N-Acetyl-*N*-trichloromethylsulphenylarenesulphonamides

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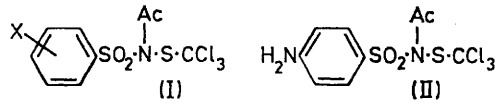
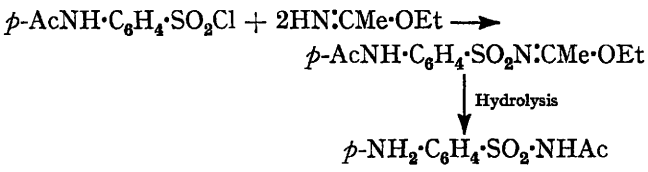
In a search for new fungicides, *N*-acetyl-*N*-trichloromethylsulphenylbenzenesulphonamide and the following derivatives have been prepared: *p*-methyl, *p*-chloro, *o*-nitro, *p*-ethoxy, *p*-acetamido, *p*-methoxy, 2,5-dimethoxy, *p*-phenylazo, 3-bromo-4-methoxy, 5-bromo-2-methoxy, 5-chloro-2-methoxy, 4-chloro-3-nitro, 2,3,4-trichloro, 4-chloro-3-methyl, and 2-chloro-5-methyl. These compounds were synthesised by condensation of trichloromethanesulphenyl chloride with the appropriate *N*-acetylarenesulphonamide; this reaction and the formation of the N-acetylsulphonamides are briefly discussed.

MANY trichloromethylsulphenyl derivatives are fungicidal;[1,2] this is particularly true of those containing the $N{\cdot}S{\cdot}Cl_3$ group and several of these compounds have been developed commercially.[3-5] Certain *N*-trichloromethylsulphenyl-sulphonamides are also fungicidal[3] and we have examined a range of their *N*-acetyl derivatives (I) as potential fungicides.

The only *N*-acetyl-*N*-trichloromethylsulphenylarenesulphonamide reported[6] is the derivative (II) which has carcinolytic activity.[7]



These compounds are closely related to the *N*-trichloromethylsulphonylsulphonamides, several of which are powerful fungicides.[8] Although several methods for the acetylation of sodium sulphonamides[9a] and free sulphonamides have been reported[10-17] acetyl chloride or acetic anhydride with catalysts are claimed to be the most satisfactory agents.[15,18] We have re-investigated three reagents and have found their effectiveness to be generally in the order acetic anhydride–sulphuric acid > acetic anhydride–pyridine > acetyl chloride. The acetylation species are probably $AcO{\cdot}SO_3H$, $Ac\overset{+}{N}C_5H_5$, and AcCl respectively.[19] Attempted preparations of *N*-acetylsulphonamides by reaction of the appropriate arenesulphonyl chloride with acetamide were unsuccessful presumably due to the very weak basic character of the latter. An analogous condensation does occur with acetimidic esters.[9b,20]

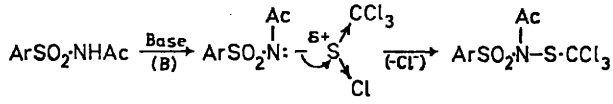


Since *N*-acetylsulphonamides are more acidic than sulphonamides they can be freed from the latter by their preferential dissolution in warm aqueous sodium hydrogen carbonate. *N*-Trichloromethylsulphenyl derivatives are prepared by condensation of trichloromethanesulphenyl chloride with a compound containing an acidic hydrogen atom:[3,21]

$$R{-}H + ClS{\cdot}CCl_3 \xrightarrow[(B)]{\text{Base}} RS{\cdot}CCl_3 + \overset{+}{B}HCl^-$$

In the synthesis of *N*-acetyl-*N*-trichloromethylsulphenylarenesulphonamides two condensation procedures were used. (1) A heterogeneous system in which a solution of the *N*-acetylsulphonamide in aqueous sodium hydroxide was treated with trichloromethanesulphenyl chloride in ether. (2) A homogeneous system in which both the *N*-acetylsulphonamide and the sulphenyl chloride were dissolved in dioxan in the presence of triethylamine. The second procedure usually gave better yields. The variable, and often unsatisfactory, yields from the first method are probably due to side reactions, such as the hydrolysis of trichloromethanesulphenyl chloride, the *N*-acetylsulphonamide (*cf.* ref. 15), or the trichloromethylsulphenyl derivative.[21,22] These reactions cause the mixture to become acid and precipitate the *N*-acetylsulphonamide; addition of further sodium hydroxide solution to redissolve the precipitate resulted in lower yields.

The formation of *N*-acetyl-*N*-trichloromethylsulphenyl arene sulphonamides involves nucleophilic attack of the *N*-acetylsulphonamide anion on the electrophilic sulphur atom in trichloromethanesulphenyl chloride:



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In the biological tests, fungicidal activity was shown by the following derivatives of *N*-acetyl-*N*-trichloromethylsulphenylbenzenesulphonamide: *p*-methyl and *p*-chloro were active against *Fusarium* wilt; also 5-bromo-2-methoxy and 2,5-dimethoxy were strongly active against Vine Downy Mildew, Potato Blight, and Apple Scab.

EXPERIMENTAL

I.r. spectra were measured with an Infracord 237 and n.m.r. spectra with a Varian A-60 for solutions in deuteriochloroform with tetramethylsilane as internal standard.

In the preparation of the *N*-acetylarene sulphonamides (Table 1) three different acetylation methods were employed, and these are illustrated by the following examples:

N-*Acetyl*-p-*chlorobenzenesulphonamide.*—*Method* (1) *with acetyl chloride.* *p*-Chlorobenzenesulphonamide (1·0 g.) was boiled under reflux with acetyl chloride (5 c.c.) and glacial acetic acid (1·5 c.c.) for 1 hr. Evaporation of the solvent left a white powder (1·1 g.) which upon treatment with warm aqueous sodium hydrogen carbonate (20 c.c.) and acidification of the filtrate (by glacial acetic acid with Congo Red indicator) gave *N*-acetyl-*p*-chlorobenzenesulphonamide as needles (0·5 g., 45%), m.p. 192° (lit.,[11] 192·5°) (from aqueous ethanol).

Method (2) *with acetic anhydride–pyridine.* *p*-Chlorobenzenesulphonamide (1·0 g.) was boiled under reflux with pyridine (2 c.c.) and acetic anhydride (2 c.c.) for 1 hr. The solution was poured on ice to give a white powder (1·1 g.) which, purified as above, gave the *N*-acetylsulphonamide as needles (0·6 g., 55%), m.p. 192°.

N-*Acetyl*-o-*nitrobenzenesulphonamide.*—*Method* (3) *with acetic anhydride–conc. sulphuric acid.* *o*-Nitrobenzenesulphonamide (10 g.) was boiled under reflux with acetic anhydride (10 c.c.) and a few drops of concentrated sulphuric acid (0·1 c.c.) for 3 hr. The mixture was poured on ice to give a fawn powder (11·5 g.) which when purified as above gave *N*-acetyl-*o*-nitrobenzenesulphonamide as a pale yellow powder (10·0 g., 80%), m.p. 189° (lit.,[10] 190°). With *p*-chlorobenzenesulphonamide this method gave a 65% yield of the *N*-acetylsulphonamide with a reaction time of 1 hr.

The following known *N*-acetylarenesulphonamides were prepared: benzene (62%), m.p. 125—126° (lit.,[15] 124—125°); *p*-toluene (80%), m.p. 135—136° (lit.,[12] 136—137°); *m*-nitrobenzene (80%), m.p. 189° (lit.,[10] 190°); *p*-methoxybenzene (45%), m.p. 143—145° (lit.,[15] 140°); *p*-ethoxybenzene (40%), m.p. 148—149° (lit.,[15] 151·5°); *p*-acetamidobenzene (42%), m.p. 251—253° (lit.,[16] 254°). The other *N*-acetylsulphonamides are listed in Table 1.

Attempted Preparation of N-*Acetyltoluene*-p-*sulphonamide by Condensation of the Sulphonyl Chloride with Acetamide* (1). A solution of toluene-*p*-sulphonyl chloride (20 g.) in hot acetone was treated with acetamide (5·9 g.) in water (50 c.c.) and 6N-sodium hydroxide (20 c.c.). The mixture was stirred for 1 hr. at 50° and acidified (glacial acetic acid), but no precipitate of the *N*-acetylsulphonamide was formed.

(2) Toluene-*p*-sulphonyl chloride was boiled with acetamide in pyridine for 3 hr.; again no *N*-acetyltoluene-*p*-sulphonamide was formed.

The i.r. spectra of the *N*-acetylarenesulphonamides in ethanol showed the SO stretching vibrations in the region 1170—1155 cm.$^{-1}$ (*cf.* ref. 23*a*); the single N–H stretching band at 3360—3125 cm.$^{-1}$ (*cf.* ref. 23*b*); and the carbonyl absorption band at 1720—1690 cm.$^{-1}$ (*cf.* ref. 23*c*).

TABLE 1

N-Acetylarenesulphonamides $RSO_2 \cdot NHAc$

R	M.p.	Yield (%)	Formula	Found (%) C	H	Cl	N	S	Required (%) C	H	Cl	N	S
p-$N_2 \cdot C_6H_5$	200—202°	43 [a]	$C_{14}H_{13}N_3O_3S$	55·4	4·1		14·1		55·5	4·3		13·9	
2,5(MeO)$_2$C$_6$H$_3$	177—178	65 [c]	$C_{10}H_{13}NO_5S$	46·1	4·9		5·2		46·3	5·0		5·4	
3-Br,4-MeOC$_6$H$_3$	146—148	71 [b]	$C_9H_{10}BrNO_4S$	35·2	3·3		4·4		35·0	3·2		4·5	
5-Cl,2-MeOC$_6$H$_3$	202—203	73 [a]	$C_9H_{10}ClNO_4S$	41·0	3·8		5·2		41·0	3·8		5·3	
4-Cl,3-O$_2$NC$_6$H$_3$	152—153	74 [c]	$C_8H_7ClN_2O_5S$			13·0		11·7			12·75		11·5
2,3,4-Cl$_3$C$_6$H$_2$	193—194	60 [b]	$C_8H_6Cl_3NO_3S$	32·0	1·9		4·7		31·7	2·0		4·6	
5-Br,2-MeOC$_6$H$_3$	219—220	68 [b]	$C_9H_{10}BrNO_4S$	34·7	3·1		4·3		35·0	3·2		4·5	
4-Cl,3-MeC$_6$H$_3$	144	53 [a]	$C_9H_{10}ClNO_3S$			14·3		13·0			14·3		12·9
2-Cl,5-MeC$_6$H$_3$	190—191	62 [c]	$C_9H_{10}ClNO_3S$			14·1		13·2			14·3		12·9
4-Cl,2-MeC$_6$H$_3$	187	51 [a]	$C_9H_{10}ClNO_3S$			13·9		12·5			14·3		12·9
4-Cl,3-AcNHC$_6$H$_3$	214—215	60 [b]	$C_{10}H_{11}ClNO_4S$			12·6		11·1			12·2		11·0
m-$HO_2C \cdot C_6H_4$	226—227	75 [c]	$C_9H_9NO_5S$	44·3	3·3		6·1		44·4	3·7		5·8	

[a] = Method (1). [b] = Method (2). [c] = Method (3).

Preparation of N-*Acetyl*-N-*trichloromethylsulphenylarenesulphonamides.*—The condensation of trichloromethanesulphenyl chloride with the *N*-acetylarenesulphonamide was effected by two procedures, as illustrated by the following examples.

N-*Acetyl*-N-*trichloromethylsulphonyltoluene*-p-*sulphonamide: method* (1). An ethereal solution of trichloromethanesulphenyl chloride (2·1 g., 1·2 c.c.) was added dropwise to a stirred solution of *N*-acetyltoluene-*p*-sulphonamide (2·0 g.) in aqueous N-sodium hydroxide (11 c.c.) at 0°. After 2 hr. the product was collected, washed with water, and recrystallised from ethanol to give the *N*-trichloromethylsulphenyl derivative as a white *powder* (2·1 g., 60%), m.p. 143—145° (Found: C, 33·5; H, 2·8; N, 3·9; S, 18·3. $C_{10}H_{10}Cl_3NO_3S_2$ requires C, 33·1; H, 2·8; N, 3·9; S, 17·9%).

N-*Acetyl*-5-*bromo*-2-*methoxy*-N-*trichloromethylsulphenylbenzenesulphonamide: method* (2). A solution of trichloromethanesulphenyl chloride (1·2 c.c.) in dioxan (10 c.c.) was added dropwise to a stirred solution of *N*-acetyl-5-bromo-2-methoxybenzenesulphonamide (3·1 g.) and triethylamine (1·0 c.c.) in dioxan at 5°. After 3 hr., water

[23] L. J. Bellamy, 'The Infra-Red Spectra of Complex Molecules,' Methuen, 2nd Edn., 1958; (*a*) p. 363; (*b*) p. 205; (*c*) p. 211.

TABLE 2

N-Acetyl-*N*-trichloromethylsulphenylarenesulphonamides $RSO_2NAc{\cdot}S{\cdot}CCl_3$

R	M.p.	Yield (%)	Formula	Found (%) C	H	Cl	N	S	Required (%) C	H	Cl	N	S
C_6H_5	159—160°	52 [a]	$C_9H_8Cl_3NO_3S_2$			30·4		18·2			30·6		18·4
p-Cl·C_6H_4	142	77 [b]	$C_9H_7Cl_4NO_3S_2$	28·35	1·8		3·55	16·9	28·2	1·8		3·65	16·7
p-MeO·C_6H_4	144	58 [a]	$C_{10}H_{10}Cl_3NO_4S_2$			27·8		17·3			28·1		16·9
p-EtO·C_6H_4	133—135	60 [a]	$C_{11}H_{12}Cl_3NO_4S_2$			26·9		16·2			27·1		16·3
o-$O_2N{\cdot}C_6H_4$	144—145	60 [a]	$C_{10}H_{10}Cl_3NO_5S_2$	33·5	2·8		3·9	18·0	33·1	2·8		3·9	17·7
p-$C_6H_5{\cdot}N_2$	200	45 [a]	$C_{15}H_{12}Cl_3N_3O_3S_2$			23·2		13·7			23·5		14·15
4-Cl,3-MeC_6H_3	138—139	70 [b]	$C_{10}H_9Cl_4NO_3S_2$			36·1		15·8			35·8		16·1
p-Ac·NH·C_6H_4	194—195	45 [a]	$C_{11}H_{11}Cl_3N_2O_4S_2$			25·9		16·15			26·3		15·8
3-Br,4-$MeOC_6H_3$	142—143	75 [b]	$C_{10}H_9BrCl_3NO_4S_2$	26·4	2·2		3·15	14·3	26·2	2·0		3·1	14·0
5-Cl,2-$MeOC_6H_3$	153—154	85 [b]	$C_{10}H_9Cl_4NO_4S_2$	29·4	2·2		3·3	15·8	29·1	2·2		3·4	15·5
2,5$(MeO)_2C_6H_3$	134—135	74 [b]	$C_{11}H_{12}Cl_3NO_5S_2$	32·6	3·1		3·4	16·0	32·3	2·9		3·4	15·7
4-Cl,3-$O_2NC_6H_3$	142	70 [b]	$C_9H_6Cl_4N_2O_5S_2$	25·5	1·5		6·5	15·1	25·1	1·4		6·5	15·0
2,3,4-$Cl_3C_6H_2$	172—173	80 [b]	$C_9H_5Cl_6NO_3S_2$	24·3	1·25		2·9	14·5	24·0	1·1		3·1	14·2
2-Cl,5-MeC_6H_3	155—157	42 [a]	$C_{10}H_9Cl_4NO_3S_2$			35·6		15·7			35·8		16·1

[a] = Method (1). [b] = Method (2).

(100 c.c.) was added and the precipitate was collected and triturated with ethanol (10 c.c.) to give the *N*-trichloromethylsulphenyl derivative as a *powder* (3·7 g., 82%), m.p. 166—168° (Found: C, 26·6; H, 2·1; N, 3·1; S, 14·2. $C_{10}H_9BrCl_3NO_4S_2$ requires C, 26·2; H, 2·0; N, 3·1; S, 14·0%).

The other *N*-acetyl-*N*-trichloromethylsulphenylarenesulphonamides prepared are listed in Table 2.

The i.r. spectra of the *N*-trichloromethylsulphenyl derivatives in ethanol showed bands at 1170—1160 cm.$^{-1}$ (SO_2) and at 1740—1720 cm.$^{-1}$ (CO); there was no band in the N–H stretching region.

The n.m.r. spectrum of *N*-acetyl-4-chloro-*N*-trichloromethylsulphenylbenzenesulphonamide showed signals at τ 2·0—2·5 (4ArH in a *p*-substituted benzene), and a singlet at τ 7·4 (CH_3 protons).

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