The Sulphoximides: an Update

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1 Introduction

The chemistry of the sulphoximides continues to be exploited and it is the objective of this review to complement and update a previous review[1] of the sulphoximides published in 1975. It is intended that the two reviews taken together will provide a comprehensive coverage of the chemistry of the sulphoximides from the first report of their preparation up until the end of 1979. Over the period covered by this survey, three other reviews[2,3,4] have appeared.

2 Synthesis

The four major routes of synthesis of sulphoximides from sulphoxides, sulphilimines, sulphonimidoyl chlorides, and sulphones are shown schematically in Figure 1. The first three of these routes had been described at the time of the

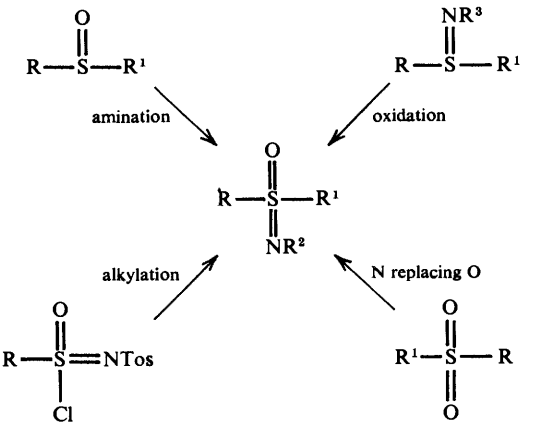


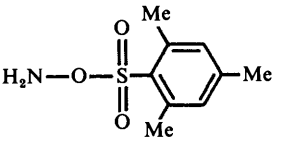
Figure 1

[1] P. D. Kennewell and J. B. Taylor, *Chem. Soc. Rev.*, 1975, **4**, 189.
[2] S. L. Huang and D. Swern, *Phosphorus and Sulfur*, 1976, **1**, 309.
[3] C. R. Johnson in 'Comprehensive Organic Chemistry', Vol. 3, ed. D. N. Jones, Pergamon Press, Oxford, 1979, p. 223.
[4] W. E. Truce, T. C. Klinger, and W. W. Brand in 'Organic Chemistry of Sulphur', ed. S. Oae, Plenum Press, New York, 1977, p. 588.

previous report and have since been further improved and modified, whilst the latter route from sulphones has recently been introduced.

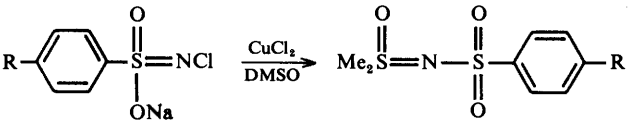
A. From Sulphoxides.—The original route[5] from sulphoxides by the action of hydrazoic acid is still being utilized but concern over the hazards involved in the handling* of this azide and of aqueous solutions of sodium azide will probably result in the decline of this method, at least on the industrial scale.

Mesitylene-*O*-sulphonyl hydroxylamine (1), MSH,[9] is an effective aminating agent, especially for the synthesis of optically active sulphoximides from optically active sulphoxides,[10] but the practical problems involved in synthesis of MSH, and doubts about its stability,[11] have reduced its appeal.



(1)

The trapping of nitrenes, generated from a number of sources by sulphoxides, especially dimethyl sulphoxide used as the concomitant solvent, continues to be used to prepare *N*-substituted sulphoximides. Thus Swern[12] has extended the early report[13] of the copper powder catalysed decomposition of chloramine-T in DMSO which yields *N*-arylsulphonyl sulphoximides (2a) to a range of sodium salts of *N*-chlorosulphonamides (Scheme 1).



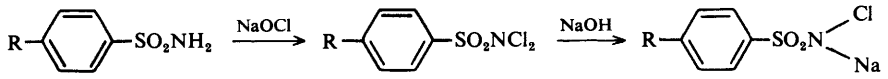
(2)a; R = Me
b; R = H
c; R = Cl
d; R = NO_2
e; R = $PhCH_2OCONH$

Scheme 1

*NaN_3 itself does not appear to be explosive[6] but HN_3 is both toxic and explosive. Explosions have been attributed to the action of HN_3 on the brass parts of vacuum gauges,[7] and in lead plumbing pipes through which dilute solutions of NaN_3 have been flushed.[8]

[5] H. R. Bentley, E. E. McDermott, and J. K. Whitehead, *Proc. R. Soc. London, Ser. B*, 1951, **138**, 265.
[6] Anonymous, *Chem. Eng. News*, 1978, **56** (47), 48.
[7] B. R. Cowley and J. F. Oughton, *Chem. Ind. (London)*, 1973, 444.
[8] J. O. Wear, *J. Chem. Educ.*, 1975, **52**, A23.
[9] Y. Tamura, K. Lumoto, J. Minamikawa, and M. Ikeda, *Tetrahedron Lett.*, 1972, 4173.
[10] C. R. Johnson, R. A. Kirchhoff, and H. G. Corkins, *J. Org. Chem.*, 1974, **39**, 2458.
[11] R. Y. Ning, *Chem. Eng. News*, 1973, **51** (50), 36.
[12] R. W. Heintzelman and D. Swern, *Synthesis*, 1976, 731.
[13] D. Carr, T. P. Siden, and R. W. Turner, *Tetrahedron Lett.*, 1969, 477.

The substituted sodium *N*-chlorosulphonamides are conveniently prepared by the action of sodium hypochlorite and base on the appropriate sulphonamide (Scheme 2). Swern greatly improved the value of the reaction by replacing the

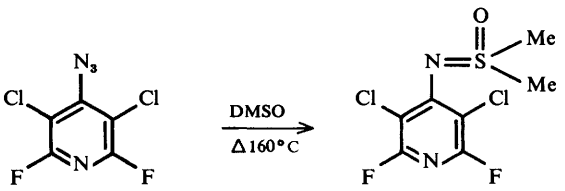


Scheme 2

copper powder catalyst, the use of which was known to give variable yields, with a soluble catalyst. The yields are then higher and more reproducible.

Oae[14] has shown that optically active butyl methyl sulphoxide reacts with chloramine-T in methanol in the presence of copper powder to give optically active *S*-butyl-*S*-methyl-*N*-tosylsulphoximide.

The thermal decomposition of two more azides in DMSO to give *N*-substituted dimethyl sulphoximides has been reported[15,16] (Schemes 3 and 4).

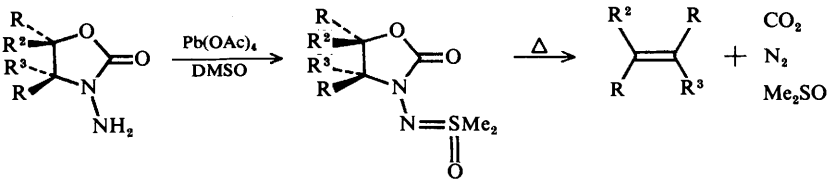


Scheme 3

Scheme 4

The preparation of *N*-substituted sulphoximides by the trapping by sulphoxides of nitrenes generated by the action of lead tetra-acetate on *N*-amino lactams was reported earlier.[17] This reaction has continued to be investigated largely because of the range of reactions undergone by the sulphoximide products. Thus White[18] applied the technique to *N*-amino-oxazolones (3) and thermolysed the sulphoximides (4) to give an elegant synthesis of highly substituted olefins (Scheme 5).

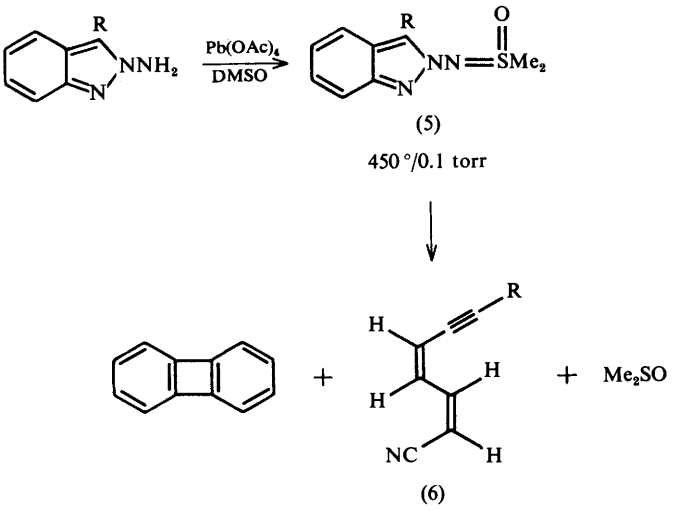
[14] M. Moriyama, T. Numato, and S. Oae, *Org. Prep; Proc. Int.*, 1974, **6**, 207.
[15] R. E. Banks, R. I. Higgins, A. Frakash, M. Rawston, and G. R. Sparks, *J. Fluorine Chem.*, 1977, **9**, 327.
[16] G. W. Kirby, J. W. M. McKinnon, and R. P. Sharma, *Tetrahedron Lett.*, 1977, 215.
[17] D. J. Anderson, D. C. Horwell, E. Stanton, T. L. Gilchrist, and C. W. Rees, *J. Chem. Soc., Perkin Trans. 1*, 1972, 1317.
[18] M. Kim and J. D. White, *J. Am. Chem. Soc.*, 1977, **99**, 1172.



(3) (4)

Scheme 5

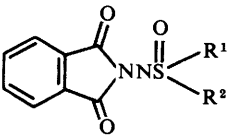
Similarly, Rees[19] decomposed the sulphoximide (5) to the acetylenic dienonitrile (6) (Scheme 6).



Scheme 6

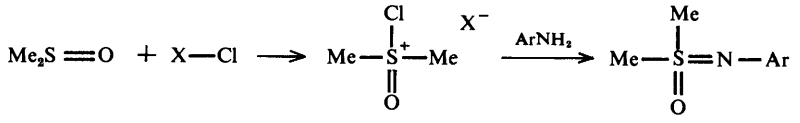
The ready base-catalysed decomposition of these sulphoximides has been used, particularly by Colonna and his associated groups, to investigate the stereochemistry of the nitrene insertion reaction. Thus the reaction of an optically active sulphoxide with the nitrene from *N*-aminophthalimide gives an optically active sulphoximide (7), decomposition of which regenerates the sulphoxide with a high degree of stereospecificity.[20] An intriguing extension of the reaction used the nearly symmetric sulphoximide (7; $R^1 = CH_2Ph$, $R^2 = CD_2Ph$)[21] and the decomposition of racemic (7) in the presence of chiral amines will be discussed in the later section on stereochemistry.

[19] B. M. Adger, M. Keating, C. W. Rees, and R. C. Storr, *J. Chem. Soc., Perkin Trans. 1*, 1975, 41.
[20] S. Colonna and C. J. M. Stirling, *J. Chem. Soc., Perkin Trans. I*, 1974, 2120.
[21] K. K. Andersen, M. Cinquini, S. Colonna, and F. L. Pilar, *J. Org. Chem.*, 1975, **40**, 3780.



(7)

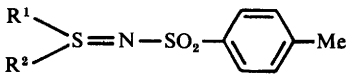
The conversion of sulphoxides to sulphoximides *via* an oxidative-amination route has been described by two groups.[22,23] Dimethyl sulphoxide reacts at low temperatures with sulphuryl chloride or t-butyl hypochlorite to give an intermediate complex (8) which is not isolated but is treated *in situ* with arylamines giving *N*-aryl sulphoximides (9) (Scheme 7). This provides an excellent route to otherwise inaccessible *N*-aryl sulphoximides.



(8) (9)

Scheme 7

B. From Sulphilimines.—The oxidation of sulphilimines (10) to sulphoximides is another long-standing method of preparation.[24] In principle, this is an attrac-



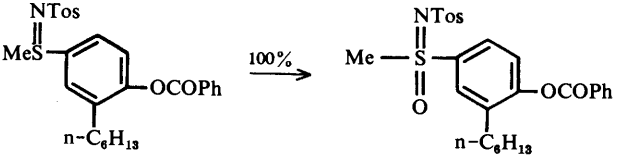
(10)

tive route since *N*-tosyl sulphilimines are readily available from the reaction of sulphides with chloramine-T. Unfortunately, the oxidants which have been described, mainly potassium permanganate or peracids, have failed to give consistent results. However, three new techniques have been described which appear to be capable of giving consistently good yields. The first of these was a biphasic system with ruthenium oxide–sodium metaperiodate as the oxidant.[25] Water-soluble ruthenium dioxide is oxidized in the aqueous layer by the metaperiodate to the tetroxide which then partitions into the organic layer. Sulphilimine is rapidly oxidized to the sulphoximide and the tetroxide is reduced to the dioxide which returns to the aqueous layer for the process to be repeated. Thus the expensive ruthenium salt is only used in catalytic quantities whilst the relatively cheap periodate is consumed. In the original report, the reaction was restricted to *N*-substituted dimethyl sulphilimines but work in the

[22] R. W. Heintzelman, R. B. Bailey, and D. Swern, *J. Org. Chem.*, 1976, **41**, 2207.
[23] P. K. Claus, W. Rieder, P. Hofbauer, and E. Vilsmaier, *Tetrahedron*, 1975, **31**, 505.
[24] H. R. Bentley and J. K. Whitehead, *J. Chem. Soc.*, 1950, 2081.
[25] H. S. Veale, J. Levin, and D. Swern, *Tetrahedron Lett.*, 1978, 503.

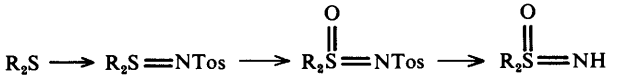
author's laboratory[26] has shown that it proceeds very satisfactorily for substituted sulphilimines (*e.g.* Scheme 8).

The other two oxidations rely on the susceptibility of *N*-tosyl sulphilimines to nucleophilic attack on sulphur. Thus the anion of *m*-chloroperbenzoic acid in



Scheme 8

ethanol-saturated aqueous potassium carbonate[27] or alkaline hydrogen peroxide[28] gives very high yields of *N*-tosyl sulphoximides. These oxidations, coupled with the introduction of a high-yield phase-transfer preparation of *N*-tosyl sulphilimines from chloramine-T and sulphides[29] and the use of sodium in liquid ammonia to remove the tosyl group from the *N*-tosyl sulphoximides,[30] make this sequence a very attractive route to sulphoximides (Scheme 9).



Scheme 9

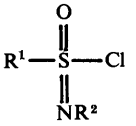
The difficulty of oxidation of *N*-tosyl sulphilimines is presumably due to the strongly electron-attracting tosyl group as is implied by the success of the latter two methods. In further support of this, Oae[31] has shown that 'free' sulphilimines (11), *i.e.* ones unsubstituted on nitrogen, can be produced by the action of strong acid on *N*-tosyl sulphilimines and then rapidly oxidized to sulphoximides with

(11) (12)

permanganate. Also, (11) can be chlorinated by *N*-chlorosuccinimide to the *N*-chloro derivatives (12)[32] which can be hydrolysed by base to sulphoximides with, in appropriate cases, retention of configuration.[33] The utility of these routes is however severely limited by the instability of all but diaryl sulphilimines (11; R^1, R^2 = aryl).

[26] W. R. Tully, unpublished observations.
[27] S.-L. Huang and D. Swern, *J. Org. Chem.*, 1979, **44**, 2510.
[28] C. R. Johnson and R. A. Kirchhoff, *J. Org. Chem.*, 1979, **44**, 2280.
[29] C. R. Johnson, K. Mori, and A. Nakanishi, *J. Org. Chem.*, 1979, **44**, 2065.
[30] R. B. Greenwald and D. H. Evans, *Synthesis*, 1977, 650.
[31] T. Yoshimura, T. Omata, N. Furukawa, and S. Oae, *J. Org. Chem.*, 1976, **41**, 1728.
[32] T. Yoshimura, N. Furukawa, T. Akasaka, and S. Oae, *Tetrahedron*, 1977, **33**, 1061.
[33] T. Akasaka, T. Yoshimura, N. Furukawa, and S. Oae, *Chem. Lett.*, 1978, 417.

C. From Sulphonimidoyl Chlorides.—The reactions of sulphonimidoyl chlorides (13), originally introduced by Levchenko,[34] have recently been investigated in more detail.[35–37] Simplified synthetic schemes involving the condensation of sulphinamides (14) with chlorine, *N*-chlorobenzotriazole,[36] or t-butyl hypochlorite[37] have made these compounds more readily accessible. Three separate sulphoximide syntheses have been identified from these reagents. The action of strong base on (13; R^1 = Me, R^2 = Tos) generates the iminosulphene (15),



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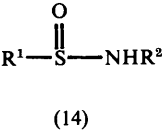
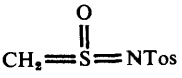
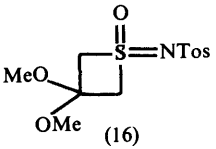


(14)

which can be trapped, albeit in low yield, by 1,1-diethoxyethylene to give the cyclic sulphoximide (16). Methoxide and phenoxide displace the chlorine atom

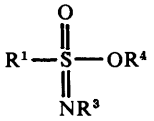


(15)



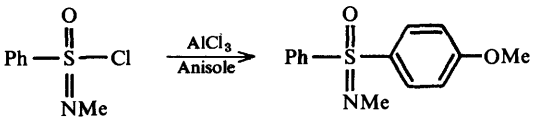
(16)

in *N*-alkyl sulphonimidoyl chlorides (13; R^1 = alkyl) to give sulphonimidates (17), which react readily with alkyl lithiums to give *N*-alkyl sulphoximides.



(17)

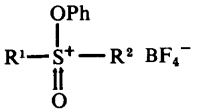
Finally the sulphonimidoyl chlorides will react with activated aromatics in the presence of aluminium chloride in a Friedel–Crafts type of reaction (Scheme 10).



Scheme 10

[34] E. S. Levchenko and A. V. Kirsanov, *Zh. Obshch. Khim.*, 1960, **30**, 1553 (*Chem. Abstr.*, 1961, **55**, 3484).
[35] C. R. Johnson, E. V. Jonsson, and C. C. Bacon, *J. Org. Chem.*, 1979, **44**, 2055.
[36] C. R. Johnson, E. V. Jonsson, and A. Wambsgans, *J. Org. Chem.*, 1979, **44**, 2061.
[37] C. R. Johnson and A. Wambsgans, *J. Org. Chem.*, 1979, **44**, 2278.

D. From Sulphones.—As stated earlier, the preparation of sulphoximides from sulphones was unknown at the time of the previous review. Two groups[38,39] have now shown that the phenoxysulphonium salts (18) produced by the reaction of sulphones with phenyl diazonium fluoroborates react with primary amines to give high yields of *N*-alkyl sulphoximides.



(18)

3 Physical Properties

The gas-phase structure of dimethyl sulphoximide, as determined by electron diffraction,[40] is shown in Figure 2. The measured bond angles clearly show

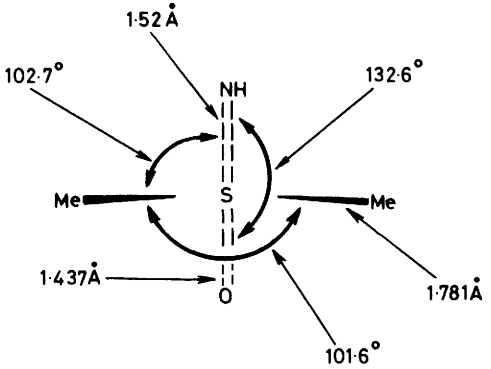
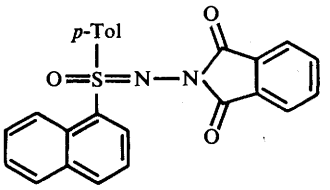


Figure 2

considerable distortion from a pure tetrahedron around the sulphur atom, whilst the S–N bond distance (1.52 Å) is close to that predicted for a 'pure' S–N double bond (1.54 Å).[41] Very similar S–N and S–O bond lengths have been found in *X*-ray crystallographic studies of (±)-*N*-phthalimido-*p*-tolyl-α-naphthylsulphoximide (19),[42] its (+)-enantiomer,[43] *S*,*S*-dimethyl-*N*-(2-oxo-1-indolinyl)-sulphoximide (20),[44] and (+)-*N*-phthalimido-2(*R*)-bromo-2-octyl-*p*-tolyl-(*R*)-sulphoximide (21).[45]

[38] M. Shimagaki, H. Tsuchiya, Y. Ban, and T. Oishi, *Tetrahedron Lett.*, 1978, 3435.
[39] G. R. Chalkley, D. J. Snodin, G. Stevens, and M. C. Whiting, *J. Chem. Soc., Perkin Trans. 1*, 1978, 1580.
[40] H. Oberhammer and W. Zeil, *Z. Naturforsch., Teil A*, 1970, **25**, 845.
[41] M. Goehring, *Quart. Rev. Chem. Soc.*, 1956, **10**, 437.
[42] G. D. Andreetti, G. Bocelli, and P. Sgarabotto, *Gazz. Chim. Ital.*, 1975, **105**, 165.
[43] G. D. Andreetti, G. Bocelli, L. Coglii, and P. Sgarabotto, *Cryst. Struct. Commun.*, 1975, **4**, 393.
[44] M. D. Cabezuelo, C. Foces-Foces, F. H. Cano, and S. Garcia-Blanco, *Acta Crystallogr.*, 1972, **B33**, 3911.
[45] G. Andreetti, G. Bocelli, and P. Sgarabotto, *Cryst. Struct. Commun.*, 1977, **6**, 761.

Despite the crystal data clearly showing the double bond character of the S–N bond, a ^{13}C n.m.r. study of *S,S*-dimethyl-*N*-(4-substituted-phenyl)aryl sulphoximides (22)[46] was interpreted as showing a high dipolar character for the S–N bond (22*a*). Whilst this characteristic was not as pronounced as in the sul-



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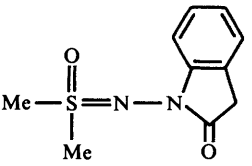

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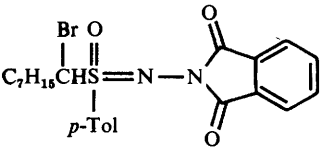
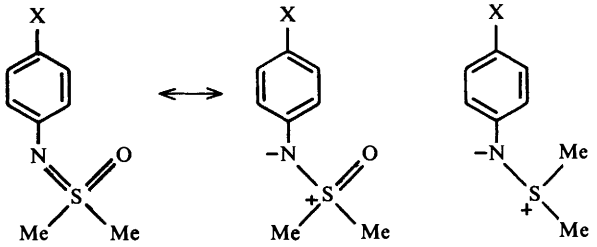


(21) S═N = 1.63Å

philimines (23), the sulphoximide group does appear to act in these molecules as a moderately strong electron donor.



(22) (22a) (23)

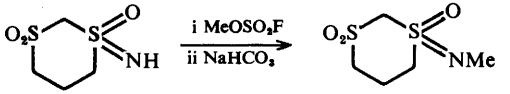
From pK_a measurements, sulphoximides can be seen to be more polar and basic than either sulphoxides or sulphones. It would therefore be expected that, like these compounds,[47] sulphoximides might act as dipolar aprotic solvents and enhance S_N2 reactions. In fact molten dimethyl sulphoximide was found to be a good solvent for inorganic salts, and in admixture with methanol to be capable of accelerating the rate of S_N2 displacement reactions to a greater extent than either dimethyl formamide or dimethyl sulphoxide under the same conditions.[48]

[46] G. Kresze, M. Berger, P. K. Claus, and W. Rieder, *Org. Magn. Reson.*, 1976, **8**, 170.
[47] A. J. Parker, *Quart. Rev. Chem. Soc.*, 1962, **16**, 163.
[48] N. Furukawa, F. Takahashi, T. Yoshimura, and S. Oae, *Chem. Lett.*, 1972, 1359.

4 Synthetic Applications

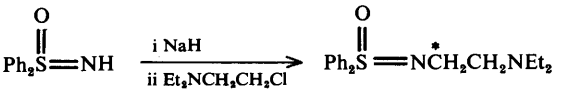
The great interest of the sulphoximide group lies in the variety of reactions available to it. The nitrogen is nucleophilic, even more so after deprotonation, and the protons α to the sulphur atom are sufficiently acidic to be readily removed with base to give very reactive anions. Combination of the two types of reaction has led to the preparation of cyclic sulphoximides of interest *per se* or as novel 'aromatic' heterocycles and these will be discussed in a later section. Further examples of most types of reaction have been described during this period.

'Magic methyl', methyl fluorosulphate, is sufficiently electrophilic to alkylate the nitrogen atom of sulphoximides without prior anion formation (Scheme 11).[30]

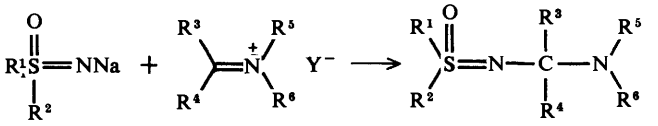


Scheme 11

Less reactive alkylating agents require prior salt formation, *e.g.* using sodium hydride in toluene (Schemes 12 and 13).[49,50]



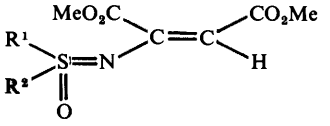
Scheme 12



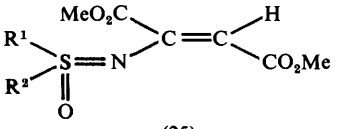
Scheme 13

The Michael addition of sulphoximides to activated double bonds has been used as the initial stage of a number of syntheses of cyclic sulphoximides as will be discussed below. Tamura[51] has studied the addition of a variety of sulphoximides to, *inter alia*, dimethyl acetylenedicarboxylate which gives in high yields mixtures of *cis* and *trans* adducts (24) and (25). The isomer distribution is highly solvent-dependent with the *cis* isomer (24) dominant when the reaction is conducted in DMSO and the *trans* isomer (25) dominating in methanol. With difunctional reagents, *e.g.* S_2Cl_2, two sulphoximides can be incorporated to give (26) for example.[52] t-Butyl hypochlorite chlorinates sulphoximides to give N–Cl deriva-

[49] B. Liedthe and K. O. Vollner, *J. Labelled Comp. Radiopharm.*, 1978, **14**, 825.
[50] Ger. Offen. 2539220 to Ludwig Heuman & Co. G.m.b.H. (*Chem. Abstr.*, 1977, **87**, 39112j).
[51] Y. Tamura, S. M. Bayomi, M. Tsunekawa, and M. Ikeda, *Chem. Pharm. Bull.*, 1979, **27**, 2137.
[52] M. Okahara, E. Yoshikawa, I. Ikeda, and S. Komori, *Synthesis*, 1975, 521.

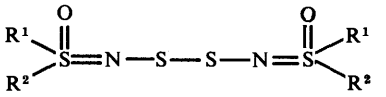


(24)

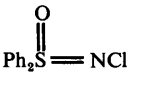


(25)

tives[53] (27) which are effective chlorinating agents[54–56] and which add

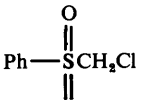


(26)

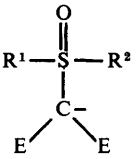


(27)

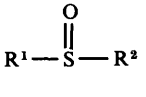
homolytically to olefins.[57] The acidic α-protons of sulphoximides can be replaced by halogen[58] (28) or deuterium[59] (Scheme 14). The alkylidene transfer reactions of these anions will be discussed later.



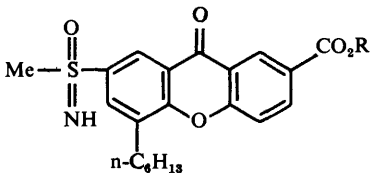
(28)



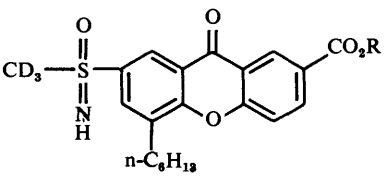
(30)



(31)



(29) R = H



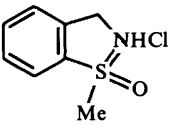
(34) R = Me

Scheme 14

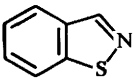
The decomposition of sulphoximides has been studied in a number of ways. Diazomalonate reacts with sulphoximides in the presence of soluble copper salts to give oxosulphonium ylides (30).[59] The reaction of optically active sulphox-

[53] C. R. Johnson and H. G. Corkins, *J. Org. Chem.*, 1978, **43**, 4136.
[54] R. Annunziata, R. Fornasier, and F. M. Montanari, *J. Chem. Soc., Chem. Commun.*, 1972, 1133.
[55] T. Akasaka, N. Furukawa, and S. Oae, *Chem. Lett.*, 1979, 529.
[56] H. Morita, H. Itoki, N. Furukawa, and S. Oae, *Chem. Lett.*, 1978, 817.
[57] T. Akasaka, N. Furukawa, and S. Oae, *Tetrahedron Lett.*, 1979, 2035.
[58] D. P. Kay, unpublished results.
[59] N. Furukawa, F. Takahashi, T. Yoshimura, and S. Oae, *Tetrahedron Lett.*, 1977, 3633; *Tetrahedron*, 1979, **35**, 317.

imides proceeds with retention of configuration and it was presumed that the sulphoxide (31) was an intermediate. The cleavage of *S*-methyl groups by thermolysis of 1-methyl-1*H*,3*H*-1,2-benzisothiazole-1-oxide hydrochloride (32) to 1,2-benzisothiazole (33)[60] and of the xanthone sulphoximide (29) to a complex mixture containing *inter alia* the corresponding methyl ester (34)[61] has been described. The role of the acidic group in the latter methyl transfer reaction was shown when phenyl methyl sulphoximide, which is stable on heating alone to 240 °C, rapidly decomposed at 230 °C in the presence of benzoic acid to give a complex mixture containing methyl benzoate.

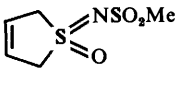


(32)

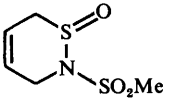


(33)

The thermal decomposition of butadiene sulphone (sulpholene) is well known[62] to give butadiene and sulphur dioxide. In the case of (35), the *N*-methanesulphonyl sulphoximide analogue of sulpholene, thermolysis without solvent results in ring expansion to (36), whilst heating in sulphur dioxide gives sulpholene and *N*-sulphinylmethanesulphonamide (37) indicating that butadiene is also produced from (35).



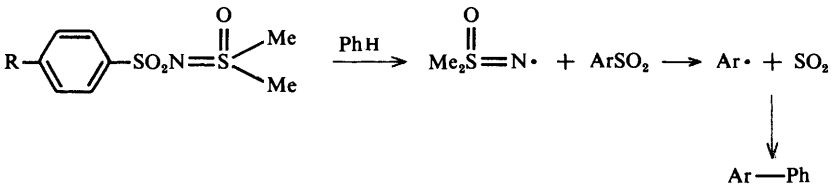
(35)



(36)

(37)

Photolysis of *N*-arylsulphonyl-*S*,*S*-dimethyl sulphoximides in benzene was found to generate mainly biphenyls[63] (Scheme 15).



Scheme 15

N-Tosyl-α-halosulphoximides (*e.g.* 38) undergo a type of Ramberg–Bäcklund

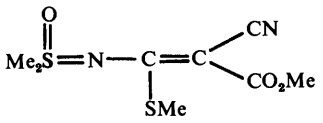
[60] R. H. Rynbrandt and D. P. Balgoyen, *J. Org. Chem.*, 1978, **43**, 1824.
[61] A. C. Barnes, P. W. Hairsine, D. P. Kay, P. J. Ramm, and J. B. Taylor, *J. Heterocycl. Chem.*, 1979, **16**, 1089.
[62] W. L. Mock and R. M. Nugent, *J. Am. Chem. Soc.*, 1975, **97**, 6526.
[63] R. A. Abramovitch and T. Takaya, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1806.

rearrangement in the presence of strong base to give *cis–trans* mixtures of olefins (39) with the expulsion of tosyl sulphonamide.[64]

(38) (39)

5 Heterocyclic Sulphoximides

Interest in the incorporation of the sulphoximide moiety into heterocycles and concern with their 'aromaticity' have continued. Dimethyl sulphoximide was condensed with methyl 3,3-bis(methylthio)-2-cyanoacrylate and the intermediate (40) cyclized by NaH–DMSO to give 1-methyl-3-methylthio-4-cyano-5-

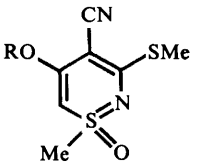


(40)

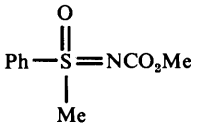
hydroxy-2-azathiabenzene-1-oxide (41).[65] Whilst the i.r. spectrum of (41) indicated that it exists, at least in the solid phase, as a mixture with the corresponding keto form, reaction with dimethyl sulphate and acetic anhydride gave exclusively (42) and (43) respectively. In a different approach[66] phenyl methyl sulphoximide was treated with methyl chloroformate, the adduct (44) isolated, and then a second carbomethoxy group (45) added. Reaction with one equivalent of a primary amine gave (46) which was cyclized to (47). In this case spectral data showed the product (47) to exist totally in the keto form. Base-catalysed alkylations readily gave *C*-alkylation (48) whilst attempted ethylation with ethyl oxonium fluoroborate caused a novel tautomerization to give (49).

The structure of (47) is fully supported by ^{1}H and ^{13}C n.m.r. and is reminiscent of a transformation found earlier in ylide work[67] (Scheme 16). Further ethylation of (49) gives (50) whose ^{13}C n.m.r. spectrum showed considerable ylidic character to the S—C-6 bond. In support of this, deuterium exchange of

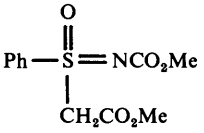
[64] C. R. Johnson and H. G. Corkins, *J. Org. Chem.*, 1978, **43**, 4140.
[65] M. Watanabe, M. Minohara, K. Masuda, T. Kinoshita, and S. Furukawa, *Heterocycles*, 1976, **4**, 1875.
[66] K. Schaffner-Sabba, H. Tomaselli, B. Henrici, and H. B. Renfroe, *J. Org. Chem.*, 1977, **42**, 952.
[67] C. R. Johnson, M. Haake, and C. W. Schroek, *J. Am. Chem. Soc.*, 1970, **92**, 6594.



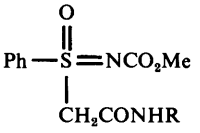
(41) R = H
(42) R = Me
(43) R = COMe



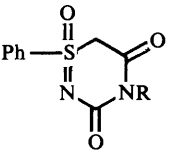
(44)



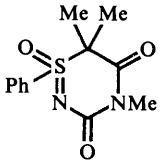
(45)



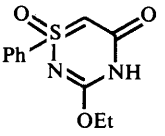
(46)



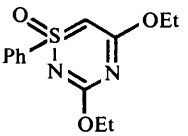
(47)



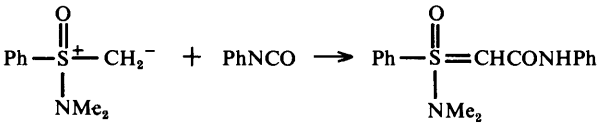
(48)



(49)

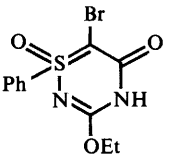


(50)



Scheme 16

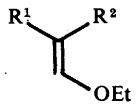
the C-6 proton occurs rapidly in acidic and basic media and bromination also occurs at this position (51).



(51)

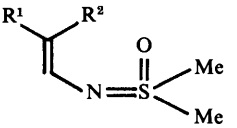
Dimethyl sulphoximide was condensed with a range of ethoxymethylene di-

carboxyl and related compounds (52) and the intermediate olefinic sulphoximides (53) were cyclized to various cyclic sulphoximides.[68] In the case of (53;



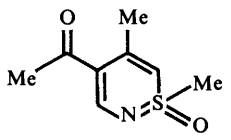
(52)

$R^1 = R^2 = CO_2Me$
$R^1 = R^2 = CO_2Et$
$R^1 = COCH_3$, $R^2 = CO_2Et$
$R^1 = R^2 = CN$
$R^1 = CN$, $R^2 = CO_2Et$

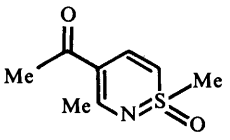


(53)

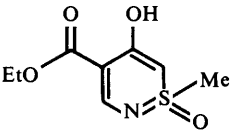
$R^1 = R^2 = COMe$), two isomeric products (54) and (55) were produced, (53; $R^1 = R^2 = CO_2Et$) gave (56), whilst (53; R = COMe, $R^1 = CO_2Et$) gave a range of products which were dependent upon the temperature, but which included (57), (58), (59), and dimers. On the other hand, (53; $R^1 = R^2 = CN$



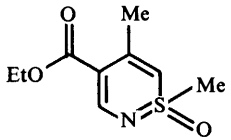
(54)



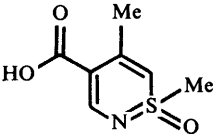
(55)



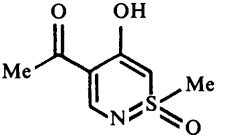
(56)



(57)



(58)

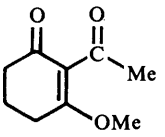


(59)

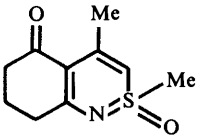
and $R^1 = CN$, $R^2 = CO_2Et$) did not cyclize whilst the cyclic enone (60) gave the bicyclic structure (61). Another bicyclic structure (62) arose from the condensation of (52; $R^1 = R^2 = CO_2Et$) with tetramethylene sulphoximide (63). Interesting comparisons were drawn between the spectra of the azathiabenzenes (54) and the analogous thiabenzenes (64).

The ^1H shifts of the Ha protons indicated less carbanionic character in the aza series, whilst the i.r. frequencies of exocyclic carbonyl groups confirmed that the betaine-like character was less in the aza series. Bromination was found to occur readily in the Ha position. It was therefore concluded from both the chemical and physical evidence that the azathiabenzenes have ylidic characteristics but that the contribution from charge separated forms, *e.g.* (65), is less than in the analogous thiabenzene-1-oxides.

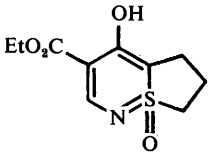
[68] Y. Tamura, M. Tsunekawa, T. Miyamoto, and M. Ikeda, *J. Org. Chem.*, 1977, **42**, 602.



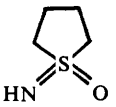
(60)



(61)



(62)



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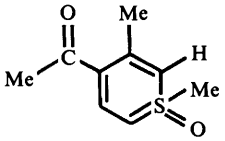
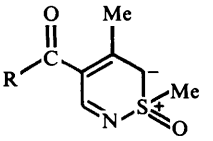


(64)



(65)

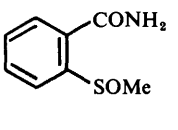
In the bicyclic sulphoximide field, 2-methylsulphinylbenzamide (66) reacts[69] with sodium azide–polyphosphoric acid to give the imino-benzisothiazole (67). Dilute base hydrolyses (67) to (68), strong base cleaves it to the amidine (69), and acid chloride and isocyanates acylate it to (70) and (71) respectively.

An alternative preparation of a derivative of (66) occurred coincidentally when (72) was found to give (73) on oxidation with hydrogen peroxide–acetic acid.[70] If this reaction were to occur in less substituted derivatives it would represent a novel sulphoximide preparation.

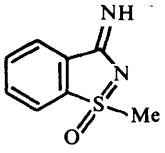
o-Amino-sulphoximides, *e.g.* (74), condense with one-carbon functionalities giving substituted benzothiadiazines which, appropriately substituted, can undergo reactions well known in quinoline chemistry. Thus (74) with carbon disulphide gives the thione (75), methylation of which produces the thiolactam (76). Formyl hydrazide can then displace the thioether and ring closure gives the triazolobenzthiadiazine (77).[71]

The use of MSH to prepare the previously unknown tricyclic sulphoximides (78) was reported earlier.[72] The same authors have now shown[73] that acyl and

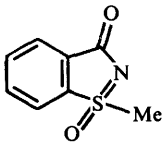
[69] P. Stoss and G. Satzinger, *Chem. Ber.*, 1975, **108**, 3855.
[70] J. R. Beck and J. A. Yahner, *J. Org. Chem.*, 1978, **43**, 2052.
[71] P. Stoss and G. Satzinger, *Chem. Ber.*, 1976, **109**, 2097.
[72] P. Stoss and G. Satzinger, *Tetrahedron Lett.*, 1974, 1973.
[73] P. Stoss and G. Satzinger, *Chem. Ber.*, 1978, **111**, 1453.



(66)

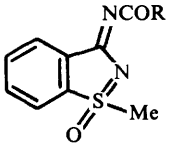


(67)

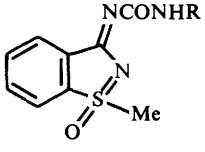


(68)

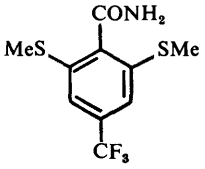
(69)



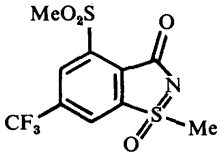
(70)



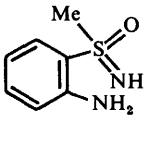
(71)



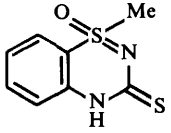
(72)



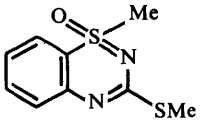
(73)



(74)



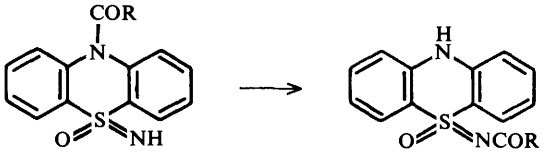
(75)



(76)

(77)

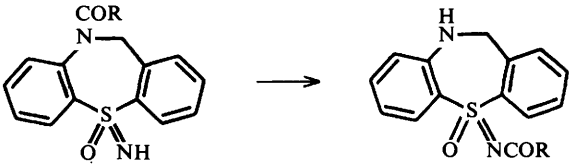
sulphonyl groups will migrate intramolecularly from ring nitrogens to the sulphoximide nitrogen (Schemes 17 and 18).



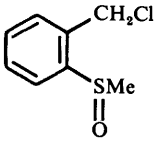
(78)

Scheme 17

2-(Methylsulphinyl)benzyl chloride (79) reacts with sodium azide–acid to produce the benzothiazole-1-oxide (32) whose decomposition was described earlier.[60]



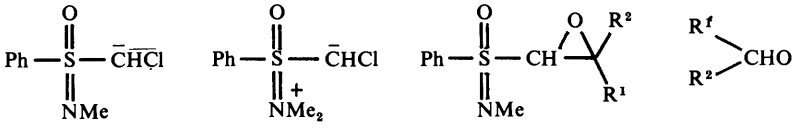
Scheme 18



(79)

6 Alkylidene Transfer Reactions

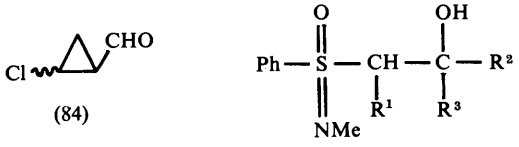
The use of ylides of sulphoximides as alkylidene transfer reagents, so well explored by Johnson,[74] represents one of the most interesting aspects of this class of compounds. Further examples of the reaction have investigated the action of the chlorinated anion (80) and ylide (81) with aldehydes and ketones.[75] With (80) the epoxides (82) were produced but it proved impossible to cleave them in such a way as to produce the homologated aldehyde (83). With α,β-unsaturated al-



(80) (81) (82) (83)

dehydes, *e.g.* acrolein, (81) gave mixtures of *cis* and *trans* substituted cyclopropanes (84).

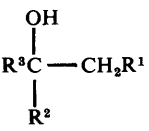
The initial condensation product from non-halogenated ylides and ketones is the hydroxy derivative (85), the reduction of which gives different products depend-



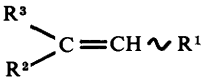
(84) (85)

ing on the metal reducing agent.[76] Thus sodium amalgam gives largely the alcohol (86) whilst aluminium amalgam gives mainly the olefin (87). If $R^1 \neq H$

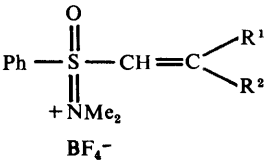
[74] C. R. Johnson, *Acc. Chem. Res.*, 1973, **6**, 341.
[75] H. G. Corkins, L. Veenstra, and C. R. Johnson, *J. Org. Chem.*, 1978, **43**, 4233.
[76] C. R. Johnson and R. A. Kirchhoff, *J. Am. Chem. Soc.*, 1979, **101**, 3602.



(86)



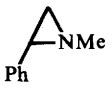
(87)



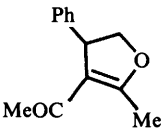
(88)

mixtures of *cis* and *trans* olefins are produced and no reaction takes place with tetra-substituted derivatives. If the alcohol (85; R^1 = H) is dehydrated and the olefinic sulphoximide methylated with trimethyloxonium fluoroborate the resulting salt (88) is a powerful Michael acceptor.[77] The reaction of (88; R^1 = Ph, R^2 = H) with difunctional reagents, *e.g.* methylamine, acetylacetone, and nitromethane gives respectively (89), (90), and (91).

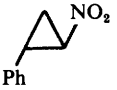
Further examination of the reaction of the methylene anion (92) with ketones,



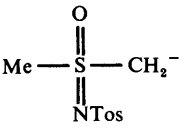
(89)



(90)



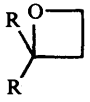
(91)



(92)

which is known to give the oxirane (93), has shown that the initially formed oxirane is very susceptible to nucleophilic attack.[78] Thus if an excess of anion is used, or if the oxirane is isolated and then treated with anion the oxetane (94) is produced.

(93)



(94)

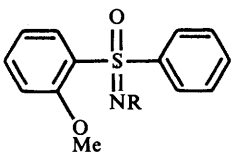
7 Stereochemistry

A circular dichroism study of (+)-*S*-(*o*-methoxyphenyl)-phenyl sulphoximide (95)[79,80] and its (−)-*N*-tosyl derivative (96) demonstrated two small Cotton effects with opposite signs near 275 nm giving near-zero rotational strengths in this region. Compared to the corresponding sulphilimines it was concluded that the addition of an oxygen atom reduces the disymmetry around the sulphur atom and that the c.d. curves are not distinctive enough for definitive stereochemical

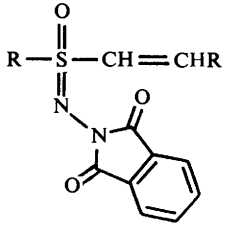
[77] C. R. Johnson, J. P. Lockard, and E. R. Kennedy, *J. Org. Chem.*, 1980, **45**, 264.
[78] S. C. Welch and A. S. C. Prakasu Rao, *J. Am. Chem. Soc.*, 1979, **101**, 6135.
[79] M. Moriyama, K. Kuriyama, T. Iwata, N. Furukawa, T. Numata, and S. Oae, *Chem Lett.*, 1976, 363.
[80] M. Moriyama, T. Yoshimura, N. Furukawa, T. Numata, and S. Oae, *Tetrahedron*, 1976, **32**, 3003.

assignments. Solvent effects on the Cotton effect were probably due to solvent-induced changes in the relative positions of the two aryl rings.

A resolution of phthalimido sulphoximides (97) *via* asymmetric selection has been reported.[81] Reaction of (97) with less than one equivalent of chiral amines gave unreacted sulphoximides with an enantiomeric excess of up to 46 %. The use of more polar solvents and chiral tertiary bases caused cleavage of the S—N bonds.



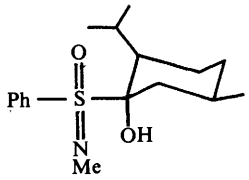
(95) R = H
(96) R = Tos



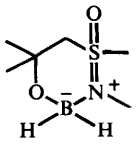
(97)

Terminating this reaction before completion allowed the isolation of optically active sulphoxides, albeit of low optical purity.

In toluene at −78 °C, diborane in the presence of (98), generated by addition of the lithiated sulphoximide to *l*-menthone, has been found to reduce ketones to alcohols enantioselectively with the optical purity of the product ranging from 30—80 %. A boron complex, partial structure (99), was tentatively suggested as being involved.[82]



(98)



(99)

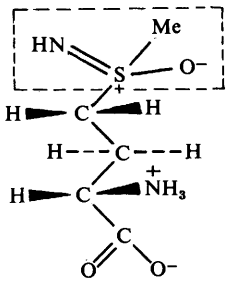
8 Applications

A. Methionine Sulphoximide.—The initial discovery of sulphoximides arose from investigations on the toxic factor produced by the action of nitrogen trichloride on wheat protein.[83] The toxic factor proved to be methionine sulphoximide (100) which subsequent work showed to be a potent convulsant in a number of animal species. This activity, which resides largely in the 2(*S*),5(*S*) isomer, probably arises from the irreversible inhibition of the enzyme glutamine synthe-

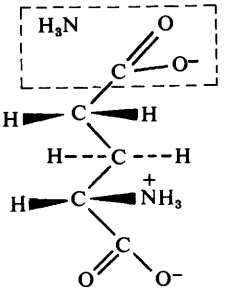
[81] R. Annunziata and M. Cinquini, *J. Chem. Soc., Perkin Trans. 1*, 1979, 1684.
[82] C. R. Johnson and C. J. Stark, *Tetrahedron Lett.*, 1979, 4713.
[83] H. R. Bentley, E. E. McDermott, T. Moran, J. Pace, and J. K. Whitehead, *Proc. R. Soc. London, Ser. B*, 1950, **137**, 402.

tase although it has proved to be very difficult to relate the onset of convulsions to reduced brain levels of glutamine. The close structural similarity between methionine sulphoximide and glutamic acid (101) can be clearly seen and the inhibition probably arises from competition between (100) and (101) for the same enzymatic site. Further studies have shown that (100) is also capable of inhibiting γ-glutamyl-cysteine synthetase.

The similarity between these two enzymes is that they both utilize glutamic acid



(100)

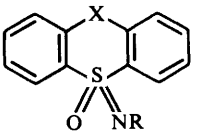


(101)

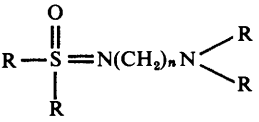
and incorporate either ammonia or cysteine to the γ-carbonyl group. There are, however, differences between the active sites since α-methyl and α-ethyl methionine sulphoximides are convulsants but are inactive against γ-glutamyl-cysteine synthetase.[84] It was argued that, reflecting the greater size of the cysteine molecule compared to ammonia, the cysteine synthetase enzyme should be less susceptible to steric effects around the γ-carboxy-group. In support of this it was found[85] that *S*-ethyl and *S*-propyl analogues of (100) are potent inhibitors of γ-glutamyl-cysteine synthetase but have little convulsant activity. It was conjectured that these inhibitors may be of use in cancer chemotherapy in view of the high levels of glutathione found in some tumours.

B. Patents.—Patents which describe the use of sulphoximides for a wide variety of physiological purposes have continued to appear. Anti-histamine, anti-tussive, and sedative activity were claimed[86] for the tricyclic sulphoximides (102) whilst the aminoalkylated sulphoximides (103)[87] and (104)[88] are spasmolytics. The bicyclic sulphoximides (105),[89] (106),[90] and (107)[91] have CNS depressant, bronchorespiratory, and anti-hypertensive activity respectively, whilst (108)[92] has

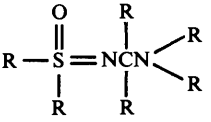
[84] O. W. Griffith and A. Meister, *J. Biol. Chem.*, 1978, **253**, 2333.
[85] A. Meister and O. W. Griffith, *Cancer Treat. Rep.*, 1979, **63**, 115.
[86] G.B. 1471898, G.B. 1468868 (1977) to Warner-Lambert.
[87] G.B. 2011404 (1979) to Warner-Lambert.
[88] G.B. 1526996 (1978) to Ludwig-Heuman & Co. G.m.b.H.
[89] U.S. 4022774 (1977) to Squibb.
[90] Swiss 599226 (1978) to Sandoz.
[91] Ger. Offen. 2530792 (1977) to Goedecke.
[92] G.B. 1418854, G.B. 1418855, G.B. 1418856 (1972) to Warner-Lambert.



(102) X = bond, S, O, NR, or CO

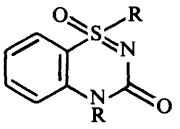


(103)

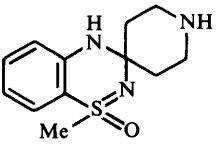


(104)

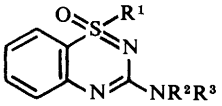
anti-inflammatory–analgesic effects. Finally, significant oral anti-allergy activity has been claimed for the xanthone (109).[93]



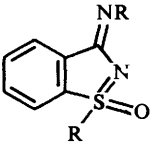
(105)



(106)



(107)



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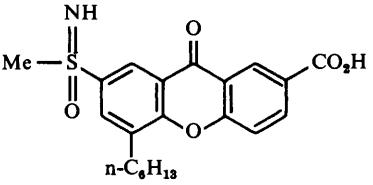

(109)

[93] A. C. Barnes, P. W. Hairsine, S. S. Matharu, P. J. Ramm, and J. B. Taylor, *J. Med. Chem.*, 1979, **22**, 418.