Synthesis of Benzocarbazoloquinones via Oxidative Cyclization

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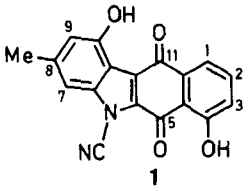
Ethyl 1-benzenesulfonyl-2-bromomethyl-5-methoxyindole-3-carboxylate (**2**) and 2-methyl-3-phenylthioindole (**5**) have been converted into benzcarbazoloquinones **4** and **10**, respectively, involving an oxidative cyclization by air during the application of polyphosphoric acid.

Prekinamycin[1] (**1**), belonging to the kinamycin group of antibiotics, has a benzcarbazoloquinone skeleton with oxygenated A and D rings. The kinamycin[1-3] family possesses a novel tetrahydrobenzcarbazoloquinone skeleton also with oxygenated A and D rings.



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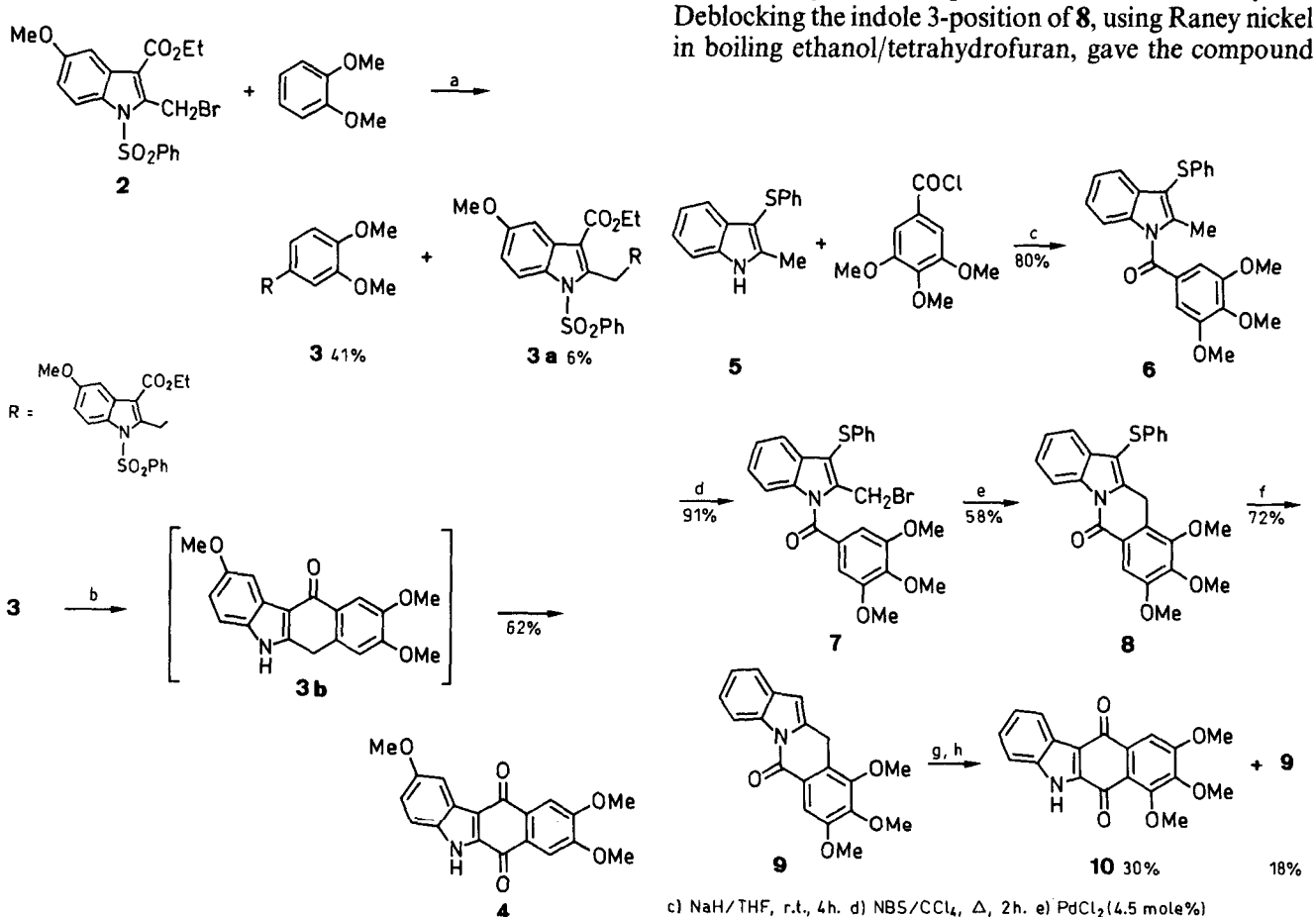
Only a few syntheses of benzcarbazoloquinones have been reported.[1,4-8] Here, we report a synthesis of benzocarbazoloquinones with oxygenated A and D rings via oxidative cyclization by polyphosphoric acid. The bromo compound[9] **2** was arylated with 1,2-dimethoxybenzene, using a catalytic amount of palladium chloride and two equivalents of cupric chloride following our earlier procedure,[10] to give ethyl 1-benzenesulfonyl-5-methoxy-2-veratrylindole-3-carboxylate (**3**) in 41 % yield together with the coupled product **3a** in 6 % yield. Polyphosphoric acid treatment of the compound **3**, in the presence of air, at 100 °C effected oxidative cyclization to give the title compound **4** in 62 % yield, presumably via the intermediate **3b**.

An intermediate similar to **3b**, lacking methoxy groups, has been known[4] to survive polyphosphoric acid treatment under the above conditions and was converted to quinone, in a subsequent step, using lead tetraacetate. Hence the presence of methoxy groups in the D ring is essential for the oxidative cyclization.

Treatment of 2-methyl-3-phenylthioindole (**5**) with sodium hydride and 3,4,5-trimethoxybenzoyl chloride in tetrahydrofuran at room temperature gave the *N*-aroylated compound **6** in 80 % yield. Treatment of **6** with *N*-bromosuccinimide in boiling carbon tetrachloride gave the bromo compound **7** in 91 % yield. Intramolecular arylation of **7** with a catalytic amount of palladium chloride and two equivalents of cupric chloride in boiling acetonitrile gave the isoquinolonoindole **8** in 58 % yield. Deblocking the indole 3-position of **8**, using Raney nickel in boiling ethanol/tetrahydrofuran, gave the compound



a) $PdCl_2$ (4.5 mole %)/$CuCl_2$ (2 eq)/MeCN, Δ, 6h. b) PPA/air, 100°C, 2h.
c) NaH/THF, r.t., 4h. d) NBS/CCl_4, Δ, 2h. e) $PdCl_2$(4.5 mole%) $CuCl_2$ (2 eq)/MeCN, Δ, 6h. f) Ra-Ni/EtOH/THF, Δ, 5h.
g) 10% NaOH/DMSO, 100°C, 2h. h) PPA/air, 100°C, 2h.

9 in 72% yield. Compound **9** was treated with 10% sodium hydroxide in dimethyl sulfoxide followed by polyphosphoric acid, in the presence of air, at 100°C to give the title compound benzocarbazoloquinone **10** in 30% yield together with recovered **9** in 18% yield.

In the above synthesis, the *N*-aroyl group is used as an *N*-protective group as well as a precursor to the oxygenated D ring of the target molecule.

All melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer 598 spectrophotometer. ^{1}H NMR spectra were recorded using either a Varian EM-390 (90 MHz) or a JEOL GSX-400 (400 MHz) instrument with tetramethylsilane as internal standard. The ^{13}C NMR spectrum was recorded using a JEOL GSX-400 (100.6 MHz) instrument. MS were recorded using a JEOL JMS-DX 303 HF spectrometer.

Arylation of 2 with 1,2-Dimethoxybenzene:
To a solution of $PdCl_2$ (40 mg, 4.5 mole%) in MeCN (50 mL) were added the bromo compound **2** (2.26 g, 5 mmol), 1,2-dimethoxybenzene (0.8 mL, 6 mmol) and $CuCl_2$ (1.34 g, 10 mmol) and the solution was refluxed for 6 h. The solvent was removed under reduced pressure, the residue was poured into H_2O and extracted with $CHCl_3$ (60 mL). The organic extract was washed with H_2O (3×25 mL), dried ($MgSO_4$) and the removal of solvent under vacuum gave the crude product. This was chromatographed on a column of silica gel using C_6H_6 and C_6H_6/EtOAc (19:1) as eluents to afford **3** (1.04 g, 41%) and **3a** (0.11 g, 6%), respectively.

Ethyl 1-Benzenesulfonyl-5-methoxy-2-veratrylindole-3-carboxylate **(3)**:

Mp 162–164°C (benzene).

IR (KBr): ν = 1695 cm^{-1} (CO).

^{1}H NMR ($CDCl_3$/TMS): δ = 1.5 (t, 3H, J = 7.5 Hz, $CO_2CH_2C\underline{H}_3$), 3.85 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 4.0 (s, 3H, OCH_3), 4.45 (q, 2H, J = 7.5 Hz, $CO_2C\underline{H}_2CH_3$), 5.04 (s, 2H, CH_2), 6.8 (m, 3H, arom), 7.0–7.8 (m, 7H, arom), 8.2 (d, 1H, J = 9.3 Hz, indole-7H).

MS: m/z (%) = 509 (34, M^+), 422 (20), 368 (45), 339 (13), 322 (37), 308 (14), 256 (17), 236 (21).

1,2-Bis(1-benzenesulfonyl-3-ethoxycarbonyl-5-methoxyindol-2-yl)ethane **(3a)**:

Mp 218–220°C (C_6H_6/EtOAc)

IR (KBr): ν = 1700 cm^{-1} (CO).

^{1}H NMR ($CDCl_3$/TMS): δ = 1.0 (t, 6H, J = 7 Hz, $CO_2CH_2C\underline{H}_3$), 3.75 (q, 4H, J = 7 Hz, $CO_2C\underline{H}_2CH_3$), 3.85 (s, 6H, OCH_3), 4.05 (s, 4H, CH_2), 7.0–8.03 (m, 14H, arom), 8.3 (d, 2H, J = 9.6 Hz, indole-7H).

2,3,9-Trimethoxybenzo[*b*]carbazole-5,11-quinone (4):
To a solution of **3** (0.51 g, 1.0 mmol) in 88% H_3PO_4 (4 mL), P_2O_5 (14 g, 98 mmol) was added and the solution was heated at 100°C for 2 h in an aerial atmosphere. Then it was cooled, and crushed ice was added to the mixture. The precipitated solid was filtered, washed with H_2O and dried over $CaCl_2$. The crude product was chromatographed on a column of silica gel using C_6H_6/EtOAc (9:1) as eluent; yield: 0.21 g (62%); mp 312–314°C (EtOAc).

IR (KBr): ν = 3210 (br, NH), 1640 cm^{-1} (CO).

^{1}H NMR ($CDCl_3$/DMSO-d_6/TMS): δ = 3.85 (s, 3H, OCH_3), 3.95 (2 s, 6H, OCH_3), 7.38–7.64 (m, 5H, arom), 12.25 (s, 1H, NH).

^{13}C NMR ($CDCl_3$/DMSO-d_6/TMS): δ = 54.11 (q, OCH_3), 54.75 (q, OCH_3), 101.14 (d), 106.84 (d), 107.09 (d), 113.32 (d), 115.75 (s), 116.47 (d), 123.93 (s), 125.89 (s), 128.03 (s), 132.13 (s), 135.91 (s), 150.76 (s), 151.76 (s), 155.69 (s), 175.63 (s), 178.93 (s).

MS: m/z (%) = 337 (100, M^+), 336 (7), 322 (18), 308 (7), 294 (13), 279 (4), 264 (5), 236 (5).

2-Methyl-3-phenylthioindole (5):
To a solution of 1-phenylthiopropan-2-one[11] (16.8 g, 100 mmol) in glacial AcOH (300 mL) was added phenylhydrazine (9.8 mL, 100 mmol). After the initial exothermic reaction subsided the solution was refluxed for 3 h. It was poured onto crushed ice and the precipitated solid was filtered, washed with H_2O (300 mL) and dried ($CaCl_2$). The crude product was recrystallized from C_6H_6/hexane (1:2); yield: 19.2 g (80%); mp 133–134°C (C_6H_6/hexane) (Lit.[12] 130°C).

2-Methyl-3-phenylthio-1-(3,4,5-trimethoxybenzoyl)indole (6):
To a suspension of NaH (0.75 g, 31 mmol) in dry THF (100 mL) was added slowly a solution of indole **5** (5.98 g, 25 mmol) in the same solvent (200 mL). After the evolution of hydrogen had ceased, a solution of 3,4,5-trimethoxybenzoyl chloride (6 g, 26 mmol) [prepared from 3,4,5-trimethoxybenzoic acid and thionyl chloride (neat) and the crude acid chloride was distilled under vacuum to give the crystalline acid chloride; mp 82–83°C (Lit.[13] 81–84°C)] in dry THF (75 mL) was added. The solution was stirred for 4 h at r.t. Then the solvent was removed under reduced pressure and the residue was poured onto ice. The separated solid was filtered, washed with H_2O and dried over $CaCl_2$. The crude product was crystallized from C_6H_6/hexane (1:3, 50 mL); yield: 8.7 g (80%); mp 142–143°C (C_6H_6/hexane).

IR (KBr): ν = 1680 cm^{-1} (CO).

^{1}H NMR (CCl_4/TMS): δ = 2.6 (s, 3H, CH_3), 3.8 (s, 6H, OCH_3), 3.9 (s, 3H, OCH_3), 6.97–7.6 (m, 11H, arom).

2-Bromomethyl-3-phenylthio-1-(3,4,5-trimethoxybenzoyl)indole (7):
To a solution of **6** (4.34 g, 10 mmol) in dry CCl_4 (200 mL) were added NBS (1.78 g, 10 mmol) and dibenzoyl peroxide (10 mg) and the solution was refluxed for 2 h. It was then cooled to 15°C and succinimide was filtered off. The filtrate was concentrated to 25 mL under reduced pressure. Hexane (5 mL) was added to the concentrated solution. The crystallized bromo compound was filtered; yield: 4.66 g (91%); mp 132–134°C (CCl_4/hexane, 5:1).

IR (KBr): ν = 1680 cm^{-1} (CO).

^{1}H NMR (CCl_4/TMS): δ = 3.75 (s, 6H, OCH_3), 3.9 (s, 3H, OCH_3), 5.1 (s, 2H, CH_2), 7.0–7.5 (m, 11H, arom).

5-Oxo-11-phenylthio-1,2,3-trimethoxyisoquinolono[2,3-*a*]indole (8):
This compound was prepared, from the bromo compound **7** (2.56 g, 5 mmol), as described above for **3**. The resulting residue was chromatographed on a column of silica gel using C_6H_6/EtOAc (9:1) as eluent; yield: 1.25 g (58%); mp 198–199°C (C_6H_6).

IR (KBr): ν = 1670 cm^{-1} (CO).

^{1}H NMR ($CDCl_3$/TMS): δ = 3.87 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.9 (s, 2H, CH_2), 3.91 (s, 3H, OCH_3), 6.9–7.15 (m, 2H, arom), 7.3–7.6 (m, 6H, arom), 8.33 (d, 2H, J = 8 Hz, arom).

5-Oxo-1,2,3-trimethoxyisoquinolono[2,3-*a*]indole (9):
To a solution of **8** (0.86 g, 2 mmol) in THF (25 mL) and EtOH (75 mL) was added Raney nickel[14] (ca. 6 g, W-2). The solution was refluxed for 5 h. The nickel was filtered off and the filtrate was concentrated to 20 mL and left at r.t. for 24 h. The crystallized isoquinolonoindole **9** was filtered off. This product was recrystallized from C_6H_6/hexane; yield: 0.46 g (72%); mp 180–191°C (C_6H_6/hexane).

IR (KBr): ν = 1670 cm^{-1} (CO).

^{1}H NMR ($CDCl_3$/TMS): δ = 3.9 (3 s, 9H, OCH_3), 4.05 (s, 2H, CH_2), 6.75 (s, 1H, indole-3H), 7.05–7.7 (m, 4H, arom), 8.6 (d, 1H, J = 9 Hz, indole-7H).

MS: m/z (%) = 323 (100, M^+), 308 (18), 293 (18), 292 (20), 280 (6), 279 (7), 265 (5), 257 (9), 256 (10), 236 (12), 222 (9), 208 (7), 194 (6), 191 (6), 183 (15), 161 (10).

2,3,4-Trimethoxybenzo[*b*]carbazole-5,11-quinone (10):
To a solution of **9** (0.32 g, 1 mmol) in DMSO (25 mL), H_2O (15 mL) and 50% NaOH (10 mL) were added and the solution was heated on a water bath for 2 h. It was cooled, poured onto crushed ice and the solution was neutralized using 10% dilute HCl (50 mL). The precipitated solid was filtered, washed with H_2O and dried. To a solution of this solid in 88% H_3PO_4 (3 mL) was added P_2O_5 (10 g, 70 mmol) followed by heating at 100°C for 2 h in an aerial atmosphere. Then, crushed ice was added to the cooled reaction

mixture. The separated solid was filtered, washed with H_2O and dried over $CaCl_2$. The crude product was chromatographed on a column of silica gel using C_6H_6 and C_6H_6/EtOAc (19:1) as eluent to afford **9** and **10**, respectively: **9**, yield: 0.06 g (18%); mp 180–181 °C (C_6H_6/hexane); **10**, yield: 0.10 g (30%); mp 300–302 °C (C_6H_6/EtOAc).

IR (KBr): ν = 3260 (NH), 1645, 1635 cm^{-1} (CO).

^1H NMR ($CDCl_3$/DMSO-d_6/TMS): δ = 4.05 (s, 6H, OCH_3), 4.15 (s, 3H, OCH_3), 7.4–8.4 (m, 5H, arom), 12.75 (br, s, 1H, NH).

MS: m/z (%) = 337 (100, M^+), 322 (36), 309 (5), 308 (22), 294 (7), 280 (5), 279 (11), 278 (5), 264 (11), 257 (5), 236 (8), 211 (5), 207 (5), 193 (5), 183 (13), 114 (5).

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