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Novel heterocyclization of 3-(2-aminophenylamino)-5,5-dimethyl-2-cyclohexen-1-one

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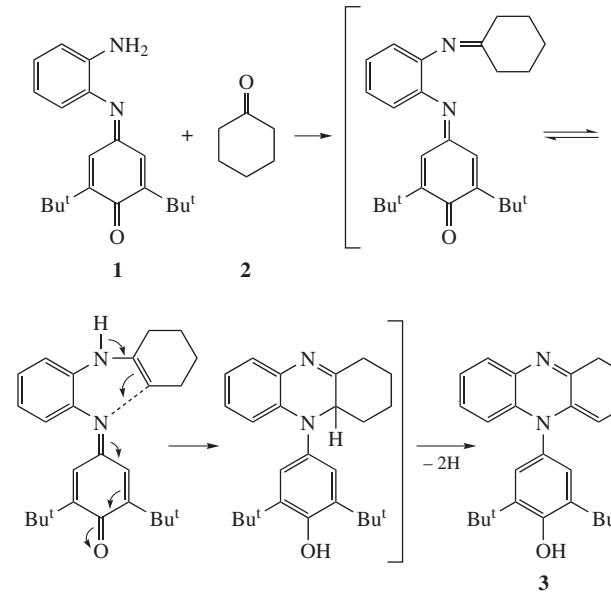
4-(1,2,3,4,10,10a-Hexahydro-3,3-dimethyl-1-oxophenazin-10a-yl)-2,6-di-*tert*-butylphenol [10a-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3,3-dimethyl-1,2,3,4,10,10a-hexahydro-1*H*-phenazin-1-one] was obtained by the condensation of 3-(2-aminophenylamino)-5,5-dimethyl-2-cyclohexen-1-one and 2,6-di-*tert*-butyl-1,4-benzoquinone.

Heterocyclic derivatives bearing 2,6-di-*tert*-butyl-4-hydroxyphenyl substituent are potential bioantioxidants. Previously, we have described the related isoquinoline and indazole derivatives, which proved to be low-toxic and efficient inhibitors of the peroxide oxidation.[1–4]

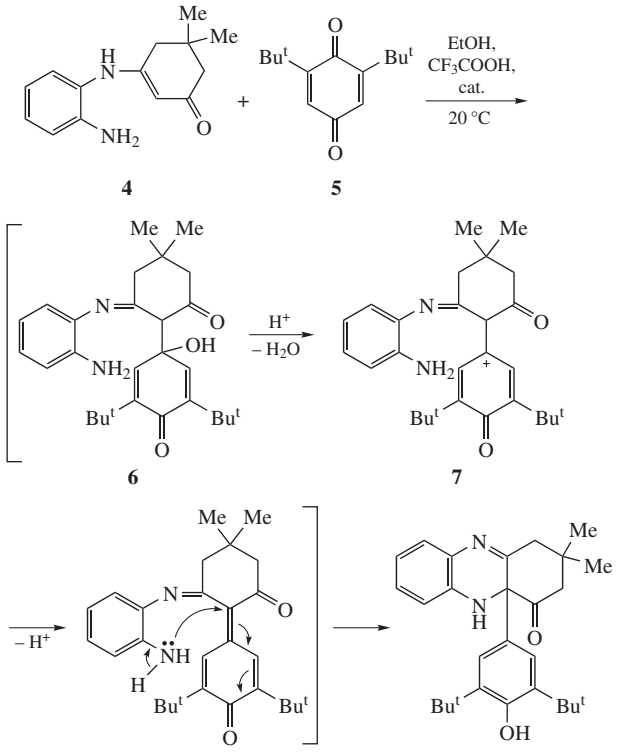
On the other hand, aromatic amines readily undergo condensation with 2,6-di-*tert*-butyl-1,4-benzoquinone to form quinonimines.[5,6] We have shown that reaction between quinonimine **1** and cyclohexanone **2** afforded 4-(1,2,3,5-tetrahydrophenazin-5-yl)-2,6-di-*tert*-butylphenol **3** (Scheme 1).[7] Formation of phenazine structure was facilitated by the *ortho* arrangement of quinonimine and enamine fragments in the intermediates.

We have supposed that 3-(2-aminophenylamino)-5,5-dimethyl-2-cyclohexen-1-one **4** would be suitable for the design of similar structure (Scheme 2).[8–11] It contains the enamine fragment and amino group, the latter being necessary for the formation of quinonimine.

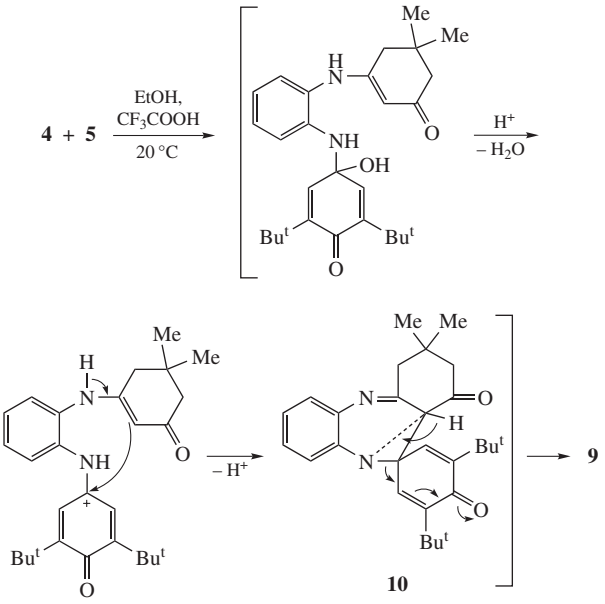
Unexpectedly, compound **4** reacts with quinone **5** giving C-substituted derivative **9** instead of N-substituted analogue of compound **3**. Apparently this transformation excludes an intermediate formation of quinonimine. It seems that the reaction starts with addition of the quinone to the enamine fragment of compound **4** to form intermediate **6**.[12] Furthermore, it was found that 3-(2-hydroxyphenylamino)-5,5-dimethyl-2-cyclohexen-1-one (oxygen analogue of **4**) did not react with quinone **2**. Therefore, it can be concluded that the presence of the amino group is crucial condition for the cyclization to proceed. We can explain the role of the amino group as an anchimeric assistance for an addition of the quinone to the enamine fragment. Taking into account the well-known fact of high activity of the quinone **5** in the reactions with aromatic amines,[6] we suppose that the reaction may occur on the amino group with intermediate formation of



Scheme 1



Scheme 2



Scheme 3

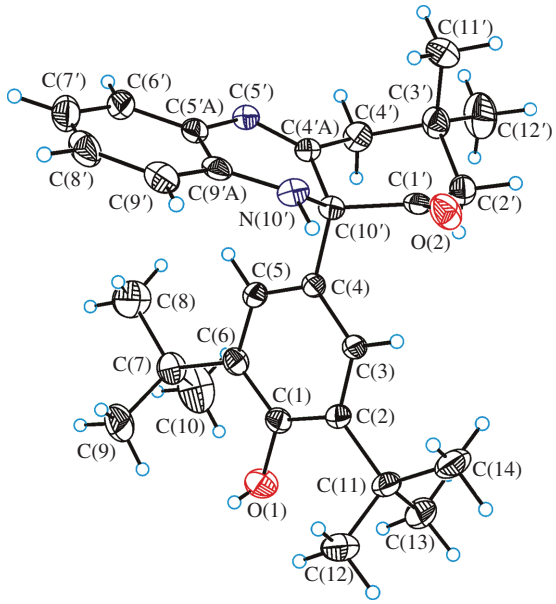


Figure 1 ORTEP view of compound **9** showing 30% probability displacement ellipsoids and the atom-numbering scheme.

spiro compound **10** (Scheme 3). Then compound **10** would rearrange into phenazine **9**.† Similar rearrangement with the formation of 3,3-dimethyl-1,2,3,4-tetrahydrophenazin-1-one from derivatives of spiro[3.7]oxindolo-7,8-dihydro-9,9-dimethyl-10*H*, 11*H*,16*H*-dibenzo[2,3:5,6][1,4]diazepin-7-one was described earlier.[13]

The structure of compound **9** was ultimately solved by single crystal X-ray diffraction (Figure 1).‡ An independent unit cell consists of **9** and ethanol in the ratio of 1 : 1. The phenyl ring along with bonded nitrogen atoms forms a planar structure, dihydropyrazine cycle adopts distorted envelope conformation while cyclohexanone is in normally observed chair conformation; the H(2′B)–C(2′)–C(3′)–C(4′)–H(4′A) fragment (equatorial hydrogen atoms) has planar structure that is in accordance with ^{1}H NMR data. The phenol cycle is oriented nearly perpendicularly to phenazine system, and the C(10′)–C(4) bond is elongated up to 1.544(4) Å which is an indication of sterically hindered molecule. In part it is confirmed by H-bonding pattern in the crystal structure of **9**. The amino group participates in the very weak N(10′)–H(10′)···O(2) bond [N···O 3.326(3) Å, H···O 2.43 Å, ∠NHO 179°] while hydroxy group is not H-bonded. Also relatively strong hydrogen acceptor [N(5′)] forms H-bond with solvate ethanol molecule (rather than with hydroxy group) [O(1S)–H(1S)···N(5′); O···N 2.943(5) Å, H···N 2.10 Å, ∠OHN 174°], and this fact is probably responsible for an inclusion of ethanol in the crystal structure.

Both of the methylene groups in the ^{1}H NMR spectrum of phenazine **9** appeared as AB systems, and also interact through four σ-bonds (*J* 2.7 Hz). This is an indication of the planar zigzag W-shaped structure H(2′)–C(2′)–C(3′)–C(4′)–H(4′). These data suggest that the cyclohexanone fragment is a rigid system which retains its structure both in solid and in solution. Another feature of compound **9** is the exchange character of the methylene protons, presumably C(2′)–H_{eq}. When in D_2O deuteration, AB-spectrum of protons of C(2′)H_2 group appears as broad singlet with δ 2.66 (~0.3–0.4 H), and dd C(4′)H δ 2.36 appears as doublet at 12.36 ppm (*J* 13.8 Hz).[14]

Here we presented the first example of new type of phenazine derivatives, containing C-conjugated phenolic substituent with space-hindered fragments. Due to potential biological activity (*prima facie* as antioxidants), investigation of similar derivatives might be of great importance and interest.

In conclusion, the advantages of the described method for the synthesis of phenazine derivatives include reagent availability and experimental simplicity. Taking into account variability in the synthesis of compound **4** of two initial components, namely aromatic *o*-diamines and cyclic β-diketones, this approach can be applied to the synthesis of a broad range of members of this class of compounds.

† *4-(1,2,3,4,10,10a-Hexahydro-3,3-dimethyl-1-oxophenazin-10a-yl)-2,6-di*-tert-*butylphenol* **9**. 3-(2-Aminophenylamino)-5,5-dimethyl-2-cyclohexen-1-one **4** (0.46 g, 2 mmol) and quinone **5** (0.44 g, 2 mmol) were dissolved in EtOH (10 ml) at room temperature. The mixture was treated with CF_3COOH (2 drops) and left for 12 h. Then the mixture was cooled on ice and the precipitate formed was filtered off, washed with a little cooled EtOH and light petroleum and dried in air. The yield of **9** was 0.37 g (yellow crystals). An additional crop of **9** (0.29 g) precipitated one day later. The total yield of yellow crystalline product **9**·EtOH was 69% (0.66 g), mp 215–220 °C (**9** was recrystallized from EtOH and dried *in vacuo* at 110 °C). IR (ATR, ν/cm^{-1}): 3605 (br., OH), 3373 (m, NH), 3335 (br., (OH_{Alk})), 2960 (m, Bu^t), 1714 (s, CO), 1621 (m), 1607 (m), 1480 (s), 1434 (s, arom.). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.98 and 1.10 (2 s, 6 H, Me), 1.22 (t, 3 H, Me, *J* 7.0 Hz), 1.31 (s, 18 H, Bu^t), 2.36 (dd, 1H, C$^{4'}$H$_2$, ^2J 13.8 Hz, ^4J 2.7 Hz), 2.62 (d, 1H, C$^{4'}$H$_2$, *J* 13.8 Hz), 2.71 (dd, 1H, C$^{2'}$H$_2$, ^2J 13.8 Hz, ^4J 2.7 Hz), 2.84 (d, 1H, C$^{2'}$H$_2$, *J* 13.8 Hz), 3.70 (q, 2 H, CH_2, *J* 7.0 Hz), 5.00 (br. s, 1H, NH), 5.23 (s, 1H, OH), 6,48 (d, 1H, CH_{arom}, *J* 7.8 Hz), 6.67 (t, 1H, CH_{arom}, *J* 7.5 Hz), 6.85 (s, 2 H, C^{3}H, C^{5}H), 6.94 (t, 1H, CH_{arom}, *J* 7.5 Hz), 7.25 (d, 1H, CH_{arom}, *J* 7.8 Hz). MS (EI, 70 eV), *m*/*z*: 432 $[M]^+$.

‡ *Crystallographic data for* **9**: $C_{28}H_{36}N_2O_2·C_2H_6O$, triclinic, space group $P\bar{1}$, *a* = 9.584(2), *b* = 11.192(2) and *c* = 14.680(2) Å, α = 79.083(3)°, β = 71.021(3)°, γ = 74.243(3)°, *V* = 1424.2(4) Å^3, *Z* = 2, *M* = 478.66, d_{calc} = 1.116 g cm^{-3}, wR_2 = 0.1867 calculated on F^2_{hkl} for 6188 independent reflections with 2θ < 54° [GOF = 1.024, *R* = 0.0787 calculated on F_{hkl} for 3274 reflections with $I > 2\sigma(I)$].

CCDC 924271 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2014.

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