Synthesis, Spectroscopic Studies and Crystal Structure of 5,5'-Dimethoxy-3,3'-methanediyl-*bis*-indole as the Inhibitor of Cell Proliferation of Human Tumors

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5,5'-Dimethoxy-3,3'-methanediyl-*bis*-indole (**3**) was synthesized in a reductive cyclisation process from (*E*)-5-methoxy-2-nitro-β-morpholinestyrene. The solid state structure was probed by single crystal X-ray diffraction and ^{13}C CP/MAS NMR methods. The results of the X-ray analysis indicate insignificantly different structure of both methoxyindole fragments of the molecule, and this is the main reason for the appearance of the double resonances in the solid state NMR spectrum. Interesting N-H$\cdots\pi$ interactions were observed which may have a functional role in biological features of **3**. 5,5'-Dimethoxy-3,3'-methanediyl-*bis*-indole at conc. $1 \cdot 10^{-4}$ M reduces the growth of MCF7 (breast), NCI-H460 (lung), and SF-268 (NCS) cells to 21, 0, and 48%, respectively.

Key words: 5,5'-Dimethoxy-3,3'-methanediyl-*bis*-indole, Anticancer Agent, Reductive Cyclisation, X-ray Diffraction, ^{13}C CP/MAS NMR

Introduction

The antiproliferative effect of 3,3'-diindolylmethane DIM (Fig. 1) on human breast and endometrial cancer cells was shown in papers [1 – 4]. DIM is a major product of acid condensation of indole-3-carbinol IC (Fig. 1), which is liberated from glucobrassicin by autolytic breakdown. However, IC and its acid condensation product DIM appeared to enhance tumor growth in some animal models, when administered at post-initiation stage [5 – 7]. Thus, the search for more selective 3,3'-diindolymethane derivatives would be a fruitful synthetic direction. The first goal of our project was 5,5'-dimethoxy-3,3'-methanediyl-*bis*-indole **3** (Fig. 1). The structure of **3** in solution was confirmed by 1D, 2D ^{1}H and ^{13}C NMR spectra in DMSO-d_6. In order to probe the molecular structure of **3** in solid state we took a ^{13}C CP/MAS NMR spectrum of the powdered sample. Double signals with intensity ratios of 1:1 were observed in the ^{13}C CP/MAS NMR spectrum (Fig. 2) for the majority of C atoms. It was not an easy task, but we were successful in growing suitable crystals of **3** for X-ray diffraction measurement. Geometric details of putative anticancer agents are crucial for their biochemical activity, and we have been analyzing them for the purpose of future synthetic work.

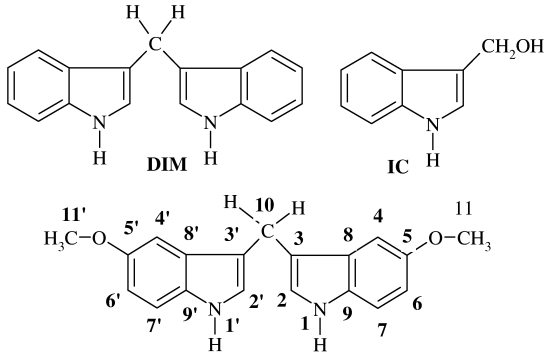
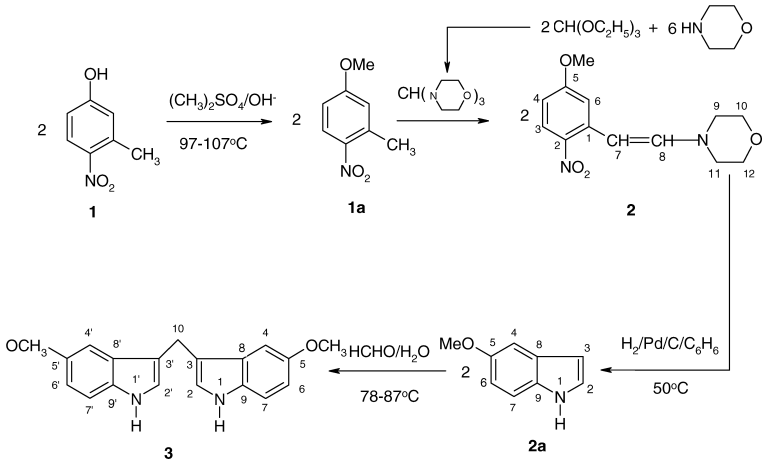
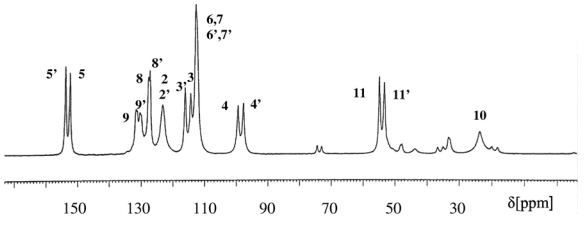


Fig. 1. Chemical formulas and atom numbering.



Scheme 1. Reagents and conditions for preparation of 5,5'-dimethoxy-3,3'-methanediyl-*bis*-indole **3**.



chemical shifts of ^{13}C in solid state, δ [ppm]

C2	C3	C4	C5	C6	C7	C8	C9	C10	C11
123.3	114.4	99.4	152.5	112.8	112.8	127.3	131.8	23.6	54.9
C2'	C3'	C4'	C5'	C6'	C7'	C8'	C9'	–	C11'
123.3	116.8	97.7	153.9	112.8	112.8	127.8	130.5		53.3

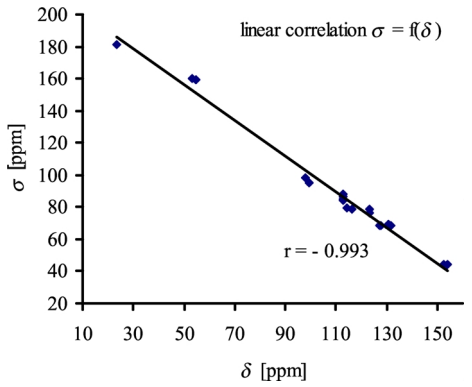


Fig. 2. The ^{13}C CP/MAS NMR spectrum of 5,5'-dimethoxy-3,3'-methanediyl-*bis*-indole **3** in solid state. A linear correlation between calculated shielding constants σ and experimental chemical shifts δ values.

A lot of synthetic procedures towards indole have been published [8]. Numerous reductive cyclisation reactions of various 2-nitrostyrene derivatives can be found in the literature [9 – 12], but some of them are not very effective for the preparation of methoxyindoles. Therefore, we modified the scheme using tripiperidinylmethane [9] by employing trimorpholylmethane in the first step. Next, we found the catalyst 10% Pd(C) to be convenient in the reductive cyclisation step (Scheme 1). The mechanism of the reaction described herein was not studied, but it should be related to the one suggested by the authors of [10], in which an initial reduction of the nitro group to an amine is followed by palladium-catalyzed cyclisation to the indole ring.

In our synthesis (*E*)-5-methoxy-2-nitro-β-morpholinestyrene **2** was originally used as reactant. It was identified as *E* isomer by ^{1}H NMR spectroscopy.

Results and Discussion

Spectroscopic study

Standard 1D and 2D hetero- and homonuclear NMR experiments were sufficient to afford complete assignment of the solution spectra of compounds **2**, **2a**, and **3**. In NMR spectra of 5,5'-dimethoxy-3,3'-methanediyl-*bis*-indole **3** in solution we have observed a simple pattern of signals (*i.e.* the number of resonances was in agreement with the number of atoms). This means that no hindered rotation takes place in solution, in opposition to the situation in the solid state, where we have observed double signals in the ^{13}C CP/MAS NMR spectrum of **3** (Fig. 2). This could have been caused by the presence of two energetically similar conformers of **3** in the solid state, or to different packing mode of both indole rings in one conformer. Crystallographic atom coordinates were used for the computation of shielding constants σ [ppm] of ^{13}C atoms to assign the resonances in solid-state NMR, employ-

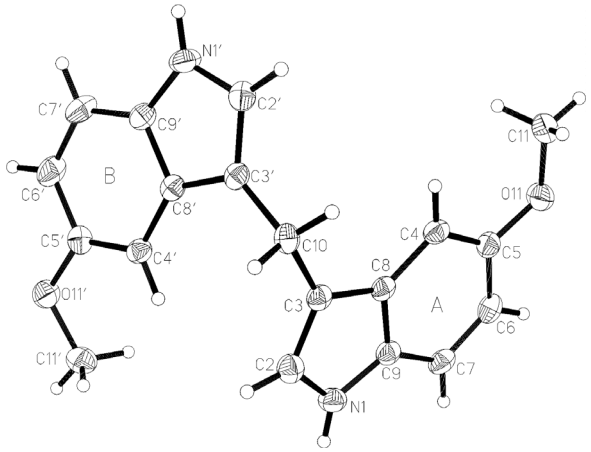


Fig. 3. The molecular structure of **3** with 50% probability displacement ellipsoids and atom-numbering scheme.

ing DFT method with B3LYP/6–31(d,p) hybrid functional using the CHF–GIAO approach [13]. The presence of a linear correlation ($r = -0.993$) between the calculated shielding constants σ and the experimental chemical shift δ values is good evidence of correctness of proposed assignments (see Fig. 2). The origin of the above-mentioned double resonances is that non-equivalent conformations of both 5-methoxy substituted indole rings are present in solid state, resulting in diversification of the C atoms shielding constants of rings A and B (see Fig. 3). This type of resonance pattern was not observed in solution because of plausible low-lying barriers of single C-O and C-C bonds rotations.

Crystallographic study

The molecular structure of **3** in the solid state was analyzed by single crystal X-ray diffraction. Crystallographic data, together with data collection and structure refinement details are listed in Table 1. Selected bond lengths, bond angles and torsion angles are listed in Table 2. Additional crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications No CCDC-238437. The displacement ellipsoid representation of the molecule, together with the atomic numbering scheme, is shown in Fig. 3 (the drawings were performed with a Stereochemical Workstation [14]).

Two methoxyindole systems (A and B, see Fig. 3) are connected through a common C atom. Both indole moieties are quite planar and their planes make an angle 68.10(3)°. The small tilts between the planes of the five-membered and six-membered rings are 3.0(1)° and 3.2(1)° in indoles A and B, respectively. Atom C10 is displaced from the mean plane of indole fragments by 0.022(2) Å and 0.195(2) Å for indole A and B, respectively. We have observed slightly different conformations of the methoxy groups. The disposition of these groups with respect to the indole fragments can be described by torsion angles C4-C5-O11-C11 of 3.14(1)° and C4'-C5'-O11'-C11' of −14.74(1)°. In consequence, the methyl carbon atom C11 is found to be only 0.067(2) Å out of the indole A plane, the other methyl carbon atom C11' is found to be −0.346(2) Å out of the indole B plane. Thus, the results of the X-ray analysis indicate an insignificantly different structure of both methoxyindole fragments of the molecule.

Table 1. Crystal data, data collection and structure refinement.

Empirical formula	$C_{19}H_{18}N_2O_2$
Formula weight	306.35
T [K]	130(2)
Wavelength [Å]	0.71073
Crystal system, space group	orthorhombic, $P2_12_12_1$
Unit cell dimensions	
a [Å]	5.932(1)
b [Å]	10.892(1)
c [Å]	23.207(2)
Volume [Å^3]	1499.4(3)
Z, D_x [Mg/m^3]	4, 1.357
μ [mm^{-1}]	0.089
$F(000)$	648
θ Range for data collection [°]	4.72 – 29.38
hkl Range	$-4 \le h \le 8$
	$-14 \le k \le 14$
	$-31 \le l \le 31$
Reflections:	
collected	10256
unique (Rint)	3820 (0.04)
observed $(I > 2((I))$	2626
Data / restraints / parameters	3820 / 0 / 210
Goodness-of-fit on $F2$	0.834
$R(F)(I > 2\sigma(I))$	0.0352
$wR(F^2)$ (all data)	0.0618
Max./min. $\Delta\rho$ [e/Å^3]	0.151 / −0.171

Table 2. Selected bond lengths [Å] and angles [deg] and selected torsion angles [deg].

C3-C10	1.503(2)	C3'-C10	1.504(2)
C5-O11	1.382(2)	C5'-O11'	1.388(2)
O11-C11	1.424(2)	O11'-C11'	1.430(2)
C3-C10-C3'	115.8(1)	C4-C5-O11	124.8(1)
C4'-C5'-O11'	124.0(1)	C5-O11-C11	116.4(1)
C5'-O11'-C11'	117.3(1)		
C2-C3-C10-C3'	−98.6(2)	C4-C5-O11-C11	3.1(2)
C3-C10-C3'-C2'	−132.7(1)	C4'-C5'-O11'-C11'	−14.7(2)

Table 3. Hydrogen-bonding geometry [Å and deg.].

D-H···A	d(D-H)	d(H···A)	d(D···A)	<(DHA)
N1-H1···O11' [i]	0.86	2.17	2.965(2)	153
N1'-H1'···Cg [ii]	0.86	2.49	3.261(2)	149
C2'-H2'···O11 [iii]	0.93	2.56	3.421(2)	154
C11-H11A···N1 [iv]	0.96	2.84	3.591(2)	136
C11-H11C···O11' [v]	0.96	2.79	3.604(2)	144

Cg represents the centroid of the five-membered ring of indole B. Symmetry transformations used to generate equivalent atoms: [i] $x+1/2, -y+3/2, -z+1$; [ii] $x-1/2, -y+5/2, -z+1$; [iii] $-x+1, y+1/2, -z+1/2$; [iv] $x-1, y, z$; [v] $-x+3/2, -y+2, z-1/2$.

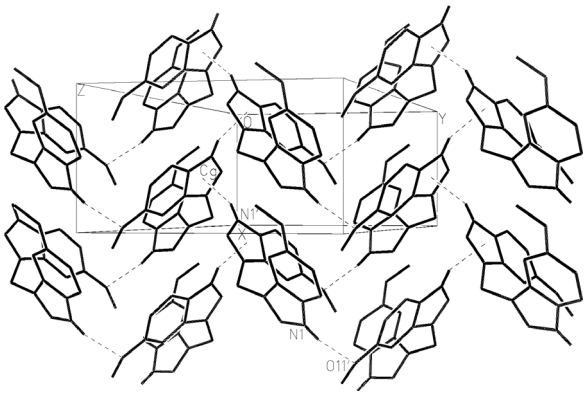


Fig. 4. Infinite helical chains along the *a* axis. H atoms, except H1 and H1', are omitted for clarity. *Cg* represents the centroid of the five-membered ring of indole B.

That is probably the reason why double resonances appear in NMR spectra of **3**.

Intermolecular hydrogen bonds determine the crystal packing of the molecules. Geometric parameters of all these bonds are listed in Table 3. The most interesting are shown in Fig. 4 and 5. In the crystal the molecules are connected *via* intermolecular hydrogen bonds N1-H1···O11' and N1'-H1'···π (Fig. 4) along the two-fold screw axis parallel to the [100] direction. The O11 atom is involved in intermolecular hydrogen bonds C2'-H2'···O11 (Fig. 5), which connect the molecules to infinite chains along the *b* axis. Similar N-H···π interactions were observed for other indole derivatives [15, 16] and for globular proteins [17]. It has been suggested that such interactions may provide stability and may contribute to the folding process or have a functional role in proteins.

Primary anticancer prescreen

5,5'-Dimethoxy-3,3'-methanediyl-*bis*-indole **3** was selected by the National Cancer Institute (NSC number 731013) [18]. As a primary anticancer assay, a 3-cell line panel consisting of the MCF7 (Breast), NCI-H460 (Lung), and SF-268 (CNS) was used. The results

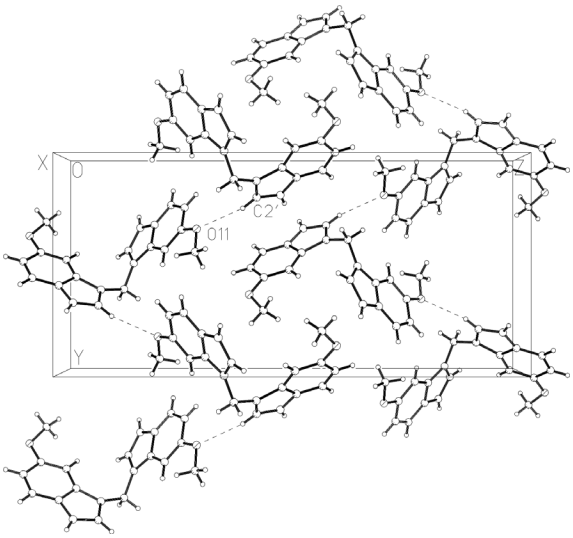


Fig. 5. Projection of crystal structure along the *a* axis.

are reported as the percentage of growth of the treated cells when compared with untreated control cells. 5,5'-Dimethoxy-3,3'-methanediyl-*bis*-indole **3** at conc. $1 \cdot 10^{-4}$ M reduces the growth of MCF7, NCI-H460, and SF-268 cell lines to 21, 0, and 48 percent, respectively.

Experimental Section

Reagents and techniques

Melting points were determined with a Digital Melting Point Apparatus 9001 and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra in solution were recorded with a Varian Unity plus-500, and standard Varian software was employed. Chemical shifts δ [ppm] were references to TMS. The solid state ^{13}C CP/MAS NMR spectrum of **3** was measured using a Bruker Avance DMX 400. A powdered sample was spun at 8 kHz. Contact time of 7 ms, repetition time of 20 s, and spectral width of 24 kHz were used for accumulation of 3,000 scans. All reported elemental analyses were averaged from two independent determinations. Prefabricated silica gel sheets (Merck Kieselgel 60 F_{254}) were used for TLC. Reagents were obtained from commercial sources.

The synthesis of 3-methyl-4-nitroanisole (**1a**) from 3-methyl-4-nitrophenole (**1**) has already been described [19, 20].

Notation used in the NMR assignments is given in Scheme 1 and Fig. 1.

Preparation

*(E)-5-Methoxy-2-nitro-β-morpholinestyrene (**2**)*

The mixture of morpholine (7.49 g, 0.105 mol) and triethyl orthoformate (7.41 g, 0.05 mol) with 0.2 ml CH_3COOH

was stirred at 105 – 120 °C for 4 h. The ethanol, forming during the reaction, and excess of orthoformate were evaporated. The residue, white precipitate of trimorpholylmethane was mixed with 3-methyl-4-nitroanisole (**1a**) (2.68 g, 0.016 mol) at 110 °C. Next, the mixture was heated at 148 – 150 °C for 7 h and cooled to 70 °C. The ethanol (2.5 ml) was added and the red solution was then allowed to cool to room temperature. After 24 h at 4 °C the red crystals were formed. They were suction-filtered, washed twice with ethanol and recrystallized from ethanol; 2.89 g, (68%) yield. M.p. 107.1 – 107.4 °C. – IR (KBr): $\tilde{\nu} = 3150 - 3000$, 300 – 2800, 1610, 1600, 1570 (NO_2), 1490, 1420, 1320 (NO_2), 1230, 1170, 1030 cm^{-1}. – ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 3.14$ (t, $J = 5$ Hz, 4 H, 9-CH_2, 11-CH_2), 3.75 (t, $J = 5$ Hz, 4 H, 10-CH_2, 12-CH_2), 3.86 (s, 3 H, OMe), 6.26 (d, $J = 14$ Hz, 1 H, 7-H), 6.60 (dd, $J_1 = 2$ Hz, $J_2 = 9$ Hz, 1 H, 4-H), 6.73 (d, $J = 14$ Hz, 1 H, 8-H), 6.84 (d, $J = 2$ Hz, 1H, 6-H), 7.97 (d, $J = 9$ Hz, 1 H, 3-H) ppm. – ^{13}C NMR (125.68 MHz, $CDCl_3$): $\delta = 48.74$ (C-10, C-12), 55.63 (3 H, OMe), 66.24 (C-9, C-11), 95.31 (C-7),108.96 (C-6), 110.11 (C-4), 128.09 (C-3), 137.92 (C-1) 139.38 (C-2), 143.90 (C-8), 162.85 (C-1) ppm.

*5-Methoxyindole (***2a***)*

Compound (**2**) (4.92 g, 0.02 m) was dissolved in benzene (150 ml) and 2 g of 10% Pd/C was added. The mixture was kept for 8 h at 50 °C and at a pressure of 6 atm in an autoclave. Finally, the catalyst was removed from light yellow solution by filtration. After evaporation of the solvent, the residue was separated chromatographically on silica gel with chloroform/methanol/diethyl ether, 3:1:1. The oily residue of (**2a**) crystallized after several hours at 4 °C. It was recrystallized from ethanol; 2.12 g (72%) yield. M.p. 51.1 – 52.1 °C. – IR (KBr): $\tilde{\nu} = 3400$ (NH), 3150 – 3000, 300 – 2800, 1620, 1590, 1490, 1450, 1440, 1350, 1230, 1040 cm^{-1}. – ^{1}H NMR (500.13 MHz, $CDCl_3$): $\delta = 3.82$ (s, 3 H, OMe), 6.45 (td, $J_1 = 1$ Hz, $J_2 = J_3 = 2$ Hz, 1 H, 4-H), 6.85 (dd, $J_1 = 2$ Hz, $J_2 = 9$ Hz, 1 H, 6-H), 7.06 (t, $J_1 = J_2 = 2$ Hz, 1 H, 2-H), 7.10 (d, $J = 2$ Hz, 1 H, 3-H), 7.17 (d, $J = 9$ Hz, 1 H, 7-H). 7.98 (s, broad, 1 H, NH) ppm. – ^{13}C NMR (125.68 MHz, $CDCl_3$): $\delta = 55.82$ (OMe), 102.19 (C-4), 102.27 (C-3), 111.78 (C-7), 112.24 (C-6), 124,97 (C-2), 128.21 (C-8), 130.94 (C-9), 154.06 (C-5) ppm.

*5,5'-Dimethoxy-3,3'-methanediyl-bis-indole (***3***)*

Compound (**2a**) (2.94 g, 0.02 m) was dissolved in water (100 ml) and formalin (0.81 g, 0.01 mol) was added. The mixture was kept out of light and stirred at 80 – 85 °C for 7 h, and then the solution was allowed to cool to room temperature. The water phase was extracted three times with diethyl ether (15 ml each). The organic phase was dried with $MgSO_4$. The solvent was evaporated *in vacuo* and red oil residue was dissolved in hot benzene (60 ml). Compound **3** (1.52 g, 50%) precipitated when the solution was allowed to cool. The crude precipitate was crystallized from benzene under exclusion of light; 0.72 g (24%) yield. M.p. 172 – 172.5 °C. Colorless crystals, suitable for X-ray analysis, were formed from methanol. – IR (KBr): $\tilde{\nu} = 3420$, 3410, 3380 (NH), 3150 – 3000, 3000 – 2800, 1620, 1590, 1480, 1450, 1440, 1300, 1210, 1060 (C-O-C), 1180 (CN) cm^{-1}. – ^{1}H NMR (500.13 MHz, DMSO-d_6): $\delta = 3.71$ (s, 6 H, OMe), 4.08 (s, 2 H, 10-CH_2), 6.73 (d, $J = 9$ Hz, 2 H, 6-H, 6'-H), 7.04 (d, $J = 2$ Hz, 2 H, 4-H, 4'-H), 7.10 (d, $J = 1$ Hz, 2 H, 2-H, 2'-H), 7.30 (d, $J = 9$ Hz, 2 H, 7-H, 7'-H), 10.60 (s, broad, 2 H, 1-NH, 1'-NH). – ^{13}C NMR (125.68 MHz, DMSO-d_6): $\delta = 20.81$ (C-10), 55.18 (OMe), 100.56 (C-4, C-4'), 110.64 (C-6, C-6'), 111.84 (C-7, C-7'), 113.87 (C-3, C-3'), 123.39 (C-2, C-2'), 127.43 (C-8, C-8'), 131.46 (C-9, C-9'), 152.68 (C-5, C-5') ppm. – $C_{19}H_{18}N_2O_2$ (306.35): calcd. C 74.49, H 5.92, N 9.14; found C 74.44, H 5.92, N 9.13.

X-ray diffraction measurements

Crystals suitable for X-ray analysis were grown from methanol solution by slow evaporation. Diffraction data were collected on an Oxford Diffraction KM4CCD diffractometer [21] at 130 K, using graphite-monochromated *Mo-*K_α radiation. A total of 532 frames were measured in four separate runs in order to cover the symmetry-independent part of reciprocal space. The ω-scan was used with a step of 0.75°, two reference frames were measured after every 50 frames, they did not show any systematic changes either in peaks positions or in their intensities. The unit-cell parameters were determined by least-squares treatment of setting angles of 3809 highest-intensity reflections, chosen from the whole experiment. Intensity data were corrected for Lorentz and polarization effects [22]. The structure was solved by direct methods with the SHELXS-97 program [23] and refined with full-matrix least-squares by the SHELXL-97 [24] program. The function $\Sigma w(|F_o|^2 - |F_c|^2)^2$ was minimized with $w^{-1} = [\sigma^2(F_o)^2 + (0.0246P)^2]$, where $P = (F_o^2 + 2F_c^2)/3$. All non-hydrogen atoms were refined anisotropically, the positions of hydrogen atoms were generated geometrically and these atoms were included in the refinement as a "riding model" with U_{iso} parameters set at 1.2 (1.5 for methyl groups) times U_{eq} of the appropriate carrier atom.

Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre, CCDC-238437. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: int.code+(1223)336-033; e-mail for inquiry: fileserv@ccdc.cam.ac.uk).

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