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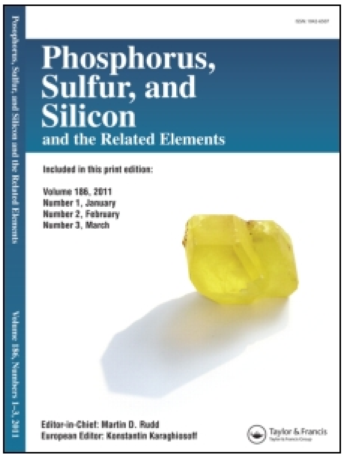

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THE CHEMISTRY OF CAMPHOR- AND 3-BROMOCAMPHOR-8-SULFONYL CHLORIDES

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THE CHEMISTRY OF CAMPHOR- AND 3-BROMOCAMPHOR-8-SULFONYL CHLORIDES

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DL-camphor and 3-bromocamphor reacted with chlorosulfonic acid and phosphorus pentachloride to give the corresponding 8-sulfonyl chlorides (**1, 10**). These were converted into 13 derivatives by reaction with amines, azide ion and hydrazine.

The spectral data of the compounds are briefly discussed, together with the results of preliminary biological screening against insects, weeds and fungi.

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INTRODUCTION

The work forms part of our general programme on the chemistry and biological activity of organic sulfonyl derivatives.[1–3] In particular, it extends previous studies[4–6] on the chemistry of camphor-10-sulfonyl chloride to the 8-sulfonyl analogues. In the late 19th century, it was shown that camphor[7] or 3-bromocamphor[8] reacted with fuming sulfuric acid or chlorosulfonic acid to give camphor- or 3-bromocamphor-π-sulfonic acid. Subsequent degradation studies[9] indicated that in these compounds, the sulfonic acid group was attached to either the 8- or 9-carbon atom of the geminal dimethyl group. There has been little recent work on camphor-π-sulfonic acids and consequently spectroscopic data is lacking. We therefore decided to reinvestigate these compounds and convert them into a range of derivatives for spectroscopic and biological examination. These compounds have intrinsic interest since camphor is produced naturally in the camphor tree (*cinnamomum camphora*) and it was therefore considered that their derivatives could well be systemic in plants and possibly prove valuable in the control of phytopathogenic fungi.

DISCUSSION

DL-camphor, by heating with chlorosulfonic acid in chloroform, gave the π-sulfonic acid; this was neutralized and the ammonium sulfonate treated with phosphorus pentachloride to yield the sulfonyl chloride (**1**, 47%) (Table I and Figure 1).

DL-3-bromocamphor, by a similar procedure afforded the corresponding sulfonyl chloride (**10**). The preparation is tedious, but unfortunately attempts to directly obtain the sulfonyl chlorides (**1, 10**) by use of a large excess of chlorosulfonic acid were unsuccessful.

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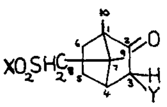
TABLE I

Physical data for 8-sulfonylcamphors

Compd no.	Yield (%)	m.p. (°C)	X	Molecular formula	Microanalysis found (calc.) % C	H	N	MS (M+)
1	47	100–101	Cl	$C_{10}H_{15}ClO_3S$	47.6 (47.9)	5.8 (6.0)	— —	250
2	42	120	NMe_2	$C_{12}H_{21}NO_3S$	55.3 (55.6)	7.8 (8.1)	5.3 (5.4)	259
3	81	77–78	$NHCH_2Ph$	$C_{17}H_{23}NO_3S$	63.3 (63.5)	7.0 (7.2)	4.2 (4.4)	321
4	56	104	C_4H_8NO	$C_{14}H_{23}NO_4S$	55.6 (55.8)	7.8 (7.6)	4.4 (4.6)	301
5	63	159–160	$N{=}PPh_3$	$C_{28}H_{30}NO_3PS$	68.2 (68.4)	6.0 (6.1)	2.9 (2.9)	491
6	65	146	$N{=}P(OEt)_3$	$C_{16}H_{30}NO_6PS$	49.0 (48.6)	7.4 (7.6)	3.4 (3.5)	395
7	36	158	$NHNH_2$	$C_{10}H_{18}N_2O_3S$	48.6 (48.8)	7.5 (7.3)	11.5 (11.4)	151†
8	46	150	$NHN{=}CMe_2$	$C_{13}H_{22}N_2O_3S$	54.3 (54.5)	7.8 (7.6)	10.0 (9.8)	—
9	59	172	$NHN{=}CHC_6H_4NO_2$-p	$C_{17}H_{21}N_3O_5S$	53.6 (53.8)	5.4 (5.5)	10.9 (11.1)	—
10	49	108–109	Cl	$C_{10}H_{14}BrClO_3S$	36.4 (36.4)	4.2 (4.2)	— —	331
11	74	156	C_4H_8NO	$C_{14}H_{22}BrNO_4S$	44.0 (44.2)	5.8 (5.8)	3.5 (3.7)	380
12	80	184–185	NMe_2	$C_{12}H_{20}BrNO_3S$	42.3 (42.6)	5.9 (5.9)	3.8 (4.1)	338
13	65	105–106	$NHN{=}CMe_2$	$C_{13}H_{21}BrN_2O_3S$ $\frac{1}{2}H_2O$	41.5 (41.7)	5.6 (5.8)	7.2 (7.4)	—
14	42	65–66	$NHN{=}CHPh$	$C_{17}H_{21}BrN_2O_3S$	49.7 (49.4)	5.3 (5.1)	7.0 (6.8)	306†
15	76	163	$N{=}PPh_3$	$C_{28}H_{29}BrNO_3PS$	58.6 (58.9)	5.1 (5.1)	2.3 (2.5)	490†

† highest mass fragment ion

The chlorides (**1**, **10**) reacted with amines to give the amides (**2–4**, **11–12**). Treatment with sodium azide afforded the corresponding azides (oils) characterized as the phosphinimines (**5**, **15** and **6**) obtained by warming with triphenylphosphine and triethylphosphite respectively. (**1**) was condensed with hydrazine hydrate to give the hydrazide (**7**); whereas the analogous reaction with (**10**) gave the crude hydrazide as an oil. The hydrazides were reacted with carbonyl compounds to give solid hydrazones (**8–9**, **13–14**).



(1-9 , Y=H)
(10-15 , Y=Br)

Originally we expected that normal carbon and proton NMR spectroscopy would identify the position of sulfonation in these compounds.

However, studies of the NMR spectra[10] of a number of camphor-10-sulfonyl derivatives indicated that the carbon and hydrogen resonances for 8- and 9-positions namely (C-8(9) 20.0, 19.5 and 8(9)-$C\underline{H}_3$, 1.0, 0.8 ppm) were too close to permit definite assignment.

On the other hand, we have recently shown[11] that application of 2D-NMR and NOE difference spectroscopy to the benzylamide (**3**) unequivocally demonstrates that sulfonation occurred on the 8-carbon atom.

Chemical support for this assignment comes from the relative stability of camphor-8-sulfonohydrazide which on warming did not undergo cyclisation to the corresponding thiadiazinedioxide as was observed[4,5] with the camphor-10-sulfonyl analogue.

The NMR spectra of the camphor-8-sulfonyl derivatives show that the resonance due the 8-methyl protons are moved downfield to ca. $\delta 3.4$ due to the deshielding effect of the attached SO_2 group. Likewise in the 3-bromo-compounds the resonance of the 3-methylene protons appears at a lower field ($\delta 4.25$) due to the presence of the adjacent electron-withdrawing bromine atom.

The IR spectra exhibited the normal bonds (1350, 1150 cm^{-1}) associated with the SO_2 group; the carbonyl absorption band appeared at ca. 1750 cm^{-1} while the azides displayed an additional sharp band at 2150 cm^{-1}; the data were in good agreement with previous observations.[12] The mass spectra of the majority of the derivatives showed the molecular ions (M^+) (Table I), except for the hydrazides and hydrazones which generally suffered extensive fragmentation (cf. Reference 12).

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The action of chlorosulfonic acid and camphor is unusual, because even when a large excess of the reagent was present only the sulfonic acid was isolated. Normally use of excess chlorosulfonic acid leads directly to formation of the sulfonyl chloride.[13] The resistance of camphor sulfonic acid towards chlorination may be associated with —O-H‴O hydrogen bonding between the carbonyl and sulfonic acid groups. Some support for this hypothesis comes from previous work,[14] which showed that those diarylurea sulfonic acids capable of participating in zwitterion formation could not be converted into the sulfonyl chlorides by treatment with excess of chlorosulfonic acid.

The compounds described here have been tested for biocidal activity against insects, weeds and fungi, there was no insecticidal or herbicidal activity but several were fungicidal. The preliminary antifungal screen was conducted with the compound (100 ppm) against grey mould on lettuce, vine downy mildew, potato late blight, wheat rust, apple and barley mildew and rice blast. In this screen, the following compounds were active: the dimethylamides (**2**, **12**) and the morpholidates (**4**, **11**) against grey mould and apple and barley mildew; the acetone hydrazones (**8**, **13**) against vine mildew and wheat rust.

EXPERIMENTAL

Melting points were determined with a Gallenkemp electric apparatus and are uncorrected. IR spectra were measured as Nujol mulls using a Unicam SP1000 spectrometer. NMR spectra were recorded using a Bruker WP80 spectrometer using TMS as internal standard, as asterisk indicates resonances that were removed by D_2O treatment. TLC was carried out on Camlab Polygram silica gel plates sensitized to UV 254 nm using ethyl acetate-cyclohexane 1:1 as eluant. MS were obtained with a VG micromass spectrometer operating at 60 eV.

DL-Camphor-8-sulfonic chloride (**1**)

Chlorosulfonic acid (43.7 ml, 0.66 mol) was added to a solution of DL-camphor (50 g, 0.32 mol) in dry chloroform (100 ml). The solution was refluxed for 12 hours, poured onto ice-water and the chloroform layer separated. The aqueous layer was neutralized with calcium hydroxide and the precipitated calcium sulfate filtered off. The hot filtrate was mixed with ammonium carbonate (31.7 g, 0.33 mol) and the precipitate of calcium carbonate removed. The solution was evaporated under reduced pressure to give a brown solid (39.8 g) which was mixed with phosphorus pentachloride (96 g, 0.54 mol) and phosphorus oxychloride (5 ml) and heated on the steam-bath for 1 hour.

The mixture was added to crushed ice to give a gummy solid; this was washed with water (4 × 100 ml) and recrystallized from methanol to give (**1**, 38 g). TLC showed 1 spot R_F 0.10. IR ν max 1750 (C=O), 1360, 1150 (SO_2) cm^{-1}. NMR ($CDCl_3$): δ 3.9–3.3 (q, 2H, CH_2SO_2), 3.0–1.4 (m, 7H, cyclohexyl H), 1.05 (s, 3H, 10-Me), 0.8(s, 3H, 9-Me). ^{13}C NMR($CDCl_3$): δ214.7 (C-2), 71.5 (C-8), 60.5 (C-1), 50.7 (C-7), 42.6 (C-4), 41.2 (C-3), 29.2 (C-6), 26.7 (C-5), 19.5 (C-9), 17.5 (C-10).

DL 3-Bromocamphor-8-sulfonyl chloride (**10**)

This compound was similarly obtained by treatment of 3-bromocamphor (100 g) with chlorosulfonic acid (75 g) in chloroform (200 ml). Heating the ammonium sulfonate (50 g) with phosphorus pentachloride (47 g)—phosphorus oxychloride (5 ml) gave **10** (70 g). IR ν_{max} 1770 (C=O), 1345, 1150 (SO_2) cm^{-1}. ^{13}C NMR($CDCl_3$)δ: 208 (C-2), 72 (C-8), 61.5 (C-3), 60.5 (C-1), 59.5 (C-7), 56.5 (C-4), 29.5 (C-5), 22.0 (C-6), 18 (C-9), 9.8 (C-10).

General procedure for the reaction of the sulfonyl chlorides (**1, 10**) *with amines*

The sulfonyl chloride (0.01 mol) was treated with the amine (0.02 mol) in methanol (30 ml) for 6 hours. (In the preparation of the benzylamide (**3**), THF was used as solvent).

The mixture was added to crushed ice (100 g); the precipitate was collected, washed with water and recrystallized from methanol to give the amides (**2–4**, **11–12**).

Compound (**3**)

IR ν_{max} 3300 (NH), 1765 (C=O), 1600 (ArC=C), 1330, 1150 (SO_2) cm^{-1}. NMR ($CDCl_3$): δ9.5* (s, H, NH), 7.36–7.25 (m, 5H, ArH), 4.3 (d, 2H, $PhCH_2N$), 3.4–1.5 (m, 9H, cyclohexyl H, CH_2SO_2), 1.05 (s, 3H, 10-Me), 0.8 (s, 3H, 9Me).

DL-Camphor-8-sulfonyl azide

A solution of sodium azide (0.02 mol) in water (10 ml) was added to stirred solution of the sulfonyl chloride (1) (0.01 mol) in acetone (15 ml) at room temperature. After 6 hours, the suspension was extracted with ether (100 ml), the ether layer was separated, washed with water (2 × 30 ml) and dried ($MgSO_4$). Evaporation of the solvent *in vacuo* afforded the azide as a pale yellow oil (1.8 g, 68%). Beilstein test $(-)^{ve}$. TLC 1 spot R_F 0.72. IR ν_{max} 2150 (N_3), 1760 (C=O), 1360, 1155 (SO_2) cm^{-1}. MS: 257 (M+), 215 (M—N_3), 200, 167, 55, 49.

DL-3-Bromocamphor-8-sulfonyl azide

3-Bromocamphor-8-sulfonyl chloride (**10**) (3.3 g, 0.01 mol) was similarly reacted with sodium azide (1.3 g, 0.02 mol) in aqueous acetone to give the azide as a pale yellow oil (1.7 g, 51%). IR ν_{max} 2160 (N_3), 1750 (C=O), 1350, 1150 (SO_2) cm^{-1}.

DL-Camphor-8-sulfonyltriphenylphosphinimine (**5**)

A mixture of camphor-8-sulfonyl azide (1 g, 0.004 mol) and triphenylphosphine (1.02 g, 0.004 mol) in toluene (30 ml) was refluxed for 8 hours to give an oil. Trituration with petroleum ether (bp. 60–80°) gave a solid which was recrystallized from chloroform to give (**5**, 1.2 g). TLC 1 spot R_F 0.88. IR ν_{max} 1750 (C=O), 1360, 1150 (SO_2) cm^{-1}.

NMR ($CDCl_3$) δ: 8.0–7.45 (m, 15H, ArH), 3.1–1.2 (m, 9H, cyclohexyl H, CH_2SO_2), 1.05 (s, 3H, 10-Me), 0.85 (s, 3H, 9-Me).

MS: 491 (M+), 400, 340, 324, 277, 223, 200, 151 (camphor), 126, 77 (Ph).

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Compound (**15**)

DL-3-Bromocamphor-8-sulfonyl azide (1.6 g, 0.005 mol) and triphenylphosphine (1.3 g, 0.005 mol) were similarly reacted to give the triphenylphosphinimine (1.9 g) (from methanol). IR ν_{max} 1760 (C=O), 1600 (ArC=C), 1345, 1140 (SO_2) cm^{-1}.

NMR ($CDCl_3$) δ: 8.0–7.5 (m, 15H, ArH), 4.5 (d, 1H, C<u>H</u>Br) (J, 5.3 H_z), 3.2–1.2 (m, 7H, cyclohexyl H, C<u>H</u>$_2SO_2$), 1.15 (s, 3H, 10-Me), 0.83 (s, 3H, 9-Me).

^{13}C NMR ($CDCl_3$) δ 211.5 (C-2), 134–128 (ArC), 59.9 (C-8), 59.3 (C-3), 53.2 (C-1), 50 (C-7), 47.1 (C-4), 30.3 (C-6), 22.1 (C-5), 18 (C-9), 9.9 (C-10). MS: no M^+ (570), 490 (M^+-Br), 348, 324, 277, 201, 183, 122, 77 (Ph).

Compound (**6**)

DL-camphor-8-sulphonyl azide (2 g, 0.008 mol) was heated with triethylphosphite (1.3 g, 0.008 mol) in benzene (20 ml) at 60° for 1 hour to give the triethoxyphosphinimine. IR ν_{max} 1750 (C=O), 1345, 1150 (SO_2) cm^{-1}.

DL-Camphor-8-sulfonohydrazide (**7**)

The sulfonyl chloride (1) (2 g, 0.0066 mol) was dissolved in THF (30 ml) and the solution added dropwise to a stirred solution of hydrazine hydrate (0.8 mol of 98%, 0.0132 mol) at 0°C. The mixture was stirred for 3 hours, THF was removed *in vacuo* and the residue triturated with ice-water. Recrystallization from methanol gave (**7**) (0.6 g). TLC 1 spot R_F 0.46. IR (KBr) ν_{max} 3360, 3280 (NH), 1740 (C=O), 1350, 1150 (SO_2) cm^{-1}.

DL-3-Bromocamphor-8-sulfonhydrazide

3-Bromocamphor-8-sulfonyl chloride (1) (3.3 g, 0.01 mol) similarly reacted with hydrazine hydrate (0.8 g, 0.02 mol) to give the hydrazide as an oil (1.62 g, 50%). IR ν_{max} 3280, 3250 (NH), 1740 (C=O), 1340, 1150 (SO_2), 675 (C—Br) cm^{-1}.

Both these hydrazides were characterized by condensation with carbonyl compounds to give the hydrazones (**8–9**, **13–14**).

Compound (**9**)

Yellow prisms (petroleum ether), TLC (EtOAc–toluene 1:1) 1 spot R_F 0.26. NMR ($CDCl_3$) δ: 9.2*(s, 1H, NH), 8.2–7.5 (q, 4H, ArH), 7.9 (s, 1H, =C<u>H</u>), 3.4 (q, 2H, C<u>H</u>$_2SO_2$), 3.1–1.2 (m, 7H, cyclohexyl H), 1.0 (s, 3H, 10-Me), 0.85 (s, 3H, 9-Me).

Compound (**13**)

TLC 1 spot R_F 0.62. IR ν_{max} 3250 (NH), 1770 (C=O), 1335, 1155 (SO_2) cm^{-1}. MS: 365 (M+), 303, 285 (M—Br), 221, 151 (camphor), 107, 91, 71, 55, 53.

Compound (**14**)

NMR ($CDCl_3$) δ: 8.8* (s, 1H, NH), 7.9 (s, 1H, =CH), 7.7–7.2(m, 5H, ArH), 4.65 (d, 1H, C<u>H</u>Br) (J, 5.3 Hz), 3.8–1.5 m (m, 7H, cyclohexyl H, C<u>H</u>$_2SO_2$), 1.25 (s, 3H, 10-Me), 1.0 (s, 3H, 9-Me). MS: 413 (M+), 333 (M—Br), 229, 202, 150 (camphor), 119, 109, 90, 64.

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