Synthesis and Diels–Alder Reactivity of ortho-Carbazolequinones

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Oxidation of 2- and 3-hydroxycarbazoles with Frémy’s salt gave the corresponding ortho-carbazolequinones. These molecules react as carbodienophiles in Diels–Alder reaction with 1-acetoxy-1,3-butadiene and 1,3-cyclopentadiene to provide the novel benzocarbazolequinone structures 15, 16, 18 and 19.

Key words ortho-carbazolequinone; Diels–Alder reaction; benzocarbazolequinone

The carbazole-3,4-quinones represent an important family of carbazole alkaloids. Carquinostatins A and B, lavanduquinocin and carbazoquinocins A—F represent the first carbazole alkaloids containing an \textit{ortho}-quinone system\(^1\) and possess various biologic activities (Chart 1).

The carquinostatins A and B were isolated from \textit{Streptomyces exfoliatus} 2419-SVT\(^2\) and were shown to be potent neuronal protecting substances.\(^2,3\) Lavanduquinocin was isolated from \textit{Streptomyces viridochromogenes} 2942-SVS\(^3\) and exhibit a strong neuronal cell protecting activity.\(^4\) The carbazoquinocins A—F were isolated from \textit{Streptomyces violaceus} 2448-SVT\(^2\) and they showed strong inhibitory activity against lipid peroxidation.\(^5\)

As part of our continuing search for biologically active compounds with a quinone moiety, we were particularly interested in the synthesis and in the Diels–Alder chemistry of carbazolequinones.\(^6\) In a previous work we reported the synthesis,\(^7,8\) the induction of caspase-dependent cell death\(^9\) and the \textit{Toxoplasma gondii} purine nucleoside phosphorylase inhibitory activity\(^10\) of some carbazole-1,4-quinones.

The purpose of this work is to obtain carbazole-1,2 and -3,4-dione derivatives and to report their behaviour as dienophiles in \([4+2]\) cycloaddition reactions.

Results and Discussion

Carbazole-1,2-quinone \(^3\)\(^{(1)}\) was obtained by oxidation of the commercially available hydroxycarbazole \(1\) with Frémy’s salt. Treatment of \(1\) with sodium hydride in the presence of methyl iodide in the solvent system THF–DMF, gave chemoselectively the N-methylated compound \(2.\)\(^{12}\) Then, oxidation of \(2\) with Frémy’s salt afforded carbazole-1,2-quinone \(4.\)

On the other hand, carbazole-3,4-quinone \(7\) was obtained in two steps from the commercially available 3-aminocarbazole \(5.\) The formation of the corresponding diazonium salt at \(0\) °C followed by heating the latter in highly acidic aqueous solution gave the 3-hydroxycarbazole \(6,\) which was oxidized as above to yield quinone \(7\) (Chart 2).

Our attempts to obtain \(7\) through a direct oxidation of \(5\) with Frémy’s salt provided the dimeric carbazole compounds \(12\) and \(13\) only. The reaction may proceed first by formation of a mixture of amino phenol \(8\) and \textit{ortho}-quinone imine \(9\). Then, a nucleophilic addition of primary amine \(5\) or \(8\) to quinone imine \(9\) led to intermediates \(10\) and \(11\) which were subsequently oxidized to the dimeric carbazoles \(12\) and \(13\) (Chart 3). Aromatic amines which have a position \textit{para} to the amino group substituted by an alkyl or alkoxy group have been reported to undergo a similar reaction.\(^13,14\)
The Diels–Alder reactions of ortho-quinones previously reported have been essentially performed with benzocarbazolequinones and 1-acetoxy-1,3-butadiene. Recently, our group reported the first examples of [4 + 2] cycloaddition of ortho-benzofurandione and ortho-indoloquinone towards 1-azadienes. Thus the ortho-benzofurandione reacts as a carbodiienophile and ortho-indoloquinone can react either as a carbodiienophile or as heterodiienophile.

In continuation of this work focused on heterocyclic ortho-quinones we planned to investigate the chemical behaviour of ortho-carbazolequinones 3 and 7 towards carbodiienophiles and 1-azadienes.

The [4 + 2] cycloaddition between carbazolequinone 3 or 7 and 1-acetoxy-1,3-butadiene 14 was performed at reflux in dry THF and provided directly the benzocarbazolequinones 15 and 16, respectively. The reaction between 1,3-cyclopen- tandiene 17 and carbazolequinone 3, carried out in dichloromethane at −10 °C for 5 h then at room temperature for 12 h led to the stable cycloadduct endo 18. In contrast, reaction of 9 with 1,3-cyclopentadiene 17 as above gave an unstable tetrahydro cycloadduct which was converted into the dihydro derivative 19 after its treatment with silica gel at 40 °C (Chart 4).

The stereochemistry endo 18 was confirmed by 1H-NMR NOE DIFF experiment (Chart 5). Irradiation at 3.42 ppm (H-4a) gives responses on H-11c at 4.12 ppm and H-12 at 1.71 ppm. Irradiation at 4.12 ppm (H-11c) gives responses on H-4a and H-12. Finally, an irradiation at 1.71 ppm (H-12) gives two responses on H-4a and H-11c.

Attempted cycloadditions of ortho-carbazolequinones 3 and 7, as dienophiles, with different 1-azadienes gave a complex mixture of products and failed to yield the expected pyridocarbazolequinones, probably due to the versatile reactivity profile of ortho-quinones in Diels–Alder reactions. Potentially they can react as carbodiienophiles, heterodiienophiles or 1-azadienes.

**Experimental**

Melting points were taken in a capillary tube using a Büchi 510 apparatus. The IR spectra were obtained on a Perkin-Elmer 1310 spectrophotometer. The NMR spectra were recorded with a Bruker AM 300 spectrometer (1H-NMR: 300 MHz, 13C-NMR: 75 MHz). Chemical shifts are reported in ppm using tetramethylsilane (TMS) as an internal reference. Coupling constant values are given in Hz. Elemental analyses were performed at the Centre de Microanalyse du CNRS at Solaize, France.

**2-Hydroxy-9-methyl-9H-carbazole (2)** A solution of 2-hydroxycarbazole 1 (0.457 g, 2.5 mmol) and DMF (0.37 ml, 4.76 mmol) in dry THF (5 ml) was added dropwise to 60% NaOH (0.25 g, 6.25 mmol) under a nitrogen atmosphere and stirring at room temperature. After 10 min, CH3I (0.17 ml, 2.75 mmol) was added and the stirring was continued for 2 h. The resulting mixture was cooled to 0 °C and quenched with water (2 ml). After removing the solvent under vacuum, the crude product was washed with acidic aqueous solution and purified by column chromatography on silica gel with CH2Cl2/MeOH (98:2) as the eluent. Compound 2 was obtained as a yellow solid in 80% yield (ref. 12, 89%), mp 162 °C (ref. 12, 166—167 °C). IR (KBr) cm⁻¹: 3360. 1H-NMR (DMSO-d₆): δ: 9.53 (1H, s, OH), 7.96 (1H, d, J = 7.7 Hz, H-5), 7.89 (1H, d, J = 8.3 Hz, H-4), 7.48 (1H, d, J = 8.2 Hz, H-8), 7.34 (1H, td, J = 8.2, 1.1 Hz, H-7), 7.13 (1H, td, J = 7.7, 1.0 Hz, H-6), 6.86 (d, J = 2.0 Hz, H-1), 6.68 (1H, dd, J = 8.3, 2.0 Hz, H-3), 3.76 (3H, s, CH₃-9).

**General Method for the Oxidation of Hydrocarbazoles with Frémy’s Salt** An aqueous solution (20 ml) of Frémy’s salt (0.37 g, 1.37 mmol) and potassium dihydrogen orthophosphate (0.02 g, 0.15 mmol) was added to a solution of hydroxycarbazole 1, 2 or 6 (0.55 mmol) in acetone (20 ml). The reaction mixture was stirred at room temperature for 30 min, extracted with CH2Cl2, dried over Na2SO4 and concentrated under vacuum.

**1,2-Dihydrocarbazole-1,2(9H)-dione (3)** The quinone 3 was obtained from hydroxycarbazole 1. The crude mixture was purified by column chromatography on silica gel using CH2Cl2/MeOH (95:5) as the eluent. Compound 3 was obtained as a dark green solid in 64% yield (ref. 11, 83%), mp 181 °C (ref. 11, 178 °C). IR (KBr) cm⁻¹: 3260, 1665, 1640. 1H-NMR (DMSO-d₆): δ: 12.61 (1H, s, NH), 7.87 (2H, m, H-4, H-5), 7.43—7.18 (3H, m, m, H-6, H-7, H-8), 5.97 (1H, d, J = 9.9 Hz, H-3).

**9-Methyl-1,2-dihydrocarbazole-1,2(9H)-dione (4)** The quinone 4 was obtained from hydroxycarbazole 2. The crude mixture was purified by column chromatography on silica gel using CH2Cl2 as the eluent. Compound 4 was obtained as a dark green solid in 42% yield, mp 177 °C. IR (KBr) cm⁻¹: 1670, 1640. 1H-NMR (DMSO-d₆): δ: 7.90 (2H, m, H-4, H-5), 7.59 (1H, d, J = 8.7 Hz, H-8), 7.45 (1H, m, H-6 or H-11), 7.26 (1H, m, H-6 or H-11), 6.01 (1H, d, J = 9.8 Hz, H-3), 4.01 (3H, s, CH₃-9). 13C-NMR (DMSO-d₆): δ: 182.7, 172.4, 141.2, 138.4, 131.9, 129.5, 126.3, 125.6, 125.5, 32.6. HR-MS m/z: 211.0636 (Calcd for C₁2H₁₂N₂O₂). 3-Hydroxy-9-ethyl-9H-carbazole (6): A solution of 3-amino-9-ethylcarbazole 5 (1 g, 4.76 mmol), ice (3 g) and concentrated H₂SO₄ (1 ml) in water (1.5 ml) was stirred at 0 °C. Then, a cooled solution of NaNO₂ (0.391 g, 5.11 mmol) in water (1 ml) was added dropwise and the stirring was continued for 10 min. The resulting mixture was added to acidic aqueous solution (3 ml of concentrated H₂SO₄ in 2.5 ml of water) heated at reflux. After 5 min the reaction mixture was poured into ice water (30 ml), extracted with CH2Cl2 and dried with Na2SO4. After removing the solvent under vacuum, the crude product was purified by column chromatography on silica gel with CH2Cl2, dried over Na2SO4 and concentrated under vacuum.
Oxidation of 3-Amino-9-ethylobenzaldehyde 5 with Frémy’s Salt
An aqueous solution (200 ml) of Frémy’s salt (3.2 g, 11.9 mmol) and potassium dihydrogen orthophosphate (0.16 g, 1.19 mmol) was added to a solution of aminocarbazole 3 (1 g, 4.76 mmol) in acetone (200 ml). The reaction mixture was stirred at room temperature for 1 h, extracted with CHCl3, dried over MgSO4 and concentrated under vacuum. The crude residue was purified by column chromatography on silica gel using CH2OEt/Petroleum ether (20:80) as the eluent to give compounds 12 and 13.

3-Amino-9-ethyl-1-[9-ethyl-9H-carbazol-3-yl]iminio-1,9-dihydropyrrolo[4,3-c]carbazole-9(1H)-dione (12) Compound 12 was obtained as a dark red solid in 10% yield, mp 236 °C. IR (KBr) cm⁻¹: 3430, 3380, 1625, 1585, 1550. H NMR (CDCl3) δ: 9.1 (1H, s, NH), 6.28 (1H, d, J = 7.4 Hz), 8.19 (1H, d, J = 7.4 Hz), 7.75 (1H, d, J = 8.1 Hz), 7.57 (1H, d, J = 8.1 Hz), 7.44—7.38 (3H, m), 7.19 (1H, m), 7.14 (1H, d, J = 8.5 Hz), 7.01 (1H, d, J = 8.5 Hz), 6.32 (2H, brs, NH2), 6.04 (1H, d, J = 4.7 Hz), 5.03 (2H, q, J = 7.0 Hz, CH2CH3), 4.42 (2H, q, J = 7.0 Hz, CH2CH3), 1.41 (3H, t, J = 7.4 Hz, CH3CH2), 1.35 (3H, t, J = 7.0 Hz, CH3CH2). Anal. Calcd for C19H15NO2 · 0.5 H2O: C, 76.06; H, 3.83; N, 5.54. Found: C, 76.38; H, 4.05; N, 5.55.

11-Ethylbenzo[c]carbazole-5,6(11H)-dione (13) Compound 13 was obtained as a dark blue solid in 30% yield, mp 248 °C. IR (KBr) cm⁻¹: 3500, 3380, 1625, 1585, 1550. H NMR (CDCl3) δ: 9.1 (1H, s, OH), 6.26 (1H, d, J = 7.4 Hz), 8.19 (1H, d, J = 7.4 Hz), 7.75 (1H, d, J = 8.1 Hz), 7.57 (1H, d, J = 8.1 Hz), 7.44—7.38 (3H, m), 7.19 (1H, m), 7.14 (1H, d, J = 8.5 Hz), 7.01 (1H, d, J = 8.5 Hz), 6.32 (2H, brs, NH2), 6.04 (1H, d, J = 4.7 Hz), 5.03 (2H, q, J = 7.0 Hz, CH2CH3), 1.41 (3H, t, J = 7.4 Hz, CH3CH2), 1.35 (3H, t, J = 7.0 Hz, CH3CH2). Anal. Calcd for C19H15NO2 · 0.5 H2O: C, 76.38; H, 4.05; N, 5.55.

References