J. CHEM. SOC. PERKIN TRANS. II 1985

Experimental and Theoretical Study of Electronic Substituent Effects in 4-Aminoaryl (4-Substituted Aryl) Sulphones

Pier G. De Benedetti,* Ugo Folli, and Dario Iarossi
Dipartimento di Chimica, Università di Modena via Campi 183, 41100 Modena, Italy
Chiara Frassineti
Istituto di Chimica Biologica, Università di Modena via Campi 287, 41100 Modena, Italy

Substituent effects on the electronic structure of 23 biologically active 4-aminoaryl (4-substituted aryl) sulphones were investigated by means of ^{1}H n.m.r., ^{13}C n.m.r., and i.r. spectroscopy, as well as by semiempirical all-valence CNDO/2 calculations, with and without sulphur *d* orbital participation. Good linear intercorrelations were found among the spectral data and between these and the computed electronic charges and the Hammett σ_p values. On this basis the substituent effects are interpreted in terms of electronic charge perturbation, which is linearly transmitted from the substituent to the whole molecule, bridging SO_2 group included. The agreement between experimental and theoretical data is good and the trends do not depend on the inclusion or exclusion, in the calculations, of the sulphur *d* orbitals. Strong and linearly related σ–π electron interactions operate between C-1 and C-1′ in the C(1)SO_2C(1′) moiety; thus Koch and Moffitt's qualitative π-electron conjugation model for Case 2 type sulphones seems inadequate.

The aryl 4-aminoaryl sulphone derivatives represent an interesting class of organic compounds from physicochemical, biological,[1,2] and pharmacological[3] points of view (which are, in turn, closely interdependent). In recent theoretical work[4] we have shown that the biological activity of these compounds is linearly related to the electronic structure of the common moiety, 4-$NH_2C_6H_4SO_2$, which is modulated by the substituents *via* intramolecular interaction. In particular, high antimycobacterial and antileprotic activity is related to substantial negative charges both on the oxygen atoms of the SO_2 group and on the *p*-NH_2 group. These results indicate that the optimization of the biological action of these sulphones (*i.e.* the inhibition, competitive with respect to the substrate *p*-aminobenzoate, of the enzyme dihydropteroate synthase[1,2]) depends on the ability of the substituents to transmit their electronic effects on and through the SO_2 group to the rest of the molecule. Furthermore, the nature of the S–O bonds is the object of a long-standing controversy[5] and much disagreement exists concerning the relative importance of the polar (inductive and/or field) and the mesomeric (resonance) effect of the sulphonyl group.[6] In this context these sulphones constitute an interesting family of compounds for testing the nature and the transmission mechanism of substituent effects, their magnitude, and the role of sulphur *d* orbitals in the conjugation.

In an effort to clarify these problems, we have investigated by means of nuclear magnetic resonance, vibrational spectroscopy, and quantum chemical calculations a wide series of sulphones of general formula 4-$NH_2C_6H_4$–SO_2–C_6H_4X-4′.

Results and Discussion

The comparative use of three different spectroscopic techniques, ^{13}C n.m.r., i.r., and ^{1}H n.m.r., can greatly help our understanding of the magnitudes and mechanisms of substituent effects in our compounds. ^{13}C N.m.r. spectroscopy has recently been shown[7] to be a powerful technique for monitoring substituent effects, in aromatic systems, by observation of substituent-induced chemical shifts. The transmission of substituent effects through the SO_2 bridge can also be easily followed by measuring the S–O stretching frequencies, both the antisymmetric and symmetric.[5] The last-named vibration mode is more suitable for our aims, giving a very strong band, so that the assignment is easier and, usually, unambiguous. Furthermore the symmetric stretching frequency [$\nu_s(SO_2)$] is more sensitive to substituent effects.[5]

Finally, the ^{1}H n.m.r. of the 4-NH_2 group [$\delta(NH_2)$] has been considered. This group, being at the extreme end of the molecule with respect to the variable substituent X, is an interesting probe of substituent effects; furthermore, it plays an indispensable role in the biological activity[3,8] of these compounds.

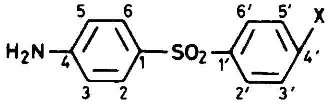
The Table presents the $\delta(NH_2)$ values, the ^{13}C chemical shifts [$\delta(^{13}C)$] of the benzene rings, and the $\nu_s(SO_2)$ values for 23 sulphones measured in dimethyl sulphoxide solutions. The $\delta(^{13}C)$ values have been generally assigned by the usual methods[9,10] and by the additivity criteria of substituent chemical shifts of substituted benzenes,[11] which can be conveniently adapted to the present case. For example, taking benzene as reference compound (128.5 p.p.m.), from the shielding values[7] of the amino and $SO_2C_6H_5$ moieties the chemical shifts in p.p.m. of the interposed ring carbons for compound (**12**) can be calculated: δC(1) 129.10; δC(2,6) 128.10; δC(3,5) 115.00; δC(4) 153.90 p.p.m.. Alternatively, with $(C_6H_5)_2SO_2$ as reference [δC(1) 141.02; δC(2,6) 129.67; δC(3,5) 127.25; and δC(4) 133.63 p.p.m. in Me_2SO], from the shielding values of the 4-NH_2 group, the following values in p.p.m. can be calculated for the same ring carbons: δC(1) 128.52; δC(2,6) 130.17; δC(3,5) 112.95; δC(4) 154.33.

As regards the X-substituted ring carbons, the additivity criterion can be applied taking as reference molecule the parent compound 4-$NH_2C_6H_4$–SO_2–C_6H_5 and the shielding values of the various 4′-X groups.[7] In this way we considered the sulphones as *para*-disubstituted benzenes with a constant group K (1′-KC_6H_4 X-4′ with K = 4-$NH_2C_6H_4SO_2$).

The predicted chemical shift values are also reported in the Table. The agreement with the observed values is variable, depending on carbon position and substituent nature, but is acceptable as an assignment aid. In particular, the agreement is worse for strong electron-donor substituents, probably because of the direct conjugation between the electron-releasing substituent and the electron-acceptor SO_2 group.

Finally for the assignments of $\delta(NH_2)$ and $\nu_s(SO_2)$ values, we followed previous literature criteria and data.[5,8] The data collected in the Table have been ordered according to decreasing values of $\delta(NH_2)$. At the end of each column are

Table. ^{13}C N.m.r.[a] and selected i.r. and ^{1}H n.m.r. data



No.	X	$\delta(NH_2)$(p.p.m.) $[(CD_3)_2SO]$	$\delta(^{13}C)$(p.p.m.) $[(CD_3)_2SO]$								$\nu_s(SO_2)$/cm^{-1} (Me_2SO)
			C(1)	C(2,6)	C(3,5)	C(4)	C(1′)	C(2′,6′)	C(3′,5′)	C(4′)	
(1)	CN	6.34	123.41	129.87	113.09	154.14	147.19 147.51	127.10 127.05	133.51 132.99	117.56 116.80	1 149
(2)	NO_2	6.33	123.19	129.67	113.24	154.22	148.65 150.21	128.34 127.95	124.65 124.49	149.60 152.00	1 150
(3)	CO_2Me	6.30	124.01	129.70	113.05	153.94	147.13 147.51	126.81 126.45	130.13 130.39	132.84 134.50	1 150
(4)	CO_2H	6.28	124.17	129.67	113.00	153.90	146.82 148.61	126.67 127.35	130.22 131.19	134.10 135.80	1 150
(5)	$COCH_3$	6.27	124.27	129.67	113.04	153.90	146.77 147.61	126.73 126.25	129.11 129.49	139.39 141.40	1 150
(6)	$CONH_2$	6.25	124.57	129.56	112.98	153.75	145.35 145.91	126.39 126.05	128.40 128.39	137.78 138.40	1 151.5
(7)	$CONEt_2$	6.25	124.59	129.56	113.00	153.74	143.45 144.21	126.64 126.15	127.01 127.89	141.01 140.50	1 148
(8)	Br	6.21	124.54	129.47	113.03	153.75	142.44 141.61	128.41 128.35	132.39 132.49	126.43 126.70	1 147
(9)	Cl	6.20	124.59	(129.47)[b]	113.02	153.74	142.01 142.01	128.32 128.35	(129.44) 129.49	137.48 137.40	1 149
(10)	F	6.17	125.05	(129.56)	112.99	153.63	139.65 138.80	(129.37) 128.35	116.47 116.19	163.80 167.25	1 147.5
(11)	Me	6.16	125.71	129.21	112.90	153.40	140.40 140.21	126.43 126.25	129.75 129.99	142.87 141.50	1 147.5
(12)	H	6.15	125.24	(129.32)	112.96	153.55	143.21	126.35	(129.39)	132.50	1 147
(13)	CO_2Na	6.12	124.03	(129.26)	112.92	153.47	144.51 145.41	125.51 125.85	(129.48) 129.89	142.89	1 144
(14)	NHAc	6.11	126.02	129.09	112.89	153.29	136.75 137.81	127.64 126.65	118.75 120.09	142.82 143.50	1 148.5
(15)	OMe	6.08	126.31	(128.99)	112.90	153.21	134.82 135.31	(128.62) 127.55	114.48 114.99	162.20 163.50	1 146.5
(16)	OH	6.04	126.77	(128.92)	112.87	153.03	133.10 135.81	(128.85) 127.70	115.68 116.39	161.01 159.40	1 144
(17)	NHOH	6.01	127.30	(128.70)	112.84	152.88	131.75	(127.85)	111.46	155.14	1 145
(18)	NH_2	6.01	128.08	128.46	112.78	152.61	128.08 130.71	128.46 126.85	112.78 115.09	152.61 153.20	1 144
(19)	NEt_2	6.01	127.29	128.41	112.76	152.69	127.98 130.21	128.41 126.95	110.40 112.89	149.88 151.80	1 143
(20)	NMe_2	5.99	127.84	128.49	112.78	(152.40)	128.19 131.71	128.08 127.25	112.78 113.59	(152.71) 155.00	1 143.5
(21)	NHEt	5.98	127.74	(128.40)	112.77	152.61	128.05 131.81	(128.35) 127.05	110.95 113.69	151.94 152.50	1 144
(22)	ONa	5.79	128.50	128.68	112.75	152.23	123.99 129.61	128.10 128.25	117.49 121.19	170.46 172.10	1 137.5
	Δ	0.55	5.31	2.02	0.49	1.99	24.66	4.05	23.11	52.90	14

[a] Observed (upper row) and predicted (lower row) chemical shift values. [b] Values in parentheses indicate ambiguities in the assignments.

reported the spectral data variation ranges (Δ), which reflect the responses of the various molecular sites to substituent effects and suggest the following analogies in the spectral variations between the carbon atoms: 1—4′; 2,6—3′,5′; 3,5—2′,6′; 4—1′.

Simple regression analysis enables us to test these trends quantitatively. The statistical indices (r = correlation coefficient; s = standard deviation of the estimate) show a poor correlation between δC(1) and δC(4′) values (r = 0.86, s =

0.82) and a fair one between δC(2,6) and δC(3′,5′) (r = 0.91, s = 0.20). No correlation at all is observed between δC(3,5) and δC(2′,6′) data, whereas a satisfactory linear relationship is obtained in the correlation between δC(4) and δC(1′), as shown by equation (1), where n is the number of data points.

	n	r	s	
$\delta C(4) = 0.070\ \delta C(1') + 143.67$	22	0.98	0.11	(1)

Finally, the linear relationship subsisting between the $\nu_s(SO_2)$ values of the bridging group and the $\delta(^{13}C)$ values of the substituted carbons [$\nu_s(SO_2)/\delta C(4')$: $r = -0.77$, s = 2.22, (**1**), (**8**), (**10**) omitted; $\nu_s(SO_2)/\delta C(1')$: r = 0.92, s = 1.01, (**13**), (**22**) omitted; $\nu_s(SO_2)/\delta C(1)$: $r = -0.89$, s = 1.17, (**13**), (**22**) omitted; $\nu_s(SO_2)/\delta C(4)$: r = 0.89, s = 1.52], which are crucial points in the molecule with regard to substituent effects, show the involvement of the SO_2 group in the substituent effect perturbations.[12]

Relationships between Spectral Data and Electronic Charge.—It is often assumed that substituent effects on spectral data in aromatic systems are determined mainly by the substituent-induced changes in electron density at the appropriate atom or group and that these quantities are linearly related.[7] In fact the linear regressions (2)—(4) show good correlations between the $\delta(^{13}C)$ values and the total ($\sigma + \pi$) net charges (q_{tot}) computed[*] in the CNDO/2 approximation[13] and parametrization.[4,14] These equations refer to the aromatic ring bearing the substituent X and, as in benzene derivatives,[7,11] the best trend is that of (4), where the *para*-position with respect to X is considered.

	n	r	s	Omitted	
$\delta C(4') = 114.70\ q_{tot}^{4'} + 133.35$	20	0.92	4.257	(**1**)	(2)
$\delta C(3',5') = 239.90\ q_{tot}^{3',5'} + 125.37$	21	0.92	3.065		(3)
$\delta C(1') = 365.47\ q_{tot}^{1'} + 138.20$	21	0.96	2.318		(4)
$\delta C(1) = -1\,744.10\ q_{tot}^{1} + 87.08$	19	0.87	0.775	(**13**),(**22**)	(5)
$\delta C(3,5) = 314.72\ q_{tot}^{3,5} + 126.20$	19	0.94	0.042	(**13**),(**22**)	(6)
$\delta C(4) = 317.65\ q_{tot}^{4} + 94.93$	19	0.84	0.292	(**13**),(**22**)	(7)
$\delta C(1) = 486.84\ q_{\pi}^{1} + 164.74$	19	0.94	0.526	(**13**),(**22**)	(8)
$\delta C(1) = -384.32\ q_{\sigma}^{1} + 148.00$	19	0.93	0.571	(**13**),(**22**)	
$\delta(NH_2) = 86.97\ q_{\pi}^{N} - 6.80$	19	0.91	0.052	(**13**),(**22**)	(9)
$\delta(NH_2) = -166.17\ q_{\sigma}^{N} - 60.27$	19	0.91	0.051	(**13**),(**22**)	
$\delta C(1') = 226.26\ q_{\pi}^{1'} + 145.99$	19	0.97	1.99	(**13**),(**22**)	(10)
$\delta C(1') = -518.70\ q_{\sigma}^{1'} + 156.63$	19	0.95	2.32	(**13**),(**22**)	

Interesting and quite unusual[7] are the results (2) and (3) where the $\delta^{13}C$ values at the *ipso*- and *ortho*-positions are successfully related to the charge density. As far as the *meta* position (C-2′,6′) is concerned, no correlation has been found. The same holds for the C-2,6 on the other ring, whereas for the remaining carbon chemical shifts fairly good correlations are obtained [equations (5)—(7)]. Interesting and unusual features emerge from these correlations too. First of all the negative slope of (5) shows opposite trends between the negative total net charge on C(1) and their chemical shift values. The rationale of this strange result is given by considering the correlations between the π and σ electronic charges and δC(1) values [equation (8)], where the opposite role played by the σ and π symmetry components of the total net charges becomes evident. This trend is observed for all the atoms of the common moiety $4\text{-}NH_2C_6H_4$, nitrogen included [equation (9)]. The opposite behaviour between σ and π charges in relation to substituent effects is typical of the *para*-carbon atom in monosubstituted benzenes[15] and, if we consider C(1′), which is in the *para*-position with respect to the variable substituent X, the trend just seen emerges again [equation (10)]. In other words, the electronic features, analysed in terms of a σ and π populations, determined on C(1′) by substituent X, are transmitted through the SO_2 bridge to the other molecular sites, with an inversely proportional relationship between the σ and π charges on each atom. This result is consistent with the conclusions obtained from the analysis of the intercorrelations between spectral data, *i.e.* the nature and the transmission mechanism of substituent effects from one aromatic ring to the other are qualitatively the same. Furthermore, the correlations with the π charge are successful in those cases where the total net charge fails [$\delta C(2,6)/q_{\pi}^{2,6}$: r = 0.95, s = 0.16; (**13**),(**22**) omitted] and, in general, an improvement in the linear regressions, in the case of the common moiety carbons, is observed.

In all cases the substituents bearing a negative charge are omitted because of their large deviation from the regressions. These exceptions are probably due to an overestimation of the calculated electronic charge transfer from the substituent to the molecule. Finally, similar equations are also obtained for the $\nu_s(SO_2)$ and $\delta(NH_2)$ values with their respective total net charges.

The computed data discussed above were obtained with inclusion in the calculations of the sulphur d orbitals. With the aim of evaluating the role of such orbitals, we have reperformed the calculations on the sulphones without sulphur d orbitals. The computed data obtained are different and, in particular, show a greater S–O bond polarization in comparison with those calculated with d orbitals;[6] nevertheless they are strictly linearly

---

[*] Extensive tabulations of numerical results, not reported in the text, are available as Supplementary Publication No. SUP 56301 (5 pp.). (For details of Supplementary Publications see Instructions for Authors, *J. Chem. Soc., Perkin Trans. 2*, Issue 1, 1985). The bromo-derivative was omitted because the parametrization is not available.

related ($r = 0.99$) so the relative trends with respect to the substituent effects are the same. This result is clearly connected to the very nature of all-valence electron calculations which do allow for σ–π interactions, so that, at variance with Koch and Moffit's π-model,[16] p_π–d_π interactions need not be invoked for producing the substituent effect transmission shown by experiment.

The extent of σ–π interaction can be estimated by the overlap integrals between the local π-orbitals on C(1), C(1′), and oxygen atoms and the hybrid σ orbitals of the sulphur atom. The relevant values are: $(\pi_C$–$\sigma_{S\rightarrow C}) = 0.1341$; $(\pi_O$–$\sigma_{S\rightarrow O}) = 0.1218$ (π_O perpendicular to the SO_2 plane) and 0.0765 (π_O lying in the SO_2 plane), where the hybrid atomic orbitals are calculated according to the maximum localization criterion.[17] The overlap integrals involving d_π sulphur orbitals are much lower: $(\pi_C$–$d_\pi) = 0.0713$; $(\pi_O$–$d_\pi) = 0.0617$, 0.0366 (π_O perpendicular to the SO_2 plane) and 0.0626, 0.0348 (π_O lying in the SO_2 plane) and can only be increased by d orbital contraction;[5,6] however, although the inclusion of d orbitals (and their contraction) is suggested by the experimental interactions through the SO_2 group, σ–π interactions, as introduced in the CNDO framework, are quite sufficient to account for the observed effects.

Correlations between Spectral Data and Substituent Constants.—Linear relationships ($r = 0.85$—0.97) are also obtained between Hammett's σ_p constants and $\delta C(1')$, $\nu_s(SO_2)$, $\delta C(1)$, $\delta C(3,5)$, $\delta C(2,6)$, $\delta C(4)$, and $\delta(NH_2)$ values. It is worth stressing that the only negative slope refers to the regression between $\delta C(1)$ and σ_p, confirming the inversely proportional relationships for this carbon atom.

For the remaining carbons and their relative $\delta(^{13}C)$ values [$\delta C(2',6')$, $\delta C(3',5')$, and $\delta C(4')$], no correlations have been obtained at all, even by considering the two variable regression analyses as dual substituent parameters equations[15,18] or by Swain and Lupton's approach.[19]

Finally, with the aim of characterizing separately the weight of polar and resonance effects, we applied Swain and Lupton's approach.[19] No significant improvements in the statistical parameters were observed with respect to simple regressions; furthermore, the blend of the resonance and polar contributions, expressed as a ratio (λ) between the resonance (ρ_R) and polar (ρ_F) weights, appears to decrease, for the crucial molecular sites, in the sequence C(1′) > C(1) > C(4) > NH_2, as equations (11)—(14) show. Here again there is an opposite trend between $\delta C(1)$ values and the substituent constants F (field efficiency[20]) and R (resonance efficiency[20]), the weight factors being negative in comparison with those of the other equations. However, the λ trend is clear in suggesting that the resonance contribution in the last two equations plays a greater role than in the first two. This result probably disguises the contribution to the resonance due to the σ and π bond interactions (hyperconjugation) of C(1′) and C(1) through the SO_2 bridge.

	n	R	s	λ	
$\delta(NH_2) = 0.307F + 0.250R + 0.613$	19	0.95	0.044	0.82	(11)
$\delta C(4) = 1.144F + 1.046R + 153.39$	19	0.98	0.128	0.92	(12)
$\delta C(1) = -2.477F - 3.564R + 125.32$	19	0.96	0.478	1.44	(13)
$\delta C(1') = 9.386F + 17.81R + 140.81$	19	0.96	2.075	1.90	(14)

Conclusions.—On the basis of the spectral data intercorrelations and of their agreement with theoretical results we can conclude that the substituent effects on the sulphones studied can be interpreted in terms of electronic charge perturbation due to the variable substituents 4′-X and linearly transmitted along the whole molecule, bridging SO_2 group included. Thus the problem of the role of this group in transmitting substituent effects does not seem qualitatively different in comparison with the other atoms or groups in the molecule. In particular, Koch and Moffitt's π-electron descriptive model of conjugation in Case 2 type sulphones seems inadequate in view of the strong interactions between the σ and π electrons which take place in the $C(1)SO_2C(1')$ moiety.

Finally the agreement between experimental and computed data renders these last data reliable and useful for predictive as well as diagnostic purposes. In particular, it is possible to design sulphone structures having the best electronic features for the common moiety in order to show highest biological activity. Furthermore, useful information can be obtained on the nature of the intermolecular forces between the sulphone inhibitors and the dihydropteroate synthase active site.

Experimental

N.m.r. spectra (^1H and ^{13}C) were recorded at 25 °C for solutions in [$^2H_6$]Me_2SO using a Varian XL-200 spectrometer. Sample concentrations were in the range 10^{-1}—10^{-2}M. The 4-NH_2 proton signals were reproducible to within less than 0.02 p.p.m. and showed no concentration dependence in the concentration range 2×10^{-1}—1.25×10^{-2}M. The same holds for ^{13}C chemical shift values.

I.r. spectra were recorded for solutions in Me_2SO with a Perkin-Elmer 180 spectrometer. The concentration of the samples was between 3×10^{-1} and 1×10^{-2}M; within the limits of experimental accuracy (± 0.5 cm^{-1}) the band positions were not affected by 1:5 dilution.

The spectroscopic measurements were performed at the Centro Strumenti of the University of Modena.

LCAO-MO results were obtained for the set of molecules reported in the Table using the CNDO/2 approximation and the parametrization of ref. 14. Standard geometries were used[4,14] for the substituents X, whereas for the common moiety $4\text{-}NH_2C_6H_4SO_2C_6H_4$ the following bond lengths (in Å) and bond angles were assumed for all the derivatives in the Table: r(S–O) = 1.436, r(S–C) = 1.764, r(C–C) = 1.397, r(C–N) = 1.397, r(C–H) = 1.080, r(N–H) = 1.030; angles OSO = 120°, CSC = 119°, CSO = 120.5°, CCH = 120°, CCN = 120°, CNH = 120° and HNH = 120°. The benzene rings lie in planes perpendicular to the C(1)SC(1′) plane (Case 2 type sulphone[16]).

The calculations were performed at the Centro di Calcolo Elettronico of the University of Modena with a modified version of the program QCPE 141.

Commercial bis-4-aminophenyl sulphone (**18**) from Ega Chemie was purified by crystallization from water.

Compounds (**4**),[21] m.p. 266—268 °C (from dioxane–acetic acid) (lit.,[21] 253—254 °C; lit.,[22] 263—264 °C); (**8**);[23] (**9**);[24] (**10**);[25] (**11**);[21,26] (**12**);[24] (**15**);[27] (**16**),[27] m.p. 174—176 °C (from benzene) (lit.,[27] 166 °C; lit.,[22] 177—178 °C); (**17**);[28] (**19**);[29] and (**20**);[29] were prepared according to literature methods and had physical properties similar to those reported except for (**4**) and (**16**), which gave correct elemental analyses.

4-*Bromophenyl* 4-*Nitrophenyl Sulphone*.—A mixture of 4-nitrobenzenesulphonyl chloride (8.8 g, 40 mmol), $AlCl_3$ (8 g, 60 mmol), and bromobenzene (15.7 g, 100 mmol), was stirred at room temperature (0.5 h) and then gradually heated (1.5 h) to the temperature of the steam-bath which was maintained for 4 h. After cooling, ice and water were added and the collected product was washed with cold isopropyl alcohol and crystallized from ethyl acetate–ethanol to yield the sulphone (8 g, 59%), m.p. 182—184 °C (lit.,[23] 181—184 °C).

4-*Cyanophenyl* 4-*Nitrophenyl Sulphone*—A mixture of 4-bromophenyl 4-nitrophenyl sulphone (7.4 g, 22 mmol), copper(I) cyanide (2.5 g, 30 mmol), dry pyridine (2.2 g, 28 mmol), and nitrobenzene (37 ml) was heated at 180 °C for 20 h. After moderate cooling, chloroform and charcoal were added and the filtered solution was evaporated. The residue was chromatographed on silica gel (benzene as eluant) to give the product (4 g, 64%), m.p. 214—215 °C (lit.,[30] 213 °C).

4-*Aminophenyl* 4-*Cyanophenyl Sulphone* (**1**).—Conc. hydrochloric acid (0.43 ml, 5 mmol) in ethanol (25 ml) was added slowly (40 min) to a stirred mixture of 4-cyanophenyl 4-nitrophenyl sulphone (2.6 g, 9 mmol), ethanol (75 ml), and iron dust (5.5 g) at reflux temperature, which was maintained for an additional 1 h. The iron sludge was filtered from the hot solution through Celite and washed with a little more boiling ethanol. The ethanolic solution was concentrated and cooled. The collected product was crystallized from ethanol to give the sulphone (**1**) (2 g, 91%), m.p. 182—184 °C (lit.,[30] 175—176 °C) (Found: C, 60.1; H, 3.8; N, 10.8; S, 12.0. Calc. for $C_{13}H_{10}N_2O_2S$: C, 60.45; H, 3.9; N, 10.8; S, 12.4%).

4-*Aminophenyl* 4-*Nitrophenyl Sulphone* (**2**).—To 4-acetylaminophenyl 4-nitrophenyl sulphone[31] (17.5 g, 54.6 mmol) in ethanol (25 ml), a solution of conc. HCl (31.7 ml, 381 mmol) in water (45 ml) was added and the mixture was refluxed for 4 h. After cooling, the collected product was crystallized from ethanol to give the amino compound (**2**) (12 g, 79%), m.p. 169—170 °C (lit.,[22] 166—169 °C).

Methyl 4-(4-*Aminophenylsulphonyl*)*benzoate* (**3**).—This was prepared (67%) from 4-(4-aminophenylsulphonyl)benzoic acid (**4**) in tetrahydrofuran with an ethereal solution of diazomethane; m.p. 189—190 °C (from benzene) (lit.,[21] 175—176 °C) (Found: C, 57.6; H, 4.4; N, 4.8; S, 10.7. Calc. for $C_{14}H_{11}NO_6S$: C, 57.7; H, 4.5; N, 4.8; S, 11.0%).

4′-(4-*Aminophenylsulphonyl*)*acetophenone* (**5**).—Crude 4-(4-nitrophenylsulphonyl)benzoyl chloride, obtained from the corresponding acid[21] with an excess of $SOCl_2$, was dissolved in tetrahydrofuran and converted (85%) into the methyl ketone by the diethyl acylmalonate method;[32] m.p. 181—182 °C [from methanol–acetonitrile (2:1)] (lit.,[33] 180—181 °C). Reduction to the amino derivative (**5**) was accomplished according to the literature method.[33]

N,N-*Diethyl*-4-(4-*nitrophenylsulphonyl*)*benzamide*.—To a stirred solution of diethylamine (3 ml, 30 mmol) in dry tetrahydrofuran (30 ml), cooled with an ice-bath, crude 4-(4-nitrophenylsulphonyl)benzoyl chloride (10 mmol) in dry tetrahydrofuran (80 ml) was slowly added. The mixture was stirred for 3 h and the volatile materials were evaporated off. The residue was treated with water and the crude product was collected and crystallized from ethanol to give the *amide* (3 g, 83%), m.p. 194—196 °C (Found: C, 56.6; H, 5.0; N, 7.8; S, 8.5. $C_{17}H_{18}N_2O_5S$ requires C, 56.3; H, 5.0; N, 7.7; S, 8.8%).

4-(4-*Aminophenylsulphonyl*)-N,N-*diethylbenzamide* (**7**).—Catalytic hydrogenation (10% Pd/C; 2 atm, room temp., 3 h) of *N,N*-diethyl-4-(4-nitrophenylsulphonyl)benzamide (0.5 g) in methanol (30 ml) gave the amino derivative (**7**) (0.3 g, 65%), m.p. 165—166 °C (from isopropyl alcohol) (Found: C, 61.8; H, 6.3; N, 8.55; S, 9.4. $C_{17}H_{20}N_2O_3S$ requires C, 61.4; H, 6.1; N, 8.4; S, 9.6%).

4-(4-*Aminophenylsulphonyl*)*benzamide* (**6**).—Catalytic hydrogenation of 4-(4-nitrophenylsulphonyl)benzamide[34] as described for compound (**7**) afforded (89%) the *sulphone* (**6**), m.p. 232—234 °C (from methanol–water) (Found: C, 56.5; H, 4.3; N, 9.8; S, 11.35. $C_{13}H_{12}N_2O_3S$ requires C, 56.6; H, 4.4; N, 10.1; S, 11.6%).

4-*Acetylaminophenyl* 4-*Aminophenyl Sulphone* (**14**).—Catalytic hydrogenation (10% Pd/C; atmospheric pressure, room temp., 4 h) of 4-acetylaminophenyl 4-nitrophenyl sulphone[31] (1.2 g) in methanol (70 ml) gave the amino compound (**14**) (0.5 g, 61%), m.p. 246—247 °C (lit.,[35] 242—243 °C).

4-*Aminophenyl* 4-*Ethylaminophenyl Sulphone* (**21**).—A mixture of 4-acetylaminophenyl 4-aminophenyl sulphone (**14**) (0.5 g, 2 mmol) and $LiAlH_4$ (0.2 g, 5 mmol) in dry tetrahydrofuran (15 ml) was stirred under reflux for 15 h. The excess of hydride was decomposed with ice and methanol and the tetrahydrofuran was evaporated off. The aqueous mixture was extracted with ether and the residue was chromatographed on silica gel (ether as eluant) to give the *sulphone* (**21**) (0.25 g, 50%), m.p. 195 °C (Found: C, 61.0; H, 6.1; N, 10.0. $C_{14}H_{16}N_2O_2S$ requires C, 60.8; H, 5.8; N, 10.1%).

References

1 G. M. Brown, *Adv. Biochem.*, 1971, **35**, 35.

2 J. L. McCullough and T. H. Maren, *Antimicrob. Agents Chemother.*, 1973, **3**, 665.

3 H. J. Scholar, R. Leimer, and R. Richle, in 'Handbook of Experimental Pharmacology', ed. W. Peters and W. H. G. Richards, Springer-Verlag, Berlin, 1984, vol. 68/II, p. 123.

4 P. G. De Benedetti and C. Frassineti, *J. Mol. Struct., Theochem.*, 1983, **92**, 191.

5 H. H. Szmant, in 'Sulfur in Organic and Inorganic Chemistry,' ed. A. Senning, Dekker, New York, 1971, vol. 1, p. 107.

6 M. J. Janssen, in 'Organic Sulphur Chemistry,' ed. C. J. M. Stirling, Butterworths, London, 1975, p. 26.

7 D. F. Ewing, *Org. Magn. Reson.*, 1979, **12**, 499.

8 P. G. De Benedetti, A. Rastelli, M. Melegari, and A. Albasini, *J. Med. Chem.*, 1978, **21**, 1325.

9 G. W. Buchanan, C. Reyes-Zamora, and D. E. Clarke, *Can. J. Chem.*, 1974, **52**, 3895.

10 C. Chang, H. G. Floss, and G. E. Peck, *J. Med. Chem.*, 1975, **18**, 505.

11 G. L. Nelson and E. A. Williams, *Prog. Phys. Org. Chem.*, 1976, **12**, 107.

12 C. Cauletti, C. Furlani, G. Nicotra, K. D. Schleinitz, and W. Wegener, *J. Chem. Soc., Perkin Trans. 2*, 1984, 533.

13 J. A. Pople and G. A. Segal, *J. Chem. Phys.*, 1966, **44**, 3289.

14 P. G. De Benedetti, S. Quartieri, and A. Rastelli, *J. Mol. Struct., Theochem.*, 1981, **85**, 45.

15 W. J. Hehre, R. W. Taft, and R. D. Topsom, *Prog. Phys. Org. Chem.*, 1976, **12**, 164.

16 W. Moffitt, *Proc. R. Soc., Ser A*, 1950, **200**, 409; H. P. Koch and W. Moffitt, *Trans. Faraday Soc.*, 1951, **47**, 7.

17 G. Del Re, *Theor. Chim. Acta*, 1963, **1**, 188; S. A. Pozzoli, A. Rastelli, and M. Tedeschi, *J. Chem. Soc., Faraday Trans. 2*, 1973, **69**, 256.

18 P. R. Wells, S. Ehrenson, and R. W. Taft, *Prog. Phys. Org. Chem.*, 1968, **6**, 147.

19 C. G. Swain and E. C. Lupton, *J. Am. Chem. Soc.*, 1968, **90**, 4328.

20 C. Hansch, A. Leo, S. H. Unger, K. H. Kim, D. Nikaitani, and E. J. Lien, *J. Med. Chem.*, 1973, **16**, 1207.

21 W. Wenner, *J. Org. Chem.*, 1957, **22**. 1808.

22 H. H. Szmant and G. Suld, *J. Am. Chem. Soc.*., 1956, **78**, 3400.

23 E. D. Amstuz, E. A. Fehnel, and J. W. Woods, *J. Am. Chem. Soc.*, 1947, **69**, 1922.

24 E. Knüsli, *Gazz. Chim. Ital.*, 1949, **79**, 621 (*Chem. Abstr.*, 1950, **44**, 4438a).

25 W. T. Calwell, G. Chan, V. H. Brown, J. I. De Graw, J. H. Peters, and N. E. Morrison, *J. Med. Chem.*, 1974, **17**, 142.

26 H. Gilman and H. Smith Broadbent, *J. Am. Chem. Soc.*, 1947, **69**, 2053.

27 H. Burton and E. Hoggarth, *J. Chem. Soc.*, 1945, 468.

28 E. L. Jackson, *J. Am. Chem. Soc.*, 1946, **68**, 1438.

29 E. Knüsli, *Gazz. Chim. Ital.*, 1950, **80**, 522 (*Chem. Abstr.*, 1951, **45**, 6596i).

30 K. Ganapathi and A. Alamela Venkataraman, *Proc. Indian Acad. Sci.*, 1945, **21A**, 30 (*Chem. Abstr.*, 1945, **39**, 3524 ^{3}).

31 C. W. Ferry, J. S. Buck, and R. Baltzly, *Org. Synth.*, 1960, Coll. Vol. III, p. 239.

32 H. G. Walkn and C. R. Hanser, *J. Am. Chem. Soc.*, 1946, **68**, 1386.

33 H. H. Szmant and G. Levit, *J. Am. Chem. Soc.*, 1954, **76**, 5459.

34 G. Leandri, L. Maioli, and L. Ruzzier, *Bull. Sci. Fac. Chim. Ind. Bologna*, 1957, **15**, 57 (*Chem. Abstr.*, 1958, **52**, 7292c).

35 H. Heymann and C. Heidelberger, *J. Am. Chem. Soc.*, 1945, **67**, 1986.

Received 30*th July* 1984; *Paper* 4/1343