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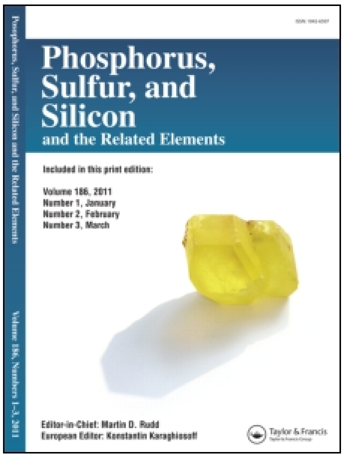

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SOME SULFONYL CRISSCROSS CYCLOADDUCTS

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SOME SULFONYL CRISSCROSS CYCLOADDUCTS

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The dipolar cycloadducts from diaryl azines and maleimides (1, 20) or maleic anhydride (18) have been reacted with chlorosulfonic acid to give the bis- (2, 19) or tetrachlorosulfonyl derivatives (21). The chorosulfonation generally required addition of thionyl chloride. The various sulfonyl chlorides were converted into a range of sulfonamides (3–11, 13–16) and the *N*-butylsulfamate (12). The *N,N*-dialkylsulfamonyl cycloadducts (23, 25) were also obtained by cycloaddition of the bis-dimethylsulfamoyl 2-methoxybenzaldehyde azine (22) and *N*-phenyl maleimide or the *N*-(*p*-diethylsulfamoylphenyl) maleimide (24) with *p*-tolualdehyde azine, although the former reaction did not go to completion.

Attempts to carry out the cycloaddition between the two sulfamoyl reactants (22 and 24) were unsuccessful. The various sulfonamide derivatives will be screened as pesticides.

Keywords: crisscross cycloadducts; chlorosulfonation; sulfonamides

INTRODUCTION

The formation of crisscross cycloadducts was first reported by Bailey and co-workers[1] in the reaction of cyanic acid or isocyanates with benzaldehyde. Later workers[2,3] showed that a similar crisscross cycloaddition occurred between an arylaldehyde azine (1 equivalent) and maleic anhydride (2 equivalents). The cycloaddition was further extended to the use of *N*-alkyl and *N*-arylmaleimides as dienophiles and the reaction was reviewed by Wagner-Jauregg[4].

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The cycloadducts have been shown to exist as a number of stereoisomers[5] and this has been confirmed by recent studies in these laboratories.[6,7] We have also demonstrated that the cycloaddition is reversible and subject to kinetic and thermodynamic control. The stereochemistry is dependant on both the nature of the substrates and the experimental conditions.

In the cycloaddition using maleic anhydride, the formation of a reasonably pure product generally required a fairly short period of reflux in xylene (≈2 hours). On the other hand, in the analogous reaction with maleimides, a much longer reaction time (≈18 hours) was successfully employed.

In the reaction between *N*-aryl maleimides (2 equivalents) and arylaldehyde azines (1 equivalent) in boiling xylene (18 hours) under a nitrogen atmosphere, the major isolated product was the symmetrical cycloadduct (thermodynamically most stable isomer), whereas in the analogous reaction using *N*-alkyl maleimides a mixture of cycloadducts was isolated.[6,7]

DISCUSSION

As part of our general program on the chemistry and biological activity of sulfonyl derivatives, especially those derived from heterocycles,[8–10] it was of interest to examine the synthesis of sulfonyl derivatives of these crisscross cycloadducts as a route to potentially biologically active molecules.

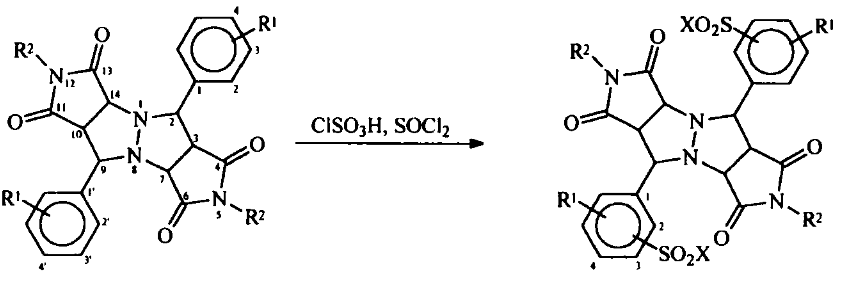
To this end, we examined the reaction of the cycloadduct (1; R^1 = 4-Me, R^2 = Ph) (Scheme 1) obtained from the cycloaddition of p-tolualdehyde azine and *N*-phenyl maleimide with a large excess of chlorosulfonic acid (24 equivalents). The product appeared to be a mixture of mainly the tri- and tetra-sulfonyl chlorides, which after condensation with dimethylamine afforded largely the tetra dimethylsulfonamide derivative involving sulfonation of all four phenyl rings.

To simplify the reaction, we decided to examine the chlorosulfonation of the adduct (1a; R^1 = 4-OMe, R^2 = Et), derived from 4-methoxybenzaldehyde azine and *N*-ethyl maleimide, since this contained only two phenyl rings capable of sulfonation which should be facilitated by the powerful electron-donating methoxy substituents. The cycloadduct (1a), a mixture of the 4 stereoisomers, was treated with a large excess of chlorosulfonic acid (12 or 18 equivalents) for one week. TLC indicated a main product which appeared to be the bis-sulfonic acid (2; R^1 = p-OMe, R^2 = Et, X = OH). The product evolved hydrogen chloride with phosphorus pentachloride and gave a precipitate with barium chloride solution. The presence of the OH group was confirmed by the IR spectrum which showed a broad absorption band at 3300 cm^{-1} and the proton NMR spectrum contained a broad singlet resonance (δ 10,4) which was reduced by D_2O treatment. Repetition of the reaction using a mixture of chlorosulfonic acid (6–8 equivalents) in excess thionyl chloride for one week afforded the desired 3,3′-bis-sulfonyl chloride (*2a*; R^1 = 4-OMe, R^2 = Et, X = Cl) in excellent yield (86%) (SCHEME 1).

The need for the more powerful chlorinating agent (thionyl chloride) is probably due to some stabilization of the hydroxyl group of the sulfonic acid intermediate by intramolecular hydrogen bonding between the 4-methoxy and the 3-sulfonic acid group. The product (2a) gave a strong green colour in the Beilstein test and positive results for Cl and S in the sodium fusion test; the IR spectrum showed no hydroxyl absorption band and additional bands at 1380, 1180 cm^{-1} which were not present in the cycloadduct (1) and were therefore indicative of the presence of the SO_2 group. The MS exhibited the molecular ion cluster (M^+, 718, 716, 714) corresponding to the bis-sulfonyl chloride. The bis-3,3′-sulfonyl chloride (2a) was condensed with nine different amines to give a range of 3-sulfonamides (3–11) for biological screening ((TABLE I)).

The sulfonyl chloride (2a) was also condensed with *n*-butanol to give the *n*-butylsulfonate derivative (12) (TABLE I). The reaction was performed under two sets of conditions; the first involved treatment with sodium butoxide as described by Chadbourne and Nunn[11]; the second was by reaction with *n*-butanol in the presence of pyridine[12]. The latter route gave the higher yield of product and was therefore favoured.

The cycloadduct (1b; R^1 = 2-OMe, R^2 = Et), a mixture of the 3 stereoisomers derived from the reaction of 2-methoxybenzaldehyde azine and *N*-ethyl maleimide, was similarly treated with a mixture of chlorosulfonic acid—thionyl chloride to give the 5,5′-bis-sulfonyl chloride (2b; R^1 = 2-OMe, R^2 = Et, X = Cl) in moderate yield (67%). The structure was supported by sodium fusion



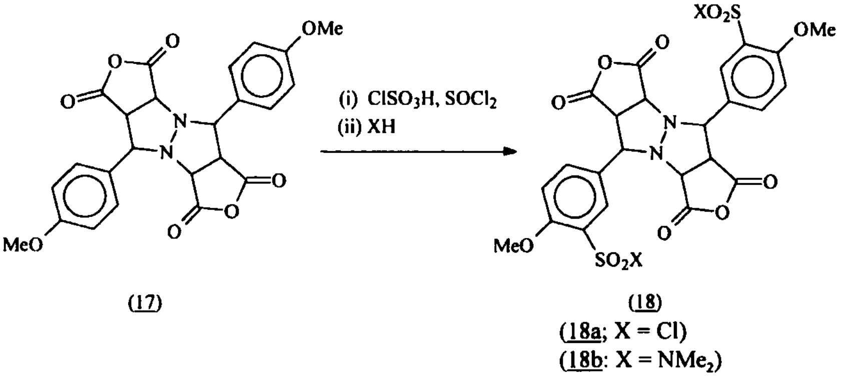
SCHEME 1

TABLE I Physical data for sulfonyl derivatives

Compound No.	*R1*	*R2*	*X*	*Yield (%)*
3	4-OMe	Et	3-NMe_2	25
4	4-OMe	Et	3-NEt_2	34
5	4-OMe	Et	3-NHEt	24
6	4-OMe	Et	3-piperidino	59
7	4-OMe	Et	3-morpholino	33
8	4-OMe	Et	3-(2,6-dimethylmorpholino)	45
9	4-OMe	Et	3-NHC_6H_4F-*p*	25
10	4-OMe	Et	3-NHC_6H_4F-*m*	16
11	4-OMe	Et	3-$NHC_6H_3F_2$-(2,4)	56
12	4-OMe	Et	3-$O(CH_2)_3Me$	46
13	2-OMe	Et	5-NMe_2	63
14	2-OMe	Et	5-(2,6-dimethylmorpholino)	82
15	H	H	4-Cl	70
16	H	H	NEt_2	25

(positive tests for sulfur and chlorine). The sulfonyl chloride was condensed with dimethylamine and 2,6-dimethylmorpholine to give the corresponding sulfonamides (13, 14) (TABLE I)).

Attempted preparation of the crisscross adduct (1; R^1 = 3-OMe, R^2 = Et) by reaction of 3-methoxybenzaldehyde azine (1 equivalent) with *N*-ethyl maleimide (2 equivalents) in boiling xylene (18 hours) caused problems: The product failed to precipitate out from the cold xylene solution and vacuum evaporation gave an oil, which eventually solidified. Recrystallization from various solvents was unsuccessful. Chlorosulfonation, under standard conditions (chlorosufonic acid—thionyl chloride), gave a solid containing sulfur and chlorine, but it decomposed in the vacuum desiccator. Repetition of the reaction did not improve the results and attempted derivatisation with excess dimethylamine failed to yield a pure product. One reason for the problems with the chlorosulfonation of the 3-methoxy cycloadduct (1; R^1 = 3-OMe, R^2 = Et) is that the substrate may be sulfonated in the 2-, 4- or 6- positions and these may also be contaminated with the sulfonic acid. The crisscross cycloadduct (1c; R^1 = R^2 = H) from benzaldehyde azine and maleimide was treated with a large excess of chlorosulfonic acid (12 equivalents) for one week, but gave mainly the 4,4′-bis-sulfonic acid with only a trace of the corresponding sulfonyl chloride. However, repetition of the chlorosulfonation using chlorosulfonic acid (6 equivalents) in thionyl chloride (one week) afforded a much improved yield (70%) of the 4,4′-bis-sulfonyl chloride (15) which was characterized as the diethylsulfonamide derivative (16) (TABLE I)).

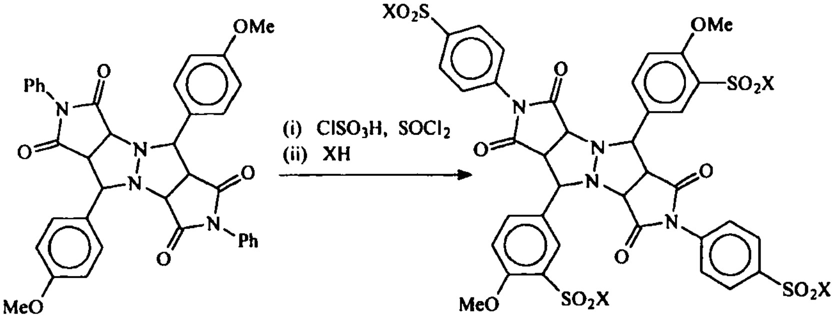


SCHEME 2

The cycloadduct (17) formed by reaction of 4-methoxybenzaldehyde azine and maleic anhydride in boiling xylene (2 hours) was reacted with excess chlorosulfonic acid (12 equivalents) to yield a mixture of the sulfonyl chloride (18a) and the sulfonic acid (18; X = OH) (Scheme 2). The optimum conditions for chlorosulfonation were discovered to be treatment with chlorosulfonic acid (12 equivalents) for one week followed by addition of excess thionyl chloride (1 day). This procedure afforded the bis-sulfonyl chloride (18a) in 55% yield, which was appreciably lower than the 86% that was obtained for the chlorosulfonation of compound (1a). The lower yield may probably be ascribed to competing ring-opening reactions of the anhydride adduct (18) under acidic conditions. The bis-sulfonyl chloride was characterized as the dimethylsulfonamide derivative (18b; X = NMe_2).

In an attempt to extend the chlorosulfonation of the crisscross adducts to obtain the tetrasulfonyl chlorides, the cycloadduct (19) from the reaction of 4-methoxybenzaldehyde azine and *N*-phenyl maleimide was heated with a large excess of chlorosulfonic acid (24 equivalents) for one week followed by addition of excess thionyl chloride. This procedure afforded the desired tetrasulfonyl chloride (20a; X = Cl) in excellent yield (86%) (Scheme 3)

In the substrate (19), the presence of the methoxy group facilitated sulfonation as compared with the analogous cycloadduct from *p*-tolualdehyde azine and *N*-phenyl maleimide which was previously studied by Williams[6]. The tetrasulfonyl chloride (20a) was characterized by formation of the tetra *N,N*-dimethylsulfonamide derivative (20b; X = NMe_2). The proton NMR spectrum of this compound showed the correct aliphatic/aromatic proton ratio (18:7) for the tetrasulfonamide.



(19)

(20)
(20a; X = Cl)
(20b; X = NMe$_2$)

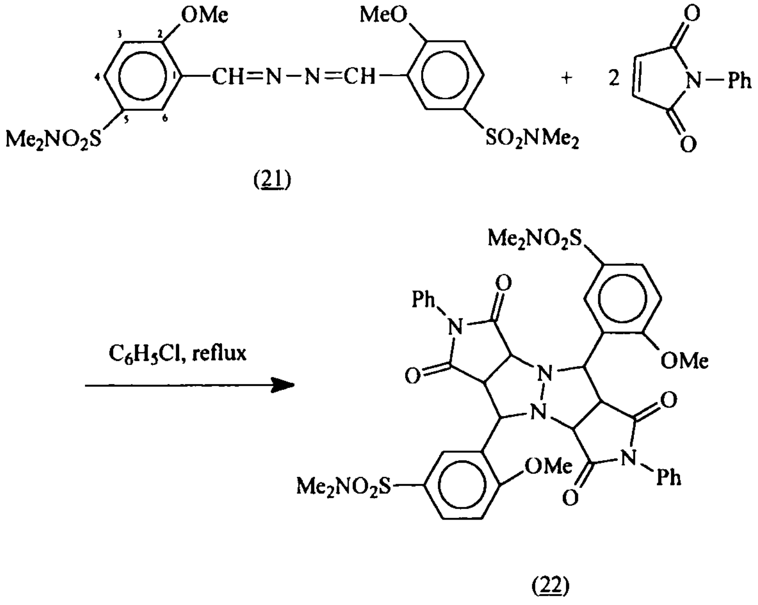
SCHEME 3

An alternative route for the synthesis of sulfonyl crisscross adducts involved carrying out the cycloaddition using sulfonyl substrates. However, electron-donor groups in the azine facilitate the cycloaddition whereas electron-withdrawing substituents, *e.g.* sulfonyl have the reverse effect. Consequently, 2,2′-dimethoxybenzaldehyde azine was selected and converted into the 5,5′-dimethylsulfonamide (21) as previously described[13]. The cycloaddition of compound (21) with *N*-phenyl maleimide was investigated in boiling chlorobenzene. However, even after 40 hours the NMR spectrum of the products, by comparison of the two methoxy proton resonances (δ 3.9, 4.0) corresponding to the original azine and the cycloadduct, indicated approximately 50% conversion to the desired cycloadduct (22). The presence of the latter was proved by the FAB MS which showed the $M^+ + 1$ ion (829) (Scheme 4).

An analogous cycloaddition between 4-methoxybenzaldehyde azine-3,3′-bis dimethylsulfonamide and *N*-phenyl maleimide resulted in a similar incomplete reaction.

The sulfonyl azines therefore appear fairly unreactive in the cycloaddition reaction and the electron donation of the methoxy group does not seem powerful enough to completely overcome the deactivating effect of the electron-withdrawing sulfonyl group.

An alternative synthetic route to the bis-sulfonyl cycloadducts involved reaction of a sulfonylphenyl maleimide derivative with the arylaldehyde azine.



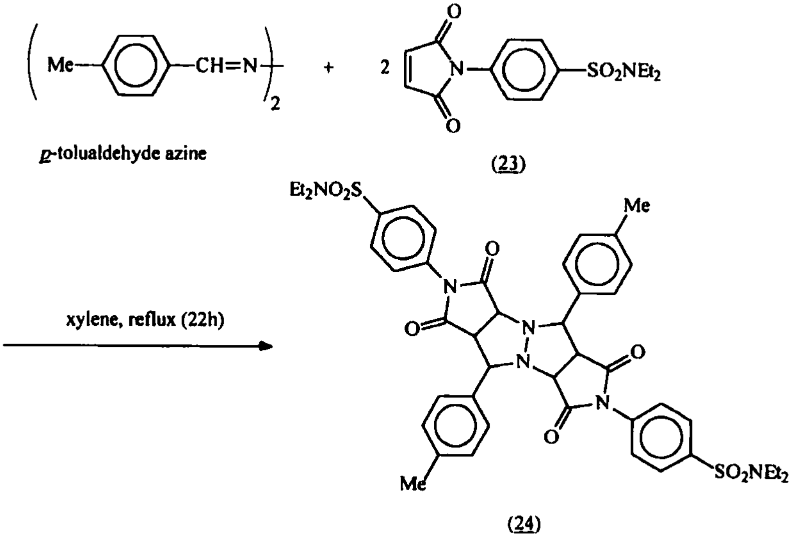
SCHEME 4

N-phenyl maleimide was converted into *N*-(p-chlorosulfonylphenyl) maleimide as previously described[14]; it was then reacted with p-tolualdehyde azine in boiling xylene (18 hours) but afforded a mixture of products possibly due to competing reactions between the chlorosulfonyl moiety and the solvent[6].

To avoid the side reactions, the analogous cycloaddition using *N*-(p-*N*,*N*-diethylsulfamoylphenyl) maleimide (23) was investigated in boiling xylene (22 hours) (Scheme 5).

The reaction afforded the required bis-sulfonyl cycloadduct (24) in 55% yield. The structure was supported by the FAB MS which showed the $M^+ + 1$ ion (853) and microanalytical data. Attempted cycloaddition between the bis-sulfonyl azine (21) and the sulfonyl phenyl maleimide (23) in boiling chlorobenzene (50 hours) was unsuccessful; the two substrates did not appear sufficiently reactive under these conditions.

On the other hand, work at the University of Aveiro (Portugal)[15] demonstrated that the cycloaddition could be achieved by fusion of the reactants in the absence of solvent.



SCHEME 5

EXPERIMENTAL

Melting points were determined with a Gallenkamp electric apparatus and are uncorrected. IR spectra were recorded as nujol mulls using a Perkin Elmer 237 Spectrophotometer. NMR Spectra were obtained with a Brucker AC 250 Spectrometer using tetramethylsilane as internal standard and unless otherwise stated DMSO-d_6 as solvent. Resonances reduced by D_2O treatment are indicated by an asterisk. EI mass spectra were measured with a V.G. Micromass 16F spectrometer operating at 70eV. TLC was carried out using Camlab silica gel plates sensitised to UV 256nm and 1:1:1 petroleum ether (30–40°C), ethyl acetate, cyclohexane mixture as eluant unless otherwise indicated.

2,9-Di (4-methoxyphenyl)-5,12-diethyl-1,5,8,12-tetraazatetracyclo [6.6.0^{3,7}.0^{10,14}] tetradecane-4,6,11,13-tetraone (1a)

4-Methoxybenzaldehyde azine (55g, 0.21 mol) was dissolved in warm xylene (60ml) and *N*-ethylmaleimide (50.1g, 0.42 mol) added. The mixture was refluxed for 10 minutes, some xylene (10ml) was distilled off and the remaining mixture was refluxed for 18 hours. On cooling a solid precipitated out from solution, and was filtered off under suction, the solid was washed with xylene (10 ml) and dichloromethane (2 × 10ml) and dried in a vacuum desiccator to give the cycloadduct (1a) (79.4g, 74 %), m.p. 206–208°C (Found: C, 64.7; H, 6.1; N, 10.9. $C_{28}H_{30}N_4O_6$ requires C, 64.9; H, 5.8; N, 10.8%). T.L.C. showed 4 spots R_F 0.02, 0.1, 0.17, 0.24. IR: υ_{max} 1790-1720, 1710-1680 (CO-NH-CO) cm^{-1}. MS: 518 (M^+).

Chlorosulfonation of 2,9-Di (4-methoxyphenyl)-5,12-diethyl-1,5,8,12-tetraazatetracyclo [6.6.0^{3,7} .0^{10,14}] tetradecane-4,6,11,13-tetraone (1a)

The above crisscross adduct (1a) (10g, 0.019 mol) was gradually added to a cold mixture of chlorosulfonic acid (19.9g, 0.154 mol) in thionyl chloride (18 ml). The reddish brown solution was left for 1 week at room temperature and was poured onto crushed ice. The fine yellow precipitate was filtered off with suction, washed with water (250ml) and dried in a vacuum desiccator to give the 3,3'-bis-sulfonyl chloride (2a) (11.8g, 86%), m.p. 214–216°C. TLC showed 3 spots, R_F 0.27, 0.52, 0.65. IR: υ_{max} 1750-1720, 1710-1690 (CO), 1600 (ArC=C), 1380, 1180 (SO_2) cm^{-1}. MS: 715 (M^+).

Derivatives of the 3,3'-bis-sulfonyl chloride (2a)

The *N,N*-Dimethylsulfonamide (3)

The bis-sulfonyl chloride (2a) (5.0g) was dissolved in methanol and dimethylamine (2.2g, 5 equivalents) was added. The mixture was stirred for 3 hours, poured onto icewater (100ml), the solid filtered off, washed with water (25ml) and recrystallized from ethanol to give the dimethylsulfonamide (3) (1.53g, 25%), m.p. 160–164°C. TLC showed 3 spots, R_F 0.31, 0.21, 0.11. IR: υ_{max}, 1750-1720, 1715-1685 (CO), 1600 (ArC=C), 1380, 1180 (SO_2) cm^{-1}. ^1H NMR δ 8.0-6.9 (m, 6H, ArH), 4.5-3.5 (m, 6H, CH), 3.7 (s, 6H, OMe), 3.30 (q, 4H, CH_2Me), 2.8 (s, 12H, NMe_2), 1.1 (t, 6H, CH_2Me). MS: 624 (M^+-SO_2NMe_2).

N,N-Diethylsulfonamide (4)

Prepared by a similar procedure using diethylamine gave 34%, m.p. 220–224°C. TLC showed 3 spots R_F 0.35, 0.23, 0.12. (Found C, 51.2; H, 5.4, N, 11.3. $C_{38}H_{46}N_6O_{10}S_2$ requires C 52.4; H 5.5; N, 11.5%). IR: υ_{max} 1750-1720, 1710-1690 (CO), 1600 (ArC=C), 1380, 1180 (SO_2) cm^{-1}. ^1H NMR: δ 8.1–7.1 (m, 6H, ArH), 4.6–3.7 (m, 6H, CH), 3.8 (s, 6H, OMe), 3.2 (q, 12H, CH_2Me), 1.0 (t, 18H, CH_2Me). FAB (+) MS: 789 (M^+ + 1).

N-Ethylsulfonamide (5)

Prepared using ethylamine: 24%, m.p. 258–260°C. TLC showed 2 spots R_F 0.23, 0.52. (Found: C 52.3; H, 5.3; N, 11.9. $C_{32}H_{38}N_6O_{10}S_2$ requires C, 52.6; H, 5.2; N, 11.5 %). MS: 622 (M^+-SO_2NHEt).

Piperidinylsulfonamide (6)

Prepared using piperidine: 59% m.p. 142–144°C. (Found: C, 52.8; H, 10.5; N, 9.5. $C_{38}H_{46}N_6O_{10}S_2$ requires C, 53.3; H, 10.7; N, 9.8%). IR: υ_{max} 1750–1735, 1715–1690 (CO), 1605 (ArC=C), 1380, 1180 (SO_2) cm^{-1}.

Morpholinosulfonamide (7)

Prepared using morpholine: 33%, m.p. 184–186°C. (Found: C, 52.8; H, 5.0; N, 10.5. $C_{36}H_{42}N_6O_{12}S_2$ requires C, 53.1; H, 5.2; N, 10.3%).

2,6-Dimethylmorpholinosulfonamide (8)

Prepared using 2,6-dimethylmorpholine: 45%, m.p. 160–161°C. (Found: C, 52.7: H, 5.0; N, 10.5. $C_{38}H_{46}N_6O_{12}S_2$ requires C, 53.1. H, 5.2; N, 10.3 %). IR: υ_{max} 1750–1720, 1715–1690 (CO), 1605 (ArC=C), 1380, 1185 (SO_2) cm^{-1}. MS: 669 (M^+-$SO_2C_6H_{12}NO$).

p-Fluorobenzenesulfonamide (9)

Prepared using p-fluoroaniline: 25%, m.p. 254–256°C. (Found: C, 55.2, H, 4.4; N, 9.9. $C_{40}H_{36}F_2N_6O_{10}S_2$ required C, 55.4; H, 4.2; N, 9.7 %).

m-Fluorobenzenesulfonamide (10)

Prepared using m-fluoroaniline: 16%, m.p. 220–222°C. (Found: C, 55.4; H, 4.5; N, 10.0 $C_{40}H_{36}F_2N_6O_{10}S_2$ requires C, 55.4; H, 4.2; N, 9.7 %).

2,4-Difluorobenzenesulfonamide (11)

Prepared using 2,4-difluoroaniline: 56%, m.p. 176–178°C. (Found: C, 53.0; H, 3.5; N, 9.7. $C_{40}H_{34}F_4N_6O_{10}S_2$ requires C, 53.4; H, 3.8; N, 9.3 %)

n-Butylsulfamate Derivative (12)

The 3,3′-bis-sulfonyl chloride was condensed with *n*-butanol in pyridine as previously described[12] to give the sulfamate (46%), m.p. 124–126°C. (Found C, 55.8; H, 2.8; N, 7.7. $C_{36}H_{24}N_4O_{12}S_2$ requires C, 56.2; H, 3.1; N, 7.3 %).

2,9-Di (2-methoxyphenyl)-5,12-diethyl-1,5,8,12 tetraazatetracyclo [6.6.03,7 .010,14] tetradecane-4,6,11,13-tetraone (1b)

2-Methoxybenzaldehyde azine (13.5g, 0.05 mol) and *N*-ethyl maleimide (12.5g, 0.1 mol) were reacted in boiling xylene as previously described to give the cycloadduct (1b) 9.25g (35%), m.p. 222–225°C. IR: υ_{max} 1790–1720, 1710–1680 (CO) cm^{-1}. MS: 518 (M^+).

Chlorosulfonation of 2,9-Di (2-methoxyphenyl)-5,12-diethyl-1,5,8,12 tetraazatetracyclo [6.6.03,7.010,14] tetradecane-4,6,11,13-tetraone (1b)

The crisscross adduct (1b) (5.0g, 9.6 × 10^{-3} mol) was reacted with chlorosulfonic acid (6 ml, 0.093 mol) in thionyl chloride (10 ml) as previously described to give the 5,5'-bis-sulfonyl chloride (2b) (6.15g, 67%), m.p. 250–253°C. TLC showed 3 spots R_F 0.11, 0.21, 0.31. IR: υ_{max} 1750, 1690 (CO), 1600 (ArC=C), 1380, 1180 (SO_2) cm^{-1}.

N,*N*-Dimethylsulfonamide (13)

Reaction of the 5,5′-bis-sulfonyl chloride with dimethylamine as previously described gave (13) (63%), m.p. 152–154°C. (Found: C, 52.3; H, 5.4; N, 11.2. $C_{32}H_{38}N_6O_{10}S_2$ requires C, 52.6; H, 5.2; H, 11.5%). ^1H NMR: δ 8.1-7.0 (m, 6H, ArH), 4.4-3.4 (m, 6H, CH), 3.9 (s, 6H, OMe), 3.30 (q, 4H, CH_2Me), 2.8 (s, 12H, NMe_2), 1.0 (t, 6H, CH_2Me). MS: 623 (M^+-SO_2NMe_2).

2,6-Dimethylmorpholinosulfonamide (14)

Prepared using 2,6-dimethylmorpholine: 82%, m.p. 187–188°C. (Found: C, 53.4; H, 5.3; N, 10.4. $C_{38}H_{46}N_6O_{12}S_2$ requires C, 53.1; H, 5.2; N, 10.3%). FAB(+) MS: 842 (M^+).

2,9-Diphenyl-5,12-dihydro-1,5,8,12-tetraazatetracyclo [6.6.03,7.010,14]-4,6,11,13-tetraone (1c; R^1 = R^2 = H)

Benzaldehyde azine (13.3g, 0.06 mol) was refluxed with maleimide (15g, 0.154 mol) in xylene (30 ml) for 18 hours to give the cycloadduct (23.4g, 91%), m.p. 263–265°C. TLC showed 2 spots R$_F$ 0.13, 0.34. IR: ν_{max} 3250 (NH), 1790-1720, 1710-1690 (CONHCO) cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 11.3*, 11.1* (bs, 2H, NH), 7.5&-7.1 (m, 10H, ArH), 4.8-3.5 (m, 6H, CH). MS: 402 (M$^+$).

Chlorosulfonation of the Cycloadduct (1c)

The cycloadduct (1c) (3.0g, 0.007 mol) was reacted with chlorosulfonic acid (3.0 ml, 0.044 mol) and thionyl chloride (20 ml) as previously described to give the 4,4'-bis-sulfonyl chloride (15) (3.11g, 70%), m.p. 210–213°C. IR: ν_{max} 1790–1725, 1710–1680 (CO), 3270 (NH), 1380, 1180 (SO$_2$) cm^{-1}. MS: 598 (M$^+$).

The *N,N*-Diethylsulfonamide Derivative (16)

Prepared by reaction with diethylamine: 25%, m.p. 164–166°C. TLC showed 2 spots R$_F$ 0.11, 0.31 (Found: C, 53.6; H, 5.25; N, 12.5. $C_{30}H_{36}N_6O_8S_2$ requires C, 53.5; H, 5.3; N, 12.5%). ^{1}H NMR: δ 11.3*, 11.1* (bs, 2H, NH), 8.0–7.1 (m, 8H, ArH), 4.9–3.7 (m, 6H, CH), 3.2 (q, 8H, CH$_2$Me), 1.1 (t, 12H, CH$_2$Me). FAB (+) MS: 673 (M$^+$ + 1).

2,9-Di (4-methoxyphenyl)-5,12-dioxa-1,5,8,12-tetraazatetracyclo [6.6.03,4.010,14]-4,6,11,13-tetrazone (17)

4-Methoxybenzaldehyde azine (10.0g, 0.03 mol) and maleic anhydride (10.0 g, 0.18 mol) was refluxed in xylene (60 ml) for 10 minutes. Some xylene (15 ml) was distilled off and the remaining mixture was refluxed for 2 hours. The precipitate was filtered off under suction and the solid was washed with xylene (10 ml), dichloromethane (2 × 10 ml) and dried in a vacuum desiccator to give the cycloadduct (17) (4.5 g, 32%), m.p. 270–271°C. Found: C, 62.4; H, 4.2; N, 6.4. $C_{24}H_{20}N_2O_8$ requires C, 62.1; H, 4.3; N, 6.0%). ^{1}H NMR: δ 8.6-6.9 (m, 8H, ArH, AA'BB' pattern), 4.8-4.1 (m, 6H, CH), 3.7 (s, 6H, OMe). MS: 464 (M$^+$).

Chlorosulfonation of the adduct (17)

The cycloadduct (17) 2.0 g, 0.0043 mol) was reacted with chlorosulfonic acid (3.5 ml, 0.05 mol) in thionyl chloride (15 ml) at room temperature (1 week) to give the 3,3′-bissulfonyl chloride (18a; X=Cl) (1.54 g, 55%), m.p. 152–154°C. IR: ν_{max} 1750, 1720 (CO), 1605 (ArC=C), 1385, 1185 (SO_2) cm^{-1}. MS: 660 (M^+).

The *N,N*-dimethylsulfonamide (18b; X = NMe_2)

Prepared using dimethylamine: 37%, m.p. 176–178°C. (Found: C, 49.2; H, 4.1; N, 8.5. $C_{28}H_{30}N_4O_{12}S_2$ requires C, 49.5; H, 4.4; N, 8.2%). ^1H NMR: δ 7.8–7.0 (m, 6H, ArH), 4.8-3.7 (m, 6H, CH), 3.4 (s, 6H, OMe), 2.8 (s, 6H, NMe_2). FAB (+) MS 678 (M^+).

Chlorosulfonation of 2,9 Di(4-methoxyphenyl)-5,12-diphenyl-1,5,8,12-tetraazatetracyclo [6.6.03,4.010,14] tetradecane-4,6,11,13-tetraone (19)

The cycloadduct (19) (1.25 g, 0.0025 mol) was reacted with chlorosulfonic acid (6.7 g, 0.058 mol) and thionyl chloride (10 ml) as previously described to give the tetrasulfonyl chloride (20, X=Cl) (2.2 g, 86%), m.p. 164–166°C. TLC showed 3 spots R_F 0.11, 0.21, 0.31. IR: ν_{max} 1750, 1700 (CO), 1600 (ArC=C), 1380, 1180 (SO_2) cm^{-1}.

N,N-Dimethylsulfonamide derivative (20b; X = NMe_2)

Prepared using dimethylamine: 46%, m.p. 210–213°C. (Found: C, 50.3; H, 4.6; N, 11.0. $C_{44}H_{50}N_8O_{14}S_4$ requires C, 50.7; H, 4.8; N, 10.7%). ^1H NMR: δ 8.1-7.1 (m, 14H, ArH), 4.5-3.7 (m, 6H, CH), 3.5 (s, 6H, OMe), 2.8 (s, 24H, NMe_2). FAB (+) MS: 1155 (M^+).

Attempted cycloaddition of 2,2′-dimethoxybenzaldehyde azine-5,5′-bis (N,N′-dimethylsulfonamide) (21) with *N*-phenyl maleimide

The azine dimethylsulfonamide (21) (3 g, 0.0062 mol) and *N*-phenyl maleimide (2.15 g, 0.012 mol) was refluxed in chlorobenzene (150 ml) for 40 hours. On cooling, the red solution deposited a fawn solid which was filtered off under reduced pressure to give a buff solid 2.2 g (43%), m.p. 243–248°C. TLC showed 2 spots R_F 0.15, 0.22 (Found: C, 54.6; H, 5.1; N, 9.9. The desired cycloadduct (22), $C_{40}H_{40}N_6O_{10}S_2$ requires C, 58.0; H, 4.8; N, 10.1%. The starting azine dimethylsulfonamide (21) $C_{20}H_{26}N_4O_6S_2$ requires C, 49.8; H, 5.4; N 11.6%). IR: ν_{max} 1710 (CO), 1610, 1595 (ArC=C), 1385, 1175 (SO_2) cm^{-1}. ^1H NMR:

δ 8.8-7.1 (m, 14H, ArH + CH azine), 4.9-3.7 (m, 3H, CH), 4.0 (s, 3H, OMe azine), 3.9 (s, 3H, OMe adduct), 2.9, 2.8 (2 × s, 12H, NMe). FAB (+) MS: 829 (M^+ + 1).

Cycloaddition of *N*-(*p*-*N*,*N*-diethylsulfamoylphenyl) maleimide (23) with *p*-tolualdehyde azine

A mixture of the diethylsulfonamide (23) (3.8 g, 0.0123 mole) and p-tolualdehyde azine (1.46 g, 0.0062 mole) in xylene (30 ml) was refluxed under an atmosphere of nitrogen for 22 hours. After cooling, the white precipitate was collected and recrystallised from ethanol to give the cycloadduct (24) (2.88g, 55%), m.p. 195–200°C. (Found: C, 60.7; H, 5.3; N, 10.3. $C_{40}H_{40}N_6O_8S_2$ requires C, 60.3; H, 5.0; N, 10.5%). ^{1}H NMR ($CDCl_3$): δ 7.8-7.2 (m, 16H, ArH), 4.7-3.4 (m, 6H, CH), 2.7 (q, 8H, CH_2Me), 2.3 (s, 6H, Ar-Me), 1.2 (t, 12H, CH_2Me). FAB (+) MS: 797 (M^+ + 1).

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