A Study of Annular Tautomerism, Interannular Conjugation, and Methylation Reactions of *ortho*-Substituted-5-aryltetrazoles using Carbon-13 and Hydrogen-1 N.M.R. Spectroscopy

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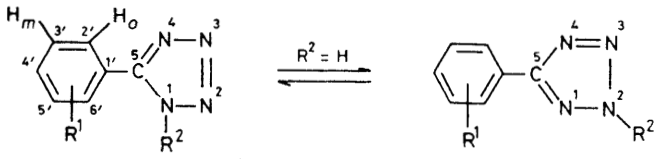
In *ortho*-substituted-5-phenyltetrazoles, Ar–CN_4H (Ar = 2′-MeC_6H_4, 2′-ClC_6H_4, or 2′,6′-$Cl_2C_6H_3$), the rings are twisted out of the planar configuration and interannular conjugation is inhibited. In each case the tetrazole 1-NH tautomer is strongly predominant. When the rings are coplanar, as in *para*-substituted-5-phenyltetrazoles, the electron-withdrawing effect of the *para*-substituents changes the tautomerism significantly back towards the 2-NH form. Methylation of the anion of 5-(*ortho*-substituted-phenyl)tetrazoles occurred equally at the 1-N- and 2-N-positions, or slightly favoured the 1-N-position, and thereby contrasted with the *p*-substituted derivatives, where 2-*N*-methylation strongly predominates.

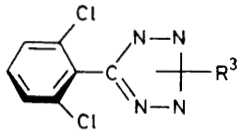
LACK of information on the influence of substituents on the annular tautomerism (I) ⇌ (II) of 5-substituted-tetrazoles [1] and the failure of attempts using hydrogen-1 [2] and nitrogen-15 n.m.r.[3] to monitor this tautomerism recently prompted us to explore [4] the chemical shift of the 5-carbon atom as a probe of the tautomerism using



(I) (II)

(1) $R^1 = R^2 = H$
(2) R^1 = 4′-Me, R^2 = H
(3) R^1 = 2′-Me, R^2 = H
(4) R^1 = 4′-NO_2, R^2 = H
(5) R^1 = 2′-NO_2, R^2 = H
(6) R^1 = 4′-Cl, R^2 = H
(7) R^1 = 2′-Cl, R^2 = H
(9) R^1 = H, R^2 = Me
(10) R^1 = 4′-Me, R^2 = Me
(11) R^1 = 2′-Me, R^2 = Me
(12) R^1 = 4′-NO_2, R^2 = Me
(13) R^1 = 2′-NO_2, R^2 = Me
(14) R^1 = 4′-Cl, R^2 = Me
(15) R^1 = 2′-Cl, R^2 = Me

(17) R^1 = H, R^2 = Me
(18) R^1 = 4′-Me, R^2 = Me
(19) R^1 = 2′-Me, R^2 = Me
(20) R^1 = 4′-NO_2, R^2 = Me
(21) R^1 = 2′-NO_2, R^2 = Me
(22) R^1 = 4′-Cl, R^2 = Me
(23) R^1 = 2′-Cl, R^2 = Me



(8) R^3 = H
(16) R^3 = 1-N-Me
(24) R^3 = 2-N-Me

N-methyl isomers as models for the individual tautomers. The 5-C chemical shift differed significantly in 1,5- and 2,5-disubstituted-tetrazoles, and allowed the tautomerism to be monitored for a number of *p*-substituted-5-phenyltetrazoles.[4] In this present work the effects of *ortho*-substituents in 5-phenyltetrazoles, the nitrogen analogues of benzoic acids, are examined and compared with the *p*-substituents. It has been previously predicted [5] that electron-withdrawing 5-substituents in tetrazoles should favour the 2-H-tautomer (II).

RESULTS AND DISCUSSION

Annular Tautomerism.—The 5-carbon shifts for the series of 5-aryltetrazoles (1)—(8) are compared with those of the corresponding 1-*N*-methyl, [(9)—(16)] and 2-*N*-methyl [(17)—(24)] isomers, in Table 1. The annular

TABLE 1

^{13}C Shifts (p.p.m. from $SiMe_4$) and tautomerism of 5-aryltetrazoles

		5-C Shifts				
Compound	5-Phenyl-substituent R^1	Parent	1-*N*-Me Derivative	2-*N*-Me Derivative	1-NH form (%)	K_T\{[1]/[11]\}
(1) [a]	H	155.6	154.2	164.25	86	6.14
(2)	*p*-Me	155.3	154.1	164.3	88	7.33
(3)	*o*-Me	155.35	153.85	164.6	86	6.14
(4) [a]	*p*-NO_2	155.8	152.7	162.5	68	2.12
(5) [a]	*o*-NO_2	153.9	151.95	160.7	78	3.54
(6)	*p*-Cl	156.5	153.1	163.3	67	2.03
(7)	*o*-Cl	153.45	152.6	162.4	91	10.1
(8)	*o*,*o*-Cl_2	151.4	150.6	159.9	91	10.1

[a] From ref. 4.

tautomerism of the tetrazoles was determined from these shifts by using the expression $\delta = N_1\delta_1 + N_2\delta_2$, in which δ is the measured 5-C shift, N_1 and N_2 represent the mole fraction of the 1-H and 2-H tautomers, and δ_1 and δ_2 the 5-C shifts of the 1-*N*-Me and 2-*N*-Me isomers, respectively. The use of the chemical shifts of the *N*-Me isomers in place of the chemical shifts of the NH tautomers is an obvious but worthwhile approximation which we have commented on previously [4,6] and which has been widely used in studies of tautomerism. A recent dipole-moment study of the *p*-tolyltetrazole set (2), (10), and (18) (Table 2) by Lumbroso *et al.*[7] was in general agreement with the carbon n.m.r. results in indicating a dominance of the 1-H tautomer (60—70%) in dioxan which, however, was not as high as in aqueous dimethyl sulphoxide. Another possible source of difficulty with the present *ortho*-substituted derivatives is the possibility that the 5-C shifts might be significantly influenced by the conformational angle between the

rings. For example the aryl C-1′ shifts of the *E* and *Z* forms of aromatic thiobenzimidate systems [Ph–C(SMe)=NMe] depend on the conformational angle of the *C*-aryl bond.[8] However, this is not the case for the imino-carbon shifts, which are the analogues of the tetrazole 5-carbon shifts of the present systems. For example the differences between imino-carbon shifts of the *E* and *Z* isomers of the system Ar–C(SMe)=NMe were 0.7, 0.7, and 0.9 p.p.m., respectively when the aryl *ortho*-substituents were H, H; H, Me; and Me, Me. These shift differences are very small and in the context of the differences in the tetrazole 5-C shifts, which are over an order of magnitude bigger, they allow us to eliminate a significant contribution to the tetrazole 5-carbon shifts from the angle of twist of the 1′-aryl–5-tetrazole bond. Furthermore the data for the phenyltetrazoles (Table 2) show no indication that even the aryl C-1′ shift is seriously influenced by the conformational angle. This is evident through all of the data, but very clear for the 2′,6′-dichloro-series (8), (16), and (24) (Table 2), where in each case the rings lie orthogonal with similar conformational angles, but the C-1′ shifts differ markedly. In fact these C-1′ shifts show a pattern we have pointed out previously,[6] namely they generally follow the trend of the tetrazole C-5 shifts. This suggests that the main factor governing both sets of shifts is the nature of the bonding in the tetrazole ring which in turn reflects the annular tautomerism.

For the series of 5-aryltetrazoles herein the carbon n.m.r. shifts suggest that the 1-NH form was dominant but *p*-electron-withdrawing groups directed the tautomerism back towards the 2-NH form [Table 1, compounds (4) and (6)]. The influence of the *ortho*-substituents relative to *para*-substituents in the 5-phenyltetrazoles [compounds (3), (5), (7), and (8), Table 1] is interesting because, although steric effects by the *ortho*-substituent might be expected to favour the 2-NH form, the results suggest that the 1-H form (I) is strongly dominant, even more so than for *p*-substituted derivatives. In these *ortho*-substituted compounds the tetrazole ring appears to be twisted out of the plane of the benzene ring, thus reducing the steric and electronic effects of the *ortho*-substituents, and the 1-H form is preferred. This was further confirmed by introducing two *ortho*-substituents as in compound (8) (Table 1). For the 5-(2′,6′-dichlorophenyl)tetrazoles the ^{1}H and ^{13}C n.m.r. spectra of the aromatic regions (see below) suggested that the tetrazole ring was twisted orthogonally to the phenyl ring. The 1-H form was strongly preferred and molecular models suggested that there is no steric interaction between the 1-H proton and the *ortho*-substituents of the phenyl ring when the rings are orthogonally oriented.

TABLE 2

^{1}H and ^{13}C Aromatic n.m.r. shifts [a]; interannular conjugation

Compound	Phenyl substituent R[1]	δ(H_m)	δ(H_o)	Δ δ_H [f]	δ(C-1′)	δ(C-2′)	ΔC-2′[g]	N–Me δ_H	N–Me δ_C
(2)	4′-Me	7.36	8.00	0.64	120.8	126.7	1.8		
(10)	4′-Me	7.34	7.64	0.30	120.4	128.5		4.16	34.95
(18)	4′-Me	7.24	8.00	0.76	124.1	126.25	2.25	4.34	39.7
(6)	4′-Cl	7.42	7.96	0.54		128.2	2.3		
(14)	4′-Cl	7.58	7.78	0.20	122.5	130.5		4.2	35.1
(22)	4′-Cl	7.44	8.04	0.60	125.8	128.0	2.5	4.4	39.7
(3)	2′Me	7.32 [b]	7.60 [c]	0.28	123.6	129.35	1.35	*h*	*h*
(11)	2-Me	7.28—7.40 [d]		0.12	123.2	130.7		3.94 [i]	34.1 [i]
(19)	2′-Me	7.34 [b]	7.92 [c]	0.58	126.2	128.9	1.8	4.45 [j]	39.5 [j]
(7)	2′-Cl	7.56 [b]	7.84 [c]	0.28	124.1	131.7	1.45		
(15)	2′-Cl	7.57—7.70 [d]		0.13	123.2	133.15		3.98	34.3
(23)	2′-Cl	7.46 [b]	7.90 [c]	0.44	126.0	131.3	1.85	4.44	39.7
(8)	2′,6′-Cl_2	7.58 [e]			124.4	134.75	0.25		
(16)	2′,6′-Cl_2	7.66 [e]			122.5	135.0		3.98	33.7
(24)	2′,6′-Cl_2	7.52 [e]			126.4	135.1	0.1	4.52	39.9

[a] $SiMe_4$ was the reference for all shifts. [b] Multiplet (3 H) including H_p. [c] Multiplet (1 H). [d] Multiplet (4 H) including H_o. [e] Singlet (3 H), all aromatic protons. [f] δ(H_o) − δ(H_m). [g] C-2′ Shift substracted from that of the corresponding 1-*N*-methyl derivative. [h] *ortho*-Me, δ_H 2.50; δ_C 20.3 p.p.m. [i] *ortho*-Me, δ_H 2.20; δ_C 19.1 p.p.m. [j] *ortho*-Me, δ_H, 2.60; δ_C 21.1 p.p.m.

Interannular Conjugation.*—The n.m.r. spectra of 5-aryltetrazoles generally show a large separation in the chemical shifts of the *ortho*- and *meta*-aryl protons when there is a strong interannular conjugation [9,10] (Table 2). Thus 2-methyl-5-(4′-substituted-phenyl)tetrazoles exhibit a shift difference δ(H_o − H_m) of 0.6—0.76 p.p.m. [Table 2, compounds (18) and (22), column headed Δ δ_H]. This effect is also observed in the ^{13}C n.m.r. spectra where conjugation results in an upfield shift in C-2′ of ⩾2.0 p.p.m.[4,11] [Table 2, compounds (18) and (22), column headed ΔC-2′]. A comparison of these parameters for the parent 5-(4′-substituted-phenyl)-tetrazoles [Table 2, compounds (2) and (6)] suggests

* The results of the n.m.r. spectra for interannular conjugation in 5-phenyltetrazoles are, as expected, in agreement with the u.v. spectra of these compounds. However, as we have pointed out previously,[1] the n.m.r. spectra are superior for studying the conjugation phenomenon because of the relatively small differences observed in the u.v. spectra: for example, the u.v. spectrum [1] of 2-methyl-5-phenyltetrazole (17), which has interannular conjugation, shows $\lambda_{max.}$ 240 nm, while that of the 1-methyl isomer (9), in which the conjugation is much reduced, shows a maximum absorption at shorter wavelengths as expected, $\lambda_{max.}$ 232 nm, but the difference is relatively small and the u.v. spectra are not as informative [4] as the proton spectra.

that this interannular conjugation is also present in these parent tetrazoles but it is strongly reduced or absent in the 1-methyl derivatives [Table 2, compounds (10) and (14), column headed $\Delta\ \delta_H$] where $\Delta\ \delta_H$ is reduced to 0.2—0.3 p.p.m. (this remaining difference being due to inductive and anisotropic effects).[10] The interannular conjugation is also reduced or absent in 5-(2′-substituted-phenyl)tetrazoles [compounds (3) and (7), Table 2] where $\Delta\ \delta_H$ is again 0.2—0.3 p.p.m. Interestingly, the interannular conjugation appears to be retained to a significant extent in 2-methyl-5-(2′-substituted-phenyl)-tetrazoles [compounds (19) and (23), Table 2], where $\Delta\ \delta_H$ is 0.44—0.58 and ΔC-2′ is 1.8 p.p.m. Introduction of two *ortho*-substituents in the 5-phenyl ring results in complete loss of interannular conjugation in all the tetrazole derivatives, *e.g.*, compounds (8), (16), and (24) (Table 2). In these compounds the rings are undoubtedly lying orthogonally. Hence, the 1-*N*-methyl substituent of compound (16) should be encroaching on the π-system of the benzene ring and should exhibit exceptional shielding, as is indeed the case, since a shielding of ⩾4.0 p.p.m. is very rare for a tetrazole *N*-methyl group.[1] It is interesting that the same high shielding of the 1-*N*-methyl group is also present in the 5-aryltetrazoles, which contain only one *ortho*-substituent [compounds (11) and (15), Table 2]. It seems likely that the presence of an *ortho*-substituent in the 5-aryl ring causes the tetrazole ring to rotate significantly out of the plane of the aryl ring, and it is in these circumstances that the 1-NH tautomer may be preferred. This rotation of the ring planes is further confirmed by the progressive increase in the shielding of the 2′-methyl protons for the series (19), (3), and (11) (Table 3, notes *j*, *h*, *i*). Due to the increased angle between the rings, these *ortho*-methyl protons show the expected shielding sequence for increasing penetration of the π-system of the tetrazole ring. Shielding shifts of similar magnitude have been observed with methyl groups of *N*-methylimine systems, Ph–CH=N–Me, in the *Z* configuration, where the methyl group also interacts with the aryl π-system.[12] The methylation reactions of the *ortho*-substituted aryl tetrazoles are also of significance in illustrating further effects of this conformational change.

Methylation of ortho-*Substituted-5-aryltetrazoles.*—Methylation of 5-aryltetrazoles occurs with a strong preference for the 2-N-position.[9,13–15] However, the introduction of an *ortho*-substituent in the 5-aryl group surprisingly orients the methylation back towards the 1-N-position. This is the reverse of what might be expected, since an *ortho*-substituent should sterically direct the incoming methyl group more so towards the 2-N-position. However, if the rings lie orthogonal to each other, molecular models show that there is then no serious steric interaction between aryl *ortho*-substituents and the 1-N-position. These methylation trends are best illustrated by the reactions of the chloro-derivatives (6), (7), and (8) (Table 3). The successive introduction of *ortho*-chloro-substituents reverts the methylation orientation towards the 1-N-position and away from the 2-position, which is favoured for the *para*-chloro-derivative. A similar trend is observed with *ortho*-Me and *ortho*-NO_2 groups (Table 3). With the latter the yield of the 1-N-Me isomer is three times higher than for a *para*-NO_2 substituent but it is still low overall, since strong electron-withdrawing 5-substituents favour[1] 2-N-methylation. Since an incoming methyl group bonds to these *ortho*-substituted 5-aryltetrazoles to a significant extent at the 1-N-position, it is not surprising that the much smaller proton may reside preferentially at the 1-N-position in the tautomeric mixture of the parent tetrazoles.

TABLE 3

Methylation of some *ortho*-substituted 5-phenyltetrazoles

5-Aryltetrazole			1-*N*-Methyl derivative			2-*N*-Methyl derivative		
Compound	Ar	M.p. (°C)	Compound	M.p. (°C)	Yield (%)	Compound	M.p. (°C)	Yield (%)
(2)	4′-Me-C_6H_4	252	(10)	117—118	30	(18)	108—109	62.0
(3)	2′-Me-C_6H_4	155—156 [a]	(11)	oil	38.7	(19)	44—45 [f]	48.3
(4)	4′-$NO_2C_6H_4$		(12)		6.0 [d]	(20)		88.0 [d]
(5)	2′-$NO_2C_6H_4$		(13)		21.0 [e]	(21)		70.0 [e]
(6)	4′-Cl-C_6H_4	252—253 [b]	(14)	89—90 [c]	23.7	(22)	108—109 [c]	64.2
(7)	2′-Cl-C_6H_4	179—180 [b]	(15)	68—69 [b]	43.1	(23)	oil [f]	42.0
(8)	2′,6′-Cl_2-C_6H_3	215—217 [b]	(16)	74—75	45.05	(24)	79 [b]	30.0

[a] From aqueous methanol. [b] Recrystallised from acetic acid. [c] From aqueous ethanol. [d] Taken from ref. 9. [e] Taken from ref. 4. [f] Purified by column chromatography.

EXPERIMENTAL

Melting points were measured on an Electro-thermal apparatus. Carbon-13 shifts (±0.1 p.p.m.) were measured at ambient probe temperature on a JEOL FX-60 spectrometer, and hydrogen-1 shifts were similarly measured on a JEOL JNM-100 spectrometer using, in each case, 30 mg of sample in a mixture of $CDCl_3$ (0.66 ml) and $(CD_3)_2SO$ (0.33 ml). When small quantities of water or deuterium oxide were added to the samples, no differences were observed in the shifts.

The known tetrazole derivatives were prepared by literature[1] procedures. Structures were proved by microanalysis and the n.m.r. spectra. The 5-(*ortho*-substituted-aryl)tetrazoles (Table 3) were prepared as follows (typical example). A mixture of *o*-toluenecarbonitrile (10 ml), sodium azide (6.5 g), butanol (10 ml), and glacial acetic

acid (6 ml) was refluxed for 5 days. The mixture was then treated with water (40 ml) and 20% NaOH solution (10 ml), cooled, and acidified with concentrated HCl, whereupon 5-(*o*-tolyl)tetrazole (3), m.p. 155—156 °C (from acetic acid) (32% yield) separated. The following compounds (Table 3) were similarly prepared: (6), 95%; (7), 70%; (8), 69%.

Methylations of 5-Aryltetrazoles.—The following is a typical example. A mixture of 5-(*o*-tolyl)tetrazole (1 g), sodium hydroxide (251 mg), water (5.0 ml), ethanol (5.0 ml),

TABLE 4

Microanalytical data on substituted-5-phenyltetrazoles

Compound	Found (%)			Formula	Required (%)		
	C	H	N		C	H	N
(3)	60.4	5.1	34.7	$C_8H_8N_4$	60.0	5.0	35.0
(11)	61.7	5.8	31.8	$C_9H_{10}N_4$	62.0	5.8	32.15
(19)	62.4	6.0	32.5	$C_9H_{10}N_4$	62.0	5.8	32.15
(6)	46.7	2.75	30.95	$C_7H_5ClN_4$	46.65	2.75	31.1
(14)	49.8	3.45	29.2	$C_8H_7ClN_4$	49.35	3.6	28.8
(22)	49.2	3.6	29.05	$C_8H_7ClN_4$	49.35	3.6	28.8
(7)	46.9	2.7	30.85	$C_7H_5ClN_4$	46.65	2.75	31.1
(15)	49.3	3.7	28.8	$C_8H_7ClN_4$	49.35	3.6	28.8
(23)	49.8	3.7	28.3	$C_8H_7ClN_4$	49.35	3.6	28.8
(8)	39.45	1.9	26.1	$C_7H_4Cl_2N_4$	39.1	1.85	26.05
(16)	42.3	2.5	25.0	$C_8H_6Cl_2N_4$	41.95	2.6	24.5
(24)	42.1	2.7	24.9	$C_8H_6Cl_2N_4$	41.95	2.6	24.5

and methyl iodide (0.5 ml) was refluxed for 12 h and then cooled and treated with water (10 ml), sodium hydroxide (10%) (5 ml), and diethyl ether (50 ml). The ethereal layer was separated and evaporated to yield an oily mixture of *N*-methyl isomers (87% yield). The isomers were separated *via* a 40-cm column of alumina in light petroleum with eluting solvents (A) light petroleum (b.p. 40—60 °C), (B) benzene–light petroleum (b.p. 40—60 °C) (1 : 1 v/v), (C) benzene, (D) diethyl ether. The 2-*N*-methyl isomer separated first in solvents (A) and (B) followed by the 1-*N*-methyl isomer in solvents (C) and (D) (*cf.* Table 3). The other methylations and isomer separations were carried out similarly, one minor difference being observed with 5-(*o*-chlorophenyl)tetrazole where the 1-*N*-methyl isomer separated from the column first in solvents (A) and (B).

Microanalytical data on all new compounds are provided in Table 4.

All carbon-13 spectral assignments were confirmed by off-resonance proton decoupling which showed the proton splitting pattern for each signal. The C-2′ signals were further identified by selective decoupling at the H_o proton frequency, thereby giving the C-2′ carbon signals as a sharp singlet among the remaining much weaker multiplets.

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