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One-pot assembly of large heterocyclic quinones through three-component reactions

Pilar López-Alvarado, Miguel Ángel Alonso, Carmen Avendaño* and J. Carlos Menéndez*

Departamento de Química Orgánica y Farmacéutica, Facultad de Farmacia, Universidad Complutense, 28040 Madrid, Spain

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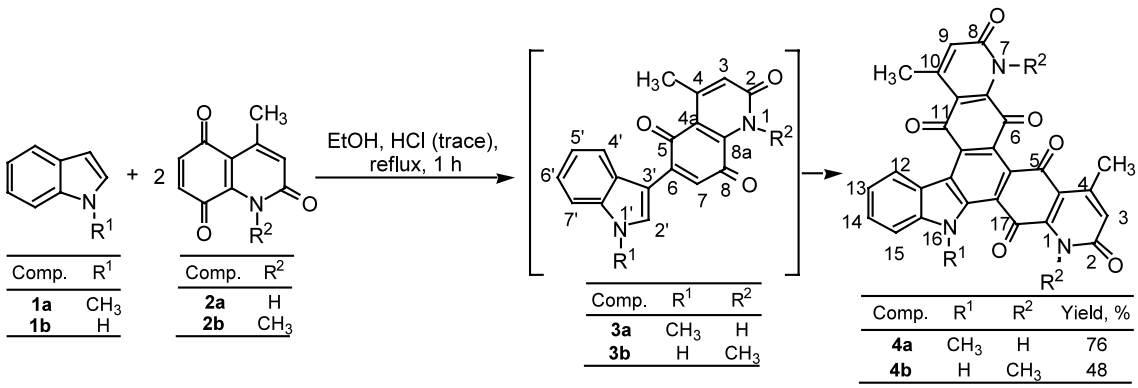
Abstract—Treatment of indoles with 2,5,8-quinolinetriones in the presence of a catalytic amount of hydrochloric acid afforded heptacyclic reaction products arising from a cascade of two regioselective Michael addition–Diels–Alder cycloaddition steps. In another approach to polyheterocyclic quinone systems, double Diels–Alder reactions between indolylquinolinetriones and 2,5- or 2,6-dihalogenated benzoquinones provided regioisomeric 11-cycle products in good yields. © 2001 Elsevier Science Ltd. All rights reserved.

Heterocyclic quinones[1] are a very important class of compounds from a biological point of view, particularly as antitumour agents.[2] On the other hand, while many polycyclic aromatic quinones are known, some of them with interesting properties,[3] their heterocyclic counterparts have received very little attention. We describe here our findings on the preparation of polyheterocyclic quinone systems by means of two different types of three-component reactions that involve the use of 3-indolyl-2,5,8-quinolinetriones as Diels–Alder dienes. Although the use of 2- and 3-vinylindoles as dienes in Diels–Alder reactions is well known,[4] indolylquinones are virtually unexplored in this regard;[5] furthermore, only symmetrical quinones (benzoquinone and naphthoquinone) have been studied as dienophiles, and thus no issues of regioselectivity have arisen in the past.

In our first series of experiments, we discovered that a simple 1-h reflux of indoles **1** with two equivalents of quinones **2** in ethanol containing a trace of HCl led to the heptacyclic derivatives **4** in a single synthetic operation. The formation of **4** can be rationalized in terms of a cascade process initiated by the Michael addition of indoles **1** onto **2** to give the corresponding 6-(3-indolylmethyl) hydroquinones, which are oxidized in situ to the corresponding quinones **3**.[6] Diels–Alder reaction of the latter compounds with a second molecule of **2** followed by a new oxidation[7] yields compounds **4**[8] (Scheme 1). It is noteworthy that the Michael and the Diels–Alder reactions were both completely regioselective. This regiocontrol can be assumed to arise from electron donation of N-1 to the C-5 carbonyl, which renders its conjugate C-7 position less electrophilic than



Comp.	R^1
1a	CH_3
1b	H

Comp.	R^2
2a	H
2b	CH_3

Comp.	R^1	R^2
3a	CH_3	H
3b	H	CH_3

Comp.	R^1	R^2	Yield, %
4a	CH_3	H	76
4b	H	CH_3	48

Scheme 1.

* Corresponding authors. E-mail: josecm@farm.ucm.es

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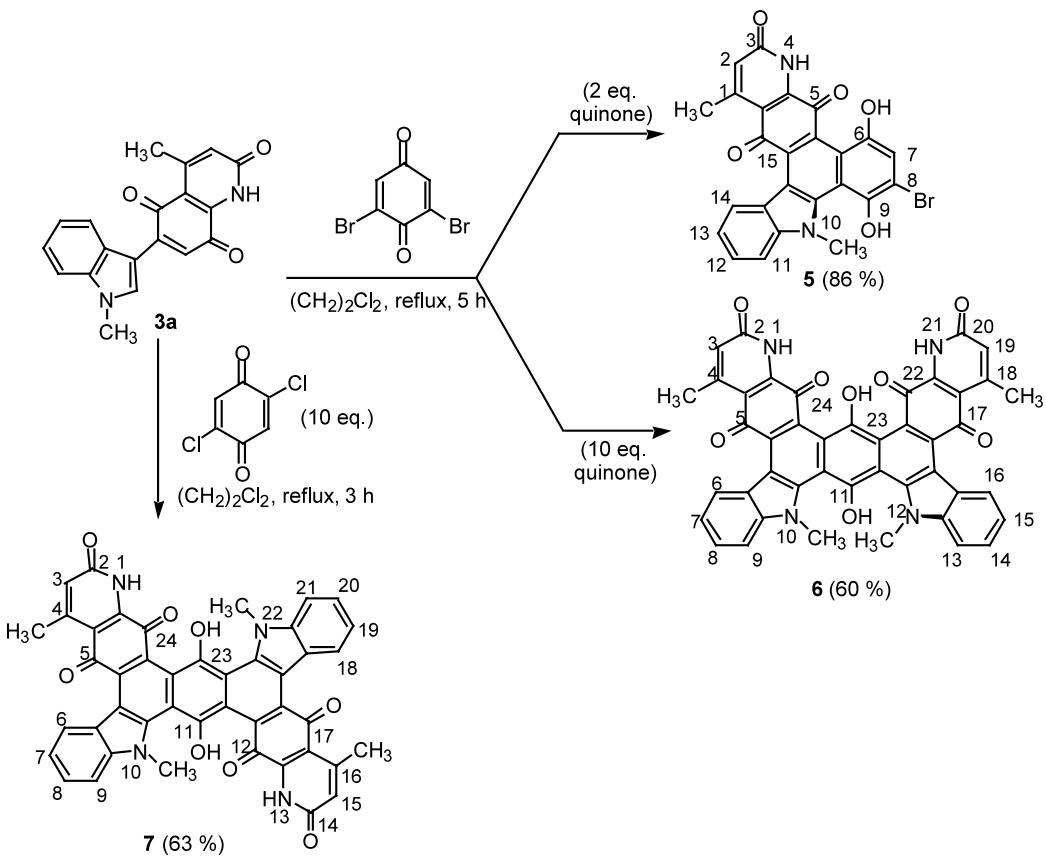
C-6,[9] directing both the initial Michael reaction and the subsequent cycloaddition of compounds **3**. To check this assumption, we performed the reaction at room temperature to isolate intermediates **3**,[6] in order to establish their structure unambiguously. The long-range couplings of quaternary carbon atoms 4a and 8a are very useful for differentiating between 6- and 7-substituted carbostiryl derivatives because of their very different chemical shifts. In the case of compound **3a**, these signals appear at 117.7 and 145.5 ppm, respectively, as expected from literature data (typical values are ca. 115 ppm for C-4a and ca. 140–145 ppm for C-8a),[10] and as confirmed by two-dimensional experiments. In the HMBC experiment, the signal due to H-7 shows a correlation with the one assigned to C-8a, but not with the C-4a signal, proving the existence of a three-bond relationship between C-8a and H-7, which is compatible with structure **3a** but not with the other possible regioisomer.

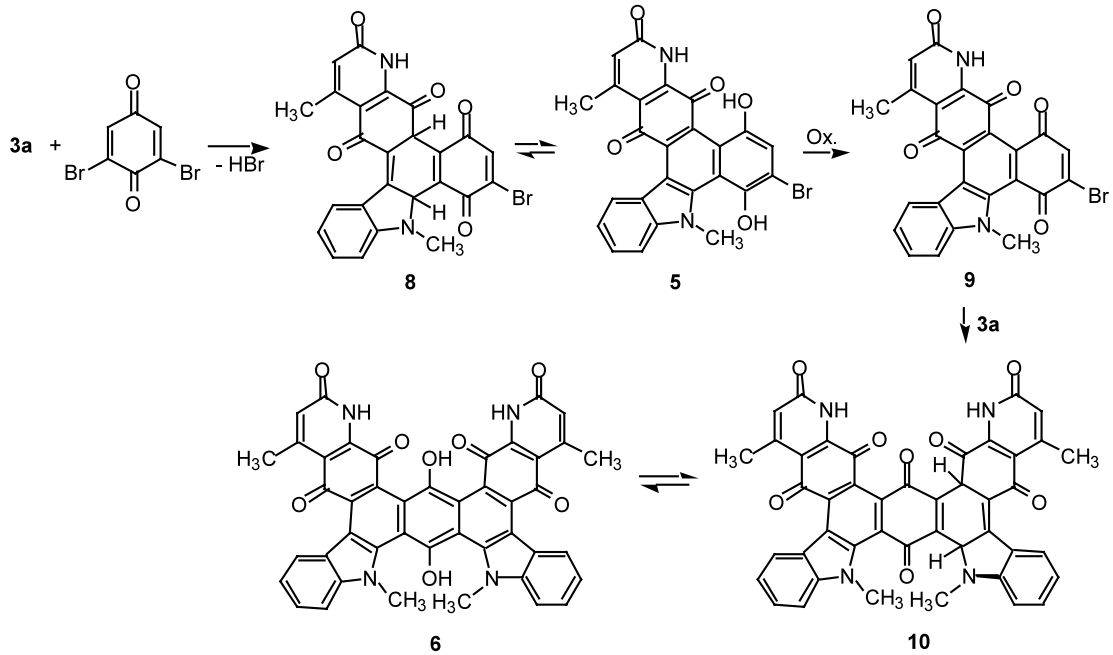
In a second approach to polyheterocyclic quinone systems, we examined the double Diels–Alder reactions of isolated indolylquinone **3a** with dihalogenated benzoquinones. In our first experiment, treatment of **3a** with 2,6-dibromobenzoquinone[11] in refluxing 1,2-dichloroethane gave hydroquinone **5**,[12] which precipitated from the reaction medium, thus preventing its oxidation and a further cycloaddition. This reaction required the use of two equivalents of 2,6-dibromobenzoquinone, which is unstable under the reaction conditions as shown in a blank run of the experiment. Use of a larger excess of the quinone allowed to isolate compound **6**,[13] from a double cycloaddition. Application of the same conditions to commercially available 2,5-dichlorobenzoquinone gave the regioisomeric compound **7**[14] (Scheme 2). To our knowledge, these are the first double Diels–Alder reactions of an indolylquinone.

The fact that compound **6** has an axis of symmetry while compound **7** has a center of symmetry should allow to differentiate these regioisomeric compounds. Indeed, the ^{1}H NMR spectrum of compound **6** showed two broad singlets centered at 10.91 and 9.82 ppm, due to two non-equivalent hydroxyl groups, while in the case of compound **7** only one signal was observed at 9.87 ppm. The regiochemistry observed for the hetero Diels–Alder reactions is the one expected for halogenated quinones, since the literature contains many examples that prove that in these compounds the nucleophilic end of the diene attacks the unhalogenated carbon of the dienophile.[15]

The formation of **5** and **6** can be rationalized by the mechanism proposed in Scheme 3. Formation of compound **5** can be easily explained through a double bond isomerization leading to aromatization of the indole ring and a tautomeric equilibrium starting from the primary adduct from the first Diels–Alder reaction (**8**). Under the conditions of our first experiment, compound **5** precipitated and further reactions were thus prevented. However, in the presence of a large excess of 2,6-dibromobenzoquinone, **5** is oxidized to **9** while still



Scheme 2.



Scheme 3.

in solution,[16] allowing the second cycloaddition to take place to give adduct **10**, which is transformed into the observed product **6** through a new isomerization-tautomerism process.

In summary, we have shown that large polyheterocyclic quinone systems can be rapidly and efficiently constructed by recourse to the Diels–Alder chemistry of indolylquinones.

Acknowledgements

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References

1. For a review of the chemistry of heterocyclic quinones, see: Middleton, R. W.; Parrick, J. In *The Chemistry of Quinonoid Compounds*; Patai, S.; Rappoport, Z., Eds.; John Wiley & Sons: Chichester, 1988; Vol. 2, pp. 1019–1066.
2. For some examples of recent research in this area, see: (a) Krapcho, A. P.; Maresch, M. J.; Hacker, M. P.; Hazelhurst, L.; Menta, E.; Oliva, A.; Spinelli, S.; Beggiolin, G.; Giuliani, F. G.; Pezzoni, G.; Tognella, S., *Curr. Med. Chem.* **1995**, *2*, 803–824; (b) Skibo, E. B. *Curr. Med. Chem.* **1996**, *2*, 900–931; (c) Jaffar, M.; Naylor, M. A.; Robertson, N.; Stratford, I. J. *Anticancer Drug Design* **1998**, *13*, 593–609; (d) Beall, H. D.; Winski, S.; Swann, E.; Hudnott, A. R.; Cotterill, A. S.; O'Sullivan, N.; Green, S. J.; Bien, R.; Siegel, D.; Ross, D.; Moody, C. J. *J. Med. Chem.* **1998**, *41*, 4755–4766; (e) Lee, K. H. *Med. Res. Rev.* **1999**, *19*, 569–596; (f) Phillips, R. M.; Naylor, M. A.; Jaffar, M.; Doughty, S. W.; Everett, S. A.; Breen, A. G.; Choudry, G. A.; Stratford, I. J. *J. Med. Chem.* **1999**, *42*, 4071–4080; (g) Schulz, W.; Skibo, E. B. *J. Med. Chem.* **2000**, *43*, 629–638.
3. See, for instance: (a) Cory, R. M.; McPhail, C. L.; Dikmans, A. J. *Tetrahedron Lett.* **1993**, *34*, 7533–7536; (b) Smirnov, A.; Fulton, D. B.; Andreotti, A.; Petrich, J. W. *J. Am. Chem. Soc.* **1999**, *121*, 7979–7988; (c) Zhang, J.; Ho, D. M.; Pascal, Jr., R. A. *Tetrahedron Lett.* **1999**, *40*, 3859–3862; (d) Watson, Jr., J. A.; Pascal, Jr., R. A.; Ho, D. M.; Kilway, K. V. *Tetrahedron Lett.* **2000**, *41*, 5005–5008.
4. (a) Pindur, U. *Chimia* **1990**, *44*, 406–412; (b) Pindur, U. *Heterocycles* **1988**, *27*, 1253–1268; (c) Pindur, U.; Pfeuffer, L. *Chem.-Ztg.* **1986**, *110*, 95–99.
5. (a) Prassad, K. K. *Tetrahedron Lett.* **1974**, *15*, 1361–1362; (b) Corradini, M. G.; Prota, G. *Gazz. Chim. It.* **1989**, *119*, 153; (c) Henrion, J. C.; Jacquet, B.; Hocquauv, M.; Lion, C. *Bull. Soc. Chim. Belg.* **1994**, *103*, 163.
6. Compound **3a** was prepared in 59% overall yield by reaction between compounds **1a** and **2a** (2 equivalents) in ethanol containing a trace of hydrochloric acid, at room temperature for 18 h. Data for **3a**: Mp 299–301°C; ν (KBr): 3437 (NH), 1631 (CO) cm^{-1}; ^1H NMR (d_5-pyridine, 250 MHz) δ 8.25 (s, 1H, H-2′); 7.92 (d, 1H, $J=7.6$ Hz, H-4′); 7.50–7.20 (m, 4H, H-5′,6′,7′,7); 6.51 (s, 1H, H-3); 3.62 (s, 3H, N–Me); 2.55 (s, 3H, C_4–Me); ^{13}C NMR (d_5-pyridine, 63 MHz) δ 187.2 (C-8); 182.4 (C-5); 164.5 (C-2); 153.2 (C-4); 145.5 (C-8a); 143.7 (C-6); 140.3 (C-7a′); 140.2 (C-2′); 129.1 (C-3a′); 128.5 (C-3); 125.3, 125.0 and 124.7 (C-7, C-6′, C-5′); 123.3 (C-4′); 117.2 (C-4a); 113.4 (C-7′); 110.4 (C-3′); 35.4 (N–Me); 24.8 (C_4–Me). Anal. Calcd for $C_{19}H_{14}N_2O_3$: C, 71.69; H, 4.43; N, 8.80. Found: C, 71.38; H, 5.11; N, 8.24.
7. These oxidation steps are coupled with reduction of the starting quinones to the corresponding hydroquinones, which were isolated by evaporation of the reaction mixtures after filtration of compounds **4**.

8. Data for **4a**: Mp >300 °C. *v* (KBr): 1648 (C=O); ^{1}H NMR (d_6-DMSO, 250 MHz) δ 9.50 (br. s, 2H, NH); 9.07 (d, 1H, $J=7.5$ Hz, H-12); 7.80–7.45 (m, 3H, H-13,14,15); 6.72, 6.70 (2 s, 2H, H-3,9); 4.00 (s, 3H, N_{16}–CH_3); 2.79, 2.68 (2 s, 6H, $C_{4,10}$–CH_3). Anal. Calcd for $C_{29}H_{17}N_3O_6$: C, 69.18; H, 3.37; N, 8.34. Found: C, 68.95; H, 3.03; N, 7.99.
9. This assumption is in agreement with our previous observations on the Diels–Alder regiochemistry of 2,5,8(1*H*)-quinolinetriones. See: (a) Pérez, J. M.; Vidal, L.; Grande, M. T.; Menéndez, J. C.; Avendaño, C. *Tetrahedron* **1994**, *50*, 7923–7932; (b) Pérez, J. M.; Avendaño, C.; Menéndez, J. C. *Tetrahedron* **1995**, 51, 6573–6586.
10. For some examples, see: (a) Blanco, M. M.; Avendaño, C.; Cabezas, N.; Menéndez, J. C. *Heterocycles* **1993**, 36, 1387–1398; (b) Alonso, M. A.; Blanco, M. M.; Avendaño, C.; Menéndez, J. C. *Heterocycles* **1993**, *36*, 2315–2325; (c) Kitahara, Y.; Nakahara, S.; Shimizu, M.; Yozenawa, T.; Kubo, A. *Heterocycles* **1993**, *36*, 1909–1924.
11. Perumal, P. T.; Bhat, M. V. *Synthesis* **1979**, 205.
12. Data for **5**: Mp >320 °C. *v* (KBr) 1652 (C=O) cm^{-1}. ^{1}H NMR (d_6-DMSO, 250 MHz) δ 9.95 (br. s, 1H, NH); 9.60 (s, 1H, OH); 9.11 (s, 1H, OH); 8.93 (d, 1H, $J=7.5$ Hz, H-14); 7.82–7.70 (m, 2H, H-11,13); 7.45 (t, 1H, $J=7.0$ Hz, H-12); 6.93 (s, 1H, H-7); 6.63 (m, 1H, H-2); 3.89 (m, 3H, N–CH_3); 2.66 (s, 3H, C_1–CH_3). MS (ESI): 527 and 525 (M^++23); 503 and 505 (M^++1); 424 (M^++1–Br); 408 (M^+–Br–CH_3). Anal. Calcd for $C_{25}H_{15}N_2O_5$: C, 59.66; H, 3.00; N, 5.57. Found: C, 59.48; H, 2.95; N, 5.62.
13. Data for **6**: Mp >320 °C. *v* (KBr) 1653 cm^{-1}. ^{1}H NMR (d_6-DMSO, 250 MHz) δ 12.30 (br. s, 2H, $N_{1,21}$–H); 10.91 (br. s, 1H, OH); 9.82 (br. s, 1H, OH); 8.92 (d, 2H, $J=7.5$ Hz, H-6,16), 7.80–7.68 (m, 4H, H-7,9,13,15), 7.44 (t, 2H, $J=7.5$ Hz, H-8,14), 6.63 (s, 2H, H-3,19), 3.88 (s, 6H, 2 N–CH_3), 2.65 (s, 6H, $C_{4,18}$–CH_3). MS (ESI), m/z: 739 (M^++1). Anal. Calcd for $C_{44}H_{24}N_4O_8$: C, 71.74; H, 3.28; N, 7.61. Found: C, 71.40; H, 3.00; N, 7.31.
14. Data for **7**: Mp >320 °C. *v* (KBr) 1653 cm^{-1}. ^{1}H NMR (d_6-DMSO, 250 MHz) δ 12.25 (br. s, 2H, $N_{1,13}$–H); 9.87 (br. s, 2H, OH); 8.93 (d, 2H, $J=7.5$ Hz, H-6,18), 7.80–7.68 (m, 4H, H-7,9,19,21), 7.44 (t, 2H, $J=7.5$ Hz, H-8,20), 6.63 (d, 2H, $J=1.2$ Hz, H-3,15), 3.89 (s, 6H, 2 N–CH_3), 2.65 (s, 6H, $C_{4,16}$–CH_3). A solid-state ^{13}C NMR experiment showed three carbonyl signals, at 211.3, 206.1 and 192.1 ppm. MS (ESI), m/z: 739 (M^++1). Anal. Calcd for $C_{44}H_{24}N_4O_8$: C, 71.74; H, 3.28; N, 7.61. Found: C, 71.40; H, 3.00; N, 7.31.
15. See, for instance: (a) Gómez-Bengoa, E.; Echavarren, A. M. *J. Org. Chem.* **1991**, *56*, 3497–3501; (b) Lévesque, S.; Brassard, P. *Heterocycles* **1994**, *38*, 2205–2218; (c) Tapia, A. R.; Quintanar, C.; Valderrama, J. A. *Heterocycles* **1996**, *43*, 447; (d) Blanco, M. M.; Avendaño, C.; Menéndez, J. C. *Tetrahedron* **1999**, *55*, 12637–12646; (e) Pérez, J. M.; López-Alvarado, P.; Avendaño, C.; Menéndez, J. C. *Tetrahedron* **2000**, *56*, 1561–1567.
16. The electrospray MS spectrum of a DMSO solution of compound **5** kept at room temperature for a few days showed peaks due to the M+1 ions of both **5** (m/z 503 and 505) and **9** (m/z 501 and 503), proving the ease of oxidation of **5**.