Reactions of some 2-aminophenyl- and 2- and 4-nitrophenyl sulfones in aqueous sodium hydroxide solution[1]

K. B. SHAW AND R. K. MILLER
Defence Research Establishment Ottawa, Defence Research Board, Ottawa 4, Ontario

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When 2-aminophenylsulfonylacetic acid (**3**) was heated under reflux in an excess of dilute sodium hydroxide solution, the only product identified was 2-methylsulfonylaniline (**6**). When 2-nitrophenylsulfonylacetic acid was treated under the same conditions, the major products identified were 2-methylsulfonylnitrobenzene (**7**), 2-nitrophenol (**8**), and orthanilic acid (**13**); minor products of this reaction were **6** and 3-methylsulfonyl-3′-nitro-4-amino-4′-hydroxybiphenyl (**12**). The same products were obtained although the yields were different when **7** was boiled with alkali, but the reaction of 4-methylsulfonylnitrobenzene (**15**) with alkali was less complex and 4-nitrophenol (**16**) was the only major product. The biphenyl **12** was also formed in small yield when *N*-(2-methylsulfonylphenyl)hydroxylamine (**19**) was treated with alkali and its formation in these reactions was investigated in detail. It was concluded that **12** arises from **7** and **19**, but it could also be prepared from **19** and 2-chloro- or better, 2-fluoronitrobenzene, in alkaline solution, and based on all these observations, a mechanism for its formation is suggested. The genesis of the various other products is also discussed. Reference is made to the infrared spectra of sulfones.

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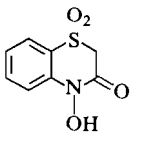
Introduction

It has been reported (1) that certain cyclic hydroxamic acids, among them **1** and **2**, are powerful reactivators in vitro of acetylcholinesterase inhibited by diisopropylphosphorofluoridate (DFP). All the compounds were said to be more potent reactivators than pyridine 2-aldoxime methiodide (2-PAM), and **1** was said to be more than twice as potent as 2-PAM and less than half as inhibitory. In view of these claims, it was necessary to extend the reactivation



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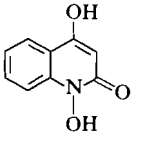

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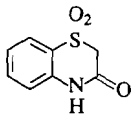
studies to cholinesterase inhibited by other organophosphorus compounds. However, we[2] were unable to demonstrate any significant reactivation by **1** or **2** of acetylcholinesterase or serum cholinesterase after inhibition by isopropyl methylphosphonofluoridate (Sarin), although these compounds, in conjunction with atropine, were found to afford some protection to mice against poisoning by Sarin above that afforded by atropine alone.[3]

Because of this protection afforded against Sarin poisoning, it was of interest to study the chemistry of some of these hydroxamic acids and the benzothiazine derivative **1**, was selected for this work. Compound **1** was unaffected by refluxing 10% hydrochloric acid, but when a solution of **1** in dilute sodium hydroxide was heated under reflux for several hours a multitude of products was formed. Before this reaction was investigated further, it seemed desirable to study the action of sodium hydroxide on some related sulfones in order to gain background information which might help in understanding the reaction of **1** with alkali. In this respect however, the information gained from these reactions, some of which were also rather complex, was of limited value. Nevertheless, interesting results were obtained and these form the subject of this and another paper (2). The reaction of **1** with sodium hydroxide is imperfectly understood and is not reported here.

Results and Discussion

It was decided initially to study the action of sodium hydroxide on 2-aminophenylsulfonylacetic acid (**3**). Although **3** could be prepared in solution, the acid could not be isolated owing to the ease with which it cyclized to the lactam, 3,4-dihydro-3-oxo-2*H*-1,4-benzothiazine-1,1-dioxide (**4**) (3, 4). Several attempts to prepare **3** by the published method ((5) reduction of 2-nitrophenylsulfonylacetic acid (**5**) with ferrous sulfate and ammonia) or by reduction of **5** with sodium

[1]Issued as DREO Report No. 612.
[2]K. B. Shaw and R. K. Miller. Unpublished work.
[3]I. W. Coleman. Personal communication.



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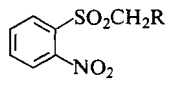


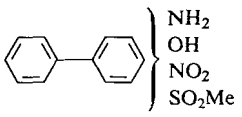
5 R = CO_2H
7 R = H

borohydride and palladium charcoal (6) gave **4** as the only identifiable product. The lactam **4** was also obtained in poor yield by the reduction of **5** with iron and hydrochloric acid (7) but could be prepared in good yield by this method from the methyl ester of **5** since this avoided difficulties arising from the formation of iron salts. The lactam has maxima in the ultraviolet (u.v.) (in water) at 251 and 295 mμ in the p*H* range 1 to about 10. At higher p*H* however, the maxima are at 257 and 305 mμ, when **4** presumably exists as the salt of **3**. The lactam **4** was recovered in high yield after being heated for 4 h with 1 molar equivalent of 0.1 *N* sodium hydroxide, but when the experiment was repeated using 2 molar equivalents of alkali, 2-methylsulfonylaniline (**6**) (7, 8, 9) was obtained in about 20% yield. The yield of **6** was increased to about 30% after a 7 h reaction period and to about 75% after 24 h. In addition, **4** was also recovered and another product appeared (u.v.) to be present but there was no evidence that orthanilic acid was formed in this reaction (see below).

When 2-nitrophenylsulfonylacetic acid (**5**) was heated under reflux in 1 molar equivalent of *N* sodium hydroxide the sole product isolated, in 50–60% yield, was 2-methylsulfonylnitrobenzene (**7**) (8) and this decarboxylation in alkaline solution is a general reaction of 2-nitrophenylsulfonylacetic acids (10). A somewhat cleaner product was obtained in rather higher yield when the decarboxylation was carried out in 0.1 *N* sodium hydroxide for 3 h, but **7** was not the only product of this reaction (cf. (10)), since the reaction mixture showed maxima in the u.v., whereas neither **5** nor **7** shows a maximum in the u.v. Subsequently, it was found that the decarboxylation of **5** takes place almost quantitatively when the acid is heated under reflux for 3 h with only 10% of 1 molar equivalent of dilute sodium hydroxide solution; but when the reaction was carried out in water for the same time, the yield of **7** was less than 20% and the remaining **5** was recovered. It is apparent from these results that in alkaline solution, the nitro acid **5** loses carbon dioxide much more readily than the amino acid **3**. Compound **7** could also be prepared in very high yield by heating under reflux for 20 h a solution of **5** in methanol containing a little piperidine, the method used by Coutts and Smith (11) for the preparation of **7** from the methyl ester of **5**.

The reaction of **5** with two molar equivalents of alkali was complex. Although in a number of runs the yields of the various products were not exactly reproducible, the variations were not large and the same products were obtained. The reaction was carried out by heating a solution of **5** in 0.1 *N* sodium hydroxide under reflux for 7 h. During this time, ammonia was evolved and the solution became deep red (cf. (10)). From this solution **7** could be isolated in about 20% yield by extraction with ether and a very small quantity of **6** was also detected in this fraction. After the solution had been acidified, steam distillation gave a yellow solid which was readily identified as 2-nitrophenol (**8**) (10%), and then extraction with ether gave a semi-solid which was not completely soluble in methanol.

Although no pure compound could be isolated from the methanol-soluble part of this fraction, the methanol-insoluble portion was an orange–red solid which crystallized readily from ethanol–acetone. Elemental analysis indicated an empirical formula $C_{13}H_{12}N_2O_5S$ which was confirmed as the molecular formula by a mass spectrum (mol. wt. 308). The infrared (i.r.) spectrum was very informative and showed peaks ascribable to NH_2, bonded OH, aromatic NO_2 and SO_2Me. In addition, peaks at 1580, 1505, 850, and 815 cm^{-1} were suggestive of a 1,2,4-substituted benzene (12*a*). The sharp NH stretching bands and the slightly broad and weak OH stretching band were well defined, and it seemed unlikely that the amino and hydroxyl groups in the unknown were ortho, since 2-aminophenol (**9**) shows broad absorption between about 3200 and 2300 cm^{-1}. The position and intensity of the OH absorption in the unknown resembled that in 2-nitrophenol. The presence of nitro and methylsulfonyl groups was further confirmed by peaks at *m/e* 292 (M – 16) and 262 (M – 46) and at *m/e* 229 (M – 79) in the mass spectrum, which was consistent with a substituted biphenyl. Hence the part structure **10** accounts for all the atoms present. The nuclear magnetic resonance (n.m.r.) spectrum of the aromatic



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protons in the unknown (Fig. 1) showed peaks in the regions A, B, and C (total 5.3 H); not shown in Fig. 1 are a peak at 6.78 τ (3.0H) assigned to the protons in a methylsulfonyl group and a broad peak centered at 3.7 τ (1.9H), assigned to an amino group. The spectrum was also consistent with a biphenyl structure and an inspection of the line positions and coupling patterns allowed the following conclusions to be drawn: (*i*) Each ring contains an electron-withdrawing and an electron-donating substituent. (*ii*) In each ring there is a proton adjacent to the electron-donating substituent, and it is

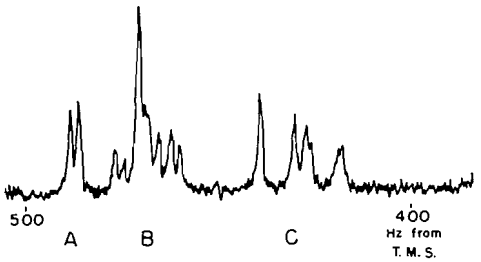
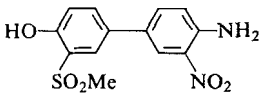


FIG. 1. The nuclear magnetic resonance spectrum of the aromatic protons in the biphenyl **12**.

split by an ortho proton but not by a meta proton (region C). (*iii*) In each ring, there is a proton adjacent to the electron-withdrawing substituent, but it is split only by a meta proton (regions A and B). The only structures which satisfy these requirements, and which are in accord with the previous observations are **11** and **12**. However, **11** may be rejected since the starting material did not contain adjacent nitrogen atoms and thus **12** is the structure of the biphenyl. The yield of **12** was about 2%.



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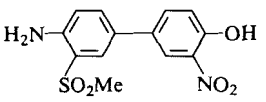


12

After the dark aqueous solution remaining after removal of the ether-soluble material had been decolorized, it showed maxima in the u.v. at 238 and 295 mμ, unchanged when the solution was made alkaline. This spectrum recalled that of 2-aminobenzenesulfonic acid (orthanilic acid) (**13**) (13) and the yield of this acid was estimated from the u.v. spectrum to be about 27%. In one experiment **13** was isolated and its identity was confirmed by u.v. and i.r. spectra and by elemental analysis.

When 2-methylsulfonylnitrobenzene (**7**) was treated with dilute sodium hydroxide solution, the products identified above were again obtained, but the yields (allowing for recovered starting material, ca. 10%) were different. It appeared that more ammonia was evolved during the reaction, and the yields of **6** (ca. 5%), **8** (22%), and **12** (8%) were all higher than in the reaction of **5** with alkali whereas the yield of **13** (13%) was lower. The methanol-soluble fraction from which **12** was isolated was shown by chromatography on alumina to be a mixture of several compounds. Although no pure compound was isolated, there was compelling evidence (comparison of i.r. and u.v. spectra in neutral and in alkaline solution with those of an authentic sample) that one fraction was 2-methylsulfonylphenol (**14**) (about 1% yield) and another fraction which showed NH_2, OH, SO_2Me, and possibly NO_2 absorptions in the i.r. may have been an isomer of **12** (see below).

The course of the reactions which occur when **5** or **7** is treated with alkali is not completely clear but a number of points can be made. The fact that the same products were isolated from **5** and **7** suggests that the decarboxylation of **5** is the first step in the reaction of that compound but, since the yields of the various products of the two reactions were dissimilar, this may not be completely true. In any event, **5** should be susceptible to the same reactions which lead to **8** and **13** from **7** (see below) and the different yields of **8** in particular, in relation to the quantity of **7** recovered, may be a reflection of the different concentrations of hydroxide ion throughout the two reactions. Thus it seems unwise to emphasize these differences in yields unduly and the discussion will be concerned with the reactions of **7**. Although it is well known

that certain substituents, e.g. nitro and chloro ortho to a nitro group, are susceptible to nucleophilic attack (14), it was uncertain whether or not the methylsulfonyl group in **7** could be displaced by a nucleophile. However the formation of **8** in the reaction of **7** with alkali indicates that such a reaction can occur and the ready displacement of the methylsulfonyl group in a number of nitrogen heterocycles by various nucleophiles, has been demonstrated recently (15). The vulnerability of a substituent ortho to a methylsulfonyl group to nucleophilic attack is very much less than that of the same substituent ortho to a nitro group (16), and 2-methylsulfonylphenol (**14**) was only a very minor product of the reaction of **7** with alkali. The formation of **14** generates nitrite ion, reduction of which would give ammonia (cf. 17); it is unlikely that ammonia was formed as a result of displacement of an aromatic amino group since both **13** and **6** were unaffected by dilute sodium hydroxide solution.

The activating effect of the ortho-nitro group in **7** is apparent in the formation of **8** (and in the ease of decarboxylation of **5** compared to **3**) and the genesis of **8** is straightforward. However, the formation of orthanilic acid (**13**) is less easily explained. Although several routes to **13** can be envisaged, it seems likely that ortho-substituent interactions (18) are involved in the formation of **13**, and also the numerous unidentified products obtained after treatment of **7** with alkali.

The ready reduction of nitro compounds under alkaline conditions is unexceptional (18 and references therein) but it is often debatable whether an external reducing agent is involved, and if so, what that agent is. A possible reducing agent in the reaction of **7** with alkali was methylsulfinate ion but this idea seemed improbable after an examination of the action of alkali on 4-methylsulfonylnitrobenzene (**15**, prepared by a series of reactions analogous to that used for **7**). In **15**, ortho-substituent interactions are not possible and the reaction of this compound with alkali was much less complex than that of **7**. The sole product isolated ($> 70\%$ yield) was 4-nitrophenol (**16**), and there was no evidence that sulfanilic acid (**17**) or other primary amines, e.g. 4-methylsulfonylaniline (**18**), were formed. In view of the high yield of **16**, and hence presumably methylsulfinate ion, **17** and **18** might have been expected if methylsulfinate ion was acting as a reducing agent.

The formation of the biphenyl **12** during the reaction of **5** or **7** with sodium hydroxide was quite unexpected and some experiments were performed in an effort to understand its mechanism of formation. The biphenyl **12** was not formed when **8** and **6** were boiled in sodium hydroxide solution for several hours (both compounds were recovered in high yield), and, when the reaction of **7** in alkali was carried out in the presence of one mole of **6**, the yield of **12** was again about 8% and **6** was recovered quantitatively. Hence it seemed unlikely that **6** was involved directly in the formation of **12**. If it is assumed that two different molecules are implicated in the formation of **12** (rather than, for example, dimerization of **7** with subsequent elaboration of the substituents) and considering what other compounds might be formed, but which could not be isolated during the reaction of **7** with alkali, one of the possible intermediates in the formation of **12** was *N*-(2-methylsulfonylphenyl)-hydroxylamine (**19**). Furthermore **19** is a part structure of the hydroxamic acid **1**, thus it was relevant to know what products were obtained when **19** was treated with dilute sodium hydroxide solution.

N-(2-Methylsulfonylphenyl)hydroxylamine (**19**), prepared by Claasz (8) by reduction of **7** with zinc and 40% acetic acid, was described as an oil. However, when **7** was reduced with zinc and ammonium chloride (19), **19** was obtained as a solid which crystallized readily. The reactions of **19** in alkali were studied in some detail and are reported elswhere (2). Here it is sufficient to state that **12** was one of several products obtained when **19** was treated with alkali, although the highest yield was about 6%. The isolation of **12** from this reaction did not prove that **19** itself was involved in the formation of **12**, in view of the numerous oxidation – reduction reactions which occur when **7** or **19** is treated with alkali but the result was at least suggestive. The nitro compound **7** was isolated in some cases after treatment of **19** with alkali (2), and since in all likelihood **19** might be formed when **7** was treated with alkali, there seemed a good possibility that these two compounds were the precursors of **12**, especially since the more obvious possibilities had been eliminated. This idea was strengthened by two facts. First, **19** is soluble in alkali in which presumably it is present in large part as the anion which might be a good nucleophile, and second,

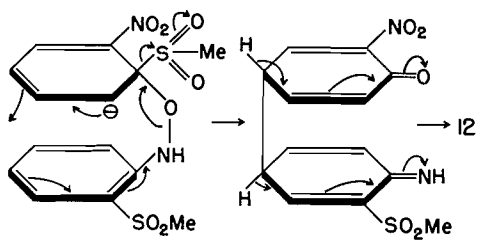
TABLE 1
Experiments on the formation of **12***

Experiment no.	**19** (mmoles)	**7** (mmoles)	Aqueous 0.1 *N* NaOH (mmoles)	**12** Isolated (mmoles)
1	0.3	0	0.3	0†
2	0	0.3	0.3	0
3	0.3	0.3	0.3	0.052
4	0.3	0.3	0.3	0.033‡
5	0.3	0.3	0.6	0.040
6	0.3	0.6	0.3	0.049
7	0.3	0.6	0.6	0.034
8	0.6	0.3	0.3	0.039
9	0.6	0.3	0.3 + 3 ml H_2O	0.046
10	0.6	0.3	0.6	0.098

*All reaction mixtures contained 3 ml of ethanol (to increase the solubility of 7) and were heated under reflux 15 min.
†On 10 times the scale, the yield of 12 was 0.072 mmoles.
‡Reaction done in presence of 0.3 mmoles of potassium acetate.

the carbon atom bearing the methylsulfonyl group in **7** is susceptible to nucleophilic attack. Thus, attack by the anion, $RNHO^-$, of **19** on **7** would lead to a reaction intermediate (**20**) which is resonance-stabilized. If this intermediate then rearranges in the manner indicated in Scheme 1, the biphenyl is produced. Alternatively, if **20** merely lost the methylsulfonyl group, an *N*,*O*-diphenylhydroxylamine (a type of compound which does not appear to be known, see below) would result, and this might also rearrange to **12**. Although other modes of joining the two rings are probably less favorable for steric reasons, it might be expected that isomers of **12**, e.g. a 2,2′- or a 2,4′-biphenyl, would also be formed. Such a possibility cannot be ruled out. In one experiment (reaction of **7** with sodium hydroxide), chromatography of the methanol-soluble fraction from which **12** was isolated, gave a fraction which had a similar i.r. spectrum to that of **12** but which could not be crystallized.

In an attempt to acquire some support for the foregoing ideas, numerous small-scale experiments were carried out using **7** and **19**. These experiments are summarized in Table 1. In each case the reaction mixture was worked up to isolate **12** only and no attempt was made to identify the other products. The following points about these results can be made: (*a*) Both **7** and **19** are involved in the formation of **12** (experiments 1–3).[4] (*b*) When one equivalent of sodium hydroxide was used, the yield of **12** was approximately the same when the quantities of **19** and **7** were 1:1 (experiment 3), 1:2 (experiment 6), or 2:1 (experiments 8 and 9). (*c*) When two equivalents of sodium hydroxide were used, and the quantities of **19** and **7** were 1:1 (experiment 5) or 1:2 (experiment 7) the yield of **12** was almost the same as in the experiments mentioned under (*b*). However, when the quantities of **19** and **7** were 2:1 (experiment 10) the yield of **12** was about twice that obtained in the other experiments. This marked difference in yield between experiments 8 and 9, and experiment 10, clearly demonstrates that the anionic form of **19** is the important one in the formation of **12**. In addition, if the first stage of the above mechanism is correct, **19** should react with other appropriate 2-substituted nitrobenzenes in alkaline solution to give **12**, and indeed, when 2-chloronitrobenzene (**22**) was used instead of **7** under the con-



20 21

SCHEME 1

[4]It should be noted that although **12** is one of the products obtained when **19** (3 mmoles) is boiled in dilute sodium hydroxide solution for 15 min (2), the amount expected (by extrapolation) on a 0.3 mmole scale (experiment 2) would be too small to isolate. However **12** was not isolated from any experiment in which **7** was boiled in alkali for only 15 min.

ditions of experiment 3, **12** was obtained, but the yield was lower than in experiment 3. However, when 2-fluoronitrobenzene (**23**) was used instead of **7** in experiments analogous to 3, 6, and 10, the yields of **12** were 0.068, 0.068, and 0.14 mmoles respectively, and in addition, because of the more favorable solubility of **23** compared with **7**, it was possible to carry out a reaction involving **23** (experiment 3) at room temperature (48 h) when the yield of **12** was 0.077 mmoles.

In an attempt to prepare *N,O*-diphenylhydroxylamine via its *N*-acetyl derivative (**24**), Cox and Dunn (20) treated *N*-acetylphenylhydroxylamine (**25**) with diphenyliodonium hydroxide, but the main product of this reaction was 4-acetyl-4′-hydroxybiphenyl (**26**) containing some of the 2′-hydroxy isomer. Cox and Dunn considered that the most likely explanation of their results was that **25** was phenylated to give **24** which then spontaneously rearranged intramolecularly to the observed products. The experiments discussed above provide good evidence that the first stage in the formation of **12** is nucleophilic attack by the anion of **19** on the carbon atom bearing the methylsulfonyl group in **7** (and that bearing the halogen atom in **22** and **23**) and an intermediate analogous to **20**, is also likely in the formation of **26**. In the absence of any evidence for the formation of an *N,O*-diphenylhydroxylamine, either in this or the earlier (**20**) work, we prefer to regard the rearrangement as proceeding in the manner outlined above. We also obtained some evidence that **12** is formed in the alkaline solution and not (e.g. by an acid-catalyzed process) during workup (cf. (20)). After completion of the reaction between **19** and **7** (e.g. experiment 3 above) the alkaline reaction mixture had a maximum in the u.v. at 286 mμ, changing to 276 mμ after acidification, and the peak at 286 mμ persisted after extraction of the alkaline solution with chloroform. In aqueous alkali **12** has a peak at 288 mμ, changing to 278 mμ on acidification. However, the reaction cannot be quite as straightforward as outlined above. If this was so, it would be expected that, in the small-scale experiments described above, doubling the quantity of **7** (experiments 6 and 7), or **19** and sodium hydroxide (experiment 10), would lead to an increase in the yield of **12** over that obtained when the reactants were 1:1 (experiment 3), whereas only when 2 parts of **19** and sodium hydroxide were used, was an increase in the yield of **12** observed. A possible explanation of this is that the anion of **19** functions as a base in some other manner e.g. by facilitating the removal of the protons from **21** (cf. (21)). However, other bases e.g. hydroxyl ion (experiment 5) and acetate ion (experiment 4) do not act similarly.

Infrared Spectra

During the course of this and other work, 30 sulfones were available for study. In all these compounds, the sulfur atom was attached to a benzene ring. Nineteen of these compounds contained a methylsulfonyl group, nine contained the group $—SO_2CH_2—$, either in a six-membered ring (e.g. as in **4**) or as in **3**, and the remaining two compounds contained the group $—SO_2CH=$. All the compounds were solids and their i.r. spectra were recorded in potassium bromide disks, and in some cases also in solution. Of the 19 compounds containing the methylsulfonyl group, 18 showed a medium to strong band in the region 950–970 cm^{-1} (very fine splitting was observed with two compounds) and one compound showed two bands in this region. Eight compounds showed a medium-strong to strong band in the region 950–960 cm^{-1} in solution. Of the 11 compounds not containing a methylsulfonyl group four showed a weak band in the region 945–970 cm^{-1}, one showed a band of medium intensity at 980 cm^{-1} and six did not show any absorption between 910 and 1000 cm^{-1}. As an extension of these observations, an inspection of the i.r. spectra of more than 60 sulfones recorded on DMS cards revealed that of 20 compounds containing a methylsulfonyl group, 18 also showed a medium to strong band in the 950–970 cm^{-1} region and two compounds showed a band 5 cm^{-1} outside this range. Of the remaining compounds, only one (a salt) showed any significant absorption in this region.

Sheppard has stated (22) that the CH_3 rocking modes in compounds containing the group $CH_3—X$, in which the atom X is in Period III or higher of the Periodic Table, give rise to strong bands in the region 700–1000 cm^{-1}; and Momose *et al.* (23) have assigned bands in the 950–980 cm^{-1} region of the i.r. spectra of phenyl methylsulfones to methyl rocking vibrations in methylsulfonyl groups. This assignment is clearly supported by the observations recorded here. Furthermore, the spectra on DMS cards indicate

that the assignment may be extended to include also alkyl methylsulfones. Since all sulfones show strong SO_2 stretching vibrations in the region 1350–1290 and 1160–1100 cm^{-1} (12*b*), the presence of an additional medium to strong band in the 950–970 cm^{-1} region of the spectrum of a sulfone of unknown structure is strong evidence for the presence of a methylsulfonyl group, although it should be noted that aliphatic *N*-oxides and *trans*-1,2-disubstituted olefines also absorb in this region (12*c*, 12*d*).

Experimental

Infrared spectra are for potassium bromide disks except where noted otherwise. The micro analyses were performed by J. G. Helie and the mass spectrum was by Morgan-Schaffer Corporation, Montreal.

2-Nitrophenylsulfonylacetic Acid (5)

This compound was prepared by oxidation of (2-nitrophenylthio)acetic acid (24, cf. also 25) (25 g) in glacial acetic acid (200 ml) with 30% hydrogen peroxide (75 ml) for 5 h at 70°. (When less peroxide was used the product was not readily purified). The reaction mixture was concentrated to small volume, the crude product was separated, washed with water, and then crystallized from water to give the pure acid (80–85%), m.p. 175–176° (lit. (3) m.p. 173–174°); ν_{max} 1720 (C=O), 1535 and 1355 (NO_2), 1335 and 1145 cm^{-1} (SO_2).

Anal. Calcd. for $C_8H_7NO_6S$: C, 39.18; H, 2.86; N, 5.71; S, 13.07. Found: C, 39.36; H, 2.97; N, 5.66; S, 13.04.

Methyl (2-Nitrophenylsulfonyl)acetate

This ester, prepared by the method of Coutts *et al.* (25) in > 90% yield, was recrystallized (thimble) from methanol, m.p. 121–122° (lit. (27) m.p. 119–120°; (11) m.p. 120–121°); ν_{max} 1745 (C=O), 1530 and 1360 (NO_2), 1330 and 1150 cm^{-1} (SO_2).

Anal. Calcd. for $C_9H_9NO_6S$: C, 41.71; H, 3.51; N, 5.40. Found: C, 41.82; H, 3.71; N, 5.15.

2-Methylsulfonylnitrobenzene (7)

(*a*) A mixture of 2-nitrophenylsulfonylacetic acid (2.45 g) and 0.1 *N* sodium hydroxide (10 ml, 10% of 1 molar equ.) was heated under reflux for 3 h and then cooled in ice. The solid was separated and crystallized from 25% (v/v) ethanol–water giving 7 as pale yellow plates (1.86 g, 93%), m.p. 106–107° (lit. (7, 8, 9) m.p. 105–106°); ν_{max} 1540 and 1355 (NO_2), 1300, 1150 and 955 cm^{-1} (SO_2Me).

Anal. Calcd. for $C_7H_7NO_4S$: C, 41.78; H, 3.51; N, 6.96. Found: C, 41.97; H, 3.48; N, 7.15.

(*b*) A solution of 2-nitrophenylsulfonylacetic acid (32.8 g) in 95% methanol (300 ml) containing piperidine (5 ml) was heated under reflux for 20 h. The hot solution was poured into water (600 ml) at ca. 60° and then left to cool. The crystalline solid was separated and washed with dilute methanol, (25.0 g, 93%), m.p. and mixed m.p. 105–106°.

3,4-Dihydro-3-oxo-2H-1,4-benzothiazine-1,1-dioxide (4)

A mixture of methyl (2-nitrophenylsulfonyl)acetate (5 g) and iron powder (12.5 g) in 50% (v/v) aqueous methanol (150 ml) containing concentrated hydrochloric acid (1 ml) was heated under reflux with stirring, for 21 h. The hot solution was filtered (Celite), the filtrate was adjusted to p*H* 1 and then concentrated to small volume. The white solid was separated (2.6 g, 68%, m.p. 206–208°) and crystallized from ethyl acetate – hexane and then, for analysis, from aqueous methanol, m.p. 208.5–209.5° (lit. (3) m.p. 207–208°; (4, 28) m.p. 208–209°); λ_{max} (H_2O) (*a*) p*H* 1: 251 and 295 mμ (log ε 3.91 and 3.67); (*b*) p*H* > 10: 257 and 305 mμ (log ε 3.92 and 3.49); ν_{max} 3290 (NH), 1695 (C=O), 1295 and 1155 and 1120 cm^{-1} (SO_2).

Anal. Calcd. for $C_8H_7NO_3S$: C, 48.72; H, 3.58; N, 7.10; S, 16.26. Found: C, 48.93; H, 3.80; N, 6.72; S, 16.33.

2-Methylsulfonylaniline (6)

(*a*) 2-Methylsulfonylnitrobenzene (5 g) was reduced following the method of Cava and Blake (7). When the concentrated reaction mixture was cooled, the product separated (80–90%, m.p. 83–84°) and extraction with chloroform was unnecessary. Recrystallization from benzene – light petroleum gave white prisms, m.p. 84.5–85.5° (lit. (7) m.p. 53.5–54.5°; (8) m.p. 85–92°; (29) m.p. 65–66°; (9) m.p. 84–85°); λ_{max} (EtOH) 245 and 313 mμ (log ε 3.93 and 3.58); ν_{max} 3470 and 3370 (NH_2), 1280, 1125 and 955 cm^{-1} (SO_2Me).

Anal. Calcd. for $C_7H_9NO_2S$: C, 49.10; H, 5.30; N, 8.18. Found: C, 49.09; H, 5.42; N, 7.96.

(*b*) 3,4-Dihydro-3-oxo-2*H*-1,4-benzothiazine-1,1-dioxide (1 g) in 0.1 *N* sodium hydroxide (100 ml) was heated under reflux for 24 h. Extraction of the solution with chloroform gave an oil (660 mg, 76%) which solidified, m.p. and mixed m.p. with the foregoing product, 83–84°.

N-(2-Methylsulfonylphenyl)hydroxylamine (19)

2-Methylsulfonylnitrobenzene (5 g) in ethanol (140 ml) and water (10 ml) was reduced with zinc (17 g) and ammonium chloride (3 g) following the method of Martinez *et al.* (19). The crude product (4.0 g) was crystallized twice from benzene giving nearly white crystals, m.p. 102–104°. Further recrystallization from benzene (charcoal) gave white needles m.p. 103.5–105°; λ_{max} (H_2O) 241 and 303 mμ (log ε 3.78 and 3.49), unchanged when the solution was acidified; λ_{max} (NaOH) 296 mμ (log ε 3.74), the peak disappeared in 15 min; ν_{max} 3400 (OH), 3280 (NH), 1300, 1140 and 1125, and 960 cm^{-1} (SO_2Me); ν_{max} ($CHCl_3$) 3610 (OH), 3315 (NH), 1310 and 1290, 1140 and 1130, 960 cm^{-1} (SO_2Me).

Anal. Calcd. for $C_7H_9NO_3S$: C, 44.91; H, 4.85; N, 7.48; S, 17.13. Found: C, 44.90; H, 4.98; N, 7.26; S, 17.14.

2-Methylsulfonylphenol (14)

2-(Methylmercapto)phenol (Aldrich) (5 g) in glacial acetic acid (50 ml) containing 30% hydrogen peroxide (25 ml) was kept at 60–70° for 3 h. The mixture was concentrated to small volume, diluted with water, and extracted with ether to give hydrated 2-methylsulfonylphenol as pale yellow prisms (3.7 g, 60%), m.p. 87–90.5° (lit. (30) m.p. 87.5°). A sublimed sample was still partly hydrated and was exposed to a moist atmosphere, giving the pure monohydrate, white prisms, m.p. 85–87°; λ_{max}

(EtOH) 285 mμ (log ε 3.60); λ_{max} (EtOH + 1 drop NaOH solution) 245 and 318 mμ (log ε 3.99 and 3.81). This spectrum in alkaline solution is rather similar to that of **6** in neutral solution (cf. (31)). ν_{max} 3200–2500 (broad, hydrogen bonded OH), 1280, 1140 and 1120, and 970 (SO_2Me), 3530, 3490, and 1640 cm^{-1} (H_2O); ν_{max} ($CHCl_3$) 3350 (OH), 1315 and 1295, 1130 and 1120, and 955 cm^{-1} (SO_2Me).

Anal. Calcd. for $C_7H_8O_3S \cdot H_2O$: C, 44.20; H, 5.30. Found: C, 44.00; H, 5.00.

(4-Nitrophenylthio)acetic Acid

This compound was prepared from 4-chloronitrobenzene and thioglycolic acid by the method used (24, 25) for the 2-isomer. The crude product was heated with ethanol, the mixture was filtered (the insoluble material was mainly di-(4-nitrophenyl)disulfide and the filtrate was diluted with water to turbidity. The product was obtained as yellow crystals (50%) m.p. 151–153°, raised to 155.5–156.5° after 2 recrystallizations from aqueous ethanol (lit. (26) m.p. 149–151°; (32) m.p. 156.7°); ν_{max} 1695 (C=O), 1575 and 1330 cm^{-1} (NO_2).

Anal. Calcd. for $C_8H_7NO_4S$: C, 45.08; H, 3.31; N, 6.57; S, 15.02. Found: C, 45.13; H, 3.42; N, 6.53; S, 15.13.

4-Nitrophenylsulfonylacetic Acid

This compound was made by oxidation of the foregoing thioacid by the method used for the preparation of **3**. The product (80–90%) after crystallization from water had m.p. 172–173° (lit. (33) m.p. 167°; (26) m.p. 171–172°); ν_{max} 1730 (C=O), 1530 and 1350 (NO_2), 1310 and 1145 cm^{-1} (SO_2).

Anal. Calcd. for $C_8H_7NO_6S$: C, 39.19; H, 2.86; N, 5.71; S, 13.07. Found: C, 39.33; H, 2.94; N, 5.69; S, 12.93.

*4-Methylsulfonylnitrobenzene (**15**)*

The foregoing acid was decarboxylated using method (*b*) described above for the preparation of **7**. The product (ca. 90%), m.p. 140–142°, crystallized from the reaction mixture and it was not necessary to add water. Recrystallization from methanol gave pale yellow needles, m.p. 142–143° (lit. (34) m.p. 139°; (11) m.p. 143°); ν_{max} 1525 and 1345 (NO_2), 1300, 1150, and 960 cm^{-1} (SO_2Me).

Anal. Calcd. for $C_7H_7NO_4S$: C, 41.78; H, 3.51; N, 6.96. Found: C, 41.91; H, 3.70; N, 6.97.

Reactions of 2-Nitrophenylsulfonylacetic Acid in Sodium Hydroxide Solution

A solution of 2-nitrophenylsulfonylacetic acid (4.9 g) in 0.1 *N* sodium hydroxide (400 ml, 2 molar equ.) was heated under reflux 7 h, during which time the solution became deep red and ammonia was evolved (Nessler's Reagent). The cooled solution was extracted several times with ether, giving a pale yellow solid which was crystallized from 25% aqueous ethanol giving 2-methylsulfonylnitrobenzene (**7**) (850 mg), m.p. and mixed m.p. 104–105.5°. The mother liquors from the crystallization were evaporated to dryness and the remaining solid (80 mg) was shown by u.v. and i.r. spectra to be **7** containing ca. 10% of 2-methylsulfonylaniline (**6**). The total yield of **7** was 23%. The aqueous solution was then acidified with concentrated hydrochloric acid and steam distilled. The distillate was extracted with ether giving a yellow solid (276 mg) shown by m.p. and mixed m.p., 45–46°, (lit. (35*a*) m.p. 45°), and i.r. to be 2-nitrophenol (10%). The aqueous solution was then extracted repeatedly with ether giving a sticky orange-red solid (368 mg), to which was added 2–3 ml of methanol. The insoluble material was separated (68 mg; 2.2%), and crystallized from ethanol–acetone giving 3-methylsulfonyl-3′-nitro-4-amino-4′-hydroxybiphenyl (**12**) as orange-red rods, m.p. 213–215°; λ_{max} (EtOH) 282 and ca. 447 mμ (log ε 4.47 and 3.34); λ_{max} (EtOH + 1 drop NaOH solution) 292 and ca. 458 mμ (log ε 4.51 and 3.79); ν_{max} 3420 and 3340 (NH_2), 3210 (bonded OH), 1530 and 1310 (NO_2) 1285, 1130, and 960 cm^{-1} (SO_2Me); n.m.r. (60 MHz)(DMSO-d_6) τ 2.18 (H-2), 2.96 (H-5), and 2.25 p.p.m. (H-6), $J_{2,5}$ 0.2, $J_{2,6}$ 2.4, $J_{5,6}$ 8.0 Hz. τ 1.88 (H-2′), 2.76 (H-5′), and 2.15 p.p.m. (H-6′), $J_{2',5'}$ 0.2, $J_{2',6'}$ 2.3, $J_{5',6'}$ 8.8 Hz.

Anal. Calcd. for $C_{13}H_{12}N_2O_5S$: C, 50.64; H, 3.92; N, 9.09; S, 10.40. Found: C, 50.50; H, 3.91; N, 9.18; S, 10.27.

The acetate of **12** (pyridine and acetic anhydride, overnight at room temperature, the use of elevated temperature gave a mixture of the acetate and its *N*-acetyl derivative) crystallized from ethanol as yellow needles, m.p. 162–163°; ν_{max} 3465 and 3370 (NH_2), 1770 (C=O), 1535 and 1345 (NO_2), 1180 (C—O), 1290, 1135, and 955 cm^{-1} (SO_2Me).

Anal. Calcd. for $C_{15}H_{14}N_2O_6S$: C, 51.42; H, 4.03; N, 8.00; S, 9.15. Found: C, 51.48; H, 4.33; N, 7.95; S, 9.31.

The original aqueous solution was treated several times with charcoal until it was pale yellow. It was estimated by u.v. spectroscopy to contain 960 mg of orthanilic acid (27%).

In one experiment the orthanilic acid was isolated as follows. The aqueous solution was evaporated to dryness *in vacuo*, the resulting dark sticky solid was rubbed well with absolute ethanol (20 ml) and the mixture was filtered giving a brown solid (3.08 g). (The filtrate, after removal of the solvent, gave a dark tar which was not investigated further.) The brown solid was dissolved in water (40 ml) and passed through a column of AG 50W-X8 cation exchange resin, hydrogen form, (Bio. Rad. Laboratories, Richmond, Calif.) (30 ml) which had been previously washed with water, dilute hydrochloric acid, and then water. The column was developed with water and 10 ml fractions were collected. Fractions 2, 3, and 4 showed λ_{max} 238 and 295 mμ and were combined and taken to dryness, giving a brown solid (740 mg). A portion of this solid was dissolved in water and treated three times with charcoal. The solvent was removed leaving a pale yellow solid which crystallized from a small volume of water giving orthanilic acid m.p. > 300° (lit. (35*b*) decomposition 325°), i.r. spectrum identical to that of an authentic sample.

Anal. Calcd. for $C_6H_7NO_3S$: C, 41.62; H, 4.08; N, 8.09; S, 18.55. Found: C, 41.47; H, 4.06; N, 7.79; S, 18.52.

Reactions of 2-Methylsulfonylnitrobenzene in Sodium Hydroxide Solution

A mixture of 2-methylsulfonylnitrobenzene (5 g) and 0.1 *N* sodium hydroxide (550 ml, 2.2 molar equ.) was

heated under reflux 7 h. Ammonia was detected within 15 min of the start of the reaction and was still being evolved at the end when the solution was deep red. The reaction mixture was worked up as described for the reaction of **5** in sodium hydroxide to give: (*a*) A sticky yellow solid (768 mg) which was crystallized from 25% aqueous ethanol, giving starting material **7** (475 mg), m.p. 104–106°. The mother liquors from the crystallization were taken to dryness giving a pale yellow solid (215 mg), shown by u.v. and i.r. spectra to be 2-methylsulfonylaniline (**6**), containing ca. 10% of **7**. Thus the recovery of **7** was ca. 10% and the yield of **6** (allowing for recovered **7**) ca. 5%; (*b*) 2-nitrophenol (680 mg, 22%) m.p. and mixed m.p. 45–46°; and (*c*), the biphenyl **12**, (275 mg, 8%), m.p. 213–215°, after crystallization from ethanol–acetone. The aqueous solution remaining, after treatment as before with charcoal, was estimated by u.v. spectroscopy to contain 500 mg of orthanilic acid (13%).

One attempt was made to purify the methanol-soluble part of the fraction from which **12** was isolated. The mixture (a red oil, 370 mg) was chromatographed in chloroform on alumina (acid 2). The major orange band passed rapidly through the column and was collected in 3 fractions which were combined (230 mg, fraction A), λ_{max} 278 and 320 mμ. Following the major band, 2 fractions were obtained (total 46 mg), which showed λ_{max} 285 mμ; λ_{max} (EtOH + 1 drop NaOH solution) 245 and 318 mμ; ν_{max} ($CHCl_3$) 3340 (OH or NH), 1315 and 1295, 1130 and 1120, and 955 cm^{-1} (SO_2Me). These spectral data are identical with those of **14**. Fraction A was rechromatographed on alumina (acid 2) in benzene. From the appearance of the column and the spectroscopic properties of the various fractions collected, it was clear that fraction A was a mixture of several compounds, and no pure compound was isolated. Most fractions contained SO_2Me (i.r.), and some also showed the presence of NH_2, OH, and possibly NO_2 and may have been (an) isomer(s) of **12**.

Reactions of 4-Methylsulfonylnitrobenzene in Sodium Hydroxide Solution

A mixture of 4-methylsulfonylnitrobenzene (2.0 g) and 0.1 *N* sodium hydroxide (220 ml, 2.2 molar equ.) was heated under reflux 6½ h and then left overnight. The solid which had separated was filtered off and washed with water giving starting material (**15**) (359 mg) m.p. 141–142°. A further quantity (101 mg) of rather less pure **15** was obtained from the alkaline reaction mixture by extraction with ether. The reaction mixture was then acidified and extracted with ether to give an orange solid (977 mg) whose spectral properties closely resembled those of 4-nitrophenol, but which did not melt sharply. The material was therefore chromatographed on alumina (Acid 3) in acetone–hexane (1:3) and the main yellow band was collected giving 4-nitrophenol (764 mg, 72% allowing for recovered **15**), m.p. and mixed m.p. 109–111°, (lit. (35*a*) m.p. 114°). The remaining aqueous solution showed only weak absorption in the u.v. and was not investigated further.

*Preparation of **12***

The experiments summarized in Table 1 were carried out as follows. A mixture of the appropriate quantities of **7**, **19**, 0.1 *N* sodium hydroxide, and ethanol (3 ml) was heated under reflux 15 min. The deep red solution was cooled, diluted with sodium hydroxide solution, filtered, and washed with chloroform. The solution was then acidified and extracted with ether giving a mixture of red solid and oil, which was treated with a little methanol and filtered, giving **12** as a red solid, m.p. in the range 206–212°. The i.r. spectra of the various crude samples of **12** were virtually the same as the spectrum of the pure compound.

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