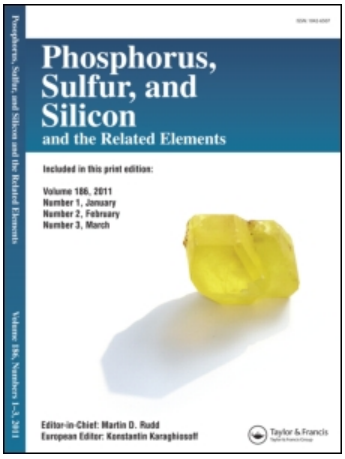

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SALICYLIC ACID SULFONYL DERIVATIVES AND RELATED COMPOUNDS

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SALICYLIC ACID SULFONYL DERIVATIVES AND RELATED COMPOUNDS

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Salicylic acid-5-sulfonohydrazide (**3**) has been condensed with β-dicarbonyl compounds to form pyrazoles (**5**). With ethyl acetoacetate, tri- and hexafluoropentane-2,4-dione the hydrazones (**4**) were obtained; although the former did cyclise in the presence of potassium carbonate-magnesium sulfate. With hexane-2,5-dione the pyrrole (**7**) was formed and not the pyridazine (**8**). Acylation of salicylic acid-5-and *p*-acetamidobenzene-sulfonohydrazides was examined; mono-acetates, benzoates and p-toleuenesulfonates and diacetates are described, but other pure diacyl derivatives could not be isolated.

Reaction with succinic and maleic anhydrides gave the corresponding amic acids (**9**, **10**), and their cylisation to pyridazines (**11**) was examined; only the maleamic acid (**10**)) was converted to the pyridazine (**11**). Maleic hydrazide (**14**) by condensation with *p*-acetamido-benzenesulfonyl chloride gave the O-sulfonyl pyridazine (**15**). 5-Chlorosalicylic acid-3-sulfonohydrazide (**18**) was prepared and characterized as the acetone and cyclohexanone hydrazones (**19**); but attempts to make aromatic hydrazones gave the azines (**20**). 5-Chlorosalicylic acid-3-sulfonyl azide (**21**) reacted with norbornene and triphenylphosphine to give the aziridine (**22**) and the phosphinimine (**23**).

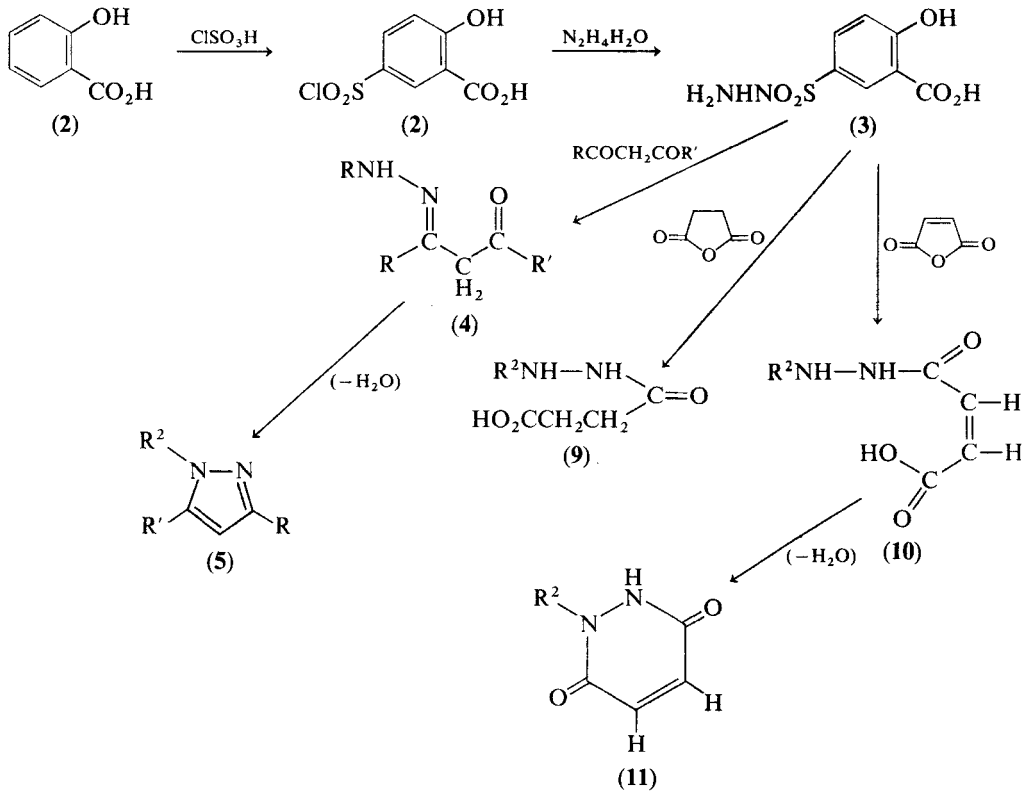
INTRODUCTION

Many sulfonyl compounds such as amides,[1] azides[2] and hydrazides[3–6] have valuable biocidal properties, for instance as antibacterials, nematicides and fungicides. Phenols are well-established biocides and have proved useful against bacteria, fungi, and insects.[7a] In addition, several salicylic acid derivatives, for example, aspirin, salicylates, and salicylamide are important bactericides, antipyretics, and analgesics.[8] Salicylanilide ("Shirlan") was also one of the earliest organic surface fungicides and 2-methylsalicylanilide ("Mebenil") is a valueable systemic fungicide against rust diseases on cereal and vegetable crops.[7b] Comparatively little work has been reported on the chemistry of salicylic acid sulfonyl derivatives and in view of the potential biological activity of these compounds, further work appeared justified. In a previous publication,[9] salicylic acid-5-sulfonyl chloride was converted into hydrazides, hydrazones, and azides for biological evaluation. The present paper examines the chemistry of salicylic acid-5-sulfonyl-pyrazoles, and some derivatives of 5-chlorosalicylic acid sulfonyl chloride. Certain pyrazoles have shown activity as analgesics, gastric secretion stimulants and sedatives.[10–11] so the combination of the salicylic acid group with the pyrazole moiety should lead to some potentially useful compounds.

p-Acetamidobenzenesulfonohydrazide has fungicidal activity[3] and the acylation of this compound has been studied. *p*-Acetamidobenzenesulfonyl chloride was also condensed with maleic hydrazide to give the O-(*p*-acetamidobenzenesulfonyl) derivative, a potential plant growth control agent (cf. Ref. 7c).

DISCUSSION

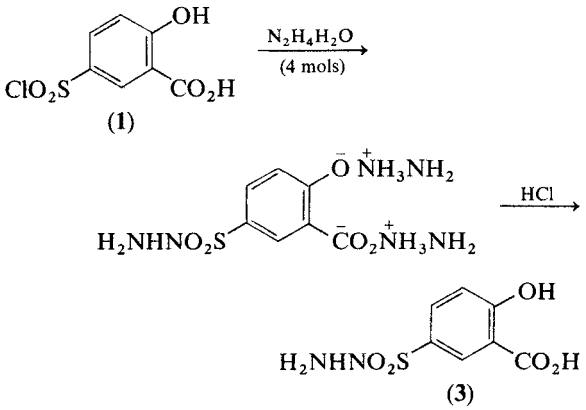
Salicyclic acid (**1**) (Scheme 1) was reacted with a large excess of chlorosulfonic acid to give the 5-sulfonyl chloride (**2**).[12–13] This was condensed with hydrazine (5 mols) using the procedure of Jaeken[14] to give the hydrazide (3) (82%). The yield of product by this method was much better than that obtained (15%) using less hydrazine (3 mols),[13]



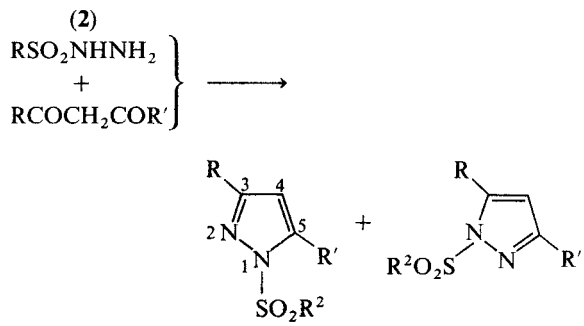
(R² = salicyclic acid-5-sulfonyl)

SCHEME 1

because at least 4 mols of hydrazine were needed since both the OH and CO_2H groups are involved in salt formation:

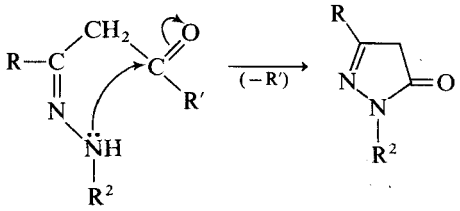


The product (m.p. 230°) reported by Jaeken[14] as the hydrazine (**3**) was probably the hydrochloride salt. The hydrazide (**3**), by condensation with β-dicarbonyl compounds, gave the β-ketohydrazones (**4**) or the corresponding sulfonylpyrazoles[15–16] (**5**). With unsymmetrical dicarbonyl compounds two isomeric pyrazoles may be formed:



The actual result depends on the stereoelectronic effects operating in a particular example; however, with 1-phenylbutane-1,3-dione nmr spectroscopy indicates that only one isomer (5; R = CH_3, R′ = C_6H_5) is isolated as there is only one pyrazole ring proton shown.

As has been previously suggested,[16] this isomer (**5**) would be favoured since steric and electronic factors combine to reduce the reactivity of the carbonyl group in C_6H_5CO as cf. the CH_3CO in phenylbutane-1,3-dione. The low yield (39%) of the pyrazole (5; R = CH_3, R′ = C_6H_5) may be partly due to steric hindrance between the bulky phenyl group and the adjacent sulfonyl group. This hindrance combined with the low reactivity of the C_6H_5CO group would account for the lower yield (23%) of the 3,5-diphenylpyrazole (5; R = R′ = C_6H_5) obtained by reaction of the hydrazide (3) with 1,3-diphenylpropane-1,3-dione. The mother liquor by evaporation and heating at 130–150° gave 3,5-diphenyl pyrazole. This is probably formed by elimination of sulfur dioxide as Nair[17] observed that *p*-toluenesulfonyl pyrazoles on heating eliminate sulfur dioxide with formation of the parent pyrazoles (cf. Ref. 16). With ethylacetoacetate, the β-ketohydrazone (**4**) (R = CH_3, R′ = OC_2H_5) was obtained, but when the reaction was carried out in the presence of potassium carbonate-magnesium sulfate, cyclisation occurred to afford a moderate yield (47%) of the pyrazolone (**6**) (R = CH_3, R′ = OC_2H_5). The structures of (**4**) and (**6**) are defined by the much greater reactivity of the carbonyl group of the acetyl moiety (cf. that in the carbothoxy group), consequently only one product is obtained:



(**4**) (**6**)

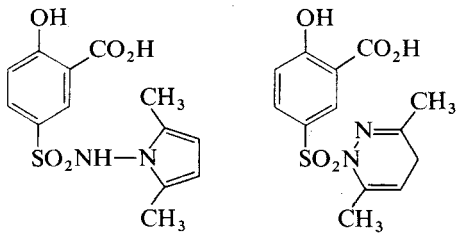
(R=CH_3, R′=OC_2H_5)

R^2 = salicyclic acid-5-sulfonyl)

In the reaction of the hydrazide (**3**) with 1,1,1-trifluoropentane-2,4-dione attack by the hydrazide occurs at the CH_3CO group rather than at the CF_3CO because the dione exists predominantly in the enol form (cf. Ref. 16). Attempts to cyclise the hydrazone (4, R = CH_3, R′ = CF_3) to the pyrazole (5; R = CH_3, R′ = CF_3) either by pyrolysis (130°/1h) or by prolonged heating in ethanol with potassium carbonate-magnesium sulfate failed, probably as a consequence of low carbonyl reactivity in the intermediate hydrazone due to extensive enolisation. With 1,1,1,5,5,5-hexafluoropentane-2,4-dione, the hydrazide (**3**) gave a mixture of products, mass spectroscopy indicated the presence of the hexafluorosulfonohydrazone (4; R = R′ = CF_3).

The yields of the pyrazoles (**5**) were appreciably lower than those obtained from pyridine-3-sulfonohydrazide;[16] this may be due to the occurrence of side reactions arising from the presence of the reactive OH and CO_2H groups.

Salicyclic acid-5-sulfonohydrazide was also condensed with hexane-2,5-dione; the n.m.r spectrum of the product showed two methyl groups in the same environment (singlet δ 1.72), indicating that the product was the pyrrole derivative (**7**) and not the pyridazine (**8**). The formation of the pyrrole



(**7**) (**8**)

(**7**) would be favoured by the aromatic character of the 5-membered ring.

Acylation of salicylic acid-5-sulfonohydrazide (**3**) was examined (Table 1). Warming (**3**) with acetic anhydride gave the N-acetyl derivative (Table I, No. 1) in which the acetyl group was attached to the most basic terminal NH_2 group. Under similar conditions, reaction of the hydrazide (**3**) with succinic anhydride afforded the succinamic acid (**9**) (Scheme 1) (Table I no 2); condensation with maleic anhydride similarly gave the maleamic acid (**10**) (no 3). Attempts to cyclise the succinamic acid (**9**) to the corresponding pyridazine derivative by boiling with acetic acid (4h) failed. This agrees with the difficulties experienced by other workers[18] in performing the analogous reaction between succinic anhydride and hydrazine hydrate.

In contrast, when the maleamic acid (**10**) was boiled with acetic acid, cyclisation occurred to give the pyridazine (**11**) (30%). Here intramolecular elimination of water and consequent cyclisation is probably facilitated by the *cis*-configuration of the double bond which holds the CO_2H and SO_2NH groups in juxtaposition (Scheme 1).

Acylation of *p*-acetamidobenzenesulfonohydrazide[19] (12; R = R′ = R^2 = R^3 = H) has been examined. Treatment with acetic anhydride (1 mol)-pyridine (15°) gave the N′-acetyl derivative (Table I, No. 4) (cf. Ref. 20); the structure was

TABLE I

Acyl sulfonohydrazides $R^1NHNR^2COR^3$

No.	R^1	R^2	R^3	Yield (%)	m.p. (°C)	Molecular formula	Analysis Found (%) C	H	N	Required (%) C	H	N
1	A	H	CH_3	72	222–224	$C_9H_{10}N_2O_6S$	39.3	4.0	9.9	39.4	3.7	10.2
2	A	H	$(CH_2)_2CO_2H$	56	195	$C_{11}H_{12}N_2O_8S$	39.6	3.9	8.1	39.8	3.6	8.4
3	A	H	$CH{=}CH$ | CO_2H	60	135–136	$C_{11}H_{10}N_2O_8S$	39.7	2.8	8.2	40.0	3.05	8.5
4	B	H	CH_3	43	167–170	(lit.[20] 166–170)						
5	B	Ac	CH_3	60	192–194	(lit.[20] 191–192)						
6	B	H	C_6H_5	34	223–224 (lit.[20] 219–220)	$C_{15}H_{15}N_5O_4S$	54.0	4.65	12.2	54.05	4.5	12.6
7	B	H	Ts (replaces R^3CO)	50	212–213 (lit.[20] 220)	$C_{15}H_{17}N_3O_5S_2$	46.7	4.5	10.9	47.0	4.4	11.0
8	B	H	$CH{=}CH$ | CO_2H	58	175–176	$C_{12}H_{13}N_3O_6S$	43.6	4.2	12.4	44.0	4.0	12.8
9	B	H	$(CH_2)_2CO_2H$	52	192–194	$C_{12}H_{15}N_3O_6S$	43.4	4.5	12.5	43.7	4.5	12.7

R^1 = Salicylic acid-5-sulfonyl (A) or *p*-acetamidobenzenesulfonyl (B)
Ac = CH_3CO Ts = *p*-$CH_3C_6H_4SO_2$.

Spectroscopic data

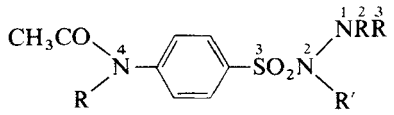
No.	N.m.r.($(CD_3)_2SO$)δ:	I.r. ($cm\Sigma^1$)
1	9.98*, brS, 1 H(NH); 9.85*, brS(OH, CO_2H); 9.7*, s(NH); 8.18–7.05, m, 3H(ArH); 1.68, s, 3H(CH_3)	3360, 3230(NH), 1700(CO), 1345, 1185(SO_2)
2	10.05*, s, 2H($CO_2H \times 2$); 9.68*, brs(2NH); 8.75*, s(OH); 8.15–7.05, m(3ArH); 2.22, brS, 4H(CH_2CH_2)	3320, 3100(NH), 1725, 1680(CO), 1340, 1185(SO_2)
3	10.4*, brS, 5 H(2CO_2H, OH); 8.28–7.05, m(3ArH); 6.16, brS, 2H(CH=CH)	3200(NH), 1720(CO), 1725(CO), 1350, 1180(SO_2)
4	9.2*, s, 1 H(NH); 9.1*, s, 1 H(NH); 8.3*, s, 1 H(NH); 7.9, m, 4H (4ArH); 2.2, s, 3H(CH_3); 1.9, s, 3H(CH_3)	3200(NH), 1690(CO), 1593(arom C=C), 1330, 1150(SO_2)
5	11.4*, s, 1H(NH); 10.4*, s, 1H(NH); 8.0, m, 4H(4ArH); 2.21, 2.15, 2.1, s, 9H($CH_3 \times 3$)	3350, 3300(NH), 1700(CO), 1360, 1180(SO_2)
6	10.8*, 10.25*, 9.45*, s, 3H(NH × 3); 7.9, m, 5H(C_6H_5CO); 7.6, m, 4H(4ArH); 2.2, s, 3H(CH_3)	3370, 3230(NH), 1665(CO), 1595(arom C=C), 1320, 1160(SO_2)
7	10.3*, brS, 1H(NH); 9.6*, m, 2H(NH × 2); 7.8, 4H, (4ArH); 7.5, m, 4H(4ArH); 2.4, s, 3H($CH_3 \cdot C_6H_4$); 2.1, s(CH_3CO)	3380, 3250(NH), 1680(CO), 1595(arom C=C), 1330, 1160(SO_2)
8	10.2*, s, 1H(NH); 9.7*, brS, 1H(NH); 7.7, m, 4H(4ArH); 6.1, s, 2H(CH=CH); 2.0, s, 3H(CH_3)	3400, 3260(NH), 1680(CO), 1360, 1160(SO_2)
9	10.4*, s, 1H(NH); 10.2*, s, 1H(NH); 9.7*, brS, 1H(NH); 7.9, m, 4H(4ArH); 2.25, m, 4H(CH_2CH_2); 2.05, 3H(CH_3)	3380, 3260(NH), 1700(CO), 1640(CONH), 1340, 1160(SO_2)

* Signals removed after D_2O treatment.

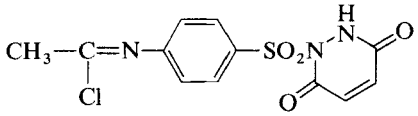
Mass spectra

1	274(M^+), 232(M-CH_2CO)$^+$, 201(salicyclic acid sulfonyl)$^+$
2	332 (M^+), 314 (M-H_2O)$^+$, 201 (salicyclic acid sulfonyl)$^+$
4	271(M^+), 198(M-$NHNHCOCH_3$)$^+$, 157, 140, 134($CH_3CONHC_6H_4$)$^+$, 108, 65 43
5	315(M^+), 271(M-CH_3CO)$^+$, 199, 198, 157, 140, 134, 43
6	333(M^+), 199(M-$NHNHCOC_6H^5$)$^+$, 140, 105(C_6H_5CO)$^+$, 77(C_6H_5)$^+$
7	383(M^+), 292(M-$CH_3C_6H_4$)$^+$, 198, 140($C_6H_4SO_2$)$^+$
8	no M^+, 312(M-CH_3)$^+$, 309(M-H_2O)$^+$, 213, 198, 134
9	no M^+, 314(M-CH_3)$^+$, 311(M-H_2O)$^+$, 198($CH_3CONHC_6H_4SO_2$)$^+$, 115($NHCOCH_2CH_2CO_2H$)$^+$

confirmed by the preparation of the same acetate by reaction of *p*-acetamidobenzenesulfonyl chloride with N,N′-diacetylhydrazide. With acetic anhydride (2 mol.)-pyridine at room temperature the hydrazide gave the N′,N′-diacetate (no. 5) (12; R = R′ = H, $R^2 = R^3 = CH_3CO$). Acetylation of the acetamido group requires more forcing conditions (cf. Ref. 21), also condensation of *p*-acetamidobenzenesulfonyl chloride with N,N′-diacetylhydrazide afforded the N^1,N^2-diacetylsulfonohydrazide (12; R = R^2 = H, $R^1 = R^3 = CH_3CO$) which was different from the diacetate obtained by reaction with acetic anhydride (no. 5); the latter is therefore concluded to be the N′,N′-diacetate. Under forcing conditions (excess of acetic anhydride-acetyl chloride, 100°) the hydrazide gave a mixture of products. The mass spectrum indicated the presence of a tetra-acetate. The structure (12; R = $R^2 = R^3 = CH_3CO$, R′ = H)



(12)

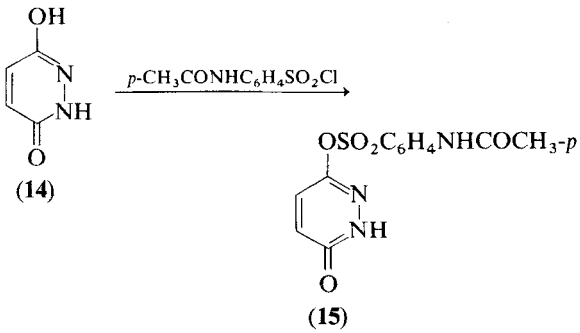


(13)

is possibly supported by the conversion of aniline to the N,N-diacetate under similar conditions.[21] In addition, steric interactions between the acetyl groups attached to the adjacent N^1, N^2 nitrogen atoms makes this structure relatively unfavourable. Reaction of the hydrazide (12; R = R^1 = R^2 = R^3 = H) with benzoyl chloride (1 mol.) or *p*-toluenesulfonyl chloride (1 mol.) in pyridine gave the N′-benzoyl or *p*-toluenesulfonyl derivatives[20] (Table I, nos. 6,7). The structure of the benzoyl derivative was confirmed by synthesis from N-acetamido-benzenesulfonyl chloride and N-benzoylhydrazide. Attempts to obtain a dibenzoate by reaction of the hydrazide with (benzoyl chloride (2 mols.)-pyridine) gave a mixtue of the mono- and dibenzoyl derivatives, and treatment with an excess of boiling benzoyl chloride caused decomposition. Acetamidobenzenesulfonyl chloride could not be condensed with N,N′-dibenzoyl hydrazide, probably due to steric hindrance by the large benzoyl groups. Similarly an effort to obtain a di-*p*-toluenesulfonyl derivative by reaction of the hydrazide (12; R = R^1 = R^2 = R^3 = H) with *p*-toluenesulfonyl chloride (2 mols.)-pyridine gave only the mono-*p*-toluenesulfonate (Table I, No. 7). Reaction of *p*-acetamidobenzenesulfonohydrazide (12; R = R^1 = R^2 = R^3 = H) with maleic anhydride (1 mol.) in acetic acid ($\frac{1}{2}$h) gave the maleamic acid (Table 1, No. 8) (10, R^2 = *p*-acetamidobenzenesulfonyl). Reaction with succinic anhydride similarly afforded the succinamic acid (Table I, No. 9) (**9**). Both compounds evolved carbon dioxide with aqueous sodium hydrogen carbonate confirming the presence of the CO_2H group.

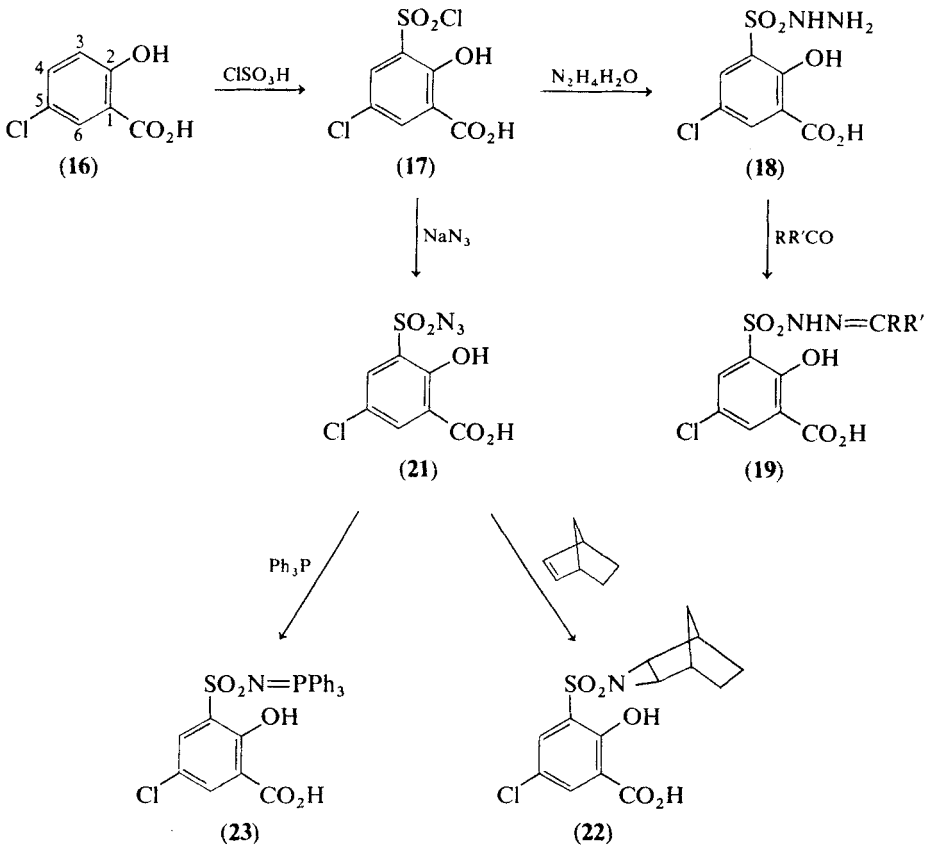
The maleamic acid (**10**), on attempted cyclisation to the pyridazine (11; R^2 = *p*-acetamidobenzenesulfonyl), by boiling xylene, acetic acid, or acetic acid-anhydrous sodium acetate (80°–90°) gave dark resinous products. However, treatment with boiling thionyl chloride afforded a yellow solid containing chlorine, which on the basis of analysis and mass spectroscopy appears to be the imidoyl chloride (**13**). In support of this structure, previous workers[22] have shown that the reaction of thionyl chloride with benzanilide gives N-phenylacetimidoyl chloride. The succinamic acid (Table I, No. 9) by boiling with xylene or acetic acid cyclised to the pyridazine. The cyclisation was supported by the mass spectrum (shows molecular ion), i.r. spectrum (absence of OH group), and the fact that the product did not evolve carbon dioxide with aqueous sodium hydrogen carbonate. Attempted cyclisation of the succinamic acid (**9**) with acetic acid-sodium acetate (80°–90°) gave a black tar.

An alternative route to pyridazines involves condensation of maleic hydrazide (**14**) with *p*-acetamidobenzenesulfonyl chloride, although this reaction would give the O-sulfonyl derivative (**15**) because in maleic hydrazide the OH has a greater nucleophilicity than the NH group.



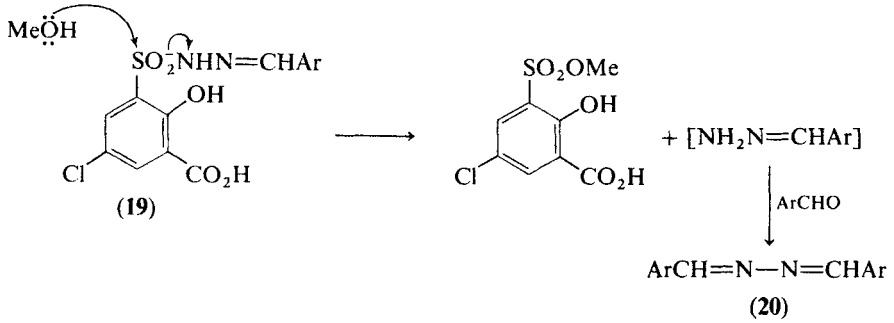
(14) (15)

O-sulfonation is confirmed by the absence of the O–H stretching absorption in the infra red spectrum of (**15**).



SCHEME 2

5-Chlorosalicylic acid (**16**) was reacted with a large excess (7 mols.) of chlorosulfonic acid to give the 3-sulfonyl chloride (17; 58%) (Scheme 2). When less chlorosulfonic acid (5 mols.) was used the yield of (**17**) decreased to 5%, suggesting that the carboxylic acid and phenolic groups both react with the reagent (cf. Ref. 13). Condensation of the sulfonyl chloride (**17**) with hydrazine (5 mols.) gave the hydrazide (**18**); this was characterized by formation of acetone (19; R = R′ = CH_3) and cyclohexanone (19; R = R′ = cyclohexyl) hydrazones. On the other hand, reaction of the hydrazide (**18**) with aromatic aldehydes in boiling methanol did not yield the expected hydrazones (19; R = H, R′ = Ar) but the aldehyde azines (**20**). These may result from methanolysis of the initially formed aldehyde hydrazones (**19**) as indicated:



5-Chlorosalicylic acid-3-sulfonyl chloride (**17**) by reaction with sodium azide gave the azide (**21**), which reacted with norbornene to give the aziridine (**22**) and with triphenylphosphine to form the phosphinimine (**23**) (Scheme 2) (cf. Ref. 2).

EXPERIMENTAL

I.r. spectra were recorded 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 obtained 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.

Microanalyses were carried out by the Butterworth Microanalytical Consultancy Limited, Teddington, England.

Salicyclic Acid 5-Sulfonyl Chloride (**2**)

The reaction of salicyclic acid (1) with chlorosulfonic acid was carried out as previously described[12,13] to give sulfonyl chloride (60%), m.p. 162° (lit.[12] 169–171°, lit.[13] 164–166°).

Salicyclic Acid 5-Sulfonohydrazide (**3**)

Salicyclic acid-5-sulfonyl chloride (30.2 g) in dioxan (100 ml) was added dropwise to a stirred solution of hydrazine hydrate (32 ml of 98%; 5 mol equivs.) in dioxan (240 ml) at 20°C. After stirring for 2 h, the dioxan layer was removed and 5 M-hydrochloric acid (100 ml) added to the residual oil and the mixture vigorously stirred for 2 h. The precipitate was filtered off, washed with water, and acetonitrile to give the *hydrazide* (24.8 g, 82%), m.p. 175–176° (decomp.) (lit.[13] 182°). (Found: C, 38.85; H, 3.1; N, 12.0. Calc. for $C_7H_8N_2O_5S$: C, 36.2; H, 3.5; N, 12.1%). ν_{max} 3330, 3300 (NH), 1690 (CO), 1360, 1160 (SO_2) cm^{-1}. N.m.r. ($(CD_3)_2SO$) δ: 8.2, m, 6H (1 ArH, 3 NH, OH, CO_2H); 7.08, d, 7.85, q (2 ArH). On treatment with D_2O, the signal at δ 8.2 collapses to doublet (1 ArH).

Reactions of Salicyclic Acid-5-Sulfonohydrazide (**3**) *with Dicarbonyl Compounds*

i) *Pentane-2,4-dione* The reaction was carried out as described by Ried and Schleimer.[15] Pentane-2,4-dione (1.7 g) was added to a stirred slurry of the hydrazide (3.9; 1 mol equiv.) in 2 M-hydrochloric acid (150 ml). After stirring the mixture for 12 h, the precipitate was filtered off and recrystallised (methanol) to give the *3,4-dimethylpyrazole* (5; R = R′ = CH_3) (2.0 g, 40%), m.p. 183–185°. (Found: C, 48.3; H, 4.1; N, 9.0. $C_{12}H_{12}N_2O_5S$ requires C, 48.6; H, 4.1; N, 9.45%). ν_{max} 3500 br (OH), 1665 (CO), 1365, 1140 (SO_2) cm^{-1}. N.m.r. ($(CD_3)_2SO$) δ: 9.15, s, 2H (CO_2H, OH); 8.22–7.1, m (3 ArH); 6.1, s, 1H (pyrazole-4H); 2.42, 2.08, s, 6H (2 × CH_3). Treatment with D_2O removed the signal at δ 9.15.

ii) *1-Phenylbutane-1,3-Dione* 1-Phenylbutane-1,3-dione (3.0 g) and the hydrazide (3) (4.6 g; 1 mol equiv) was refluxed in ethanol (50 ml) for 6 h. Evaporation under reduced pressure gave a gummy solid which solidified on trituration with ethyl acetate. Recrystallisation (water) gave the *methyl phenyl pyrazole*) (5; R = CH_3, R′ = C_6H_5) (2.8 g, 39%) m.p. 232°. (Found: C, 57.1; H, 3.6; N, 7.5. $C_{17}H_{14}N_2O_5S$ requires C, 57.0; H, 3.9; N, 7.8%). ν_{max} 2800 br (OH), 1675 (CO), 1340, 1440(SO_2)cm^{-1}. N.m.r. ($(CD_3)_2SO$)δ: 10.9, s, 2H (CO_2H, OH); 8.1, 6.8, d, 2H (salicylate H); 7.8–7.45, m, 6H (C_6H_5 and 1 salicylate H); 6.78, s. 1H (pyrazole-4H); 2.35, s, 3H (CH_3). The signal at δ 10.9 was removed by D_2O treatment. Ms. does not show the molecular ion (M^+, 358) but major fragment ions at 200 (salicyclic sulfonyl) and 158 (methylphenylpyrazole).

iii) *1,3-Diphenylpropane-1,3-Dione* Reaction under similar conditions to (ii) afforded the *3-5-diphenylpyrazole* (from ethyl acetate) (5; R = R′ = C_6H_5) (23%), m.p. 234–236°. (Found: C, 58.8; H, 4.2; N, 6.2. $C_{22}H_{16}N_2O_5S$, 1.5 H_2O requires C, 59.1; H, 4.25; N, 6.3%). ν_{max} 1670 (CO), 1355, 1140 (SO_2) cm^{-1}. N.m.r. ($(CD_3)_2SO$) δ: 9.82, s, 5H(CO_2H, OH, 1.5 H_2O), 8.1, d, 1H (salicylate H), 7.82–7.4, m, 11H(C_6H_5 × 2, 1 salicylate H); 7.20, s, 1H (salicylate H), 6.9, d. 1H (pyrazole-4H). The signal at δ 9.82 disappears after D_2O treatment. Evaporation of ethyl acetate gave a yellow glass, this was heated at 130–150° for ½ h. Cooling and trituration with ethyl acetate gave a white solid. Recrystallization (50% aqueous methanol) afforded 3,5-diphenylpyrazole, m.p. 197° (lit.[23a] 200°). (Found: C, 81.6; H, 5.2; N. 13.0. Calc. for $C_{15}H_{22}N_2$: C, 81.8; H, 5.5; N, 12.7%). N.m.r. ($CDCL_3$) δ: 7.9–7.4, m, 10H (C_6H_5 × 2); 7.18 s, 1H (pyrazole-4H).

iv) *Ethyl Acetoacetate Method 1.* Reaction in boiling ethanol (6 h) gave the *ethyl acetoacetate hydrazone* (67%) (4; R = CH_3, R′ = OC_2H_5), m.p. 146–147°. (Found: C, 45.3; H, 4.6; N, 8.1. $C_{13}H_{16}N_2O_7S$ requires C, 45.35; H, 4.7; N, 8.1%). ν_{max} 3190 (NH), 1710 (CO), 1340, 1175 (SO_2) cm^{-1}. N.m.r. ($CDCl_3$) δ: 10.4, s, 2H (CO_2H, OH), 10. 1, s, 1H (NH); 8.25–7.10, m (3 ArH); 3.18, 4.0, 4H, (CH_2—O—CH_2); 1.82, s, 3H (CH_3); 1.10 t, 3H (CH_2CH_3). The signals at δ 10.4, 10.1 disappear after D_2O treatment.

Method 2. The hydrazide (3) (4.6 g) and ethyl acetoacetate (2.6 g, 1 mol equiv.) was refluxed in ethanol (75 ml) in the presence of potassium carbonate (5.5 g) and magnesium sulfate (5 g) for 12 h. The mixture was cooled and the precipitate dissolved in water (50 ml) and acidified (conc. hydrochloric acid) to pH3. The precipitate after recrystallization (methanol) gave the *3-methylpyrazol-5-one* (6) (2.8 g, 47%), m.p. 102–103°.[3] (Found: C, 40.2; H, 3.8; N, 8.5 $C_{11}H_{10}N_2O_6S$ 1.5 H_2O requires C, 40.6; H, 4.0; N, 8.6%). N.m.r. ($(CD_3)_2SO$ δ: 8.35, m, 5H (1 ArH, CH_2, CO_2H, OH); 7.95–7.18, m (2 ArH); 5.06 (1H, H_2O); 2.06, s, 3H (CH_3).

v) *1,1,1-Trifluoropentane-2,4-Dione* Reaction in boiling ethanol (6 h) gave the *hydrazone* (4; R = CH_3, R′ = CF_3) (from ethyl acetate-light petroleum 60–80° (72%), m.p. 144–145°. (Found: C, 39.4; H. 2.7; N, 7.8. $C_{12}H_{11}F_3N_2O_6S$ requires C, 39.1; H, 3.0; N, 7.6%) ν_{max} 3380 (NH), 1670, 1645 (CO), 1380, 1160 (SO_2) cm^{-1}. N.m.r. ($(CD_3)_2SO$) δ: 9.3, br s, 2H (CO_2H, OH); 8.25–7.15, m. (3 ArH); 3.1, q, 2H (CH_2); 1.88, s, 3H (CH_3). The signal at δ 9.3 disappeared on treatment with D_2O. Ms. showed the molecular ion (M^+, 368) and a fragment ion at 150 (trifluoromethylpyrazole).

vi) *1,1,1,5,5,5-Hexafluoropentane-2,4-Dione* Boiling in ethanol (5 h) gave an impure product (61%), m.p. 152–146,. T.l.c. (ethyl acetate-methanol 6:1) showed 3 spots, R_F 0, 0.25, 0.42. ν_{max} 3400 (NH), 1675 (CO), 1380, 1180 (SO_2) cm^{-1}. N.m.r. ($(CD_3)_2SO$) δ: 8.92, br s, (CO_2H, OH); 8.32–6.9, m (ArH);

1.12, m (CH_3). The signal at δ 8.92 disappears after D_2O treatment. M.s. showed the molecular ion (M^+, 422) for the hydrazone (4; R = R' = CF_3).

vii) *Hexane-1,4-Dione* Boiling in ethanol (5 h) gave the *2,5-dimethylpyrrole* (7) 79%), m.p. 180–181°. (Found: C, 50.0; H, 4.2; N, 8.8. $C_{13}H_{14}N_2O_5S$ requires C, 50.3; H, 4.5; N, 9.0%). ν_{max} 3275 (NH), 1685 (CO), 1350, 1175 (SO_2) cm^{-1}. N.m.r. ($(CD_3)_2SO$)δ: 11.0, br. s, 2H (OH, CO_2H); 10.7, br s, 1H (NH); 8.08–7.10, m, 3H (3 phenyl H); 5.54, d, 2H (2 pyrrole H); 1.72, s, 6H (2 × CH_3). The signals at δ 11.0, 10.7 were removed by D_2O treatment. Ms. showed the molecular ion (M^+, 310), and fragment ions at 109 (M-salicyclic acid sulfonyl), and 94 (2,5-dimethyl-pyrrole).

N'-(Salicyclic Acid-5'-Sulfonyl)Pyridazine-3,6-Dione (**11**)

Maleic anhydride (0.85 g) and salicyclic acid-5-sulfonohydrazide (3) (2 g) were refluxed in glacial acetic acid for 4 h. Evaporation gave an oil which solidified on trituration with ice-water to give the *pyridazine* (11) (0.8 g, 30%), m.p. 209–211°. (Found: C, 42.0; H, 2.8; N, 8.6. $C_{11}H_8N_2O_7S$ requires C, 42.0; H, 2.6; N, 8.9%). ν_{max} 1740, 1685 (CO), 1350, 1170 (SO_2) cm^{-1}. N.m.r. ($(CD_3)_2SO$) δ: 10.75, s, 1H(NH); 10.05 brs, 2H(CO_2H, OH); 8.23–7.90, m, 3H (3ArH); 7.1, m, 2H (CH=CH). Ms. shows the molecular ion (M^+, 312) and a major fragment ion at 201 (salicyclic-5'-sulfonyl.

p-Acetamidobenzenesulfonohydrazide (12; R = R' = R^2 = R^3 = H) This was prepared by reaction of *p*-acetamidobenzenesulfonyl chloride with hydrazine hydrate as previously described.[19,24] Yield (95%, m.p. 178° (decomp.) (lit.[19] 176–178, lit.[23a] 188–190°). ν_{max} (KBr) 3580, 3500, 3300 (NH), 1692 (CO), 1595 (arom C=C), 1350, 1140 (SO_2) cm^{-1}. N.m.r. ($(CD_3)_2SO$) δ: 10.3, s, 1H (CONH); 7.9, s, 4H (4ArH); 3.7, brs, 3H ($NHNH_2$); 2.2, s, 3H (CH_3). The signals at δ 10.3, 3.7 were removed after D_2O treatment. Ms. showed the molecular ion (M^+, 229) and fragment ions at 214 ($M-CH_3$), 198 ($M-NH-NH_2$), 157 ($NH_2-C_6H_4SO_2H$), 140 ($C_6H_4SO_2$), 108, 64 (SO_2), 43 (CH_3CO).

N'N²-Diacetyl p-Acetamidobenzenesulfonohydrazide (12; R = R' = R^2 = CH_3CO, R^3 = H). *p*-Acetamidobenzenesulfonyl chloride (2.4 g) was reacted with N,N'-diacetylhydrazide (1.2 g) in pyridine (15 ml) for 24 h at room temperature. Evaporation under reduced pressure, trituration with water, and recyrstallization (ethanol) afforded the *N',N²-diacetate* (0.3 g), m.p. 237–239° (decomp.) (Found: C, 45.7; H, 4.5; N, 13.3. $C_{12}H_{15}N_3O_5S$ requires C, 46.0; H, 4.8; N, 13.4%). ν_{max} (KBr) 3350 (NH), 1685 (CO), 1595 (arom C=C), 1330, 1160 (SO_2) cm^{-1}. N.m.r. ($CDCl_3$) δ: 10.5, s, 1H ($CONHC_6H_5$); 9.7, s, 1H (NH); 7.95, s, 4H (4ArH); 2.38, 2.25, 2.20, s, 9H (CH_3 × 3). Ms. (chemical ionization) showed the (M^+ + 1) ion at 314.

Reaction of p-Acetamidobenzenesulfonohydrazide with Excess of Acetyl Chloride and Acetic Anhydride

The hydrazide (3 g) was refluxed with acetyl chloride (6.3 ml) and acetic anhydride (25 ml) for 1 h. The mixture was evaporated under reduced pressure and the residual oil, triturated with ice-water (100 ml) and the precipitate collected. The solid was washed with water and ether, and dried to give (1.3 g), m.p. 178–183° (decomp.). ν_{max} (KBr) 3350–3300 (NH), 1700 (CO), 1595 (arom C=C), 1360, 1160 (SO_2) cm^{-1}. Ms. showed the molecular ion (M^+, 355) for the tetraacetate (12, R = R^2 = R^3 = CH_3CO, R' = H); other ions were at 313 ($M-CH_2CO$), 271 ($M-2CH_2CO$), 198 ($CH_3CONHC_6H_4SO_2$), 140, 133, 43.

Attempted Formation of a Dibenzoyl Derivative of p-Acetamidobenzenesulfonohydrazide

p-Acetamidobenzenesulfonohydrazide (3 g) was reacted with benzoyl chloride (3.67 g; 2 mol. equivs.) in pyridine (15 ml) for 1 week at room temperature. Evaporation under reduced pressure and trituration of the residue with ice-water gave a solid which was collected and washed with water. Recrystallization (ethanol) gave plates (1.86 g), m.p. 188–190° (decomp.). (Found: C, 56.0; H, 4.2; N, 10.60. The *dibenzoate*, $C_{22}H_{19}N_3O_5S$ requires C, 60.4; H, 4.35; N, 9.60). Concentration of the filtrate gave the *monobenzoate* (Table 1, no. 6) (1.58 g), m.p. 215–217° (m.m.p. with authentic monobenzoate = 217–219°). Ms. did not show the molecular ion of the dibenzoate (M^+, 437), fragment ions: 333 (monobenzoate), 140, 105, 77, 43. In chemical ionization, the ions observed were sensitive to the sample and probe temperatures: at 150° and 200° respectively the highest ion was the monobenzoate + 1 (334); while at 160°, 210°, and at 160°, 250° the M + 1 ion of the dibenzoate (438) was observed.

Reaction of p-Acetamidobenzenesulfonyl Chloride with Benzoylhydrazine

p-Acetamidobenzenesulfonyl chloride (2.3 g) was reacted with benzoylhydrazine (1.4 g) in pyridine (15 ml) for 12 h. The solvent was evaporated off under reduced pressure; the residual oil solidified by trituration with dilute hydrochloric acid. Recrystallization (aqueous ethanol) afforded the *N-benzoylhydrazide* (12; R = R' = R^2 = H, R^3 = C_6H_5CO) (1.8 g), m.p. 225–228°. (m.m.p. with the compound formed by benzoylation of the hydrazide = 222–227°).

Reaction of the Maleamic Acid (Table I, no. 8) with Thionyl Chloride

The maleamic acid (10; R^2 = *p*-acetamidobenzenesulfonyl) (3 g) was refluxed with thionyl chloride (30 ml) for 1½ h. Cooling (ice-water) gave crystals, which were filtered off, washed with chloroform, and triturated with ethanol to give the *imidoyl chloride* (13) as a canary-yellow solid (1.5 g), m.p. 181–183°. (Found: C, 43.9; H, 3.4; N, 12.6. $C_{12}H_{10}ClN_3O_4S$ requires C, 44.0; H, 3.1; N, 12.8%). ν_{max} (KBr) 3320 (NH), 1683 (CO), 1660 (CO), 1588 (arom C=C), 1160 (SO_2) cm^{-1}.

N.m.r. ($(CD_3)_2SO$) δ: 10.5, s, 1H (NH); 7.9, s, 4H (4ArH); 6.8, 7.7, dd, J 5.5 Hz, 2H (CH=CH); 2.1 s, 3H (CH_3). Ms. gave the molecular ion (M^+, 327) and fragment ions at 291.5 (M—Cl), 198, 154.

Cyclisation of the Succinamic Acid (Table I, no. 9)

The succinamic acid (9; R^2 = *p*-acetamidobenzenesulfonyl) (4 g) was refluxed with glacial acetic acid (20 ml) for 2 h. The crystalline precipitate was collected, washed with water, and triturated with ethanol to give the *p-acetamidobenzenesulfonyl pyridazine* (2.8 g) as plates, m.p. 239–241° (decomp.). (The identical compound was obtained by refluxing the succinamic acid with xylene (11 h).) (Found: C, 46.0; H, 4.2; N, 13.4. $C_{12}H_{13}N_3O_5S$ requires C, 46.3; H, 4.2; N, 13.5%). ν_{max} (KBr)

3320 (NH), 1730 (CO), 1680 (CO), 1595 (arom C=C), 1380, 1180 (SO_2) cm^{-1}. N.m.r. ($(CD_3)_2SO$: δ 10.6, s, 1H (NH); 10.3, s. 1H (NH); 7.8, s, 4H (4ArH); 2.7, s. 4H (CH_2CH_2); 2.1, s, 3H (CH_3). The signals at δ 106, 10.3 were removed by D_2O treatment.

Ms. showed the molecular ion (M^+, 311) and fragment ions at 198 ($CH_3C_6H_4SO_2$), 156, 55.

O-(p-Acetamidobenzenesulfonyl)Maleic Hydrazide (**15**)

Maleic hydrazide (**14**) (0.9 g) was dissolved in pyridine (10 ml) and treated with *p*-acetamidobenzenesulfonyl chloride (1.9 g; 1 mol equiv.). After 12 h, pyridine was evaporated off under reduced pressure, and the residue was triturated with water and ethanol to give the *O-sulfonyl derivative* (**15**) (1.2 g, 48%), m.p. 186–190°. (Found: C, 46.8; H, 3.6; N, 13.7. $C_{12}H_{11}N_3O_5S$ requires C, 46.6; H, 3.6; N, 13.7%). ν_{max} (KBr) 3250 (NH), 1685, 1650 (CO), 1360, 1180 (SO_2) cm^{-1}. N.m.r. ($(CD_3)_2SO$ δ: 12.7 brs, 1H (NH); 10.4, s, 1H (NH); 7.9, s, 4H (4ArH); 7.35–6.95 q, 2H (CH=CH), 2.1, s, 3H (CH_3). Treatment with D_2O removed the signals at δ 12.7, 10.4. Ms. (chemical ionization) only showed the M + 1 ion at 310 and fragment ions at 244, 198, 113.

5-Chlorosalicyclic Acid-3-Sulfonyl Chloride (**17**)

5-Chlorosalicyclic acid (31.5 g) was heated with chlorosulfonic acid (85 ml; 7 mol equivs.) at 65–80° for 3h. Trituration with ice-water and light petroleum (30–40° gave the *sulfonyl chloride* (28 g), m.p. 204°. (Found: C, 30.7; H, 1.8; N, 25.9. $C_7H_4Cl_2O_5S$ requires C, 31.0; H, 1.5; N, 26.2%). ν_{max} 3500 br (·OH), 1680 (CO), 1370 1162 (SO_2) cm^{-1}. Ms showed the molecular ion (M^+, 270) and fragment ions at 253 (M—OH), 235 (M—Cl), 218.

5-Chlorosalicyclic Acid-4-Sulfonohydrazide (**18**)

Reaction of the sulfonyl chloride (**17**) with hydrazine hydrate (5 mol equivs.) in dioxan as previously described gave the *hydrazide* (70%), m.p. 158° (decomp.). (Found: C, 31.3; H, 2.8; N, 10.8. $C_7H_7ClN_2O_5S$ requires C, 31.5; H, 2.6; N, 10.5%). ν_{max} 3360, 3330 (NH), 1690 (CO), 1370, 1160 (SO_2) cm^{-1}.

The hydrazide was converted to the following hydrazones:

i) *Acetone* (19; R = R′ = CH_3), (80%), m.p. 197° (decomp.). (Found: C, 39.0; H, 3.6; N, 8.8. $C_{10}H_{11}ClN_2O_5S$ requires C, 39.15; H, 3.6; N, 9.1%). ν_{max} 3270 (NH), 1680 (CO), 1379, 1179 (SO_2) cm^{-1}. Ms showed the molecular ion (M^+, 306) and fragment ions at 217, 209, 186, 172, 154, 71.

N.m.r. ($CDCl_3$) δ: 9.63, s, 1H (NH), 8.0–7.8, m, 2H (2ArH); 2.04, s, 6H (2 × CH_3). The signal at δ 9.63 was removed by D_2O treatment.

ii) *Cyclohexanone* (19; R = R′ = cyclohexyl) (55%), m.p. 170° (decomp.). (Found C, 44.8; H, 4.5; N, 8.3. $C_{13}H_{15}ClN_2O_5S$ requires C, 45.0; H, 4.3; N, 8.1%). ν_{max} 3240 (NH), 1680 (CO), 1360, 1170 (SO_2) cm^{-1}. N.m.r. ($CDCl_3$-$(CD_3)_2SO$) δ: 8.9 brs, 1H, NH; 8.0–7.8, m, 2H (2ArH), 2.6–2.1, d, 4H (cyclohexane H); 1.65, s, 6H (cyclohexane H).

Benzaldehyde Azine (20; Ar=C_6H_5)

5-Chlorosalicyclic acid-3-sulfonohydrazide (18) (1.3 g) was boiled with freshly distilled benzaldehyde (0.9 g, 1.8 mol equivs.) in methanol (35 ml) for 2 h. Cooling and recrystallization (methanol) gave the azine (1 g), m.p. 180° (decomp.) (lit.[23b] 93°). (Found: C, 80.4; H, 6.0; N, 13.8. $C_{14}H_{12}N_2$ requires C, 80.8; H, 5.8; N, 13.5%). Ms. shows the molecular ion (M^+, 208), and fragment ions at 180 (M—N_2) 131, 104 (C_6H_5—CH=N), 78 (C_6H_5). ν_{max} 1640 (C=N), 1600, 1590 (arom C=C) cm^{-1}.

The following azines were similarly prepared:

i) *p-Chlorobenzaldehyde* (20; Ar = *p*-ClC_6H_4) (50%), m.p. 217°. (Found: C, 60.3; H, 3.45; N, 10.05. $C_{14}H_{10}Cl_2N_2$ requires C, 60.6; H, 3.6; N, 10.1%). ν_{max} 1630(C=N), 1610, 1590 (arom C=C) cm^{-1}. Ms. showed the molecular ion (M^+, 276) and fragment ions at 241 (M—Cl), 165, 138, 111.

ii) *p-Nitrobenzaldehyde* (75%) yellow platelets, m.p. 310° (lit.[23c] 300°). (Found: C, 56.1; H, 3.5; N, 18.5. $C_{14}H_{10}N_4O_4$ requires C, 56.4; H, 3.35; N, 18.8%). ν_{max} 1660 (C=N), 1600 (arom C=C), 1510, 1340 (aryl NO_2) cm^{-1}.

N.m.r. ($(CD_3)_2SO$ (130°) δ: 8.67, s, 2H (2 × CH=N); 8.4–7.88, m, 8H (8ArH). Ms. (chemical ionization) showed the M + 1 ion at 299 and fragment ions at 206, 154, 152, 149, 130, 103.

iii) *p-Methoxybenzaldehyde* (70%), m.p. 170° (lit.[25] 168°). (Found: C, 71.3; H, 6.3; N, 10.4. $C_{16}H_{16}N_2O_2$ requires C, 71.6; H, 6.0; N, 10.4%). ν_{max} 1660 (C=N), 1610, 1600 (arom C=C), 1225 (C—O—C) cm^{-1}. Ms. shows molecular ion (M^+, 268) and fragment ions at 253 (M—CH_3), 241, 161 (M—C_6H_5-OCH_3), 134. N.m.r. ($CDCl_3$) δ 7.9–6.9, m, 8H (8ArH); 4.35, s, 2H (2 × CH=N); 3.81, s, 6H (2 × OCH_3). The identical compound (m.p. 170°) was made by reacting *p*-methoxybenzaldehyde (2 mols) with hydrazine hydrate (1 mol) in methanol at 10°.

5-Chlorosalicyclic Acid-3-Sulfonyl Azide (**21**)

5-Chlorosalicyclic-3-Sulfonyl chloride (**17**) (13.2 g) was treated with sodium azide (7.2 g; 2 mol equivs.) in 50% aqueous acetone (40 ml). After 2½ h, the mixture was diluted with ice-water (450 ml), acidified (conc. hydrochloric acid) to pH3. After 30 min. at 5°, the precipitate was filtered off and recrystallized (ethanol) to give *the azide* (8.6 g), m.p. 172° (decomp.). (Found: C, 30.5; H, 1.5; N, 14.95. $C_7H_4ClN_3O_5S$ requires C, 30.3; H, 1.4; N, 15.1%). ν_{max} 2140 (N_3), 1685 (CO), 1600 (arom C=C), 1380, 1180 (SO_2) cm^{-1}. Ms. showed the molecular ion (M^+, 277) and fragment ions at 235 (M—N_3), 217, 200.

Reactions of the Sulfonyl Azide (**21**)

i) *With Norbornene* The azide (17) (0.7 g) was heated with norbornene (0.25 g; 1 mol. equiv.) in toluene-acetone (30 ml of 2:1 mixture) at 75° for 11 h. The solvents were evaporated and recrystallization of the residue (ethanol) gave the *aziridine* (**22**) (0.6 g), m.p. 258° (decomp.). (Found: C, 48.6; H, 4.3; N, 4.0. $C_{14}H_{14}ClNO_5S$ requires C, 48.9; H, 4.1; N, 4.1%). ν_{max} 1685 (CO), 1600 (arom C=C), 1380, 1180 (SO_2) cm^{-1}.

ii) *With Triphenylphosphine* The azide (**17**) (1.5 g) was refluxed with triphenylphosphine (1.5 g; 1 mol. equiv.) in acetone (40 ml) for 3 h. The solid was filtered off and washed with ether to give the *phosphinimine* (**23**) (1.2 g), m.p. 300–302° (decomp.). (Found: C, 58.4; H, 3.5; N, 2.6. $C_{25}H_{19}ClNO_5PS$ requires C, 58.65; H, 3.7; N, 2.7%). ν_{max} 3500 (br, OH), 1700 (CO), 1600 (br, arom C=C), 1385, 1180 (SO_2) cm^{-1}.

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