; H, 5.11; N, 6.32.

4-Methoxy-2,7-dimethyl-6-oxo-6*H*,7*H*,8*H*-indeno[4,5-*d*]-oxazole 2c was prepared as shown above for **2a**. Demethylation of 5,6-dimethoxy-2-methyl-1-indanone (**1c**, 2 g, 9.70 mmol) yielded 1.61 g (86%) of **5-hydroxy-6-methoxy-2-methyl-1-indanone** as white prisms, mp 136–138 °C (CH_2Cl_2). IR (KBr): 3150, 1670, 1580, 1470, 1440, 1300, 1170 cm^{-1}. ^1H NMR: 7.19 (s, 1 H), 6.93 (s, 1 H), 3.92 (s, 3 H), 3.29 (dd, 1 H, J = 16.9 and 8.8 Hz), 2.67 (m, 1 H), 2.59 (dd, 1 H, J = 16.9 and 3.4 Hz), 1.28 (d, 3 H, J = 7.3 Hz) ppm. ^{13}C NMR: 208.28, 152.69, 149.08, 147.01, 128.34, 110.95, 104.29, 55.89, 41.96, 34.35, 16.34 ppm. EIMS: m/e 192 (M^+, 62), 177 (100), 149 (29), 121 (11), 103 (13), 91 (15), 77 (15), 65 (10). Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.75; H, 6.25. Found: C, 68.59; H, 6.29.

This compound (0.30 g, 1.56 mmol) on nitration yielded 0.28 g (75%) of **5-hydroxy-6-methoxy-2-methyl-4-nitro-1-indanone** as a yellow solid, mp 185–187 °C (prisms/AcOH). IR (KRr): 3150, 1690, 1590, 1530, 1340, 1220 cm^{-1}. ^1H NMR: 11.57 (broad s, 1 H), 7.44 (s, 1 H), 3.99 (s, 3 H), 3.78 (dd, 1 H, J = 18.9 and 7.4 Hz), 3.04 (dd, 1 H, J ≠ 18.9 and 3.4 Hz), 2.72 (dt, 1 H, J = 7.4 and 3.4 Hz), 1.33 (d, 3 H, J = 7.4 Hz) ppm. EIMS: m/e 237 (M^+, 100), 202 (31), 191 (29), 174 (11), 146 (11), 120 (11), 91 (18), 77 (20), 65 (11). Anal. Calcd for $C_{11}H_{11}NO_5$: C, 55.70; H, 4.64; N, 5.91. Found: C, 55.96; H, 4.64; N, 5.77.

Reduction of the nitro compound (0.15 g, 0.56 mmol) provided 0.11 g (82%) of **4-amino-5-hydroxy-6-methoxy-2-methyl-1-indanone** as a white solid, mp 162–164 °C (CH_2Cl_2). IR (KBr): 3320, 2950, 1670, 1620, 1580, 1480, 1140 cm^{-1}. ^1H NMR: 6.80 (s, 1 H), 3.89 (s, 3 H), 3.16 (dd, 1 H, J = 15.5 and 7.0 Hz), 2.74 (ddt, 1 H, J = 7.1, 7.0 and 3.0 Hz), 2.43 (dd, 1 H, J = 15.5 and 3.0 Hz), 1.30 (d, 3 H, J = 7.1 Hz) ppm. EIMS: m/e 207 (M^+, 90), 192 (100), 164 (12), 147 (10), 146 (12), 136 (10), 118 (16), 65 (12).

The amino compound (0.30 g, 1.45 mmol) on treatment with acetic acid furnished 0.25 g (75%) of **2c** as white needles, mp 141–143 °C (CH_2Cl_2). IR (KBr): 2920, 1700, 1500, 1420, 1320, 1190, 1150 cm^{-1}. EIMS: m/e 231 (M^+, 45), 217 (14), 216 (100), 202 (8), 188 (22), 77 (11). Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.53; H, 5.63; N, 6.06. Found: C, 67.44; H, 5.65; N, 5.98.

Synthesis of Indenooxazoles 3. General Procedure. 4-Methoxy-2,8-dimethyl-8*H*-indeno[4,5-*d*]oxazole (3a). To a THF (50 mL) solution of **2a** (0.48 g, 2.07 mmol) was added $NaBH_4$ (0.1 g, 2.6 mmol) portionwise, and the mixture was stirred at room temperature during 15 h. Excess $NaBH_4$ was destroyed with a concentrated solution of NH_4Cl. Extractive workup provided 0.385 g (80%) of a diastereoisomeric mixture of indanols as a white solid, mp 97–99 °C (CH_2Cl_2). IR (KBr): 3400–3100, 2700, 1630, 1570, 1490, 1320, 1130 cm^{-1}. EIMS: m/e 233 (M^+, 32), 219 (11), 218 (100), 190 (16), 176 (19), 77 (11). This crude material (0.59 g, 2.53 mmol) was treated with refluxing glacial acetic acid (15 mL) during 16 h. The pH was then adjusted to 4–5. The usual workup procedure provided 0.39 g (72%) of **3a** as a clear oil, bp 175–180

(17) Marquardt, F. H. *Helv. Chim. Acta* **1965**, 1476. Castedo, L.; Novo, J. M.; Guitián, E.; Saá, J. M.; Suau, R. *An. Quim.* **1983**, *79C*, 262.

°C (0.2 mmHg). IR (KBr): 2940, 1610, 1570, 1470, 1430, 1370, 1290, 1180, 1120 cm^{-1}. EIMS: *m/e* 215 (M^+, 100), 200 (61), 173 (11), 159 (25), 145 (15), 131 (20), 103 (15), 77 (15). Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.56; H, 6.04; N, 6.51. Found: C, 72.50; H, 6.17; N, 6.46.

4-Methoxy-2-methyl-8*H*-indeno[4,5-*d*]oxazole (3b): white prisms (81% yield), mp 80–82 °C (CH_2Cl_2). IR (KBr): 1590, 1440, 1370, 1280, 1190, 1120, 920 cm^{-1}. EIMS: *m/e* 201 (M^+, 100), 186 (46), 145 (54), 132 (18), 131 (20), 117 (19), 89 (43), 63 (12). Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.64; H, 5.47; N, 6.96. Found: C, 71.45; H, 5.49; N, 6.89.

4-Methoxy-2,7-dimethyl-8*H*-indeno[4,5-*d*]oxazole (3c): white prisms (90% yield), mp 64–66 °C (CH_2Cl_2). IR (KBr): 2850, 1610, 1570, 1470, 1430, 1350, 1180, 1120 cm^{-1}. EIMS: *m/e* 215 (M^+, 100), 200 (59), 159 (40), 145 (13), 131 (18), 103 (25), 77 (18). Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.56; H, 6.04; N, 6.51. Found: C, 72.51; H, 6.17; N, 6.30.

Synthesis of Formylindoles 4. General Procedure. 2*H*,3*H*-*N*-Acetyl-2,7-dihydroxy-4-formyl-6-methoxy-3-methylindole (4a). A solution of **3a** (200 mg, 0.93 mmol) in 40 mL of absolute methanol and 10 mL CH_2Cl_2 was cooled to −78 °C. A gentle stream of O_3(20%)/O_2 was maintained during 5 min. The solution was purged with argon, and dimethyl sulfide (0.2 mL) was added. Stirring was continued at room temperature for 20 h. Standard workup yielded a crude material (0.25 g) which was then dissolved in 50 mL of THF, 1 mL of water, and two drops of H_2SO_4 and stirred under argon for 21 h. Extractive workup provided 160 mg (65%) of **4a** as a white solid, mp 139–141 °C (prisms/CH_2Cl_2). IR (KBr): 3300, 2850, 1620, 1590, 1440, 1400, 1270, 1130 cm^{-1}. ^1H NMR: 10.75 (s, 1 H), 9.79 (s, 1 H), 6.97 (s, 1 H), 5.35 (s, 1 H), 3.82 (s, 3 H), 3.72 (q, 1 H, J = 7.2 Hz), 2.51 (s, 3 H), 1.26 (d, 3 H, J = 7.2 Hz) ppm. ^{13}C NMR ($CDCl_3$ + CD_3OD): 189.69, 172.60, 164.48, 149.43, 133.78, 127.85, 122.60, 111.69, 92.19, 56.13, 42.41, 22.02, 18.49 ppm. EIMS: *m/e* 265 (M^+, 100), 223 (75), 219 (28), 218 (24), 208 (60), 195 (21), 194 (21), 190 (26), 180 (32), 176 (43), 167 (30), 149 (78), 134 (12), 77 (23). Anal. Calcd for $C_{13}H_{15}NO_3$: C, 58.87; H, 5.66; N, 5.28. Found: C, 58.89; H, 5.47; N, 5.11.

2*H*,3*H*-*N*-Acetyl-2,7-dihydroxy-4-formyl-6-methoxyindole (4b): yellowish solid (63% yield), mp 152–154 °C (prisms/CH_2Cl_2). IR (KBr): 3450, 1685, 1630, 1600, 1450, 1270, 1110 cm^{-1}. ^1H NMR ($CDCl_3$–CD_3OD): 9.80 (s, 1 H), 7.05 (s, 1 H), 5.78 (d, 1 H, J = 6.2 Hz), 3.84 (s, 3 H), 3.51 (dd, 1 H, J = 18.2 and 6.2 Hz), 3.35 (d, 1 H, J = 18.2 Hz), 2.43 (s, 3 H) ppm. ^{13}C NMR (acetone-d_6): 190.54, 173.44, 150.68, 143.89, 129.80, 128.94, 124.27, 113.06, 86.79, 56.97, 37.57, 22.84 ppm. EIMS: *m/e* 251 (M^+, 75), 233 (30), 209 (100), 192 (90), 191 (80), 181 (64), 180 (60), 176 (74), 152 (30), 148 (36), 132 (33), 120 (26), 92 (29), 63 (23), 43 (72). HRMS for $C_{12}H_{13}NO_5$: calcd 251.07936, found 251.08000 (deviation 2.5 × 10^{-6}).

Preparation of 4-Formyl-7-hydroxyindoles 5 and 6. General Procedure. *N*-Acetyl-4-formyl-7-hydroxy-6-methoxy-3-methylindole (5a). A solution of **4a** (160 mg, 0.60 mmol) in 50 mL of CH_2Cl_2, under argon, was treated with two drops of H_2SO_4 and stirred for 10 min. The standard extractive workup furnished 106 mg (71%) of **5a** as a white solid, mp 162–164 °C (prisms/CH_2Cl_2). IR (KBr): 3600–3200, 1700, 1600, 1400, 1350, 1315, 1250, 1150, 1100 cm^{-1}. ^1H NMR: 10.98 (s, 1 H), 10.43 (s, 1 H), 7.57 (s, 1 H), 7.12 (d, 1 H, J = 1.2 Hz), 3.96 (s, 3 H), 2.66 (s, 3 H), 2.43 (d, 3 H, J = 1.2 Hz) ppm. ^{13}C NMR: 187.54, 170.85, 146.78, 141.64, 129.56, 125.97, 125.29, 121.20, 119.85, 109.29, 56.51, 23.60, 14.95 ppm. EIMS: *m/e* 247 (M^+, 70), 205 (100), 190 (95), 162 (25), 134 (8), 104 (10), 77 (12). HRMS for $C_{13}H_{13}NO_4$ calcd 247.08445, found 247.08510 (deviation 2.6 × 10^{-6}).

***N*-Acetyl-4-formyl-7-hydroxy-6-methoxyindole (5b)**: white prisms (65% yield), mp 128–130 °C (CH_2Cl_2). IR (KBr): 3100, 1650, 1565, 1380, 1260, 1130 cm^{-1}. ^1H NMR: 11.16 (s, 1 H), 10.01 (s, 1 H), 7.42 (d, 1 H, J = 2.5 Hz), 7.39 (s, 1 H), 7.36 (d, 1 H, J = 2.5 Hz), 3.98 (s, 3 H), 2.72 (s, 3 H) ppm. ^{13}C NMR: 189.48, 171.70, 146.36, 141.50, 127.96, 127.21, 124.62, 118.79, 115.16, 110.08, 56.89, 23.59 ppm. EIMS: *m/e* 233 (M^+, 38), 191 (75), 176 (100), 148 (40), 120 (15), 92 (11), 91 (12), 63 (11). Anal. Calcd for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.72; N, 6.01. Found: C, 61.97; H, 4.74; N, 5.91.

4-Formyl-7-hydroxy-6-methoxy-3-methylindole (6a). A solution of **5a** (103 mg, 0.41 mmol) in 50 mL of methanol was mixed with a small amount of silica gel and stirred at room temperature (TLC monitoring). After filtration, the solvent was evaporated and the resulting residue flash chromatographed on silica gel (CH_2Cl_2), thus providing 60 mg (70%) of **6a** as a pale yellow solid, mp 205–207 °C (prisms/CH_2Cl_2). IR (KBr): 3420, 3120, 1610, 1400, 1380, 1300, 1100 cm^{-1}. ^1H NMR ($CDCl_3$ + CD_3OD): 10.40 (s, 1 H), 7.51 (s, 1 H), 7.06 (d, 1 H, J = 0.8 Hz), 3.93 (s, 3 H), 2.47 (d, 3 H, J = 0.8 Hz) ppm. ^{13}C NMR ($CDCl_3$ + CD_3OD): 189.10, 160.95, 143.05, 129.14, 128.16, 125.36, 119.46, 116.63, 112.75, 57.34, 12.65 ppm. EIMS: *m/e* 205 (M^+, 100), 190 (63), 162 (35), 144 (9), 134 (12), 105 (8), 77 (15), 51 (7). Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.39; H, 5.36; N, 6.83. Found: C, 64.28; H, 5.40; N, 6.60.

4-Formyl-7-hydroxy-6-methoxyindole (6b). A solution of the indole **5b** (83 mg, 0.36 mmol) in 20 mL of methanol and 10 mL of 2 N NaOH was stirred at room temperature for 2 h. The standard extractive workup yielded 51 mg (75%) of **6b** as an unstable yellow solid, mp 177–179 °C (prisms/CH_2Cl_2). IR (KBr): 3400, 1620, 1560, 1410, 1400, 1300, 1120 cm^{-1}. ^1H NMR ($CDCl_3$ + CD_3OD): 10.01 (s, 1 H), 7.35 (s, 1 H), 7.33 (d, 1 H, J = 3.1 Hz), 7.13 (d, 1 H, J = 3.1 Hz), 3.97 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$ + CD_3OD): 191.09, 162.52, 142.80, 130.08, 127.34, 127.26, 119.01, 113.92, 113.77, 57.36 ppm. EIMS: *m/e* 191 (M^+, 100), 176 (77), 148 (60), 120 (38), 92 (27), 91 (30), 65 (28), 63 (22). HRMS for $C_{10}H_9ON_3$: calcd 191.0582, found 191.0580 (deviation 1.2 × 10^{-6}).

Synthesis of Indoloquinones 7. 6-Methoxy-3-methyl-4,7-indoloquinone (7a). Fremy's salt (0.3 g) in 8.5 mL of buffer (pH = 6.1) solution (NaH_2PO_4 0.2 M/Na_2HPO_4 0.2 M 8.5/1.5) was added to a solution of **6a** (60 mg, 0.29 mmol) in 10 mL of CH_2Cl_2. The mixture was vigorously stirred for 45 min (TLC monitoring). Extractive workup furnished 53 mg (95%) of **7a** as orange plates, mp 174–176 °C (acetone). IR (KBr): 3150, 1665, 1625, 1590, 1400, 1380, 1330, 1250, 1050 cm^{-1}. EIMS: *m/e* 191 (M^+, 100), 173 (31), 162 (34), 148 (12), 134 (71), 105 (18), 78 (21). HRMS for $C_{10}H_9NO_3$: calcd 191.0582, found 191.0594 (deviation 6.1 × 10^{-6}).

6-Methoxy-4,7-indoloquinone (7b): red prisms (95% yield) (acetone), mp 210–212 °C dec. IR (KBr): 3150, 1660, 1630, 1580, 1400, 1380, 1330, 1250, 1100 cm^{-1}. EIMS: *m/e* 177 (M^+, 76), 149 (46), 148 (48), 120 (100), 119 (28), 93 (49), 91 (55), 69 (24), 67 (23), 64 (28). HRMS for $C_9H_7NO_3$: calcd 177.0426, found 177.0424 (deviation 1.1 × 10^{-6}).

6-Methoxy-3-methyl-4,7-indoloquinone (7c). Ozonolysis of indene **3c** (0.2 g, 0.93 mmol) as illustrated for **3a** furnished ***N*-acetyl-4-formyl-7-hydroxy-6-methoxy-2-methylindole (5c)** as an unstable solid (all purification attempts led to destruction). ^1H NMR: 11.41 (broad s, 1 H), 9.94 (s, 1 H), 7.27 (s, 1 H), 7.15 (s, 1 H), 3.93 (s, 3 H), 2.71 (s, 1 H), 2.60 (s, 3 H) ppm. EIMS: *m/e* 247 (M^+, 16), 205 (70), 191 (12), 190 (100), 162 (24), 132 (10), 117 (6), 77 (13). Due to its instability, correct combustion analysis for this compound could not be obtained.

Crude 5c was deacetylated as described for **5a**, thus yielding **4-formyl-7-hydroxy-6-methoxy-2-methylindole (6c)** as an unstable solid. ^1H NMR: 10.07 (s, 1 H), 7.27 (s, 1 H), 6.89 (broad s, 1 H), 3.97 (s, 3 H), 2.47 (s, 3 H) ppm. EIMS: *m/e* 205 (M^+, 100), 191 (12), 190 (89), 162 (35), 134 (25), 104 (12). No combustion analysis could be obtained for this unstable compound.

Fremy's salt oxidation of **6c** as shown above for **6a** gave 60 mg of **7c** (34% from **3c**) as a red solid, mp 193–195 °C (prisms/acetone). IR (KBr): 3150, 1650, 1610, 1580, 1420, 1220, 1140, 1020, 800 cm^{-1}. EIMS: *m/e* 191 (M^+, 100), 163 (25), 162 (63), 134 (66), 133 (21), 107 (14), 105 (21). HRMS for $C_{10}H_9NO_3$: calcd 191.05824, found 191.05860 (deviation 1.9 × 10^{-6}).

7-(Benzyloxy)-4-formyl-6-methoxyindole (8b). A mixture of **6b** (12 mg, 0.063 mmol), 0.1 g of K_2CO_3, and 16 mg (0.094 mmol) of benzyl bromide in 10 mL anhydrous acetone was gently refluxed for 1 h. Filtration and solvent evaporation gave a crude material which was purified by column chromatography thus yielding 16 mg (91%) of **8b** as yellow prisms (CH_2Cl_2), mp 117–119 °C (lit.[18] mp 117–119 °C). IR (KBr): 3300–3100, 1630, 1540, 1500, 1400, 1350, 1290, 1230, 1210, 1130, 1080, 1010, 940, 750, 710 cm^{-1}. ^1H NMR ($CDCl_3$): 10.17 (s, 1 H), 8.26 (broad s, 1 H), 7.40 (s, 1 H), 7.43–7.34 (m, 5 H), 7.23 (m, 1 H), 7.16 (m, 1 H), 5.34 (s, 2 H), 4.02 (s, 3 H) ppm. EIMS (DIP): *m/e* 281 (M^+, 13), 252 (16), 190 (17),

(18) Bolton, R. E.; Moody, C. J.; Rees, C. W.; Tojo, G. *J. Chem. Soc., Perkin Trans. 1*, 1987, 931.

91 (100). This compound was found to be identical to a sample provided by Prof. C. W. Rees.[14]

Acknowledgment. Financial support by the DGICYT (PB87/0019) is gratefully acknowledged. Thanks are also due to Prof. J. D. Martin (U. de La Laguna) and Dr. G. Tojo (U. de Santiago de Compostela) for carrying out our HRMS.

Registry No. **1a**, 4082-25-1; **1b**, 2107-69-9; **1c**, 137542-56-4; **2a**, 137542-52-0; **2b**, 137542-55-3; **2c**, 137542-59-7; **3a**, 137542-60-0; **3b**, 137542-61-1; **3c**, 137542-62-2; **4a**, 137542-63-3; **4b**, 137542-64-4; **5a**, 137542-65-5; **5b**, 137542-66-6; **5c**, 137542-71-3; **6a**, 137542-67-7; **6b**, 137542-68-8; **6c**, 137542-72-4; **7a**, 137542-69-9; **7b**, 137542-70-2; **7c**, 137542-73-5; **8b**, 102357-91-5; PDE-I, 62497-62-5; PDE-II, 62874-94-6; 5-hydroxy-6-methoxy-1-indanone, 127399-78-4; 5-hydroxy-6-methoxy-4-nitro-1-indanone, 137542-53-1; 4-amino-5-hydroxy-6-methoxy-1-indanone, 137542-54-2; 5-hydroxy-6-methoxy-3-methyl-1-indanone, 71653-30-0; 5-hydroxy-6-methoxy-3-methyl-4-nitro-1-indanone, 137542-50-8; 4-amino-5-hydroxy-6-methoxy-3-methyl-1-indanone, 137542-51-9; 5-hydroxy-6-methoxy-2-methyl-1-indanone, 137542-56-4; 5-hydroxy-6-methoxy-2-methyl-4-nitro-1-indanone, 137542-57-5; 4-amino-5-hydroxy-6-methoxy-2-methyl-1-indanone, 137542-58-6.

Supplementary Material Available: ^{1}H NMR spectra for compounds **5c** and **6c** (2 pages). This material is contained in many 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.

Novel Carbocyclic Nucleosides Related to Oxetanocin

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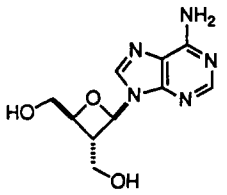
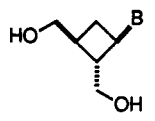
Received March 21, 1991 (Revised Manuscript Received September 20, 1991)

Carbocyclic oxetanocin analogues 9-[*trans*-2,*cis*-3-bis(hydroxymethyl)-5,9-dithiaspiro-[3.5]non-*r*-1-yl]adenine, 9-[4,4-dimethyl-*trans*-2,*cis*-3-bis(hydroxymethyl)cyclobut-*r*-1-yl]adenine, and related compounds have been prepared by a strategy utilizing nucleophilic addition of heterocyclic bases to dimethyl 4,4-disubstituted 2-cyclobutene-1,2-dicarboxylates. The latter were prepared by a process involving [2 + 2] cycloadditions of enamines and dimethyl maleate.

In 1986, Shimada and co-workers isolated oxetanocin (Oxt-A) (1) from a strain of bacteria, *Bacillus megaterium* NK84-0218;[1] oxetanocin is the first and only known example of a naturally occurring four-membered ring nucleoside.[2] Among other activities, biological testing



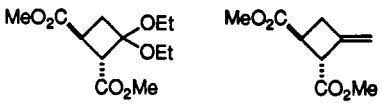
1 (Oxt-A)



2 BH = Adenine (C-Oxt-A)
3 BH = Guanine (C-Oxt-G)
4 B = NH_2

showed that oxetanocin was active against human immunodeficiency virus (HIV).[3] We began a program to synthesize carbocyclic analogues of oxetanocin. At the outset of our investigation there were no published reports of any carbocyclic analogues of oxetanocin; however, since June 1989 a number groups have published syntheses of carbocyclic oxetanocin (C-Oxt-A) (2) and related substances, e.g., 3.

Honjo and co-workers utilized cyclobutane 5[4] as starting material in their nonstereoselective synthesis of racemic C-Oxt-A (2).[5] The adenine ring was assembled from a protected 4 using the three-step sequence of Montgomery.[6]



5 6

Slusarchyk and co-workers have reported a synthesis of racemic as well as optically pure cyclobutyl nucleoside analogues from cyclobutane 5.[7] The synthesis involved an improved synthesis of 5 as well as the direct introduction of a protected guanine. Norbeck and co-workers' synthesis of racemic C-Oxt-A and C-Oxt-G[8] utilized the cyclobutane product 6 from the cyclization of allene and diethyl fumarate.[9] Katagiri and co-workers have reported the preparation of carbocyclic oxetane intermediates in the form of protected derivatives of 4 beginning with irradia-

(1) Shimada, N.; Hasegawa, S.; Harada, T.; Tomisawa, T.; Fujii, A.; Takita, T. *J. Antibiot.* **1986**, *39*, 1623. Nakamura, H.; Hasegawa, S.; Shimada, N.; Fujii, A.; Takita, T.; Iitaka, Y. *Ibid.* **1986**, *39*, 1626.

(2) For synthetic oxetanocin analogues see: Reference 1 and (a) Nishiyama, Y.; Yamamoto, N.; Yamada, Y.; Daikoku, T.; Ichikawa, Y.-I.; Takahashi, K. *J. Antibiot.* **1989**, *42*, 1854. (b) Jacobs, G. A.; Tino, J. A.; Zahler, R. *Tetrahedron Lett.* **1989**, *30*, 6955. (c) Nishiyama, S.; Ohgiya, T.; Yamamura, S.; Kato, K.; Nagai, M.; Takita, T. *Ibid.* **1990**, *31*, 705.

(3) Hoshino, H.; Shimizu, N.; Shimada, N.; Takita, T.; Takeuchi, T. *J. Antibiot.* **1987**, *40*, 1077.

(4) Brannock, K. C.; Burpitt, R. D.; Thweatt, J. G. *J. Org. Chem.* **1964**, *29*, 940.

(5) Honjo, M.; Maruyama, T.; Sato, Y.; Horii, T. *Chem. Pharm. Bull.* **1989**, *37*, 1413.

(6) Montgomery, J. A.; Temple, C., Jr. *J. Am. Chem. Soc.* **1957**, *79*, 5238.

(7) (a) Slusarchyk, W. A.; Young, M. G.; Bisacchi, G. S.; Hockstein, D. R.; Zahler, R. *Tetrahedron Lett.* **1989**, *30*, 6453. (b) Bisacchi, G. S.; Braitman, A.; Cianci, C. W.; Clark, J. M.; Field, A. K.; Hagen, M. E.; Hockstein, D. R.; Malley, M. F.; Mitt, T.; Slusarchyk, W. A.; Sundeen. J. E.; Terry, B. J.; Tuomari, A. V.; Weaver, E. R.; Young, M. G.; Zahler, R. *J. Med. Chem.* **1991**, *34*, 1415.

(8) Norbeck, D. W.; Kern, E.; Hayashi, S.; Rosenbrook, W.; Sham, H.; Herrin, T.; Plattner, J. J.; Erickson, J.; Clement, J.; Swanson, R.; Shipkowitz, N.; Hardy, D.; Marsh, K.; Arnett, G.; Shannon, W.; Broder, S.; Mitsuya, H. *J. Med. Chem.* **1990**, *33*, 1281. See also: Norbeck, D.; Rosenbrook, W.; Plattner, J.; Erickson, J.; Arnett, G.; Shannon, W. Abstract of Papers. V International Conference on AIDS, Montreal, June 4-9, 1989; M.C.P. 65, p 552. Hayashi, S.; Norbeck, D. W.; Plattner, J.; Broder, S.; Mitsuya, H. *Ibid.* M.C.P 135, p 564.

(9) Cripps, H. N.; Williams, J. K.; Sharkey, W. H. *J. Am. Chem. Soc.* **1959**, *81*, 2723.

0022-3263/92/1957-0594$03.00/0