The first example of the synthesis of 1-aminoindole derivatives by the Nenitzescu reaction

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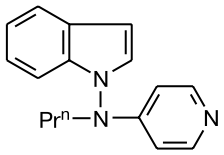
The Nenitzescu reaction with 1-methyl-2-nitrovinylhydrazine was studied for the first time. 1-Amino-6-hydroxyindole derivatives containing a nitro group in position 3 were synthesized.

Key words: nitro enehydrazines, Nenitzescu reaction, 1-aminoindoles, X-ray diffraction analysis.

1-Aminoindoles attract considerable attention of the researchers because some of them are biologically active,[1] exhibiting, *e.g.*, psychotropic,[2] antispasmodic,[3] and analgesic effects.[4] 1-Aminoindole derivatives have been extensively studied as potential therapeutic agents for treatment of Alzheimer's disease.[5] An 1-arylaminoindole derivative has been clinically approved and recommended as a symptomatic means.[5]



At present, there are a number of routes to 1-aminoindole derivatives; however, the most commonly used method for the synthesis of compounds of this type and primarily unsubstituted 1-aminoindole is direct amination of indoles with hydroxylamine-*O*-sulfonic acid[6] or, less often, *O*-(diphenylphosphinyl)hydroxylamine proposed later as an aminating agent.[7] A rather serious limitation of this method is its applicability only to indoles containing no strong electron-withdrawing substituents. Among other techniques, reduction of 1-nitrosoindoles to 1-aminoindoles[8,9] is worth noting. A number of investigations was devoted to contraction of the pyridazine ring in cinnoline derivatives.[1,10]

In the present study, 1-aminoindole derivatives were synthesized by the Nenitzescu reaction (Scheme 1); this approach has been recently published by us in a brief communication.[11] The Nenitzescu reaction, which is the most accessible method for the synthesis of 5-hydroxyindole and 5-hydroxybenzofuran derivatives, allows a wide variation in the structures of the starting quinones and enamines.[12—14] Use of nontrivial starting reagents often leads to uncommon products.[15,16] We carried out the Nenitzescu reaction with an *N*-amino derivative of nitro enamine, namely, 1-methyl-2-nitrovinylhydrazine (**2**) prepared by transamination of 2-dimethylamino-1-nitroprop-1-ene (**1**)[17] with hydrazine hydrate. Note that enehydrazines have not been used hitherto as enamine components in the Nenitzescu reaction. With hydrazine **2** as the starting reagent, one could obtain 1-aminoindole derivatives bearing such a strong electron-withdrawing substituent in position 3 as the nitro group. As noted above, the synthesis of such compounds by conventional methods is quite problematic.

We assumed that the presence of such a substituent as the amino group in enamine could complicate condensation of the enamine component with quinone.

Indeed, the condensation of enamine **2** with *p*-benzoquinone follows a different pathway: the Michael C—C addition indispensable for the Nenitzescu reaction does not occur in this case, compound **2** behaving like a hydrazine derivative rather than an enamine. The reaction gave the corresponding hydrazone, namely, 4-[(1-methyl-2-nitrovinyl)hydrazono]cyclohexa-2,5-dienone (**3**) (see Scheme 1). For this reason, we synthesized *N*-benzylidene-*N*′-(1-methyl-2-nitrovinyl)hydrazine (**4**) containing no primary amino group by condensation of compound **2** with benzaldehyde. The Nenitzescu reaction of

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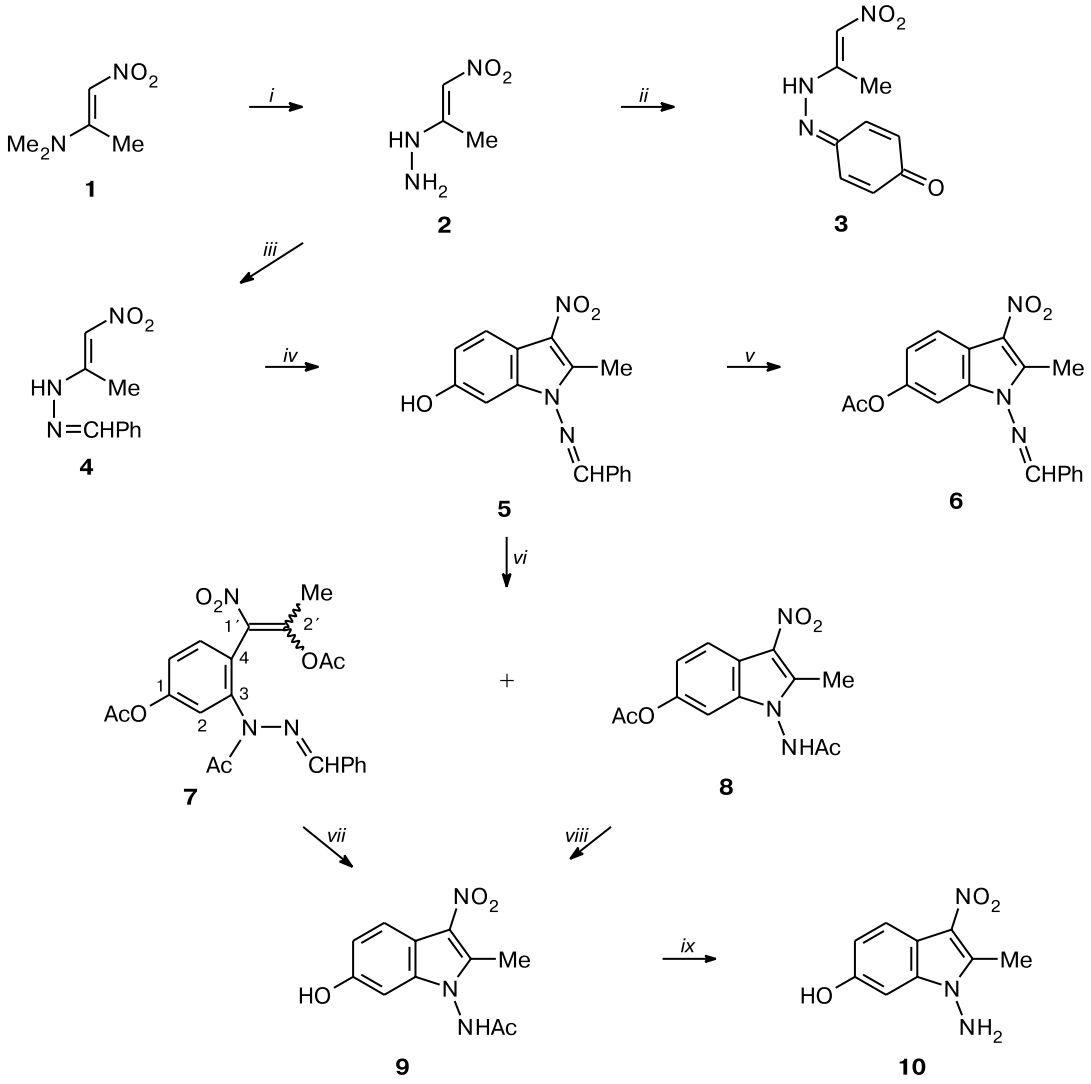
Scheme 1

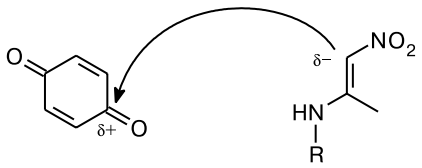


Reagents and conditions: *i*. $NH_2NH_2 \cdot H_2O$, 20 °C, 1 h; *ii*. *p*-Benzoquinone, 20 °C, 2 h; *iii*. Benzaldehyde, 20 °C, 1 h; *iv*. *p*-Benzoquinone, TsOH, 20 °C, 3 h; *v*. Ac_2O, refluxing, 1 h; *vi*. Ac_2O, H_2SO_4 (one drop), 20 °C, 1.5 h; *vii*. HCl, EtOH, H_2O, refluxing, 30 min; *viii*. Piperidine, benzene, EtOH, refluxing, 6 h; *ix*. HCl, Bu^nOH, H_2O, refluxing, 45 min.

compound **4** with *p*-benzoquinone yielded indole **5**. The indole structure of compound **5** was confirmed by ^1H NMR data; however, the position of the hydroxy group (5 or 6) requires special evidence since nitro enamines in the Nenitzescu reaction are known to give 6-hydroxyindoles.[18] A probable reaction mechanism and reasons for the formation of 6-hydroxy derivatives in the reactions of quinones with nitro enamines were analyzed in detail earlier.[13,14,18] An initial attack of the C_β atom of nitro enamines on the C(1) atom of the quinone is shown in Scheme 2.

Being insufficiently soluble for HMBC NMR study, compound **5** was *O*-acetylated in boiling acetic anhydride to give derivative **6**. Its HMBC spectrum shows correlation peaks of the signal at δ 117.3 (C(3a)) with the signals at δ 7.20 (dd, H(5), J_1 = 8.6 Hz, J_2 = 1.2 Hz) and 7.59 (d, H(7), J_2 = 1.2 Hz), which unambiguously indicates the formation of 6-hydroxy (**5**) and then 6-acetoxy derivatives (**6**). In a structure containing the 5-acetoxy group,

Scheme 2



the signal for C(3a) would show only one correlation peak with the signal for H(7) (for complete spectroscopic data, see Experimental).

In the reaction with acetic anhydride in the presence of a catalytic amount of conc. H_2SO_4 (*i.e.*, under the conditions used earlier for *O*-acylation of 6-hydroxy-3-nitroindoles[18]), compound **5** undergoes opening of the pyrrole ring through cleavage of the 1,2-bond with accompanying acetylation of the OH and NH groups to give 4-(2-acetoxy-1-nitroprop-1-enyl)-3-[(1-acetyl-2-benzylidene)hydrazino]phenyl acetate (**7**). The above behavioral differences between *N*-aminoindole derivative **5** and the corresponding deaminated compounds should be most reasonably associated with the destabilized ground state of the former. Indeed, the presence of the electron-withdrawing substituent (N=CHPh) at the indole N atom partially excludes its lone electron pair from the aromatic system, thus reducing the aromaticity of the molecule. As the result, the indole system easily degrades to give compound **7**. Such an opening of the pyrrole ring was detected as an intermediate step in the transformation of an *N*-aminoindole derivative into substituted quinolines.[19]

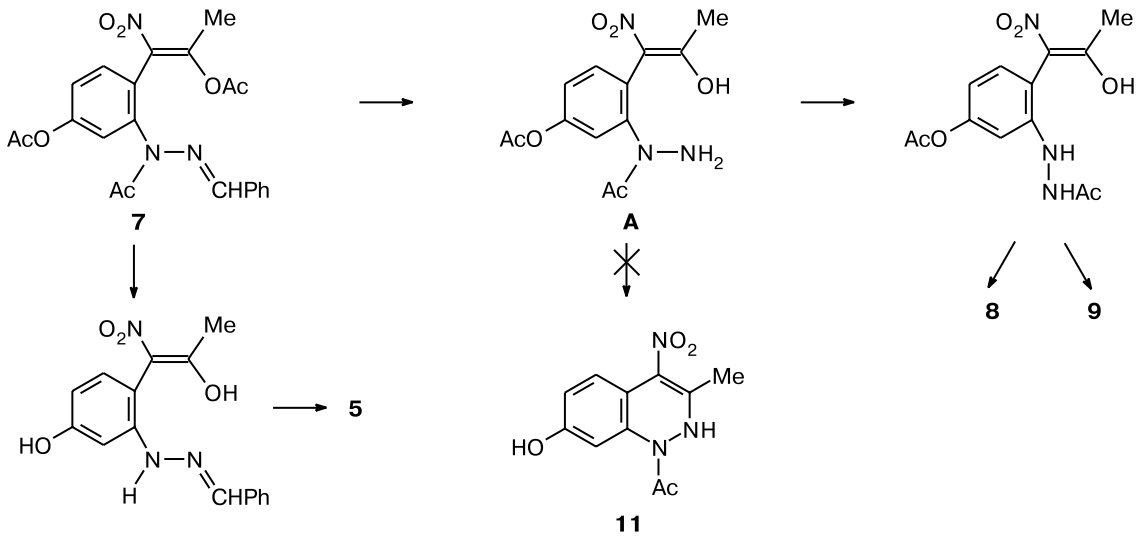
The structure of compound **7** was proved by ^1H and ^{13}C NMR spectra, which substantially differ from those of compound **6**. First, the spectra of compound **7** show a double set of signals due to geometrical isomers; the signals were assigned from the COSY, NOESY, HSQC and HMBC NMR spectra. Second, its ^1H NMR spectrum contains signals for four methyl groups three of which are in acetyl radicals. In the HMBC spectrum, the latter methyl groups show correlation peaks with signals for C=O at δ 168.0—171.0. The signals for the 2′-methyl group are strongly shifted upfield (δ 1.81 and 1.90) compared to the signals for the 2-methyl group in compound **6** (δ 2.87). A similar shift was observed when acyclic intermediates (hydroquinone adducts) were converted into final Nenitzescu products (*e.g.*, indoles).[20] The ^1H and ^{13}C chemical shifts of the signal for the benzylidene proton also differ largely: δ 9.14 and 166.6 for compound **6** and δ 7.88, 8.06 and 79.1, 83.1 for compound **7**, respectively. 6-Acetoxy-1-acetylamino-2-methyl-3-nitroindole (**8**) was obtained as a by-product.

Acid hydrolysis of compound **7** unexpectedly gave 1-acetylamino-6-hydroxy-2-methyl-3-nitroindole (**9**) in high yield; in addition, a small amount of indole **5** was isolated.

The hydrolysis aimed at the azomethine fragment and the acetoxy groups in compound **7** is accompanied by migration of the acyl residue (acylotropic rearrangement). Such rearrangements were reported earlier.[21,22] Apparently, the same scheme is valid in the formation of indole **8** from compound **7** (rather than from compound **5** as we assumed earlier[11]). This is evident from our unsuccessful attempts to hydrolyze compound **5** to 1-unsubstituted aminoindole. In this reaction, indole **5** is probably formed according to a simplified scheme: *N,O*-deacylation in compound **7** is followed by closure of the indole system (Scheme 3).

Solid proof was required to confirm the structure of compound **9** since the hypothetical intermediate **A** could undergo cyclization into cinnoline derivative **11** containing a six-membered pyridazine ring. The elemental compositions of compounds **9** and **11** are the same; moreover, ^1H NMR data for compound **9** are not in conflict with structure **11**. However, a comparison of the ^1H and ^{13}C NMR spectra of compounds **8** and **9** suggests the formation of the indole derivative **9**. For instance, most of the chemical shifts for compound **9** differ only slightly

Scheme 3



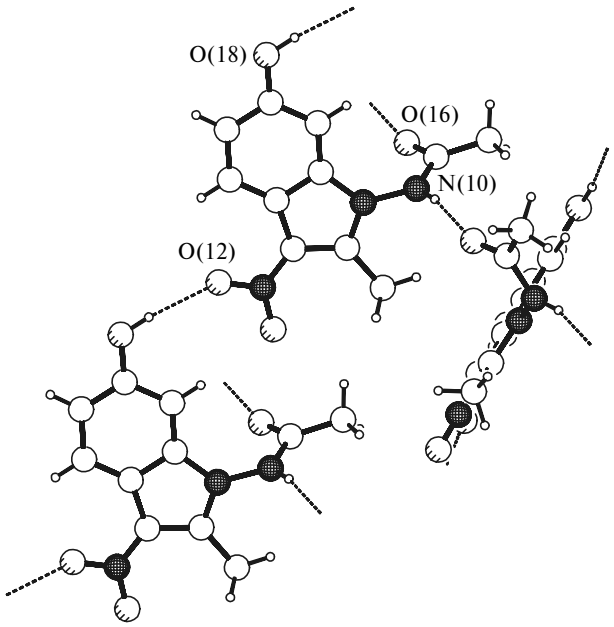


Fig. 1. Crystal packing of compound **9**.

from those for compound **8**, while the signals for H(5), H(7), C(5) and C(7) are shifted upfield by 0.29, 0.61, 5.0, and 8.4 ppm, respectively; this is due to the presence of different substituents in position 6 of compounds **8** and **9**. This was confirmed by the difference NOE data for compound **9**: when the Ac protons (δ 2.18) are preirradiated, the spectra show signals for H(7) (δ 6.71) and C(2)H_3 (δ 2.64), which are possible only for compound **9**.

The structure of compound **9** was finally proved by X-ray diffraction analysis. The three-dimensional structure of its molecule was determined from X-ray powder diffraction data. Crystals of compound **9** are monoclinic (space group $P2_1/c$, unit cell volume 1168(1) Å^3). The crystal packing of compound **9** is stabilized by N—H...O and O—H...O intermolecular hydrogen bonds (Fig. 1). Their geometric parameters are given in Table 1.

Compound **9** was also synthesized from indole **8** by its *O*-deacetylation in boiling benzene in the presence of piperidine.

Indole **10** with the unsubstituted amino group in position 1 was obtained in high yield by acid hydrolysis of its *N*-acyl derivative **9**.

Table 1. Geometric parameters of the hydrogen bonds in compound **9**

Hydrogen bond D—H...A	*d*/Å			Angle/deg D—H...A
	D—H	H...A	D...A	
N(10)—H(10)...O(16)^{i}	0.86	1.89	2.73(1)	162
O(18)—H(18)...O(12)^{ii}	0.87	2.10	3.00(1)	169

Symmetry operation codes: (*i*) x, $1/2 - y$, $1/2 + z$; (*ii*) $1 + x$, y, z.

Experimental

Mass spectra were recorded on a Finnigan SSQ-710 mass spectrometer (direct inlet probe). ^{1}H NMR spectra were recorded on a Bruker AC-200 spectrometer; 2D HMBC NMR spectra were recorded on a Bruker DRX-500 spectrometer in DMSO-d_6 with the use of Bruker standard procedures. The course of the reactions was monitored and the purity of compounds was checked by TLC on Silufol UV-254 plates in ethyl acetate (spot visualization in UV light). Reflection intensities were measured on a XPert PRO powder diffractometer (CuKα_1 radiation). The crystal structure of compound **9*** was solved by the systematic search method[23] and refined by the Rietweld method with the MRIA program.[24] The physicochemical characteristics, yields, and elemental analysis data for the compounds obtained are given in Table 2.

1-Methyl-2-nitrovinylhydrazine (2). Hydrazine hydrate (5.3 mL, 106 mmol) was added at 20 °C to a stirred suspension of enamine **1**[17] (12.2 g, 94 mmol) in 50 mL of isopropyl alcohol. the reaction mixture was kept for 1 h and concentrated. The residue was triturated with cooled isopropyl alcohol and the precipitate was filtered off. The yield of compound **2** was 9.37 g. ^{1}H NMR, δ: 2.01 (s, 3 H, Me); 5.00 (br.s, 2 H, NH_2); 6.31 (s, 1 H, H(2)); 11.23 (br.s, 1 H, NH).

4-[(1-Methyl-2-nitrovinyl)hydrazono]cyclohexa-2,5-dienone (3). Compound **2** (0.58 g, 5 mmol) was added to a solution of *p*-benzoquinone (0.54 g, 5 mmol) in 5 mL of AcOH. The reaction mixture was stirred at 20 °C for 2 h. The precipitate that formed was filtered off, washed with AcOH and water, and dried to give compound **3** (0.38 g). ^{1}H NMR, δ: 2.45 (d, 3 H, Me, J = 1.2 Hz); 6.90, 7.70 (both m, 2 H each, C_6H_4); 7.95 (q, 1 H, H(2), J = 1.2 Hz, $J_{CH,NH}$ = 1.2 Hz); 10.37 (br.s, 1 H, NH).

***N*-Benzylidene-*N*´-(1-methyl-2-nitrovinyl)hydrazine (4).** Benzaldehyde (2.2 g, 21 mmol) was added at 20 °C to a stirred suspension of compound **2** (2.5 g, 21 mmol) in 60 mL of ethanol. The reaction mixture was stirred for an additional 1 h. The precipitate that formed was filtered off, washed with ethanol, and dried to give compound **4** (3.8 g). ^{1}H NMR, δ: 2.22 (s, 3 H, Me); 6.74 (s, 1 H, H(2)); 7.49, 7.75 (m, 5 H, Ph); 8.61 (s, 1 H, C<u>H</u>Ph); 12.43 (br.s, 1 H, NH).

1-Benzylideneamino-6-hydroxy-2-methyl-3-nitro-1*H*-indole (5). Toluenesulfonic acid (3.1 g, 18 mmol) and then enamine **4** (3.7 g, 18 mmol) were added at 20 °C to a stirred suspension of *p*-benzoquinone (1.94 g, 18 mmol) in 20 mL of AcOH. The reaction mixture was stirred for 3 h. The precipitate that formed was filtered off, washed with AcOH and water, and dried to give compound **5** (1.26 g). ^{1}H NMR, δ: 2.85 (s, 3 H, Me); 6.87 (dd, 1 H, H(5), J_1 = 8.6 Hz, J_2 = 1.2 Hz); 6.97 (d, 1 H, H(7), J_2 = 1.2 Hz); 7.60 (m, 3 H, H(3´), H(4´), H(5´)); 8.03 (d, 2 H, H(2´), H (6´), J_1 = 7.4 Hz); 7.98 (d, 1 H, H(4), J_1 = 8.6 Hz); 9.12 (s, 1 H, C<u>H</u>Ph).

6-Acetoxy-1-benzylideneamino-2-methyl-3-nitro-1*H*-indole (6). A suspension of compound **5** (1.9 g, 6.4 mmol) in 20 mL of

* All crystallographic data, including atomic coordinates and bond lengths and angles have been deposited with the Cambridge Crystallographic Database (No. CCDC239829). Copies can be made available upon request to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44(0) 1223 336033. E-mail: deposit@ccdc.cam.ac.uk).

Table 2. Yields, melting points, elemental analysis data, and mass spectra of compounds **2**—**10**

Compound	Yield (%)	M.p./°C (solvent)	Found / Calculated (%)			Molecular formula	MS, m/z (I_{rel} (%))
			C	H	N		
2	85	83—85 (benzene)	30.97 30.77	5.96 6.03	35.65 35.88	$C_3H_7N_3O_2$	117 $[M]^+$ (58), 101 $[M - NH_2]^+$ (42), 71 $[M - NO_2]^+$ (100)
3	37	111—113 (decomp.)	51.94 52.17	4.38 4.38	—	$C_9H_9N_3O_3$	207 $[M]^+$ (26), 161 $[M - NO_2]^+$ (71), 121 $[M - MeC{=}CHNO_2]^+$ (100)
4	88	175—177 (EtOH)	58.49 58.53	5.40 5.40	19.95 20.48	$C_{10}H_{11}N_3O_2$	205 $[M]^+$ (29), 159 $[M - NO_2]^+$ (100), 119 $[M - MeC{=}CHNO_2]^+$ (93)
5	24	263—265 (EtOH)	65.63 65.08	4.47 4.44	13.75 14.23	$C_{16}H_{13}N_3O_3$	295 $[M]^+$ (100), 248 $[M - HNO_2]^+$ (10), 191 $[M - PhCH{=}N]^+$ (17)
6	70	182—183 (EtOH)	64.09 64.09	4.51 4.48	12.31 12.46	$C_{18}H_{15}N_3O_4$	337 $[M]^+$ (25), 295 $[M - COCH_2]^+$ (100), 248 $[M - HNO_2]^+$ (6), 191 $[M - PhCH{=}N]^+$ (13)
7	63	183—185 (EtOH)	59.88 60.13	4.82 4.81	9.64 9.56	$C_{20}H_{19}N_3O_6$	439 $[M]^+$ (21), 397 $[M - COCH_2]^+$ (18), 291 $[M - CHPh, -OCOCH_3]^+$ (79), 249 $[M - CHPh, -OCOCH_3, -COCH_2]^+$ (100)
8	18	239—240 (EtOH)	53.48 53.61	4.55 4.50	14.15 14.43	$C_{13}H_{13}N_3O_5$	291 $[M]^+$ (27), 249 $[M - COCH_2]^+$ (100), 207 $[M - 2\,COCH_2]^+$ (24)
9	65 (*A*), 90 (*B*)	262 (decomp.) (Pr^iOH)	53.03 53.01	4.60 4.45	16.49 16.86	$C_{11}H_{11}N_3O_4$	249 $[M]^+$ (100), 207 $[M - COCH_2]^+$ (25), 190 $[M - H_2NCOCH_3]^+$ (59), 160 $[M - H_2NCOCH_3, -NO]^+$ (27), 145 $[M - H_2NCOCH_3, -NO, -CH_3]^+$ (70)
10	84	295 (decomp.) (Bu^nOH)	52.28 52.17	4.68 4.38	19.96 20.28	$C_9H_9N_3O_3$	207 $[M]^+$ (100), 190 $[M - NH_3]^+$ (37), 160 $[M - OH, -NO]^+$ (30), 145 $[M - OH, -NO, -CH_3]^+$ (70)

acetic anhydride was refluxed for 1 h. The reaction mixture was cooled and diluted with water (100 mL). The precipitate that formed was filtered off, washed with water, and dried to give compound **6** (1.5 g). ^{1}H NMR, δ: 2.27 (s, 3 H, AcO); 2.87 (s, 3 H, Me); 7.20 (dd, 1 H, H(5), J_1 = 8.6 Hz, J_2 = 1.2 Hz); 7.59 (d, 1 H, H(7), J_2 = 1.2 Hz); 7.60 (t, 2 H, H(3′), H(5′), J_1 = 7.4 Hz); 7.67 (t, 1 H, H(4′), J_1 = 7.4 Hz); 8.05 (d, 2 H, H(2′), H(6′), J_1 = 7.4 Hz); 8.20 (d, 1 H, H(4), J_1 = 8.6 Hz); 9.14 (s, 1 H, CHPh). ^{13}C NMR, δ: 12.3 (Me); 20.6 (CH_3COO); 104.6 (C(7)); 117.3 (C(3a)); 118.8 (C(5)); 120.1 (C(4)); 125.0 (C(3)); 128.9, 131.9, 130.6 (Ph); 130.6 (C(7a)); 141.2 (C(2)); 147.7 (C(6)); 166.6 (CHPh); 169.1 (CH_3COO).

4-(2-Acetoxy-1-nitroprop-1-enyl)-3-[(1-acetyl-2-benzylidene)hydrazino]phenyl acetate (7) and 6-acetoxy-1-acetylamino-2-methyl-3-nitroindole (8). One drop of conc. H_2SO_4 was added at 20 °C to a stirred suspension of indole **5** (3.54 g, 12 mmol) in 40 mL of acetic anhydride. Stirring was continued for 1.5 h. The reaction mixture was diluted with water (300 mL). The precipitate that formed was filtered off, washed with water, dried, and chromatographed on silica gel with ethyl acetate as the eluent. Compounds **7** (3.32 g) and **8** (0.65 g) were isolated in succession.

Compound **7**. ^{1}H NMR, δ: 1.90, 1.81 (both s, 3 H each, C(2′)Me); 1.74, 2.10, 2.19, 2.70 (all s, 3 H each, NAc, C(2′)OAc); 2.34 (s, 6 H, C(1)OAc); 7.70, 7.75 (both d, 1 H each, H(2), J = 1.7 Hz); 7.06—7.37 (m, 6 H, Ph, H(5)); 7.88, 8.06 (both s, 1 H each, CHPh); 8.09, 8.15 (both d, 1 H each, H(5), J = 8.6 Hz). ^{13}C NMR, δ: 11.4, 11.5 (Me(2′)); 20.1, 20.4, 20.5, 20.6, 20.9, 21.12 ($NCOCH_3$, C(2′)CH_3COO, C(1)CH_3CO); 79.1, 83.1 (CHPh); 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(2)); 144.4, 145.2 (C(2′)); 148.5 (C(1)); 168.0—171.0 ($NCOCH_3$, C(2′)CH_3COO), C(1)CH_3CO).

Compound **8**. ^{1}H NMR, δ: 2.19 (s, 3 H, C(1)NAc); 2.30 (s, 3 H, OAc); 2.66 (s, 3 H, Me); 7.16 (dd, 1 H, H(5), J_1 = 8.6 Hz, J_2 = 1.2 Hz); 7.32 (d, 1 H, H(7), J_2 = 1.2 Hz); 8.12 (d, 1 H, H(4), J_1 = 8.6 Hz); 11.55 (br.s, 1 H, NH). ^{13}C NMR, δ: 11.4 (Me); 20.4, 20.8 ($NCOCH_3$); $OCOCH_3$); 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 ($NCOCH_3$, $OCOCH_3$).

1-Acetylamino-6-hydroxy-2-methyl-3-nitroindole (9).

A. Concentrated HCl (1.2 mL, 14 mmol) and water (1.2 mL, 70 mmol) were added to a suspension of compound **7** (0.63 g, 1.4 mmol) in 40 mL of ethanol. The reaction mixture was refluxed for 30 min and concentrated. The residue was recrystallized from ethanol to give compound **5** (0.02 g). The ethanolic mother liquor was concentrated, the residue was refluxed in ethyl acetate, and the suspension was filtered hot to give compound **9** (0.23 g). ^{1}H NMR, δ: 2.18 (s, 3 H, NAc); 2.64 (s, 3 H, Me); 6.71 (d, 1 H, H(7), J_2 = 1.2 Hz); 6.87 (dd, 1 H, H(5), J_1 = 8.6 Hz, J_2 = 1.2 Hz); 7.90 (d, 1 H, H(4), J = 8.6 Hz); 9.56 (br.s, 1 H, OH); 11.35 (br.s, 1 H, NH). ^{13}C NMR, δ: 11.4 (Me); 20.3 ($NCOCH_3$); 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 ($NCOCH_3$).

B. A mixture of compound **8** (0.64 g, 2.2 mmol), benzene (30 mL), ethanol (5 mL), and piperidine (0.37 g, 4.4 mmol) was refluxed for 6 h and concentrated. The residue was triturated

with benzene and the precipitate was filtered off and dried to give compound **9** (0.49 g).

1-Amino-6-hydroxy-2-methyl-3-nitroindole (10). Concentrated HCl (4.2 mL, 50 mmol) and water (4.5 mL, 250 mmol) were added to a suspension of compound **8** (1.25 g, 5 mmol) in 70 mL of Bu^nOH. The reaction mixture was refluxed for 45 min. The resulting solution was cooled and the precipitate that formed was filtered off, washed with Bu^nOH, and dried to give compound **10** (0.76 g). The mother liquor was concentrated and the residue was recrystallized from Bu^nOH to give an additional amount of compound **10** (0.116 g). ^{1}H NMR, δ: 2.80 (s, 3 H, Me); 5.91 (br.s, 2 H, NH_2); 6.77 (dd, 1 H, H(5)); 6.95 (d, 1 H, H(7), J = 2.0 Hz); 7.85 (d, 1 H, H(4), J = 8.4 Hz); 9.34 (br.s, 1 H, OH).

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