# Synthesis and Structural Analysis of (*E*)-2-(2'-Nitrovinyl)indoles from the Corresponding 2-Formylindole Derivatives



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Preparation of 2-formylindoles was carried out from the appropriate methylindole by oxidation with selenium dioxide and by Vilsmeier formylation. The 2-(2'-nitrovinyl)indoles have been obtained by condensation of 2-formylindoles with nitroalkanes in the presence of ammonium chloride in good yields. In this reaction, only the (*E*)-isomer of the 2-(2'-nitrovinyl)indoles was observed by $^1$H nmr and NOE experiments. Evidence for an extended conjugation through the double bond and the nitro group can be evaluate by the deshielding effect on the olefinic protons. Moreover, the non-Beer's law behaviour in the uv-visible spectra suggest the existence of some sort of complex for these compounds.

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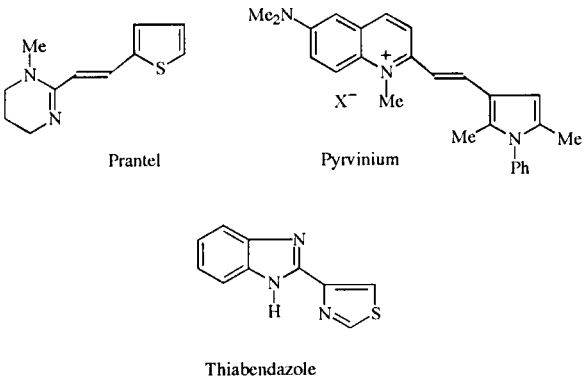
Many previously reported drugs [1a-e] such as pyrantel, pyrvinium salts and thiabendazole, used as therapeutic agents due to their broad parasiticide activity, have a system of extended conjugation through an ethylene bridge, which has one 5-membered heterocycle with high π–charge density and one withdrawing heterocycle ring (ionophoric group) as substituents at either end of the double bond. The 3-(2'-nitrovinyl)indoles derivatives show *in vitro* important parasiticide action, some of them are more active than the reference drug [2]. This electronic π-extended structure could be responsible for the biological activity of the drug, Scheme 1.

Scheme 1

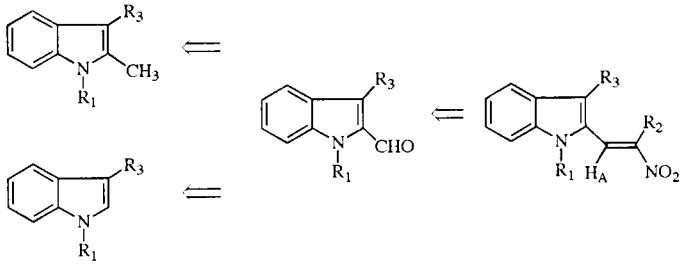



To verify this hypothesis [2], we undertook the preparation of 2-(2'-nitrovinyl)indoles, **17-24**, Table 1, in which the extreme of high charge density is the position 2 of an indole ring, while the withdrawing (ionophoric extreme $N^+O^-$) is always the nitro group. Moreover, a structural study of these compounds was performed to verify the extended conjugation through the ethylene bridge. The different $R_1$ $R_2$ and $R_3$ groups could affect the conjugation and hence, the biological activity of the compound.

Results and Discussion.

A retrosynthetic pathway from the 2-(2'-nitrovinyl)-indole derivatives show as the starting products the 2-methylindole derivatives, for a selective oxidation, and the 2-unsubstituted indole derivatives, for a selective formylation, Scheme 2.

Scheme 2




However, there are few cases in the literature for selective oxidation of an alkyl substituent on position 2 of the indole ring. Thus, 2,3-dimethylindole was treated with periodic acid to give 2-formyl-3-methylindole in low yield [3a].

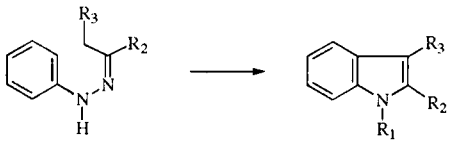
The indole ring is sensitive to some oxidants such as: hydrogen peroxide; oxygen; peracetic acid; Fremy's salt, giving oxidative dimerization products; chromium trioxide to give C2-C3 oxidative ring cleavage to *o*-acylamine phenylketones or *N*-anthranylic acids using potassium permanganate [3b]. Selective oxidation of methylindoles can be carried out by DDQ [3c], and photooxidation [3d]. Some active indoles suffer autooxidation in the presence of oxygen to give 3-hydroperoxyindolenines [3e]. Recently, were obtained the indole-3-carboxaldehyde derivatives and their acids by oxidative transformation with air of the corresponding indole-3-acetonitrile [3f].

The 2-formylindoles were prepared by selective oxidation of the appropriate 2-methylindoles with selenium dioxide [4], and alternatively by the Vilsmeier-Haack reaction on 3-methyl or 3-phenylindoles [5], Scheme 2. The preparation of the alkylindole derivatives was carried out by means of the Fischer reaction, starting from the phenylhydrazone of the convenient ketone in the presence of an acid catalyst. In this reaction isomers in position 2- or 3- were formed in relative amount, which depends on the catalyst used [6].

Fischer indolisation of methyl alkyl ketones provides the 3-substituted 2-methylindoles as the sole or major product [7]. However, the 3-unsubstituted indoles were prepared under very strongly acidic conditions. Thus, the phenylhydrazone of ethyl methyl ketone gives exclusively 2,3-dimethylindole under weak acid conditions, but 2,3-dimethyl and 2-ethyl isomers are formed in equal amounts with use of polyphosphoric acid or sulfuric acid in ethanol [8]. Changes in regiochemistry are recently interpreted by kinetic and solvent isotope effects as a diprotonation mechanism on the nitrogen and the aromatic ring of the phenylhydrazone followed by the rate-determining ene-hydrazine formation and depends on the neat acid conditions [9].

On this basis, the phenylhydrazone of ethyl methyl ketone and benzyl methyl ketone was respectively transformed in anhydrous acetic acid into the corresponding 2-methylindole derivative as the only product in 85 and 86% yield respectively, Table 1.

Table 1



| Phenylhydrazone | $R_2$ | $R_3$ | Indole | % | Catalyst | t (hours) | T(°) |
|---|---|---|---|---|---|---|---|
| **1** | $CH_3$ | $CH_3$ | **4** | 85 | [a] | 3 | 80 |
| **2** | $CH_3$ | $C_6H_5$ | **5** | 86 | [a] | 3 | 100 |
| **3** | H | $C_6H_5$ | **6** | 81 | [b] | 1 | 100 |
| **3** | H | $C_6H_5$ | **6** | 48 | [c] | 3 | 25 |

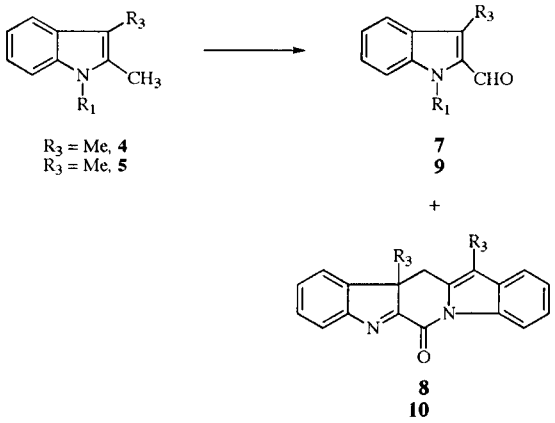
[a] Anhydrous acetic acid; [b] HCl/EtOH; c. $ZnCl_2$.

The *N*-methylindole derivatives were obtained from the appropriate NH indole (**4-6**), by treatment with methyl iodide in anhydrous DMF and sodium hydride, in good yields.

Oxidation of 2-Methylindoles with selenium dioxide.

There are references in the literature on the oxidation of 3-unsubstituted 2-methylindoles with selenium dioxide giving a complex mixture of organoselenium compounds [4]. However, oxidation of 3-methylindole derivatives with freshly sublimed selenium dioxide in dioxane gives the corresponding 3-formyl derivatives in moderate yield [2]. The reaction of 2,3-dimethylindole (**4**) with selenium dioxide gives the expected 2-formyl-3-methylindole (**7**) in low yield (23%) as the main product. Moreover, a secondary product was isolated and identified as 5,6,11b,12-tetrahydro-11b,13-dimethylpyrido[1,2-*a*:5,4-*b*']diindol-6-one (**8**) (5%), Scheme 3. The structure for **8** was established on the basis of the following facts: a) in the $^1H$ nmr spectrum appear at 7.92 and 8.59 ppm two doublet of doublets with the same intensity for aromatic protons, with coupling constants of *ortho* and *meta* type which were assigned to the peri-hydrogens of the benzene rings. Moreover, also appear two singlets for two methyl groups and an AB system integrating for two protons with a coupling constant of the geminal type (J = 15.4 Hz) for a methylene group. In the ir spectrum appears an intense absorption at 1690 $cm^{-1}$ for a CO group and at 760 $cm^{-1}$ for an *ortho* substitution. Thus, the frequencies for the peri-hydrogens referred must be due to the anisotropic influence of the CO group. The dimeric structure was confirmed by the mass spectrum, showing the molecular ion peak at 300 and the base peak at 285 Da as the loss of a methyl group.

Scheme 3



$R_3$ = Me, **4**
$R_3$ = Me, **5**

**7**
**9**

+

**8**
**10**

A possible interpretation above the formation of compound **8**, would be from 2-formyl-3-methylindole by condensation with a NH of a 2-formyl indole intermediate followed by intramolecular 2-formylation on position 3 occupied by a methyl group.

The same oxidation reaction with 2-methyl-3-phenylindole (**5**) gives the 2-formyl-3-phenylindole (**9**) in low yield (11%) and two products that, were identified as 5,6,11b,12-tetrahydro-11b,13-diphenylpyrido[1,2-*a*:5,4-*b*']diindol-6-one (**10**) (5%), and 3-phenylindole-2-carboxylic acid (2%), Scheme 3.

Compound **10** shows structural analogy with **8** in the nmr spectrum. Thus, the two peri-hydrogens appear at 8.0 and 8.6 ppm, but the AB system appears at more downfield than **8**, which can be explain by the anisotropic effect of the phenyl substituents. The dimeric structure was confirmed by the mass spectrum, showing the molecular peak at 424 Da which is also the base peak.

Formylation of indoles through Vilsmeier-Haack reaction.

Because the selective oxidation gave poor yields in 2-formylindoles, the direct formylation through the Vilsmeier-Haack reaction in 3-substituted indoles was complementary employed [5]. Thus, in the 1*H*-3-substituted indole derivatives, positions 1 and 2 can be active to the intermediate electrophile ($ClCH=N^+Me_2$), although at a temperature of 110°, the attack on position 2 is favoured [10].

In this way, the 3-methylindole was treated, with phosphorus oxychloride and *N,N*-dimethylformamide at 120-140° to give the expected 2-formyl-3-methylindole (**7**) (36%) and 1-formyl-3-methylindole (**13**) (63%). The 3-phenylindole under the same treatment gave a mixture of 2-formyl-3-phenylindole (**9**) (46%), and 1-formyl-3-phenylindole (**14**) (53%).

Moreover, the Vilsmeier-Haack reaction for the *N*-methylindole derivatives give excellent yield in the corresponding 2-formyl product. Thus, 1,3-dimethylindole and 1-methyl-3-phenylindole gave respectively 2-formyl-1,3-dimethylindole (**15**) (91%) and 2-formyl-1-methyl-3-phenylindole (**16**) (95%).

The *N*-formyl derivatives **13** and **14** exhibit a conformational *cisoid* and *transoid* equilibrium through the nitrogen-carbonyl bond. Structural evidence of this equilibrium was obtained from the $^1$H nmr spectra. The aromatic H-7 proton suffers an important anisotropic effect for the *cisoid* isomer by the formyl group. Moreover, the 1-formylindoles exhibit two singlet signals for the formyl hydrogen that confirmed the presence of two rotamers in solution.

The proton of the CHO group in the nmr spectrum shows the absorption at the most downfield for the *transoid* conformation, probably due to the anisotropy effect of the benzene ring of the indole nucleus [11].

Synthesis of 3-substituted-2-(2'-nitrovinyl)indoles (**17-24**).

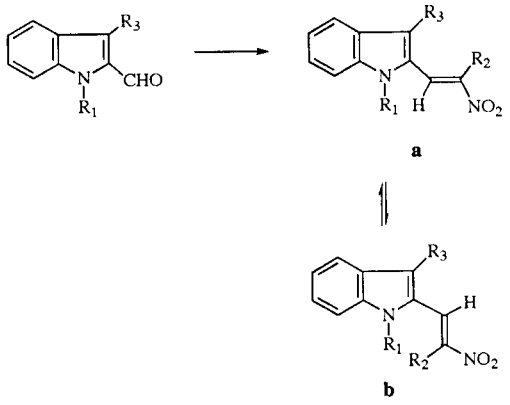
The synthesis of the 3-substituted-2-(2'-nitrovinyl)indoles (**17-24**) have been carried out by means of the Henry reaction. To avoid secondary products in this reaction, the condensation of a stoichiometric amount of the aliphatic or aromatic aldehydes with nitroalkanes has been recently reported in an aqueous solution of sodium hydroxide (0.025 *M*) in the presence of cetyltrimethylammonium chloride as cationic surfactant to give the β-nitroalkanol derivative in good yield [12a]. Moreover, the use of a polymer-supported strong base for the condensation of an aldehyde in excess of nitroalkane (normally used neat) to obtain the nitroaldol product in a very clean fashion has been recently described [12b].

However, the nitrovinylation of the 3-formylindoles with nitromethane (or nitroethane) in a great excess was carried out at 120-140° with ammonium acetate as a mild acid catalyst to give the corresponding nitrovinylindole (among one to three hours) in good yield [2]. This procedure was applied to the aldolisation of 2-formylindoles, **7**, **9**, **12**, **15** and **16**, with nitromethane (or nitroethane) to obtain the 3-substituted-2-(2'-nitrovinyl)indoles **17-24**, in good yield (with the exception of nitroethane with the 2-formyl-1-methyl derivatives; $R_3$ = $CH_3$, 56%; $R_3$ = Ph, 63%). In general the 3-phenylindole derivatives, show highest kinetic of reaction than the 3-methylindole derivatives, Table 2.

Structure of 3-substituted-2-(2'-nitrovinyl)indoles.

The nitrovinylation of 2-formylindoles always gives the corresponding (*E*)-2-(2'-nitrovinyl)indole which can be unequivocally identified from the $^1$H nmr spectra. The same (*E*)-stereochemistry for the 1'-methyl-2'-nitrovinylindoles has been assigned by comparison of its nmr and ir spectra. The vinyl $H_A$ proton on position 1' appears in all the cases with an important deshielding effect at frequencies between 8.07-8.30 ppm in 2-(2'-nitrovinyl)-indoles and in 2-(2'-methyl-2'-nitrovinyl)indoles. For $R_2$ = H, the signal is always a doublet with a coupling constant among 13.4 to 13.7 Hz, assigned to the *E*-isomer. The *E* stereochemistry in 2-(2'-methyl-2'-nitrovinylindoles was confirmed by irradiation at the $H_A$ and methyl ($R_2$) frequencies in $^1$H nmr-NOE experiments. On this basis, the proton $H_A$ is close to the NH proton and the methyl ($R_2$) to the methyl ($R_3$) in compound **19**, but $H_A$ and $R_2$ are in a trans configuration relative to each other.

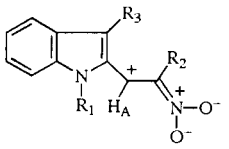
Table 2




| Compound | $R_1$ | $R_2$ | $R_3$ | Product | Yield %, | a:b |
|---|---|---|---|---|---|---|
| **7** | H | H | Me | **17** | 77 | |
| **15** | Me | H | Me | **18** | 87 | |
| **7** | H | Me | Me | **19** | 84 | |
| **15** | Me | Me | Me | **20** | 56 | |
| **9** | H | H | Ph | **21** | 82 | |
| **16** | Me | H | Ph | **22** | 90 | |
| **9** | H | Me | Ph | **23** | 89 | 95:5 |
| **16** | Me | Me | Ph | **24** | 63 | |
| **9** | H | Et | Ph | **25** | 79 | 74:26 |
| **9** | H | Pr | Ph | **26** | 65 | 79:21 |

Taking in account the planarity of the nitrovinyl chain in compounds **17-24** [13,14b,c], the deshielding effect observed on $H_A$ must be produced by the resonance of the nitro group where the polar formula with a positive charge on the 1' position shows an important contribution. However, when $R_2$ is a methyl group, $H_A$ also shows a deshielding effect, but in minor extent.

A noteworthy question is the important anisotropic effect on the $R_2$ group by the phenyl at position 3, which increases when $R_1$ = Me, probably by the steric effect of $R_1$ pushing the chain towards the phenyl substituent, that is



virtually orthogonal to the indole plane [13,14]. This anisotropic effect confirms that the methyl ($R_2$) is close to the Ph ($R_3$) as the assigned structure by NOE experiments.

In the ir spectra the same conjugation effect for the asymmetric stretching bands of the $NO_2$ group was observed. Thus, for $R_2$ = H, the two bands appear at 1480 and 1470 $cm^{-1}$ while for $R_2$ = $CH_3$, leave as is appear at 1510 and 1480 $cm^{-1}$, due to the partial loss of the conjugation by the steric hindrance of both methyl and nitro groups.

For $R_1$ = Me a hipsochromic effect on the visible band was observed which increases when $R_2$ = Me and $R_3$ = Me or Ph. Moreover, the ε value decreases for $R_2$ = Me but the hypochromic effect is still more when $R_3$ = Me or Ph, Table 3. By analogy with the X-ray structural data of some 3-nitrovinylindoles [2], both effects can be explained by partial loss of conjugation of the vinyl chain with the indole ring. Thus, for the *N*-methyl derivatives the torsion angle between the plane of the nitrovinyl chain, $R_2$ = H, or $R_2$ = Me, and the plane of indole ring is among 2.8-6.1 or 20.0-33.3 (°) respectively [13,14b,c].

Table 3

| Compound | $R_1$ | $R_2$ | $R_3$ | λ | (ε) |
|---|---|---|---|---|---|
| **17** | H | Me | H | 406 | (27371) |
| **18** | Me | H | Me | 400 | (17037) |
| **19** | H | Me | H | 406 | (12241) |
| **20** | H | Me | Me | 384 | (10387) |
| **21** | H | H | Me | 404 | (17310) |
| **22** | Me | Me | Me | 392 | (16180) |
| **23** | Me | Me | Ph | 412 | (11892) |
| **24** | Ph | Ph | Ph | 362 | (8201) |

(*) MeOH, $l.mol^{-1}cm^{-1}$.

Moreover, the existence of a self charge-transfer complex in compounds **17-24**, is confirmed in solution, where the representation of the absorbance versus concentration for the visible absorption band of the compounds (although the true charge-transfer band is probably masked) do not follow Beer's law. The bimolecular association in the 3-nitrovinylindole derivatives show a self-charge-transfer complex of the π,π–type between the plane of the nitrovinyl chain (acceptor) and the plane of indole ring (donor) [14b,c].

## EXPERIMENTAL

Melting points were determined using a Reichert hotstage microscope and are uncorrected. The ir spectra (FT) were obtained as neat films between sodium chloride plates or potassium bromide pellets or a Nujol suspension. The nmr spectra were recorded at 200 MHz. Chemical shifts are given in δ units. Deuteriochloroform with tetramethylsilane as internal standard was used as the solvent. Mass spectral analyses were recorded by electron impact at 70 eV. Yields are given on isolated products. All substituted indoles were prepared satisfactorily by the Fischer reaction from the phenylhydrazones of the appropriate ketones and were purified by column chromatography.

2,3-Dimethylindole (**4**).

i. Preparation of the Phenylhydrazone of 2-Butanone **1**.

In a Dean-Stark system was placed 2-butanone, 29.8 ml (0.33 moles), phenylhydrazine freshly distilled, 32.8 ml (0.33 moles) and 100 ml of anhydrous benzene. The mixture was warmed at 110-120° and water removed (2 hours) and then, solvent was evaporated at reduced pressure. The phenylhydrazone **1**, was obtained as an orange oil (93%). $^1$H-nmr (deuteriochloroform): 7.30-6.70 (5H, m, Ar-H), 2.23 (2H, q, J = 7.4 Hz, $CH_2$-$CH_3$), 1.63 (3H, s, $CH_3$), 1.06 (3H, t, J = 7.4 Hz, $CH_2$-$CH_3$); ir (nujol): 1605 (C= N), 750 and 690 $cm^{-1}$ (Ar-H-monosubst.).

ii. Fischer reaction of phenylhydrazone (**1**).

A mixture of phenylhydrazone **1**, 49.72 g (0.31 moles), and anhydrous acetic acid, 105 ml (1.84 moles), was warmed at 80° in argon atmosphere for 3 hours. After cooling, water, 100 ml, was added and the mixture extracted with dichloromethane. The organic layer was dried with anhydrous sodium sulfate, and after filtration, solvent was removed and the residual product was purified by silica gel column chromatography, using dichloromethane as the eluent. The 2,3-dimethylindole, **4**, was obtained as a pale yellow solid, mp 103° [15] (85%). $^1$H-nmr (deuteriochloroform): 7.68 (1H, s br, NH), 7.50-7.42 (1H, m, H-7), 7.28-7.01 (3H, m, Ar-H), 2.35 (3H, s, $CH_3$-2), 2.25 (3H, s, $CH_3$-3); ir (potassium bromide): 3400 (N-H st), 1620 (C=C conj.), 1465 (C-H, $CH_3$), 1300 (C-N st), 740 $cm^{-1}$ (ArH *o*-disubst.); ms: (70 eV) m/z 145 ($M^+$, 83), 144 (100), 115 (13), 54 (18).

2-Methyl-3-phenylindole (**5**)

i. Phenylhydrazone of 1-phenyl-2-propanone (**2**).

Following the general procedure, phenylhydrazone **2** was prepared, starting of 1-phenyl-2-propanone (10 ml, 74.6 mmoles) and phenylhydrazine (7.4 ml, 74.6 mmoles) in 75 ml of benzene. The mixture was warmed at 140° for 2 hours. The phenylhydrazone **2**, was obtained as a yellow oil (89%). $^1$H-nmr (deuteriochloroform): 7.80-6.80 (10H, m, Ar-H), 3.65 (2H, s, $CH_2$), 1.80 (3H, s, $CH_3$).

ii. Fischer reaction of the phenylhydrazone of 1-phenyl-2-propanone.

A mixture of the phenylhydrazone **2**, 14.87 g (66.4 mmoles) and 22.8 ml of anhydrous acetic acid, under argon atmosphere, was warmed at 100° for 3 hours. The 2-methyl-3-phenylindole was isolated as a brown solid, mp 57-59° [16] (86%). $^1$H-nmr (deuteriochloroform): 7.98 (1H, br s, NH), 7.70-7.60 (1H, m, H-7), 7.55-7.02 (8H, m, Ar-H), 2.49 (3H, s, $CH_3$); ir (potassium bromide): 3400 (N-H st), 1605 and 1500 (C=C conj.), 1460 (C-H, $CH_3$), 1310 (C-N st), 750, (ArH o-disubst.), 775 and 705 $cm^{-1}$ (ArH monosubst.); ms: (70 eV) m/z 207 ($M^+$, 100), 206 (54), 178 (13), 165 (9), 130 (17).

3-Phenylindole.

A mixture of phenylacetaldehyde (4.4 ml, 37.4 mmoles) and phenylhydrazine (3.7 ml, 37.4 mmoles) was stirred for 1 hour and then warmed at 100° for 30 minutes. Then, a solution of $ZnCl_2$ (9.06 g, 66.5 mmoles) in ethanol (40 ml) was added and the mixture stirred at 100° for 1 hour. After cooling, the mixture was filtered and the solvent removed at reduced pressure, and an aqueous solution of hydrochloric acid (4%, 40 ml) was added. The mixture was extracted with dichloromethane (40 ml). The organic layer was dried on sodium sulfate and after filtration the solvent was removed to give a brown solid, which was purified by silica gel column chromatography using toluene as the eluent. The 3-phenylindole was obtained as a yellow crystalline solid, mp 83° [17] (81%). $^1H$ nmr (deuteriochloroform): 8.00 (1H, br s, NH), 7.92 (1H, m, H-7), 7.68-7.10 (9H, m, Ar-H), ir (potassium bromide): 3410 (N-H st), 1600 (C=C conj.), 1335 (C-N st), 750 (ArH o-disubst.), 770 and 700 $cm^{-1}$ (ArH monosubst.); ms: (70 eV) m/z 193 ($M^+$, 100), 192 (60), 165 (94), 139 (13).

1,3-Dimethylindole.

To a suspension of sodium hydride (1.28 g, 53.36 mmoles) in anhydrous *N,N*-dimethylformamide (10 ml), under an argon atmosphere, was dropped a solution of 3-methylindole, 7.0 g (53.36 mmoles) in *N,N*-dimethylformamide (5 ml) and then a solution of methyl iodide, 3.4 ml (54.61 mmoles) in *N,N*-dimethylformamide (5 ml). The mixture was stirred at room temperature for 1 hour and then hydrolysed with water-ice and extracted with dichloromethane (25 ml). The organic layer was dried on sodium sulfate and after filtration, the solvent was removed at reduced pressure. The yellow oil obtained was purified by silica gel column chromatography using hexane:chloroform (3:1) as the eluent. The 1,3-dimethylindole, was isolated as an orange oil, bp 72°/10mmHg [18] (76%). $^1H$ nmr (deuteriochloroform): 7.55 (1H, d, J = 6.9Hz, H-7), 7.49-6.84 (3H, m, ArH), 6.62 (1H, s, H-2), 3.62 (3H, s, N-$CH_3$), 2.26 (3H, s, $CH_3$); ir (film): 3060 (C-H st ArH), 2920 (C-H, $CH_3$), 1465 (C-H, $CH_3$), 1365 (C-H, $CH_3$), 1330 (C-N), 740 $cm^{-1}$ (ArH o-disubst.); ms: (70 eV) m/z 145 ($M^+$, 60), 144 (100), 128 (8), 115 (7), 102 (7).

1-Methyl-3-phenylindole (**5**).

Following the above procedure, 1-methyl-3-phenylindole, was prepared starting with 3-phenylindole (3.46 g, 17.95 mmoles), sodium hydride (430.8 mg, 17.95 mmoles) and methyl iodide (1.14 ml, 18.37 mmoles). The crude product was purified by silica gel column chromatography, using toluene: hexane (3:1) as the eluent. The 1-methyl-3-phenylindole was isolated as a pale-brown solid, mp 63-64° [19] (89%). $^1H$ nmr (deuteriochloroform): 7.93 (1H, d, J = 7.1Hz, H-7), 7.64-7.11 (9H, m, Ar-H), 3.70 (3H, s, N-$CH_3$); ir (potassium bromide): 3060 (C-H st ArH), 2930 (C-H, $CH_3$), 1610 (C=C conj.), 1475 (C-H, $CH_3$), 1380 (C-H, $CH_3$), 1335 (C-N), 750 (ArH o-disubst.), 770 and 700 $cm^{-1}$ (ArH monosubst.); ms: (70 eV) m/z 207 ($M^+$, 100), 206 (27), 192 (12), 165 (30).

2-Formyl-3-methylindole (**7**).

a) Oxidation of 2,3-dimethylindole with Selenium Oxide.

To a solution of selenium oxide (0.84 g, 7.58 mmoles) in 20 ml of 1,4-dioxane-water 9:1, was added a solution of 2,3-dimethylindole, 1 g (6.9 mmoles) in 30 ml of 1,4-dioxane and the mixture was warmed at 50° for 4 hours with stirring, under an argon atmosphere. After cooling, the mixture was filtered, and the filtered solid extracted with dichloromethane. The organic layer was dried with anhydrous sodium sulfate and after filtration the solvent was removed at reduced pressure to give a brown oil which was purified by silica gel column chromatography, using hexane:ethyl acetate (3:1) as the eluent. The 2-formyl-3-methylindole was isolated as a brown-yellow solid mp 140° [20], 362 mg (33%). Another product was isolated from this reaction and identified as 5,6,11b,12-tetrahydro-11b,13-dimethylpyrido-[1,2-*a*:5,4-*b'*]diindole-6-one, as a pale-yellow crystalline solid, mp 194-196° [21], 104 mg (5%).

2-formyl-3-methylindole, **7**: $^1H$ nmr (deuteriochloroform): 10.05 (1H, s, CHO), 8.75 (1H, br s, NH), 7.71 (1H, d, J = 7.9 Hz, H-7), 7.40-7.11 (3H, m, Ar-H), 2.65 (3H, s, $CH_3$); ir (potassium bromide): 3310 (N-H), 2930 (C-H, $CH_3$), 1645 (CO), 1455 (C-H, $CH_3$), 1335 (C-N), 745 (ArH o-disubst.); ms: (70 eV) m/z 159 ($M^+$, 77), 158 (62), 131 (10), 130 (100), 77 (30).

5,6,11b,12-Tetrahydro-11b,13-dimethylpyrido[1,2-*a*:5,4-*b'*]diindole-6-one, **8**: $^1H$ nmr (deuteriochloroform): 8.59 (1H, dd, J = 6.2 Hz, J = 2.8 Hz, H-4), 7.92 (1H, dd, J = 7.1 Hz, J = 2.9 Hz, H-8), 7.70-7.21 (6H, m, Ar-H), 3.54 (1H, AB system, $J_{AB}$ = 15.4 Hz, $H_A$, $CH_2$-12), 2.49 (1H, AB system, $J_{AB}$ = 15.4 Hz, $H_B$, $CH_2$-12), 2.25 (3H, s, $CH_3$-13), 1.37 (3H, s, $CH_3$-11b); ir (potassium bromide): 1690 (CO), 1650 (C= N), 1460 (C-H, $CH_3$), 1370 (C-H, $CH_3$), 1330 (C-N), 760 $cm^{-1}$ (ArH o-disubst.); ms: (70 eV) m/z 300 ($M^+$, 53), 299 (37), 285 (100), 256 (11), 143 (64), 128 (42), 115 (27), 102 (29), 77 (38).

b) Vilsmeier-Haack reaction of 3-Methylindole.

To a solution of phosphorus oxychloride (5.5 ml, 60.6 mmoles) in anhydrous *N,N*-dimethylformamide (18.9 ml, 245.4 mmoles), after stirring for 20 minutes, at room temperature, was added a solution of 3-methylindole, 7.3 g, (55.7 mmoles) in 6 ml of anhydrous *N,N*-dimethylformamide. The mixture was warmed at 100-120° for 3 hours and hydrolysed with 25 ml of an aqueous solution of sodium acetate (15%) with stirring at room temperature for 30 minutes. Then, was extracted with dichloromethane and the organic layer dried on anhydrous sodium sulfate. After filtration, the solvent was removed and the crude product was purified by silica gel column using dichloromethane as the eluent. Two products were isolated and identified as the 1-formyl-3-methylindole (**13**) as an orange oil, bp 75°/2mmHg [10] 5.6 g (63%) and 2-formyl-3-methylindole, **7**, as pale-yellow crystals, mp 138°, 3.2 g (36%).

1-Formyl-3-methylindole. $^1H$ nmr (deuteriochloroform): 9.30 (1H, s, CHO), 8.95 (1H, s, CHO), 8.40 (1H, d, J = 7.0 Hz, H-7), 7.70-7.20 (3H, m, Ar-H), 7.00 (1H, s, H-2), 2.20 (3H, s, $CH_3$); ir (film): 3100 (C-H st ArH), 2920 (C-H, $CH_3$), 1700 (CO), 1605 (C=C conj.), 1455 (C-H, $CH_3$), 1370 (C-H, $CH_3$), 745 $cm^{-1}$ (ArH o-disubst); ms: (70 eV) m/z 159 ($M^+$, 55), 130 (100), 77 (12).

2-Formyl-1,3-dimethylindole (**15**).

Following the above procedure, phosphorus oxychloride (4.1 ml, 44.70 mmoles) in *N,N*-dimethylformamide, 13.8 ml (178.8 mmoles) and 1,3-dimethylindole, **15**, 5.89 g (40.62 mmoles). The mixture was warmed at 120-140° for 1 hour. The crude product was purified by silica gel column chromatography using dichloromethane:toluene 2:1 as the eluent. The 2-formylindole **15**, was isolated as yellow crystals mp 35-36° [22], 6.4 g (91%). $^1H$ nmr (deuteriochloroform): 10.18 (1H, s, CHO), 7.70 (1H, d,

J = 8.0 Hz, H-7), 7.50-7.10 (3H, m, Ar-H), 4.05 (3H, s, N-$CH_3$), 2.60 (3H, s, $CH_3$); ir (potassium bromide): 2930 (C-H, $CH_3$), 1660 (CO), 1460 (C-H, $CH_3$), 1340 (C-N), 745 $cm^{-1}$ (ArH o-disubst); ms: (70 eV) m/z 173 ($M^+$, 100), 172 (35), 145 (7), 144 (49), 130 (9).

3-Phenyl-2-formylindole (**9**).

a) Oxidation of 3-Phenyl-2-methylindole (**5**) with Selenium Dioxide.

Following the procedure referred above, a mixture of 3-phenyl-2-methylindole, 0.83 g, (4.01 mmoles) in 5 ml of 1,4-dioxane and selenium dioxide, 0.49 g, (4.41 mmoles) was warmed at 130° for 5 hours. The residual oil obtained was purified by silica gel column chromatography, using dichloromethane as the eluent. The 3-phenyl-2-formylindole was obtained as a yellow solid, mp 194° [23] (11%). Another product was isolated and identified as 5,6,11b,12-tetrahydro-11b,13-diphenylpyrido[1,2-*a*:5,4-*b'*]diindole-6-one, yellow crystalline solid, mp 183-184°.

3-Phenyl-2-formylindole. $^1H$ nmr (deuteriochloroform): 9.90 (1H, s, CHO), 9.15 (1H, br s, NH), 7.75 (1H, d, J = 8.2 Hz, H-7), 7.60-7.10 (8H, m, Ar-H); ir (potassium bromide): 3340 (N-H), 1640 (CO), 1330 (C-N), 750 (ArH o-disubst), 770 and 710 $cm^{-1}$ (ArH monosubst.); ms: (70 eV) m/z 221 ($M^+$, 100), 220 (94), 193 (23), 192 (28), 165 (70).

5,6,11b,12-Tetrahydro-11b,13-diphenyl-pyrido[1,2-*a*:5,4-*b'*]-diindole-6-one, **10**. $^1H$ nmr (deuteriochloroform): 8.60 (1H, dd, J = 6.0 Hz, J = 3.0 Hz, H-4), 8.00 (1H, dd, J = 6.5, J = 3.0 Hz, H-8), 7.60-7.00 (16H, m, Ar-H), 4.38 (1H, AB system, $J_{AB}$ = 17.2 Hz, H-12), 3.01 (1H, AB system, $J_{AB}$ = 17.2 Hz, H-12); ms: (70 eV) m/z 424 ($M^+$, 100), 423 (61), 396 (87), 143 (53), 128 (319), 115 (10), 102 (40), 77 (43).

3-Phenylindole-2-carboxylic acid. $^1H$ nmr (deuteriochloroform): 14.52 (1H, s, COOH), 8.10-7.10 (9H, m, Ar-H).

b) Vilsmeier-Haack Reaction of 3-Phenylindole.

Following the procedure indicated above, a mixture of anhydrous *N,N*-dimethylformamide, 6.1 ml (79.01 mmoles), phosphorus oxychloride, 1.8 ml (19.75 mmoles) and 3-phenylindole, 3.46 g (17.95 mmoles), was warmed at 120-140° for 1 hour. The crude reaction product was purified by silica gel column chromatography, using dichloromethane as the eluent. Two products were isolated: the 2-formyl-3-phenylindole **9**, yellow neddles mp 196°, 1.8 g (46%); and 1-formyl-3-phenylindole **14**, transparent crystals, mp 84-85°, 2.1 g (53%).

1-Formyl-3-phenylindole, **14**. $^1H$ nmr (deuteriochloroform): 9.43 (1H, s, CHO), 9.08 (1H, s, CHO), 8.52 (1H, d, J = 6.6 Hz, H-7), 8.05-7.30 (9H, m, Ar-H); ir (potassium bromide): 3100 (C-H, ArH), 1730 (CO), 1610 (C=C conj.), 730 (ArH o-disubst.), 760 and 705 $cm^{-1}$ (ArH monosubst.); ms: (70 eV) m/z 221 ($M^+$, 76), 193 (100), 165 (71), 139 (11).

2-Formyl-1-methyl-3-phenylindole (**16**).

Following the procedure indicated above, a mixture of anhydrous *N,N*-dimethylformamide, 5.4 ml (70.38 mmoles), phosphorus oxychloride, 1.6 ml (17.59 mmoles) and 3-phenylindole, 3.31 g (15.99 mmoles) was warmed at 130° for 1 hour. The crude reaction product was purified by silica gel column chromatography, using toluene as the eluent. The 2-formyl-1-methyl-3-phenylindole **16**, was isolated as the unique product, pale-yellow solid, mp 65-66°, 3.57 g (95%). 2-formyl-1-methyl-3-phenylindole, **16**. $^1H$ nmr (deuteriochloroform): 9.87 (1H, s, CHO), 7.70 (1H, d, J = 7.0 Hz, H-7), 7.50-7.10 (8H, m, Ar-H), 4.10 (3H, s, N-$CH_3$); ir (potassium bromide): 1660 (CO), 1465 (C-H, $CH_3$), 1375 (C-H, $CH_3$), 740 (ArH o-disubst.), 770 and 700 $cm^{-1}$ (ArH monosubst.); ms: (70 eV) m/z 235 ($M^+$, 100), 234 (76), 207 (59), 206 (28), 165 (29).

3-Methyl-2-(2'-nitrovinyl)indole (**17**).

To a solution of 2-formyl-3-methylindole, 841.7 mg (5.29 mmoles) in nitromethane (3 ml), under argon atmosphere, was added ammonium acetate (214.6 mg, 2.78 mmoles) and the mixture was warmed at 120° with stirring, for 3 hours. The excess of nitromethane was removed under reduced pressure and the crude product was purified by silica gel column chromatography, using dichloromethane as the eluent. The 3-methyl-2-(2'-nitrovinyl)-indole **17**, was obtained as orange neddles mp 184° [14a] (77%). $^1H$ nmr (deuteriochloroform): 8.19 (1H, d, J = 13.5 Hz, $H_A$), 8.06 (1H, br s, NH), 7.62 (1H, d, J = 8.3 Hz, H-7), 7.43 (1H, d, J = 13.5 Hz, $H_B$), 7.37-7.12 (3H, m, Ar-H), 2.50 (3H, s, $CH_3$); ir (potassium bromide): 3320 (N-H), 1605 (C=C conj.), 1310 and 1265 (N-O), 950 (C=C trans), 810 (C-N, $NO_2$), 745 $cm^{-1}$ (ArH o-disubst.); ms: (70 eV) m/z 202 ($M^+$, 87), 185 (15), 154 (100), 128 (46), 115 (17).

*Anal.* Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85%. Found: C, 65.74; H, 4.98; N, 13.40%.

1,3-Dimethyl-2-(2'-nitrovinyl)indole (**18**).

Following the procedure indicated above, a mixture of 2-formyl-1,3-dimethylindole (3.19 g, 18.4 mmoles), in 9 ml of nitromethane and ammonium acetate (746.5 mg, 9.68 mmoles), was warmed at 120-130° for 2 hours. The crude product was purified by silica gel column chromatography using dichloromethane-toluene (2:1) as the eluent. The 1,3-dimethyl-2-(2'-nitrovinyl)indole 18, was isolated as an orange solid mp 155-158° [14a] (87%). $^1H$ nmr (deuteriochloroform): 8.29 (1H, d, J = 13.6 Hz, $H_A$), 7.65 (1H, d, J = 8.0 Hz, H-7), 7.61 (1H, d, J = 13.6 Hz, $H_B$), 7.42-7.11 (3-H, m, Ar-H), 3.87 (3H, s, N-$CH_3$), 2.52 (3H, s, $CH_3$); ir (potassium bromide): 1610 (C=C conj.), 1480 (N-O), 1300 and 1280 (N-O), 950 (C=C trans), 815 (C-N, $NO_2$), 740 $cm^{-1}$ (ArH o-disubst.); ms: (70 eV) m/z 216 (M+50), 199 (21), 168 (100), 154 (61), 144 (32), 128 (34).

*Anal.* Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.84; H, 5.46; N, 12.95.

3-Methyl-2-(2'-methyl-2'-nitrovinyl)indole (**19**).

Following the procedure indicated above, a mixture of 2-formyl-3-methylindole (841.7 mg, 5.29 mmoles), in 4 ml of nitroethane and ammonium acetate, 271.8 mg (3.53 mmoles) was warmed at 120° for 3 hours. The crude product was purified by silica gel column chromatography using dichloromethane-toluene (1:1) as the eluent. The 3-methyl-2-(2'methyl-2'-nitrovinyl)indole **19**, was isolated as red crystals, mp 165° (84%). $^1H$ nmr (deuteriochloroform): 8.30 (1H, s, $H_A$), 8.12 (1H, br s , NH), 7.62 (1H, d, J = 8.0 Hz, H-7), 7.45-7.10 (3H, m, Ar-H), 2.63 (3H, s, $CH_3$-2'), 2.45 (3H, s, $CH_3$-3); ir (potassium bromide): 3420 (N-H), 1615 (C=C conj.), 1480 (N-O), 1275 (N-O), 850 (C=CH), 750 $cm^{-1}$ (ArH o-disubst.); ms: (70 eV) m/z 216 ($M^+$, 100), 199 (7), 168 (81), 154 (43), 128 (28), 77 (19).

*Anal.* Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.68; H, 5.58; N, 12.94.

1,3-Dimethyl-2-(2'-methyl-2'-nitrovinyl)indole (**20**).

Following the procedure indicated above, a mixture of 2-formyl-1,3-dimethylindole, 3.19 g (18.4 mmoles), in 12 ml of

nitroethane and ammonium acetate 948.1 mg (12.3 mmoles), was warmed at 140° for 1 hour. The crude product was purified by silica gel column chromatography using n-hexane:ethyl acetate (9:1) as the eluent. The 1,3-dimethyl-2-(2'methyl-2'-nitrovinyl)indole **20**, was isolated as an orange solid mp 123-124° (56%). $^1$H nmr (deuteriochloroform): 8.10 (1H, s, $H_A$), 7.65 (1H, d, J = 8.6 Hz, H-7), 7.40-7.00 (3H, m, Ar-H), 3.70 (3H, s, N-$CH_3$), 2.32 (3H, s, $CH_3$-2'), 2.28 (3H, s, $CH_3$-3); ir (potassium bromide): 1645 (C=C conj.), 1500 (N-O), 1305 (N-O), 845 (C=CH), 750 cm$^{-1}$ (ArH o-disubst.); ms: (70 eV) m/z 230 ($M^+$, 100), 213 (15), 196 (15), 182 (73), 173 (49), 168 (83).

*Anal.* Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.92; H, 6.02; N, 11.98.

3-Phenyl-2-(2'-nitrovinyl)indole (**21**).

Following the procedure indicated above, a mixture of 2-formyl-3-phenylindole, 895 mg (4.04 mmoles), in 3 ml of nitromethane and ammonium acetate, 164.2 mg (2.13 mmoles), was warmed at 120° for 2 hours. The crude product was purified by silica gel column chromatography, using dichloromethane as the eluent. The 3-phenyl-2-(2'-nitrovinyl)indole **21**, was isolated as red crystals mp 198-200° (82%). $^1$H nmr (deuteriochloroform): 8.64 (1H, br s, NH), 8.07 (1H, d, J = 13.4 Hz, $H_A$), 7.70 (1H, d, J = 9.3 Hz, H-7), 7.65 (1H, d, J = 13.4 Hz, $H_B$), 7.55-7.10 (8H, m, Ar-H); ir (potassium bromide): 3320 (N-H st), 1610 (C=C conj.), 1475 (N-O), 1310 and 1265 (N-O), 940 (C=C trans), 805 (C-N, $NO_2$), 735 (ArH o-disubst.), 750 and 710 cm$^{-1}$ (ArH monosubst.); ms: (70 eV) m/z 264 ($M^+$, 39), 217 (100), 190 (17), 189 (22), 108 (24), 57 (42).

*Anal.* Calcd. for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.81; H, 4.54; N, 10.60.

3-Phenyl-1-methyl-2-(2'-nitrovinyl)indole (**22**).

Following the procedure indicated above, a mixture of 2-formyl-1-methyl-3-phenylindole, 1.78 g (7.57 mmoles) in 6 ml of nitromethane and ammonium acetate, 307.1 mg (3.98 mmoles), was warmed at 110° for 1 hour. The crude product was purified by silica gel column chromatography, using dichloromethane:toluene (1:1) as the eluent. The 3-phenyl-1-methyl-2-(2'-nitrovinyl)indole **22**, was isolated as orange neddles mp 156-158° (90%). $^1$H nmr (deuteriochloroform): 8.20 (1H, d, J = 13.7 Hz, $H_A$), 7.60 (1H, d, J = 8.1 Hz, H-7), 7.53 (1H, d, J = 13.7 Hz, $H_B$), 7.54-7.11 (8H, m, Ar-H), 3.97 (3H, s, N-$CH_3$); ir (potassium bromide): 1610 (C=C conj.), 1470 (N-O st as), 1300 and 1290 (N-O), 930 (C=C trans), 825 (C-N, $NO_2$), 750 (ArH o-disubst.), 780 and 710 cm$^{-1}$ (ArH monosubst.); ms: (70 eV) m/z 278 ($M^+$, 51), 231 (57), 217 (100), 189 (21), 115 (39).

*Anal.* Calcd. for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.73; H, 5.01; N, 9.82.

3-Phenyl-2-(2'-methyl-2'-nitrovinyl)indole (**23**).

Following the procedure indicated above, a mixture of 2-formyl-3-phenylindole, 895 mg (4.04 mmoles), in 4 ml of nitroethane and ammonium acetate, 207.3 mg (2.69 mmoles), was warmed at 120° for 1 hour. The crude product was purified by silica gel column chromatography using dichloromethane: toluene (6:1) as the eluent. The 3-phenyl-2-(2'-methyl-2'-nitrovinyl)indole was isolated as red neddles (89%) as two rotamers, **a** and **b** (95:5 by $^1$H nmr), mp 176.5° and 157.4° respectively (by DSC). $^1$H nmr (deuteriochloroform): 8.41 (1H, br s, NH), 8.28 (1H, s, $H_A$, **b**), 8.18 (1H, s, $H_A$, **a**), 7.74 (1H, d, J = 8.0 Hz, H-7), 7.56-7.10 (8H, m, Ar-H), 2.67 (3H, s, $CH_3$, **a**), 2.53 (3H, s, $CH_3$, **b**); ir (potassium bromide): 3420 (N-H), 1630 (C=C conj.), 1485 (N-O), 1290 (N-O), 850 (C=C), 750 (ArH o-disubst.), 780 and 705 cm-1 (ArH monosubst.); ms: (70 eV) m/z 278 ($M^+$, 80), 230 (100), 217 (71), 204 (26), 165 (28).

*Anal.* Calcd. for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.56; H, 5.06; N, 9.96.

1-Methyl-3-phenyl-2-(2'methyl-2'-nitrovinyl)indole (**24**).

Following the procedure indicated above, a mixture of 1-methyl-3-phenyl-2-formylindole, 1.78 g (7.57 mmoles), in 8 ml of nitroethane and ammonium acetate, 389 mg (5.05 mmoles), was warmed at 110° for 1 hour. The crude product was purified by silica gel column chromatography using dichloromethane: toluene (1:1) as the eluent. The 1-methyl-3-phenyl-2-(2'methyl-2'-nitrovinyl)indole **24**, was isolated as a red crystalline solid mp 102° (63%). $^1$H nmr (deuteriochloroform): 8.20 (1H, s, $H_A$), 7.75 (1H, d, J = 8.12 Hz, H-7), 7.60-7.10 (8H, m, Ar-H), 3.80 (3H, s, N-$CH_3$), 1.72 (3H, s, $CH_3$); ir (potassium bromide): 1650 (C=C conj.), 1510 (N-O), 1315 and 1260 (N-O), 860 (C=CH), 750 (ArH o-disubst.), 780 and 705 cm$^{-1}$ (ArH monosubst.); ms: (70 eV) m/z 292 ($M^+$, 100), 275 (2), 245 (91), 231 (99), 216 (30), 202 (46).

*Anal.* Calcd. for $C_{18}H_{16}N_2O_2$: C, 73.96; H, 5.52; N, 9.58. Found: C, 74.33; H, 5.37; N, 9.84.

3-Phenyl-2-(2'-ethyl-2'-nitrovinyl)indole (**25**).

Following the procedure indicated above, a mixture of 2-formyl-3-phenylindole, 90 mg (0.39 mmoles), in 0.6 ml of nitropropane and ammonium acetate, 21 mg (0.27 mmoles), was warmed at 140° for 2 hours. The crude product was purified by silica gel column chromatography using dichloromethane: toluene (6:1) as the eluent. The 3-phenyl-2-(2'-ethyl-2'-nitrovinyl)indole **25**, was isolated as red neddles (79%) as a mixture of two rotamers **a** and **b** (79:21, by $^1$H nmr), mp 102-106° (broad peak by DSC). $^1$H nmr (deuteriochloroform): 8.39 (1H, br s, NH), 8.23 (1H, s, $H_A$, **b**), 8.13 (1H, s, $H_A$, **a**), 7.75 (1H, d, J = 8.0 Hz, H-7), 7.58-7.17 (8H, m, Ar-H), 3.09 (2H, q, J = 7.2 Hz, $CH_2$, **a**), 2.72 (2H, q, J = 7.2 Hz, $CH_2$, **b**), 1.39 (3H, t, J = 7.2 Hz, $CH_3$, **a**), 1.17 (3H, t, J = 7.2 Hz, $CH_3$, **b**); ir (potassium bromide): 3423 (N-H), 1535 (C=C conj.), 1421 (N-O), 1265 (N-O), 896 (C=C), 739 (ArH o-disubst.), 705 cm$^{-1}$ (ArH monosubst.); ms: (70 eV) m/z 278 ($M^+$, 80), 230 (100), 217 (71), 204 (26), 165 (28).

*Anal.* Calcd. for $C_{18}H_{16}N_2O_2$: C, 73.96; H, 5.52; N, 10.94. Found: C, 73.68; H, 5.42; N, 10.79.

3-Phenyl-2-(2'-propyl-2'-nitrovinyl)indole (**26**).

Following the procedure indicated above, a mixture of 2-formyl-3-phenylindole, 60 mg (0.26 mmoles), in 0.4 ml of nitrobutane and ammonium acetate, 14 mg (0.18 mmoles), was warmed at 140° for 2 hours. The crude product was purified by silica gel column chromatography using dichloromethane: toluene (6:1) as the eluent. The 3-phenyl-2-(2'-propyl-2'-nitrovinyl)indole **26**, was isolated as a viscous red oil (65%) as a mixture of two rotamers **a** and **b** (74:26, by $^1$H nmr), mp 173.2 and 151.5° respectively (by DSC). $^1$H nmr (deuteriochloroform): 8.32 (1H, br s, NH), 8.26 (1H, s, $H_A$, **b**), 8.17 (1H, s, $H_A$, **a**), 7.75 (1H, d, J = 8.1 Hz, H-7), 7.58-7.14 (8H, m, Ar-H), 3.03 (2H, q, J = 7.2 Hz, $CH_2$, **a**), 2.65 (2H, q, J = 7.2 Hz, $CH_2$ **b**), 1.79 (2H, sext, J = 7.2 Hz, $CH_2$, **a**), 1.60 (2H, sext, J = 7.2 Hz, $CH_2$, **b**), 1.13 (3H, t, J = 7.2 Hz, $CH_3$, **a**), 0.97 (3H, t, J = 7.2 Hz, $CH_3$, **b**); ir (potassium bromide): 3432 (N-H), 1616 (C=C conj.), 1487 (N-O), 1265 (N-O), 896

(C=C), 739 (ArH o-disubst.) and 705 $cm^{-1}$ (ArH monosubst.); ms (70 eV) m/z: 278 ($M^+$, 80), 230 (100), 217 (71), 204 (26), 165 (28).

*Anal.* Calcd. for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.14. Found: C, 74.52; H, 5.76; N, 9.22.

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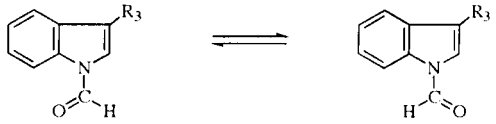
[11] The relative intensity of the proton of each CHO group in the nmr spectrum, permits to evaluate the conformation ratio *cisoid:transoid*, in solution of **13** or **14**.


| Compound | **13** ($R_3$ =$CH_3$) | | **14** ($R_3$ =$C_6H_5$) | |
|---|---|---|---|---|
| Conformation | *cisoid* | *transoid* | *cisoid* | *transoid* |
| –CHO (ppm) | 8.95 | 9.30 | 9.08 | 9.43 |
| Rotamer (%) | 55 | 45 | 63 | 37 |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