The use of enehydrazines in the Nenitzescu reaction

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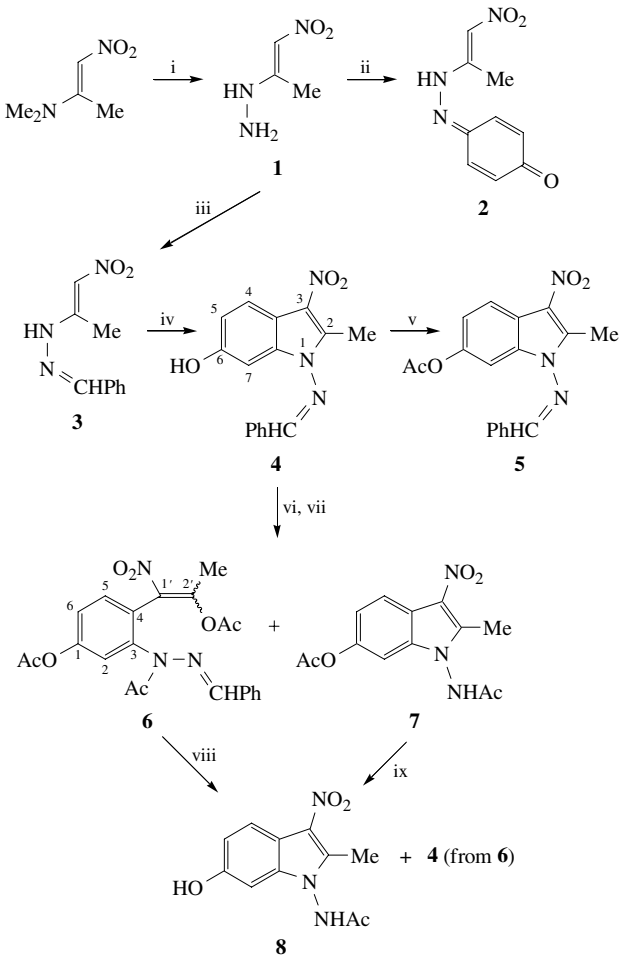
The Nenitzescu reaction involving a nitroenehydrazine 1 has been studied for the first time, and novel 1-aminoindole derivatives have been synthesised.

The Nenitzescu reaction, which is the basis for the synthesis of 5-hydroxyindole and 5-hydroxybenzofuran derivatives, allows the structures of starting compounds, *i.e.*, quinones and enamines, to be varied over a wide range.[1–3] Nontraditional final products can often be obtained from nontrivial starting compounds.[4,5] In this work, we synthesised 1-methyl-2-nitrovinylhydrazine **1**† by the transamination of 2-dimethylamino-1-nitroprop-1-ene.[6] To date, enehydrazines have not been used as enamine components in the Nenitzescu reaction. It was found that the condensation of compound **1** with *p*-benzoquinone results in corresponding hydrazone 4-[(1-methyl-2-nitrovinyl)-hydrazono]cyclohexa-2,5-dienone **2**.‡ Thus, the Michael C–C addition, which is mandatory for the Nenitzescu reaction, does not occur in this case; compound **1** acts as a hydrazine derivative rather than an enamine. Therefore, the condensation of compound **1** with benzaldehyde gave *N*-benzylidene-*N*′-(1-methyl-2-nitrovinyl)hydrazine **3**.§ The interaction of the latter with *p*-benzoquinone occurred as a Nenitzescu reaction to give 1-(benzylideneamino)-2-methyl-3-nitro-1*H*-indol-6-ol **4**.¶ The acetylation of the latter gave an *O*-acetyl derivative, 1-benzylidenamino-2-methyl-3-nitro-6-acetoxy-1*H*-indole **5**.†† The position of the hydroxy (or acetoxy) group in compounds **4** and **5** was determined using the HMBC spectra of compound **5**. The C_{3a} signal (δ 117.3 ppm) has correlation peaks with 5-H signals of 7.20 (dd, J_1 8.6 Hz, J_2 1.2 Hz) and with 7-H signals of 7.59 (d, J_2 1.2 Hz), which show unambiguously that 6-hydroxy (**4**) and then 6-acetoxy (**5**) derivatives are formed.



Scheme 1 *Reagents and conditions*: i, hydrazine hydrate (22 mmol) was added to a suspension of 2-dimethylamino-1-nitroprop-1-ene (20 mmol) in 10 ml of isopropanol; the mixture was stirred (20 °C, 1 h) and evaporated. The residue was triturated with cold isopropanol and the precipitate was filtered off; ii, a mixture of *p*-benzoquinone (5 mmol) and compound **1** (5 mmol) in 5 ml of AcOH (20 °C, 2 h), and the precipitate was filtered off; iii, a mixture of compound **1** (2 mmol), EtOH (10 ml), and benzaldehyde (2 mmol) was stirred (20 °C, 1 h) and the precipitate was filtered off; iv, a mixture of *p*-benzoquinone (4.6 mmol), *p*-toluenesulfonic acid (4.6 mmol), and compound **3** (4.6 mmol) in 12 ml of AcOH was stirred (20 °C, 3 h) and the precipitate was filtered off; v, a mixture of compound **4** (6.4 mmol) and Ac_2O (20 ml) was refluxed for 1 h, diluted with water, and filtered; vi, a mixture of compound **4** (1.1 mmol), Ac_2O (3 ml), and 1 drop of H_2SO_4 was stirred for 1.5 h at 20 °C; compound **6** was filtered off; the mother liquor was diluted with water and the precipitate formed was chromatographed on a column with silica gel (ethyl acetate) to isolate compounds **6** and **7**; vii, a mixture of compound **4** (1.5 mmol), Ac_2O (4.5 mmol), a drop of H_2SO_4, and 10 ml of AcOH was stirred for 2 h at 50 °C; viii, a mixture of compound **6** (1.4 mmol), HCl (1 ml), EtOH (40 ml), and H_2O (1 ml) was refluxed for 20 min and evaporated; the residue was triturated with ethanol; compound **4** was filtered off and compound **8** was isolated from the mother liquor; ix, a mixture of compound **7** (1.4 mmol), piperidine (2.8 mmol), benzene (20 ml), and EtOH (5 ml) was refluxed for 6 h and evaporated; the residue was triturated with benzene and the precipitate was filtered off.

† ^{1}H NMR spectra were recorded on AC-200 (Bruker) and DRX-500 (Bruker) spectrometers. Mass spectra were recorded on a Finnigan SSQ mass spectrometer with direct sample injection into the ion source.

For compound **1**: yield 73%, mp 83–85 °C (benzene). ^{1}H NMR ([$^2H_6$]DMSO) δ: 2.01 (s, 3H, 1-Me), 5.00 (br. s, 2H, NH_2), 6.31 (s, 1H, 2-H), 11.23 (br. s, 1H, NH). MS, *m*/*z*: 117. Found (%): C, 30.97; H, 5.96; N, 35.65. Calc. for $C_3H_7N_3O_2$ (%): C, 30.77; H, 6.03; N, 35.88.

‡ For compound **2**: yield 37%, mp 111–113 °C (decomp.). ^{1}H NMR ([$^2H_6$]DMSO), δ: 2.45 (d, 3H, 1-Me, *J* 1.2 Hz), 6.90, 7.70 (2m, 2×2H, C_6H_4), 7.95 (q, 1H, 2-H, *J* 1.2 Hz, $J_{CH–NH}$ 1.2 Hz), 10.37 (br. s, 1H, NH). MS, *m*/*z*: 207.

§ For compound **3**: yield 88%, mp 175–177 °C (EtOH). ^{1}H NMR ([$^2H_6$]DMSO) δ: 2.22 (s, 3H, 1-Me), 6.74 (s, 1H, 2-H), 7.49, 7.75 (m, 5H, Ph), 8.61 (s, 1H, C*H*Ph), 12.43 (br. s, 1H, NH). MS, *m*/*z*: 205. Found (%): C, 58.49; H, 5.40; N, 19.95. Calc. for $C_{10}H_{11}N_3O_2$ (%): C, 58.53; H, 5.40; N, 20.48.

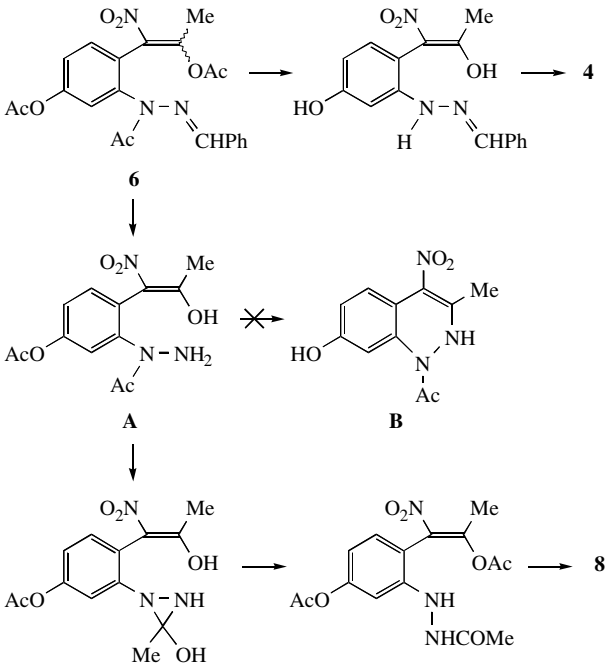
¶ For compound **4**: yield 22%, mp 263–265 °C (EtOH). ^{1}H NMR ([$^2H_6$]DMSO) δ: 2.85 (s, 3H, 2-Me), 6.87 (dd, 1H, 5-H, J_1 8.6 Hz, J_2 1.2 Hz), 6.97 (d, 1H, 7-H, J_2 1.2 Hz), 7.60 (m, 3H, 3′-H, 4′-H, 5′-H), 8.03 (d, 2H, 2′-H, 6′-H, *J* 7.4 Hz), 7.98 (d, 1H, 4-H, *J* 8.6 Hz), 9.12 (s, 1H, C*H*Ph). MS, *m*/*z*: 295. Found (%): C, 65.63; H, 4.47; N, 13.75. Calc. for $C_{16}H_{13}N_3O_3$ (%): C, 65.08; H, 4.44; N, 14.23.

†† For compound **5**: yield 70%, mp 182–183 °C (EtOH). ^{1}H NMR ([$^2H_6$]DMSO) δ: 2.27 (s, 3H, 6-OCOMe), 2.87 (s, 3H, 2-Me), 7.20 (dd, 1H, 5-H, J_1 8.6 Hz, J_2 1.2 Hz), 7.59 (d, 1H, 7-H, J_2 1.2 Hz), 7.60 (t, 2H, 3′-H, 5′-H, *J* 7.4 Hz), 7.67 (t, 1H, 4′-H, *J* 7.4 Hz), 8.05 (d, 2H, 2′-H, 6′-H, *J* 7.4 Hz), 8.20 (d, 1H, 4-H, J_1 8.6 Hz), 9.14 (s, 1H, C*H*Ph). ^{13}C NMR ([$^2H_6$]DMSO) δ: 12.3 (2-Me), 20.6 (6-OCO*Me*), 104.6 (C_7), 117.3 (C_{3a}), 118.8 (C_5), 120.1 (C_4), 125.0 (C_3), 128.9, 130.6, 131.9 (Ph), 130.6 (C_{7a}), 141.2 (C_2), 147.7 (C_6), 166.6 (*C*HPh), 169.1 (O*C*OMe). MS, *m*/*z*: 337. Found (%): C, 64.09; H, 4.51; N, 12.31. Calc. for $C_{18}H_{15}N_3O_4$ (%): C, 64.09; H, 4.48; N, 12.46.

One correlation peak of the C_{3a} signal with H-7 is possible for the structure with 5-OAc. Note that a 6- (rather than 5-) hydroxyindole is formed, which is typical of the Nenitzescu reaction involving nitroenamines.[7] The reaction of compound **4** in acetic anhydride in the presence of a catalytic amount of concentrated H_2SO_4 results in the cleavage of the indole ring at the 1,2-bond accompanied by the acetylation of OH and NH groups and the formation of 3-[acetyl-2-(benzylidene)-hydrazino]-4-[2-(acetoxy)-1-nitropropen-1-yl]phenyl acetate **6**.‡‡ The structure of compound **6** was proven by ^{1}H and ^{13}C NMR spectra, which differ considerably from those of compound **5**. First, owing to the existence of geometric isomers, the spectra of compound **6** contain a double set of signals, which were assigned on the basis of COSY, NOESY, HSQC and HMBC spectra. Furthermore, the ^{1}H NMR spectrum contains double signals of four methyl groups, three of which are acetyl groups. The latter have correlation peaks with C=O signals in the region δ 168.0–171.0 of the HMBC spectrum. On the other hand, signals of the 2′-methyl group are considerably upfield shifted (1.81, 1.90 ppm) in comparison with the methyl group signals in the spectrum of compound **5** (2.87 ppm). We observed a similar shift on transition from non-cyclic intermediates (hydroquinone adducts) to final compounds (*e.g.*, indole-type ones) formed in the Nenitzescu reaction.[7] The chemical shifts of the benzylidene proton differ significantly in both ^{1}H and ^{13}C NMR spectra: δ 9.14 and 166.6 (**5**); δ 7.88, 8.06 and 79.1, 83.1 (**6**). The reaction also gives 1-acetylamino-2-methyl-3-nitro-6-acetoxyindole **7**,§§ *i.e.*, a hydrolysis product of the Shiff base and an O- and N-acetylation product. Acetylation under different conditions (AcOH, Ac_2O, H_2SO_4, heating) also gives compounds **6** and **7**, but their ratio changes essentially: indole **7** becomes the main reaction product. The acid hydrolysis of compound **6** gives unexpectedly 1-acetylamino-2-methyl-3-nitro-6-hydroxyindole **8**¶¶ in a high yield. A small amount of indole **4** was isolated as a by-product.

To explain the transformation of compound **6** into indole **8** (acyl migration is observed), we propose a scheme according to which the hydrolysis of the Schiff base and acetoxy groups is accompanied by an acylotropic rearrangement. Such rearrangements were observed before.[9,10]

The formation of indole **4** in this reaction probably occurs by a simpler scheme, *viz.*, N-deacylation and hydrolysis of acetoxy groups in compound **6**, and the indole ring closure. Thorough proof was required to determine the structure of compound **8**, since possible transformation of hypothetical intermediate product **A** (Scheme 2) into cinnoline derivative **B** with the closure of a six-membered pyridazine ring could not be ruled out. Compounds **8** and **B** have identical elemental compositions;



Scheme 2

furthermore, the ^{1}H NMR spectra of compound **8** do not contradict to the assumed structure of **B**. However, a comparison of ^{1}H and ^{13}C NMR spectra of compounds **7** and **8** makes it possible to assume that indole derivative **8** is formed. In fact, while the majority of chemical shifts in compound **8** do not change considerably in comparison with compound **7**, the H-5, H-7 and C_5, C_7 signals are shifted upfield by 0.29, 0.61 and 5.0, 8.4 ppm, respectively. These data allow us to assume that compounds **7** and **8** only differ by substituents at the position 6. This is also confirmed by the difference NOE spectra of compound **8**: H-7 (δ 6.71 ppm) and 2-Me (δ 2.64 ppm) signals are observed upon pre-irradiation of COMe protons (2.18 ppm), which is only possible in compound **8**.

The structure of compound **8** was also confirmed by an independent synthesis. The deacetylation of indole **7** by refluxing in benzene in the presence of piperidine gave indole **8**. The TLC characteristics of the samples are identical; a mixing test did not show any melting point depression. The derivatives of 1-amino-6-hydroxyindole, which were synthesised for the first time using the Nenitzescu reaction, are of interest in terms of their chemical and biological properties.

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‡‡ For compound **6**: yield 63% (vi) or 18% (vii), mp 183–185 °C (EtOH). ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.90, 1.81 (2s, 2×3H, 2′-Me), 1.74, 2.10, 2.19, 2.70 (4s, 4×3H, NAc, 2′-OAc), 2.34 (s, 6H, 1-OAc), 7.70, 7.75 (2d, 2×1H, 2-H, *J* 1.7 Hz), 7.06–7.37 (m, 6H, Ph, 5-H), 7.88, 8.08 (2s, 2×1H, C*H*Ph), 8.09, 8.15 (2d, 2×1H, 5-H, *J* 8.6 Hz). ^{13}C NMR ([$^2H_6$]DMSO) δ: 11.4, 11.5 (2′-Me), 20.1, 20.4, 20.5, 20.6, 20.9, 21.12 (NCO*Me*, 2′-OCO*Me*, 1-CO*Me*), 79.1, 83.1 (*C*HPh), 105.5, 105.6 (C_2), 116.3 (C_4), 118.9, 119.4 (C_5), 119.9, 120.3 (C_6), 125.0 (C_1'), 128.9, 128.4, 128.6, 130.0 (Ph), 135.0 (C_3), 144.4, 145.2 (C_2'), 148.5 (C_1), 168.0–171.0 (N*C*OMe, 2′-O*C*OMe, 1-*C*OMe). MS, m/z: 439. Found (%): C, 59.88; H, 4.82; N, 9.64. Calc. for $C_{20}H_{19}N_3O_6$ (%): C, 60.13; H, 4.81; N, 9.56.

§§ For compound **7**: yield 48% (vi) or 37% (vii), mp 239–240 °C (EtOH). ^{1}H NMR ([$^2H_6$]DMSO) δ: 2.19 (s, 3H, 1-NCOMe), 2.30 (s, 3H, 6-OCOMe), 2.66 (s, 3H, 2-Me), 7.16 (dd, 1H, 5-H, J_1 8.6 Hz, J_2 1.2 Hz), 7.32 (d, 1H, 7-H, J_2 1.2 Hz), 8.12 (d, 1H, 4-H, J_1 8.6 Hz), 11.55 (br. s, 1H, NH). ^{13}C NMR ([$^2H_6$]DMSO) δ: 11.4 (2-Me), 20.4, 20.8 (1-NCO*Me*, 6-OCO*Me*), 103.8 (C_7), 116.3 (C_{3a}), 118.9 (C_5), 120.1 (C_4), 124.2 (C_3), 134.2 (C_{7a}), 144.4 (C_2), 147.9 (C_6), 169.2, 169.3 (1-N*C*OMe, 6-O*C*OMe). MS, *m/z*: 291. Found (%): C, 53.48; H, 4.55; N, 14.15. Calc. for $C_{13}H_{13}N_3O_5$ (%): C, 53.61; H, 4.50; N, 14.43.

¶¶ For compound **8**: yield 92% (viii) or 90% (ix), mp 262 °C (decomp., Pr^{i}OH). ^{1}H NMR ([$^2H_6$]DMSO) δ: 2.18 (s, 3H, 1-NCOMe), 2.64 (s, 3H, 2-Me), 6.71 (d, 1H, 7-H, J_2 1.2 Hz), 6.87 (dd, 1H, 5-H, J_1 8.6 Hz, J_2 1.2 Hz), 7.90 (d, 1H, 4-H, J_1 8.6 Hz), 9.56 (br. s, 1H, 6-OH), 11.35 (br. s, 1H, NH). ^{13}C NMR ([$^2H_6$]DMSO) δ: 11.4 (2-Me), 20.3 (1-NCO*Me*), 95.4 (C_7), 111.4 (C_{3a}), 113.9 (C_5), 120.4 (C_4), 124.4 (C_3), 135.3 (C_{7a}), 142.3 (C_2), 155.6 (C_6), 169.0 (1-N*C*OMe). MS, m/z: 249. Found (%): C, 53.03; H, 4.60; N, 16.49. Calc. for $C_{11}H_{11}N_3O_4$ (%): C, 53.01; H, 4.45; N, 16.86.