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THE aza-NENITZESCU REACTION. SYNTHESIS OF INDAZOLE DERIVATIVES BY CONDENSATION OF QUINONES WITH HYDRAZONES

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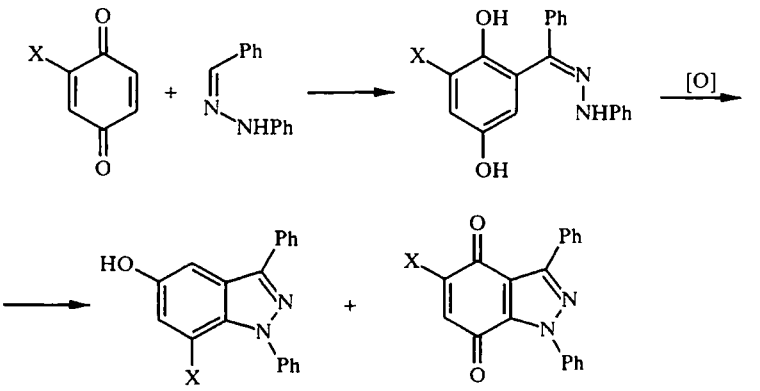
In a continuation of the study of the aza-Nenitzescu reaction new derivatives of 5-hydroxyindazole, 4,7-dioxoindazole, and 4,9-dioxobenzindazole have been obtained from the reaction of p-benzoquinone and naphthoquinone with substituted hydrazones.

One of the most fruitful uses of enamines in organic synthesis is to prepare various derivatives of 5- and 6-hydroxyindoles and 5-hydroxybenzofurans from them via the Nenitzescu reaction [1, 2]. We have recently demonstrated [3] that hydrazones – azaenamines – can be used instead of enamines in condensation with quinones. A new reaction thus observed we named the aza-Nenitzescu reaction, which provided a new synthesis for various derivatives of indazole. Apart from the theoretical interest of the process, the possibility of routes to 5-hydroxyindazole and indazoylquinones [3] could be of practical interest because a large group of biologically active compounds is found among this type of heterocycle [4-6].



In [3] the aza-Nenitzescu reaction was exemplified only by the reactions of benzoquinone and chlorobenzoquinone with phenylhydrazone. To establish the utility of this new process it is essential to increase the range of reagents to include such quinones as naphthoquinone and such azaenamines as substituted hydrazones.

The reactions of *p*-benzoquinone (I) with the phenylhydrazones of *p*-bromo- (IIa), *p*-nitro- (IIb), and *p*-methoxybenzaldehyde (IIc) and with benzaldehyde *p*-nitrophenylhydrazone (IId) have now been studied. The reactions of quinone I with the hydrazones IIa and IIb occur as in the Nenitzescu reaction, i.e., by attack of the

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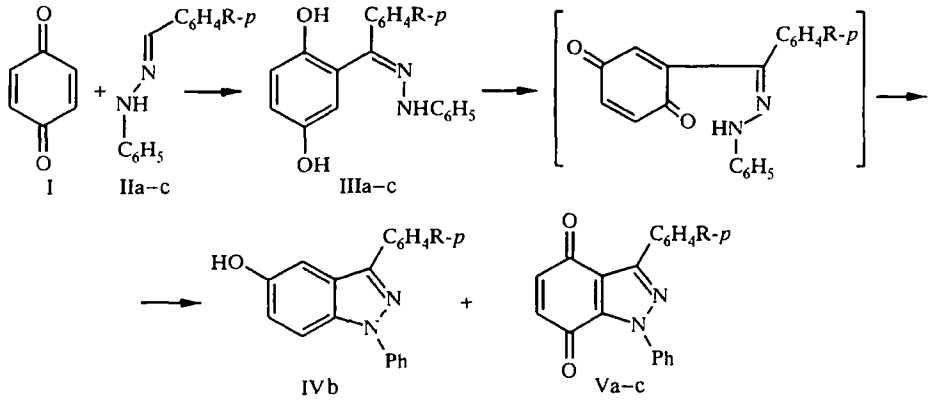
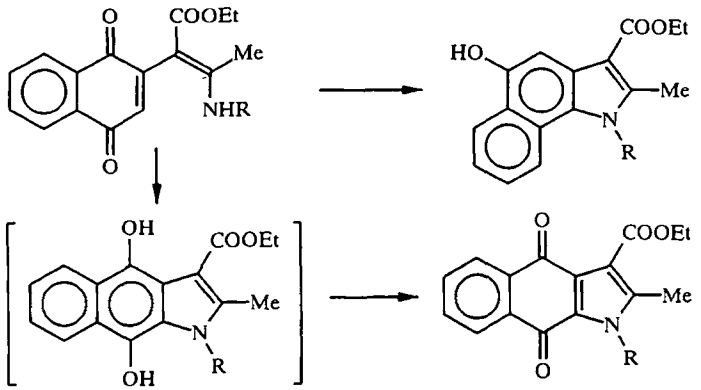
electrophilic carbon atom of the quinone on the nucleophilic carbon atom of the hydrazone. The condensation products IIIa and IIIb may be called "aza-hydroquinone adducts" by analogy with the Nenitzescu reaction products. When hydrazone IIb was used a small quantity of 5-hydroxyindazole IVb was isolated from the condensation reaction together with the adduct IIIb. Compounds IIIa and IIIb were oxidized with potassium ferrocyanide under usual conditions. Only the indazolquinone Va was isolated from the oxidation of compound IIIa, whereas 3-(4-nitrophenyl)-1-phenylindazoldione-4,7 (Vb) and 5-hydroxy-3-(4-nitrophenyl)-1-phenylindazole (IVb) were isolated and identified from the oxidation of compound IIIb.



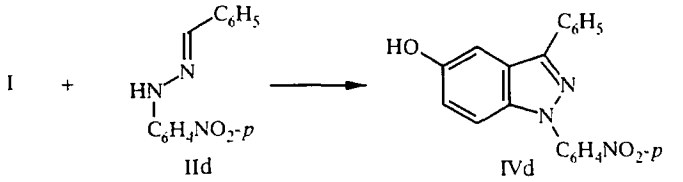
IIa, IIIa, Va R = Br; IIb, IIIb, IVb, Vb R = NO_2;
IIc, IIIc, Vc R = OMe

Evidently the initially formed hydroquinone fragment is transformed into the quinone as the oxidation proceeds. Subsequent indazole ring closure occurs in two directions characteristic of the quinone – attack of the unshared pair of the NH group electrons at the carbonyl carbon atom or at atom $C_{(3)}$. The first case is the true aza-Nenitzescu reaction while the second is the formation of indazoloquinones. There is a analogy with the usual Nenitzescu reaction: cyclization of the enaminoquinones also occurs in directions which give as final products derivatives of 5-hydroxyquinone and pyrrolonaphthoquinone [7].



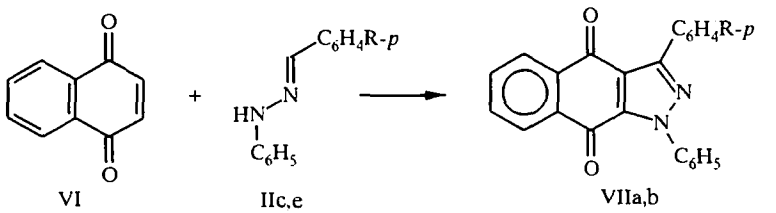
An important aspect of the aza-Nenitzescu reaction is that the "aza-hydroquinone adducts" are very stable and usually require an external reagent for oxidation. In the normal Nenitzescu reaction oxidation occurs at the same time as condensation of the quinones with the enamines [1, 2] although a number of exceptions have been observed [8]. Evidently the presence of the electron accepting aza group hinders the oxidation process and quinone is an insufficiently strong oxidizing reagent to convert the "aza-hydroquinone adduct" into the "azaquinone adduct."

The reaction of quinone I with the phenylhydrazone of methoxybenzaldehyde IIc occurred extremely ambiguously (TLC) and only a small yield of the corresponding "aza-hydroquinone adduct" IIIc was isolated. Oxidation of IIIc did not give products of cyclization. A tar-like substance was formed and the corresponding indazoloquinone Vc ($M^{+\cdot}$ 330) was only detected among the reaction products by mass spectrometry. The reaction of quinone I with benzaldehyde *p*-nitrophenylhydrazone (IId) proceeded extremely slowly. Even when the reaction was considerably prolonged most of the starting hydrazone IId remained unreacted. After its removal a very small yield of the aza-Nenitzescu reaction product – 5-hydroxy-1-(4-nitrophenyl)-3-phenylindazole (IVd) – was isolated.



The reduced reactivity of compound IId in comparison with hydrazone IIb is probably caused by the great proximity of the nitro group in the former to the secondary NH group, the electron donor effect of which determines the increased electron density on the carbon atom and the corresponding possibility of condensation with the quinone.

The final stage of this work deals with the use of naphthoquinone (VI) as the quinone component in the aza-Nenitzescu reaction. Reaction the quinone VI with benzaldehyde phenylhydrazone IIe and with hydrazone IIc gave the dioxobenzindazoles VIIa and VIIb but isolation of the intermediate "aza-hydroquinone adducts" was not successful in this case.



IIc, VIIb, R = OMe; IIe, VIIa R = H

Thus this study shows that the aza-Nenitzescu reaction is general and may be used to synthesize new derivatives of 5-hydroxyindazole and indazol-4,7-diones.

EXPERIMENTAL

^{1}H NMR Spectra were recorded in DMSO-d_6 solution with TMS as internal standard with Varian Unity Plus 400 MHz instrument. Mass spectra were recorded with a Finnigan SSQ-710 chromato-mass spectrometer with direct injection of the sample into the ionization source. Progress of reactions and purity of products were monitored by TLC on Silufol UV-254 strips with UV detection.

Phenylhydrazone of 4-Bromophenyl-2',5'-dihydroxyphenylketone (III a). *p*-Toluenesulfonic acid (0.12 g, 0.65 mmol) and quinone I (0.78 g, 7 mmol) were added with stirring at 20°C to a suspension of phenylhydrazone IIa (1.8 g, 6.5 mmol) in acetic acid (10 ml). Stirring was continued for 3 h. The precipitate was filtered off, washed with AcOH and water, and dried to give compound IIIa (1.05 g, 42%); mp 114-116°C (from 1:1 benzene–petroleum ether). $M^{+\cdot}$ 383. Found, %: C 59.1; H 4.0; Br 20.3; N 7.3. $C_{19}H_{15}BrN_2O_2$. Calculated, %: C 59.5; H 3.9; Br 20.8; N 7.3.

Phenylhydrazone of 2,5-Dihydroxyphenyl-4'-nitrophenylketone (IIIb) and 5-Hydroxy-3-(4-nitrophenyl)-1-phenylindazole (IVb). *p*-Toluenesulfonic acid (0.14 g, 0.8 mmol) and quinone I (0.99 g, 9 mmol) were added with stirring at 20°C to a suspension of hydrazone IIb (2.0 g, 8.3 mmol) in acetic acid (15 ml). Stirring

was continued for 12 h. The reaction mass was diluted with water, the precipitate was filtered off, washed with water and dried to give 2.5 g of crude product, which was dissolve in a minimum amount of dichloroethane and the insoluble crystals were filtered off to give compound IIIb (0.13 g); mp 132-135°C (dichloroethane), $M^{+\cdot}$ 349. The filtrate was chromatographed on a silica gel column with dichloroethane as eluent. Subsequently compound IVb (0.05 g, 0.2%); mp 146-149°C (dichloroethane), $M^{+\cdot}$ 331, and compound IIIb (0.8 g, 32% overall) were isolated.

Compound IIIb. ^{1}H NMR spectrum: 6.44 (1H, d, J = 2.8 Hz, 6-H), 6.8 (1H, q, J_1 = 8.8, J_2 =2.8 Hz, 4-H), 6.87 (1H, d, J = 8.8 Hz, 3-H); 6.82 (1H, m), 7.23 (2H, m) and 7.32 (2H, m) (C_6H_5); 7.67 (2H) and 8.18 (2H) (A_2B_2, C_6H_4); 9.02 (1H, s, OH), 9.06 (1H, s, OH), 9.18 ppm (1H, br. s, NH). Found, %: C 65.3; H 4.3; N 11.9. $C_{19}H_{15}N_3O_4$. Calculated, %: C 65.3; H 4.3; N 12.0.

Compound IVb. ^{1}H NMR spectrum: 7.14 (1H, q, J_1 = 9.2, J_2 = 2.4 Hz, 6-H), 7.46 (1H, d, J = 2.4 Hz, 4-H), 7.78 (1H, d, J = 9.2 Hz, 7-H); 7.45 (1H, m), 7.62 (2H, m) and 7.83 (2H, m) (C_6H_5); 8.27 (2H) and 8.40 (2H) (A_2B_2, C_6H_4); 9.71 ppm (1H, s, OH). Found, %: C 68.6; H, 4.2; N 12.5. $C_{19}H_{13}N_3O_3$. Calculated, %: C 68.9; H 4.0; N 12.7.

Phenylhydrazone of 2,5-Dihydroxyphenyl-4′-methoxyphenylketone (IIIc). *p*-Toluenesulfonic acid (0.17 g, 1 mmol) and quinone I (1.08 g, 10 mmol) were added with stirring at 20°C to a suspension of hydrazone IIc (2.26 g, 10 mmol) in acetic acid (10 ml). Stirring was continued for 3 h. The reaction mixture was diluted with water, the water was carefully decanted from the oily material which was stirred with chloroform, and the crystals were filtered to give compound IIIc (0.2 g). The filtrate was washed with water, dried over $MgSO_4$, and chromatographed on a silica gel column with chloroform as eluent. An additional amount of IIIc* was obtained (0.03 g). Yield 0.23 g, (7%); mp 142-145°C (benzene). $M^{+\cdot}$ 334.

^{1}H NMR spectrum: 3.74 (3H, s, CH_3), 6.38 (1H, d, J = 3.2 Hz, 6-H), 6.40 (1H, d, J = 9.2 Hz, 3-H), 6.74 (1H, q, J_1 = 9.2, J_2 = 3.2 Hz, 4-H); 6.72 (1H, m) and 7.16 (4H, m) (C_6H_5); 6.88 (2H) and 7.40 (2H) (A_2B_2, C_6H_4); 8.33 (1H, s, OH), 8.92 (1H, s OH), 8.98 ppm (br. s, NH). Found, %: C 72.0; H 5.6; N 8.0. $C_{20}H_{18}N_2O_3$. Calculated, %: C 71.8; H 5.4; N 8.4.

5-Hydroxy-3-(4-nitrophenyl)-1-phenylindazole (IVb) and 3-(4-nitrophenyl)-4,7-dioxo-1-phenylindazole (Vb). An oxidizing mixture, prepared from potassium ferrocyanide (0.5 g), sodium bicarbonate (0.12 g) and water (4 ml), was added to a vigorously stirred mixture of compound IIIb (0.28 g, 0.8 mmol), chloroform (25 ml), sodium bicarbonate (0.12 g) and water (1.8 ml) at 20°C. Stirring was continued for 7 h, then the organic layer was separated, washed with water, and the chloroform evaporated. The residue was recrystallized from benzene to give compound Vb (0.09 g). The filtrate was chromatographed on a silica gel column and compound Vb (0.03 g, overall yield 0.12 g, 44%) and compound IVb (0.03 g, 12%,) were consecutively isolated from the benzene eluate.

Compound Vb. Mp 228-230°C (benzene). $M^{+\cdot}$ 345. 1H NMR spectrum: 6.91 (2H, AB, J = 10 Hz, 5-H, 6-H); 7.59 (3H, m) and 7.73 (2H, m) (C_6H_5); 8.38 ppm (4H, A_2B_2, C_6H_4). Found, %: C 65.6; H 3.1; N 12.0. $C_{19}H_{11}N_3O_4$. Calculated, %: C 66.1; H 3.2; N 12.2.

5-Hydroxy-1-(4-nitrophenyl)-3-phenylindazole (IVd). *p*-Toluenesulfonic acid (0.17 g, 1 mmol) and quinone I (1.08 g, 10 mmol) were added with stirring at 20°C to a suspension of hydrazone IId (2.41 g, 10 mmol) in acetic acid (15 ml). Stirring was continued for 48 h. The precipitate was filtered off, washed with AcOH and water, and dried to give the starting material IId (2.0 g). The filtrate was diluted with water, the precipitate formed was filtered off, washed with water, dried, and dissolved in benzene. The solution was chromatographed on a silica gel column. Elution with benzene gave a small amount of starting material IId. Elution with chloroform gave compound IVd (0.1 g, 3%); mp 248-250°C (chloroform), M^+ 331. ^{1}H NMR spectrum: 7.16 (1H, q, J_1 = 9.2, J_2 = 2.4 Hz, 6-H), 7.40 (1H, d, J = 2.4 Hz, 4-H), 7.98 (1H, d, J = 9.2 Hz, 7-H); 7.50 (1H, m), 7.59 (2H, m) and 7.98 (2H, m) (C_6H_5); 8.15 (2H) and 8.41 (2H) (A_2B_2, C_6H_4); 9.73 ppm (1H, s, OH). Found, %: C 68.9; H 4.1; N 12.6. $C_{19}H_{13}N_3O_3$. Calculated, %: C 68.9; H 4.0; N 12.7.

3-(4-Bromophenyl)-4,5-dioxo-1-phenylindazole (Va). An oxidizing solution, prepared from potassium ferrocyanide (0.8 g), sodium bicarbonate (0.2 g), potassium carbonate (0.25 g) and water (6.6 ml) was added to a vigorously stirred mixture of compound IIIa (0.5 g, 1.3 mmol), chloroform (5 ml), sodium bicarbonate (0.2 g), and water (3 ml) at 20°C. Stirring was continued for 1 h, the organic layer was separated, washed with water, and

* The first fractions contained mostly compound Vc ($M^{+\cdot}$ 330) mixed with other compounds.

chloroform was evaporated. The residue was dissolved in benzene and chromatographed on a silica gel column. Compound Va was isolated from the benzene eluate: 0.08 g (16%); mp 192-194°C (propanol), M^+ 379. ^1H NMR spectrum: 6.87 (2H, AB, J = 10 Hz, 5-H, 6-H); 7.56 (3H, m) and 7.68 (2H, m) (C_6H_5); 7.71 (2H) and 8.06 ppm (2H) (A_2B_2, C_6H_4). Found, %: C 60.0; H 3.0; Br 20.6; N 7.4. $C_{19}H_{11}BrN_2O_2$. Calculated, %: C 60.2; H 2.9; Br 21.1; N 7.4.

4,9-Dioxo-1,3-diphenylbenzindazole (VIIa). *p*-Toluenesulfonic acid (0.34 g, 2 mmol) and quinone VI (3.16 g, 20 mmol) were added with stirring at 20°C to a suspension of hydrazone IIe (3.92 g, 20 mmol) in acetic acid (20 ml). Stirring was continued for 24 h. The precipitate was filtered off, washed with AcOH and water, dried, and dissolved in benzene. The solution was chromatographed on a silica gel column. Compound VIIa was isolated from the benzene eluate: 1.6 g (23%); mp 254-255°C (acetone). M^+ 350. ^1H NMR spectrum: 7.53 (3H, m), 7.59 (3H, m), 7.76 (2H, m), 8.12 (2H, m) (two C_6H_5); 7.88 (1H, m), 7.94 (1H, m), 8.08 (1H, m), 8.19 ppm (1H, m) (5-H, 6-H, 7-H, 8-H). Found, %: C 78.3; H 4,3; N 8.0. $C_{23}H_{14}N_2O_2$. Calculated, %: C 78.8; H 4.0; N 8.0.

Compound VIIb was prepared analogously from quinone VI and hydrazone IIc. Yield 6%; mp 274-275°C. M^+ 380. ^1H NMR spectrum: 3.84 (3H, s, CH_3); 7.07 (2H) and 8.12 (2H) (A_2B_2, C_6H_4); 7.57 (3H, m) and 7.74 (2H, m) (C_6H_5); 7.86 (1H, m), 7.92 (1H, m), 8.06 (1H, m), 8.18 ppm (1H, m) (5-H, 6-H, 7-H, 8-H). Found, %: C 76.0; H 4.3; N 7.1. $C_{24}H_{16}N_2O_3$. Calculated, %: C 75.8; H 4.2; N 7.4.

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