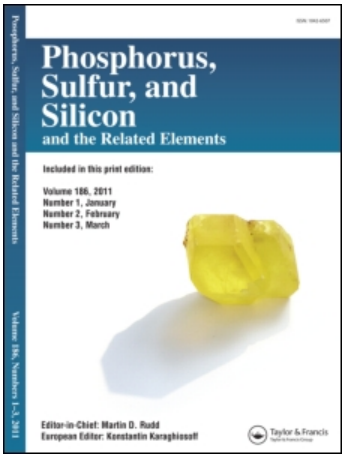


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

SOME SULFONYL DERIVATIVES OF SALICYLIC ACID AND RELATED COMPOUNDS

Richard Cremlyn[a]; Frederick Swinbourne[a]; John Atherall[a]; Lynn Courtney[a]; Theo Cronje[a]; Paul Davis[a]; Stuart Langston[a]; Michael Rogers[a]
[a] School of Natural Sciences, Hatfield Polytechnic, Hatfield, Hertfordshire, England

To cite this Article Cremlyn, Richard , Swinbourne, Frederick , Atherall, John , Courtney, Lynn , Cronje, Theo , Davis, Paul , Langston, Stuart and Rogers, Michael(1980) 'SOME SULFONYL DERIVATIVES OF SALICYLIC ACID AND RELATED COMPOUNDS', Phosphorus, Sulfur, and Silicon and the Related Elements, 9: 2, 155 — 164
To link to this Article: DOI: 10.1080/03086648008078234
URL: http://dx.doi.org/10.1080/03086648008078234

Phosphorus and Sulfur, 1980, Vol. 9, pp. 155–164
0308-664X/80/0902-0155$06.50/0

SOME SULFONYL DERIVATIVES OF SALICYLIC ACID AND RELATED COMPOUNDS

RICHARD CREMLYN, FREDERICK SWINBOURNE, JOHN ATHERALL, LYNN COURTNEY, THEO CRONJE, PAUL DAVIS, STUART LANGSTON, and MICHAEL ROGERS

School of Natural Sciences, Hatfield Polytechnic, Hatfield, Hertfordshire, England.

(*Received November 3, 1979; in final form January 18, 1980*)

o-Methoxybenzamide, salicyclic acid, salicylamide and N-acetylsalicylamide have been converted to the corresponding 5-sulfonyl chlorides, and *p*-hydroxybenzoic acid to the 3-sulfonyl chloride. The sulfonyl chlorides were characterized by the preparation of various derivatives, e.g. amides, hydrazides, hydrazones and azides. Chlorosulfonation of O-acetyl compounds showed either complete or partial deacetylation. O-Acetyl compounds were therefore obtained by subsequent acetylation. O-Acetylsalicylamide on heating was converted to the N-acetyl derivative and the isomerization was followed by h.p.l.c. In contrast both *m*- and *p*-acetoxybenzamides were relatively stable. Salicylanilide and O-methylsalicylanilide, with chlorosulfonic acid gave the 1,4′-disulfonyl chlorides. On the other hand, 4′-chloro- and 4′-chloro-O-methyl-salicylanilides afforded the corresponding monosulfonyl chlorides. The i.r., n.m.r. and mass spectra, together with the algaecidal and antibacterial results are briefly discussed.

INTRODUCTION

Many sulfonyl derivatives, such as amides,[1] azides,[2] and hydrazides[3–5] have shown useful biological activity as for instance antibacterials, fungicides, and nematicides. Phenols are important biocides[6] and accordingly hydroxybenzenesulfonyl derivatives are of particular interest as candidate biocides. In addition the value of aspirin, and related derivatives, such as salicylates and salicylamide, as bactericides, antipyretics, and analgesics are well known.[7] Salicylanilide ("Shirlan") was also one of the earliest organic fungicides.[6] Comparatively little has been reported on the chemistry of the sulfonyl derivatives of salicylic acid, aspirin, salicylamide and salicylanilide and these compounds were therefore worthy of further investigation.

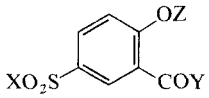
DISCUSSION

o-Methoxybenzamide with excess of chlorosulfonic acid (4 mols) gave 3-amido-4-methoxybenzenesulfonyl chloride (86%) (**1**) (Table I) which was converted to the amide (**2**), hydrazide (**3**) and hydrazones (**4–10**). Chlorosulfonation of salicyclic acid gave the 5-sulfonyl chloride (**11**),[8–9] the optimum yield (90%) was obtained using a large excess (6 mols) of chlorosulfonic acid, which agrees with the proposed mechanism[9] for the chlorosulfonation of aromatic carboxylic acids. Reaction of the sulfonyl chloride (**11**) with aromatic amines (1–2 mols) as previously described[10] gave the amides (**12–15**). However the procedure was unsuccessful with aliphatic amines which are sufficiently basic to break the intramolecular hydrogen-bonding between the OH and CO_2H groups. Consequently formation of the cyclohexylamide (**16**) needed more amine (at least 3 mols).

Acetylation of the sulfonamides (excess acetic anhydride) gave the N,O-diacetyl derivatives (**17–19**). The sulfonyl chloride (**11**) with sodium azide gave the azide (**20**) acetylated to the O-acetylazide (**21**); both azides with triphenylphosphine gave the phosphinimines (**22, 23**). The sulfonyl chloride (**11**) was also converted to the phenylhydrazide (**24**), hydrazide (**25**) and hydrazones (**26–33**). The O-acetyl derivative (**34**) of compound (**11**) was prepared by acetylation; subsequent condensation with amines caused deacetylation so the O-acetyl-amides (**35–38**) were prepared by acetylation (1 mol of acetic anhydride) of the salicylic acid-5-sulfonamides. Salicylamide with chlorosulfonic acid (3 mols) gave the sulfonyl chloride (**39**) (55%). Reaction with N,N-dimethyl- and phenylhydrazine afforded the hydrazides (**40,**

TABLE I

Salicylic acid sulfonyl derivatives



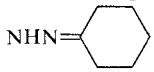
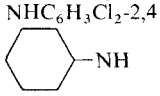
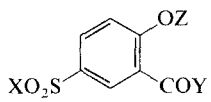
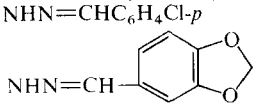
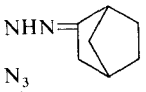
No.	X	Y	Z	m.p.	Formula	Found (%) C	H	N	Required (%) C	H	N
1	Cl	NH_2	Me	140°	$C_8H_8ClNO_4S$	38.3	3.4	5.8	38.5	3.2	5.6
2	NH_2	NH_2	Me	200°	$C_8H_{10}N_2O_4S$	41.3	4.4	12.2	41.3	4.3	12.0
3	$NHNH_2$	NH_2	Me	180°	$C_8H_{11}N_3O_4S$	39.0	4.4	22.5	38.85	4.4	22.5
4	NHN=CHPh	NH_2	Me	160°	$C_{15}H_{15}N_3O_4S$	53.8	4.7	12.5	54.05	4.5	12.6
5	NHN=CHC_6H_4Me-*m*	NH_2	Me	192°	$C_{16}H_{17}N_3O_4S$	55.5	4.8	12.3	55.3	4.9	12.1
6	NHN=CHC_6H_4Br-*p*	NH_2	Me	188°	$C_{15}H_{14}BrN_3O_4S$	47.2	3.9	11.2	47.4	3.7	11.0
7	NHN=$CHC_6H_4NO_2$-*p*	NH_2	Me	214°	$C_{15}H_{14}N_4O_6S$	47.7	3.8	15.1	47.6	3.7	14.8
8	NHN=CH−CH=CHPh	NH_2	Me	178°	$C_{17}H_{18}N_3O_4S$	56.5	5.2	11.9	56.7	5.0	11.7
9	NHN=CMe_2	NH_2	Me	205°	$C_{11}H_{15}N_3O_4S$	46.4	5.3	14.8	46.3	5.3	14.7
10	NHN= 	NH_2	Me	186°	$C_{14}H_{19}N_3O_4S$	52.0	5.9	12.7	51.7	5.8	12.9
11	Cl	OH	H	162–164°[a]							
12	NHPh	OH	H	208°[b]	$C_{13}H_{11}NO_5S$	53.0	4.0	4.9	53.2	3.7	4.8
13	NHC_6H_4Cl-*p*	OH	H	222°[b]	$C_{13}H_{10}ClNO_5S$	47.8	3.0	4.3	47.7	3.1	4.3
14	NHC_6H_4I-*p*	OH	H	223°	$C_{13}H_{10}INO_5S$	37.6	2.5	3.6	37.2	2.4	3.3
15	$NHC_6H_3Cl_2$-2,4	OH	H	214–215°	$C_{13}H_9Cl_2NO_5S$	43.1	2.4	4.0	43.1	2.5	3.9
16	 −NH	OH	H	176–178°	$C_{13}H_{17}NO_5S$	52.5	6.0	5.1	52.2	5.7	4.7
17	N(Ac)Ph	OH	Ac	180°	$C_{17}H_{15}NO_7S$	54.5	4.3	3.7	54.1	4.0	3.7
18	N(Ac)C_6H_4Cl-*p*	OH	Ac	183–185°	$C_{17}H_{14}ClNO_7S$	49.4	3.3	3.4	49.6	3.4	3.4
19	N(Ac)C_6H_4I-*p*	OH	Ac	179°	$C_{17}H_{14}INO_7S$	40.4	2.9	3.1	40.6	2.8	2.8
20	N_3	OH	H	135°[c]							
21	N_3	OH	Ac	207°	$C_9H_7N_3O_6S$	37.8	2.7	14.5	37.9	2.5	14.7
22	Ph_3P=N	OH	H	104–106°	$C_{25}H_{20}NO_5PS$	62.6	4.4	3.2	62.9	4.2	2.9
23	Ph_3P=N	OH	Ac	185°	$C_{27}H_{22}NO_6PS$	62.1	4.3	2.8	62.4	4.3	2.7
24	NHNHPh	OH	H	161°	$C_{13}H_{12}N_2O_5S$	50.8	4.2	8.7	50.6	3.9	9.1
25	$NHNH_2$	OH	H	182–183°[e]							
26	NHN=CHPh	OH	H	193°[d]	$C_{14}H_{12}N_2O_5S$	52.3	3.9	8.9	52.5	3.75	8.75
27	NHN=$CHC_6H_4NO_2$-*p*	OH	H	208°	$C_{14}H_{11}N_3O_7S$	45.7	3.3	11.5	46.0	3.0	11.5
28	NHN=CHC_6H_4Cl-*p*	OH	H	214°[f]							
29	NHN=CMe_2	OH	H	178°[g]							
30	NHN=CEtMe	OH	H	152°	$C_{11}H_{14}N_2O_5S$	52.4	3.8	8.8	52.5	3.75	8.75
31	NHN=CH−CH=CHPh	OH	H	162–164°	$C_{16}H_{14}N_2O_5S$	55.7	4.0	7.9	55.5	4.0	8.0
32	NHN=CHPh	OH	Ac	144°	$C_{16}H_{14}N_2O_6S$	53.2	3.8	7.9	53.0	3.85	7.7
33	NHN=CEtMe	OH	Ac	162°	$C_{13}H_{16}N_2O_6S$	48.0	5.1	8.6	47.55	4.9	8.5
34	Cl	OH	Ac	137–138°	$C_9H_7ClO_6S$	38.6	2.7	12.9	38.8	2.5	12.75
35	NHPh	OH	Ac	176–177°	$C_{15}H_{13}NO_6S$	53.9	4.0	4.0	53.7	3.9	4.2
36	NHC_6H_4Cl-*p*	OH	Ac	179–180°	$C_{15}H_{12}ClNO_6S$	49.3	3.5	3.9	49.2	3.5	4.1
37	$NHC_6H_3Cl_2$-2,4	OH	Ac	160–162°	$C_{15}H_{11}Cl_2NO_6S$	44.3	3.0	3.4	44.5	2.7	3.5
38	NHNHPh	OH	Ac	240–241°	$C_{15}H_{14}N_2O_6S$	51.6	3.8	8.2	51.4	4.0	8.0
39	Cl	NH_2	H	178–180°	$C_7H_6ClNO_4S$	35.5	2.7	6.1	35.7	2.55	5.9
40	$NHNMe_2$	NH_2	H	148–149°	$C_9H_{13}N_3O_4S$	41.7	5.1	15.9	41.7	5.0	16.2
41	NHNHPh	NH_2	H	160°	$C_{13}H_{13}N_3O_4S$	50.7	4.2	13.6	50.8	4.2	13.7
42	NHC_6H_4Cl-*p*	NH_2	H	238–239°	$C_{13}H_{11}ClN_2O_4S$	47.5	3.2	8.7	47.8	3.4	8.6
43	NHC_6H_4Cl-*o*	NH_2	H	205–206°	$C_{13}H_{11}ClN_2O_4S$	47.9	3.5	8.5	47.8	3.4	8.6
44	NHC_6H_4Cl-*m*	NH_2	H	217–218°	$C_{13}H_{11}ClN_2O_4S$	47.8	3.6	8.3	47.8	3.4	8.6
45	NHPh	NH_2	H	216°	$C_{13}H_{12}N_2O_4S$	53.0	3.8	9.9	53.4	4.1	9.6
46	$NHC_6H_3Cl_2$-2,4	NH_2	H	217°	$C_{13}H_{10}Cl_2N_2O_4S$	42.8	3.1	7.9	43.2	2.8	7.8
47	$NHC_6H_3Cl_2$-2,5	NH_2	H	160–162°	$C_{13}H_{10}Cl_2N_2O_4S$	42.9	2.7	8.0	43.2	2.8	7.8
48	$NHC_6H_3Cl_2$-2,6	NH_2	H	179°	$C_{13}H_{10}Cl_2N_2O_4S$	43.0	3.1	7.6	43.2	2.8	7.8
49	$NHC_6H_3Cl_2$-3,4	NH_2	H	215–216°	$C_{13}H_{10}Cl_2N_2O_4S$	43.1	3.1	7.7	43.2	2.8	7.8

TABLE I (*continued*)



No.	X	Y	Z	m.p.	Formula	Found (%) C	H	N	Required (%) C	H	N
50	$NH\overset{+}{N}H_3Cl^-$	NH_2	H	175°	$C_7H_{10}ClN_3O_4S$	31.4	3.8	15.9	31.4	3.7	15.7
51	$NHN{=}CMe_2$	NH_2	H	157°	$C_{10}H_{13}ClN_3O_4S$	44.7	4.8	15.5	44.3	4.4	15.5
52	$NHN{=}C(Ph)C_6H_4NO_2$-*p*	NH_2	H	232°	$C_{15}H_{14}N_4O_6S$	47.4	3.7	14.7	47.6	3.7	14.8
53	$NHN{=}CHC_6H_4NO_2$-*p*	NH_2	H	220–222°	$C_{14}H_{12}N_4O_6S$	46.3	3.2	15.6	46.1	3.3	15.4
54	$NHN{=}CHC_6H_4Cl$-*p*	NH_2	H	188°	$C_{14}H_{12}ClN_3O_4S$	47.8	3.0	12.1	47.5	3.4	11.9
55		NH_2	H	200–201°	$C_{15}H_{13}N_3O_6S$	49.8	3.8	11.7	49.6	3.6	11.6
56		NH_2	H	190–191°	$C_{14}H_{17}N_3O_4S$	51.9	5.3	12.6	52.0	5.3	13.0
57	N_3	NH_2	H	179°	$C_7H_6N_4O_4S$	35.0	2.8	22.9	34.7	2.5	23.1
58	Cl	NHAc	H	146°	$C_9H_8ClNO_5S$	38.7 (Cl, 12.3; S, 11.7)	3.0	5.0	39.0 (Cl, 12.8; S, 11.5)	2.9	5.0
59	$NHC_6H_3Cl_2$-2,4	NHAc	H	230–231°	$C_{15}H_{12}Cl_2N_2O_5S$	44.8	2.7	7.0	44.7	3.0	6.9
60	NHPh	NHAc	H	194–196°	$C_{15}H_{14}N_2O_5S$	54.0	4.2	8.6	53.9	4.2	8.4
61	NHNHPh	NHAc	H	160°	$C_{15}H_{15}N_3O_4S$	54.1	4.3	12.8	53.9	4.5	12.6
62	N_3	NHAc	H	169–170°	$C_9H_8N_4O_5S$	38.3	2.8	19.8	38.0	2.8	19.7
63	N_3	NH_2	Ac	128°	$C_9H_8N_4O_5S$	38.1	3.0	20.0	38.0	2.8	19.7

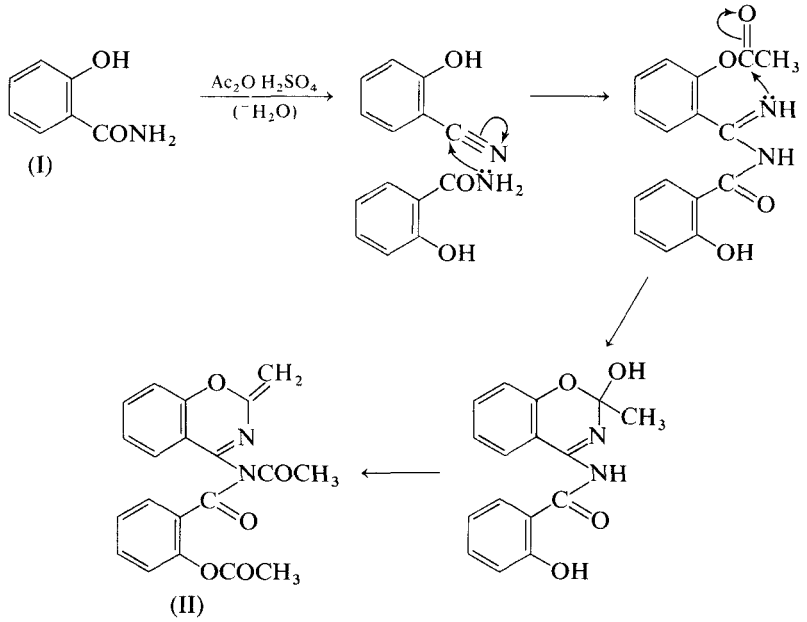
[a] Lit.[9] 164–166°.
[b] Lit.[10] 216–218, 235–237°.
[c] Lit.[9] 138–140°.
[d] Lit.[9] 229–230°.
[e] Lit.[9] 182°.
[f] Lit.[9] 217–218.
[g] Lit.[9] 180°.

41); the sulfonyl chloride (**39**) was also converted to the amides (**42–49**), azide (**57**) and the acetylazide (**63**). 3-Amido-2-hydroxybenzenesulfonohydrazide was obtained as the hydrochloride (**50**) and was characterized as the hydrazones (**51–56**).

O-Acetylsalicylamide was obtained in excellent yield (95%) by acetylation of salicylamide with acetic anhydride-pyridine;[11] under basic conditions salicylamide probably exists substantially in the phenoxy form which favours O- rather than N-acetylation. This is supported by the lower yield obtained (67%) in the presence of a little sulfuric acid. In contrast, N-acetylsalicylamide was prepared (50%) by acetylation of salicylamide (**1**) under acidic conditions (acetic anhydride-acetic acid).[12] An effort was made to improve the yield of N-acetylsalicylamide by using more drastic conditions (acetic anhydride-sulfuric acid at 120° for 3 h); however this gave an unknown compound, m.p. 193°. This compound did not contain a phenolic OH group and the mass spectrum showed a molecular ion (M^+, 364), suggesting the formation of the tricyclic compound (**11**), possibly by the mechanism shown later (p. 162).

The provisional structure (II) is supported by the microanalytical data and the i.r. spectrum which shows the presence of the O-Ac and N-Ac groups (bands at 1750 and 1680 cm^{-1}), these two acetyl groups are also indicated by the n.m.r. and mass spectra. Further work on this interesting compound is proposed, to definitely establish the structure and to examine biological activity.

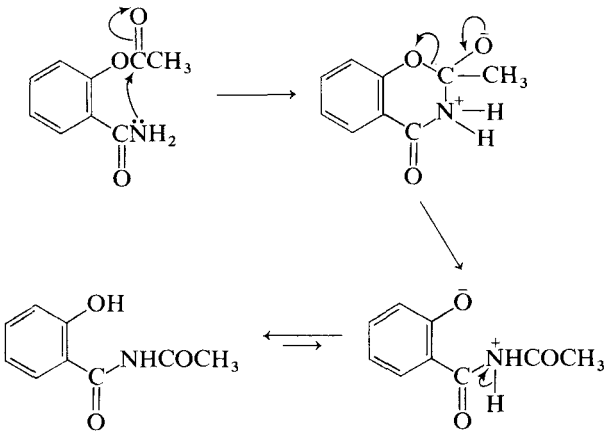
O-Acetylsalicylamide with boiling methanol is known[13] to be converted to the N-acetyl derivative. The isomerization was followed using high performance liquid chromatography and was virtually complete after $1\frac{1}{2}$ h; previously[14] the reaction was followed by n.m.r. spectroscopy. We found that isomerization of O-acetylsalicylamide to the N-acetyl derivatives was the best method for the preparation of the latter compound. Early



(I)

(II)

workers[13] suggested that the process was intramolecular which may be rationalised by the mechanism:



The reaction could take place intermolecularly, but we found that *m*-acetoxy- and *p*-acetoxybenzamide were relatively stable in boiling methanol. This supports the intramolecular mechanism as neighbouring group participation is not possible in the *m*- and *p*-compounds.

Standard texts in practical organic chemistry (e.g.[15,16]) indicate that hydroxybenzoic acids can be converted to the hydroxybenzamides by successive treatment with thionyl chloride and ammonia. The procedure was successful with salicylic acid (60%), and *m*-hydroxybenzoic acid (40%), but *p*-hydroxybenzoic acid gave mainly ammonium 3-chloro-4-hydroxybenzoate. Previous workers[17,18] showed that the conversion of hydroxybenzoic acids to amides is complex yielding several by products, but that excellent yields can be obtained by acetylation of the hydroxyl group. By this route *p*-acetoxybenzamide was prepared (90%). Salicyclic acid gives a reasonable yield of the amide by the standard procedure, probably because the hydroxyl group is protected by intramolecular hydrogen bonding with the carbonyl group.

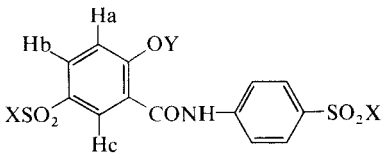
N,O-Diacetylsalicylamide was prepared (54%) by treatment of the N-acetyl derivative with acetic anhydride-pyridine, but direct acetylation (acetyl chloride-sodium acetate) of salicylamide was unsatisfactory (cf. Ref. 12).

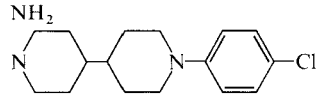
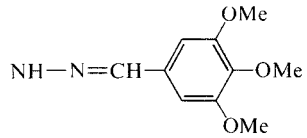
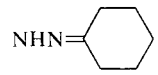
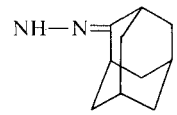
N-Acetylsalicylamide on chlorosulfonation gave the sulfonyl chloride (**58**) which was characterized as the amides (**59–61**) and azide (**62**). The relative lability of the O-acetyl derivatives was demonstrated on chlorosulfonation: N, O-diacetylsalicylamide gave the N-acetyl sulfonyl chloride (**58**); O-acetylsalicylamide gave a mixture of the O-acetyl- and N-acetyl- benzenesulfonyl chlorides; and aspirin gave 5-chlorosulfonylsalicylic acid (**11**). The O-deacetylation is a very interesting reaction, but we have not proposed a formal mechanism.

p-Hydroxybenzoic acid has been converted to the 3-sulfonyl chloride, which was characterized as the hydrazide and acetone hydrazone: the

TABLE II

Salicylanilide disulfonyl derivatives



No.	X	Y	m.p.	Formula	Found (%) C	H	N	S	Required (%) C	H	N	S
64	OH	H	103°	$C_{13}H_{11}NO_6S_2$	32.6	4.5	2.9	—	32.9	4.3	2.7	—
65	Cl	H	300°	$C_{13}H_9Cl_2NO_6S_2$	37.6	2.2	3.4	—	38.0	2.2	3.4	—
66	$NHCH_2Ph$	H	239°	$C_{27}H_{25}N_3O_6S_2$	58.4	4.3	7.4	11.7	58.8	4.6	7.6	11.6
67	$N(C_4H_9)_2$	H	159–160°	$C_{29}H_{45}N_3O_6S_2$	58.7	7.8	7.0	10.8	58.5	7.6	7.05	10.8
68	NMe_2	H	268°	$C_{17}H_{21}N_3O_6S_2$	47.5	4.8	9.7	14.8	47.8	4.9	9.8	15.0
69	NHPh	H	225°	$C_{25}H_{21}N_3O_6S_2$	57.1	3.9	7.7	12.7	57.4	4.0	8.0	12.3
70	NHNHPh	H	200°	$C_{25}H_{23}N_5O_6S_2$	54.2	4.1	12.3	11.6	54.2	4.2	12.6	11.6
71		H	>300°	$C_{21}H_{25}N_3O_8S_2$	49.3	4.9	8.4	—	49.3	4.9	8.2	—
72	NH_2	H	180°	$C_{13}H_{13}N_3O_6S_2$	41.6	3.6	11.1	16.9	42.0	3.5	11.3	17.3
73		H	>300°	$C_{33}H_{33}Cl_2N_5O_6S_2$	54.2	4.6	9.5	—	54.3	4.6	9.6	—
74	$NHNH_2$	H	182°	$C_{13}H_{15}N_5O_6S_2$	38.9	3.7	18.0	—	38.9	3.8	17.5	—
75	$NHN{=}CHC_6H_4NO_2$-*p*	H	190°	$C_{27}H_{21}N_7O_{10}S_2$ 1.5 H_2O	46.7	3.4	13.8	9.3	46.7	3.5	14.1	9.2
76	$NHN{=}CHC_6H_4OMe$-*p*	H	191°	$C_{29}H_{27}N_5O_8S_2$ 2 H_2O	51.6	4.3	10.4	9.8	51.7	4.6	10.4	9.5
77	$NHN{=}CHC_6H_4NO_2$-*o*	H	225°	$C_{31}H_{25}N_7O_{10}S_2$	51.4	3.7	13.4	—	51.7	3.5	13.6	—
78		H	168°	$C_{33}H_{35}N_5O_{12}S_2$ 1 MeOH	51.8	5.0	8.9	—	51.7	5.0	8.9	—
79	$NH{-}N{=}CHC_{11}H_{23}$	H	181°	$C_{37}H_{59}N_5O_6S_2$	60.8	8.6	9.3	8.5	60.5	8.1	9.5	8.7
80		H	153°	$C_{25}H_{31}N_5O_6S_2$ 2 H_2O	50.1	5.6	11.6	10.9	50.2	5.9	11.7	10.7
81		H	191 192°	$C_{33}H_{39}N_5O_6S_2$ 1 $HCONMe_2$	58.4	6.5	11.3	—	58.5	6.3	11.4	—
82	Cl	Me	168°	$C_{14}H_{11}Cl_2NO_6S_3$	39.4	2.9	3.0	15.1	39.6	2.6	3.3	15.1
83	$NHNH_2$	Me	180°	$C_{14}H_{17}N_5O_6S_2$	40.4	4.2	16.5	15.3	40.5	4.1	16.8	15.4
84	$NHN{=}CHC_6H_4Cl$-*p*	Me	192°	$C_{28}H_{23}Cl_2N_5O_6S_2$ $\frac{1}{2}$ C_5H_5N	52.2	3.7	11.0	—	52.3	3.7	11.0	—
85	$(C_4H_9)_2N$	Me	147°	$C_{30}H_{47}N_3O_6S_2$	59.2	8.0	6.7	—	59.1	7.8	6.9	—

hydrazide did not undergo cyclisation in hot dioxan; this treatment was expected to cause intramolecular dehydration with consequent cyclisation.

Salicylanilide with chlorosulfonic acid (4 mols.) at 50° gave the 1,4′-disulfonic acid (**64**); with more chlorosulfonic acid (at least 6 mols.) the disulfonyl chloride (**65**) was obtained (84%); the latter was also prepared (91%) from the disulfonic acid with phosphorus pentachloride. Efforts to achieve selective sulfonation *para* to more electron-donating hydroxyl group were unsuccessful, which suggests that both aromatic rings have similar reactivity to the reagent. The disulfonyl chloride was charac-

terized as the amides (**66–73**), hydrazide (**74**) and hydrazones (**75–81**).

O-Methylsalicylanilide with chlorosulfonic acid (6 mols.) similarly gave the disulfonyl chloride (**82**) (87%) which was characterized as the hydrazide (**83**), *p*-chlorobenzaldehyde hydrazone (**84**) and the dibutylamide (**85**). 4′-Chlorosalicylanilide with chlorosulfonic acid (4 mols.) gave the sulfonyl chloride (**86**) (83%); this was converted into the derivatives (**87–89**). Chlorosulfonation of 4′-chloro-O-methylsalicylanilide similarly gave the sulfonyl chloride (**90**) which was characterized as the derivatives (**91–93**).

The i.r. spectra of the amidobenzenesulfonyl derivatives often showed two carbonyl stretching absorptions associated with the $CONH_2$ group in the ranges 1680–1660 and 1635–1610 cm^{-1} (cf. Ref. 19a). The compounds containing the O-acetyl group exhibited an appreciably higher carbonyl stretching absorption band in the range 1780–1735 cm^{-1} which was clearly distinguishable from the lower carbonyl absorptions associated with the *CO*OH or *CO*NH groups.[19b]

The n.m.r. spectra showed the deshielded SO_2NH protons as a broad singlet at low field within the range δ12.5–9.5 (cf. Ref. 20). In the aromatic sulfonohydrazones, the presence of electron-withdrawing substituents tended to move the resonance further downfield to δ12.5–11.0, whereas with electron-donating substituents and in the aliphatic sulfonohydrazones the signal appeared at $\simeq\delta$9.5. In contrast, the N=C*H* signal in the aromatic hydrazones was little affected by the nature of the substituents and always appeared within the range δ8.0–7.5. The aromatic protons generally showed as a broad multiplet (δ8.5–7.0); however in the salicylanilide sulfonyl derivatives, the aromatic proton resonances exhibited a characteristic pattern. The protons Ha and Hb are *ortho*-coupled (J, 9 Hz) and also the proton Hb appears as a double doublet since it is also *meta*- coupled (J, 3 Hz) to the proton Hc. The protons of the anilide moiety appeared as a sharp singlet (δ7.75–7.6).

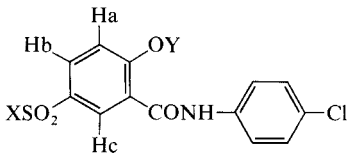
The mass spectra of the various sulfonyl derivatives generally showed the molecular ions and fragment ions corresponding to nitrogen-sulfur bond cleavage with base peaks representing the parent aromatic compounds.

Salicylanilide 1,4′-disulfonyl chloride (Table II, **65**) and the diamides showed the molecular ions, but the corresponding dihydrazide (**74**), hydrazones and the phenylhydrazide (**70**) failed to give satisfactory mass spectra by either chemical ionization or electron impact. The total observed ion current was low with respect to the amount of sample and the ions had low masses. A graph of total ion current against time showed a sharp peak instead of the usual gradual hump as the temperature of the probe was increased, suggesting explosive decomposition.

Studies of 20 electron impact mass spectra of the disulfonohydrazide (**74**) using source temperatures varying between 100 and 260° and probe temperatures of 60–400° showed that with a large sample and a source temperature of 200° and a probe temperature of 250 or 275°, a fragment ion of mass 371 (M—NH=NH) was sometimes observed.

The salicylic acid sulfonyl derivatives were tested against two species of freshwater algae:

TABLE III



No.	X	Y	m.p.	Formula	Found (%) C	H	N	S	Cl	Required (%) C	H	N	S	Cl
86	Cl	H	121°	$C_{13}H_9Cl_2NO_4S$	45.0	2.6	4.0	9.1	—	45.1	2.6	4.0	9.2	—
87	$N(C_4H_9)_2$	H	142–143°	$C_{21}H_{27}ClN_2O_4S$	57.6	6.5	6.4	—	—	57.5	6.2	6.4	—	—
88	$NHNH_2$	H	145°	$C_{13}H_{12}ClN_3O_4S$	45.7	3.6	12.0	9.9	10.5	45.7	3.5	12.3	9.4	10.4
89	$NHN{=}CHC_6H_4Cl$-*p*	H	232°	$C_{20}H_{15}Cl_2N_3O_4S$	52.0	3.3	9.2	7.2	15.3	51.7	3.3	9.1	6.9	15.3
90	Cl	Me	135°	$C_{14}H_{11}Cl_2NO_4S$	46.4	3.0	3.8	—	—	46.7	3.1	3.9	—	—
91	$NHNH_2$	Me	150°	$C_{14}H_{14}ClN_3O_4S$	47.2	4.0	11.6	9.1	10.1	47.3	4.0	11.8	9.0	10.0
92	$NHN{=}CHC_6H_4Cl$-*p*	Me	233°	$C_{21}H_{17}Cl_2N_3O_4S$	52.8	3.6	8.8	6.9	15.0	52.7	3.6	8.8	6.7	14.8
93	$N(C_4H_9)_2$	Me	163°	$C_{22}H_{29}ClN_2O_4S$	58.1	6.1	6.1	—	—	58.3	6.4	6.2	—	—

Chlorella fusca and *Anabaena variabilis;* and the bacteria *Escherichia coli* (gram $(-)^{Ve}$ species) and *Staphylococcus aureus* (gram $(+)^{Ve}$ species). The compounds generally showed little algaecidal activity, indeed they often caused an initial enhancement of algal growth followed by slight inhibition, e.g. the acetamido-azide (Table I, **62**) at 1 mg/l after 10 days caused 50% stimulation in the growth of *C. fusca*, but after 19 days resulted in 15% inhibition. The 2,4-dichlorosulfonamide (**15**) at 10 mg/l after 7 days gave 100% stimulation of growth and after 19 days 30% inhibition. In the antibacterial tests the majority of compounds were inactive. The most active were the N-acetamido 2,4-dichlorosulfonamide (**59**) and the corresponding O-acetyl derivative (**37**) which gave 50% inhibition of *E. coli* and 67% inhibition of *S. aureus* at 100 mg/l.

EXPERIMENTAL

I.r. spectra were determined as Nujol mulls using a Perkin Elmer 237 spectrophotometer. N.m.r. spectra were measured with a Varian HA 100 spectrometer using tetramethylsilane as internal standard. Mass spectra were determined with an AEI MS9 spectrometer at 70 eV. Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. T.l.c. was carried out on silica gel G plates developed with iodine vapour. High performance liquid chromatography (h.p.l.c.) was carried out with a stainless steel column (150 × 5 mm) with Spherisorb detector and a chart speed of 15 cm/h. Microanalyses were carried out by the Butterworth Microanalytical Consultancy Limited, Teddington, England.

The following preparative details are representative examples for the different types of sulfonyl derivatives described.

3-Amido-4-Methoxybenzenesulfonyl Chloride (**1**)

o-Methoxybenzamide (14g) was added portionwise to chlorosulfonic acid (4 mol. equivs.) in tetrahydrofuran (20 ml) at 0°. The solution was warmed at 50° for 30 min. and poured onto ice to give the *sulfonyl chloride* (19.8g, 86%). ν_{max} 3480 (NH_2), 1685 (CO), 1580, 1490 (arom C—H), 1380, 1170 (SO_2), 1260, 1030 (C—O—C) cm^{-1}. Ms showed the molecular ion (M^+, 251, 249) and a fragment ion at 150 (2-Methoxybenzamide). N.m.r. ($(CD_3)_2SO$) δ7.59–8.50 m (3 ArH), 7.2 br s (2H, $CONH_2$), 4.0 s (3H, CH_3). The signal at δ7.2 was removed by D_2O treatment.

3-Amido-4-Methoxybenzenesulfonohydrazine (**3**)

The sulfonyl chloride (**1**) (6g) was reacted with hydrazine hydrate (2.2 mol. equiv.) in tetrahydrofuran (25 ml) at 0° and left at room temperature for 12 h. Addition of ice-water (150 ml) gave the *hydrazide* (5g, 86%). ν_{max} 3550 (NH_2) 3450 (NH), 1650 (CO), 1580, 1490 (arom C—H), 1380, 1170 (SO_2), 1260, 1030 (C—O—C) cm^{-1}. Ms gave the molecular ion (M^+, 245) and fragment ions at 214 (M—$NHNH_2$), 150 (2-methoxybenzamide). The acetone hydrazone (**9**) showed M^+(285), 214 (M—NHN=CMe_2), 200, and 150.

2-Hydroxy-5-(N-Phenyl) Sulfonamidobenzoic Acid (**12**).

This was obtained (49%) by reaction of 2-hydroxy-5-chlorosulfonylbenzoic acid (**11**) with aniline (1 mol. equiv.) in boiling benzene as previously described.[10] The yield was improved (78%) by using more aniline (2 mols.). The other aromatic amides (13–15) were similarly prepared, but the method was unsuccessful with aliphatic amines.

2-Hydroxy-5-N-(cyclohexyl)sulfonoamidobenzoic Acid (**16**)

2-Hydroxy-5-chlorosulfonylbenzoic acid (5g) was reacted with cyclohexylamine (6.3g; 3 mol. equivs.) and triethylamine (21.3g, 10 mol. equivs.) in tetrahydrofuran (50 ml) at room temperature for 24 h. Triethylamine hydrochloride was filtered off and evaporated under reduced pressure. The residue was acidified (dilute HCl) and the oil extracted with ether. Evaporation gave a solid which was recrystallised from aq. ethanol to give the *N-cyclohexylsulfonamide* (16) (40%). ν_{max} 3350 (NH), 1695 (CO), 1340, 1160 (SO_2) cm^{-1}. N.m.r. ($(CD_3)_2CO$) δ10.6 s (2H, CO_2H, OH) 7.05–8.40 m (3 ArH), 1.50 m (11 cyclohexyl H). The NH signal was not located.

Acetylation of the sulfonamides (**12–14**) was carried out by heating the sulfonamides (2g) with acetic anhydride (10 ml) and concentrated sulfuric acid (3 drops) on a stream-bath for 15 min. Dilution with ice-water (150 ml) and crystallisation (ethyl acetate) afforded the corresponding N,O-diacetyl derivatives (**17–19**). Attempted acetylation of the N-cyclohexylsulfonamide (**16**) only gave a brown gum.

17 (98%), ν_{max} 1770 ($OCOCH_3$), 1730 (N-$COCH_3$), 1695 ($COOH$), 1360, 1170 (SO_2) cm^{-1}.

18 (31%), ν_{max} 1775 ($OCOCH_3$), 1720 ($NCOCH_3$), 1770 ($COOH$), 1360, 1180 (SO_2) cm^{-1}.

19 (83%), ν_{max} 1780 (O.$COCH_3$), 1730 ($NCOCH_3$), 1710 ($COOH$), 1360, 1160 (SO_2) cm^{-1}. In all cases no N—H stretching bands at ≃3300 cm were observed.

In contrast, when acetylation of the amides was carried out with less acetic anhydride (1 mol. equiv.) with concetrated sulfuric acid (2 drops) the corresponding O-acetylsulfonamides (**35–38**) were obtained.

2-Hydroxy-5-(sulfonylazido)benzoic Acid (**20**)

2-Hydroxy-5-chlorosulfonylbenzoic acid (**11**) was reacted with sodium azide as described by Cremlyn[9] to give the azide (87%), ν_{max} 2120 (N_3), 1665 (CO), 1365, 1170 (SO_2) cm^{-1}. Heating the azide (**20**) (2g) with acetic anydride (10 ml)-concentrated sulfuric acid (3 drops) on the steam-bath for 15 min. gave the *2-acetoxy azide* (**21**) (2.1g, 91%) as needles from toluene. ν_{max} 2120 (N_3), 1785 ($OCOCH_3$), 1695 ($COOH$), 1370, 1180 (SO_2) cm^{-1}. N.m.r. ($(CD_3)_2SO$) δ7.60–8.40 m (3 ArH), 2.30 s (3H, CH_3).

Reaction of the Azide (*20*) *with Triphenylphosphine*

The azide (2g) was boiled with triphenylphosphine (2.1g) in dry ether (40 ml) for 30 min. Cooling gave the *triphenyliminophosphorane* (**22**) as a pale yellow powder (1.8g). ν_{max} 1680 (CO), 1360 (SO_2) cm^{-1} (no azide band at ≃2100 cm^{-1}). N.m.r. ($(CD_3)_2SO$) δ7.1–8.25 m (18 ArH). The acetoxy-azide (**21**) also reacted with triphenylphosphine to give the *imino-phosphorane* (23) (17%), ν_{max} 1770 ($OCOCH_3$), 1720 ($COOH$), 1365 (SO_2) cm^{-1}. N.m.r. ($(CD_3)_2SO$) δ7.1–7.9 m (18 ArH), 2.25 s (3H, CH_3).

O-Acetylsalicylamide

Salicylamide (8.2 g) was reacted with acetic anhydride (20 ml)- pyridine 5 ml) as previously described[11] to give O-acetylsalicylamide as plates (92%), m.p. 144–145° (lit.[11] 145°). (Found: C, 60.1; H, 5.1; N, 7.8. Calc. for $C_9H_9NO_3$: C, 60.3; H, 5.0; N, 7.8%). ν_{max} 3400, 3190 (NH), 1745 ($OCOCH_3$), 1680 ($CONH_2$) cm^{-1}. N.m.r. ($CDCl_3$) δ7.10–7.90 m (4ArH), 6.10 s (2H, $CONH_2$), 2.38 s (3H, $COCH_3$). The signal at δ2.38 was removed by D_2O treatment. T.l.c. (Me_2CO-Et_2O 1:9) gave a single spot, R_F 0.41) and the product gave a $(-)^{Ve}$ ferric chloride test.

O-Acetylsalicylamide was also obtained (67%) by acetylation of salicylamide using acetic anhydride-concentrated sulfuric acid (3 drops).

N-Acetylsalicylamide

Salicylamide (14g) was boiled with acetyl chloride (25 ml)–acetic acid (25 ml) for 20 min. to give N-acetylsalicylamide (50%), m.p. 147° (lit.[12] 146°). (Found: C, 60.3; H, 5.2; N, 7.7. Calc. for $C_9H_9NO_3$: C, 60.3; H, 5.0; N, 7.8%). ν_{max} 3270 (NH), 3200–2800 br (OH), 1720 ($NCOCH_3$), 1650 (CONH). N.m.r. ($CDCl_3$) δ7.20–7.81 m (4ArH), 6.10 s (1H, CONH), 2.63 s (3H, $COCH_3$), T.l.c. (Me_2CO-Et_2O 1:9) showed a single spot, R_F 0.81, and the product gave a $(+)^{Ve}$ ferric chloride test.

N-Acetylsalicylamide was best obtained (95%) by boiling the O-acetyl derivative with methanol (10% w/v) for 3 h. It was also prepared (85%) by heating the O-acetyl derivative at 120° for 2 h (cf. Ref. 14).

Attempted Preparation of N-Acetylsalicylamide

Salicylamide (**1**) (20g) was boiled under reflux with acetic anhydride (50 ml)-concentrated sulfuric acid (10 drops) at 120° for 3 h. Cooling and shaking with ether gave a reddish-brown solid which was crystallised (benzene-ethyl acetate) to give an unknown product (12g), m.p. 193°. (Found: C, 66.3; H, 4.6; N, 7.6. Calc. for N-Acetylsalicylamide $C_9H_9NO_3$: C, 60.3; H, 5.0; N, 7.8%). The suggested structure (**11**) (see discussion p. 157), $C_{20}H_{16}N_2O_5$ requires: C, 65.9; H, 4.4; N, 7.7%. The product gave a $(-)^{Ve}$ ferric chloride test. Molecular mass = 364 M.s. showed an ion of mass 364 and major fragment ions at 321 ($M-CH_3CO$), 303 ($M-CH_3CO-H_2O$), 121, 77 (C_6H_5). ν_{max} 1760 ($OCOCH_3$), 1680 (CON—) cm^{-1}. N.m.r. ($CDCl_3$) δ8.20–7.21 m (8ArH), 5.20 q (2H, C=CH_2), 4.72 s (1H, OH ?), 2.64 s (3H, CH_3CON), 2.34 s (3H, CH_3COO). The signal at δ4.72 was removed by D_2 treatment.

Examination of the Conversion of O-Acetylsalicylamide to N-Acetylsalicylamide

O-Acetylsalicylamide (0.5g) was boiled under reflux with methanol (50 ml) and samples were removed at ½ h intervals and analysed by high pressure liquid chromatography (h.p.l.c.). A small peak corresponding to the N-acetyl derivative appeared after ½ h and after 2 h the conversion was practically complete as shown below:

Time (h)	% N-Acetyl derivative
0	0
0.5	21
1.0	73
1.5	99
2.0	100

N,O-Diacetylsalicylamide

N-Acetylsalicylamide (14g) in pyridine (40 ml) was treated with acetic anhydride (14 ml) at 0°. After 2½ h at room temperature, pyridine was evaporated under reduced pressure and the oil extracted with ether (100 ml). The extract was washed with dilute HCl (2 × 40 ml), dried ($MgSO_4$), and evaporated to give the N,O-diacetyl derivative (9.4g, 54%), m.p. 63–64° (lit.[13] 68°). (Found: C, 59.7; H, 5.0; N, 6.4. Calc. for $C_{11}H_{11}NO_4$: C, 59.7; H, 5.0; N, 6.3%). ν_{max} 3280 (NH), 1765, 1735 ($COCH_3$), 1680 (CONH) cm^{-1}. N.m.r. ($CDCl_3$) δ8.90 b r s (1H, CONH), 7.11–7.80 m (4ArH), 2.48 s (3H, CH_3CON), 2.30 s (3H, CH_3COO). The signal at δ8.90 was removed by D_2O treatment. Ms showed the molecular ion (M^+, 221) with major fragment ions at 178 ($M-CH_3CO$), 135 ($M-2CH_3CO$) and 119. T.l.c. (Me_2CO-Et_2O 1:9) showed a single spot, R_F 0.85 and the product gave a $(-)^{Ve}$ ferric chloride test.

N,O-Diacetylsalicylamide was also prepared in very poor yield (≃1%) by reaction of salicylamide with acetyl chloride-anhydrous sodium acetate (cf. Ref. 13).

3N-Acetamido-4-Hydroxybenzenesulfonyl Chloride (**58**)

N-Acetylsalicylamide (5.6 g) was heated with chlorosulfonic acid (9 ml; 4 mol. equivs.) at 60° for 2 h. to give the *sulfonyl chloride* (6.0g, 69%). ν_{max} 3460 (NH), 3200–2300 br (OH), 1730 ($COCH_3$), 1660 (CONH), 1370, 1170 (SO_2) cm^{-1}. N.m.r. ($CDCl_3$) δ10.80 br s (1H, OH), 8.90 br s (1H, CONH), 7.10–7.80 m (3ArH), 2.48 s (3H, CH_3CON). The signals at δ10.80 and 8.90 were removed by D_2O treatment. T.l.c. ($Pr^iOH-C_6H_5CH_3$-EtOAc—H_2O 5:1:2.5:1.25) showed a single spot, R_F 0.75.

This product also resulted (50%) from attempted chlorosulfonation of N,O-diacetylsalicylamide.

3N-Acetamido-4-Hydroxybenzenesulfonyl Azide (**62**)

This was obtained (89%) from the sulfonyl chloride (58) by reaction with sodium azide. ν_{max} 3450, 3260 (NH), 3250–3100 (OH), 2140 (N_3), 1680, 1625 (CO), 1590 (arom C=C), 1365, 1180 (SO_2) cm^{-1}.

Chlorosulfonation of O-Acetylsalicylamide

O-Acetylsalicylamide (5.6g) was warmed with chlorosulfonic acid (8.9 ml, 4 mol. equivs.) at 50–60° for 2 h. Recrystallisation (petroleum ether 60–80°) gave a mixture of O-acetyl and N-acetyl-benzenesulfonyl chlorides (5.6g), m.p. 144–160°. ν_{max} 3500, 3250 (NH), 3350–3150 (OH), 1750 (CH_3COO), 1680, 1630 (CONH), 1590 (arom C=C), 1390, 1330, 1195 (SO_2) cm^{-1}. T.l.c. ($Pr^iOH-C_6H_5CH_3$-EtOAc—H_2O 5:1:2.5:1.25) showed two spots, R_F 0.60, 0.77 corresponding to O- and N-acetyl derivatives respectively. The product showed a $(+)^{Ve}$ ferric chloride test.

Attempted Chlorosulfonation of O-Acetylsalicylic Acid

O-Acetylsalicyclic acid with chlorosulfonic acid (4 mol. equivs.) at room temperature for 2 h gave 5-chlorosulfonylsalicylic acid (**11**) (51%), m.p. 165–166° (m.m.p. with an authentic sample 164–167°) (lit.[9] 164–166°). ν_{max} 3500–2500 (OH), 1675 (CO), 1610, 1580 (arom C=C), 1380, 1180 (SO_2) cm^{-1}. The product gave a $(+)^{Ve}$ ferric chloride test.

2-Acetoxy-5-Chlorosulfonylbenzoic Acid (**34**)

5-Chlorosulfonylsalicylic acid (**11**) (1.5g) was heated with acetic anhydride (10 ml)-concentrated sulfuric acid (2 drops) at 50–60° for 15 min. Dilution with ice-water and recrystallisation (aq. acetic acid) gave the *acetoxy-sulfonyl chloride* (1.6g, 91%). ν_{max} 3100–2500 (OH), 1780 ($OCOCH_3$), 1700 (*C*OOH), 1600 (arom C=C), 1365, 1170 (SO_2) cm^{-1}. The product gave a $(-)^{Ve}$ ferric chloride test.

m-Acetoxybenzamide

m-Hydroxybenzoic acid (10g) was boiled with thionyl chloride (15 ml; 3 mol. equivs.) for 4 h. Treatment of the residual oil with ammonium hydroxide (15 ml of 0.88) at 0° and acidification (concentrated HCl) gave *m*-hydroxybenzamide (4g, 40%), m.p. 169° (lit.[21] 170.5°). ν_{max} 3400, 3250 (NH_2), 3300–3150 (OH), 1650 ($CONH_2$), 1615, 1580 (arom C=C) cm^{-1}. Treatment with acetic anhydride (16 ml)-pyridine (4 ml) at 0° for 4 h gave *m*-acetoxybenzamide (1.1 g, 58%), m.p. 139–140. (Found: C, 60.4; H, 5.2; N, 7.9. $C_9H_9NO_3$ requires: C, 60.3; H, 5.0; N, 7.8%). ν_{max} 3400, 3190 (NH_2), 1765 (CH_3COO), 1650 ($CONH_2$), 1585 (arom C=C), cm^{-1}. The product gave a $(-)^{Ve}$ ferric chloride test.

Stability of m-Acetoxybenzamide in Ethanol

When *m*-acetoxybenzamide was boiled with ethanol (10% w/v) for 1 h, the compound was recovered (98%) unchanged (cf. the behaviour of O-acetylsalicylamide (p. 159).

Attempted Preparation of p-Hydroxybenzamide

p-Hydroxybenzoic acid (30g) was boiled with thionyl chloride (135 ml) for 3 h. Acidification gave an unknown product (35g) m.p. >300° (lit.[16] m.p. of *p*-hydroxybenzamide 162°). Sodium fusion was $(+)^{Ve}$ for Cl and ammonia was evolved with cold NaOH indicating an ammonium salt. ν_{max} 3700–3000 br ($\overset{+}{N}H_3$), 3200–2800 (OH), 1740 (CO), 1580 (arom C=C) cm^{-1}. (Found: C, 42.6; H, 4.6; N, 7.4; Cl, 17.4. *Ammonium 3-chloro-4-hydroxybenzoate*, $C_7H_8ClNO_3 \frac{1}{2}H_2O$ requires: C, 42.3; H, 4.6; N, 7.4; Cl, 17.8%).

p-Acetoxybenzamide

p-Hydroxybenzoic acid (50g) was acetylated (acetic anhydride-concentrated sulfuric acid) to give *p*-acetoxybenzoic acid (90%), m.p. 183° (lit.[18] 181°). (Found: C, 60.2; H, 4.5. Calc. for $C_9H_8O_4$: C, 60.0, H, 4.4.).

p-Acetoxybenzoic acid (10g) was boiled with thionyl chloride (8 ml; 2 mol. equivs.) and the product reacted with ammonia as previously described[18] to give *p*-acetoxybenzamide (90%), m.p. 181° (lit.[18] 181°). (Found: C, 60.2; H, 5.0; N, 7.8. Calc. for $C_9H_9NO_3$: C, 60.3; H, 5.0; N, 7.9%). ν_{max} 3400, 3192 (NH_2), 1760 ($OCOCH_3$), 1650 ($CONH_2$). N.m.r. ($CDCl_3$) δ7.0–8.20 m (4 ArH), 4.40 s (2H, $CONH_2$), 2.32 s (3H, $COCH_3$). D_2O treatment removed the signal at δ4.40.

Stability of p-Acetoxybenzamide in Methanol

When *p*-acetoxybenzamide was boiled with methanol (10% w/v) for 3 h, the starting material (92%) was recovered (cf. the behaviour of O-acetylsalicylamide p. 159).

3-Chlorosulfonyl-4-Hydroxybenzoic Acid

p-Hydroxybenzoic acid (10g) was heated with chlorosulfonic acid (24 ml, 5 mol. equivs.) at 65° for 4 h. The solution was poured onto crushed ice (100g) to give the *sulfonyl chloride* (10.2g, 60%), m.p. 159–162°. (Found: C, 35.0; H, 2.4; Cl, 14.5; S, 13.8. $C_7H_5ClO_5S$ requires: C, 35.2; H, 2.1; Cl, 14.8; S, 13.6%). ν_{max} 3540, 3200–2800 (OH), 1715 (*C*OOH), 1370, 1170, (SO_2) cm^{-1}.

3-Hydrazinosulfonyl-4-Hydroxybenzoic Acid

3-Chlorosulfonyl-4-hydroxybenzoic acid (5g) was treated with hydrazine hydrate (4 ml, 4 mol. equivs.) in ethanol (20 ml) at 0°. After 12 h at room temperature, ethanol was decanted off and the oily solid freeze dried to give a hygroscopic solid. (Found: C, 24.4; H, 5.4; N, 25.2; S, 9.9, there was no Cl). This appeared to be the dihydrazinium salt of the sulfonohydrazide, $C_7H_{16}N_6O_5S$ requires: C, 28.4; H, 5.4; N, 28.4; S, 10.8%. The product (4g) was acidified (concentrated HCl) to pH4 and left at 5° for 3 days to give the *3-sulfonohydrazide* (2.3 g), m.p. 218°. (Found: C, 36.0; H, 3.7; N, 12.1; S, 13.5. $C_7H_8N_2O_5S$ requires: C, 36.2; H, 3.5; N, 12.1; S, 13.8%). ν_{max} 3340 (NH_2), 3300 (NH), 3200–2600 (OH), 1700 (*C*OOH), 1370, 1175 (SO_2) cm^{-1}. This was characterized as the *acetone hydrazone* (65%), m.p. 256°. (Found: C, 43.9; H, 4.5; N, 10.6. $C_{10}H_{13}N_2O_5S$ requires: C, 44.1; H, 4.7; N, 10.3%). ν_{max} 3300 (NH), 3200–2600 (OH), 1690 (*C*OOH), 1370, 1170 (SO_2) cm^{-1}. Ms. did not show the molecular ion (M^+, 273), the highest fragment ion was 256, there were also intense ions at 135 ($SO_2NHN = CMe_2$) and 71 ($NHN^+ = CMe_2$).

Attempted Cyclisation of 3-Hydrazinosulfonyl-4-Hydroxybenzoic Acid

3-Hydrazinosulfonyl-4-hydroxybenzoic acid (0.5g) was boiled under reflux with dioxan (20 ml) for 8 h. Evaporation and trituration with ethanol gave the unchanged hydrazide (0.4g), m.p. 218° (m.m.p. with the authentic hydrazide 218–219°). (Found: C, 36.3; H, 3.8; N, 12.0; S, 13.4. The hydrazide, $C_7H_8N_2O_5S$ requires: C, 36.2; H, 3.5; N, 12.1; S, 13.8%).

Salicylanilide-1,4'-Disulfonic Acid (**64**)

Salicylanilide (10g) was heated with chlorosulfonic acid (22g, 4 mol. equivs.) at 50° for 2 h to give the *disulfonic acid hexahydrate* (from concentrated hydrochloric acid (14.2 g, 63%) and the solid was dried *in vacuo* (50°, P_2O_5). N.m.r. ($(CD_3)_2SO$) δ13.95 s (1H, OH), 10.6 s (1H, CON*H*), 8.3 d J 2.5 Hz (1H, Hc), 7.75 m (5H, 1H Hb, 4 anilino H), 7.1 d J 8.5 Hz (1H, Ha). D_2O treatment removed signals at δ13.95, 10.6.

Salicylanilide-1,4'-Disulfonyl Chloride (**65**)

Salicylanilide (10g) was reacted with chlorosulfonic acid (50 ml) at 0° for 7 h to give the *disulfonyl chloride* (16.2g, 84%). M.s. showed the molecular ion (M^+, 410) and ions at 374 (M—Cl), 192 $(NH_2C_6H_4SO_2Cl)^+$, 156 $(NH_2C_6H_4SO_2)^+$. The disulfonyl chloride was also prepared (91%) be heating the disulfonic acid (64) with phosphorus pentachloride (3 mol. equivs.) at 50° for 1 h.

Salicylanilide-1,4'-Dibenzylsulfonamide (**66**)

The disulfonyl chloride (**65**) (3g) was reacted with benzylamine (4.25g; 5.2 mol. equivs.) in tetrahydrofuran (20 ml) at room

temperature for 2 h. Benzylamine hydrochloride was filtered off and the filtrate concentrated and acidified (dil. HCl) to pH6. The precipitate (3.4g) was recrystallised (EtOH) to give the *dibenzylsulfonamide* (2g, 70%). ν_{max} 3300, 3250 (NH), 1642 (CO), 1350, 1160 (SO_2) cm^{-1}. N.m.r. ($(CD_3)_2SO$) δ13.9 (1H, O*H*), 10.75 s (1H, CONH), 8.3 d J 2.5Hz (1H, Hc), 8.15 d, J 7Hz (2H, 2 × SO_2NH), 8.0–7.7 m (5H, 1Hb, anilino H), 7.3 s (10H, 2 × $C_6H_5CH_2$), 7.2 d J 8.5Hz (1H, Ha), 4.05 d J, 7Hz (4H, 2NHCH_2). Treatment with D_2O removed the signals at δ13.9; 10.75 and 8.15. Ms. (chemical ionization) showed the molecular ion ($M^+ + 1$, 552). T.l.c. ($CHCl_3$-MeOH 10:1) showed a single spot, R_F 0.30.

The other amides (67–69, 72, 73) also showed ions corresponding to M + 1 in their mass spectra by chemical ionization.

Salicylanilide-1,4'-Disulfonohydrazide (**74**)

The disulfonyl chloride (65) (10g) was reacted with hydrazine hydrate (6.6g of 9.8%; 5 mol. equivs.) in methanol (15 ml) at room temperature for ½ h. Water (50 ml) was added and the solution acidified (concentrated HCl) to pH6. After 1 h at 0°, the precipitate was collected, washed with water, methanol, and ether to give the *disulfonohydrazide* (7.4 g, 76%). ν_{max} 3300, 3260, 3180 (NH), 1678 (CO), 1340, 1155 (SO_2) cm^{-1}. Ms. showed fragment ions at 371 (M—NH=NH), 354, 324, 307, 292, 277, 245, 217, 200, 173, 125, 93, 79, 74, 64 (SO_2).

The *p-Nitrobenzaldehyde hydrazone* (**75**). ν_{max} 3320, 3190 (NH), 1675 (CO), 1340, 1167 (SO_2) cm^{-1}. N.m.r. ($(CD_3)_2SO$) δ13.9 s (1H, OH) 1075 s (1H, CONH), 8.3 d J 2.5 Hz (1H, Hc), 8.2–7.7 m (15H, 13ArH, 2 × N=C*H*), 7.2 d J 9Hz (1H, Ha), 3.51 s (2H, 2 × SO_2NH). Treatment with D_2O removed the signals at δ13.9, 10.75 and 3.51. T.l.c. ($CHCl_3$-MeOH 10:1) gave one spot, R_F 0.25.

Attempted Preparation of the p-Chlorobenzaldehyde Hydrazone

Only 1 mol. of the aldehyde condensed with the disulfonohydrazide (**74**) to give the *monohydrazone* m.p. 222–223°. (Found: C, 46.1; H, 3.4; N, 13.0; Cl, 6.9; S, 12.5. $C_{20}H_{18}ClN_5O_6S_2$ requires: C, 45.9; H, 3.5; N, 13.4; Cl, 6.8; S, 12.2%). ν_{max} 3560 (HN_2), 3310, 3190 (NH), 1610 (CO), 1350, 1168 (SO_2) cm^{-1}. N.m.r. ($(CD_3)_2SO$) δ13.95 s (1H, OH), 10.8 s (1H, CONH), 8.35 d J 3Hz (1H, Hc), 8.20–7.31 m (10H, 9ArH, 1N=C*H*), 7.20 d J 9Hz (1*H*, Ha), 5.2 s (4H, 2SO_2NH, NH_2). Treatment with D_2O removed the signals at δ13.95, 10.8 and 5.2. T.l.c. ($CHCl_3$-MeOH 10:1) showed a single spot, R_F 0.50.

O-Methylsalicylanilide-1,4'-Disulfonyl chloride (**82**)

O-Methylsalicylanilide (10 g) was reacted with chlorosulfonic acid (50 ml) at room temperature for 7 h to give the *disulfonyl chloride* (87%). ν_{max} 3440 (NH), 1684 (CO), 1375, 1169 (SO_2) cm^{-1}. N.m.r. ($(CD_3)_2SO$) δ13.95 s (1H, OH), 10.2 s (1H, CONH), 7.9 d J 3Hz (1H, Hc), 7.85–7.50 m (5ArH), 7.2 d J 9Hz (1H, Hb), 3.95 s (3H, CH_3). The signals at δ13.95, and 10.2 were removed by D_2O treatment.

4'-Chlorosalicylanilidesulfonyl Chloride (**86**)

4'-chlorosalicylanilide with chlorosulfonic acid (4 mol. equivs.) at room temperature (5 h) gave the *sulfonyl chloride* (83%), ν_{max} 3400 (NH), 1650 (CO), 1360, 1172 (SO_2) cm^{-1}. N.m.r. ($(CD_3)_2SO$) δ13.9 s (1H, OH), 10.55 s (1H, CONH), 8.31 d J 3 Hz (1H, Hc), 7.68 d J 9 Hz (1H, Hb), 7.60 d (4H, anilino H), 7.0 d, J 9Hz (1H, Ha). D_2O treatment removed the signals at δ13.9 and 10.55.

REFERENCES

1. L. Weinstein, *Sulfonamides* in *The Pharmacological Basis of Therapeutics*, L. S. Goodman and A. Goodman (Eds.) (Macmillan, New York 1975), 5th ed., p. 1113.
2. R. J. Cremlyn, *Int. J. Sulfur Chem.*, **8** (1), 133 (1973).
3. R. J. Cremlyn, *J. Chem. Soc.*, 1132 (1965).
4. R. J. Cremlyn, *J. Chem. Soc.* (C), 77 (1967).
5. R. J. Cremlyn, *J. Chem. Soc.* (C), 1341 (1969).
6. R. J. Cremlyn, *Pesticides: Preparation and Mode of Action* (Wiley, Chichester 1978), p. 117.
7. A. Berger, *Medicinal Chemistry* (Wiley, New York 1970), 3rd ed., p. 958.
8. J. Stewart, *J. Chem. Soc.* **121**, 2555 (1922).
9. R. J. Cremlyn, *J. Chem. Soc.*, 11 (1968).
10. A. M. Islam, I. B. Hannout and M. M. Atwa, *Egypt. J. Chem.*, **17**, 689 (1974); *Chem. Abstr.*, **86**, 171047a (1977).
11. J. McConnan and A. Titherley, *J. Chem. Soc.*, **89**, 1318 (1906).
12. Belg. Patent 496,438 (1950); *Chem. Abstr.*, **49**, 11015i (1955).
13. A. Titherly and W. L. Hicks, *J. Chem. Soc.*, **99**, 869 (1911).
14. A. J. Gordon, *Tetrahedron*, **23** (2), 863 (1967).
15. A. I. Vogel, *A Text-Book of Practical Organic Chemistry*, (Longmans, London, 1966), 3rd ed., p. 791.
16. P. A. Claret, *Experimental Chemistry*, (Pitman Press, Bath, (1961), Pt. 3, p. 45.
17. F. Becke and J. Gnad, *Liebigs Ann. Chem.*, 713, 212 (1968).
18. H. Schoenenberger, J. H. Eckardt, and E. Bamann, *Arzeimittel-Forsch.*, **14** (4), 324 (1964); *Chem. Abstr.*, **61**, 9430b (1964).
19. L. J. Bellamy, *The Infra-Red Spectra of Complex Molecules*, (Methuen, London, 1964), 2nd ed., (a) p. 205, (b) p. 162.
20. L. M. Jackman and S. Sternhell, *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, Vol. 5 (Pergamon Press, Oxford, 1969), 2nd ed., p. 215.
21. J. R. A. Pollock and R. Stevens (Eds.), *Dictionary of Organic Compounds*, Vol. 3 (Eyre and Spottiswoode, London, 1965), 4th ed., p. 1652.