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# Synthesis of 2-(2-quinoxalyl)-β-tropolones

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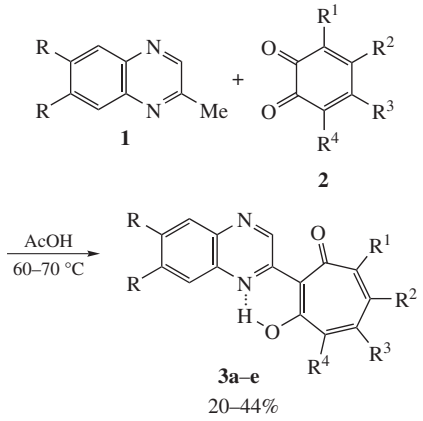
2-(2-Quinoxalyl)-β-tropolones have been prepared by the oxidizing condensation of 2-methylquinoxalines with 3,5-di(*tert*-butyl)-1,2-benzoquinone in an acetic acid solution and their structure has been studied using X-ray diffraction and DFT B3LYP/6-31G** calculations.

Tropolone natural compounds and synthetic tropolone derivatives have attracted significant interest due to the unique structure and properties of a seven-membered tropolone ring and a wide range of potent biological activities. The vast majority of the currently studied tropolones relates to α-tropolones, whereas β-tropolones (3-hydroxytropones) have yet received much less attention mostly because of the lack of expedient methods for their synthesis.[1–3] Currently, the most promising approach to functionalized β-tropolones is based on the acid-catalyzed reaction between methylene-active compounds and *o*-quinones occurring with the expansion of the six-membered aromatic ring.[4,5] This reaction is highly sensitive to the structural environment of the methylene group. Whereas 2-methylquinolines readily react with 3,5-di(*tert*-butyl)-1,2-benzoquinone to give 2-(2-quinolyl)-β-tropolone derivatives,[5] the reactions of 3,5-di(*tert*-butyl)-1,2-benzoquinone and 4,6-di(*tert*-butyl)-3-nitro-1,2-benzoquinone with 2-methylbenzimidazole[6] and 1,2,3-trimethylbenzimidazolium iodide[7] under the same conditions yield no β-tropolones resulting in the formation of polycyclic or spiroheterocyclic compounds.




**a** R = $R^2$ = $R^4$ = H, $R^1$ = $R^3$ = $Bu^t$
**b** R = $R^2$ = H, $R^1$ = $R^3$ = $Bu^t$, $R^4$ = $NO_2$
**c** R = F, $R^1$ = $R^3$ = $Bu^t$, $R^2$ = $R^4$ = H
**d** R = F, $R^1$ = $R^3$ = $Bu^t$, $R^2$ = H, $R^4$ = $NO_2$
**e** R = F, $R^1$ = $R^2$ = $R^3$ = $R^4$ = Cl

**Scheme 1**

Here, we report on the synthesis of new 2-hetaryl derivatives of β-tropolones obtained by coupling quinones **2** with 2-methylquinoxaline and 2-methyl-6,7-difluoroquinoxaline (Scheme 1). The maximal yields of β-tropolones were obtained when heating acetic acid solutions with quinones **2** taken in a double excess at 60–70 °C for 5–30 h. The excessive amount of **2** serves as an oxidant at the final stage of the reaction (Scheme 2). In spite of mild conditions of the reaction, it is accompanied by significant tarring and affords 2-(2-quinoxalyl)-β-tropolones **3**† in yields (20–44%) lower than those of 2-(2-quinolyl)-β-tropolones.[5] Along with β-tropolones **3b**, **3d**, the reaction of 2-methylquinoxalines **1** with 4,6-di(*tert*-butyl)-3-nitro-1,2-benzoquinone affords tropolones **3a**, **3c** isolated in trace amounts (2–3%).

The mechanism of the formation of 2-(2-quinoxalyl)-β-tropolones **3** corroborated by detailed quantum chemical calculations of critical parts of the potential energy surface for the model reaction of 2-methylquinoline with an *o*-quinone[5] is depicted in Scheme 2. No formation of isomers **7** was detected under the reaction conditions because at the initial stage of the reaction, the attack of **1** at the alternative unsubstituted position of a molecule of **2** is sterically hindered by a neighboring bulky *tert*-butyl group. The molecular structure of 2-(2-quinoxalyl)-β-tropolone **3c** was determined by X-ray crystallography‡ (Figure 1).

Compound **3c** acquires *s-cis* conformation with respect to the C(2)–C(8) bond that ensures the formation of a stable six-membered chelate ring due to the formation of a strong O–H···N ≡ O···H–N hydrogen bond. The N(1)–H(1) distance (0.86 Å) is typical of covalent N–H bonds, whereas the H(1)–O(2) distance (1.81 Å) is much longer than that expected for a covalent O–H bond. These data point to stabilization in crystal of the aminoenone tautomeric form **3c**(NH). The O···N distance in **3c** is very short, being 0.45 Å shorter than the corresponding van der Waals contact and the signals of the chelated proton appear in the low-field region (16–18 ppm) of the $^1$H NMR spectrum. These structural features are characteristic of the resonance assisted[8] intramolecular O···H···N bonds. The H-bonded chelate ring, the quinoxalyl fragment and the C(2) atom of the tropolone moiety of **3c**(NH) lie in common plane A (with a deviation of less than 0.010 Å). Another plane B (with a deviation of less than 0.052 Å) is formed by the C(2), C(4), C(5), C(6) and C(7) atoms

of the tropolone ring. The O(1), C(1), C(2) and C(7) atoms lie in common plane C (deviations are less than 0.014 Å), which is turned off plane B by 49.1°. The tropolone ring of **3c**(NH) is folded along the C(1)–C(4) line. The X-ray structural data (Figure 1) suggest that the aminoenone structure represents the most stable tautomeric form of 5,6-difluoro-2-(2-quinoxalyl)-β-tropolone **3c** in a crystal.

To check whether this stabilization is an intrinsic property of the molecule or it is provided by intermolecular interactions in the crystal lattice, we performed DFT B3LYP/6-31G** calculations[§]

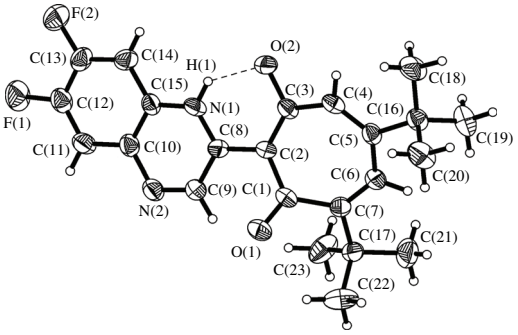
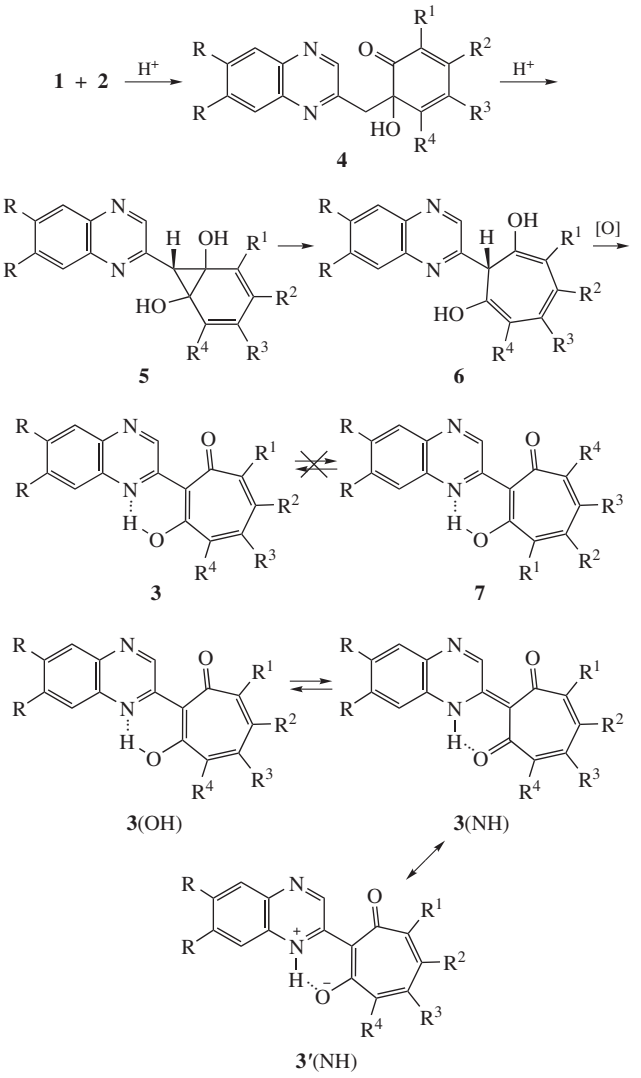



**Figure 1** Molecular structure of **3c**(NH). Thermal ellipsoids are drawn on the 30% probability level. The O(2)···N(1) distance is 2.508°. Selected bond lengths (Å): N(1)–H(1) 0.915, O(1)–C(1) 1.214(7), O(2)–C(3) 1.367(7), N(1)–C(8) 1.324(7), C(1)–C(2) 1.466(8), C(1)–C(7) 1.505(8), C(2)–C(3) 1.360(8), C(2)–C(8) 1.471(8), C(3)–C(4) 1.457(8), C(4)–C(5) 1.345(8), C(5)–C(6) 1.449(8), C(6)–C(7) 1.331(8), F(1)–C(12) 1.349(7), F(2)–C(13) 1.349(7). Selected bond angles (°): O(1)–C(1)–C(2) 120.7(6), C(3)–C(2)–C(1) 121.3(6), C(3)–C(2)–C(8) 121.2(6), C(1)–C(2)–C(8) 117.2(6), C(2)–C(8)–C(9) 123.8(6), N(1)–C(8)–C(2) 119.0(6).

of the (NH) and (OH) tautomeric forms of 2-(2-quinoxalyl)-β-tropolones **3a** and **3c** in a gas phase and DMSO solution. The computed energetic characteristics of the tautomeric forms **3a** and **3c** are given in Table 1.




**Scheme 2**

† *General procedure for the synthesis of 2-(2-quinoxalyl)-1,3-tropolones* **3a–e**. A solution of 3,5-di(*tert*-butyl)-1,2-benzoquinone **2** (10 mmol) and 2-methylquinoxaline **1** (5 mmol) in 10 ml of acetic acid was heated at 60–70 °C for 5 h. After cooling the solution and diluting it with water, the precipitate was filtered off and dissolved in chloroform (20 ml). The chloroform solution was washed with water (3×50 ml), dried over $Na_2SO_4$ for 3–4 h and passed through an aluminium oxide column (eluent: hexane–chloroform, 1:1). A bright yellow fraction was collected to give **3a** in 44% yield after removing the solvent and crystallization. Yellow crystals, mp 126–127 °C (from propan-2-ol). $^1$H NMR ($CDCl_3$) $\delta$: 1.29 (s, 9H, 5-$CMe_3$), 1.45 (s, 9H, 7-$CMe_3$), 6.71 (d, 1H, 4-H, *J* 1.7 Hz), 6.92 (d, 1H, 6-H, *J* 1.7 Hz), 7.6–8.2 (m, 4H, arom.), 9.44 (s, 1H, 3′-H), 17.17 (s, 1H, 3-OH). IR ($\nu$/cm$^{-1}$): 1633 (CO). MS, *m*/*z* (%): 363 (100) $[M + H]^+$, 335 (76) $[M - CO]^+$, 307 (74) $[M - CH_2{=}CMe_2]^+$, 289 (24) $[M - CH_2{=}CMe_2 - H_2O]^+$, 279 (9) $[M - CH_2{=}CMe_2 - CO]^+$, 251 (16) $[M - (CH_2{=}CMe_2)_2]^+$. Found (%): C, 76.44; H, 7.11; N, 7.82. Calc. for $C_{23}H_{26}N_2O_2$ (%): C, 76.21; H, 7.23; N, 7.73.

*5,7-Di*(tert-*butyl*)*-2-(2-quinoxalyl)-4-nitro-3-hydroxytropone* **3b** (yield 40%). Yellow crystals, mp 187–189 °C (from propan-2-ol). $^1$H NMR ($CDCl_3$) $\delta$: 1.35 (s, 18H, 5,7-$CMe_3$), 6.52 (s, 1H, 6-H), 7.70–8.10 (m, 4H, quinoxaline), 9.54 (s, 1H, 3′-H), 18.17 (s, 1H, 3-OH). Found (%): C, 67.62; H, 5.94; N, 10.12. Calc. for $C_{23}H_{25}N_3O_4$ (%): C, 67.80; H, 6.18; N, 10.31.

*5,7-Di*(tert-*butyl*)*-2-(6,7-difluoro-2-quinoxalyl)-3-hydroxytropone* **3c** (yield 20%). Yellow crystals, mp 127–129 °C (from ethanol). $^1$H NMR ($CDCl_3$) $\delta$: 1.29 (s, 9H, 5-$CMe_3$), 1.44 (s, 9H, 7-$CMe_3$), 6.71 (d, 1H, 4-H, *J* 1.75 Hz), 6.95 (d, 1H, 6-H, *J* 1.75 Hz), 7.66 (m, 1H, 5′-H), 7.81 (m, 1H, 8′-H), 9.40 (s, 1H, 3′-H), 16.28 (s, 1H, 3-OH). Found (%): C, 69.44; H, 6.11; F, 9.43; N, 7.22. Calc. for $C_{23}H_{24}F_2N_2O_2$ (%): C, 69.33; H, 6.07; F, 9.54; N, 7.03.

*5,7-Di*(tert-*butyl*)*-2-(6,7-difluoro-2-quinoxalyl)-4-nitro-3-hydroxytropone* **3d** (yield 28%). Yellow crystals, mp 255–257 °C (from propan-2-ol). $^1$H NMR ($CDCl_3$) $\delta$: 1.37 (s, 18H, 5,7-$CMe_3$), 6.68 (s, 1H, 6-H), 7.62 (m, 1H, 5′-H), 7.88 (m, 1H, 8′-H), 9.52 (s, 1H, 3′-H), 17.97 (s, 1H, 3-OH). Found (%): C, 62.12; H, 5.14; F, 8.27; N, 9.42. Calc. for $C_{23}H_{23}F_2N_3O_4$ (%): C, 62.30; H, 5.23; F, 8.57; N, 9.48.

*2-(6,7-Difluoro-2-quinoxalyl)-4,5,6,7-tetrachloro-3-hydroxytropone* **3e** (yield 20%). Yellow crystals, mp 212–214 °C (from ethanol). $^1$H NMR ($CDCl_3$) $\delta$: 7.65 (m, 1H, 5′-H), 7.95 (m, 1H, 8′-H), 9.42 (s, 1H, 3′-H), 18.05 (s, 1H, 3-OH). MS, *m*/*z* (%): 396 (20) $[M - CO]^+$, 360 (15), 296 (15), 261 (10), 183 (17), 165 (40), 150 (30), 138 (35), 131 (25), 118 (35), 112 (100), 88 (53), 75 (45), 62 (74), 50 (20), 37 (30). Found (%): C, 42.34; H, 0.81; Cl, 33.24; F, 8.73; N, 6.32. Calc. for $C_{15}H_4Cl_4F_2N_2O_2$ (%): C, 42.49; H, 0.95; Cl, 33.44; F, 8.96; N, 6.61.

‡ *X-Ray diffraction data*. Compound **3c**(NH): $C_{23}H_{24}F_2N_2O_2$, $M$ = 398.44, orthorhombic, $a$ = 9.310(2), $b$ = 12.182(3) and $c$ = 36.362(6) Å, $V$ = = 4124.0(15) Å$^3$, $Z$ = 8, $d_{calc}$ = 1.283 g cm$^{-3}$, space group *Pbca*, $\mu$(MoK$\alpha$) = = 0.94 cm$^{-1}$. The data were measured on a Bruker P-4 autodiffractometer with graphite monochromated MoK$\alpha$ radiation using an $\omega/2\theta$ scan technique, $2\theta < 50.02°$. The structure was solved by a direct method using the SHELXS-97[9] program package and refined by a full-matrix least-squares procedure in an anisotropic approximation for all non-hydrogen atoms. H atoms were located from difference Fourier syntheses and their positions were refined using the riding model.[9] The final refinement converged at $R_1$ = 0.074, $wR_2$ = 0.169 for 1038 observed reflections with $I > 2\sigma(I)$; $R_1$ = 0.220, $wR_2$ = 0.247 for all measured reflections, GOF = = 0.907.

CCDC 664872 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2008.

§ The calculations were performed by using the B3LYP[10–12] hybrid functional with 6-31G** basis set using the GAUSSIAN 03 set of programs. Calculations in solution were performed using the CPCM model[13] with parameters of DMSO solute ($\varepsilon$ = 46.7).

**Table 1** Total energies with zero point energy (ZPE) corrections [$E_{tot}$ + ZPE (a.u.)] and relative energies ($\Delta E$/kcal mol$^{-1}$) of the (NH) and (OH) isomers of 2-(quinoxalinyl)-β-tropolones **3a** and **3c** calculated by the B3LYP/6-311G** method for the gas phase and DMSO solution.

| Structure | $E_{tot}$ + ZPE (gas) | $\Delta E_{gas}$ | $E_{tot}$ + ZPE (sol) | $\Delta E_{sol}$ |
|---|---|---|---|---|
| **3a**(OH) | –1151.647138 | 0 | –1151.653435 | 0 |
| **3a**(NH) | –1151.644598 | 1.59 | –1151.651425 | 1.26 |
| **3c**(OH) | –1350.119151 | 0 | –1350.125055 | 0 |
| **3c**(NH) | –1350.115623 | 2.21 | –1350.122021 | 1.90 |

The hydroxyvinylimino structure of **3**(OH) corresponds to the most stable tautomeric form of an individual molecule in the gas phase and a DMSO-solvated molecule. The energy difference between the (OH) and (NH) tautomers decreases with the increase in the polarity of the environment. The electron withdrawing substituents in the benzene ring of the quinoxaline moiety of 2-(2-quinoxalyl)-β-tropolone **3c** provide for the additional stabilization of the hydroxyvinylimino form as compared to parent compound **3a**. Therefore, the zwitterionic form of **3′**(NH) in a crystal may be regarded as the result of intermolecular interactions in the crystal lattices of tropolone **3c**(NH) (Scheme 2).

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