The Sulphoximides

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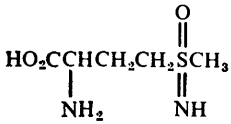
1 Introduction

It was demonstrated by Mellanby[1] that when dogs are fed a diet rich in flour pre-treated with the commercial flour improver 'Agene' (which is essentially nitrogen trichloride), they develop a condition known as canine hysteria. The manifestations of this disorder are bouts of hysterical barking and aimless running leading to epileptiform fits in severe cases.

Moran established that the toxic factor is produced by the interaction of nitrogen trichloride with the protein fraction of wheaten flour, namely gluten, and that the proteins zein and casein also become toxic when treated with the gas.[2] Not all proteins are rendered toxic by interaction with nitrogen trichloride and it was concluded by Bentley that the proteins which become toxic are relatively rich in methionine.[3] Subsequent work by Bentley led to the isolation of the toxic factor as a pure substance and to its characterization as methionine sulphoximide (1), the first member of a new family of sulphur compounds.[4]



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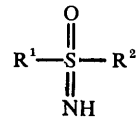

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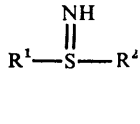

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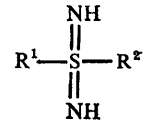


(4)

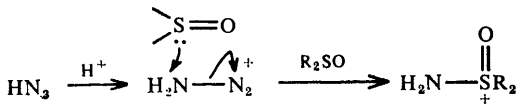
Since their initial discovery by Bentley, considerable work has been carried out on this versatile class of compounds, and it is the aim of this article to review concisely the major aspects of progress to date in this field. The nomenclature of sulphur–nitrogen compounds is highly confusing and for the purpose of this review the IUPAC convention will be followed, according to which the members of the family (2) are termed sulphoximides and the related families (3) and (4) are termed sulphimides and sulphur di-imides respectively.

[1] E. Mellanby, *Brit. Med. J.*, 1946, **2**, 885.
[2] T. Moran, *Lancet*, 1947, **2**, 289.
[3] H. R. Bentley, R. G. Booth, E. N. Greer, J. G. Heathcote, J. B. Hutchinson, and T. Moran, *Nature*, 1948, **161**, 126.
[4] H. R. Bentley, E. E. McDermott, T. Moran, J. Pace, and J. K. Whitehead, *Proc. Roy. Soc.*, 1950, **B137**, 402; J. K. Whitehead and H. R. Bentley, *J. Chem. Soc.*, 1952, 1572.

2 Synthesis

The initial synthesis of methionine sulphoximide (1) was accomplished by treatment of methionine sulphoxide with hydrazoic acid. The general applicability of the reaction was demonstrated by Reiner and his co-workers who prepared aryl and alkyl sulphoximides from the corresponding sulphoxides and showed that reaction proceeded best under conditions essentially similar to those used for the Schmidt reaction.[5] This method remains one of the most convenient general methods for preparing sulphoximides, providing that the sulphoxide used is stable to the strong acid conditions employed and not susceptible to heterolysis. In a modification of the method, Stoss and Satzinger used polyphosphoric acid as both acid catalyst and solvent to prepare a large number of sulphoximides in good yields.[6]

Although the reaction of hydrazoic acid with sulphoxides is formally related to the Schmidt reaction, it seems unlikely that the same mechanism applies. The mechanism proposed by Bentley[7] and extended by Johnson,[8] who established the necessity for two equivalents of acid in the reaction, involves nucleophilic attack by sulphoxide on a protonated hydrazoic acid intermediate (Scheme 1).

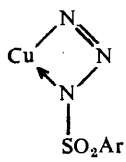


Scheme 1

A general route to *N*-substituted sulphoximides is provided by trapping, with sulphoxides, the 'nitrenes' generated by photolytic, thermolytic, and α-elimination reactions from appropriate precursors. Such a reaction was first described by Kwart and Kahn[9] and extended by others,[10] and depends on the trapping, by a suitable sulphoxide, of the transient nitrene generated from the copper-catalysed decomposition of an aryl sulphonyl azide. The catalysis by copper was suggested to be due to the formation of a 4-centre azide–copper complex (5) which could conceivably give rise to an intermediate copper–nitrene ultimately captured by the sulphoxide.[9]

In an extension of the work of Kwart and Kahn, Carr and his co-workers prepared *N*-arylsulphonylsulphoximides (6) by heating a sulphoxide with chloramine-T in the presence of copper powder.[11] Evidence for the formation of an intermediate copper–sulphonyl nitrene was provided by an insertion reaction with dioxan to give the sulphonamide (7). When copper was absent or when zinc dust was used as an alternative catalyst, little or no reaction took

[5] F. Misani, T. W. Fair, and L. Reiner, *J. Amer. Chem. Soc.*, 1951, **73**, 459.
[6] G. Satzinger and P. Stoss, *Arzneim.-Forsch.*, 1970, **20**, 1214.
[7] H. R. Bentley, E. E. McDermott, and J. K. Whitehead, *Proc. Roy. Soc.*, 1951, **B138**, 265.
[8] C. R. Johnson and E. R. Janiga, *J. Amer. Chem. Soc.*, 1973, **95**, 7692.
[9] M. Kwart and A. A. Kahn, *J. Amer. Chem. Soc.*, 1967, **89**, 1950.
[10] C. R. Johnson, R. A. Kirchhoff, R. J. Reischer, and G. F. Katekar, *J. Amer. Chem. Soc.*, 1973, **95**, 4287.
[11] D. Carr, T. P. Siden, and R. W. Turner, *Tetrahedron Letters*, 1969, 477.



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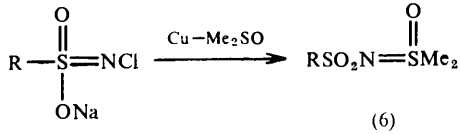
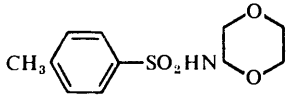


(6)

place. For high-yield preparative purposes the reaction appears to be limited to dimethyl sulphoxide. It has recently been shown that soluble copper salts are more convenient catalysts, providing the simplest preparation of *SS*-dimethyl-*N*-*p*-tolylsulphonylsulphoximide.[10]



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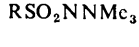


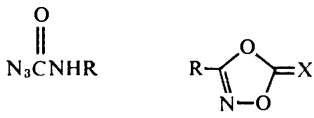
(8)

(9)

Horner and Christmann prepared a series of *N*-arylsulphonylsulphoximides by photolysis or thermolysis of arylsulphonyl azides in the presence of sulphoxides.[12] The yields were low and the reaction worked best when the sulphoxide was used as solvent. The same authors found that photolysis of benzoyl azide in DMSO resulted in the trapping of the generated nitrene by the solvent to give the *N*-benzoylsulphoximide. In an extension of this work Robson and Speakman generated nitrenes thermally, but not photolytically, from alkanesulphonamidates (8) in DMSO solution, enabling them to prepare the hitherto unknown alkyl sulphonylsulphoximides.[13] Conversely the related alkanamidates (9) did not decompose to give sulphoximides under photolytic or thermolytic conditions. The reaction of carbamoyl azides (10) with aryl sulphoxides provided the corresponding *N*-carbamoylsulphoximides in low yields.[14] Thermolysis of the dioxazolines (11) in DMSO gave the *N*-aroylsulphoximides in good yields.[15] The base-catalysed elimination reactions of the *N*-arylsulphonoxysulphonamides (12) with DMSO gave the related *N*-arylsulphonylsulphoximides, albeit in poor yields.[16]

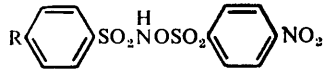
Pentafluorophenyl azide[17] and 4-azidotetrafluoropyridine[18] decompose

[12] L. Horner and A. Christmann, *Chem. Ber.*, 1963, **96**, 388.
[13] G. Robson and P. R. H. Speakman, *J. Chem. Soc.* (*B*), 1968, 463.
[14] V. J. Bauer, W. J. Fanshawe, and S. R. Safir, *J. Org. Chem.*, 1966, **31**, 3440.
[15] J. Sauer and K. K. Mayer, *Tetrahedron Letters*, 1968, 319.
[16] M. Okahara and D. Swern, *Tetrahedron Letters*, 1969, 3301.
[17] R. E. Banks and A. Prakash, *J. C. S. Perkin I*, 1974, 1365.
[18] R. E. Banks and G. R. Sparkes, *J. C. S. Perkin I*, 1972, 2964.



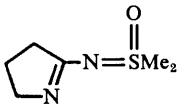
$R = Bu^n, Pr^n$ (10)

$X = O, S$ (11)



$R = H, Me$ (12)

thermally in DMSO at high temperatures to give moderate yields of the *N*-arylsulphoximides. 2-(*p*-Tolylsulphonyloxyimino)pyrrolidine decomposes in DMSO to give, after basification, the sulphoximide (13) in high yield.[19]



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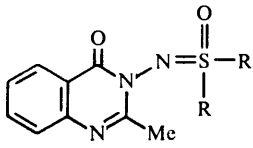

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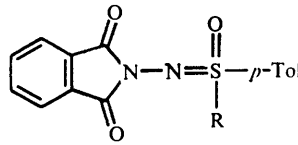


(15)

Rees and his co-workers have prepared a series of *N*-aminosulphoximides such as (14) from the corresponding *N*-aminolactams by lead tetra-acetate oxidation in the presence of a wide variety of sulphoxides.[20] The reaction has been used to synthesize the optically active sulphoximides (15) in high yield from optically active sulphoxides.[21]

The formation of analogous *N*-amino-*SS*-dimethylsulphoximides has been used to assign the structure to cyclic products obtained from 1,2-dicarboxylic anhydrides with hydrazine.[22]

Ohashi and his colleagues synthesized *N*-sulphonylsulphoximides (16) by oxidation of primary sulphonamides with lead tetra-acetate in DMSO,[23] but the reaction could not be extended to the synthesis of *N*-sulphamoylsulphoximides (17).[24]

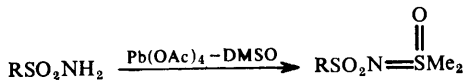
Perhaps the most versatile method of preparing sulphoximides has been introduced by Tamura and his co-workers who demonstrated that a wide variety of sulphoxides undergo ready amination under mild conditions with *O*-mesitylenesulphonylhydroxylamine (MSH).[25] The main restriction is the limited stability

[19] A. Le. Berne, C. Renault and P. Giraudeau, *Bull. Soc. chim. France*, 1971, 3245.
[20] D. J. Anderson, D. C. Horwell, E. Stanton, T. L. Gilchrist, and C. W. Rees, *J. C. S. Perkin I*, 1972, 1317.
[21] S. Colonna and C. J. M. Stirling, *Chem. Comm.*, 1971, 1591; *J. C. S. Perkin I*, 1974, 2120.
[22] B. Stanovnik and M. Tisler, *Org. Prep. and Proc.*, 1973, **5**, 87.
[23] M. Okahara, K. Matsunaga, and S. Komori, *Synthesis*, 1971, 96.
[24] M. Okahara, K. Matsunaga, and S. Komori, *Synthesis*, 1972, 203.
[25] Y. Tamura, K. Lumoto, J. Minamikawa, and M. Ikeda, *Tetrahedron Letters*, 1972, 4173.

of MSH even in solution at room temperature which prevents the use of more forcing conditions. Stoss and Satzinger have used MSH to prepare some previously unobtainable tricyclic sulphoximides (18) in good yields.[26]

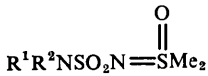
Recently it has been established that sulphoxides react with *O*-acetyl-*p*-nitrobenzohydroxamic acid to give the *N*-(*p*-nitrobenzoyl)sulphoximides, base hydrolysis of which liberates the free sulphoximides.[27]

The direct oxidation of sulphimides (19), readily accessible by a variety of



$R = p\text{-Tol}, Et$

(16)



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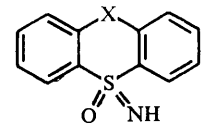
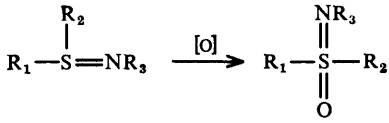


$X = CH_2, C{=}O, O, S, NR$

(18)

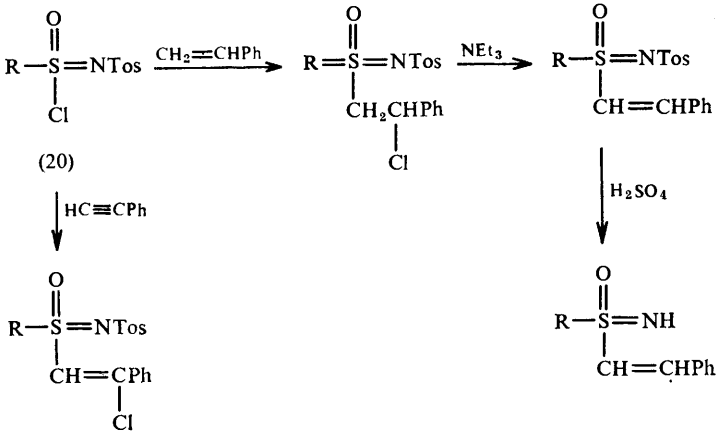


(19)

synthetic methods, in principle offers an attractive route to the sulphoximides. To date, no oxidant offers any improvement over potassium permanganate or the peracids, both of which frequently give poor yields.[28,29,30]

A route to αβ-unsaturated sulphoximides is provided by the reaction of olefins and acetylenes with *N*-tosylalkyliminosulphonyl chlorides (20).[31]

[26] P. Stoss and G. Satzinger, *Tetrahedron Letters*, 1974, 1973.
[27] Goedecke A.-G., Ger. P. 2 220 256 (Chem. Abs. 1974, **80**, 26 991).
[28] H. R. Bentley and J. K. Whitehead, *J. Chem. Soc.*, 1950, 2081.
[29] G. Kresze and B. Wustrow, *Chem. Ber.*, 1962, **95**, 2652.
[30] D. R. Rayner, D. M. von Schriltz, J. Day, and D. J. Cram, *J. Amer. Chem. Soc.*, 1968, **90**, 2721.
[31] Ya. N. Derkach, N. A. Pasmurtseva, L. N. Markovskii, and E. S. Levchenko, *Zhur. org. Khim.*, 1973, **9**, 1411.



3 Physical Properties

Since the first reports by Bentley and Reiner describing the sulphoximides very few spectral data have been published. Some i.r., n.m.r., and m.s. studies have been published by Oae and his group,[32] who reported that all the sulphoximides studied exhibited strong i.r. absorption bands at 3200—3250 cm^{-1} (N—H stretch) and 1200—1230 cm^{-1} (N—S=O stretch) not correlatable with changes in structure. In addition further characteristic bands were observed around 1100 and 1000 cm^{-1}. The chemical shifts in the n.m.r. spectra were similar to those for the corresponding sulphones, the increased acidity of the α-methylene protons in the sulphoximides being reflected in a small downfield shift. The sulphoximide group thus appears to be slightly more electron-withdrawing than the sulphone and considerably more so than the sulphoxide. The chemical shift of the imino proton appears at nearly the same position (7—8 τ) regardless of substitution on sulphur, and the proton is readily exchanged with D_2O. The marked solvent effects observed in the n.m.r. study, namely pronounced downfield shifts in protic as compared with aprotic solvents, indicate strong solvation of the sulphoximide groups. Corroborative data was obtained in a u.v. study by Barash.[33]

The ready solubility of sulphoximides in protic solvents, such as water and alcohols, compared with that of the corresponding sulphones is considered to result from the relatively large p*K*a values for the sulphoximides. (Typical p*K*a values are in the range 1.5—2.9.[34])

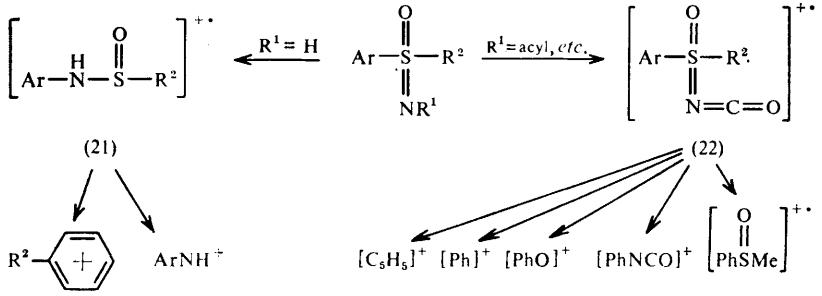
The mass spectra of some arylalkylsulphoximides have been rationalized in terms of an initial aryl to nitrogen migration giving the sulphinyl anilide cation

[32] (*a*) N. Furukewa, K. Taujihara, Y. Kawakatsu, and S. Oae, *Chem. and Ind.*, 1969, 266; (*b*) S. Oae, K. Harada, K. Tsufihara and N. Furukawa, *Internat. J. Sulphur Chem.* (*A*), 1972, 2, 49

[33] M. Barash, *Chem. and Ind.*, 1964, 1261.

[34] S. Oae, K. Tsufihara, and N. Furukawa, *Chem. and Ind.*, 1968, 1569.

(21) which subsequently fragments.[32] For *N*-substituted sulphoximides, in the absence of competitive rearrangements, the mass fragments are largely derived from the ion (22). Phenyl to nitrogen migration does take place, but the rearrangement no longer predominates.[35]



Hydrogen-exchange reactions of sulphoximides and sulphimides with D_2O in alkaline media indicate that the α-protons in sulphoximides are markedly less acidic.[36]

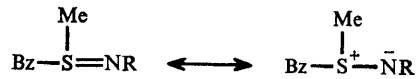
The nature of the bonding to S^{IV} has been the subject of debate for some considerable time.[37] Mixan and Lambert carried out an ESCA study on a series of derivatives of benzyl methyl suphide to provide information on the nature of the sulphur–nitrogen bond.[38] From the measurement of the S(2*p*) binding energies for the compounds they concluded that, although the actual nature of the bonds must lie between the covalent and semipolar extremes (23 and 24), the *N*-tosylsulphimide (23, R = Tos) is more polar than the sulphoxide (24) and that the *N*-tosylsulphoximide (25) is more polar than the corresponding sulphone. Their work suggested that there is little difference in polarity between the S=NH and S=O bond. The N(1*s*) binding energies indicated that although the S=N bond is more polar in (25, R = Tos) than in the parent sulphoximide (25, R = H), the electron-withdrawing nature of the *N*-tosyl group leaves a smaller negative charge on nitrogen.

4 Synthetic Applications

The sulphoximide group is an extremely versatile one for organic synthesis by virtue of the amphoteric nitrogen, the acidic α-methylene protons, and the chiral sulphur atom. The reactions of sulphoximides can be conveniently divided into their use as a versatile source of new ring systems and, alternatively, as alkylidene transfer reagents.

The first new ring system incorporating the sulphoximide group was reported by Stoss and Satzinger who obtained the benzoisothiazoles (26) *via* the Schmidt

[35] C. P. Whittle, C. G. MacDonald, and G. F. Katekar, *Org. Mass Spectrometry*, 1974, **9**, 422.
[36] M. Kobayashi, A. Mori, and H. Minato, *Bull. Chem. Soc. Japan*, 1974, **47**, 891.
[37] A. W. Johnson in 'Organic Compounds of Sulphur, Selenium, and Tellurium', ed. D. H. Reid (Specialist Periodical Reports), The Chemical Society, London, 1973, Vol. 2, p. 322.
[38] C. E. Mixan and J. B. Lambert, *J. Org. Chem.*, 1973, **38**, 1350.



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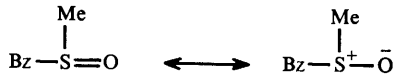

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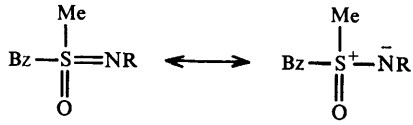


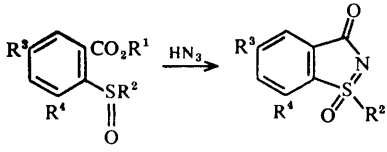
(25)

reaction of the esters (27).[39] The products exhibit remarkable chemical stability. In a subsequent extension of this work the same authors synthesized the analogous 6- and 7-ring systems (28 and 29).[40] The generation of a sulphoximide group during ring closure was also used by Cram and Williams to synthesize the ring systems (28), (30), and (31).[41]

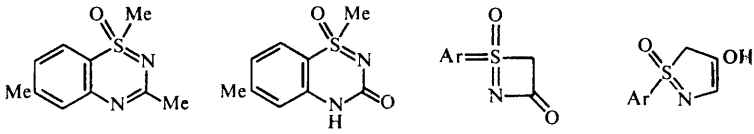
Other ring systems (32), (33), (34), (35),[42] and (36)[43] have been synthesized utilizing the nucleophilic character of the sulphoximide nitrogen and the acidity of the α-methylene protons. The thiazine (34) was synthesized in an optically pure form starting from (−)-(*R*)-*p*-tolyl-methyl-sulphoximide. In a recent publication Stoss and Satzinger have described the synthesis of a series of tricyclic sulphoximides (18).[26]

Alkylidene Transfer Reagents.—Although Johnson has recently reviewed the work of his group on the synthesis and reactions of the ylides derived from sulphoximides,[44] it is felt that the importance of this work in synthetic chemistry is such that a short review of the work is relevant. The general principle involves the reaction of an ylide (37), in which the carbanion is stabilized by resonance with an electron-deficient sulphur atom, with a carbonyl group or an electrophilic double bond. The first-formed betaine (38) collapses to give a three-membered ring with the expulsion of a sulphur species (Scheme 2).

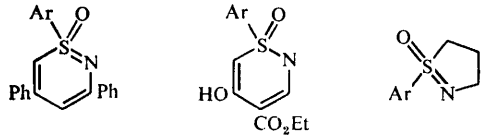
[39] P. Stoss and G. Satzinger, *Angew. Chem. Internat. Edn.*, 1971, **10**, 76.
[40] P. Stoss and G. Satzinger, *Chem. Ber.*, 1972, **105**, 2575.
[41] T. R. Williams and D. J. Cram, *J. Org. Chem.*, 1973, **38**, 20.
[42] A. C. Barnes, P. D. Kennewell, and J. B. Taylor, *J.C.S. Chem. Comm.*, 1973, 776.
[43] C. R. Johnson, G. F. Katekar, R. F. Huxol, and E. R. Janiga, *J. Amer. Chem. Soc.*, 1971, **93**, 3771.
[44] C. R. Johnson, *Accounts Chem. Res.*, 1973, **6**, 341.



(27) (26) (28) (29)

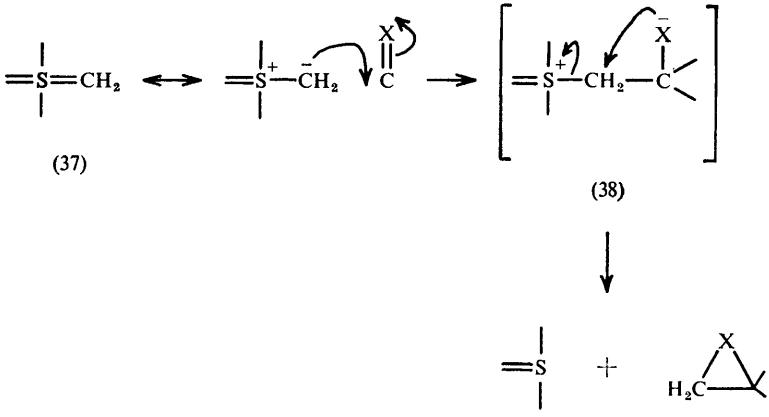


(30) (31) (32) (33)



(34) (35) (36)

It can be seen that the sulphur group in (37) needs to provide the ylide with the correct degree of stability. If the ylide is too stable then formation of the betaine is too slow and if it is too reactive then α-elimination to give a carbene becomes the dominant reaction. The function also needs to be a good leaving group to facilitate breakdown of the betaine. Corey and Chaykovsky first showed



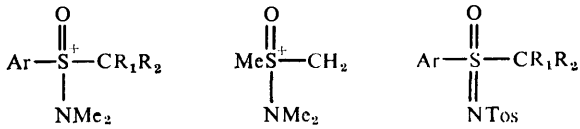
(37) (38)

Scheme 2

that ylides (39) and (40) generated by strong bases from trimethyloxosulphonium chloride and trimethylsulphonium iodide would act as methylene transfer reagents with aldehydes and ketones to give oxirans.[45]

(39) (40)

Although (39) and (40) are readily prepared and furnish high yield reactions, the extension from methylide to alkylide is not easy owing to the difficulty of *S*-alkylation of sulphoxides and the extreme instability of the corresponding ylides.[46,47] Consequently Johnson introduced the three sulphoximide-derived reagents (41),[48] (42),[49] and (43)[50] which are prepared by the strong base deprotonation of dialkylaminoalkylaryloxosulphonium fluoroborates, dialkylaminodimethyloxosulphonium fluoroborate, and alkyl aryl *N*-tosylsulphoximides. Such reagents are not only readily prepared, but are also very stable, the ylide (41) ($R^1 = R^2 = H$) remaining unchanged in DMSO solution at room temperature for two months.

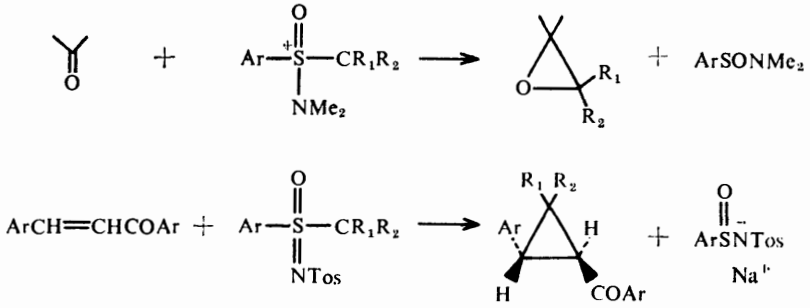


(41) (42) (43)

Whilst ylide (42) was introduced specifically as a methylene transfer reagent, (41) and (43) are more versatile and the groups studied include methyl, ethyl, isopropyl, cyclohexyl, and cyclopentyl. The precursors (41) are readily prepared by exhaustive alkylation of the appropriate alkyl aryl sulphoximide with trialkyloxonium fluoroborates, whilst alkyl aryl *N*-tosylsulphoximides are available by the synthetic routes discussed earlier. The reagents react with aldehydes and ketones to give oxirans, with imines to give aziridines, and with electrophilic olefins to give acyl cyclopropanes (Scheme 3). In the latter reaction, it is found

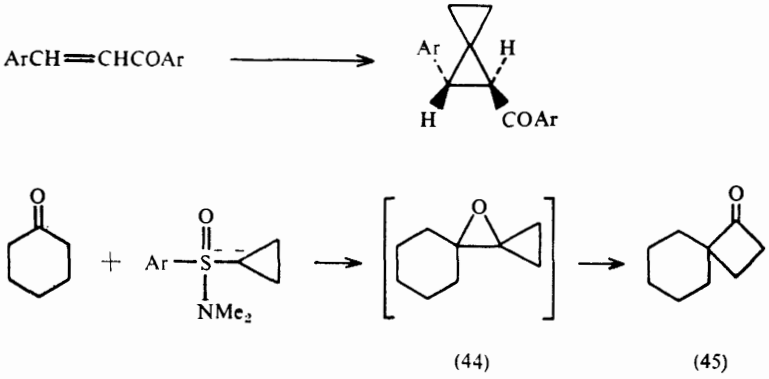
[45] E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, 1962, **84**, 867; *ibid.*, 1965, **87**, 1353.
[46] E. J. Corey, M. Jautelat and W. Oppolzer, *Tetrahedron Letters*, 1967, 2325; E. J. Corey and M. Jautelat, *J. Amer. Chem. Soc.*, 1967, **89**, 3912.
[47] For the preparation and uses of the much more stable diphenyl sulphonium cyclopropylide see B. M. Trost and M. J. Bogdanowicz, *J. Amer. Chem. Soc.*, 1971, **93**, 3773.
[48] C. R. Johnson, E. R. Janiga and M. Haake, *J. Amer. Chem. Soc.*, 1968, **90**, 3890; C. R. Johnson, M. Haake, and C. W. Schroeck, *ibid.*, 1970, **92**, 6594; C. R. Johnson and E. R. Janiga, *ibid.*, 1973, **95**, 7692.
[49] C. R. Johnson and P. E. Rogers, *J. Org. Chem.*, 1973, **38**, 1793.
[50] C. R. Johnson and G. F. Katekar, *J. Amer. Chem. Soc.*, 1970, **92**, 5753.

that irrespective of the geometry of the starting olefin, the stereochemistry of the cyclopropane is *trans*.



Scheme 3

The cyclopropyl ylide (41) (R^1R^2 = $-CH_2CH_2-$) is especially interesting because it reacts with electrophilic olefins to give spiropentanes (*e.g.* Scheme 4), but does not add to carbonyl groups except that of cyclohexanone, when the presumed intermediate oxaspirapentene (44) rearranges to the cyclobutanone (45). These results should be contrasted with those of Trost who succeeded in transferring cyclopropyl groups from diphenyl sulphonium cyclopropylide to carbonyl groups to give oxaspiropentanes.[47]



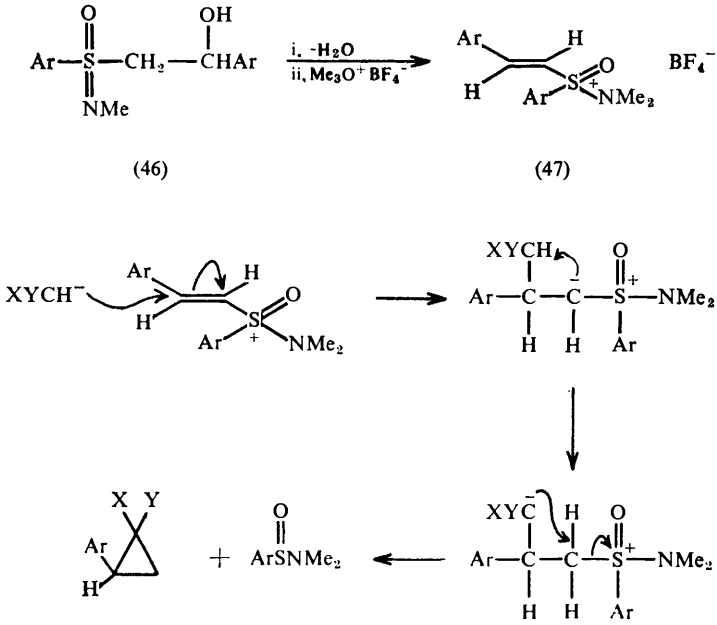
Scheme 4

Whilst the different ylides discussed have many reactions in common, there are some intriguing differences between them; in particular the ylide (40) appears to be a species apart. Thus with 4-t-butyl-cyclohexanone the ylide (40) gives the

E oxiran and the others the *Z* isomer; and with αβ-unsaturated ketones the ylide (40) gives vinyl oxirans whereas the rest give acyl cyclopropanes.[51]

A further advantage of (41) and (43), over (39) and (40) is that the sulphur atoms are chiral and the resultant ylides can be obtained in optically active forms. The reactions of these optically active ylides with achiral olefins, aldehydes and ketones lead to the induction of optical activity in the resultant oxirans and cyclopropanes. This point will be discussed in greater detail in the section on stereochemistry.

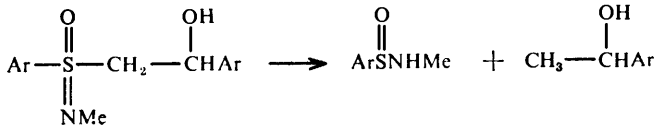
Reactions of Sulphoximide Carbanions.—In addition to the transfer reactions described above, a number of other reactions involving sulphoximides have been described. As has been shown previously, the alkyl protons of an alkylsulphoximide are sufficiently acidic to be removed by strong bases. Condensation with aldehydes such as benzaldehyde gives the isolable hydroxy alkyl sulphoximides (46) which undergo three new reactions.[52,53,54] Dehydration followed by alkylation gives the salt (47), a powerful Michael receptor, which with dibasic nucleophiles produces a range of novel products (Scheme 5).



Scheme 5

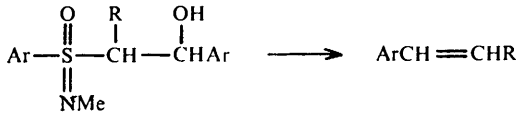
[51] C. R. Johnson and C. W. Schroeck, *J. Amer. Chem. Soc.*, 1971, **93**, 5303; C. R. Johnson, C. W. Schroeck and J. R. Shanklin, *ibid.*, 1973, **95**, 7424.
[52] C. R. Johnson and J. P. Lockard, *Tetrahedron Letters*, 1971, 4589.
[53] C. W. Schroeck and C. R. Johnson, *J. Amer. Chem. Soc.*, 1971, **93**, 5305.
[54] C. R. Johnson, J. R. Shanklin, and R. A. Kirchhoff, *J. Amer. Chem. Soc.*, 1973, **95**, 6462.

The sulphoximide (46) can also be reduced by aluminium amalgam in aqueous THF, this reaction removing the sulphur and generating an alcohol (Scheme 6). The condensation product (46) contains two asymmetric centres; the diastereo-



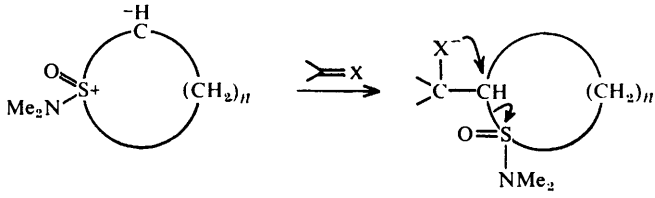
Scheme 6

mers can be separated, and subsequently reduced to yield the optically pure alcohols. Under these conditions no hydrogenolysis or racemization of the benzylic position occurs. When acetic acid is added to the reaction mixture in the reduction step dehydration results, giving rise to olefins (Scheme 7).



Scheme 7

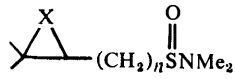
When R ≠ H the olefinic products are mixtures of *cis*- and *trans*-isomers. Further transformations result when the ylide is contained in a ring structure (48).[55]



(48) (49)

In these cases, the betaine (49) is readily formed on reaction with an olefin or a carbonyl group, but its breakdown now involves ring opening and the sulphinimide is part of the final structure (50).

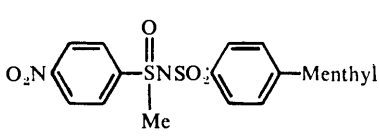
[55] C. R. Johnson and L. J. Pepoy, *J. Org. Chem.*, 1972, **37**, 671.



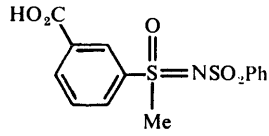
(50)

5 Stereochemistry

In one of their original publications, Bentley's group suggested that, by analogy with sulphones, the sulphur atom in a sulphoximide should be tetrahedral and that when the groups on sulphur are different the molecule should be chiral.[56] The tetrahedral orientation of the atoms around the sulphur atom has been verified by *X*-ray crystallography[57,58] and electron-diffraction studies,[59] whilst chirality was first demonstrated by the separation of the diastereomers of (51) prepared by condensing racemic *S*-*p*-nitrophenyl-*S*-methyl-sulphoximide with optically active 4-(3-menthyl)benzenesulphonyl chloride.[60] Subsequently *S*-methyl-*S*-(3-carboxyphenyl)-*N*-benzenesulphonyl sulphoximide (52) was resolved



(51)



(52)

via salt formation with (−)-α-phenylethylamine,[29] and *S*-phenyl-*S*-methyl-sulphoximide *via* salt formation with (+)-10-camphorsulphonic acid.[61] The preparation of optically active sulphoximides from both sulphoxides and sulphilimines using the various synthetic methods discussed previously has been the subject of a number of papers. It has recently been shown that the reaction of MSH with optically active sulphoxides is the best general method for preparing, in high yield, sulphoximides with high optical purity.[62]

The resolved sulphoximides have, to date, found two principal applications in asymmetric induction, particularly during alkylidene transfer reactions, and in the investigations of the stereochemistry of reactions on the sulphur atom.

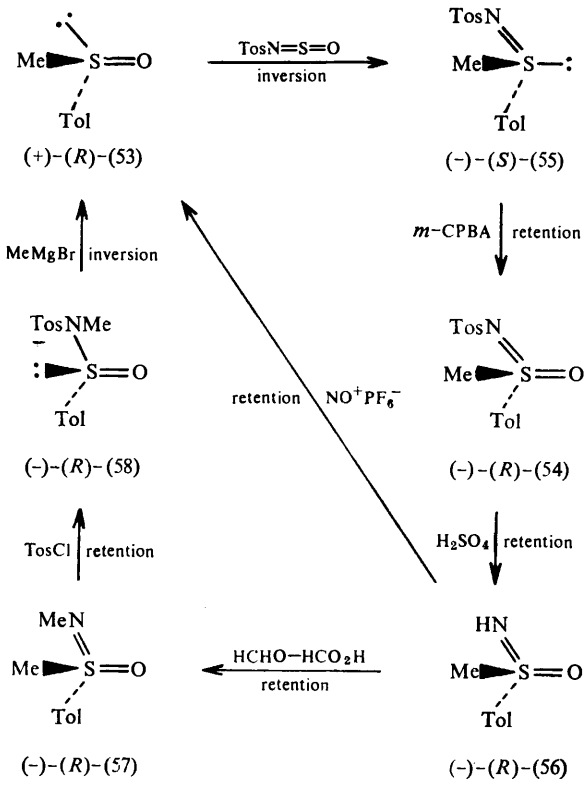
The alkylidene transfer reactions from racemic dialkylamino phenyloxosulphonium alkylides to alkenes, aldehydes, and ketones have been discussed previously. Alkylation of sulphoximides with trialkyloxonium fluoroborates

[56] H. R. Bentley, E. E. McDermott, and J. K. Whitehead, *Proc. Roy. Soc.*, 1951, **B138**, 265.
[57] B. W. Christensen, A. Kjaer, S. Neidle, and D. Rogers, *J.C.S. Chem. Comm.*, 1969, 169.
[58] G. D. Andreetti, G. Bocelli, and P. Sgarabotto, *Cryst. Struct. Comm.*, 1973, **2**, 171.
[59] M. Oberhammer and W. Zeil, *Z. Naturforsch.*, 1970, **25a**, 845.
[60] M. Barash, *Nature*, 1960, **187**, 591.
[61] R. Fusco and F. Tenconi, *Chimica e Industria*, 1965, **47**, 61.
[62] C. R. Johnson, R. A. Kirchhoff, and H. G. Corkins, *J. Org. Chem.*, 1974, **39**, 2458.

proceeds with retention of configuration and the resultant ylides, generated by sodium hydride in THF or DMSO, react with electrophilic olefins, aldehydes, and ketones to yield optically active cyclopropanes and oxirans.[63] In all cases where comparative data are available the optical purities of the products are the highest reported during asymmetric synthesis. Thus the ylide from dimethylamino-methyl-*p*-tolyloxosulphonium fluoroborate reacts with *trans*-methyl cinnammate to give (+)-(1*S*, 2*S*)-*trans*-methyl-2-phenyl-cyclopropanecarboxylate in 30.4% optical purity. Even greater asymmetric induction results when a substituted methylide is transferred to a symmetrical ketone or a terminal methylene group since here the carbon of the ylide becomes the chiral centre. An example is the reaction of (+)-(*R*)-dimethylamino-ethyl-*p*-tolyloxosulphonium fluoroborate with methyl acrylate which gives, after hydrolysis, (+)-(1*S*, 2*S*)-*trans*-2-methyl-cyclopropane-carboxylic acid with an optical purity of 43%. A different type of asymmetric induction is involved in the chlorine transfer reaction between (+)-(*S*)-*N*-chloro-methyl-phenyl-sulphoximide and 2,2-diphenylaziridine to give (+)-*N*-chloro-2,2-diphenylaziridine.[64] The extent of asymmetric induction in this case is not known.

The mechanisms and stereochemistry of reactions on tetrahedral sulphur are of considerable interest.[65] The ease and variety of methods for preparing sulphoximides from sulphoxides and sulphilimines, and the versatility of their reactions have resulted in sulphoximides being widely used in such studies. The work of Cram[66] on stereochemical reaction cycles involving, *inter alia*, sulphoximides, has been recently reviewed[67] and attention will here be concentrated on those reactions involving sulphoximides. The sequence of reactions which constitutes the first example of a monoligostatic stereochemical reaction cycle, *i.e.* one in which only one ligand is common to all the chiromers in the cycle is outlined (Scheme 8).[68] This represents the culmination of a number of smaller cycles. The absolute configuration of (+)-(*R*)-*p*-tolyl-methyl-sulphoxide (53) has been established by *X*-ray crystallography,[69] that of (−)-(*R*)-*S*-methyl-*S*-*p*-tolyl-*N*-tosylsulphoximide (54) by *X*-ray crystallography of its *N*-(3-*endo*-bromo-2-oxo-9-bornane-sulphonyl) derivative, and that of the sulphilimine (55) by the phase-diagram method.[66] Once the configurations of (55) and (54) were known it could be shown that the conversion of (53) to (55) occurs with inversion of configuration and those from (53) to (54) and (55) to (54) with retention. Deimidation of the sulphoximide (56) to sulphoxide (53) also proceeds with retention as has also been found in the deimidation of L-methionine-*S*-(or *R*)-sulphoximide

[63] C. R. Johnson and C. W. Schroeck, *J. Amer. Chem. Soc.*, 1973, **95**, 7418.
[64] R. Annunziata, R. Fornasier, and F. Montanari, *J.C.S. Chem. Comm.*, 1972, 1133.
[65] K. K. Andersen, *Internat. J. Sulphur Chem.* (*B*), 1971, **6**, 69.
[66] D. J. Cram, J. Day, D. R. Rayner, D. M. von Schriltz, D. J. Duchamp, and D. C. Garwood, *J. Amer. Chem Soc.*, 1970, **92**, 7369.
[67] G. C. Barrett, ref. 37 p. 45.
[68] T. R. Williams, A. Nudelman, R. E. Booms, and D. J. Cram, *J. Amer. Chem. Soc.*, 1972, **94**, 4684.
[69] (*a*) M. Axelrod, P. Bickart, J. Jacobus, M. M. Green, and K. Mislow, *J. Amer. Chem. Soc.*, 1968, **90**, 4835; (*b*) M. Hope, U. de la Camp, G. D. Homer, A. W. Messing, and L. H. Sommer, *Angew. Chem. Internat. Edn.*, 1969, **8**, 612.



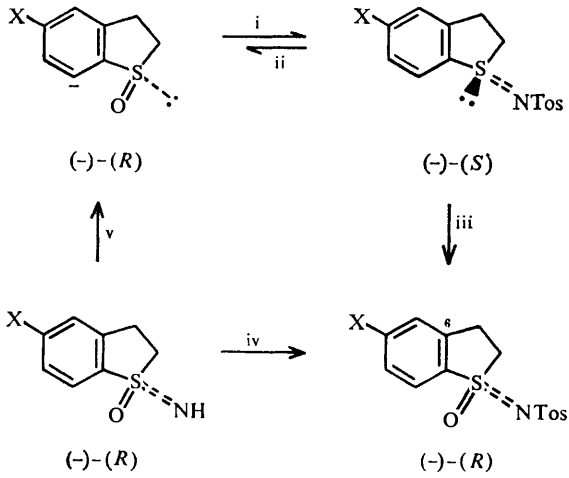
Scheme 8

to L-methionine-*S*(or *R*)-sulphoximide with nitrous acid.[70] Detosylation of (54) to (56) and methylation of (56) to (57) do not involve the chiral centre and are assumed to proceed with retention of configuration. For further verification (−)-(*R*)-(56) was tosylated to (−)-(*R*)-(54). By analogy with other nucleophilic substitutions on sulphinamides if it was assumed that the conversion of (58) to (53) involves inversion, the cycle then requires that the curious demethylation of (57) to (58) occurs with retention of configuration. It was therefore concluded that the substitution reactions leading to the sulphoximides studied can be regarded as electrophilic attack on the sulphur lone-pair electrons proceeding with retention of configuration. The desubstitution reactions which leave a lone pair of electrons on the sulphur atom also proceed with retention of configuration.

The conclusions reached from studies of acyclic compounds have recently been confirmed for the cyclic compound shown in Scheme 9.[71] The generalization

[70] R. A. Stephani and A. Meister, *Tetrahedron Letters*, 1974, 2307.
[71] F. G. Yamagishi, D. R. Rayner, E. T. Zwicker, and D. J. Cram, *J. Amer. Chem. Soc.*, 1973, **95**, 1916.

that electrophilic attack on sulphur proceeds with retention of configuration is found to hold.



Reagents: i, TosN=S=O; ii, H_2SO_4; iii, $KMnO_4$; iv, TosCl; v, HNO_2.

Scheme 9

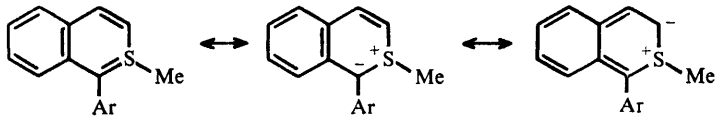
6 The Aromaticity of Azathiabenzene-*S*-oxides

The preparation, reactions, and electronic structures of the S^{IV} and S^{VI} heterocycles, thiabenzenes and thiabenzene-*S*-oxides, have been the subject of a number of studies.[72,73,74] Of particular interest is the nature of p_π–d_π bond between the sulphur atom and its adjacent atom, and the possibility of conjugation through this bond in potentially 'aromatic' cyclic conjugated systems.[75]

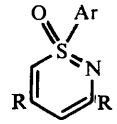
The reactions, stabilities, and proton and ^{13}C n.m.r. spectra of such compounds have shown that genuine thiabenzenes (59) and thiabenzene-*S*-oxides (34) are not aromatic and that ylidic forms (59b, c) are significant contributors to their resonance structure.

The synthesis of conjugated cyclic sulphoximides has been described and those proton n.m.r. shifts which provide information pertaining to the aromaticity of these azathiabenzene-*S*-oxides are listed (Table 1).[41,42,76] From the results available 3-H lies between 1.5 and 1.8τ, 4-H between 3.3 and 3.4τ and 6-H between 3.9 and 4.7τ. For the interpretation of such chemical shifts in terms of aromaticity the choice of model compounds is always a matter of contention,

[72] G. H. Sinkler, Jun., J. Stackhouse, B. E. Maryanoff, and K. Mislow, *J. Amer. Chem. Soc.*, 1974, **96**, 5648, 5650, and 5651.
[73] A. G. Hortmann, R. L. Harris, and J. A. Miles, *J. Amer. Chem. Soc.*, 1974, **96**, 6119.
[74] A. G. Hortmann and R. L. Harris, *J. Amer. Chem. Soc.*, 1971, **93**, 2471.
[75] D. H. Reid, ref. 37 p. 341; W. G. Salmond, *Quart. Rev.*, 1968, **22**, 253.
[76] Y. Tamura, T. Miyamoto, H. Taniguchi, K. Sumoto, and M. Ikeda, *Tetrahedron Letters*, 1973, 1729.

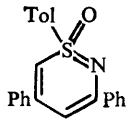
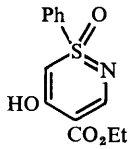
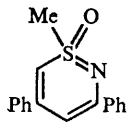
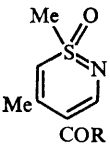


(59a) (59b) (59c)



(34)

Table ($CDCl_3$ *solution; shifts in* τ *values*)

Compound	*3-H*	*4-H*	*6-H*	*Reference*
	—	3.3	4.1	41
 (62)	1.50	—	4.7	42
	—	3.4	3.9	41
	1.74	4.2	—	76

but 3-carbethoxy-4-hydroxypyridine (60) and vinyl methyl sulphoxide (61) were chosen as models for 4-carbethoxy-3-hydroxy-1-phenyl-1,2-thiazabenzene (62). It can be seen that whereas 3-H of (62) lies close to 2-H of (60), 6-H lies upfield of 1-H in (61); a logical explanation is that the 6-H shift reflects the lack of aromaticity of the system whilst the low-field shift of 3-H results from the inductive effect of the nitrogen atom. Furthermore, in the benzo-[*e*]-1,2,4-thiadiazine (63) the shift of 3-H is clearly closer to the open-chain model (64) than the aromatic quinazoline (65).

These conclusions are supported by the ^{13}C n.m.r. shifts for (62). The low solubility of the pyridine model (60) prevented its ^{13}C n.m.r. spectrum from being recorded and shifts had to be compared with those in ethyl salicylate (66) and 1,3,5-trimethylthiabenzene-1-oxide (67). However, C-4 (97.48) in (62) is considerably shielded relative to C-2 in (66) (78.66), and C-6 (113.88) can be directly compared with C-6 in (67) (109.1). These high shieldings were interpreted as showing the considerable carbanionic nature of C-4 and C-6, suggesting significant contribution from the ylide structures (62a, b).

All these studies, coupled with the more complete analysis of thiabenzene-*S*-oxides strongly indicate that the compounds are not aromatic and that ylidic structures are a better representation of their true nature.

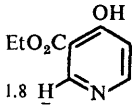
7 Applications of Sulphoximides

Patents have appeared claiming a wide variety of uses for sulphoximides. Thus methionine sulphoximide,[77] its salts,[78] and amides have been suggested as cotton defoliants and herbicides, whilst simple long-chain alkylsulphoximides (68) have been patented as detergents,[79] lubricating oil additives,[80] corrosion inhibitors for ferrous metals in contact with acids,[81] and as one element of a three-element catalytic system for polymerization of olefins.[82] Patented alkyl *N*-substituted sulphoximides include the anti-bacterial and anti-fungal *S*-methyl-*S*-decyl-*N*-chlorosulphoximide,[83] the phosphorus-substituted sulphoximides (69) claimed as pesticides,[84] and a fabric softener (70).[85]

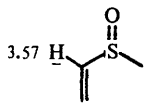
Amongst applications mentioned for arylalkylsulphoximides, (71) has herbicidal and pesticidal activity[86] whilst the *SS*-diphenyl-*N*-(alkylaminoalkyl)sulphoximides (72) are anti-spasmodics.[87] Other pharmacologically active sulphoximides include the indole derivative (73)[88] (claimed as a muscle-stimulant), the benzo-

[77] Monsanto, U.S.P. 3 179 510; American Cyanamide, U.S.P. 3 323 895.
[78] American Cyanamide, U.S.P. 3 295 949.
[79] The Proctor and Gamble Company, U.S.P. 3 255 116.
[80] The Chevron Research Company, U.S.P. 3 376 338.
[81] The Proctor and Gamble Company, U.S.P. 3 535 240.
[82] Eastman Kodak Company, U.S.P. 3 026 311.
[83] The Proctor and Gamble Company, U.S.P. 3 557 206.
[84] Roussel-Uclaf, Ger. P. 2 247 191.
[85] The Proctor and Gamble Company, U.S.P. 3 637 496.
[86] Shell International Research, Ger. P. 2 129 678.
[87] Warner Lambert, B.P. 1 168 700; see also ref. 6.
[88] Merck, Sharpe and Dohme Corporation, Ger. P. 2 062 017.

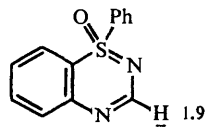
thiodiazines (74) (antihypertensives),[89] the benzothiazines (75)[90] (anti-secretory agents), and the benzisothiazolones (26) which are claimed to reduce blood sugar levels.[39] The benzothiadiazepine-*S*-oxides (76) have been claimed to have CNS-depressant activity albeit at a much lower level than the corresponding benzo-1,4-diazepines.[91]



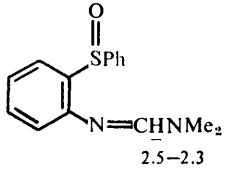
(60)



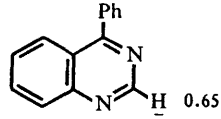
(61)



(63)

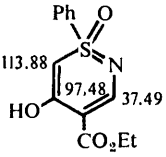


(64)

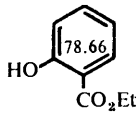


(65)

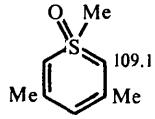
^{1}H *n.m.r. shifts in* τ *values*



(62)

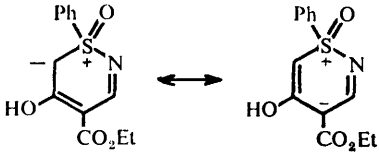


(66)



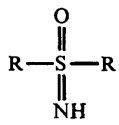
(67)

^{13}C *n.m.r. shifts in p.p.m. from* CS_2



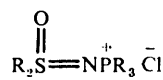
(62a) (62b)

[89] Beiersdorf A.G., Belg.P. 814 400.
[90] Warner Lambert, U.S.P. 3 803 131.
[91] E. Cohen and J. Mahnke, *Chem. Ber.*, 1972, **105**, 757.



(68)

(69)



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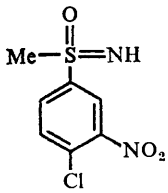
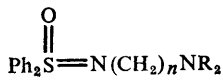
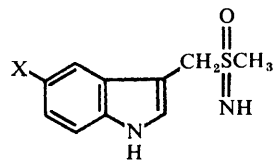


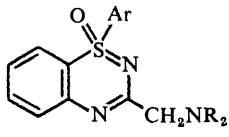
(71)



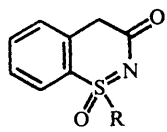
(72)



(73)



(74)



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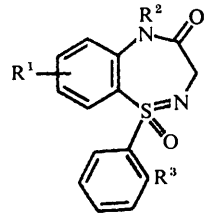

(76)