Quninone Chemistry. Synthesis of 3-Methoxy[2,1]benzisoxazole- and 3-Methoxynaphth[2,3-*c*]isoxazolequinones

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[2,1]Benzisoxazole-4,7-quinones **4** are prepared by an improved method using oxidative amination of **1** to give **2**, followed by amine exchange to **3** and cyclization with lead tetraacetate. Naphth[2,3-*c*]isoxazole-4,9-quinone **7** is obtained from **5** by an analogous procedure.

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In continuation of our interest in the synthesis and the chemistry of heterocyclic quinones [1-6] we report here an improved procedure for the preparation of 3-alkoxy-5-arylamino[2,1]benzisoxazole-4,7-quinones **4** and the synthesis of 3-methoxy-2,1-naphth[2,3-*c*]isoxazole-4,9-quinone (**7**). In the course of our work it was also necessary to prepare substituted isoxazolequinones **4a,b,d** and also the deuterium labeled quinone **4c**.

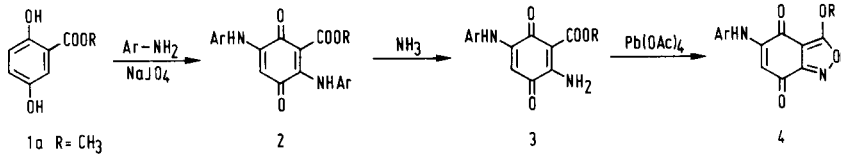
Compounds **4** were prepared in a three step synthesis: a) oxidative amination [2] of the appropriate ester **1** of gentisic acid with aniline or *p*-toluidine in the presence of sodium iodate gave the corresponding 3-substituted 2,5-bisarylamino-1,4-benzoquinone **2**; b) substitution of the arylamino group on C-2 with ammonia in methanol yielded the 2-amino-5-arylamino-1,4-benzoquinone **3**; and c) oxidative cyclization to the quinone **4** was accomplished using lead tetraacetate.

The original procedure [4] of cyclization was modified in order to obtain better yields and better quality of crude isoxazolequinones **4a, 4b** and **4c**. These compounds present many difficulties on purification. Recrystallization suffers from the low solubility in most inert solvents at room temperature. The quinones cannot be heated, because they undergo thermal rearrangement [7], and also partial decomposition occurs during purification by chromatography on silica gel. Instead, **4d** is a more soluble product, recrystallizes without difficulty and has an improved thermal stability compared with **4a,b,c**. The deuterium labeled gentisic acid methylester **1b** was obtained by treatment of *O*-deuteriomethyl-*N,N'*-dicyclohexylisourea with 2,5-dihydroxybenzoic acid [8,9].

The synthesis of 3-methoxy-2,1-naphth[2,3-*d*]isoxazole-4,9-quinone (**7**) was carried out starting from **5** by oxidative amination with ammonia in methanol in the presence of silver carbonate and silver(I) oxide followed by lead tetraacetate cyclisation in tetrahydrofuran at reflux temperature. While in the benzoquinone series oxidative amination is only possible with aromatic amines, this reaction works well in the naphthoquinone series also with ammonia and aliphatic amines.

Comparison of the nmr spectra of compounds of type **4** and **7** with those of their precursors **3** and **6** respectively showed that oxidative cyclisation resulted in a remarkable downfield shift of the methoxy group. This shift is consis-

Scheme I

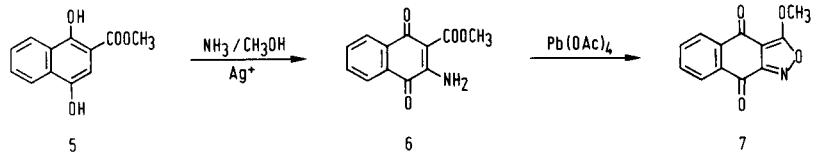


1a R= CH_3
1b R= CO_3
1c R= C_2H_5

2 3 4

2,3,4a R = CH_3 Ar = C_6H_5
2,3,4b R = CH_3 Ar = C_6H_4-CH_3
2,3,4c R = CO_3 Ar = C_6H_5
2,3,4d R = C_2H_5 Ar = C_6H_5

Scheme II



5 6 7

tent with the deshielding effect of the carbonyl group on C-4.

All products were characterized by ir, uv, nmr, ms and elemental analysis.

From the chemistry of these compounds [7] that will be published in the following papers, it will come out that isoxazolequinones could be interpreted as intramolecular stabilized nitrenes.

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. The following spectroscopic apparatus were used: for ir the spectrometer Model EM 250 from Perkin Elmer, for nmr the Bruker WH 90 spectrometer, equipped with a Nicolet TT data system and a frequency synthesizer, for ms the Varian CH 7A and 312 machines coupled with the datasystem Varian SS 200, for uv the Gilford 240 spectrophotometer. Microanalyses were conducted by the Peptide Chemistry Division of Max-Planck-Institute of Biochemistry, Munich. All thin layer chromatographic separations were performed on Merck precoated silica gel F-254 plates with fluorescent backing. Data for nmr are reported as follows: chemical shift, multiplicity (s, singlet, d, doublet, t, triplet, br, broad, m, multiplet); coupling constant, assignment and integration.

O-Deuteriomethyl-*N,N'*-dicyclohexylisourea.

According to described methods [8] a mixture of 4.5 g (0.125 mole) of perdeuteriomethanol, 25.75 g (0.125 mole) of dicyclohexylcarbodiimide and 25.0 mg of copper(I) chloride after 72 hours standing was filtered with hexane over aluminium oxide (activity III) to give 28.72 g (95%) of colorless crystals, mp 35° (lit [8b] 32-33°); ir (potassium bromide): 3440 cm^{-1}, 2930, 2854, 1660, 1358, 1337, 1100; nmr (deuteriochloroform): δ 0.8-2.2 (m, methylene, 20H), 2.76 (m, methin-1', 1H), 3.39 (m, methin-1'', 1H), 3.45 (broad, exchangeable by deuterium oxide, NH, 1H).

2,5-Dihydroxybenzoic Deuteriomethyl Ester (**1b**).

A mixture of 7.70 g (50 mmoles) of 2,5-dihydroxybenzoic acid and 12.05 g (50 mmoles) of *O*-deuteriomethyl-*N,N'*-dicyclohexylisourea in 25 ml of dimethylformamide was heated for 4 hours at 60° [9]. After cooling, the precipitate of *N,N'*-dicyclohexylurea was filtered by suction and washed with methylene chloride. The filtrates were washed with water, the organic solvent was evaporated and the residue was treated with water. The precipitate was collected by filtration, dissolved in a small volume of chloroform and the solution was filtered, to eliminate the insoluble material. The solvent was evaporated at reduced pressure to give 5.32 g (62%) of **1b**. The product was recrystallized from chloroform/*n*-hexane to yield colorless crystals, mp 86°; ir (potassium bromide): 3340 cm^{-1} (OH), 3500-3200 (OH), 2926, 1684 (C=O), 1620, 1502; nmr (deuteriochloroform): δ 5.4 (broad, exchangeable by deuterium oxide, OH, 1H), 6.88 Hz (dd, $J_{3,4}$ = 9 Hz, $J_{3,6}$ = 2.8 Hz, C_3, 1H), 7.02 (dd, $J_{3,4}$ = 9 Hz, $J_{4,6}$ = 0.7 Hz, C_4, 1H), 7.31 (dd, $J_{3,6}$ = 2.8 Hz, $J_{4,6}$ = 0.7 Hz, C_6, 1H), 10.34 (broad, exchangeable by deuterium oxide, OH, 1H).

Anal. Calcd. for $C_8H_5D_3O_4$: C, 56.13; H + D, 6.47. Found: C, 56.38; H + D, 6.61.

2,5-Bis-*p*-toluidino-3-carbomethoxy-1,4-benzoquinone (**2b**).

To a stirred solution of 2.52 g (15 mmoles) of **1a** in a mixture of 200 ml of methanol and 400 ml of water the solution of 4.28 g (40 mmoles) of *p*-toluidine in 50 ml of methanol was added at once. Followed the addition of 12.0 g of sodium iodate in 100 ml of hot water the mixture was strongly stirred for 24 hours. The precipitate was filtered by suction, washed with 1 *N* hydrochloric acid and water, dried and recrystallized from ethyl acetate-hexane to give 4.4 g (78%) of **2b** as brown red crystals, mp 223° dec; ir (potassium bromide): 3240 cm^{-1}, 3215 (NH), 1720 (C=O), 1635, 1565, 1508; nmr (deuteriochloroform): δ 2.36 and 2.37 (s, Ar-CH_3, 6H), 3.17 (s, $COOCH_3$, 3H), 6.05 (s, quinone-H, 1H), 6.9-7.4 (m, aromatic, 8H), 8.16 and 8.69 (broad, exchangeable by deuterium oxide, NH, 2H); ms: 376 (M^+, 71), 345 (30), 344 (M-32, 100), 158 (90), 130 (41).

Anal. Calcd. for $C_{22}H_{20}N_2O_4$: C, 70.20; H, 5.36; N, 7.44. Found: C, 70.07; H, 5.44; N, 7.42.

2,5-Bisanilino-3-deuteriocarbomethoxy-1,4-benzoquinone (**2c**).

Following the method described above 5.13 g (30 mmoles) of **1b** in 400 ml of methanol and 800 ml of water, 7.44 g (80 mmoles) of aniline in 100 ml of methanol and 24.0 g of sodium iodate in 200 ml of water gave on recrystallization from ethyl acetate/hexane 8.66 g (82%) of brown red crystals, mp 200° dec; ir (potassium bromide): 3260 cm^{-1} (NH), 3240 (NH), 1722, 1634, 1600, 1568, 1490; nmr (deuteriochloroform): δ 6.10 (s, quinone-H, 1H), 7.0-7.6 (m, aromatic, 10H), 8.19 and 8.,72 (broad, exchangeable by deuterium oxide, NH, 2H); ms: 351 (M^+, 31), 318 (M-33, 11), 317 (M-34, 17), 288 (M-63, 79), 144 (100).

Anal. Calcd. for $C_{20}H_{13}D_3N_2O_4$: C, 68.36; H + D, 5.45; N, 7.97. Found: C, 68.27; H + D, 5.38; N, 8.10.

2,5-Bisanilino-3-carboethoxy-1,4-benzoquinone (**2d**).

This was prepared from **1c** as described above for **2b**, in 85% yield. Recrystallization from ethyl acetate/*n*-hexane gave brown red crystals, mp 175° dec; ir (potassium bromide): 3235 cm^{-1} (NH), 3210 (NH), 1718 (C=O), 1555; nmr (deuteriochloroform): δ 0.96 (t, OCH_2CH_3, 3H), 3.50 (q, OCH_2CH_3, 2H), 6.05 (s, quinone-H, 1H), 6.8-7.6 (m, aromatic, 10H), 8.28 and 8.73 (broad, exchangeable by deuterium oxide, NH, 2H); ms: 362 (M^+, 64), 316 (M-C_2H_5OH, 66), 288 (100), 144 (80).

Anal. Calcd. for $C_{21}H_{18}N_2O_4$: C, 69.60; H, 5.01; N, 7.73. Found: C, 69.82; H, 5.12; N, 7.67.

2-Amino-3-carbomethoxy-5-(*p*-toluidino)-1,4-benzoquinone (**3b**).

To a stirred solution of 4.2 g (11.2 mmoles) of **2b** in 120 ml of chloroform, 20 ml of 2.5 *N* ammonia in methanol was added at room temperature. Stirring was continued for 6 hours, the red precipitate was filtered, washed with chloroform, dried and recrystallized from acetone to give 2.20 g (69%) of **3b** as red crystals, mp 242-243° dec; ir (potassium bromide): 3352 cm^{-1} (NH), 3200 (NH), 1658 (C=O), 1615, 1570, 1510; nmr (deuteriochloroform): δ 2.37 (s, Ar-CH_3, 3H), 3.91 (s, $COOCH_3$, 3H), 6.06 (s, quinone-H, 1H), 7.0-7.4 (m, aromatic, 4H), 7.65, 8.36, 9.7 (broad, exchangeable by deuterium oxide, NH, 3 × 1H); ms: 286 (M^+, 100), 271 (M-15, 14), 254 (M-32, 42), 158 (17).

Anal. Calcd. for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.78. Found: C, 62.81; H, 5.05; N, 9.69.

2-Amino-5-anilino-3-deuteriocarbomethoxy-1,4-benzoquinone (**3c**).

By the same method described above for **3b**, starting from 7.0 g (20 mmoles) of **2c** in 200 ml of chloroform and 25 ml of 2.5 *N* ammonia in methanol, 3.60 g (66%) of **3c** were obtained. Recrystallization from ethylacetate gave red crystals, mp 261° dec; ir (potassium bromide): 3350 cm^{-1} (NH), 3200 (NH), 1650 (C=O), 1560, 1500, 1440; nmr (deuteriodimethylsulfoxide): δ 5.79 (s, quinone-H, 1H), 7.1-7.6 (m, aromatic, 5H), 8.65, 9.24, 9.54 (broad, exchangeable by deuterium oxide, NH, 3 × 1H); ms: 275 (M^+, 100), 240 (M-35, 73), 144 (93).

Anal. Calcd. for $C_{14}H_9D_3N_2O_4$: C, 61.09; H + D, 5.49; N, 10.18. Found: C, 60.94; H + D, 5.21; N, 10.02.

2-Amino-5-anilino-3-carboethoxy-1,4-benzoquinone (**3d**).

This was prepared from **2d**, as described above for **3b**, in 72% yield. Recrystallization from dimethylformamide gave red crystals, mp 290-292° dec; ir (potassium bromide): 3340 cm^{-1} (NH), 3200 (NH), 1650 (C=O), 1565, 1495; nmr (trifluoroacetic acid): δ 1.43 (t, OCH_2CH_3, 3H), 4.49 (q, OCH_2CH_3, 2H), 6.37 (s, quinone-H, 1H), 7.2-7.8 (m, aromatic, 5H); ms: 286 (M^+, 100), 240 (M-C_2H_5OH, 44), 144 (50).

Anal. Calcd. for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.78. Found: C, 63.05; H, 4.97; N, 9.69.

5-Arylamino-3-methoxy[2,1]benzisoxazole-4,7-quinones **4**. General Procedure.

To a stirred suspension of the corresponding quinone **3** in chloroform-

tetrahydrofuran lead tetraacetate (10-20% content of acetic acid) was added. According to tlc-control, starting material had disappeared after about 30 minutes. The mixture was evaporated to dryness, the residue was resuspended in acetic acid (10 ml per mmole of quinone), diluted with water (200 ml per mmole of quinone) and the orange precipitate was filtered. The residue was resuspended in a small volume of methanol and the quinone again filtered by suction and dried over phosphorous pentoxide. The products were pure enough to be used without further purification. Analytical samples were obtained by recrystallization from methylene chloride/*n*-hexane but without heating. It is not possible to chromatograph the quinones **4** on silica gel.

5-Anilino-3-methoxy[2,1]benzisoxazole-4,7-quinone (**4a**).

From 6.0 g (22 mmoles) of **3a** [2] in 400 ml of chloroform and 250 ml of tetrahydrofuran using 19.0 g of lead tetraacetate, the quinone **4a**, 4.7 g (79%), was obtained and crystallized as orange crystals, mp 127-130° dec; ir (potassium bromide): 3285 cm^{-1} (NH), 1679 (C=O), 1638, 1610, 1565, 1514; uv (ethanol): λ 329 nm (log ε 3.88), 439 (3.74); nmr (deuteriochloroform): δ 4.45 (s, OCH_3, 3H), 6.30 (s, quinone-H, 1H), 7.1-7.6 (m, aromatic, 5H), 7.77 (broad, exchangeable by deuterium oxide, NH, 1H); ms: 270 (M^+, 33), 211 (M-59, 44), 144 (100).

Anal. Calcd. for $C_{14}H_{10}N_2O_4$: C, 62.23; H, 3.73; N, 10.37. Found: C, 62.05; H, 3.86; N, 10.30.

3-Methoxy-5-*p*-toluidino[2,1]benzisoxazole-4,7-quinone (**4b**).

By the general method, starting from 6.3 g (22 mmoles) of **3b** in 460 ml of chloroform and 270 ml of tetrahydrofuran and 20.7 g of lead tetraacetate, 4.6 g (74%) of **4b** was isolated as orange crystals, mp 136-137° dec; ir (potassium bromide): 3295 cm^{-1} (NH), 1680, 1639, 1605, 1585, 1568, 1518; nmr (deuteriochloroform): 2.37 (s, Ar-CH}, 3H), 4.44 (s, OCH}, 3H), 6.24 (s, quinone-H, 1H), 7.0-7.4 (m, aromatic, 4H), 7.70 (broad, exchangeable by deuterium oxide, NH, 1H); ms: 284 (M^+, 40), 225 (M-59, 36), 158 (100).

Anal. Calcd. for $C_{15}H_{12}N_2O_4$: C, 63.38; H, 4.26; N, 9.85. Found: C, 63.41; H, 4.38; N, 9.67.

5-Anilino-3-deuteriomethoxy[2,1]benzisoxazole-4,7-quinone (**4c**).

By the same method using half the material as for the preparation of **4a** starting from **3c**, 2.41 g (81%) of **4c** was obtained as orange crystals, mp 127-129° dec; ir (potassium bromide): 3285 cm^{-1} (NH), 1679 (C=O), 1638, 1608, 1565, 1514; nmr (deuteriochloroform): δ 6.30 (s, quinone-H, 1H), 7.1-7.6 (m, aromatic, 5H), 7.78 (broad, exchangeable by deuterium oxide, 1H); ms: 273 (M^+, 43), 211 (M-62, 51), 144 (100).

Anal. Calcd. for $C_{14}H_7D_3N_2O_4$: C, 61.54; H+D, 4.79; N, 10.25. Found: C, 61.30; H+D, 4.98; N, 9.98.

5-Anilino-3-ethoxy[2,1]benzisoxazole-4,7-quinone (**4d**).

Following the general method, from 5.72 g (20 mmoles) of **3d** in 400 ml of chloroform and 250 ml of tetrahydrofuran and 18.0 g of lead tetraacetate, 4.1 g (72%) of **4d** was obtained. Recrystallization from methylene chloride/*n*-hexane gave orange crystals, mp 123-125° dec; ir (potassium bromide): 3285 cm^{-1} (NH), 1676 (C=O), 1634, 1606, 1588, 1560, 1512; uv (ethanol): λ 251 nm (log ε 4.09), 278 (4.08), 328 (3.87), 439 (3.74); nmr (deuteriochloroform): δ 1.56 (t, J = 7.5 Hz, OCH_2CH_3, 3H), 4.82 (q, J = 7.5 Hz, O-CH_2CH_3, 2H), 6.26 (s, quinone-H, 1H), 7.1-7.6 (m, aromatic, 5H), 7.77 (broad, exchangeable by deuterium oxide, NH, 1H); ms: 284 (M^+, 31), 211 (M-73, 51), 144 (100).

Anal. Calcd. for $C_{15}H_{12}N_2O_4$: C, 63.38; H, 4.26; N, 9.85. Found: C, 63.12; H, 4.36; N, 9.76.

2-Amino-3-carbomethoxy-1,4-naphthoquinone (**6**).

To a solution of 5 g (22.9 mmoles) of **5** in 400 ml of chloroform, 2.0 g of silver carbonate, 2.0 g of silver(I) oxide and 4.0 g of anhydrous sodium sulfate were added. Following the addition of 100 ml of 2.5 *N* ammonia in methanol the mixture was stirred vigorously for 24 hours. The mixture was filtered, the inorganic residue washed with chloroform and the combined filtrates were evaporated. The residue was stirred with a small volume of ether, filtered and recrystallized from benzene-cyclohexane to give 3.6 g (68%) of **6** as yellow crystals, mp 145-146°; ir (potassium bromide): 3375 cm^{-1} (NH), 3240-2000 (NH), 1689 (C=O), 1652, 1645, 1595, 1574; uv (ethanol): λ 227 nm (log ε 4.28), 270 (4.29), 331 (343), 413 (3.43); nmr (deuteriochloroform): δ 3.96 (s, $COOCH_3$), 7.0 (broad, exchangeable by deuterium oxide, NH, 1H), 7.5-8.3 (m, aromatic, 4H), 9.0 (broad, exchangeable by deuterium oxide, NH, 1H); ms: 231 (M^+, 76), 200 (M-31, 43), 173 (M-58, 100), 172 (M-59, 71), 171 (M-60, 33).

Anal. Calcd. for $C_{12}H_9NO_4$: C, 62.34; H,3.92; N, 6.06. Found: C, 62.37; H, 3.90; N, 6.07.

3-Methoxynaphth[2,3-*c*]isoxazole-4,9-quinone (**7**).

A stirred mixture of 3.0 g (13 mmoles) of **6** in 300 ml of tetrahydrofuran and 15.0 g of lead tetraacetate was refluxed for 30 minutes. After cooling, the mixture was filtered, the inorganic product washed with tetrahydrofuran, and the combined filtrates were brought to dryness. The residue was suspended in 100 ml of acetic acid and following the addition of 1 ℓ of water the yellow product was isolated by filtration. The raw material was dried, recrystallized from acetone yielding 2.36 g (79%) of yellow crystals, mp 158-159°; ir (potassium bromide): 1685 cm^{-1}, 1605, 1592, 1507; uv (ethanol): λ 237 nm (log ε 4.28), 267 (4.24), 325 (3.54); nmr (deuteriochloroform): δ 4.46 (s, OCH_3, 3H), 7.6-8.0 (m, aromatic C_6, C_7, 2H), 8.1-8.4 (m, aromatic, C_5, C_8, 2H); ms: 229 (M^+, 22), 198 (M-31, 100).

Anal. Calcd. for $C_{12}H_7NO_4$: C, 62.89; H, 3.08; N, 6.11. Found: C, 62.61; H, 3.00; N, 6.00.

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