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Synthesis and structural characterization of novel β-tropolone derivatives

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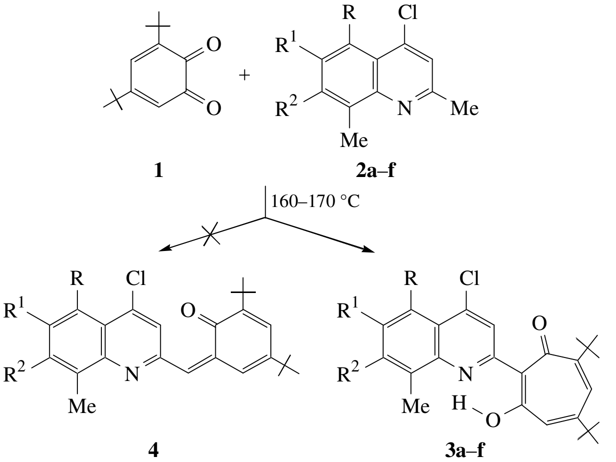
A novel method for the synthesis of β-tropolone derivatives by coupling 3,5-di(*tert*-butyl)-1,2-benzoquinone 1 with 2-methylquinolines 2 was developed, and a series of 2-(quinolin-2′-yl)-5,7-di(*tert*-butyl)-1,3-tropolones 3 were prepared.



a R = R¹ = R² = H
b R = R² = H, R¹ = Me
c R = R¹ = H, R² = Me
d R = NO_2, R¹ = R² = H
e R = NO_2, R¹ = Me, R² = H
f R = NO_2, R¹ = H, R² = Me

Scheme 1

Although the base-promoted condensation of carbonyl-containing compounds with methylene active compounds is one of the best studied routes to the formation of carbon–carbon bonds, no *o*-quinones have been thus far brought into this reaction. With the goal of the synthesis of 1-(2′-quinolyl)methylene-3,5-di(*tert*-butyl)-2-benzoquinones **4**, we studied the condensation of 3,5-di(*tert*-butyl)-1,2-benzoquinone **1** with a series of 2-methylquinolines **2**. The reaction proceeds under refluxing *o*-xylene solutions of equimolar amounts of **1** and **2** for 6 h or on melting the reactants and holding the melt at 160–170 °C for 15–20 min to give previously unknown β-tropolones **3** in 10–15% yields† rather than expected o-methylenequinones **4** (Scheme 1).

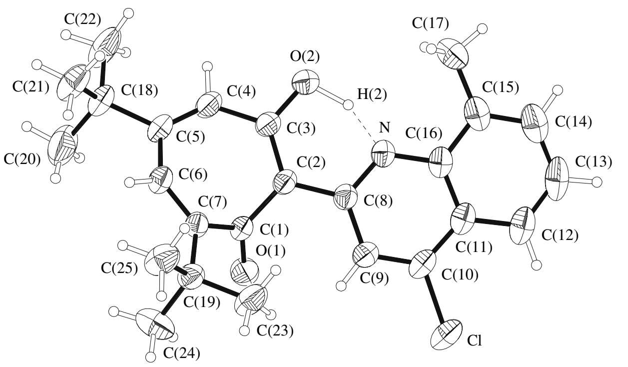
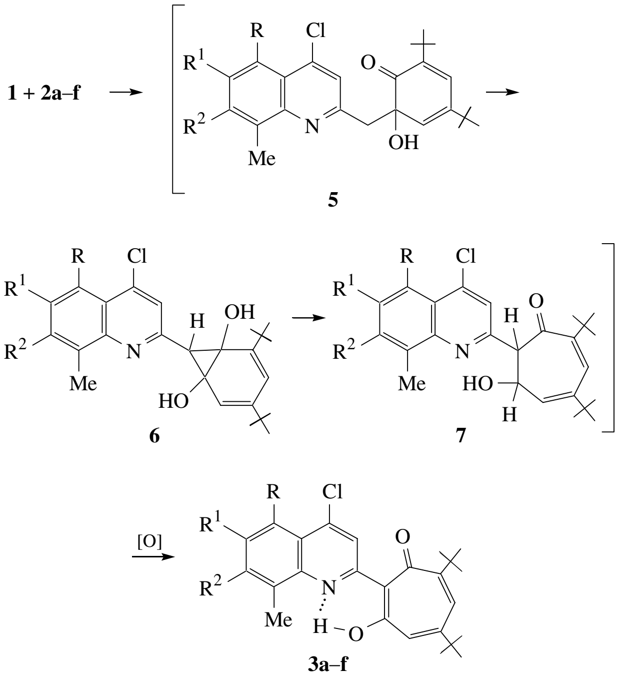


Figure 1 Molecular structure of compound **3a**. Selected bond lengths (Å): O(1)–C(1) 1.225(2), O(2)–C(3) 1.317(3), O(2)–H(2) 1.040(3), N–C(8) 1.340(3), C(1)–C(2) 1.476(3), C(1)–C(7) 1.476(3), C(2)–C(3) 1.400(3), C(2)–C(8) 1.462(3), C(3)–C(4) 1.453(3), C(4)–C(5) 1.350(3), C(5)–C(6) 1.451(3), C(6)–C(7) 1.342(3), C(8)–C(9) 1.423(3); selected bond angles (°): C(3)–O(2)–H(2) 103.8(13), C(8)–N–H(2) 101.5(9), O(1)–C(1)–C(2) 127.2, C(3)–C(2)–C(1) 120.7(2), C(3)–C(2)–C(8) 119.4(2), O(2)–C(3)–C(2) 122.0(2), N–C(8)–C(2) 117.5 (2).



Scheme 2

Compounds **3** were characterised by ¹H NMR and IR spectroscopy and mass spectrometry. The hydroxyl group of the seven-membered ring is H-bonded to the quinoline nitrogen, which explains the unusually high downfield chemical shifts (18–19 ppm) of the chelated hydroxyl protons of **3**.

The structure of one of the β-tropolones, **3a**, was determined by X-ray crystallography‡ (Figure 1). The compound acquires an *s-cis* conformation with respect to the C(2)–C(8) bond, which ensures the formation of a stable six-membered chelate ring due to the strong O–H···N hydrogen bond. The O···N distance of 2.455(7) Å is among the shortest O···N distances known for similar systems with intramolecular O–H···N bonds.[1] The H-bonded chelate ring, the quinolyl fragment and C(1)–C(4) atoms of the tropolone moiety of the molecule lie in a common plane [with a small deviation of the C(4) centre], whereas the molecule is folded along the C(1)–C(4) line with a dihedral angle of 37.9°.

The mechanism of the transformation involves, most probably, the intermediacy of norcaradiene derivatives **6** undergoing thermal isomerization to 2,3-dihydrotropones **7**, which are then oxidised by quinones **1** to the final products. In accordance with this mechanism, the yields of β-tropolones **3** can be doubled when doubling the amount of quinone **1**, *i.e.*, using reactants **1** and **2** in a 2:1 ratio.

The above reaction represents a novel method for the synthesis of the derivatives of β-tropolones. The previously known approach to this class of compounds is based on the multistep transformation that starts from the reduction of 3,4,5-trimethoxybenzoic acid to 3,5-dimethoxy-4,4-dihydrobenzoic acid followed by thermal expansion of the six-membered ring of the latter to give 3,6-dimethoxy-4,5-dihydrotropone and the subsequent oxidation of the latter.[2] The method has a very narrow scope. In contrast, the above reactions are expected to open a way to the preparation of a wide variety of 2-substituted 1,3-tropolones.

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† *Synthesis and spectroscopic properties of 2-(quinolin-2′-yl)-5,7-di-(*tert*-butyl)-1,3-tropolones* **3a**–**f**.

General procedure. Method A. A mixture of 10 mmol of 3,5-di(*tert*-butyl)-1,2-benzoquinone **1**, 5 mmol of 2-methylquinolines **2a**–**f** and 0.2 g of *p*-toluenesulfonic acid was melted and held at 160–170 °C for 15–20 min. After cooling, the melt was dissolved in hexane–chloroform (2:1) and passed through an aluminum oxide column ($d = 15$ mm, $l = 750$ mm); the above solution was used as an eluent. The first colourless fraction did not contain compounds **3**, which appeared in the second bright yellow fraction. It was collected and evaporated. The precipitates were crystallised from nitromethane to give high melting yellow crystals of **3a**–**f**.

Method B. A solution of 10 mmol of **1**, 5 mmol of 2-methylquinolines **2a**–**f** and 200 mg of *p*-tolenesulfonic acid in 10 ml of *o*-xylene was refluxed for 6 h. The subsequent isolation and purification of compounds **3a**–**f** was similar to that in *Method A*.

^{1}H NMR spectra were recorded on a Varian Unity-300 Spectrometer with TMS as a standard. Mass spectra were measured on a Finnigan MAT.INOS 50 mass spectrometer.

*2-(4′-Chloro-8′-methylquinolin-2′-yl)-5,7-di(*tert*-butyl)-1,3-tropolone* **3a**: 23% yield, mp 189–191 °C. ^{1}H NMR (CDCl$_3$) δ: 1.24 (s, 9H, 5-CMe$_3$), 1.37 (s, 9H, 7-CMe$_3$), 2.72 (s, 3H, 8′-Me), 6.65 (d, 1H, 4-H, J 1.7 Hz), 6.72 (d, 1H, 6-H, J 1.7 Hz), 7.41 (t, 1H, 6′-H, J 7.7 Hz), 7.54 (d, 1H, 7′-H, J 7.6 Hz), 7.95 (d, 1H, 5′-H, J 7.6 Hz), 8.23 (s, 1H, 3′-H), 19.12 (s, 1H, 3-OH). IR (ν/cm^{-1}): 1640 (CO). MS, m/z, (%): 409.9 (10) [M$^+$], 381 (90), 366 (100), 350 (40), 338 (40), 310 (45), 57 (40), 41 (50). Calc.: M$^+$ 409.93. Found (%); C, 73.2; H, 6.7; Cl, 8.6; N, 3.4. Calc. for C$_{25}$H$_{28}$ClNO$_2$ (%): C, 73.3; H, 6.7; Cl, 8.4; N, 3.4.

*2-(4′-Chloro-6′,8′-dimethylquinolin-2′-yl)-5,7-di(*tert*-butyl)-1,3-tropolone* **3b**: 26% yield, mp 198–201 °C. ^{1}H NMR (CDCl$_3$) δ: 1.23 (s, 9H, 5-CMe$_3$), 1.37 (s, 9H, 7-CMe$_3$), 2.51 (s, 3H, 8′-Me), 2.68 (s, 3H, 6′-Me), 6.65 (d, 1H, 4-H, J 1.88 Hz), 6.73 (d, 1H, 6-H, J 1.88 Hz), 7.43 (s, 1H, 7′-H), 7.78 (s, 1H, 5′-H), 8.23 (s, 1H, 3′-H), 19.19 (s, 1H, 3-OH). IR (ν/cm^{-1}): 1641 (CO). MS, m/z (%): 423.9 (8) [M$^+$], 395 (88), 380 (100), 352 (25), 57 (50). Calc.: M$^+$ 423.99. Found (%); C, 73.6; H, 7.0; Cl, 8.1; N, 3.3. Calc. for C$_{26}$H$_{30}$ClNO$_2$ (%): C, 73.7; H, 7.1; Cl, 8.4; N, 3.3.

*2-(4′-Chloro-7′,8′-dimethylquinolin-2′-yl)-5,7-di(*tert*-butyl)-1,3-tropolone* **3c**: 24% yield, mp 174–176 °C. ^{1}H NMR (CDCl$_3$) δ: 1.23 (s, 9H, 5-CMe$_3$), 1.37 (s, 9H, 7-CMe$_3$), 2.52 (s, 3H, 8′-Me), 2.63 (s, 3H, 7′-Me), 6.64 (d, 1H, 4-H, J 1.86 Hz), 6.68 (d, 1H, 6-H, J 1.86 Hz), 7.37 (d, 1H, 6′-H, J 8.5 Hz), 7.89 (d, 1H, 5′-H, J 8.5 Hz), 8.20 (s, 1H, 3′-H), 19.31 (s, 1H, 3-OH). IR (ν/cm^{-1}): 1637 (CO). MS, m/z (%): 423.9 (2) [M$^+$], 385 (88), 380 (100), 352 (28), 338 (13), 57 (35), 41 (38). Calc.: M$^+$ 423.99. Found (%); C, 73.6; H, 6.9; Cl, 8.2; N, 3.2. Calc. for C$_{26}$H$_{30}$ClNO$_2$ (%): C, 73.7; H, 7.1; Cl, 8.4; N, 3.3.

*2-(4′-Chloro-5′-nitro-8′-methylquinolin-2′-yl)-5,7-di(*tert*-butyl)-1,3-tropolone* **3d**: 20% yield, mp 210–212 °C. ^{1}H NMR (CDCl$_3$) δ: 1.23 (s, 9H, 5-CMe$_3$), 1.37 (s, 9H, 7-CMe$_3$), 2.73 (s, 3H, 8′-Me), 6.68 (d, 1H, 4-H, J 1.82 Hz), 6.83 (d, 1H, 6-H, J 1.82 Hz), 7.57–7.64 (m, 2H, 6′,7′-H), 8.32 (s, 1H, 3′-H), 19.0 (s, 1H, 3-OH). IR (ν/cm^{-1}): 1640 (CO). Found (%); C, 65.9; H, 5.9; Cl, 7.8; N, 6.0. Calc. for C$_{25}$H$_{27}$ClN$_2$O$_4$ (%): C, 66.0; H, 5.9; Cl, 7.8; N, 6.2.

*2-(4′-Chloro-5′-nitro-6′,8′-dimethylquinolin-2′-yl)-5,7-di(*tert*-butyl)-1,3-tropolone* **3e**: 21% yield, mp 223–225 °C. ^{1}H NMR (CDCl$_3$) δ: 1.25 (s, 9H, 5-CMe$_3$), 1.38 (s, 9H, 7-CMe$_3$), 2.40 (s, 3H, 8′-Me), 2.70 (s, 3H, 6′-Me), 6.68 (d, 1H, 4-H, J 1.82 Hz), 6.82 (d, 1H, 6-H, J 1.82 Hz), 7.50 (s, 1H, 7′-H), 8.28 (s, 1H, 3′-H), 18.02 (s, 1H, 3-OH). IR (ν/cm^{-1}): 1635 (CO). Found (%); C, 66.6; H, 6.2; Cl, 7.4; N, 5.9. Calc. for C$_{26}$H$_{29}$ClN$_2$O$_4$ (%): C, 66.6; H, 6.2; Cl, 7.6; N, 6.0.

*2-(4′-Chloro-5′-nitro-7′,8′-dimethylquinolin-2′-yl)-5,7-di(*tert*-butyl)-1,3-tropolone* **3f**: 19% yield, mp 234–236 °C. ^{1}H NMR (CDCl$_3$) δ: 1.24 (s, 9H, 5-CMe$_3$), 1.39 (s, 9H, 7-CMe$_3$), 2.54 (s, 3H, 8′-Me), 2.65 (s, 3H, 7′-Me), 6.67 (d, 1H, 4-H, J 1.87 Hz), 6.81 (d, 1H, 6-H, J 1.87 Hz), 7.51 (s, 1H, 6′-H), 8.25 (s, 1H, 3′-H), 18.30 (s, 1H, 3-OH). IR (ν/cm^{-1}): 1637 (CO). Found (%); C, 66.6; H, 6.1; Cl, 7.5; N, 5.9. Calc. for C$_{26}$H$_{29}$ClN$_2$O$_4$ (%): C, 66.6; H, 6.2; Cl, 7.6; N, 6.0.

‡ *X-Ray crystal data*. Compound **3a**: C$_{25}$H$_{28}$NO$_2$Cl, $M = 409.93$, monoclinic, $a = 14.057(8)$, $b = 13.199(9)$, $c = 11.923(7)$ Å, $\beta = 90.95(5)°$, $V = 2212(2)$ Å^3, $z = 4$, $d_\text{calc} = 1.231$ g cm^{-3}, space group $P2_1/c$, μ(MoKα) = 1.93 cm^{-1}.

The data were measured on a KUMA-DIFFRACTION (Poland) KM-4 autodiffractometer with graphite monochromated MoKα radiation using an $\omega/2\theta$ scan technique, $2\theta \leq 52.18°$. The structure was solved by direct methods using the SHELXS-97 program package and refined by a full-matrix least-squares procedure in an anisotropic approximation for all non-hydrogen atoms with the use of the SHELXL-97 program. The final refinement converged at $R_1 = 0.034$, $wR_2 = 0.090$ for 3459 observed reflections with $I \geq 2\sigma(I)$; $R_1 = 0.062$, $wR_2 = 0.115$ for all measured reflections, GOOF = 1.085.

Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). These data can be obtained free of charge *via* www.ccdc.cam.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference number 223129. For details, see ‘Notice to Authors’, *Mendeleev Commun.*, Issue 1, 2003.