Synthesis and Structure of DL-Camphor-10-Sulphonanilide and the N-Methylthiadizinedioxide

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Summary: Camphor-10-sulphonanilide (3) has been prepared and the structure confirmed by X-ray crystallography. Camphor-10-sulphonyl chloride reacts with N-methylhydrazine to give the N-methylthiadiazine dioxide (4) and not the expected N-methylhydrazide (6). The reasons for this reaction are discussed. The structure of (4) was confirmed by X-ray analysis; the structures (3) and (4) were also supported by ^{1}H and ^{13}C-NMR spectroscopy.

The work forms part of our general programme on the chemistry and biocidal activity of novel organic sulphonyl derivatives [1-4]. Camphor sulphonyl derivatives were of special interest since comphor is produced naturally in the Camphor tree, (Cinnamomum camphora), and it was therefore felt that these derivatives may be systemic in plants and could be useful in the control of phytopathogenic fungi. Camphor, by reaction with concentrated sulphuric acid-acetic anhydride, is reported [5] to give the 10-sulphonic acid, which with phosphorus pentachloride affords the sulphonyl chloride. Previous studies [6,7], showed that camphor-10-sulphonyl chloride with hydrazine hydrate at room temperature did not give the hydrazide (1) but the thiadiazine dioxide (2). On the other hand, when the reaction was performed at 0°C, the hydrazide (1) was isolated.

In the present work, DL-camphor-10-sulphonyl chloride was condensed with aniline to give the anilide (3). The IR, PMR, ^{13}C-NMR and mass spectral data of (3) are included in the experimental section. 10-sulphonation was indicated by the PMR spectrum which showed the 8- and 9-methyl protons as singlets (δ 0.9, 1.0) respectively. The 9-methyl protons are in closer proximity to the deshielding influence of the carbonyl group and consequently probably appear at slightly lower field than the 8-methyl protons. The resonance (δ 3.6-2.9, 2H) is assigned to the 10-methylene protons which are deshielded by the attached sulphonyl group. The ^{13}C-NMR spectrum of (3) is shown in Table 1; the chemical shifts were determined by comparison with the ^{13}C-NMR spectrum of camphor [8] and the off-resonance decoupled spectrum. The resonances are in good agreement with those of camphor except for the 10-carbon signal which was shifted to lower field (δ48.7 ppm) by the attached sulphonyl group. The aromatic carbons appeared at 137.5(1'), 129.6 (3',5'), 125.8 (4') and 122.5 ppm (2',6'). The structure of the anilide (3) was determined by X-ray crystallography which confirmed 10-sulphonation.

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Camphor-10-sulphonyl chloride was reacted with N-methylhydrazine, but on addition of ice-water no solid product separated, concentrated hydrochloric acid was added when crystals slowly separated from solution. The product was shown by the IR spectrum not to contain a carbonyl group and did not condense with aldehydes or ketones. Analysis and the mass spectrum supported the N-methylthiadiazine dioxide structure (4) ; the latter showed the molecular ion (M^+, 215).

The PMR spectrum was also in argument with the assigned structure (4). The ^{13}C-NMR spectrum of (4) (Table 1) shows that the resonance of the 2-carbon atom (164.1 ppm) is at higher field than in camphor (218.4) or the anilide (3) (217.6). This agrees with expectation since the absence of the carbonyl oxygen atom should reduce the deshielding effect on the 2-carbon atom; the other carbon resonances appear in comparable positions. The carbon atom of the N-methyl moiety (C11) resonates at slightly lower field (35 ppm) as compared with the 8- and 9-geminal methyl carbons (Table 1), due to the deshielding influence of the adjacent nitrogen atom.

In contrast to the analogous reaction with hydrazine, the N-methylhydrazide (5) was not isolated even when the reaction of comphor-10-sulphonyl chloride and N-methylhydrazine was carried out at 0°C.

The reaction of camphor-10-sulphonyl chloride with N-methylhydrazine probably involves competitive attack on the chlorine atom by both the more nucleophilic N(1) and the less sterically hindered N(2) nitrogen atoms of the reagent leading to a mixture of the methyl hydrazides (5) and (6).

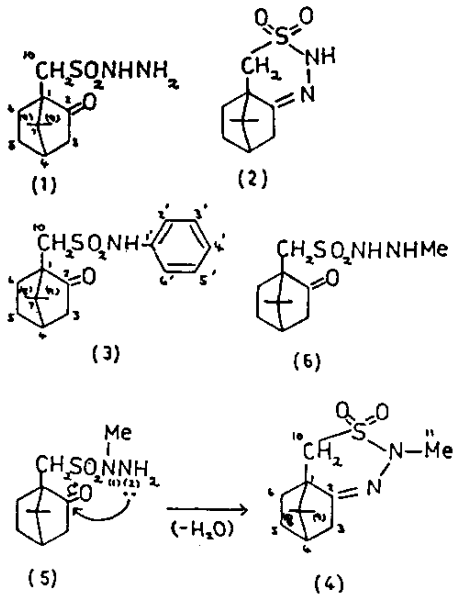
When concentrated hydrochloric acid is added, the carbonyl group is activated by protonation, facilitating intramolecular nucleophilic attack by the amino group in (5) with cyclisation to the N-methylthiadizine (4) by subsequent elimination of water (Scheme 1). The product (4) separates out from the mixture. Such elimination of water would not be possible for the isomeric N-methylhydrazide (6) and since the yield of (4) is only moderate (48%), it is possible that some of the hydrazide (6) may remain in solution.

X-ray crystallography:

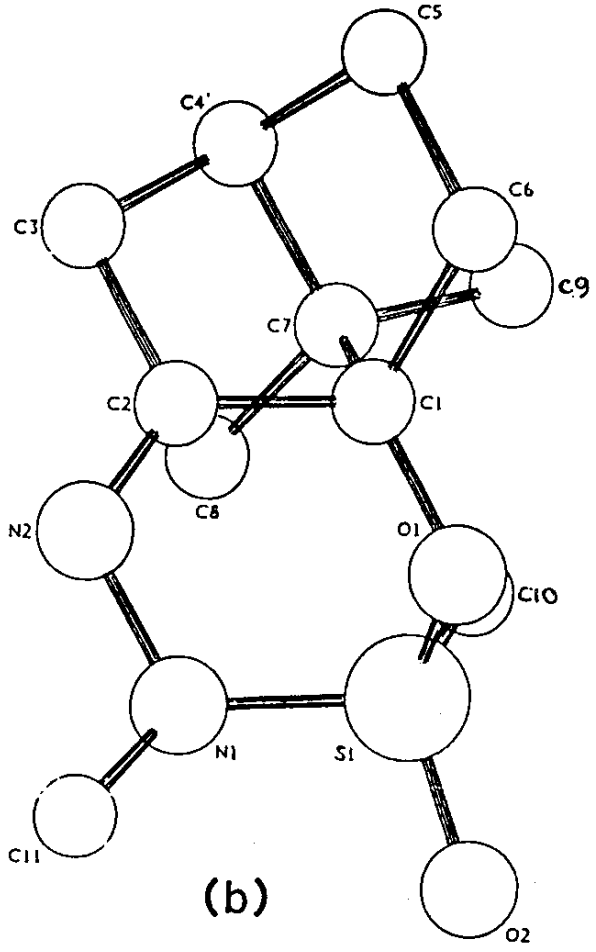
The crystal structures confirmed the molecular structures to be as indicated by NMR spectroscopy. In spite of the presence of the hetero-ring in (4) the configuration of the camphor fragment, as described by its various

Table-1: ^{13}C-NMR Data

Compound	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11
Camphor	57.0	218.4	43.2	42.2	27.4	30.1	46.6	19.5	20.0	9.7	-
(3)	59.6	217.6	43.1	42.7	27.0	27.7	48.7	19.1	19.5	48.7	-
(4)	58.4	164.1	36.7	44.8	27.2	31.5	49.4	18.1	20.2	48.3	35.0



SCHEME 1



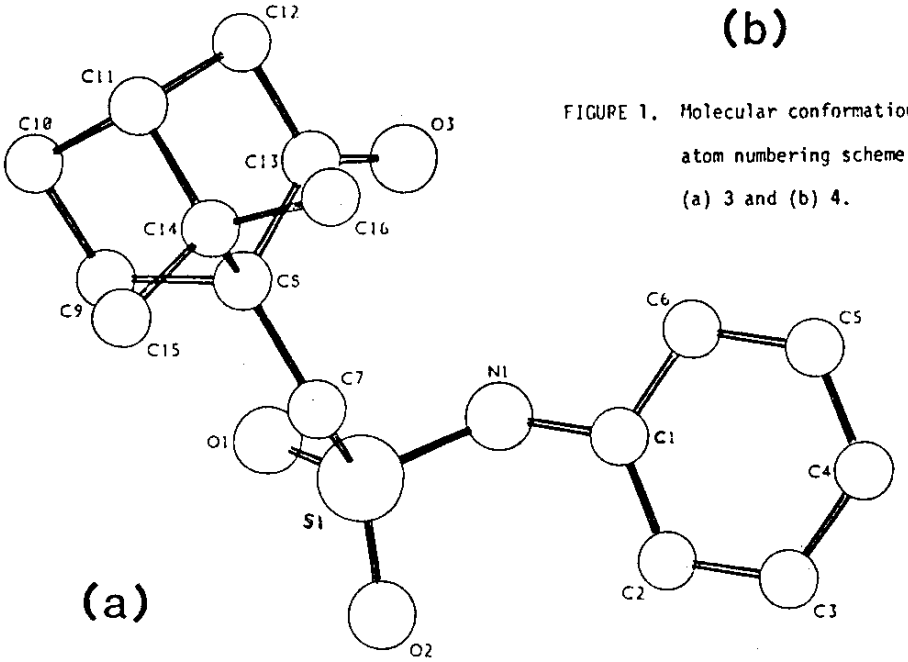


FIGURE 1. Molecular conformation and atom numbering scheme for (a) 3 and (b) 4.

torsional angles is the same in both molecules. Bond lengths and angles are normal in both structures.

The final atomic parameters are given for (3) and (4) in Tables 2 and 3 respectively with the complete atom numbering scheme in Figure 1. Structure factors and other parameters are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Rd., Cambridge CB2 1EW. Please cite full reference.

An explanation to the formation of (4) rather than, as expected, (5) or (6) may be found from the structure (3). In this later molecule, the conformation of the side chain is such that the carbonyl group lies very close to the hydrazide nitrogen (2.9Å). It is possible that in solution (5) and (6) have a configuration similar to that of (3). This will bring the hydrazide fragment close to the camphoric carbonyl group, allowing cyclization to occur. This (5) will yield (4), which is a stable cyclic structure, whereas the equivalent entity derived from (6) would be sterically hindered and therefore break-up. The difference in stability may then steer the reaction of camphor-10-sulphonylchloride with N-methylhydrazine for the production of (5), rather than (6) as expected.

Experimental

Melting points were determined with a Gallenkemp electric melting point apparatus and are uncorrected. Infrared spectra were recorded on a Unicam SP1000 spectrophotometer. NMR spectra were obtained with a Bruker WP80 spectrometer using deuteriochloroform as solvent and tetramethylsilane as internal standard; an asterisk indicates signals that were removed by treatment with D_2O. Mass spectra were recorded on a VG micromass V15 instrument. TLC was carried out using Camlab silica gel plates sensitized to UV 254 nm.

DL-Camphor-10-sulphonanilide (3):

DL-camphor-10-sulphonyl chloride (15g, 1 mol. equiv.) was added portionwise to a stirred solution of aniline (11.2g, 2 mol. equiv.) in ether (200ml) and the mixture was stirred at room temperature for 24 hours. The precipitate was filtered off and the solvent evaporated under reduced pressure to give a solid which was recrystallised from methanol to give the sulphonanilide (14g, 76%), m.p. 118-119°, (lit.[7] m.p. 119-120°).

Tlc. (ethyl acetate : petroleum ether (40-60) 1:1) showed one spot (R_F, 0.77).

(Found : C. 62.3; H, 6.9; N, 4.5. $C_{16}H_{21}NO_3S$ requires C, 62.5; H, 6.8; N, 4.6%).

ν_{max}. 3270 (NH), 1740(C=O), 1600 (ArC=C), 1345, 1140 (SO_2) cm^{-1}.

MS: the molecular ion (M^+) was not observed, fragment ions at 215 (M-NHPh), 151(M-SO_2NHPh)(camphor), 132, 123, 104, 91 (NHC_6H_5), 81, 67, 55 and 28.

PMR : δ 8.9,* (s, 1H (NH)); 7.5 - 7.0, (m, 5H, (ArH)); 3.6 - 2.9, (q, 2H(CH_2SO_2)); 2.6 - 1.2, (m, 7H (aliphatic ring H)); 1.0, (s, 3H (9-methyl)); 0.9, (s, 3H (8-methyl)).

Reaction of DL-camphor-10-sulphonyl chloride with methylhydrazine:

Methylhydrazine (1.46 g, 4 mol. equiv.) was added dropwise to a solution of the sulphonyl chloride (2 g,

Table-2: Atom co-ordinates ($x10^4$) and isotropic temperature factors ($Å^2 \times 10^3$) for (3)

	x/a	y/b	z/c	U
C(1)	2346(5)	1456(6)	-1122(4)	
C(2)	1321(5)	2275(7)	-1480(4)	
H(2)	907(5)	2875(7)	-1059(5)	78(9)
C(3)	815(6)	2337(7)	-2375(5)	
H(3)	11(6)	2992(7)	12654(5)	78(9)
C(4)	1334(6)	1561(8)	-2916(4)	
H(4)	938(6)	1602(8)	-3617(4)	78(9)
C(5)	2352(7)	742(8)	-2553(3)	
H(5)	2768(7)	148(8)	-2974(5)	78(9)
C(6)	2859(6)	661(8)	-1656(4)	
H(6)	3649(6)	-18(8)	-1377(4)	78(9)
C(7)	1928(5)	-908(6)	450(4)	
H(71)	1667(5)	-1181(6)	-238(4)	71(13)
H(72)	1164(5)	-1055(6)	695(4)	71(13)
C(8)	2878(5)	-2041(6)	916(4)	
C(9)	3358(6)	-1927(8)	1933(4)	
H(91)	2638(6)	-1634(8)	2202(4)	103(17)
H(92)	4072(6)	-1111(8)	2131(4)	103(17)
C(10)	3849(6)	-3512(8)	2232(4)	
H(101)	3332(6)	-4035(8)	2611(4)	91(16)
H(102)	4791(6)	-3474(8)	2612(4)	91(16)
C(11)	3683(5)	-4320(7)	1377(4)	
H(111)	3760(5)	-5513(7)	1458(4)	40(15)
C(12)	4585(6)	-3638(7)	951(5)	
H(121)	4663(6)	-4313(7)	412(5)	90(16)
H(122)	5467(6)	-3504(7)	1422(5)	90(16)
C(13)	4018(5)	-2151(7)	636(4)	
C(14)	2467(5)	-3702(7)	785(4)	
C(15)	1396(5)	-4092(8)	1127(5)	
H(151)	1598(5)	-3748(8)	1802(5)	101(13)
H(152)	1243(5)	-5279(8)	1081(5)	101(13)
H(153)	595(5)	-3522(8)	739(5)	101(13)
C(16)	2146(7)	-4201(7)	-161(4)	
H(161)	2883(7)	-3942(7)	-420(4)	131(17)
H(162)	1340(7)	-3631(7)	-540(4)	131(17)
H(163)	1988(7)	-5387(7)	-198(4)	131(17)
H(1)	3678(45)	1140(57)	-81(32)	48(18)
O(1)	3181(4)	1295(4)	1361(2)	
O(2)	1153(3)	1781(5)	324(3)	
O(3)	4388(3)	-1234(5)	229(3)	
S(1)	2294(2)	1025(2)	540(1)	
N(1)	2942(4)	1491(6)	-205(3)	

Anisotropic temperature factors ($Å^2 \times 10^3$) for (3)

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C(1)	32(3)	40(4)	42(4)	-5(3)	4(3)	-6(3)
C(2)	41(4)	59(4)	46(4)	-2(3)	4(3)	10(3)
C(3)	46(4)	63(5)	66(5)	2(4)	-7(4)	5(4)
C(4)	70(5)	80(5)	44(4)	1(4)	4(4)	-9(4)
C(5)	73(5)	83(6)	68(5)	-4(5)	27(4)	14(5)
C(6)	57(4)	68(5)	46(4)	2(4)	13(4)	16(4)
C(7)	37(3)	40(3)	54(4)	0(3)	11(3)	3(3)
C(8)	40(3)	37(3)	44(3)	-4(3)	18(3)	-1(3)
C(9)	76(5)	69(5)	40(4)	-1(4)	12(4)	10(4)
C(10)	81(5)	78(6)	59(5)	14(4)	13(4)	11(4)
C(11)	55(4)	46(4)	69(5)	14(3)	28(4)	7(3)
C(12)	64(4)	54(5)	102(6)	22(4)	42(4)	20(4)
C(13)	38(4)	50(4)	59(4)	7(3)	16(3)	-1(3)
C(14)	52(4)	42(4)	63(5)	3(3)	23(4)	-2(3)
C(15)	61(4)	76(5)	116(6)	36(5)	43(4)	4(4)
C(16)	105(6)	58(5)	74(5)	-19(4)	-19(5)	-16(4)
D(1)	66(3)	44(3)	44(3)	-7(2)	1(2)	-11(2)
D(2)	52(3)	59(3)	80(3)	16(2)	35(2)	24(2)
D(3)	45(3)	70(3)	105(4)	35(3)	36(3)	9(2)
S(1)	47(1)	39(1)	49(1)	-2(1)	15(1)	0(1)
N(1)	27(3)	55(3)	50(3)	6(3)	11(3)	2(3)

1 mol.equiv. in methanol (20ml) at room temperature. The mixture was warmed on a steam bath for 5 min.,cooled and poured onto crushed ice. No precipitate was observed when the ice melted. Concentrated hydrochloric acid (5 drops) was added to the reaction solution when crystals slowly precipitated out, the precipitation was complete after 4 days and the suspension was filtered off to give the thiadizine dioxide (4) (1.0 g, 48%), m.p. 110-112°.

Tlc. (ethyl acetate: petroleum ether (40-60) 1:1) showed one spot (R_F, 0.65).

Found : C, 54.6; H, 7.5; N, 11.3; S, 13.6
$C_{11}H_{18}N_2O_2S$ requires C, 54.5; H, 7.5; N, 11.6; S, 13.2%)

ν_{max} 1650(C=N), 1370, 1140, (SO_2) cm^{-1}, no NH and C=O absorption bands were observed.

MS showed the molecular ion (M^+, 242) and fragment ions at 215 ($M-N_2$), 177 (M^+-SO_2), 163 ($M^+ - CH_2SO_2$), 151 (camphor), 135 ($M^+ - SO_2NMe$), 109, 93, 79, 67, 55.

PMR : δ 3.95, (s, 3HN-C$\underline{H}_3$)); 3.7-2.85, (q, 2H,CH_2SO_2)); 2.6-1.3, (m, 7H alphatic ring H)); 1.1, (s, 3H, 9-methyl); 0.9 (s, 3H, 8-methyl).

Crystallography Compound (3) : $C_{16}H_{21}NO_3S_2S$, M = 437.42; Monoclinic, a = 11.592 (2), b = 8.986 (1),

Table-3: Atom co-ordinates ($x10^4$) and isotropic temperature factors ($Å^2 \times 10^3$) for (4)

	x/a	y/b	z/c	U
C(1)	1338(7)	8539(2)	-2147(5)	
C(2)	3533(8)	8564(2)	-1786(5)	
C(3)	4424(8)	8261(3)	-3127(6)	
H(31)	5440(8)	8591(3)	-3601(6)	100(14)
H(32)	5169(8)	7808(3)	-2807(6)	100(14)
C(4)	2584(8)	8143(3)	-4247(6)	
H(41)	2909(8)	8100(3)	-5423(6)	101(19)
C(5)	1548(9)	7542(3)	-3651(6)	
H(51)	359(9)	7380(3)	-4471(6)	90(14)
H(52)	2576(9)	7145(3)	-3401(6)	90(14)
C(6)	749(8)	7798(2)	-2167(6)	
H(61)	-831(8)	7741(2)	-2221(6)	66(11)
H(62)	1437(8)	7548(2)	-1169(6)	66(11)
C(7)	1194(8)	8709(2)	-3885(5)	
C(8)	2029(8)	9389(2)	-4200(5)	
H(81)	3500(8)	9433(2)	-3624(5)	66(9)
H(82)	1097(8)	9762(2)	-3779(5)	66(9)
H(83)	-2079(8)	9452(2)	-5419(5)	66(9)
C(9)	-862(8)	8663(3)	-4703(5)	
H(91)	-1478(8)	8189(3)	-4495(5)	104(12)
H(92)	-798(8)	8729(3)	-5918(5)	104(12)
H(93)	-1780(8)	9039(3)	-4278(5)	104(12)
C(10)	225(7)	8968(2)	-1097(4)	
H(101)	209(7)	9467(2)	-1503(4)	66(11)
H(102)	-1270(7)	8793(2)	-1101(4)	66(11)
C(11)	4951(9)	9346(3)	1776(6)	
H(111)	4162(9)	9610(3)	2589(6)	123(13)
H(112)	6147(9)	9644(3)	1446(6)	123(13)
H(113)	5537(9)	8898(3)	2296(6)	123(13)
D(1)	1450(6)	8271(2)	1316(3)	
D(2)	610(6)	9422(2)	1721(4)	
N(1)	3605(7)	9190(2)	419(4)	
N(2)	4592(6)	8838(2)	-694(5)	
S(1)	1395(2)	8935(1)	767(1)	

Anistropic temperature factors ($A^2 \times 10^3$) for (4)

C(1)	45(3)	35(3)	38(3)	-1(2)	9(2)	2(3)
C(2)	52(4)	35(3)	46(3)	3(2)	2(3)	0(3)
C(3)	57(4)	65(4)	80(4)	-16(3)	26(4)	8(3)
C(4)	70(5)	66(4)	60(3)	-28(3)	20(3)	-5(3)
C(5)	94(6)	51(4)	93(5)	-30(3)	18(4)	-9(4)
C(6)	72(4)	40(3)	70(4)	-2(3)	11(3)	-13(3)

C(7)	54(4)	52(3)	37(3)	-8(2)	9(3)	-7(3)
C(8)	84(5)	63(3)	34(2)	4(3)	9(3)	-8(3)
C(9)	61(4)	97(5)	47(3)	-1(3)	4(3)	-8(4)
C(10)	60(4)	43(3)	35(2)	4(2)	11(2)	5(3)
C(11)	104(6)	85(5)	55(3)	-13(3)	-19(4)	-25(4)
O(1)	116(4)	51(2)	54(2)	22(2)	16(2)	-10(2)
O(2)	128(4)	71(3)	43(2)	-10(2)	32(2)	13(3)
N(1)	66(3)	47(3)	45(2)	-3(2)	2(2)	-11(2)
N(2)	62(3)	46(3)	56(3)	6(2)	4(3)	-4(2)
S(1)	77(1)	51(1)	35(1)	2(1)	13(1)	0(1)

The temperature factor exponent takes the form:

$-2A^2(U_{11}.h^2.a^{2*2} + \ldots + 2U_{12}.h.k.a^*.b^*)$

c = 16.018 (3)Å, β = 107.39(1)°, Z = 4, D_c = 1.34 g cm^{-3}, space group $P2_1/n$. Weighting scheme used was $[\sigma^2F + 0.003\ F^2]^{-1}$. Total unique data was 2600 reflections of which 1098 were classed as observed with F_o 3σ (F). 202 parameters were refined to give a final R = 0.0418 and R_w = 0.0417.

Compound (4) : $C_{11}H_{18}N_2O_2S$, M = 242.46; Monoclinic, a = 6.816(1), b = 20.445(2), c = 8.719(1)Å, β = 95.75(1)°, Z = 4, D_c = 1.32 g cm^{-3}, space group $P2_1/n$. Weighting scheme used was $[\sigma^2F + 0.0004\ F^2]^{-1}$. Total unique data was 2090 reflections of which 1062 were classed as observed with F_o 3σ (F). 153 parameters were refined to give a final R=0.0423 and R_ω = 0.046.

Full intensity data for both crystals were collected on an Enraf-Nonius CAD-4 diffractometer, using CuK_α (λ=1.54178A) radiation in the manner that has been described elsewhere [9]. Crystals suitable for X-ray crystallography were prepared by slow evaporation of an appropriate solution. No absorption corrections were made for (3), μ=21.5 cm^{-1}; for (4), μ=17.8 cm^{-1}). Both structures were solved by direct methods and refined using full matrix least squares techniques, scattering factors were obtained from the International Tables for X-ray Crystallography. All non-hydrogen atoms were assigned anisotropic thermal parameters, whilst hydrogens, which were located from difference Fourier maps, were refined isotropically with constrained ideal bond lengths. Calculations were carried out on an IBM-3081 computer (University of Cambridge) using SHELX-76 (G.M. Sheldrick), PLUTO-78 (W.P.S. Motherwell and W. Clegg) and private programs.

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