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# Structural study of nitrovinylindoles: (I) 2-methyl-3-(2′-methyl-2′-nitrovinyl)indole and (II) 3-(2′-nitrovinyl)indole

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## Abstract

Compound (I) is 2-methyl-3-(2′-methyl-2′-nitrovinyl)indole, $C_{12}H_{12}N_2O_2$, $M_r = 216.24$, monoclinic, $P2_1/n$, $a = 16.710(1)$, $b = 7.627(1)$, $c = 17.646(1)$ Å, $\beta = 104.8(1)°$, $V = 2174.7(1)$ Å$^3$, $Z = 8$. $D_x = 1.321$ g cm$^{-3}$, Mo $K\alpha$, $\lambda = 0.71073$ Å, $\mu = 0.858$ cm$^{-1}$, $F(000) = 912$, room temperature, $R = 0.061$ for 1956 observed reflections. Compound (II) is 3-(2′-nitrovinyl)indole, $C_{10}H_8N_2O_2$, $M_r = 188.18$, monoclinic, $P2_1/n$, $a = 10.178(1)$, $b = 10.608(1)$, $c = 8.411(1)$ Å, $\beta = 105.5(2)°$, $V = 875.0(1)$ Å$^3$, $Z = 4$, $D_x = 1.4284$ g cm$^{-3}$, Cu $K\alpha$, $\lambda = 1.5418$ Å, $\mu = 8.068$ cm$^{-1}$, $F(000) = 392$, room temperature, $R = 0.040$ for 1330 observed reflections. Compounds (I) and (II) have a similar geometry, the only significant difference lying in the rotation of the nitrovinyl chain. This feature could be responsible for the difference in biological activity. In both compounds, the molecules are associated, forming charge-transfer complexes.

## Introduction

Many of the common drugs used in the clinic (J. G. Rodriguez and J. B. Subirats, private communication) as parasiticides consist of a heterocyclic system and an ionophoric one, both connected through an ethylene bridge. Nitro-

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vinylindoles show these characteristics, and a number of them have been prepared as potential antiparasite drugs (Fonseca *et al.*, 1987). Compound (I) is very effective in low concentration against *ameba* and *Candida albicans* parasites, while (II) shows a moderate activity. We are interested in the molecular and crystallographic study of compounds (I) and (II) in order to understand the possible molecular parameters determining the biological activity.

## Experimental

### *Preparation*

Condensation of 2-methyl-3-formylindole with excess nitroethane (Ash and Wragg, 1958) was carried out under a nitrogen atmosphere in the presence of solid ammonium acetate, at 120–130°C during 4 h, giving 2-methyl-3-(2′-methyl-2′-nitrovinyl)indole (I), mp 429–431 K, as a brown, solid material in 60% yield. Condensation of 3-formylindole with excess nitromethane (Ash and Wragg, 1958) was carried out under a nitrogen atmosphere in the presence of solid ammonium acetate, at 110–120°C during 2 h, giving 3-(2′-nitrovinyl)indole (II), mp 442–445 K, as a yellow crystalline material in 65% yield.

### *Elemental analysis*

Compound (I). Found: C, 66.45; H, 5.84; N, 13.04. Required: C, 66.65; H, 5.59; N, 12.95%. 2-Methyl-3-formylindole, mp 200–202°C, was prepared by the Vilsmeier–Haak reaction of 2-methylindole with dimethylformamide and phosphorous oxichloride. Compound (II). Found: C, 63.60; H, 4.35; N, 15.03. Required: C, 63.83; H, 4.29; N, 14.89%. 3-Formylindole was prepared by the oxidation of 3-methylindole with 1,2-dichloro-4,5-dicyanoquinone in the presence of water (molar relation 9 : 1) in a similar manner to that described previously (Rodriguez *et al.*, 1985).

### *Spectral analysis*

*IR (KBr,* $cm^{-1}$*).* Compound (I): 3350(NH); 3090(=CH); 1630, 1585, 1490, 1430(C=N and C=C); 1280 and 1235($NO_2$); 870(=CH) and 750, 730(Ar. substitution). Compound (II): 3450(NH); 3140(=CH); 1620, 1580, 1525, 1480 and 1440 (C=N and C=C); 1320 and 1250 ($NO_2$); 975(=CH) and 750(Ar. substitution).

$^1H$*-NMR (200 MHz,* $DCCl_3$*-TMS, δ).* Compound (I): 8.38(broad s,1H,NH); 8.33(s,1H,vinylic); 7.52–7.34(m,1H,H-4); 7.30–7.17(m,3H, H-5,H-6,H-7); 2.50(s,3H,$CH_3$ position 2); 2.39(s,3H,$CH_3$ position 2′). Compound (II): 8.38(d,1H,A part of AB, vinylic-proton system, $J_{AB}$ = 13.4 Hz); 8.16(d,1H,H-2); 7.99–7.96(m,1H,H-4); 8.05(bd s,1H,NH); 7.91(d,1H,B part of AB vinylic-proton system, $J_{AB}$ = 13.4 Hz); 7.60–7.27(m,3H,H-5,H-6, H-7).

*Ultraviolet-visible ($CH_3OH$, nm).* Compound (I): 412.8($\epsilon$ = 14486); 286.4($\epsilon$ = 11027); 228.2($\epsilon$ = 33632). Compound (II): 393($\epsilon$ = 19429); 297($\epsilon$ = 8286); 221($\epsilon$ = 20571).

*MS/GC (70 eV).* Compound (I): 216(95); 168(base peak); 169(92) $M^+ - NO_2H$; 154(72). Compound (II): 188(base peak); 141(78) $M^+ - NO_2H$; 115(97).

### *Structural solution*

*Compound (I).* A crystal of 0.20 × 0.10 × 0.20 mm was used to determine the lattice parameters by least-squares fitting of setting angles of 86 reflections ($8 < 2\theta < 89$) measured on a Philips PW1100 diffractometer with Cu $K\alpha$ ($\lambda$ = 1.5418 Å). Intensities were collected on a CAD-4 diffractometer equipped with graphite monochromator and Mo $K\alpha$ radiation; $\omega/2\theta$ scan mode; $\theta_{\max} = 30°$. Two intensity control reflections showed no significant variation in intensity. A total of 6312 reflections was measured, $R_{\text{int}} = 0.01$: 1956 observed [$I > 3\sigma(I)$] and 385 parameters used in refinement. Index range: $h$ 0/23, $k$ 0/10, $l$ −24/23. Lorentz and polarization corrections were applied, but no absorption correction.

*Compound (II).* A crystal of 0.38 × 0.33 × 0.28 mm was mounted on a Philips PW1100 diffractometer with graphite monochromator and Cu $K\alpha$ radiation. Lattice parameters were obtained from least-squares refinement of 77 reflections ($12 < 2\theta < 90°$). $\omega/2\theta$ scan mode; $\theta_{\max} = 65°$ ($h$ −11/12, $k$ 0/13, $l$ 0/10). No absorption correction was applied. There were no significant intensity variations of standard reflections. A total of 1467 reflections was measured: 1330 observed with [$I > 3\sigma(I)$]. Both structures were solved by direct methods using MULTAN 80 (Main *et al.*, 1980). Full-matrix, least-squares anisotropic refinement was performed on all nonhydrogen atoms. H-atom positions were determined from a difference map and included with isotropic temperature factors. Final values: compound (I) $R = 0.061$, $wR = 0.053$; $S = 0.97$, $\Delta/\sigma(\text{av.}) = 0.28$, $\Delta\rho$ within $\pm 0.26$ e Å$^{-3}$. Compound (II) $R = 0.040$, $wR = 0.045$; $S = 10.2$, $\Delta/\sigma = 0.03$, $\Delta\rho$ within $-0.25$, $+0.16$ e Å$^{-3}$. Computations were made at the Instituto Rocasolano, using the VAX 11/750 computer. The computer programs used were: XRAY System (Stewart *et al.*, 1970); PESOS (Martinez-Ripoll and Cano, 1975) for the weighting scheme; PARST (Nardelli, 1983) for the molecular geometry calculations. Atomic scattering factors were from *International Tables for X-ray Crystallography* (1974).

## Discussion

Final atomic coordinates and derived bond lengths and angles of both compounds are given in Tables 1 and 2. The structures of the molecules are shown in Figs. 1 and 2. Compound (I) has two independent molecules in the asym-

**Table 1.** Coordinates and thermal parameters as $U_{eq} = (1/3)\Sigma(U_{ij} a_i{}^* a_j{}^* a_i a_j \cos(a_i, a_j)) \cdot 10^3$

| Atom | $x/a$ | $y/b$ | $z/c$ | $U_{eq}$ |
|---|---|---|---|---|
| Compound (I) | | | | |
| N1(1) | 1.0804(2) | 0.3031(6) | 0.0383(3) | 51(2) |
| C2(1) | 1.1094(3) | 0.2587(6) | 0.1165(3) | 46(2) |
| C3(1) | 1.1870(3) | 0.2886(8) | 0.1658(4) | 68(3) |
| C4(1) | 1.2011(4) | 0.2217(9) | 0.2407(4) | 78(3) |
| C5(1) | 1.1411(3) | 0.1250(8) | 0.2643(3) | 67(3) |
| C6(1) | 1.0644(3) | 0.0969(7) | 0.2147(3) | 51(2) |
| C7(1) | 1.0458(3) | 0.1696(6) | 0.1389(3) | 39(2) |
| C8(1) | 0.9763(3) | 0.1641(6) | 0.0704(3) | 37(2) |
| C9(1) | 1.0021(3) | 0.2457(6) | 0.0099(3) | 42(2) |
| C10(1) | 0.8959(3) | 0.0841(6) | 0.0558(3) | 42(2) |
| C11(1) | 0.8517(3) | 0.0431(6) | 0.1070(3) | 43(2) |
| C12(1) | 0.8660(4) | 0.0946(10) | 0.1902(3) | 59(2) |
| C13(1) | 0.9570(5) | 0.2744(10) | −0.0736(3) | 60(3) |
| N2(1) | 0.7756(3) | −0.0513(6) | 0.0756(3) | 65(2) |
| O21(1) | 0.7558(2) | −0.0981(7) | 0.0064(3) | 97(2) |
| O22(1) | 0.7314(2) | −0.0841(6) | 0.1200(3) | 91(2) |
| N1(2) | 0.4297(2) | 0.2018(5) | 0.0118(2) | 43(2) |
| C2(2) | 0.4592(3) | 0.1729(6) | 0.0917(3) | 41(2) |
| C3(2) | 0.4160(3) | 0.1156(7) | 0.1448(3) | 54(2) |
| C4(2) | 0.4614(4) | 0.0870(8) | 0.2209(3) | 57(2) |
| C5(2) | 0.5465(4) | 0.1127(7) | 0.2424(3) | 55(2) |
| C6(2) | 0.5885(3) | 0.1703(7) | 0.1886(3) | 48(2) |
| C7(2) | 0.5446(3) | 0.2057(6) | 0.1122(3) | 36(2) |
| C8(2) | 0.5657(3) | 0.2577(6) | 0.0400(2) | 36(2) |
| C9(2) | 0.4927(3) | 0.2478(6) | −0.0195(3) | 39(2) |
| C10(2) | 0.6403(3) | 0.3159(6) | 0.0227(3) | 42(2) |
| C11(2) | 0.7067(3) | 0.3964(6) | 0.0678(3) | 41(2) |
| C12(2) | 0.7201(4) | 0.4685(8) | 0.1486(3) | 52(2) |
| C13(2) | 0.4780(4) | 0.2857(8) | −0.1046(3) | 50(2) |
| N2(2) | 0.7719(2) | 0.4421(6) | 0.0301(3) | 51(2) |
| O21(2) | 0.7671(2) | 0.3995(6) | −0.0378(2) | 76(2) |
| O22(2) | 0.8324(2) | 0.5231(5) | 0.0695(2) | 65(2) |
| Compound (II) | | | | |
| N1 | 0.4114(2) | −0.2879(1) | 1.0195(2) | 50(5) |
| C2 | 0.3046(2) | −0.2062(2) | 0.9554(2) | 41(5) |
| C3 | 0.1737(2) | −0.2062(2) | 0.9757(2) | 48(6) |
| C4 | 0.0883(2) | −0.1098(2) | 0.9026(2) | 52(6) |
| C5 | 0.1320(2) | −0.0167(2) | 0.8109(2) | 53(6) |
| C6 | 0.2619(2) | −0.0185(2) | 0.7891(2) | 46(6) |
| C7 | 0.3514(2) | −0.1146(2) | 0.8622(2) | 38(5) |
| C8 | 0.4924(2) | −0.1457(2) | 0.8737(2) | 41(5) |
| C9 | 0.5222(2) | −0.2519(2) | 0.9719(2) | 49(6) |
| C10 | 0.5904(2) | −0.0871(2) | 0.8049(2) | 42(6) |
| C11 | 0.5744(2) | 0.0190(2) | 0.7166(2) | 43(6) |
| N2 | 0.6818(1) | 0.0668(1) | 0.6546(2) | 45(5) |
| O21 | 0.7865(1) | 0.0044(1) | 0.6671(2) | 64(6) |
| O22 | 0.6657(2) | 0.1713(1) | 0.5890(2) | 69(6) |

**Table 2.** Bond distances, bond angles, and significant torsion angles

| | Compound (I) | | Compound (II) |
|---|---|---|---|
| | Mol. 1 | Mol. 2 | |
| | (a) Bond distances (Å) | | |
| N1-C2 | 1.383(7) | 1.388(6) | 1.382(2) |
| N1-C9 | 1.350(6) | 1.354(7) | 1.349(3) |
| C2-C3 | 1.383(7) | 1.391(8) | 1.388(3) |
| C2-C7 | 1.401(7) | 1.403(6) | 1.410(2) |
| C3-C4 | 1.379(10) | 1.380(7) | 1.375(3) |
| C4-C5 | 1.392(10) | 1.388(8) | 1.398(3) |
| C5-C6 | 1.371(7) | 1.387(8) | 1.383(3) |
| C6-C7 | 1.407(7) | 1.387(6) | 1.395(2) |
| C7-C8 | 1.446(5) | 1.461(7) | 1.451(2) |
| C8-C9 | 1.396(7) | 1.394(5) | 1.382(2) |
| C8-C10 | 1.438(6) | 1.427(7) | 1.422(3) |
| C9-C13 | 1.490(7) | 1.487(7) | — |
| C10-C11 | 1.341(8) | 1.339(6) | 1.335(2) |
| C11-C12 | 1.479(8) | 1.491(7) | — |
| C11-N2 | 1.444(6) | 1.455(7) | 1.424(3) |
| N2-O21 | 1.233(8) | 1.224(6) | 1.234(2) |
| N2-O22 | 1.233(9) | 1.237(5) | 1.229(2) |
| | (b) Bond angles (deg) | | |
| C2-N1-C9 | 110.6(4) | 110.2(4) | 109.8(2) |
| N1-C2-C7 | 107.6(4) | 107.9(4) | 107.6(2) |
| N1-C2-C3 | 128.4(5) | 128.6(4) | 129.3(2) |
| C3-C2-C7 | 124.0(5) | 123.5(4) | 123.1(2) |
| C2-C3-C4 | 116.5(6) | 117.0(5) | 117.2(2) |
| C3-C4-C5 | 121.5(6) | 120.9(5) | 121.1(2) |
| C4-C5-C6 | 121.3(6) | 121.3(5) | 121.3(2) |
| C5-C6-C7 | 119.3(5) | 119.5(5) | 119.1(2) |
| C2-C7-C6 | 117.4(4) | 117.8(4) | 118.1(2) |
| C6-C7-C8 | 135.9(4) | 135.7(4) | 135.5(2) |
| C2-C7-C8 | 106.5(4) | 106.3(4) | 106.3(1) |
| C7-C8-C10 | 132.5(4) | 133.6(4) | 131.5(2) |
| C7-C8-C9 | 106.7(4) | 106.4(4) | 106.3(2) |
| C9-C8-C10 | 120.6(4) | 119.9(4) | 122.3(2) |
| N1-C9-C8 | 108.6(4) | 109.2(4) | 110.0(2) |
| C8-C9-C13 | 130.2(5) | 129.6(5) | — |
| N1-C9-C13 | 121.1(5) | 121.1(4) | — |
| C8-C10-C11 | 128.9(5) | 130.7(4) | 126.9(2) |
| C10-C11-N2 | 116.1(5) | 116.3(4) | 120.8(2) |
| C10-C11-C12 | 129.0(5) | 129.5(5) | — |
| C12-C11-N2 | 114.6(4) | 113.7(4) | — |
| C11-N2-O22 | 118.0(5) | 117.6(4) | 117.5(2) |
| C11-N2-O21 | 121.2(5) | 120.9(4) | 120.5(2) |
| O21-N2-O22 | 121.2(5) | 121.5(4) | 122.0(2) |
| | (c) Some significant torsion angles (deg) | | |
| C7-C8-C10-C11 | 25.5(9) | −25.6(9) | 3.9(3) |
| C9-C8-C10-C11 | −160.1(5) | 152.2(5) | −176.1(2) |
| C8-C10-C11-N2 | −174.6(5) | 178.4(5) | −179.8(2) |
| C10-C11-N2-O21 | 3.6(7) | −3.9(7) | 7.4(3) |
| C10-C11-N2-O22 | −176.7(5) | 177.0(4) | −172.6(2) |

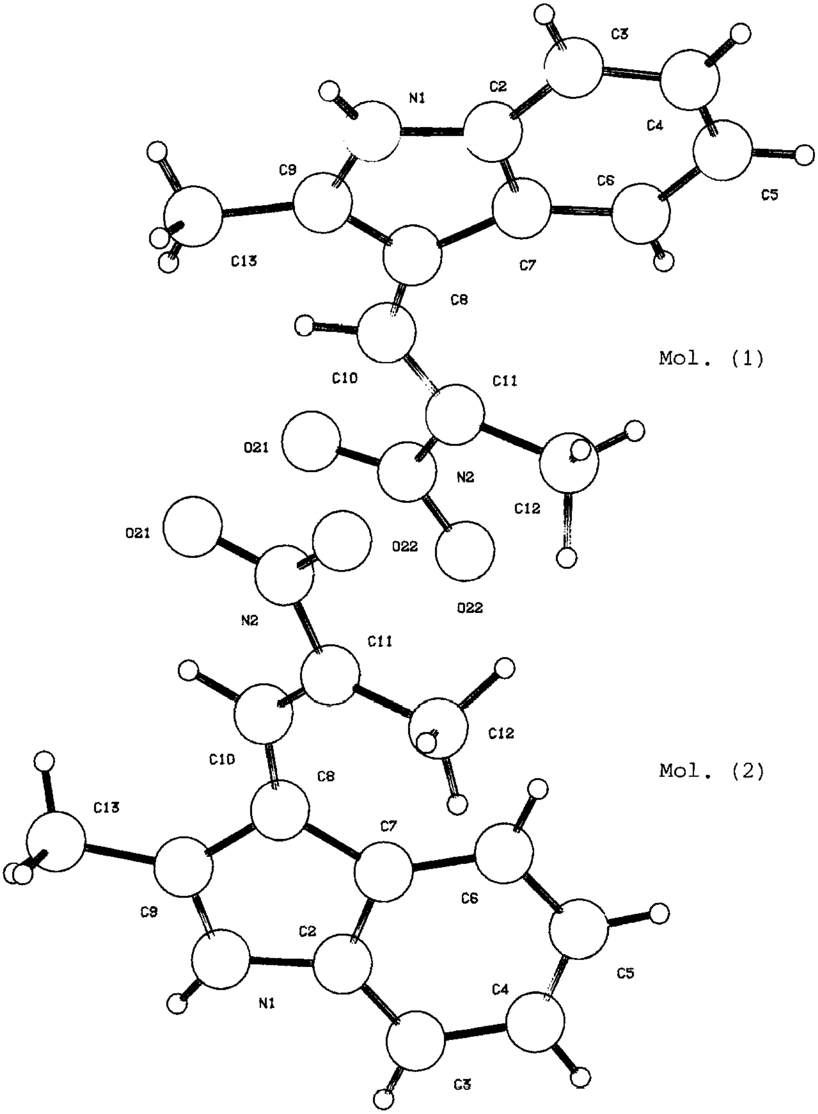


Fig. 1. Molecular structures showing the atomic numbering.

metric unit; both molecules show very similar geometries as also does compound (II). The indole nucleus is nearly planar in all compounds [dihedral angles between benzene and pyrrole rings: compound (I) 3.9(2), 4.1(2); compound (II) 2.04(6)]. Bond distances in the pyrrole ring show some deviation from the

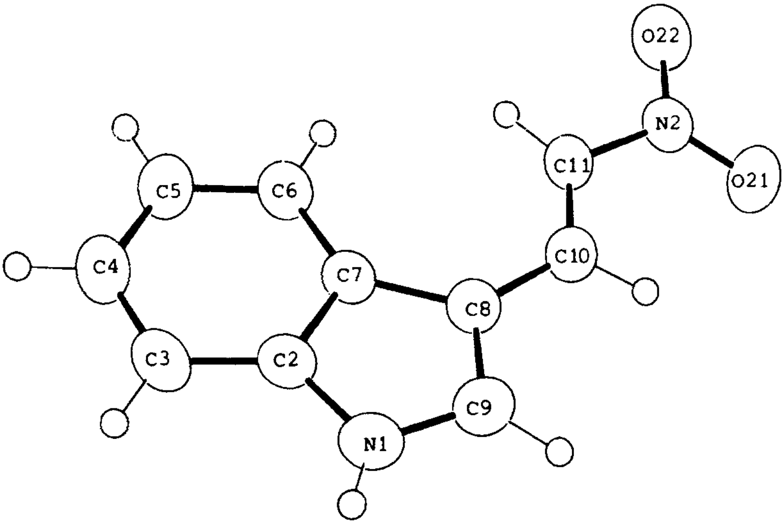
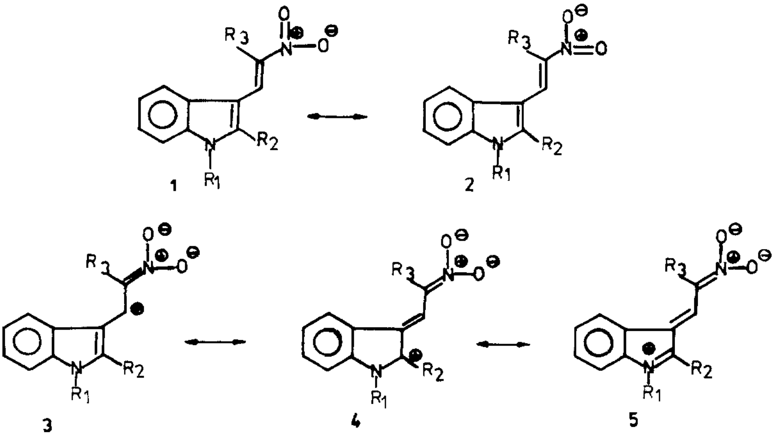


**Fig. 2.** Molecular packing.

expected values (Rodriguez *et al.*, 1985); thus N(1)–C(9) is shortened while C(7)–C(8) is lengthened; C(10)–C(11) shows double-bond character and N(1)–C(2) and C(8)–C(9) have an intermediate value between those expected for single and double bonds. The existence of hydrogen bonds as well as short intermolecular contacts (see Table 3) is clear. From the above, it can be deduced that the best structural representation for both compounds would be a resonance hybrid of the structures 1–5:



**Scheme I.** Compound 1 $R_1 = H$, $R_2 = R_3 = CH_3$; Compound 2 $R_1 = R_2 = R_3 = H$

Table 3. Hydrogen bonds and short intermolecular contacts

| | | | | | |
|---|---|---|---|---|---|
| | | (a) Hydrogen bonds | | | |
| Compound (I) | | | | | |
| N1(1)-H1(1) | 0.88(6) Å | N1(1) · · · O22(2)(i) | 2.985(6) Å | N1(1)-H1(1) · · · O22(2)(i) | 174(5)° |
| (i) $-x + 2, -y + 1, -z$ | | | | | |
| Compound (II) | | | | | |
| N1-H1 | 0.87(3) Å | N1 · · · O21(i) | 3.045(2) Å | N1-H1 · · · O21(i) | 152(3)° |
| (i) $x - \frac{1}{2}, -y - \frac{1}{2}, z + \frac{1}{2}$ | | | | | |
| | | (b) Short contacts | | | |
| Compound (I) | | | | | |
| N1(1)-H1(1) | 0.88(6) Å | N1(1) · · · O21(2)(i) | 3.414(6) Å | N1(1)-H1(1) · · · O21(2) (i) | 135(4)° |
| N1(2)-H1(2) | 0.90(5) | N1(2) · · · O21(1)(ii) | 3.136(6) | N1(2)-H1(2) · · · O21(1) (ii) | 146(5) |
| N1(2)-H1(2) | 0.90(5) | N1(2) · · · O22(1)(ii) | 3.205(5) | N1(2)-H1(2) · · · O22(1) (ii) | 159(5) |
| (i) $-x + 2, -y + 1, -z$ | | | | | |
| (ii) $-x + 1, -y, -z$ | | | | | |

We can consider a possible conjugation from the pyrrole ring to the nitrovinyl chain; thus, in (I), structures 4 and 5 should be dominant. Structure 5 shows the acid character of H(1) [it forms a hydrogen bond with O(22), which also shows the basic character of the latter (Bucki and Ching-Pong Mak, 1977)]. It should be noted that the indole parts of the molecules are arranged in pairs about the centers of symmetry, alternately parallel to the *c* axis and along the *ac* diagonal of the unit cell forming a charge-transfer complex, the shortest distances between non-H atoms of adjacent molecules varying from 3.371(9) to 3.499(8) Å; the nitrovinyl group is oriented nearly parallel to the *a* axis, the ensemble forming chains along this axis (Fig. 3). In (II) also the molecules are associated by means of a charge-transfer complexation from the nitrovinyl side chain to the aromatic benzene ring, the interplanar distance varying from 3.355(2) to 3.489(3) Å, which is common to this type of charge-transfer complexes (Foster, 1973). The packing of the structures is viewed in Figs. 3 and 4.

Spectral data—IR, UV-visible, and NMR—show some evidence of the above charge-transfer complex between the indole nuclei. Polar solvents produce a shift of the absorption band of the $n$–$\pi^*$ transition type toward the blue (I) and of the 393 nm absorption band in the UV-visible spectrum toward the red (II) (Patai, 1969). In the NMR, the AB components in the NMR spectrum and the H-2 protons are strongly shifted downfield, but no additive effect originating in the electron-releasing nitro group is observed. The existence of a charge-transfer complex is confirmed in apolar solvents such as *n*-hexane, where dilutions of both compounds do not follow Beer's law for the absorption band

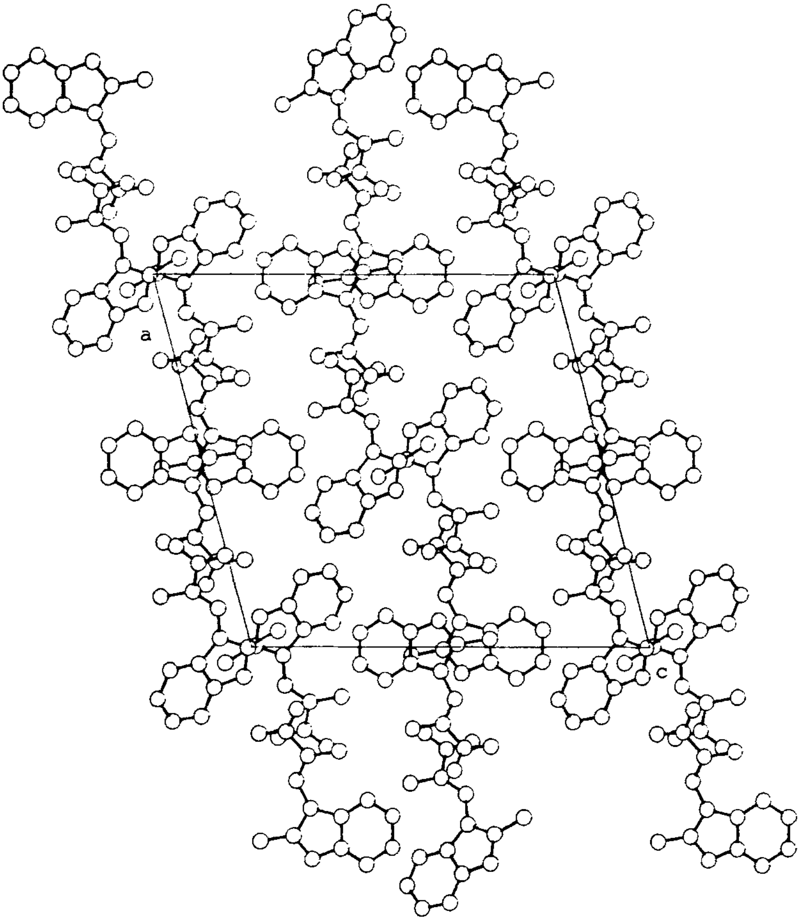


**Fig. 3.** Molecular packing of the compound (I).

at 412.8 nm (I) and at 393 nm (II) (although the true charge-transfer absorption is probably masked by these two bands). In compound (II) the nitrovinyl chain C(8)-C(10)-C(11)-N(2) is coplanar with the indole nucleus [dihedral angle 2.8(1)], which is a significant difference with respect to compound (I) (for which the dihedral angle in the two molecules is about 152°) and with respect to other substituted nitrovinylindoles (Fonseca *et al.*, 1987). We suspect that this difference in the torsion (Table 2) of the nitrovinyl chain with respect to the indole nucleus may be the reason for the different biological activities of the indoles studied.

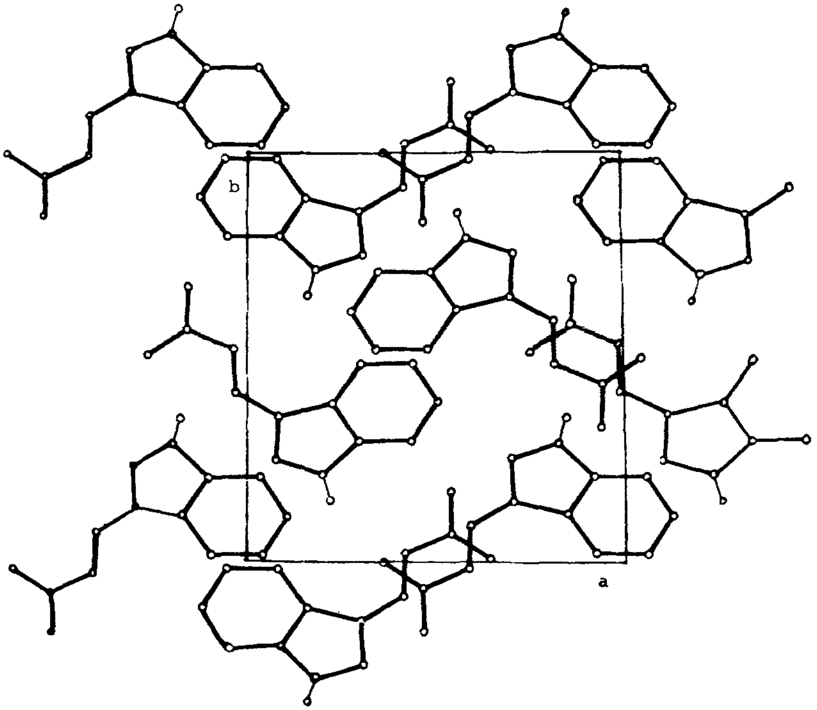


Fig. 4. Molecular packing of the compound (II).

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