# Synthesis of β-tropolone and fused heterocycles by acid-catalyzed and photoreactions of *o*-quinones with quinolines and benzimidazoles

**Vladimir I. Minkin,* Vitaly N. Komissarov, and Yurii A. Sayapin**

*Institute of Physical and Organic Chemistry. Rostov University, 194/2 Stachka St. 344090 Rostov on Don. Russian Federation*
*E-mail: minkin@ipoc.rsu.ru*

**Abstract**

The condensation of 3,5-di-(*tert*-butyl)-1,2-benzoquinone **1** with 2-methylquinolines **2** proceeding on refluxing *o*-xylene solutions of the components in the presence of catalytic amounts of *p*-toluenesulfonic acid gives rise to previously unknown β-tropolones **3**. In the case of quinolines **2** containing amino or nitro groups in position 4, the reaction with quinone **8** also leads to the formation of derivatives of a novel heterocyclic system of 2-azabicyclo[3.3.0]octa-2,7-dien-4,6-dione-*N*-oxide **10**. β-Tropolones **3,** under UV-irradiation, in heptane solution undergo an irreversible rearrangement leading to the formation of derivatives of 3-[(1H)-quinolinylidene]-1,6-di-(*tert*-butyl)-bicyclo[3.2.0]hept-6-ene-2,4-dione ring system **14**. The reaction of *o*-quinone **1** with 2-methylbenzimidazole affords the derivatives of a novel condensed heterocyclic system [benzimidazo-(1,2-*b*)][benzimidazo-(1,2-*a*)-pyrrolo(3,4,5-j,i]-13,16-dihydro-16-oxoisoquinoline **17**.

**Keywords**: 2-Azabicyclo[3.3.0]octa-2,7-dien-4,6-dione-*N*-oxides, 3,5-di-(*tert*-butyl)-1,2-benzo-quinone, 2-methylquinolines, photolysis, 2-quinolyl-β-tropolones, X-ray crystallography

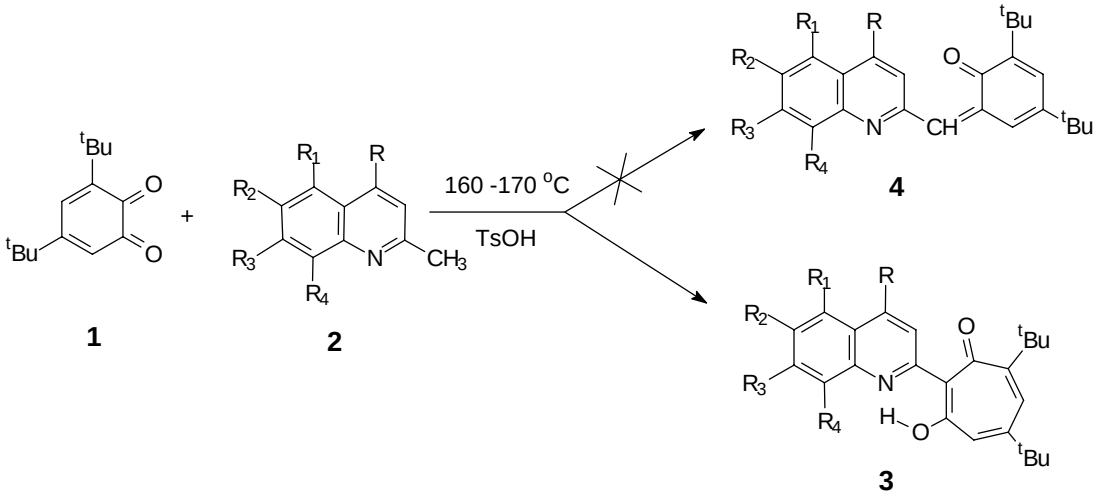
## Contents

## 1. Introduction

The vast majority of currently studied tropolone natural compounds and their synthetic derivatives belong to the class of α-tropolones, i.e. 2-hydroxytropones, whereas β-tropolones (3-hydroxytropones) have hitherto received much less attention, even though such biologically active products as stipitatic (2,6-dihydroxy-4-carboxytropone) and puberulic (2,3,7-trihydroxy-5-carboxytropone) acids, which are mould metabolites of Penicillium family, may be equally assigned to both α- and β-tropolone derivatives.[1] The principal reason for this is the lack of expedient methods for the synthesis of derivatives of β-tropolones. A general approach to β-tropolones is based on the multistep transformation that starts from the reduction of 3,4,5-trimethoxybenzoic acid to 3,5-dimethoxy-1,4-dihydrobenzylic alcohol followed by thermal expansion of the six-membered ring of its tosyl ester to give a mixture of 1,3-dimethoxycycloheptatrienes and the subsequent oxidation of the latter.[2] Other methods include a sequence of procedures[3] employing photooxygenation of cyclohepta-1,3,5-triene with singlet oxygen, the condensation of diazoacetic ester with 1,2-dimethoxybenzene or 1,2,4-trimethoxybenzene[4] and coupling 2-methylfuran with symmetric tetrachloroacetone.[5] We have recently found that an alternative approach to derivatives of β-tropolone derivatives may be based on the acid-catalyzed condensation of *o*-quinones with 2-methylquinolines.[6] Here we report on the further development of this ring-expansion reaction, investigation into its mechanism, a study of the photoinitiated rearrangement of the formed β-tropolones and an extension of the reaction to another heterocyclic system: the benzimidazole.

## 2. Results and Discussion

The condensation of 3,5-di-*tert*-butyl-1,2-benzoquinone **1** with 2-methylquinolines **2** occurs by melting the reactants and holding the temperature at 160–170 $^{o}$C for 15 minutes (method **A**) or under refluxing *o*-xylene solutions of **1** and **2** for 3-6 hours (method **B**) to afford 2-quinolyl-β-tropolones **3** rather than expected o-methylenequinones **4** (Scheme 1). The yields of the products vary from low to moderate in the range of 10-50%. Table 1 contains representative examples of compounds **3** currently obtained and structurally characterized. The maximal yields of the products are achieved at two fold excess of the quinone **1** which also acts as the oxidizer at the final stage of the reaction (Scheme 2). In some cases (e.g. R = Cl, $R_1$=$R_2$=$R_3$=H, $R_4$=$CH_3$) it was possible to isolate the initial intermediate **5** which, treated with *p*-toluenesulfonic acid, gave the corresponding 2-quinolyl-β-tropolones **3** in 80-90% yields.




**Scheme 1**

Compounds **3** were characterized by $^1$H NMR, and IR-spectroscopy and mass-spectrometry. Molecular structures of some of 2-quinolinyl-β-tropolones were determined by X-ray crystallography, two of them being shown in Figures 1 and 2. The compounds **3** acquire *s-cis* conformation with respect to the C(2)-C(8) bonds which ensures the formation of stable six-membered chelate rings due to the strong O-H…N (Fig. 1) or O…H-N (Fig. 2) hydrogen bonds. The O….N distances in the compounds are very short being approximately 0.5Å shorter than the corresponding van der Waals contact. These are among the shortest O…N distances known for similar systems[7] and the H-bonds in the compounds **3** belong to the strongest so-called resonance assisted[8] intramolecular O…H…N bonds. The protons in the hydrogen bridges are characterized by the unusually high downfield chemical shifts 18.00-19.30 ppm (Table 1). The H-bonded chelate rings, the quinolyl fragments and C(1) – C(4) atoms of the tropolone moieties of the molecule lie in a common plane (with a small deviation of the C(4) center), whereas the molecules are folded along the C(1) – C(4) lines (Figs. 1, 2) with the dihedral angles in the range 36-40$^o$. The performed DFT (B3LYP/6-31G**) calculations well reproduce the experimentally determined geometries of the compounds **3** and their main structural features: the very short O…N distances and the folding of the seven-membered rings. The difference between the experimental and calculated bond lengths is 0.01 Å in average. As stems from the X-ray structural data (Figs. 1, 2) and DFT calculations, the hydroxyvinylimino (OH) structure represents the most stable tautomeric form of 2-quinolyl-β-tropolones bearing an electron-withdrawing substituent in the position 4 (R=Cl) in both crystal and the gas phase, whereas the compounds with an electron-releasing substituent (R=NR'R") in that position prefer the aminoenone (NH) tautomeric structure.

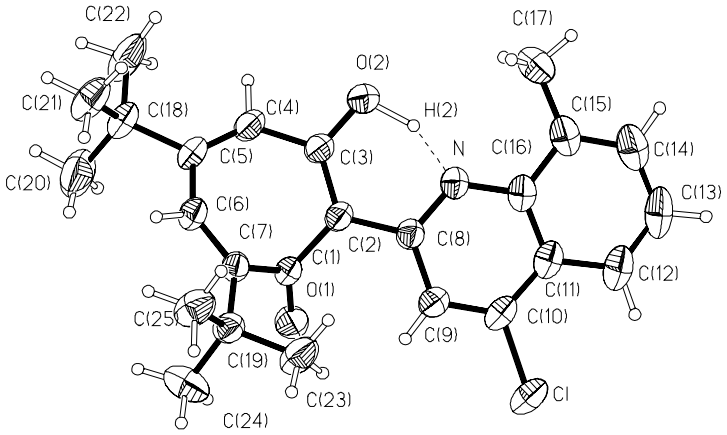



**Figure 1.** Molecular structure of compound **3** (R=Cl, $R_1$=$R_2$=$R_3$=H, $R_4$=$CH_3$) Thermal ellipsoids are drawn on the 50% probability level. The O…N distance is 2.455Å. Selected bond lengths (Å): O(1)-C(1) 1.225(2), O(2)-C(3) 1.317 (3), N-C(8) 1.340 (3), C(1)-C(2) 1.476 (3), C(1)-C(7) 1.476 (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).

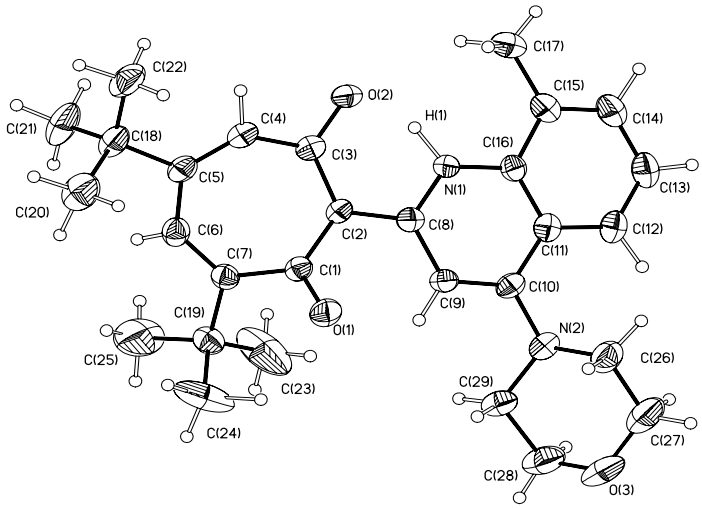
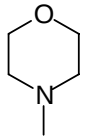



**Figure 2.** Molecular structure of compound **3** (R=$N(CH_2)_4O$, $R_1$=$R_2$=$R_3$=H, $R_4$=$CH_3$). Thermal ellipsoids are drawn on the 50% probability level. The O…N distance is 2.455Å. Selected bond lengths (Å): O(1)-C(1) 1.233(4), O(2)-C(3) 1.305(4), N(1)-H(1) 0.99(4), N(1)-C(8) 1.341 (4), C(1)-C(2) 1.465 (5), C(1)-C(7) 1.504 (4), C(2)-C(3) 1.376 (4), C(2)-C(8) 1.468 (4), C(3)-C(4) 1.470 (4), C(4)-C(5) 1.333 (4), C(5)-C(6) 1.441 (5), C(6)-C(7) 1.333 (4), C(8)-C(9) 1.401 (4); selected bond angles (°) C(3)-O(2)-H(1) 100 (2), C(8)-N(1)-H(1) 108(2), O(1)-C(1)-C(2) 122.9(3), C(3)-C(2)-C(1) 121.9(3), C(3)-C(2)-C(8) 120.3 (3), O(2)-C(3)-C(2) 122.3 (3), N-C(8)-C(2) 115.9 (3).

**Table 1.** 5,7-Di(*tert*-butyl)-2-(quinolyl)-3-hydroxytropones **3**

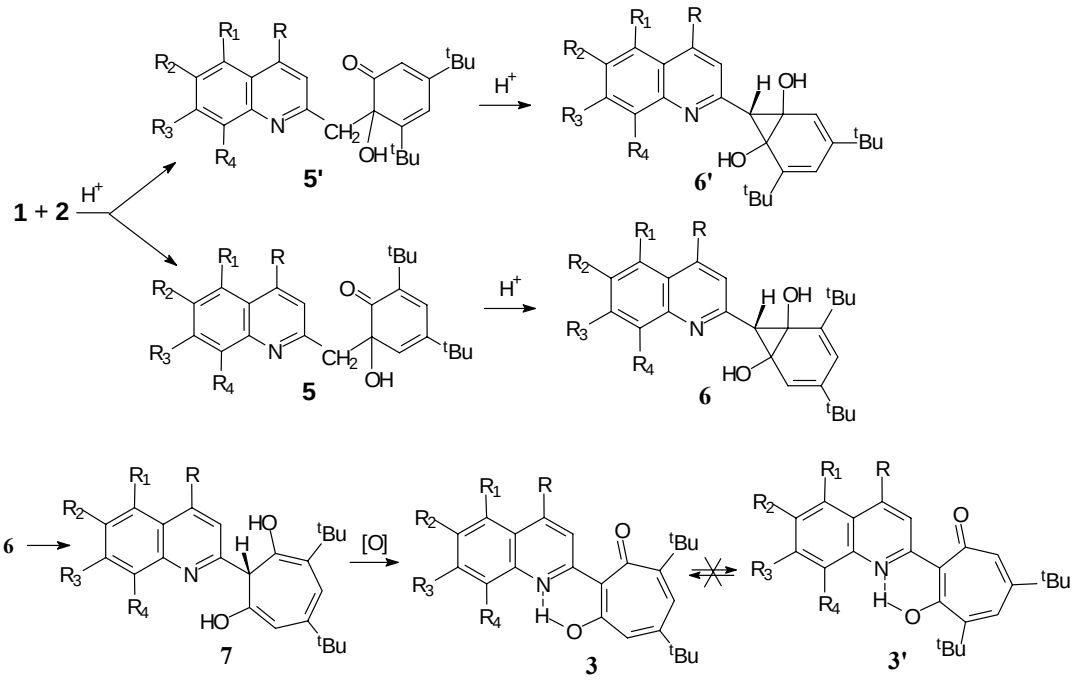
| **3** | R | $R_1$ | $R_2$ | $R_3$ | $R_4$ | Yield, % Method | M.p.,ºC | $\delta_{OH(NH)}$ ppm |
|---|---|---|---|---|---|---|---|---|
| a | H | H | H | H | H | 10 (B) | 126-128 | 19.30 |
| b | Cl | H | H | H | $CH_3$ | 23 (A) 50 (B) | 189-191 | 19.12 |
| c | Cl | H | $CH_3$ | H | $CH_3$ | 26 (A), 36 (B) | 198-201 | 19.19 |
| d | Cl | H | H | $CH_3$ | $CH_3$ | 24 (A), 35 (B) | 174-176 | 19.31 |
| e | Cl | $NO_2$ | H | H | $CH_3$ | 20 (A) | 210-212 | 18.02 |
| f | Cl | $NO_2$ | $CH_3$ | H | $CH_3$ | 21 (A) | 223-225 | 18.02 |
| g | Cl | $NO_2$ | H | $CH_3$ | $CH_3$ | 22 (A) | 234-236 | 18.30 |
| h | | H | H | H | $CH_3$ | 34 (B) | 200-202 | 19.15 |
| i |  | H | $CH_3$ | H | $CH_3$ | 26 (B) | 222-224 | 19.09 |
| j | | $NO_2$ | H | H | $CH_3$ | 26 (B), | 272-274 | 18.90 |
| k | | $NO_2$ | $CH_3$ | H | $CH_3$ | 24 (B) | 203-205 | 18.80 |
| l | $NHC_6H_3(OMe)_2$-2,5 | H | H | H | $CH_3$ | 9 (B) | 235-237 | 18.80 |
| m | $NHC_6H_4Me$-4 | $NO_2$ | H | $CH_3$ | $CH_3$ | 7 (B) | 220-222 | 18.98 |
| n | $CH_3$ | H | H | H | $NO_2$ | 11(B) | 223-225 | 18.00 |

On heating a mixture of a β-tropolone **3** (R=Cl) with an aliphatic, aromatic or heterocyclic amines at 120-130 $^oC$ for 1-3 hours the nucleophilic substitution of a chlorine readily occurs to give various 4-amino derivatives of **3** obtained in 75-95%

The mechanism for the condensation reaction resulting in the formation of 2-quinolyl-β-tropolones **3** is depicted in Scheme 2. At the initial stage of the reaction the aldol condensation of 2-methylquinolines **2** with 3,5-di(*tert*-butyl)-1,2-benzoquinone **1** affords the intermediate adducts **5** some of which were isolated in preparative yields and their structure proved using $^1H$, $^{13}C$ NMR spectroscopy and mass spectra. Compounds **5** undergo cyclization reaction to the norcaradiene derivatives **6** which then rearrange to the dihydrotropolone derivatives **7**. Oxidation of the latter by the excessive amount of 3,5-di-(*tert*-butyl)-1,2-benzoquinone **1** gives rise to the 2-quinolyl-5,7-di(*tert*-butyl)-β-tropolones **3** as the final products. The highest yields of **3** were achieved at the twofold excess of the quinone and its role as the oxidizer was confirmed by the isolation of the corresponding catechol from the reaction mixture.[9] The condensation of 2-methylquinolines **2** with another carbonyl group of **1** is sterically hindered by the vicinal *tert*-butyl substituent which prevents the formation of the isomeric adduct **5'** and blocks the alternative reaction course that would lead to the isomeric 2-quinolinyl-4,6-di-(*tert*-butyl)-β-tropolones **3'**. Other possible routes to **3'** from the energy favorable intermediates **5** are impeded by the high energy barriers against rotation about C(2)-CH bonds in **3**, **6** and **7** (according to the DFT B3LYP/6-31G** estimation their values exceed 22 kcal/mol). According to the B3LYP/6-31G** and HF/6-31G** calculations β-tropolone **3** (R=Cl, $R_4$=$CH_3$, $R_1$-$R_3$=H) is 2-4 kcal/mol

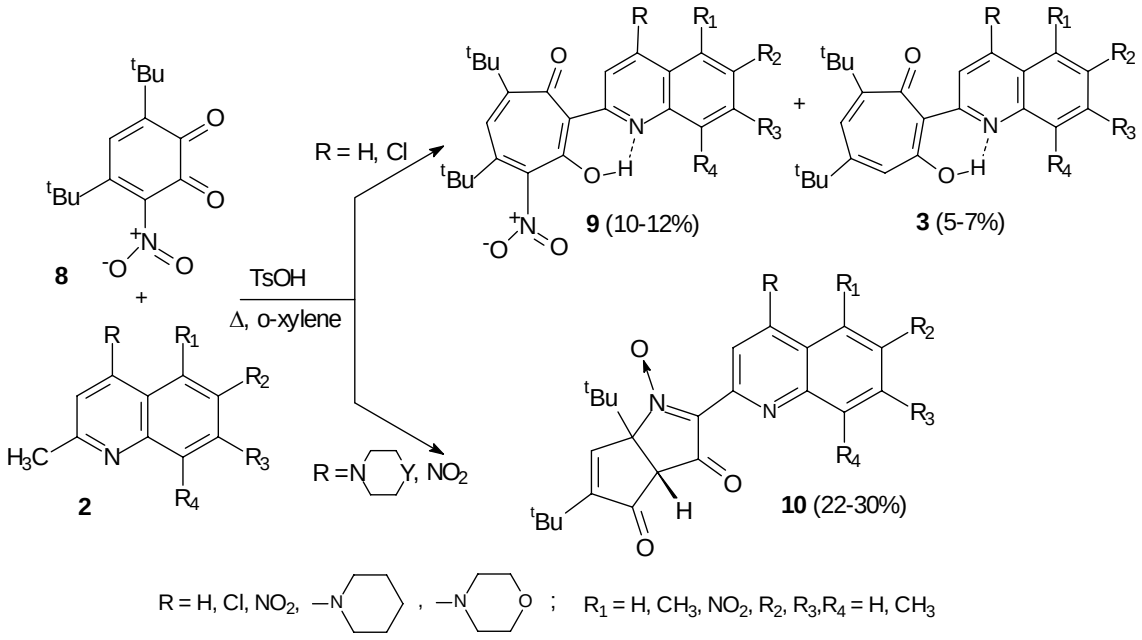
energy preferred compared to their positional isomers **3'**, whereas the opposite tendency is characteristic of the morpholinyl analogues **3** and **3'** [R= -N(CH$_2$)$_4$O], in which case the latter isomer is the energy favored by 7 kcal/mol.

The detailed mechanism for the formation of β-tropolones has been studied using the theoretical (DFT B3LYP/6-31G**) modeling of the minimal energy reaction paths of all principal stages of the reaction featured by Scheme 2. By thorough computational scanning of various possible reaction channels it has been found that for the essential ring-closing step (**5**→ **6** in Scheme 2) to occur with the energy barrier surmountable at thermal conditions it must be preceded by the proton transfer from the methylene group to the heterocyclic nitrogen. The calculated energy for the CH…N proton transfer, which represents the rate-limiting step of the whole transformation, amounts to 22.4 kcal/mol. The 1,6-dihydroxynorcaradiene intermediate **6** smoothly (with the energy barrier of only 1.3 kcal/mol) expands its six-membered ring to give the dihydro-β-tropolone **7**. Subsequent oxidation of **7** by quinone **1** affords β-tropolone **3** as the final product.




**Scheme 2**

By coupling quinolines **2** (R=H, Cl) with 6-nitro-3,5-di-(*tert*-butyl)-1,2-benzoquinone **8** under reflux for 1 hour *o*-xylene solutions of the equimolar amounts of the components 4-nitro-2-quinolyl-5,7-di-*tert*-butyl-β-tropolones **9** were obtained in low yields along with 2-quinolyl-5,7-di-*tert*-butyl-β-tropolones **3**.




**Scheme 3**

Under the same conditions quinolines **2** with the substituents R = $N(CH_2)_4O$, $NO_2$ react differently affording readily isolated crystalline products the structure of which was identified by X-ray crystallography as 2-azabicyclo[3.3.0]octa-2,7-dien-4,6-dione-*N*-oxides **10** (Table 2). These transformations are depicted in Scheme 3 and the molecular structure of a representative of this new heterocyclic system **10** is shown in Fig. 3.

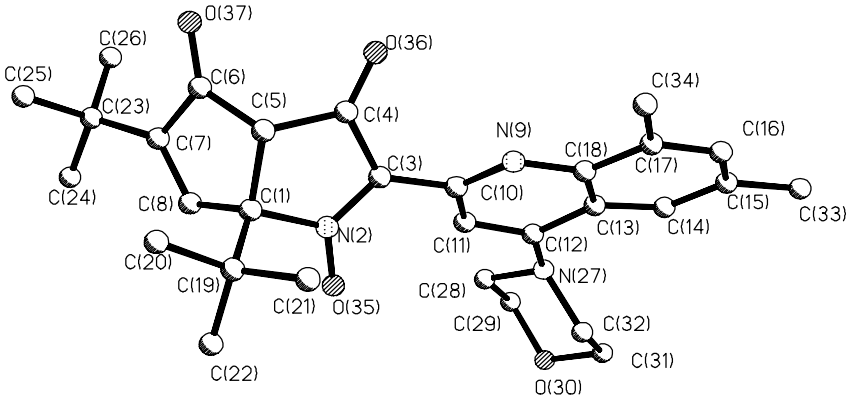
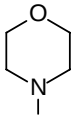
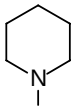


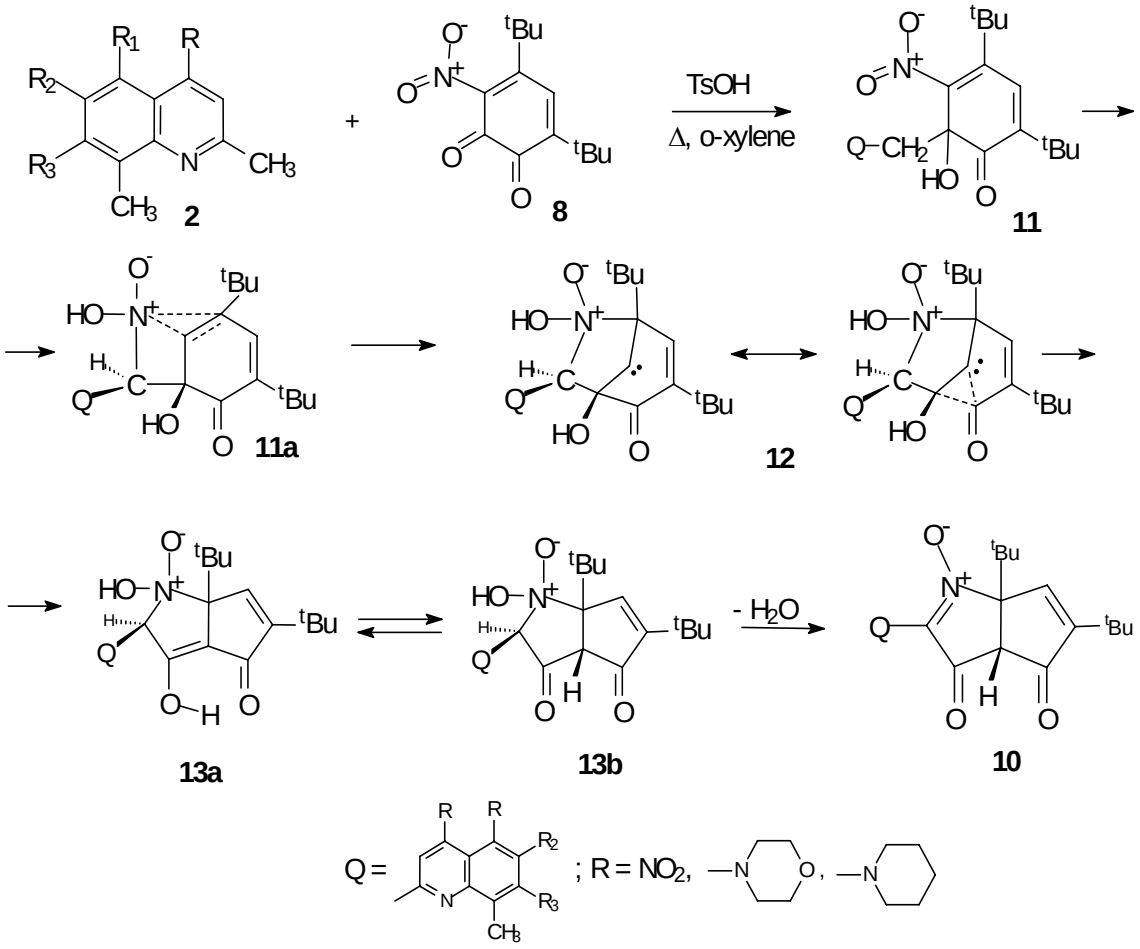

**Figure 3**. Molecular structure of 2-azabicyclo[3.3.0]octa-2,7-dien-4,6-dione-*N*-oxide **10** (R = $N(CH_2)_4O$, $R_1$=$R_2$, $R_3$=H, $R_4$=$CH_3$. Thermal ellipsoids are drawn on the 50% probability level. Selected bond lengths (Å): C(1)-C(8) 1.512(5), C(1)-C(5) 1.522(4), C(1)-N(2) 1.532(4), C(1)-C(19) 1.536(5), N(2)-O(35) 1.252(3), N(2)-C(3) 1.322(4), C(3)-C(4) 1.473(5), C(3)-C(10)

1.474(5), C(4)-O(36) 1.198(4), C(4)-C(5) .516(5), C(6)-O(37) 1.204(4), selected bond angles (°) : C(8)-C(1)-C(5) 104.1(3), C(8)-C(1)-N(2) 109.0(3), C(5)-C(1)-N(2) 102.1(2), C(8)-C(1)-C(19) 114.9(3), C(5)-C(1)-C(19) 116.1(3), N(2)-C(1)-C(19) 109.7(3), O(35)-N(2)-C(3) 126.7(3), O(35)-N(2)-C(1) 118.5(3) C(3)-N(2)-C(1) 114.7(3), N(2)-C(3)-C(4) 108.2(3), N(2)-C(3)-C(10) 123.3(3), C(4)-C(3)-C(10) 128.5(3), O(36)-C(4)-C(3) 126.6(3), O(36)-C(4)-C(5) 125.1(3), C(3)-C(4)-C(5) 108.3(3), C(10)-N(9)-C(18) 117.6(3), N(9)-C(10)-C(11) 124.5(3), N(9)-C(10)-C(3) 115.1(3), C(11)-C(10)-C(3) 120.3(3).

**Table 2.** 2-azabicyclo[3.3.0]octa-2,7-dien-4,6-dione-*N*-oxides **10**

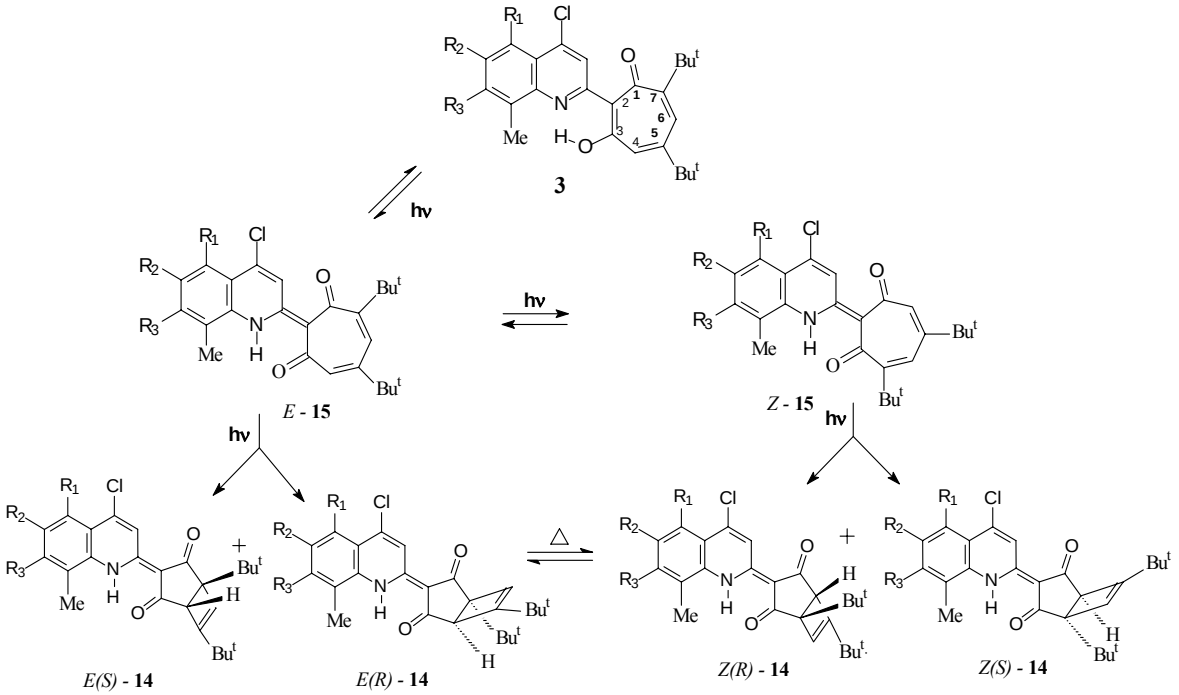
| Compound **10** | R | $R_1$ | $R_2$ | $R_3$ | $R_4$ | Yield, % | M.p.,ºC |
|---|---|---|---|---|---|---|---|
| a | | H | H | H | $CH_3$ | 28 | 210-212 |
| b |  | H | $CH_3$ | H | $CH_3$ | 26 | 220-222 |
| c | | H | H | $CH_3$ | $CH_3$ | 22 | 237-239 |
| d |  | $NO_2$ | H | H | $CH_3$ | 12 | 233-235 |
| e | | $NO_2$ | H | $CH_3$ | $CH_3$ | 14 | 234-236 |

A likely mechanism for the formation of the bicyclic compounds **10** is given in Scheme 4. The crucial step of the reaction is the intramolecular electrophilic addition of the positively charged nitrogen of the nitro group to the methine carbon occurring within the initially formed product **11** of the aldol condensation of quinoline **2** with the nitroquinone **8**. This reaction has a direct analogy with the intramolecular cyclization of the product of aldol condensation of o-nitrobenzaldehyde with acetone, which is a limiting stage of the classic Bayer-Drewsen synthesis of indigo.[10] The further route to the formation of 2-azabicyclo[3.3.0]octa-2,7-dien-4,6-dione-*N*-oxides **10** may be conceived as the sequence of the transformations **11**→**12**→**13**→**10**.




**Scheme 4**

The photolysis of hexane solutions of 2-quinolinyl-β-tropolones **3** results in a sequence of rearrangements that start from the excited state O-H…N → O…H-N proton transfer and follow by the disrotatory electrocyclization leading to 3-[2(1H)-quinolinylidene]-bicyclo[3.2.0]hept-6-ene-2,4-diones **14**.[11] These transformations are depicted by Scheme 5. The evolution of the spectral pattern occurring during the photolysis (irradiation of hexane solutions of **3** by the filtered 365 nm light of a high pressure mercury lamp for 5-6 hours) is portrayed in Fig. 4. The growth of the new long wavelength absorption band is also accompanied by the appearance of strong fluorescence of the formed compounds **14**. The fluorescence is characterized by the anomalously large Stokes shift. The compounds **14a-e** obtained in 60-70% yields were preparatively isolated and the molecular structure of one of these, 1,6-di-*tert*-butyl-3-(4-chloro-8-methyl-quinolin-2(1*H*)-ylidene)bicyclo[3.2.0]hept-6-ene-2,4-dione **14a**, was determined by X-ray crystallography.




$R_1$=$R_2$=$R_3$=H (**a**); $R_1$=$R_2$=H, $R_3$=Me (**b**); $R_1$=$R_3$=H, $R_2$=Me (**c**), $R_1$=$NO_2$, $R_2$=H, $R_3$=Me (**d**); $R_1$=$NO_2$, $R_2$=Me, $R_3$=H (**e**)

**Scheme 5**

When attempting to expand the reaction of methylene-active heterocycles from quinolines (Schemes 1, 2) to other heterocyclic systems we have found that the condensation of *o*-quinone **1** with 2-methylbenzimidazoles **16** proceeding under reflux of their solutions in *o*-xylene for 2 h yields polycyclic isoquinolines **17** rather than the expected derivatives of β-tropolones. Molecular structure of one of the compounds, **17a**, was determined by X-ray crystallography.[12] Scheme 6 shows the possible mechanism of the reaction. A initial stage of the reaction corresponds to the nucleophilic substitution of a hydrogen atom in the intermediate *o*-quinonemethide by a second methylbenzimidazole molecule. Examples of this reaction, proceeding through addition of an uncharged nucleophile, and resulting in the formation of hydroquinones oxidized then to substituted quinones are known in the literature.[13]

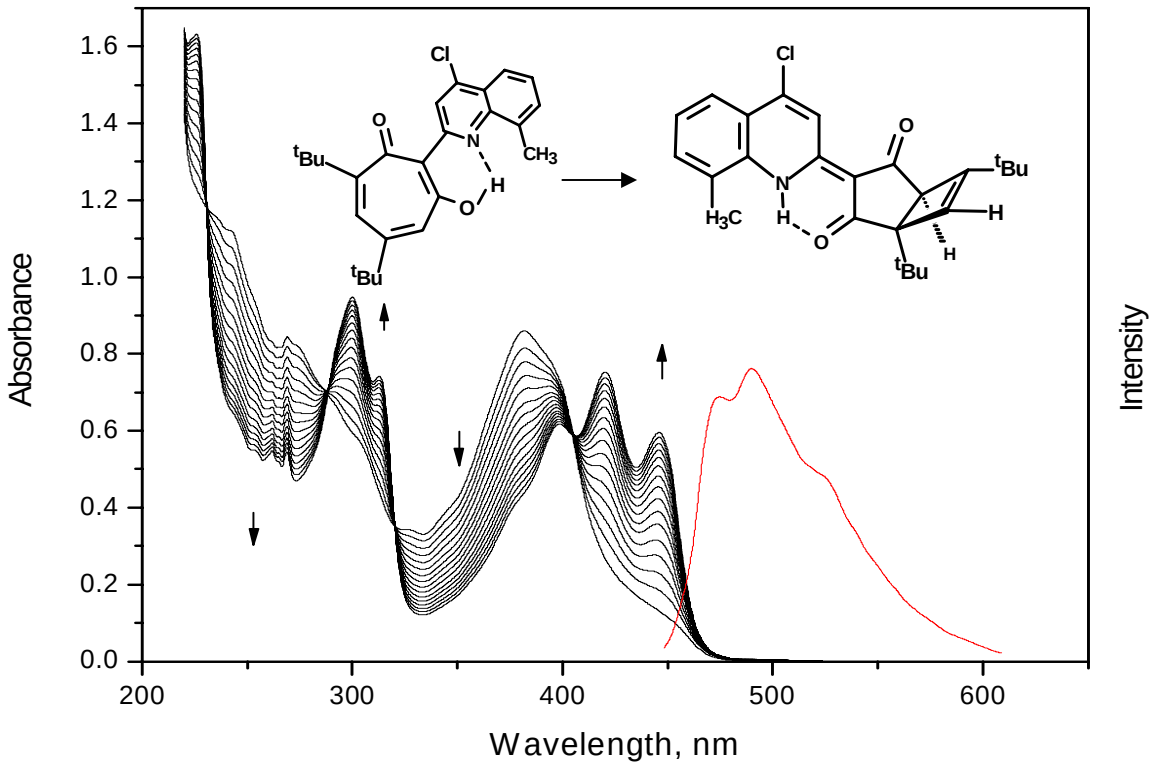
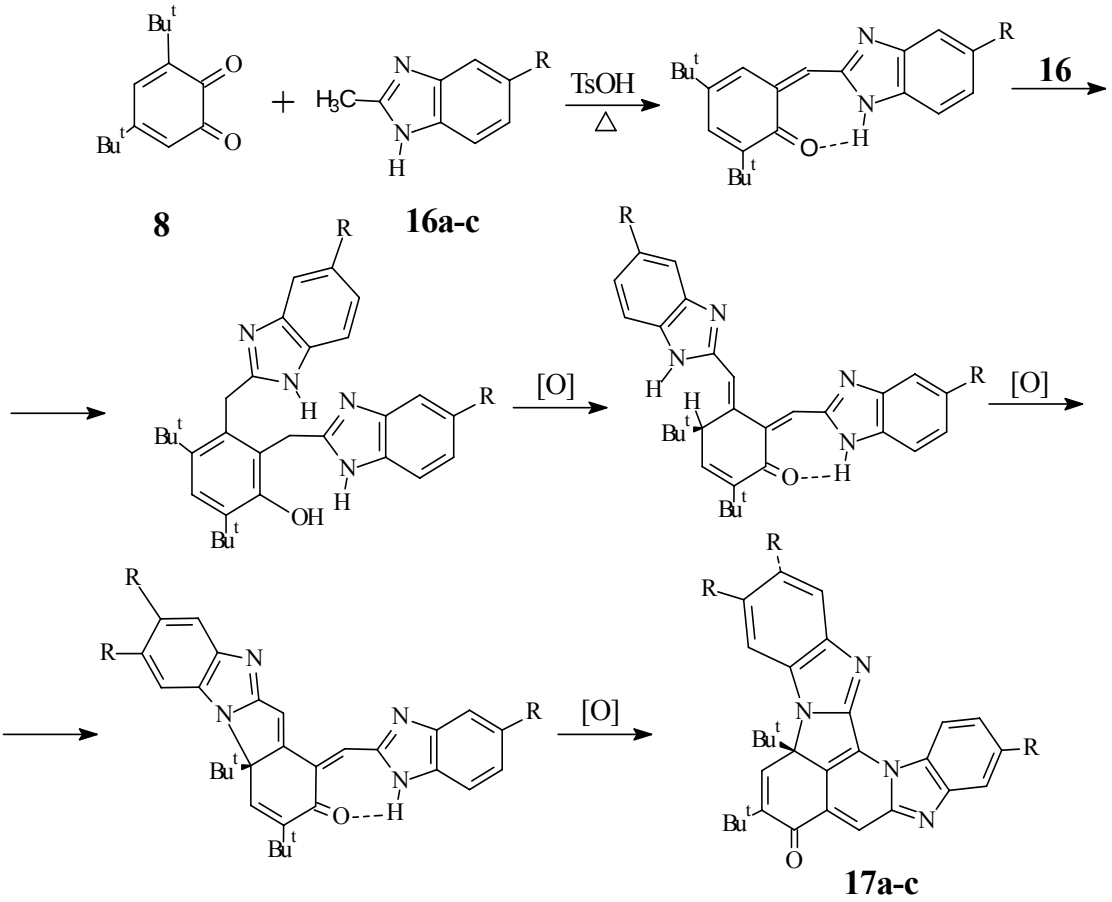



**Figure 4.** The phototoinduced changes (shown in 5 min intervals) in the absorption spectra of a hexane solution ($C$ = 4.68 $\cdot 10^{-5}$ mole$\cdot$l$^{-1}$) of 2-quinolinyl-β-tropolone **3** (R=Cl, $R_1$=$R_2$=$R_3$=H) during irradiation with the filtered (365 nm) UV-light at 293 K. The long wavelength shifted spectral curve is the fluorescence of the formed 1,6-di(*tert*-butyl)-3-[4-chloro 8-methyl-2(1*H*)-quinoinylidene]bicyclo[3.2.0]hept-6-ene-2,4-dione **14a**.




R = H (a); R = $CH_3$ (b); R = Cl (c)

**Scheme 6**

## Acknowledgements

This work was supported by the Russian Foundation for Basic Research (grant no. 05-03-32081) and Ministry of Science and Education of RF (N. Sh. 945. 2003.3). The X-ray structures shown in Figs. 1-3 were obtained by V.V. Tkachev and S.M. Aldoshin in the Institute of Problems of Chemical Physics of the Russian Academy of Sciences.

## References

1. Pietra, F. *Chem. Rev*. **1973**, *73*, 295; *Acc. Chem. Res*. **1979**, *12*, 132.
2. Chapman, J.L.; Fitton, P. *J. Am. Chem. Soc*. **1961**, *83*, 1005; **1963**, *85*, 41.
3. Becker, A.M.; Rickards, R.W. *Org. Prep. Proceed.* **1983**, *15*, 239.
4. Johns, R.B.; Johnson, A.W.; Tisler, M. *J. Chem. Soc*. **1954**, 4605.

5. Zinser, H.; Henkel, S.; Föhlish, B. *Eur. J. Org. Chem*. **2004**, 1344.
6. Komissarov, V.N.; Bang, D.N.; Minkin, V.I.; Aldoshin, S.M.; Tkachev, V.V.; Shilov, G.V. *Mendeleev Commun*. **2003**, 219.
7. (a) Sosnovskikh, V.Ya.; Vorontsov, I.I.; Kutsenko, V.A. *Russ. Chem. Bull., Int. Ed.* **2001**, *50*, 1430; (b) Dominiak, P.M.; Grech, E.; Barr, G.; Teat, S.; Mallinson, P.R.; Wozniak, K. *Chem. Eur. J*. **2003**, *9*, 963.
8. Gilli, P.; Ferretti, V.,Bertolasi, B.; Gilli, G. *Advances in Molecular Structure Research*; Hargittai, M.; Hargittai, I, Eds.; JAI Press: Greenwich CT, 1996, Vol. 2, pp 67-102.
9. Tkachev, V.V.; Aldoshin, S.M.; Shilov, G.V. Sayapin, Yu.A.; Komissarov, V.N. Minkin, V.I. *Zh. Org. Khim*. **2005**, *41*, in press.
10. Bayer, A; Drewsen, W. *Berichte.* **1882**, *15*, 2856.
11. Makarova, N.I.; Metelitsa, A.V;Besugliuy, S.O.; Sayapin, Yu.A.; Komissarov, V.N.; Starikov, A.G.; Korobov, M.S.; Borodkin, G.S.; Minkin, V.I.; Starikova, Z.A.; Antipin, M.Yu. *Russ. Chem. Bull*. 2005, in press.
12. Sayapin, Yu.A.; Komissarov, V.N.; Kobtsev, S.V.; Minkin, V.I.; Starikova, Z.A.; Antipin, M.Yu. *Dokl. Akad. Nauk (Chemistry)*. **2005**, *403* (I), 121.
13. Chupakhin, O.M.; Postovskii, I.Ya. *Usp. Khim. (Russ. Chem. Rev.).* **1976**, *45*, 908.