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The First Example of Aza-Nenitzescu Reaction. A New Approach to the Heterocyclic Quinones Synthesis

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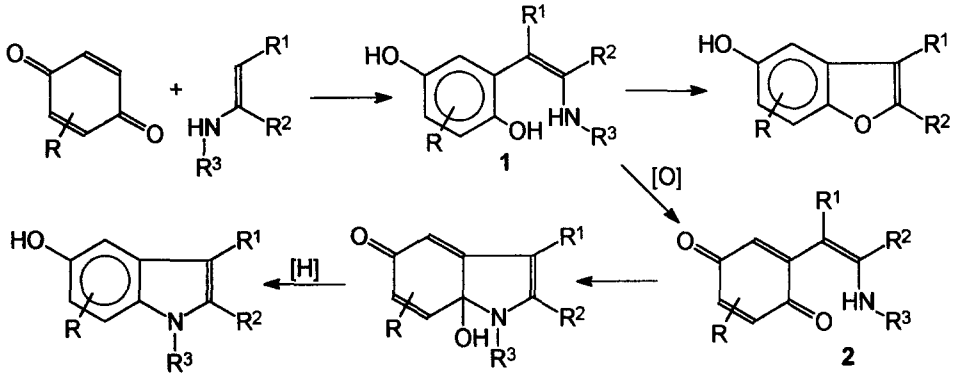
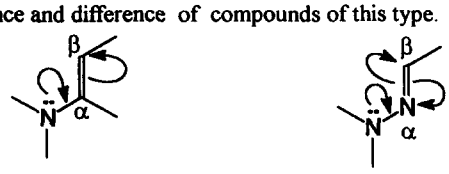
Abstract. The first example of aza-Nenitzescu reaction is described. The interaction of azaenamine - benzaldehyde phenylhydrazone with *p*-benzoquinone and chlorobenzoquinone leads to a new synthesis of 5-hydroxyindazoles and indazole quinones. © 1997 Elsevier Science Ltd.

The Nenitzescu reaction is the most expedient approach to 5-hydroxyindoles and 5-hydroxybenzofurans[1-3]. The essense of this process is the initial condensation of quinones in the electron-rich β-position of enamines with the formation of so-called hydroquinone-adducts **1**, which are either transformed into 5-hydroxybenzofurans or oxidized into quinone-adducts **2** with the further cyclization of the latter into indole:



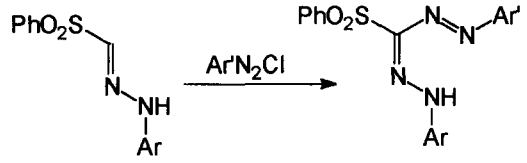
The rate of initial condensation depends greatly on electron density in the β-position of enamines and therefore on the structure and nature of substituents R-R^3. The stage 1 →2 is determined by the degree of electron donor influence of the enamine fragment - the higher this effect is, the easier is the oxidation and it is often impossible to isolate both hydroquinone-adducts and quinone-adducts. The reaction goes spontaneously to the corresponding 5-hydroxy heterocycles.

The influence of substituents in enamines on the Nenitzescu reaction has been profoundly discussed in scientific literature[1-3]. However the drastic change of enamine structure, for example the use of azaenamines - hydrazones has not been investigated. At the same time the comparison of enamine and azaenamine structures shows both resemblance and difference of compounds of this type.

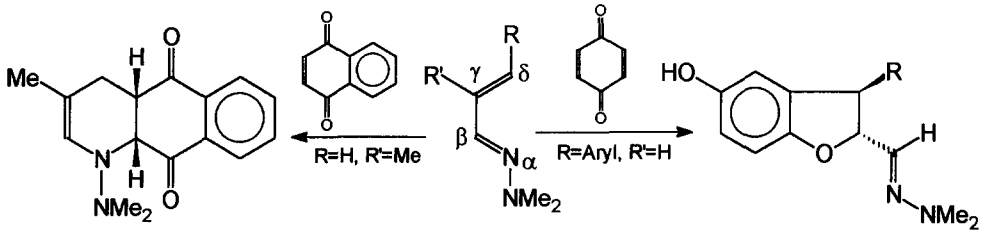


The resemblance is the following: in both cases the conjugation of the nitrogen lone pair with the double bond increases electron density in the β-position. The difference is determined by electron withdrawing

influence of C=N - bond in azaenamines and the corresponding decrease in nucleophility of this system in comparison with enamines. However, numerous literature data have demonstrated that electrophilic attack can proceed in the β-position of hydrazones. For example, it has been found recently that diazonium salts react with phenylsulfonyl azaenamines with the corresponding formation of azocompounds[4].



Recently it has been also shown that α,β-unsaturated N,N-dimethylhydrazones can interact with quinones in electron-rich δ-position with the formation of indole and benzofuran derivatives[5] or as azadienes with the formation of annelated pyridines[6].

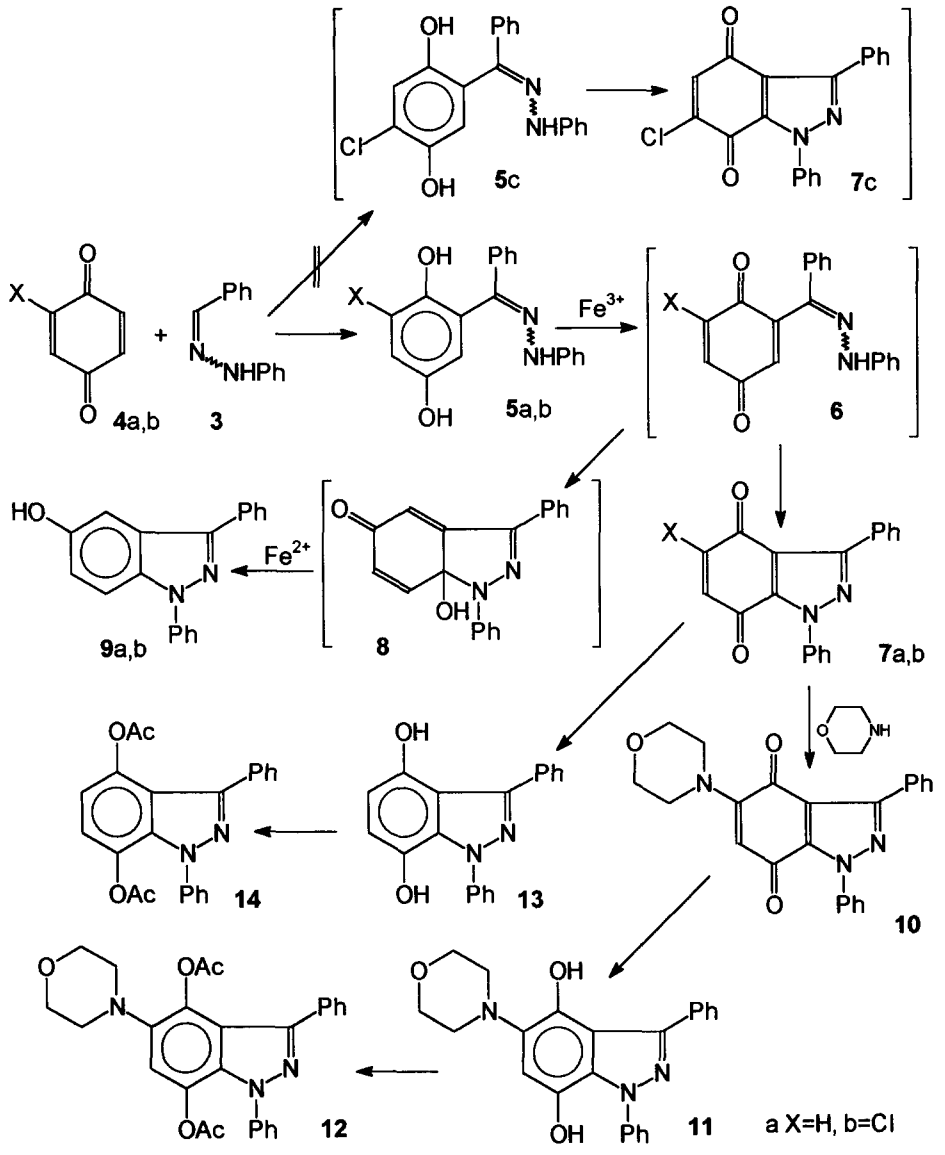


Based on these considerations, we supposed that azaenamines could to be promising starting compounds for condensation with quinones in the Nenitzescu reaction. Actually, the interaction of benzaldehyde phenylhydrazone **3** with benzoquinone **4a** gives the corresponding azahydroquinone adduct **5a**, structurally similar to hydroquinone adduct **1**, which is typical of the Nenitzescu reaction. The decrease in electron density in the β-position of hydrazone **3** in comparison with enamines caused the need for additional activation of quinone component, which has been achieved by *p*-toluene sulfonic acid catalysis, similar to the condensation with nitroenamines[7].

It is also essential that the more acceptor azaenamine moiety causes a decrease in electron density in hydroquinone nucleus and this does not make possible the oxidation of azahydroquinone-adduct **5a** under the reaction conditions. On the other hand, the further closure of cycle (similar to indole synthesis in the Nenitzescu reaction) requires the formation of the system similar to quinone-adduct **2**. The oxidation of compound **5a** by potassium ferricyanide proceeds in two directions. The first is the addition of hydrazone NH-group to the 3-C atom of quinone intermediate **6** with indazole-4,7-dione **7a** formation. Compounds of this type have been described in a series of papers[8-10], based on the preliminary isolation of the carbonyl containing hydrazinoquinones with their further cyclization with participation of carbonyl substituents and hydrazine NH group or based on 1,3-dipolar addition of diazomethane derivatives[11] or nitrilimines[12] to quinones. In the latter case[12], the reaction of diphenylnitrilimine with *p*-quinone gave the compound, which is identical in its physical constants and spectral data to the above compound **7a**, isolated under oxidation of adduct **5a**.

The second direction of oxidation of azahydroquinone-adduct **5a** is typical for the aza-Nenitzescu reaction. In this case, the addition of NH group to the 1-C carbonyl leads to the formation of carbinolamine intermediate **8**, which is reduced (probably by Fe^{2+}) with formation of 5-hydroxy-1,3-diphenylindazole **9a**. This compound has been obtained previously[13] by a multi-step synthesis from 2-chloro-5-nitrobenzophenone[13,14].

The isolation of indazole **9a** in our case confirms the possibility of the use of enamine heteroanalogs in the aza-Nenitzescu (and similar) reaction.



The condensation of chlorobenzoquinone **4b** with hydrazone **3** could follow in two directions with the formation of either azahydroquinone adduct (**5b** or **5c**). The obtained adduct was oxidized without purification with the further formation of the corresponding indazole-4,7-diones **7b** or **7c**. The reaction mixture also contained the usual product of the aza-Nenitzescu reaction 5-hydroxy-7-chloroindazole (**9b**)

together with by-products. We failed to isolate pure **9b**, however its presence was shown by mass-spectrometry (M^+ 320).

To prove the structure of chloroindazoledione 7b or 7c and also to extend the possibilities for synthetic use of the obtained heterocyclic quinones, compound **10** was obtained by the reaction of indazoledione **7a** with morpholine. Compound **10** was reduced to the corresponding hydroquinone **11 and** transformed into the diacetoxy derivative **12**. This transformation is necessary because the derivatives (**10** and **11**) do not have enough solubility for ^{13}C NMR spectroscopy. On the other hand, nucleophilic substitution of Cl in the isolated chloro derivative 7b or 7c in the reaction with morpholine leads to the same compound **10**, which is obtained from dione 7a (for details of substitution of halogen atoms in the indazole-4,7-dione derivatives by amine groups see[15-17]). The proof of the structure of bicycle **12** as 5-morpholinoindazole-4,7-dione comes from the comparison of its ^{13}C NMR with the spectrum of the diacetoxy derivative **14** unsubstituted in benzene cycle which is obtained by the reduction of quinone 7a with the further acetylation of the intermediate hydroquinone **13**. In the ^{13}C NMR spectrum of **14** in D_6-DMSO without proton interaction suppression, signals of atoms 3a-C in δ 117,9 (d, $J_{3a\text{-}C,5\text{-}H}$=6,9 Hz) and 7a-C in 134,2 (d, $J_{7a\text{-}C,6\text{-}C}$=9,4 Hz) are present. In the ^{13}C NMR spectrum of compound **12,** the signals of these quarternary carbon atoms practically do not change their position, but their multiplicity changes: 3a-C in δ 118,8(s), 7a-C in δ 134,4 (d, $J_{7a\text{-}C,6\text{-}H}$=8,5 Hz). This confirms the presence of morpholine group in position 5. Therefore the above chloro derivative has structure 7b.

Thus aza-analogs of enamines hydrazones can be easily involved in the Nenitzescu reaction, which opens a new route to 5-hydroxyheterocycles and heterocyclic quinones.

Experimental

NMR-spectra were recorded using "Unity plus 400 MHz" (Varian) with TMS as internal standard in D_6-DMSO. Mass-spectra were performed using SSQ-710 Finnigan chromatomass-spectrometer under direct introduction of the samples to ion-source. TLC control: "Silufol UV-254", UV-detection.

2,5-Dihydroxybenzophenone phenylhydrazone (5a). *p*-Toluene sulfonic acid (0,85 g, 5 mmol) and *p*-benzoquinone (5,4 g, 50 mmol) were added to a suspension of benzaldehyde phenylhydrazone (9,8 g, 50 mmol) in glacial acetic acid (50 ml) under stirring at 20°C. The reaction mixture was kept for 24 h. The precipitate was filtered, washed with AcOH and water, dried and **5a** (5,85 g, 38,5%) is obtained, m.p. 120-122°C (benzene), M^+304. ^1H NMR (D_6-DMSO): 6,41 (d, 1H, 6-H), 6,76 (dd, 1H, 4-H), 6,86 (d, 1H, 3-H), 7,20-7,55 (m, 10 H, two C_6H_5); 8,54 (s, 1H, NH); 8,95 (s) and 8,98 (s) (2H, two OH). Found: C 75,3; H 5,4; N 9,2. $C_{19}H_{16}N_2O_2$ requires: C 75,0; H 5,3; N 9,2.

1,3-Diphenylindazole-4,7-dione (7a); 1,3-diphenyl-5-hydroxyindazole (9a). A solution of potassium ferricyanide (6,2 g, 18 mmol), sodium bicarbonate (1,45 g, 17 mmol), potassium carbonate (2,3 g, 17 mmol) in water (50 ml) was added to a mixture of **5a** (3,04 g, 10 mmol), chloroform (90 ml), sodium bicarbonate (1,45 g, 17 mmol) and water (20 ml) under stirring at 20°C. The stirring was continued for 5 h. The organic layer was washed with water and evaporated. The crude product was dissolved in benzene and chromatographed on silica gel (eluent benzene). Under elution the compounds **7a** (1,0 g,33%) and **9a** (0,3 g, 10,5%) were separated consecutively. For **7a**: m.p.195-196°C (benzene) (Lit.[12] 192-194°C), M^+300. ^1H NMR (D_6-DMSO): 6,86 (AB, 2H, 5-H,6-H); 7,36-7,57 (m, 6H), 7,70 (m, 2 H), 8,07 (m, 2H) (two C_6H_5). Found: C 75,7; H 4,0; N 9,3. $C_{19}H_{12}N_2O_2$ requires: C 76,0; H 4,0; N 9,3. For **9a**: m.p.194-196°C (benzene) (Lit.[13] 196°C). M^+286. ^1H NMR (D_6-DMSO): 7,09 (dd, 1H, 6-H); 7,38 (d, 1H, 4-H); 7,75 (d, 1H, 7-H); 7,39 (m,

1H), 7,44 (m, 1H), 7,57 (m, 4H), 7,80 (m, 2H), 7,96 (m, 2H) (two C_6H_5); 9,50 (br.s, 1H, OH). Found: C 80,0; H 5,1; N 9,4. $C_{19}H_{14}N_2O$ requires: C 79,7; H 4,9; N 9,8.

1,3-Diphenyl-5-chloroindazole-4,7-dione (7b). *p*-Toluene sulfonic acid (0,85 g, 5 mmol) and *p*-chlorobenzoquinone (7,1 g, 50 mmol) were added to a suspension of benzaldehyde phenylhydrazone (9,8 g, 50 mmol) in glacial acetic acid (50 ml) under stirring at 20°C. The reaction mixture was kept for 48 h and was diluted with water. The crude product was extracted with chloraform, washed with water and evaporated to volume 150 ml. The oxidation of the hydroquinone intermediate was similar to the synthesis of 7a from 5a. Compound 7b (0,94 g, 5,6%) was obtained by the chromotography of the mixture on silica gel (eluent benzene), m.p. 212-215°C (benzene), M^+334. ^{1}H NMR (D_6-DMSO): 7,33 (br.s, 1H, 6-H); 7,51 and 7,57 (m, 6H; 7,70 (m, 2H), 8,02 (m, 2H) (two C_6H_5). Found: C 68,6; H 3,6; Cl 10,6; N 8,3. $C_{19}H_{11}ClN_2O_2$ requires: C 68,2; H 3,3; Cl 10,6; N 8,4.

1,3-Diphenyl-5-morpholinoindazole-4,7-dione (10). A. Morpholine (0,16 g, 1,8 mmol) was added to a solution of 7a (0,47 g, 1,6 mmol) in benzene (25 ml) an 40°C. The mixture was refluxed for 15 min and was kept for 20 h. The precipitate was collected, washed with benzene, dried to yield **10** (0,29 g, 47%), m.p. 247-250°C (2-propanol), M^+385. ^{1}H NMR (D_6-DMSO): 3,52 (t, 4H) and 3,71 (t, 4H) (four CH_2); 5,73 (s, 1H, 6-H); 7,46-7,54 (m, 6H), 7,62 (m, 2H) and 7,98 (m, 2H) (two C_6H_5). Found: C 71,9; H 4,9; N 10,5. $C_{23}H_{19}N_3O_3$ requires: C 71,7; H 5,0; N 10,9.

B. Morpholine (0,087 g, 1 mmol) was added to a solution 7b (0,17 g, 0,5 mmol) in benzene (20 ml) at 40°C. The mixture was refluxed for 15 min and was kept for 20 h. The precipitate was collected, washed with benzene, dried to yield **10** (0,17 g, 86,7%), m.p. 248-250°C. The samples, obtained according to methods A and B are identical (IR and ^{1}H NMR-spectra).

1,3-Diphenyl-4,7-diacetoxy-5-morpholinoindazole (12). A solution of **10** (0,38 g, 1 mmol) in ethyl acetate (150 ml) was shaken with saturated solution of $Na_2S_2O_4$ (150 ml) untill the discolouration of solution. Organic layer was washed with water and evaporated. The residue is crystallized from benzene to yield **11** (0,35 g, 90,4%), M^+387. ^{1}H NMR (D_6-DMSO): 2,78 (br.s, 4H) and 3,80 (br.s, 4H) (four CH_2); 6,75 (s, 1H, 6-H); 7,36-7,58 (m, 8H) and 7,94 (m, 2H) (two C_6H_5); 8,32 (br.s, 1H) and 9,50 (br.s, 1H) (two OH). The mixture of **11** (0,35 g, 0,9 mmol), acetic anhydride (0,9 g, 9 mmol) and anhydrous benzene (20 ml) was refluxed for 2,5 h. Benzene was evaporated, the solid was recrystallized from benzene-petroleum ether, 2:1 to yield **12** (0,23 g, 54,2%), m.p. 215-218°C, M^+471. ^{1}H NMR (D_6-DMSO): 1,67 (s, 3-H,) and 1,93 (s, 3H,) (two $CO\underline{C}H_3$); 2,85 (br.t, 4-H) and 3,68 (t, 4-H) (four CH_2); 7,26 (s, 1H, 6-H); 7,49-7,67 (m, 10-H, two C_6H_5). ^{13}C NMR (D_6-DMSO) (without proton interaction): 19,7 (q) and 20,0 (q) (two $COCH_3$); 39,2 (t, two NCH_2); 40,0 (t, two OCH_2); 115,6 (d, 6-C); 118,8 (s, 3a-C); 126,3(m), 128,2(m), 128,3(m), 128,5(m), 128,9(m), 129,2(m), 132,0(t), 139,1(t) (two C_6H_5); 131,0 (d, 4-C); 132,2 (d, 7-C); 134,4 (d, 7a-C); 138,0 (s, 5-C); 145,1 (t, 3-C); 168,1 (q, $\underline{C}OCH_3$); 168,5 (q, $\underline{C}OCH_3$). Found: C 68,4; H 5,3; N 8,9. $C_{27}H_{25}N_3O_5$ requires: C 68,8; H 5,3; N 8,9.

1,3-Diphenyl-4,7-dioxyindazole (13) was synthesized in the manner of **11** from 7a. Yield 59,6%, m.p. 209-211°C, M^+302. ^{1}H NMR (D_6-DMSO): 6,51 (AB, 5-H, 6-H); 7,36 (s, 3H, $0{,}5C_6H_6$); 7,36- 7,48 (m, 6H), 7,57 (m, 2H) and 7,92 (m, 2H) (two C_6H_5); 9,30 (s, 1H) and 9,53 (s, 1H) (two OH). Found: C 76,8; H 5,2; N 8,1. $C_{19}H_{14}N_2O_2 + 0{,}5\ C_6H_6$ requires: C 77,4; H 5,0; N 8,2.

1,3-Diphenyl-4,7-diacetoxyindazole (14). A mixture of **13** (0,58 g, 1,9 mmol), acetic anhydride (1,9 g, 1,9 mmol) and anhydrous benzene (40 ml) was refluxed for 2,5 h. Benzene was evaporated, the solid was recrystallized from 2-propanol to yield **14** (0,57 g, 77,7%), m.p. 213-215°C, M^+386. ^{1}H NMR (D_6-DMSO): 1,64 (s, 3H) and 1,89 (s, 3H) (two $COCH_3$); 7,26 (AB, 2H, 5-H, 6-H); 7,53-7,67 (m, 10H, two C_6H_5). ^{13}C NMR (D_6-DMSO) (without proton interaction): 19,7 (q) and 20,3 (q) (two $CO\underline{C}H_3$); 114,8 (d, 5-C); 117,9 (d,

3a-C); 121,3 (d, 6-C); 126,6(m), 128,4(m), 128,5(m), 128,6(m), 129,0(m), 129,2(m), 131,9(t) and 139,1(t) (two C_6H_5); 132,7 (dd, 7-C); 134,2 (d, 7a-C); 141,2 (dd, 4-C); 145,2 (br.t, 3-C); 168,6 (q) and 168,8 (q) (two $\underline{C}OCH_3$). Found: C 71,8; H 4,9; N 7,1. $C_{23}H_{18}N_2O_4$ requires: C 71,5; H 4,7; N 7,2.

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