Metal-assisted reactions. Part 29.[1] Structure and hydrogenolysis of C–N bonds in derivatives of aromatic amines. Bond length and electronegativity changes from X-ray crystallographic data

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Pseudosaccharyl and phenyltetrazolyl derivatives **1**–**6** were prepared with the aim of weakening the originally strong C–N bond in aromatic amines and facilitating its hydrogenolysis. Structural analyses of the amines **1**–**6** by ^{1}H and ^{13}C NMR spectroscopy and X-ray diffraction methods have revealed major changes in C–N bond lengths on derivatization as a result of changes in conjugation. These changes are discussed in relation to the observed reactivity of compounds **1**–**6** towards catalytic and non-catalytic C–N bond hydrogenolysis.

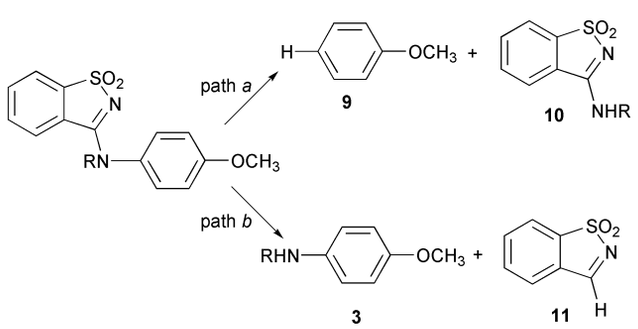
Introduction

The use of X-ray structure determination to aid understanding of reaction mechanism by considering bond lengths and angles in relation to chemical reactivity has been used in both theoretical and experimental contexts.[2] For example, a simple aliphatic C–C single bond length of *ca*. 1.53 Å is considered normal with bond order, $n = 1$, as is a C=C double bond of 1.34 Å with bond order, $n = 2$;[3] any formal single bond length lying between 1.53 and 1.34 Å suggests a degree of double bond character, with a partial bond order between 1 and 2.[4a,b] Changes in bond lengths and angles for a series of compounds have been used successfully to explain chemical reactivity by relating ground-state structure, as observed by X-ray analysis, to supposed transition state structures.[2,5]

For 3-aryloxy-1,1-dioxo-1,2-benzisothiazoles (3-aryloxy-pseudosaccharins) **7** and 5-aryloxy-1-phenyl-1*H*-tetrazoles **8**, the central ether C–O–C bond has been shown to be quite exceptional amongst aromatic ethers in having one very long C–O bond (*a* in structures **7**, **8**) and one very short C–O bond (*b* in structures **7**, **8**).[6] In effect, the heterocyclic groups in **7**, **8** siphon off electron density from the original phenolic bond *a* so that its bond order becomes, $n = 1$ and the ether bond *b* to the heterocycle becomes a partial double bond with $n = 1.4$. It was found that the combined bond lengths $a + b$ for a wide variety of diaryl ethers were always close to 2.78 Å, so that the available electron density from oxygen must be limited and the total bond energy, $D(a) + D(b)$, is constant.

The withdrawal of electron density from the original phenolic C–OH partial double bond on conversion into a heterocyclic ether weakens it so that it becomes more like a C–O single bond in aliphatic alcohols or ethers. The effect at the original aryl ring of the phenol is as if the electronegativity of the oxygen has been increased to such an extent that it becomes similar to that of fluorine. Apart from the X-ray results, evidence for this effective change in electronegativity can be found in ^{1}H and ^{13}C NMR spectra of ethers **7**, **8**, which show that the original electron-donating effect of oxygen in phenols or simple phenolic ethers has been changed into a strongly electron-withdrawing effect in the heterocyclic ethers.[6] The chemical effects of these changes can be seen in the ease with which the bond *a* in ethers **7**, **8** undergoes catalytic hydrogenolysis,[7] solvolytic reactions[8] and cross-coupling.[9] However, the bond length changes appear to be only part of the explanation for the observed ease of the catalytic reactions and the nature of the heterocycles themselves plays an important role.[7]

Although C–O bonds have been widely investigated by X-ray analysis, there does not appear to have been a similar interest in C–N bonds,[3] possibly because it is known that hydrogenolytic or nucleophilic displacement of a C–N bond in an aromatic amine is difficult.[10] Compared with S_N2 reactions of ethers and alcohols or their derivatives, similar reactions at an aromatic C–N bond are difficult because of the smaller electronegativity of nitrogen compared with oxygen and therefore its greater delocalisation of electron density into an aryl ring.[11] Generally, extreme conditions are needed to effect hydrogenolytic or solvolytic removal of the amino group in aromatic amines. For example, even conversion of a primary amine into its *N*,*N*-bis-sulfonamide does not make C–N bond cleavage easy and reaction with $NaBH_4$ at 175 °C in HMPA is required for hydrogenolysis.[11] Simple direct *ipso* displacement of the amino group from the C–N bond of an aromatic amine, as in Scheme 1



Scheme 1

(path *a*), remains an elusive goal. The result of attempted catalytic hydrogenolysis of the C–N bond of aromatic amines with molecular hydrogen is normally the formation of a cyclic alkylamine in high yield.[12] Indeed, the easiest way to cleave a C–N bond in primary aromatic amines lies indirectly through

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Table 1 Selected bond lengths, bond orders and bond bond energies for amines **1**–**6**

Amine	Bond[a]	Bond length[b]/Å	Bond order[c] (n)	Bond energy[d] D_n/kJ mol^{-1}
1	*a*	1.460(5)	1.04	365
	b	1.320(4)	1.71	574
	c	1.323(4)	1.69	567
2	*a*	1.501(2)	0.89	317
	b	1.385(2)	1.35	463
	b′	1.394(3)	1.31	450
	c	1.287(3)	1.92	637
	c′	1.295(3)	1.87	622
3	*a*	1.430(2)	1.15	400
	b	1.329(2)	1.65	555
	c	1.311(2)	1.76	589
4	*a*	1.448(2)	1.08	378
	b	1.393(2)	1.32	453
	b′	1.397(2)	1.30	447
	c	1.288(2)	1.92	637
	c′	1.288(2)	1.92	637
5	*a*	1.421(2)	1.19	412
	b	1.338(2)	1.60	540
	c	1.315(2)	1.74	583
6	*a*	1.403(2)	1.27	438
	b	1.3559(19)	1.50	509
	c	1.3280(19)	1.66	558
	d	1.343(2)	1.57	531
	e	1.4357(19)	1.13	393

[a] These are the CN bonds indicated in structures **1**–**6**. [b] Obtained by X-ray crystallographic analysis (esd's in brackets). [c] Obtained from $\ln(n) = (1.47 - \text{bond length})/0.28$; see text. [d] Estimated from $\ln(D_n/352) = 0.91\ln(n)$; see text.

diazotisation.[13a] Because of this marked contrast between aromatic ethers and amines in resistance to hydrogenolysis, the present study was undertaken to examine the structures and chemistry of several heterocyclic derivatives of aliphatic and aromatic amines.

Results and discussion

Carbon–nitrogen bond lengths in amines, imines and nitriles

By addition of covalent radii, the average length of an aliphatic C–N single bond is expected to be 1.47 Å, for a C–N double bond 1.28 Å and for a C–N triple bond 1.15 Å.[4] Reference to compilations of measured bond lengths indicates that these values are reasonably accurate and that the C–N bond length in an aromatic amine (an aniline) is usually about 1.38–1.39 Å.[3] A survey of the Cambridge Crystallographic Database[14] revealed that the mean Ph–N bond length for a range of over 500 substituted anilines was 1.418 Å (sd 0.026) and for saturated N–C bonds in the same molecules was 1.465 Å (sd 0.020). These values for bond length permit the derivation of the simple bond order (n)/bond length (r) relationship shown in eqn. (1).[4]

$$r = 1.47 - 0.28 \ln(n) \qquad (1)$$

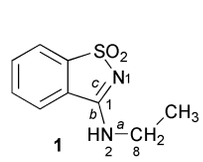
From this equation, an aromatic C–N bond in an aniline has a partial bond order of about 1.35. Eqn. (1) was used to calculate bond orders for the compounds reported here from bond lengths determined by X-ray crystallography (Table 1) to show how bond order changes markedly with structure in the present heterocyclic derivatives of amines.

Carbon–nitrogen bond energies in amines, imines and nitriles

Compilations of bond strengths[15] indicate that an average value for the C–N bond of an aliphatic amine is about 352 kJ mol^{-1}. Data for C–N bonds in aliphatic imines are sparse but some heats of hydrogenation are known.[16] From these values and known heats of formation of amines,[17] a C–N double bond strength of 657 kJ mol^{-1} may be estimated.[18] For a C–N triple bond, a value of 955 kJ mol^{-1} can be estimated from the geometric mean of C–C and N–N triple bonds,[4] a figure which is close to the 960 kJ mol^{-1} calculated from heats of formation of CH, N and HCN.[15] From these values, the linear relationship (2) was derived.[2,4,6]

$$\ln(D_n/D_1) = p\ln(n) \qquad (2)$$

For any C–N bond of order n its strength may be estimated reasonably accurately through eqn. (2), in which $p = 0.91$. For example, using an aniline C–N bond length of 1.386 Å,[18] a bond order of 1.35 may be calculated from eqn. (1), suggesting that its C–N bond strength should be 462 kJ mol^{-1}. A commonly suggested average C–N bond strength for anilines is 427 kJ mol^{-1}.[15] The bond strength relationship (2) was used to calculate C–N bond strengths in the compounds described here (Table 1; bond *a* in structures **1**–**6**). These bond strengths are important for consideration of reactivity towards hydrogenolysis (see later).



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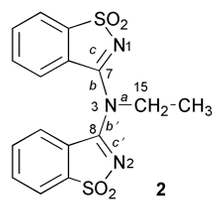

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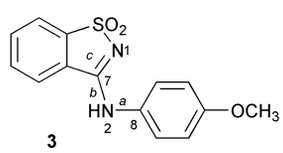

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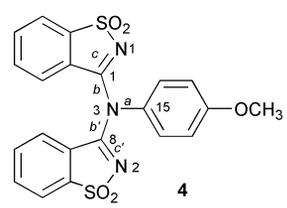

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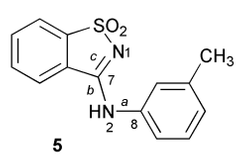

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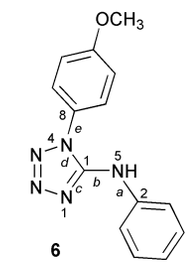

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Table 2 ^{1}H NMR signals (δ) for 4-methoxyaniline and amines **1**–**4**, **12**[a]

4-Methoxyaniline[b]	**1**	**2**	**3**	**4**	**12**
3.62 (CH_3O)	1.26 (t, J = 6 Hz, CH_3)	1.45 (t, J = 7 Hz, CH_3)	3.81 (CH_3O)	3.87 (CH_3O)	1.29 (t, J = 5.9 Hz, CH_3)
6.53 (d, J = 8.7 Hz, H3,5)	3.51 (q, J = 6 Hz, CH_2)	4.45 (q, J = 7 Hz, CH_2)	7.07 (d, J = 7 Hz) (H3′,5′)	7.17 (d, J = 9 Hz, H3′,5′)	3.55 (q, J = 5.9 Hz, CH_2)
6.61 (d, J = 8.7 Hz, H2,6)	7.82 (m, H5,6)	7.71 (d, J = 8 Hz, H4)	7.76 (d, J = 7 Hz (H2′,6′)	7.23 (d, J = 7.5 Hz, H4)	4.2 (br s, NH)
	7.98 (m, H4)	7.85 (t, J = 8 Hz, H5)	7.88 (m, H5,6)	7.63 (d, J = 9 Hz, H2′,6′)	7.52 (m, 5H)
	8.17 (m, H7)	7.96 (t, J = 8 Hz, H6)	8.05 (d, J = 6 Hz, H4)	7.77 (t, J = 7.5 Hz, H5)	
		8.28 (d, J = 8 Hz, H7)	8.45 (d, J = 6 Hz, H7)	7.92 (t, J = 7.5 Hz, H6)	
				8.26 (d, J = 7.5 Hz, H7)	

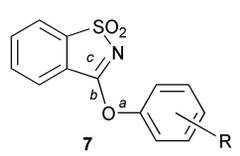
[a] The δ values (TMS = 0) are given first in each column, followed in parentheses by the carbon number to which the hydrogens are attached. For numbering used (non-conventional) see structures. The CH_3 and CH_2 groups are shown as such. Assignments in the benzisothiazole ring system followed from cross-coupling experiments. [b] The carbon atom numbering is conventional and is shown in structures **12**, **13**.

Measurement of electronegativity by ^{1}H and ^{13}C NMR spectroscopy

Although use of ^{1}H NMR spectroscopy to estimate electronegativities may be questioned because of variations in chemical shifts due to anisotropic terms, nevertheless such shifts have been used successfully to give an indication of effective electronegativity of any grouping X through use of eqn. (3),

$$\text{Electronegativity} = 0.564\,\delta_{\text{internal}} + 2.00 \qquad (3)$$

applied to substituted ethanes, C_2H_5X.[19] The same technique was used to estimate the effective electronegativity of oxygen in aryloxy ethers of pseudosaccharins and phenyltetrazoles.[6] In eqn. (3), δ_{internal} is the difference in chemical shifts of the methyl and methylene groups in the substituted ethanes. From ^{1}H NMR spectra of *N*-(1,1-dioxo-1,2-benzisothiazol-3-yl)ethylamine **1** and *N*,*N*-bis(1,1-dioxo-1,2-benzisothiazol-3-yl)ethylamine **2**, the chemical shift differences δ_{internal} were 2.26 and 2.94 ppm respectively, giving effective electronegativities of 3.27 and 3.66 for the substituted amino nitrogen. For the corresponding phenyltetrazolyl ethylamine **12**, the effective electronegativity of the amino nitrogen is calculated similarly to be 3.27 [Table 2 and eqn. (3)]. These estimates may be compared with a typical value for the electronegativity of nitrogen of 3.0.[13b] Thus, one pseudosaccharyl or one phenyltetrazolyl group causes a shift of 0.27 units of electronegativity at nitrogen but two pseudosaccharyl groups cause a shift of 0.66 units. These movements in electronegativity are not so impressive as the effect of just one pseudosaccharyl group or one phenyltetrazolyl group on the electronegativity of oxygen in their ethers of phenols, for which the shift in electronegativity is about 0.5 units.[6] Whereas the oxygen shift in pseudosaccharyl **7** or phenyltetrazolyl ethers **8** gives the oxygen an effective electronegativity about equivalent to that of fluorine, in the case of similar substitution into amines even two pseudosaccharyl groups leave the effective electronegativity of nitrogen only about the same as that of the normal value for oxygen (3.5).[13b] These considerations of electronegativity changes become important when considering *ipso* replacements of the amine group in anilines.



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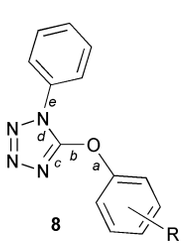

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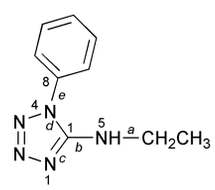
The changes in effective electronegativity are revealed even more so on comparing the ^{1}H and ^{13}C NMR spectra of the two 4-methoxyaniline derivatives **3**, **4** with that of 4-methoxyaniline



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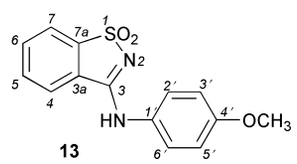

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itself. In the latter, the amino and methoxy groups are both electron-donating. This is reflected in the upfield shifts of the protons *ortho* to the two substituent groups (Table 2). In the mono-*N*-pseudosaccharyl-substituted 4-methoxyaniline **3**, the protons *ortho* to the nitrogen have been shifted downfield strongly by 1.26 ppm compared with the corresponding protons in 4-methoxyaniline itself; the protons *meta* to the amino group are shifted by 0.42 ppm and even the methyl protons on the methoxy group have been moved downfield by about 0.18 ppm. These are the effects expected of a strongly electron-withdrawing amino group rather than one having its usual electron-donating properties. The shifts indicate an abrupt change in effective electronegativity of the amino nitrogen in 4-methoxyaniline on substitution into the amino group of a pseudosaccharyl unit and is in keeping with the estimated change in electronegativity derived from eqn. (3). For compound **4** containing two pseudosaccharyl substituents on the amino nitrogen, these proton shifts are similar to those in the mono-substituted amine **3**. There is no large increase in effective electronegativity as might have been expected for substitution of two strongly electron-withdrawing pseudosaccharyl systems onto the amino nitrogen. This unexpected result is echoed by the ^{13}C shifts and is explained by significant structural changes (see later).

Long-range paramagnetic or diamagnetic shielding by neighbouring groups is important for protons and it could be argued that the apparent electronegativity effects are simply due to long-range shielding and/or deshielding. However, these long range effects are much less important for nuclei other than hydrogen (or deuterium) and measurement of ^{13}C shifts has been suggested as a better guide to electronegativity in aromatic systems.[20] Accordingly, the ^{13}C NMR spectra of compounds **3**, **4** were examined and compared with those of 4-methoxyaniline itself (Table 3). The ^{13}C shifts of all the carbons in compounds **1**–**4** were assigned (Table 4).[21,22] These ^{13}C signals reveal a very large downfield change for the aromatic carbon attached to nitrogen (C8 in structure **3** and C15 in **4**) with δ-values of 156.8 and 160.8 ppm respectively, compared with the carbon attached to nitrogen in 4-methoxyaniline (δ = 145.0 ppm). The shift of this carbon is about 8 ppm for the addition of one pseudosaccharyl group and a further 4 ppm on addition of a second pseudosaccharyl group. These results are in keeping with the amine of the original 4-methoxyaniline becoming electron-withdrawing in marked contrast to its usual electron-donating

Table 3 ^{13}C NMR signals (δ) for 4-methoxyaniline and amines **1**–**4**, **12**[a,b]

4-Methoxyaniline	**1**	**2**	**3**	**4**	**12**
57.9 (CH_3)	13.9 (CH_3)	13.4 (CH_3)	55.5 (CH_3O)	55.9 (CH_3O)	15.0 (CH_3)
117.2 (3,5,CH)	37.8 (CH_2)	47.9 (CH_2)	114.4 (3′,CH)	116.0 (3′,CH)	39.5 (CH_2)
117.7 (2,6,CH)	121.4 (7,CH)	123.1 (4,CH)	121.6 (7,CH)	122.9 (7,CH)	124.1 (CH)
145.0 (1,C)	123.1 (4,CH)	126.6 (7,CH)	123.6 (4,CH)	127.0 (3a,C)	129.9 (CH)
153.5 (4,C)	128.0 (3a,C)	126.9 (3a,C)	123.9 (2′,CH)	127.3 (4,CH)	130.4 (CH)
	133.3 (6,CH)	134.5 (5,CH)	128.5 (3a,C)	129.9 (2′,CH)	133.5 (8,C)
	133.6 (5,CH)	135.2 (6,CH)	130.6 (1′,C)	130.9 (1′,C)	155.0 (1, C)
	142.5 (7a,C)	141.7 (7a,C)	133.5 (6,CH)	134.2 (5,CH)	
	159.2 (3,C)	164.3 (3,C)	133.8 (5,CH)	135.0 (6,CH)	
			141.2 (7a,C)	141.8 (7a,C)	
			156.8 (4′,C)	160.8 (4′,C)	
			157.3 (3,C)	163.8 (3,C)	

[a] The δ values (TMS = 0) are given first in each column, followed in parentheses by the carbon number in each formula and the number of hydrogen atoms attached to that carbon. The CH_3 and CH_2 groups are shown as such. The numbers of attached hydrogens were determined by ^1H–^{13}C coupling and by DEPT experiments. Assignments in the benzisothiazole ring system were as given in ref. 22, except for positions 6, 7 which were deduced as shown in the note presented as ref. 21. [b] The carbon atom numbering is conventional and is illustrated in structures **12**, **13**.

Table 4 ^{13}C shift values (ppm) assigned to the SO_2 and C=N groups of the 1,1-dioxo-1,2-isothiazole section of 1,1-dioxo-1,2-benziso-thiazoles.[a,b]

Group	α-Position	*ortho*	*meta*	*para*
–SO_2–	+11.9	−7.1	0.0	+5.2
–C=N–	+6.9	−0.5	0.0	+4.8

[a] These values were determined as in ref. 21. The α-position is that carbon in the benzene ring of 1,1-dioxo-1,2-benzisothiazoles to which the group SO_2 or C=N is attached; the *ortho*, *meta* and *para* shifts then refer to such positions in the benzene ring *relative to the chosen α-position*. The shift at the meta positions was constrained to be zero.[20] [b] All shifts are relative to the ^{13}C atoms in benzene, for which δ = 128.5 in DMSO [c] These shifts resemble those for –NMe_3^+ (SO_2) and –CH=O (–C=N), both of which are electron-withdrawing.[20]

properties. The total shift in electronegativity does not give the nitrogen in the original aromatic amine an electronegativity near to that of fluorine but it does become more like the normal value for oxygen.

Bond lengths, bond angles and bond orders from X-ray crystallographic analysis

With the bond order/bond energy relationships outlined above [eqns. (1), (2)], bond lengths derived from X-ray crystallographic analysis can be used to estimate bond strengths. In pseudosaccharyl ethers of phenols, the original phenolic C–OH bond strength was found to be considerably reduced in its ethers **7**, **8**.[6] The relevant bond length data for the amines considered here are shown in Table 1, together with those for an analogue **5**, which does not have a conjugating group in the 4-position of the substituted aniline and also for an analogous phenyltetrazole derivative **6**. Generally, corresponding bond lengths in the monosubstituted amines are very similar (bonds *a*, *b*, *c* in structures **3**,**5**) and suggest that the methoxy group has little effect on the conjugation of nitrogen (N2) to the benzenoid ring. Therefore, bond length changes around the central nitrogen of the amino group can be considered in isolation from other potential conjugation effects of substituents in the aniline ring.

On introducing one pseudosaccharyl substitutent into 4-methoxyaniline to give **3**, the original arylamino C–N bond of the aniline is stretched from being a partial double bond of order 1.35 to one of order 1.15. Although the electron-withdrawing effects of the pseudosaccharyl group in these amines is similar to its effect in pseudosaccharyl aryl ethers,[6] the C7–N2 bond of compound **3** still appears to be partly conjugated to the aniline ring. In the bis-pseudosaccharylamine **4** the corresponding C15–N3 bond of the aniline is stretched until it is virtually a single bond (n = 1.08). Thus, to obtain similar bond length (bond order) changes for C–N in aromatic amines to those observed for the C–O bonds in the corresponding phenyl ethers, two pseudosaccharyl substituents are needed, compared with only one for the phenols. This result from X-ray crystallographic analysis in the solid state is in agreement with the changes observed in effective electronegativity in solution from NMR shifts in that one pseudosaccharyl group changes the effective electronegativity of the amino nitrogen from 3.00 to 3.26 (a shift of 0.26 units) but two pseudosaccharyl groups produce a shift of +0.66 units in electronegativity. It seems that the inherently smaller electronegativity of nitrogen compared with oxygen leads to it being more difficult to stop the nitrogen continuing to conjugate with the aryl ring to which it is attached. This effect of two pseudosaccharyl groups on a C–N bond are sufficient to cause even the C–N single bond in the ethylamine derivative **2** to stretch until it has a bond order *n* of only 0.89 rather than 1.0. The mono-tetrazolyl substituted compound **6** exhibits similar but smaller changes, with the C–N bond of the aniline (C2–N5) having a bond order of 1.27, indicating significant residual conjugation from nitrogen into the aryl ring.

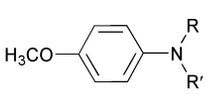
The combined bond lengths, $a + b$, in the four amines **1**, **3**, **5**, **6** average 2.76 Å, very close to the 2.78 Å found in the aryl ethers of phenyltetrazoles and pseudosaccharins.[6] The combined length in the disubstituted compounds **2**, **4** is significantly different at about 2.85 Å. The bond lengths shown in Table 1 reveal that, in the mono-pseudosaccharyl and phenyltetrazolyl derivatives **3**, **5**, **6**, the C–N bond to the heterocyclic system is considerably shorter by some 0.03–0.04 Å than is a typical C–N bond in an aniline. The similarity in the combined bond lengths $a + b$ in monosubstituted ethers and amines appears to be due to the better conjugation of nitrogen compared with oxygen to a pseudosaccharyl or tetrazolyl ring system in addition to its concomitant continued conjugation to another aryl ring.

The other C–N bonds in the pseudosaccharyl compounds **2**, **4** show even more remarkable changes. In the mono-pseudosaccharyl substituted aniline **3**, the C–N bond *b* to the pseudosaccharyl ring shows strong partial double bond character (bond order 1.65) but, with two pseudosaccharyl substituents on nitrogen, as in compound **4**, the C–N bond *b* lengthens again to give a bond order of about 1.31. In this bis-substituted compound, there are cross-conjugated π-orbital systems, *viz*., one through nitrogen between the aniline ring and either one of the two pseudosaccharyl groups (path *a*–*b*–*c* or *a*–*b*′–*c*′ in structure **4**) and the other between the two pseudosaccharyl groups themselves (path *c*–*b*–*b*′–*c*′ in structure **4**). The second conjugation path is equivalent to that of a triazapentadienyl anion system of 6 π-electrons, in which the phenyl ring is simply pendant as a non-conjugating susbstituent on the central nitrogen

Table 5 Crystallographic data

Compound	**1**	**2**	**3**	**4**	**5**	**6**
Formula	$C_9H_{10}N_2O_2S$	$C_{16}H_{13}N_3O_4S_2$	$C_{14}H_{12}N_2O_3S$	$C_{21}H_{15}N_3O_5S_2$	$C_{14}H_{12}N_2O_2S$	$C_{14}H_{13}N_5O$
M	210.3	375.4	288.3	453.5	272.3	267.3
Crystal system	Monoclinic	Triclinic	Monoclinic	Triclinic	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P\bar{1}$	$P2_1$	$P\bar{1}$	$P2_1/n$	$P2_1/c$
a/Å	7.141(5)	8.165(2)	7.111(1)	8.1028(8)	7.2916(16)	17.689(3)
b/Å	6.946(2)	8.224(3)	6.863(1)	8.3652(8)	21.129(5)	6.6556(13)
c/Å	18.886(5)	12.933(4)	13.231(3)	15.7507(16)	8.0546(18)	11.735(2)
α/°	90	98.513(16)	90	96.111(3)	90	90
β/°	95.12(4)	107.370(18)	90.00(3)	90.830(3)	97.246(5)	105.61(2)
γ/°	90	100.413(17)	90	93.793(3)	90	90
U/Å^3	932.9(7)	796.1(4)	645.7(2)	1058.97(18)	1231.0(5)	1330.6(4)
Z	4	2	2	2	4	4
D_c/g cm^{-3}	1.497	1.566	1.483	1.422	1.469	1.334
μ/mm^{-1}	0.31	3.30	0.21	0.29	0.26	0.73
T/K	153	160	213	160	160	160
$R(F, F^2 > 2\sigma)$	0.037	0.037	0.028	0.039	0.040	0.042
R_w (F^2, all data)	0.043	0.101	0.062	0.111	0.110	0.103
Data, parameters	1063, 127	2803, 228	2011, 184	4706, 281	2654, 173	2290, 183

15. This feature is enhanced by the torsional angles (22 and 135°; Table 5; structure **2**, **4**) of the planes of the pseudosaccharyl rings about the central nitrogen (N3) and the near sp^2 geometry of this nitrogen, which precludes effective conjugation between the aniline ring and either of the two pseudosaccharyl groups. In the bis-pseudosaccharyl ethylamine **2**, for which the central nitrogen (N3) is not even formally π-conjugated to the ethyl group, the conjugation path *c*–*b*–*b*′–*c*′ has similar bond orders to those in compound **4**. Since this is the only conjugated pathway involving N3 in compound **2** and it is almost identical in bond ordering as the corresponding pathway in compound **4**, it must be presumed that both pathways are essentially of the triazapentadienyl type **15** and that all formal conjugation from the central nitrogen to the aryl ring has been lost. Thus, the introduction of a second electron-withdrawing group into a mono-substituted aromatic amine simply leads to strong conjugation between the two substituting heterocyclic groups through the central nitrogen and leads also to the original aryl group becoming a non-conjugating appendage.



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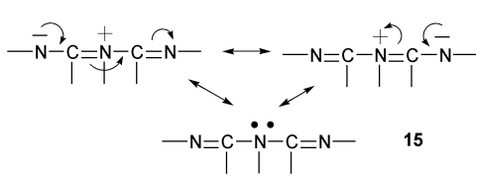


15

In this second triazapentadienyl conjugation pathway **15** for compounds **2**, **4**, the N–C–N–C–N system is not completely coplanar and cannot itself fully conjugate. The inability of this system to conjugate completely is due to steric interferences between the pseudosaccharyl and aryl rings. Structural minimization based on calculation at the B3LYP level[23] using the basis set 6–311G*, produced molecular geometries similar to those found experimentally by X-ray diffraction methods. For bis-*N*-pseudosaccharyl substituted aniline, it was confirmed that the two pseudosaccharyl groups could not be co-planar because of steric hindrance and therefore that they cannot be fully conjugated through the path *c*–*b*–*b*′–*c*′. The triazapentadienyl system **15** may be compared formally with the all-carbon pentadienyl anion. [24]

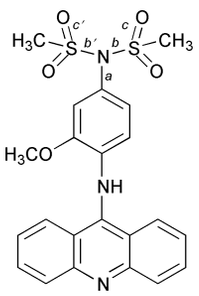
Whereas general structural features for pseudosaccharyl ethers **7** of phenols and *N*-mono-pseudosaccharyl substituted arylamines **3**, **5** are broadly similar (conjugation from the aryl ring through the oxygen or nitrogen to the pseudosaccharyl group), the effect of adding a second pseudosaccharyl ring system to the arylamine is to change the conjugation pattern entirely so as to by-pass the aryl ring. This explains the anomalies discussed above for the NMR shifts. With the new conjugation path, the central amino nitrogen has only an inductive effect on the aryl ring. It would be expected that two alkyl- or aryl-sulfonyl groups attached to an arylamine might behave similarly because the double substitution opens up a new more favourable conjugation system. This deduction suggests that a search for X-ray structures, in which there is a similar "pentadienyl" system, might prove informative. The Cambridge Crystallographic Database provided relevant comparisons, some of which are shown in structures **16**–**21**.[25] In five examplar compounds (**16**–**20**) having an aniline-like nitrogen doubly substituted by methylsulfonyl or 4-methylphenylsulfonyl groups, the aryl C–N bond has a bond order of about1 1.07, rather than the value of 1.35 expected for an aniline exhibiting partial conjugation of nitrogen to the aryl ring (Table 6). This stretching and decrease in bond order exactly parallels the behaviour of the bis-saccharyl compound **4** and is in keeping with the stretching of the C–N single bond *a* in the bis-saccharyl compound **2**. Similarly, the phthalimido compound **21** has an aryl C–N bond *a* that is also single rather than conjugated. In this last compound, there are two other aryl C–N anilino bonds in the same molecule but these other C–N bonds have bond orders of about 1.35, typical of partly conjugated anilino C–N bonds. Thus, when an anilino nitrogen is doubly substituted by potentially conjugating groups, the central nitrogen loses all delocalisation along the C–N bond into the original aryl ring and becomes instead a simple single bond. At the same time, the two new substituents conjugate through the nitrogen and attain a "pentadienyl" anion-like conjugated pathway. In all of the compounds **2**, **4**, **16**–**21**, the four bonds making up the "linear" system **15** are partial double bonds having lengths significantly different from simpler compounds. For example, the C=O bonds in compound **21** have bond lengths that are shorter than those of a simple amide, while the C–N bonds are considerably longer than those found in simple amides. Similar arguments apply to the N–S and S–O bonds in the sulfonamides **16**–**20**.

The above evidence suggests that, when compared with pseudosaccharyl or phenyltetrazolyl ethers of phenols, substitution of these heterocyclic systems into the amino group of arylamines might not be expected to have the same profound effect on ease of *ipso* substitution. The effective electronegativity of oxygen in the pseudosaccharyl aryl ethers **7** is near to that of fluorine but, for nitrogen in amines **3**, **4**, the introduction of one pseudosaccharyl group does not produce a shift to carry the

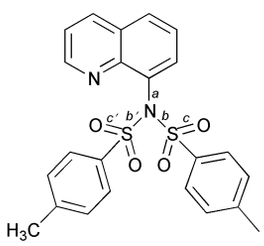
Table 6 Bond lengths/Å for some "pentadienyl" systems, **16**–**21**

Bond	16	17	18	19	20	21
a[a]	1.450 (1.07)	1.458 (1.04)	1.453 (1.06)	1.446 (1.09)	1.455 (1.06)	1.451 (1.07)
b	1.689	1.671	1.687	1.680	1.679	1.416
b′	1.678	1.672	1.670	1.678	1.679	1.392
c[b]	1.382, 1.416	1.431, 1.408	1.427, 1.421	1.425, 1.423	1.429, 1.421	1.171
c′[b]	1.421, 1.430	1.414, 1.414	1.421,1.420	1.425, 1.425	1.426, 1.439	1.214

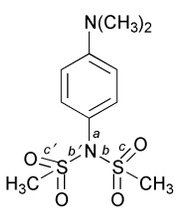
[a] Calculated bond order is shown in parentheses. [b] Both S=O bonds are given.



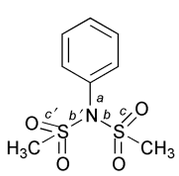
16; DAYDEM



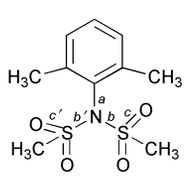
17; LATWEI



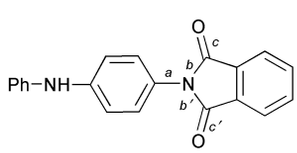
18; JEXREJ



19; RIJBIV



20; YOYYOA



21; PAPPHI

electronegativity of nitrogen even to that of oxygen let alone to fluorine. Further, the introduction of a second pseudosaccharyl group onto nitrogen leads to development of a new conjugation pattern and the effective electronegativity at nitrogen is still not close to that of fluorine. In such circumstances, easy hydrogenolysis of amino C–N bonds in amines **3**, **4** analogous to the easy hydrogenolysis of C–O bonds in pseudosaccharyl **7** or phenyltetrazolyl ethers **8** of phenols might not be expected. The experimental attempts described below to effect cleavage of such C–N bonds were designed to test their reactivity under typical hydrogenolytic conditions.

Hydrogenation of amines 3, 4

Based on the extremely easy catalytic transfer hydrogenolysis of pseudosaccharyl aryl ethers **7** to give arenes and saccharin, it was hoped that similar reduction of the anilino compounds **3**, **4** would give anisole (**9**; Scheme 1, path *a*) and a bis-pseudosaccharyl amine **10**. For all of the mono-pseudosaccharyl or mono-phenyltetrazolyl derivatives of aromatic amines, no hydrogenolysis of the C–N bond *a* to give the desired products (Scheme1, path *a*) could be effected. However, hydrogenolysis of bis-pseudosaccharyl amine **4** did occur elsewhere. In this last case, catalytic transfer reduction using hydrogen donors had no effect but, for catalytic reduction with hydrogen gas at a temperature of 150 °C and a moderately high pressure, a hydrogenolytic reaction was observed. This was not the desired hydrogenolysis of the C–N bond (*a* in structures **3**, **4**; Scheme 1, path *a*) but, instead, a different C–N bond (*b* in structure **4**) was cleaved to give the mono-pseudosaccharyl amine **3** and the reduced product **11** (Scheme 1, path *b*). When attempts were made to effect hydrogenolysis with hydride reagents, reduction was observed exclusively *via* reaction path *b* (Scheme 1) and not by path *a*. The result is not surprising in view of the structural evidence presented here for a change in conjugation pattern on substituting two heterocyclic groups onto the nitrogen of an aromatic amine (see below).

ipso Cleavage of aryl–X bonds

The removal of a substituent from an aryl ring by *ipso* replacement is generally not easy. Aromatic amines are inert except under a few reported extreme conditions. Phenols are largely inert and fluorine amongst other groups is resistant to *ipso* displacement unless the aromatic ring is extensively activated by strongly electron-withdrawing groups. Easy hydrogenolysis is found for heteroaromatic ethers of phenols **7** under heterogeneous catalytic conditions,[6] for homogeneously catalysed cross-coupling,[9] for displacement of fluorine by hydroxy under catalysed conditions[26] and most notably for diazonium compounds, which may be reduced to arene with phosphinic acid under non-catalytic conditions.[13a] Simple effects of bond energies cannot account for these differences. An energy balance of bond-forming and bond-breaking reactions at the heart of aryl–X bond displacement suggests that it should be exothermic and, specifically for C–O and C–N cleavage, that it should be about equally exothermic in the two cases, with small activation energies.[27,28] This inference is clearly incorrect for amines and, since the bond energy terms are well-established, it indicates that there must be an energy of activation barrier that is small in some reactions but sufficiently large in others as to make bond-breaking difficult. A consideration of the bonding and non-bonding orbitals in aryl–X compounds suggests a reason for such changes in activation energy.

It has been shown that, for substituents providing *p*-orbital overlap with the π-system in a benzene ring, the resultant π-orbitals are arranged as 4 bonding (π_1–π_4) and 3 antibonding (π_5–π_7).[29] Most *ipso* displacements are nucleophilic reactions, in which the incoming nucleophile may be H^- or OH^- for example and require attack at the aromatic carbon. Frontier orbital theory indicates that such reactions are governed mostly by two factors, one of which concerns the Coulombic attraction or repulsion between an incoming nucleophile and the *ipso* carbon (the first term of eqn. (4)) and the other concerns bonding between LUMO and HOMO orbitals of electrophile and nucleophile (the second term of eqn. (4), in which ΔE is the interaction energy, q represents the net charge of nuclei and electrons, R is the distance apart of incoming nucleophile and electrophilic centre, β is a resonance integral, c is the orbital coefficient and E_{HOMO} and E_{LUMO} are the energies of the HOMO and LUMO orbitals).[30] The second term on the right-hand side becomes zero if the outermost π-electron density in the nucleophile or at the *ipso* carbon in the π_5 orbital of the

aromatic system is zero. The latter is exactly the case[29] for π_5 and so the LUMO–HOMO interaction can be ignored in this *ipso* series. In contrast to this negligible effect, it can be seen that the overall (orbitals π_1 to π_4) density at the *ipso* carbon does vary significantly, depending on the electronegativity of the group X in aryl–X.[24b,31] As the electronegativity of the substituent X increases, there is an increasing inductive effect on the *ipso* carbon, making it more and more positive. Thus, easy nucleophilic displacement at the *ipso* carbon should be characteristic of groups having high effective electronegativities, so that the first term in eqn. (4) becomes significant. This

$$\Delta E = \frac{q_{nuc}\, q_{elec}}{\varepsilon R} + \frac{2(c_{nuc}\, c_{elec}\beta)^2}{E_{HOMO(nuc)} - E_{LUMO(elec)}} \qquad (4)$$

deduction runs parallel to the observed trend towards increasing susceptibility to nucleophilic displacement at the *ipso* carbon as the effective electronegativity of the group X in Aryl–X increases. This indicates that a major reason for the failure of aromatic amines to undergo hydrogenolysis when substituted by pseudosaccharyl or phenyltetrazolyl groups, in complete contrast to the very easy analogous hydrogenolysis of these heteroaromatic ethers of phenols, lies in the large initial inherent difference in electronegativities between nitrogen and oxygen and the failure of the heterocyclic derivatives to push the electronegativity of the amine nitrogen to a sufficiently high value. The theoretical considerations covered here are being investigated in greater detail through estimations of activation energies by semi-empirical and *ab initio* methods.[32] The new conjugation pathway **15** provides an easier but still difficult route to hydrogenolysis than does hydrogenolysis of the original anilino C–N bond but then leads to reversal of the original substitution to return to the original aniline.

Experimental

Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Mass spectra were recorded on a Trio 1000 Quadrupole Mass Spectrometer using electron ionisation at 70 eV or on a VG Analytical 7070E double focusing high resolution mass spectrometer. Infrared spectra were recorded on a Perkin Elmer 883 instrument as Nujol mulls. ^{1}H NMR spectra were obtained on either a Bruker ACE200 (200 MHz) or on a Varian Gemini (300 MHz) instrument, using tetramethylsilane as internal standard and $CDCl_3$ as solvent, except for the series shown in Tables 2, 3 for which d_6-dimethyl sulfoxide was the solvent. Gas–liquid chromatograms were obtained with a Dani 3800 gas chromatograph or with a Phillips PU 4600 gas chromatograph, both equipped with flame ionisation detector and using Carbowax capillary columns. Microanalyses were performed on a Carlo Erba 1106 elemental analyser, equipped with an electrical detector. Thin layer chromatography was performed on silica gel $60F_{250}$ plates (Merck).

Crystals were examined at reduced temperature on a variety of diffractometers: Stoe IPDS image-plate system at Liverpool University for compounds **1** and **3** (Mo-Kα radiation, $\lambda = 0.71073$ Å), Stoe-Siemens AED at Newcastle University for compounds **2** and **6** (Cu-Kα radiation, $\lambda = 1.54184$ Å), Bruker AXS SMART at Newcastle for compound **4** (Mo-Kα radiation, $\lambda = 0.71073$ Å), and Bruker AXS SMART at Daresbury Laboratory for compound **2** (synchrotron radiation, $\lambda = 0.6879$ Å, for a very small crystal). The structures were solved by direct methods and were refined on F^2 values for all unique reflections (except for compound **1**, for which refinement on F was used). Hydrogen atoms were constrained to idealised positions.†

† CCDC reference numbers 161957–161962 for compounds **1**–**6**, respectively. See http://www.rsc.org/suppdata/p2/b1/b102571f/ for crystallographic files in .cif format.

Synthesis of *N*-substituted amines

***N*-(1,1-Dioxo-1,2-benzisothiazol-3-yl)ethylamine 1.** A solution of ethylamine in THF (2 mL; 4.0 mmol of amine; Aldrich) was added to 3-chloro-1,1-dioxo-1,2-benzisothiazole (pseudosaccharyl chloride; 1.08 g, 5.32 mmol) in THF (10 mL) and the mixture was stirred at room temperature for 1.5 h, after which it was made alkaline with aqueous sodium hydroxide (5% w/w) and then an excess of cold water was added. The resulting precipitate was filtered off and recrystallised to give the required compound **1**, mp 280–281 °C (from methanol–water; 0.65 g; 78% yield). Found: C, 51.3; H, 4.8; N, 13.4. Calculated for $C_9H_{10}N_2O_2S$: C, 51.4; H, 4.8; N, 13.3%); ν_{max}. 1153, 3332, 1525 cm^{-1}; ms: [M$^+$], *m*/*z* 210.

***N*-(1,1-Dioxo-1,2-benzisothiazol-3-yl)-4-methoxyaniline 3.** A solution of 4-methoxyaniline (0.32 g; 2.60 mmol) and 3-chloro-1,1-dioxo-1,2-benzisothiazole (pseudosaccharyl chloride; 0.53 g, 2.56 mmol) in THF (10 mL) was heated under reflux for 2.5 h, after which the solvent was evaporated off under pressure. The residual solid was washed with water, dried *in vacuo* at room temperature and recrystallised to give the required product, mp > 330 °C (from acetone–ethanol; 0.57 g; 72% yield). Found: C, 58.5; H, 4.2; N, 9.7. Calculated for $C_{14}H_{12}N_2O_3S$: C, 58.3; H, 4.2; N, 9.7%; ν_{max}. 1350, 1154 (SO_2), 3328 (NH), 1617, 1571, 1513 (Ar) cm^{-1}; ms: [M$^+$], *m*/*z* 288.

***N*-(1,1-Dioxo-1,2-benzisothiazol-3-yl)-3-methylaniline 5.** This was prepared as for compound **3**. Colourless crystals (from THF–water; 51% yield), mp 311–312 °C (lit.[33] 296–297 °C). Found: C, 61.7; H, 4.4; N, 10.3. $C_{14}H_{12}N_2O_2S$ requires: C, 61.8; H, 4.4; N, 10.3 %; ^{1}H NMR: δ 8.49 (1H, m), 8.08 (1H, m), 7.91 (2H, m), 7.67 (2H, d, $J = 8$ Hz), 7.38 (1H, t, $J = 8$ Hz), 7.10 1H, d, $J = 8$ Hz), 2.38 (3H, s); ^{13}C NMR (H-decoupled): δ 157.0, 141.0, 138.7, 137.6, 134.0, 133.6, 129.1, 128.5, 126.7, 123.7, 122.7, 121.7, 119.6, 21.3; ν_{max}. 1345, 1157, 3330, 1624, 1485, 1572 cm^{-1}; ms: [M$^+$], *m*/*z* 272.

***N*,*N*-Bis-(1,1-dioxo-1,2-benzisothiazol-3-yl)-4-methoxyaniline 4.** *Method A*. Neat 4-methoxyaniline (2.4 g; 19 mmol) and trifluoroacetic anhydride (11.4 g; 54 mmol) were stirred at room temperature for 1 h, after which the whole reaction mixture was evaporated *in vacuo* to gave a solid, which was recrystallised to give *N*-(4-methoxyphenyl)-1,1,1-trifluoroacetamide, mp 110–112 °C (small needles from methanol; 4.1 g; 98.3% yield). ^{1}H NMR: δ 7.63 (2H, d, $J = 9$ Hz), 6.98 (2H, d, $J = 9$ Hz), 3.77 (3H, s); ν_{max}. 3300 (N–H), 1690 (CO–NH–) 822 (C–H, Ar) cm^{-1}; ms: [M$^+$], *m*/*z*: 219. To a stirred solution of this trifluoroacetamide (0.24 g; 1.11 mmol) in dry THF (10 mL) was added portionwise sodium hydride (60% w/w; 0.4 g; 10 mmol). After a further 20 min, pseudosaccharyl chloride (0.44 g; 2.2 mmol) was added and the mixture was left to stir for 24 h at room temperature. The resulting sodium chloride was filtered off and the solution was evaporated to dryness to leave a residue, which was dissolved in ethyl acetate (10 mL) and washed with aqueous sodium hydroxide (5%; 3 × 10 mL), water and finally dried (Na_2SO_4); the final solution was evaporated under reduced pressure and the residual crude solid was crystallised from acetone to give the required amine **4** in 27% yield. Analytical details for **4** appear in the following method.

Method B. To a stirred solution of *N*-(1,1-dioxo-1,2-benzisothiazol-3-yl)-4-methoxyaniline **3** (1.6 g; 5.5 mmol) in dry THF (10 mL) was added portionwise sodium hydride (60 % w/w; 0.32 g; 8.0 mmol). After a further 20 min, pseudosaccharyl chloride (1.3 g; 6.3 mmol) was added. After 1 h the mixture was examined by TLC (ethyl acetate), which showed complete conversion of the amine **3** ($R_f = 0.46$) to give a single new product ($R_f = 0.5$). The reaction mixture was added to cold water and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with water, dried (Na_2SO_4) and evaporated

to give a residual solid (2.1 g; 4.6 mmol), which was recrystallised to give the required product **4**, mp >330 °C (square yellow transparent plates from ethanol–acetone; 1.7 g; 68% yield). Found: C, 55.7; H, 3.3; N, 9.3. Calculated for $C_{21}H_{15}N_3O_5S_2$: C, 55.7; H, 3.3; N, 9.3 %; ν_{max}. 1601, 1587, 1511, 1313, 1128 cm^{-1}; ms: $[M^+]$, *m*/*z* 453.

***N*,*N*-Bis-(1,1-dioxo-1,2-benzisothiazol-3-yl)ethylamine 2.** To a stirred solution of *N*-(1,1-dioxo-1,2-benzisothiazol-3-yl)-ethylamine **1** (0.23 g; 1.1 mmol) in dry THF (10 mL) as added portionwise sodium hydride (60% w/w; 0.14 g; 3.6 mmol). After a further 20 min, pseudosaccharyl chloride (0.24 g, 1.3 mmol) was added and the mixture was stirred at room temperature. After 5 h, cold water (10 mL) was added to quench the reaction and the mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with water (3 × 10 mL) and dried (Na_2SO_4). After evaporation under reduced pressure, the residual oily solid was recrystallised to give the required bis-amine **2**, mp >250 °C (small colourless needles from ethanol–acetone; 0.22 g, 53.3%). Found: C, 51.4; H, 3.6; N, 11.0. Calculated for $C_{16}H_{13}N_3O_4S_2$: C, 51.2; H, 3.5; N, 11.2%; ν_{max}. 1326, 1132, 1601, 1531, 3441 cm^{-1}; ms: $[M^+]$, *m*/*z* 375.

***N*-[1-(4-Methoxyphenyl)-1*H*-tetrazol-5-yl)aniline 6.** 5-Chloro-1-phenyl-1*H*-tetrazole (0.99 g; 5.5 mmol) and 4-methoxyaniline (1.51 g; 12.3 mmol) were melted together and stirred under a nitrogen atmosphere at 140 °C for five hours. The reaction mixture was cooled and the resulting purple solid was shaken with dichloromethane (100 mL) and filtered from 4-methoxyanilinium chloride. The filtrate was evaporated under reduced pressure and the resulting solid was recrystallized to give the amine **6** (pale pink plates from ethanol; 0.7582 g, 52% yield), mp 146–150 °C. Found: C, 62.8; H, 4.9; N, 26.5%. Calculated for $C_{14}H_{13}N_5O$: C, 62.9; H, 4.9; N, 26.2%; ν_{max} (Nujol mull), 3162–3310, 1590, 1532 and 1235 cm^{-1}; δ_H 3.88 (s, 3H), 6.20 (br s, 1H), 7.09 (d, 2H, J = 8.8 Hz), 7.41 (d, 2H, J = 8.8 Hz), 7.26–7.57 (m, 5H); ms $[M^+]$ *m*/*z* 267; accurate mass 267.11198 Da, $C_{14}H_{13}N_5O$ requires 267.11200. A further sample of this material was recrystallized by slow diffusion of petroleum ether (bp 60–80 °C) into a solution of the amine **6** in ethanol in a closed vessel. X-Ray crystallographic diffraction analysis showed that, as a result of a Dimroth rearrangement,[34] structure **6** is correct and is not that expected of simple substitution of chlorine in 5-chloro-1-phenyl-1*H*-tetrazole by aniline.

***N*-(1-Phenyl-1*H*-tetrazol-5-yl)ethylamine 12.** To a solution of 5-chloro-1-phenyl-1*H*-tetrazole (1.00 g; 5.5 mmol) in THF (1.8 mL) at room temperature was added a 2.0 M solution of ethylamine in THF (6 mL; 12 mmol; 2 M, Aldrich) *via* a syringe under dry nitrogen. The reaction mixture was stirred at room temperature for 4 h before being poured into ice–water (200 mL). The mixture was allowed to warm to room temperature and extracted with diethyl ether (3 × 40 mL). The combined ethereal extracts were washed with saturated aqueous $NaHCO_3$ (30 mL) and dried ($MgSO_4$). Removal of the solvent *in vacuo* yielded a pale yellow solid, which was recrystallised to give the required amine **12**, mp 162–164 °C (colourless plates from toluene, 0.333 g; 32% yield). Found: C, 57.1; H, 5.8; N, 37.3%. Calculated for $C_9H_{11}N_5$: C, 57.1; H, 5.8; N, 37.0%; ms, *m*/*z* 189 $[M^+]$, *m*/*z* 160 (41%).

Attempted reduction of *N*-[1-(4-methoxyphenyl)-1*H*-tetrazol-5-yl]aniline 6 using palladium-on-charcoal as catalyst and sodium phosphinate as hydrogen donor

Pd/C catalyst (10% w/w; 120 mg) in absolute ethanol (3 mL) was added to a vigorously stirred solution of *N*-[1-(4-methoxyphenyl)-1*H*-tetrazol-5-yl]aniline **6** (150 mg; 0.56 mmol) in toluene (8 mL). A solution of sodium phosphinate (150 mg) in distilled water (2.5 mL) was added and the mixture was stirred vigorously and heated under reflux. The reaction was monitored by TLC (diethyl ether) but no reduction of the amine **6** had occurred after five hours, despite addition of more catalyst and hydrogen donor.

Attempted hydrogenolysis of *N*,*N*-bis(1,1-dioxo-1,2-benzisothiazol-3-yl)-4-methoxyaniline 4

(i) By catalytic transfer reduction. (a) To a stirred solution of the bis-pseudosaccharylamine **4** (0.058 g; 0.127 mmol) and dodecane (internal standard; 0.020 g) in THF (8 mL) containing Pd-on-charcoal catalyst (Pd/C; 10%, 0.077 g) at 60 °C was added a solution of sodium phosphinate (0.1952 g; 2.22 mmol) in water (2 mL). The reaction was monitored by TLC and GC but, after 12 h, no reaction had occurred and starting material was recovered.

(b) To a solution of the bis-pseudosaccharylamine **4** (71.4 mg; 0.157 mmol) in propan-2-ol (5 mL) was added Raney nickel (W2; 0.083 mL) and the mixture was heated under reflux for 12 h. As in (a), no reaction was observed.

(ii) By catalytic reduction with hydrogen gas. The bis-pseudosaccharylamine **4** (0.062 g, 0.136 mmol) and Pd/C catalyst (10% w/w; 0.08 g) in THF (10 mL) were stirred with hydrogen at 150 °C at a pressure of 125 psi (9 atm). After 7 days, the reaction was stopped and cooled to room temperature and the catalyst was filtered off. GC analysis of the filtrate revealed no volatile components other than solvent. However, on TLC, one new component appeared, the R_f of which (R_f = 0.46) was consistent with the presence of *N*-(1,1-dioxo-1,2-benzisothiazol-3-yl)-4-methoxyaniline **3**. The solvent was evaporated under reduced pressure and the residual solid (37.44 mg; 95.6% recovered material) was analysed. ^{1}H NMR spectroscopy confirmed that the isolated product was the amine **3**.

(iii) Using hydride reagents. (a) Sodium tetrahydroborate (38.0 mg, 1.00 mmol) was added gradually in small amounts to a stirred solution of *N*,*N*-bis(1,1-dioxo-1,2-benzisothiazol-3-yl)-4-methoxyaniline **4** (54.2 mg, 0.12 mmol) in methanol (5 mL) at room temperature. The whole was heated to 60 °C and, after two days, TLC (ethyl acetate) showed one new component had been formed. Water was added to stop the reaction and the organic product was extracted with ethyl acetate (3 × 10 mL). The combined organic phases were washed with water, dried (Na_2SO_4) and the solvent was evaporated under reduce pressure to give a residual solid (0.032 g; 93% recovered material). ^{1}H NMR spectroscopy showed that *N*-(1,1-dioxo-1,2-benzisothiazol-3-yl)-4-methoxyaniline **3** had been formed. A small amount of this residue was dissolved in THF and the resulting solution was examined by GC for the presence of 4-methoxyaniline but only solvent was found, a result which was confirmed by GC/MS.

(b) The above reaction (a) was repeated with the bis-pseudosaccharylamine **4** (50.1 mg, 0.11 mmol) and sodium tetrahydroborate (35.9 mg, 0.95 mmol) but with THF (5 mL) as solvent. After 12 h, TLC showed a new component had formed (R_f = 0.46), in addition to a small amount of starting material (R_f = 0.5). Reaction was stopped by addition of cold water and then hydrochloric acid (2 M) to destroy excess of reducing agent. The aqueous layer was made alkaline with aqueous $NaHCO_3$ and extracted with diethyl ether (2 × 10 mL). The combined extracts were dried (Na_2SO_4), filtered and the solvent removed under reduced pressure to give a residual solid (12.2 mg, 90%), which was shown to be almost entirely 4-methoxyaniline by GC/MS and ^{1}H NMR, δ 3.75 (s, 3H), 6.65 (d, 2H, J 9Hz), 6.75 (d, 2H, J 9 Hz).

(c) Reaction (a) above was repeated with the bis-pseudosaccharylamine **4** (37.5 mg, 0.083 mmol), sodium tetrahydroborate (36.6 mg, 0.97 mmol) and 1,4-dioxane (5 mL)

as solvent. After 2 days at 60 °C, TLC showed that no reaction had occurred.

(d) Reaction (a) above was repeated using the amine **4** (23.6 mg, 0.052 mmol), sodium tetrahydroborate (23.6 mg, 0.623 mmol) in DMF (5 mL) as solvent. After 12 h, TLC showed only one spot ($R_f = 0.46$), corresponding to *N*-(1,1-dioxo-1,2-benzisothiazol-3-yl)-4-methoxyaniline **3**. Water was added to stop the reaction and the resulting mixture was extracted with diethyl ether (3 × 10 mL). The combined diethyl ether extracts were dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. A ^{1}H NMR spectrum of the residual solid (15.6 mg) in d_6-DMSO verified the formation of the compound **3**.

(e) Reaction (a) above was repeated but with lithium tetrahydroaluminate (8.8 mg, 0.23 mmol) in place of $NaBH_4$ and THF (5 mL) at room temperature. After 12 h, TLC showed two spots with $R_f = 0.46$, 0.5, corresponding respectively to *N*-(1,1-dioxo-1,2-benzisothiazol-3-yl)-4-methoxyaniline **3** and starting material **4**. Water was added to stop the reaction and the mixture was extracted with diethyl ether. The combined extracts were dried (Na_2SO_4), filtered and the solvent was evaporated under reduced pressure to give a solid (29.1 mg). ^{1}H NMR spectroscopy of this solid verified it to be a mixture of amines **3**, **4**. From the integrals for the characteristic peaks at $\delta = 1.1$, 2.8 ppm the compounds **3**, **4** were estimated to be present in a ratio of 72 : 28.

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21 Ref. 22 gives assignments of ^{13}C shifts for most positions in 1,1-dioxo-1,2-benzisothiazoles, except for positions 6, 7 (conventional numbering) which are listed as uncertain. By using the extra information in the present series of compounds, it has been possible to confirm these existing assignments and to assign positions 6, 7 exactly. The SO_2 and C=N groups of the 1,1-dioxo-1,2-benzisothiazole section were regarded as substituents of a benzene ring. It was then assumed that these electron-withdrawing substituents had no effect on their respective meta positions in the benzene ring. For ^{13}C shifts of similar substituents, this assumption is sufficiently close to actuality as to make little or no difference to the final results. Knowing the assignments for positions 4–7a in the benzene ring of some 1,1-dioxo-1,2-benzisothiazoles,[22] it was then possible to treat the effects on the *ortho* and *para* positions to the SO_2 and C=N groups as unknowns in a series of simultaneous equations. Solution of these equations gave the results shown in Table 4, from which it was then possible to make definite assignments for all positions in the 1,1-dioxo-1,2-benzisothiazole system, as given in Table 3.

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