Isomerism of 1- and 2-(*NN*-Disubstituted aminomethyl)benzotriazoles; an Investigation by Nuclear Magnetic Resonance Spectroscopy

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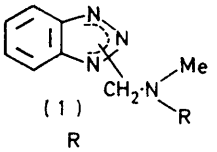
N.m.r. spectroscopy of a selection of (aminomethyl)benzotriazoles prepared by a standard Mannich reaction reveals the ready isomerism between 1- and 2-(aminomethyl)benzotriazoles. The proportions of the two isomers are sensitive to changes in solvent polarity but independent of temperature. In almost all the equilibria the 1-(aminomethyl)benzotriazole is the predominant isomer.

DURING investigations of the oxidation of amines [1] we wished to synthesise 1- and 2-(*NN*-disubstituted aminomethyl)benzotriazoles, suspected intermediates in the reaction of tertiary amines with 1-chlorobenzotriazole. The synthetic work revealed the ready isomerisation of these benzotriazole derivatives.

Benzotriazole is acylated, alkylated, and aminoalkylated predominantly at the 1-position although there are a few reports of 2-alkylation.[2,3] The 1- and 2-substituted benzotriazoles can be distinguished by u.v.,[3,4] i.r.,[4,5] and n.m.r.[6,7] spectroscopy.

The (aminomethyl)benzotriazoles were prepared by standard Mannich reactions. For those derived from diphenylamine (3b) and dicyclohexylamine (3c), satisfactory analytical data could not be obtained.

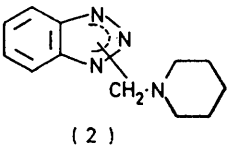
Each of the resonances attributable to the exocyclic protons (NCH_2N, NCH_2Ph, and CH_3) in the 60 MHz n.m.r. spectra of solutions of the Mannich base (1a) appears as two singlets of unequal intensity with the lower field absorption in each pair being the less intense. The ratio of the intensity of the larger peak to that of the smaller is constant for the three pairs of singlets in any one spectrum and the ratios of intensity of the



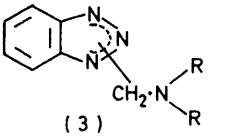
(1)

R

a; $PhCH_2$
b; $p-ClC_6H_4\cdot CH_2$
c; $p-O_2N\cdot C_6H_4\cdot CH_2$
d; Me
e; *cyclo*-C_6H_{11}
f; Ph



(2)



(3)

R

a; $PhCH_2$
b; Ph
c; *cyclo*-C_6H_{11}

aromatic resonances with respect to the combined intensities of each pair of singlets are 9 : 2 : 2 : 3 (aromatic : NCH_2N : NCH_2Ph : CH_3). Although changing the solvent alters the relative intensities and chemical shifts of the singlets, changes in temperature (−30 to +40 °C in [^{2}H]chloroform) have little or no effect. These results are consistent with isomerisation of 1- and 2-(*N*-methylbenzylaminomethyl)benzotriazole in solution, with the proportions of the two isomers being controlled by the solvent.

The investigation was extended to include 1-(chloro- and 1-(hydroxy-methyl)benzotriazole and a selection of Mannich bases related to that derived from *N*-methylbenzylamine. The 60 MHz n.m.r. data reveal that the (chloro- and hydroxy-methyl)benzotriazoles are pure 1-substituted benzotriazoles, whereas almost all the solutions of the Mannich bases contain mixtures of two isomers (Table 1). The *N*-methylaniline (1f) and diphenylamine (3b) derivatives in [$^2H_6$]benzene unexpectedly give only one set of exocyclic proton resonances and with several of the other Mannich bases in [$^2H_6$]acetone the resonances of the minor component either appear as shoulders or are merged with those of the major isomer. By use of mixed solvents it was shown for the benzotriazole (1a) that the same isomer is the minor component in [$^2H_6$]acetone and in [$^2H_6$]-benzene. Further with each of the Mannich bases, increasing the polarity of the solvent increases the proportion of the major isomer.

It has been reported that the relative intensities of the aromatic multiplets in the n.m.r. spectra of 1- and 2-methylbenzotriazoles in [^{2}H]chloroform are 1 : 3 and 1 : 1, respectively.[7] In a mixture of the two isomers the aromatic resonances overlap to produce two multiplets, the relative intensity of which will depend on the proportion of each isomer in the mixture. The relative intensities of the aromatic proton resonances in the 60 MHz spectra of selected Mannich bases in [^{2}H]-chloroform, carbon tetrachloride, or carbon disulphide agree with the values calculated from analyses of isomer mixtures based on the exocyclic proton singlets, assuming that the major component is the 1-isomer.

The 220 MHz n.m.r. spectrum of the dimethylamine derivative (1d) in [^{2}H]chloroform confirms the presence of the two isomers. The aromatic region of the spectrum consists of four major multiplets with a splitting pattern expected for the 1-substituted benzotriazole, and a minor multiplet which is the lower field resonance of the 2-isomer. In [$^2H_6$]acetone the aromatic resonances of

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the 2-substituted benzotriazole are almost totally obscured by those of the 1-isomer (Table 2).

In the spectrum of compound (1d) in carbon disulphide, in common with that in [^{2}H]chloroform only the lower field aromatic multiplet of the 2-isomer is visible, the higher field one being obscured by the highest field aromatic absorption of the 1-substituted benzotriazole. Scale expansion of the spectrum reveals that the aromatic absorption attributed to the 2-isomer has the AA'BB' symmetrical splitting pattern expected of a 2-substituted benzotriazole. Equilibration in carbon disulphide is relatively slow and spectra recorded soon after dissolution show that the solution initially contains almost exclusively the 1-isomer.

The 220 MHz n.m.r. spectrum of the methiodide of the dimethylamino-derivative (1d) in [$^2H_6$]dimethyl sulphoxide shows that this salt exists entirely as the 1-substituted benzotriazole.

The intensities of the aromatic resonances of 1-(chloromethyl)benzotriazole in [^{2}H]chloroform are in the ratio 1 : 3; however, in [$^2H_6$]acetone this ratio is 1 : 1. Likewise for 1-(hydroxymethyl)benzotriazole in [$^2H_6$]acetone this ratio is also 1 : 1. The splitting patterns of the multiplets in [$^2H_6$]acetone do not resemble the symmetrical AA'BB' spectrum typical of a 2-substituted benzotriazole. Thus a 1 : 1 distribution of the intensities of the aromatic proton absorptions is not always diagnostic of a 2-substituted benzotriazole. In agreement with this, the spectra of the *N*-methylbenzylamine derivative (1a) in [$^2H_6$]benzene–[$^2H_6$]acetone mixtures show that one of the high field multiplets of the 1-isomer moves downfield as the acetone content increases. For 1-methylbenzotriazole in [^{2}H]chloroform the C-4 proton absorbs at the lowest field [7] and it seems likely that the multiplet that shifts downfield in [$^2H_6$]acetone arises from the C-7 proton, for any specific solvation of the substituent on the benzotriazole nucleus would be more likely to affect the environment of the C-7 proton than of those on positions 5 and 6.

The influence of solvent on the chemical shifts and

TABLE 1

60 MHz N.m.r. data of equilibrium mixtures of 1- and 2-(*NN*-disubstituted aminomethyl)benzotriazoles at 40 °C

		Chemical shifts of exocyclic protons (δ)						
		1-Isomer *			2-Isomer *			% 2-Isomer at equilibrium
Compound	Solvent	(i)	(ii)	(iii)	(i)	(ii)	(iii)	
(1a)	$(CD_3)_2SO$	2·24	3·73	5·70	2·33	3·80	5·74	10
	$(CD_3)_2CO$	2·31	3·76	5·69	2·39	3·83	5·71	21
	$CDCl_3$	2·35	3·70	5·46	2·40	3·81	5·59	23
	C_6D_6	2·01	3·40	4·94	2·25	3·72	5·29	28
	CCl_4	2·35	3·66	5·39	2·39	3·78	5·52	45
	CS_2	2·30	3·62	5·36	2·35	3·74	5·47	43
(1b)	$CDCl_3$	2·32	3·64	5·40	2·36	3·74	5·51	20
	C_6D_6	1·93	3·21	4·85	2·15	3·50	5·18	27
(1c)	$CDCl_3$	2·42	3·85	5·53	2·46	3·94	5·60	23
	C_6D_6	1·88	3·23	4·85	2·12	3·48	5·17	33
(1d)	$(CD_3)_2CO$	2·23		5·48	2·37		5·50	
	$CDCl_3$	2·36		5·35	2·43		5·47	22
	C_6D_6	1·98		4·81	2·24		5·19	27
	CS_2	2·30		5·24	2·36		5·36	43
(1e)	$(CD_3)_2CO$	2·41		5·58				
	$CDCl_3$	2·39		5·46	2·58		5·69	20
	C_6D_6	2·08		5·00	2·48		5·40	34
	CS_2	2·32		5·33	2·49		5·46	47
(1f)	$(CD_3)_2CO$	3·03		6·29	3·29		6·33	17
	$CDCl_3$	2·98		6·09	3·28		6·13	25
	C_6D_6	2·42		5·41				
	CS_2	2·84		5·93	3·20			28
(2)	$CDCl_3$			5·40			5·51	18
	C_6D_6		2·17 † 2·29 2·37	4·89		2·49 † 2·58 2·66	5·26	23
	CS_2			5·24			5·36	34
(3a)	$CDCl_3$		3·77	5·40		3·82	5·52	21
	C_6D_6		3·55	5·03		3·75	5·30	31
(3b)	$CDCl_3$			6·43			6·47	16
	C_6D_6			5·95				
(3c)	$(CD_3)_2CO$						5·71	
	$CDCl_3$						5·63	
	CCl_4						5·50	

* Proton assignments: (i) N·CH_3; (ii) N·CH_2Ph; (iii) benzotriazole–CH_2·N. † Piperidine α-protons.

TABLE 2

220 MHz N.m.r. data of equilibrium mixtures of 1- and 2-(dimethylaminomethyl)benzotriazoles (1d)

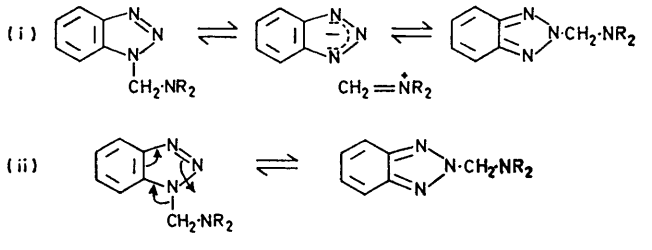
	Aromatic proton resonances (δ)					
	1-Isomer				2-Isomer	
Solvent						
$CDCl_3$	7·37	7·49	7·63	8·07	7·39	7·91
$(CD_3)_2CO$	7·39	7·54	7·9	8·02	7·43	7·92
CS_2	7·23	7·35	7·50	7·88	7·24	7·72

on the position of the equilibria between 1- and 2-(dialkylaminomethyl)benzotriazoles could be related to the differences in polarity of the two isomers. Dipole moment measurements indicate that 1-substituted triazoles are more polar than their 2-substituted isomers.[8] This might explain why the former isomer is favoured by the more polar solvents and its proton resonances show the greater solvent dependence.

The greater proportion of 2- over 1-substitution in the reactions of 4,5,6,7-tetrachlorobenzotriazole by comparison with benzotriazole has been attributed to a *peri*-interaction.[9,10] In this context the effect of increasing the bulk of the aminomethyl group on the equilibrium composition was investigated briefly; however, the results are inconclusive. Thus, for (*NN*-dimethyl-, (*N*-cyclohexyl-*N*-methyl-, and (*NN*-dicyclohexyl-aminomethyl)benzotriazoles in [^{2}H]chloroform the proportions of the 2-isomer are 22, 20, and >90%, respectively, suggesting that increased bulk favours the 2-isomer. However, the proportion of the 2-isomer is the same for [^{2}H]chloroform solutions of (*NN*-dimethyl-, (*N*-methyl-*N*-benzyl-, and (*NN*-dibenzyl-aminomethyl)-benzotriazoles.

1-Substituted benzotriazoles have u.v. absorptions around 255 and 283 nm (some compounds have two peaks in the former region), with relative absorbances ($\varepsilon_{255}/\varepsilon_{283}$) between 1·44 and 1·58. The 2-substituted compounds absorb at *ca.* 275 nm.[3,4] The u.v. spectra of the Mannich bases in methanol and chloroform have $\lambda_{max.}$ values which are indistinguishable from those of a 1-substituted benzotriazole. The absorption of the 2-isomer enhances the longer wavelength absorption of the 1-isomer causing the observed change in the relative absorbances. This effect is more pronounced in the less polar solvent chloroform which contains the greater proportion of the 2-substituted benzotriazole.

The results provide little information on the mechanism of the isomerisation; however, it seems more likely that the process is a dissociation–recombination [reaction (i)] than a concerted reaction (ii). The former mechanism



resembles that of the Mannich reaction and (aminomethyl)benzotriazoles have been shown to dissociate to iminium ions in trifluoroacetic acid.[11] The comparatively slow equilibration in carbon disulphide, a non-polar solvent, may be an indication that the process involves ionisation; however, more information on the influence of solvents on the rate of equilibration is needed.

EXPERIMENTAL

^{1}H N.m.r. spectra were measured on Perkin-Elmer R1 60 MHz and Varian A60A and 220 MHz spectrometers. Tetramethylsilane was used as an internal standard. U.v. spectra were recorded on a Pye Unicam SP 800 and i.r. spectra on a Pye Unicam SP 200 spectrophotometer.

1- *and* 2-(NN-*Disubstituted Aminomethyl*)*benzotriazoles*.—These were prepared by the general procedure of Bachmann and Heisey[12] from the secondary amine, formaldehyde, and benzotriazole. Any product that did not separate as a solid was precipitated with water. (N-*Methylbenzylaminomethyl*)*benzotriazole* (1a) (75%) had m.p. 61—61·5° (from aqueous methanol) (Found: C, 71·1; H, 6·4; N, 22·3. $C_{15}H_{16}N_4$ requires C, 71·4; H, 6·4; N, 22·2%), $\lambda_{max.}$ (MeOH) 253, 257, and 276 (rel. log ε 1·23, 1·23, and 1·00); ($CHCl_3$) 257 and 281 nm (1·12 and 1·00). (N-*Methyl*-p-*chlorobenzylaminomethyl*)*benzotriazole* (1b) (70%) had m.p. 45—53° [from petroleum (b.p. 40—60°)] (Found: C, 62·8; H, 5·3; N, 19·9. $C_{15}H_{15}ClN_4$ requires C, 62·8; H, 5·3; N, 19·5%). (N-*Methyl*-p-*nitrobenzylaminomethyl*)-*benzotriazole* (1c) (55%) had m.p. 141—142° (from methanol) (Found: C, 60·3; H, 5·2; N, 23·9. $C_{15}H_{15}N_5O_2$ requires C, 60·6; H, 5·1; N, 23·6%). (Dimethylaminomethyl)-benzotriazole (1d) (60%) had m.p. 98—100° (from diethyl ether) (lit.,[13] 99—100·5°), $\lambda_{max.}$ (MeOH) 254, 258, and 275 (rel. log ε 1·20, 1·20, and 1·00); ($CHCl_3$) 260 and 282 nm (1·07 and 1·00). (N-*Methylcyclohexylaminomethyl*)*benzotriazole* (1e) (72%) had m.p. 57—58° [from petroleum (b.p. 40—60°)] (Found: C, 68·6; H, 8·25; N, 22·8. $C_{14}H_{20}N_4$ requires C, 68·8; H, 8·25; N, 22·9%). (N-*Methylanilinomethyl*)*benzotriazole* (1f) (43%) had m.p. 76—78° (from diethyl ether) (Found: C, 70·8; H, 6·0; N, 23·8. $C_{14}H_{14}N_4$ requires C, 70·6; H, 5·9; N, 23·5%). (Piperidinomethyl)-benzotriazole (2) (70%) had m.p. 89·5—90·5° (from diethyl ether) (lit.,[12] 92·5—93·5°) (Found: C, 66·8; H, 7·55; N, 26·0. Calc. for $C_{12}H_{16}N_4$: C, 66·6; H, 7·5; N, 25·9%), $\lambda_{max.}$ (MeOH) 254, 259, and 275 (rel. log ε 1·15, 1·15, and 1·00); ($CHCl_3$) 260 and 282 nm (1·07 and 1·00). (*Dibenzylaminomethyl*)*benzotriazole* (3a) (64%) had m.p. 121—122° (from methanol) (Found: C, 76·5; H, 6·25; N, 17·3. $C_{21}H_{20}N_4$ requires C, 76·8; H, 6·1; N, 17·1%). (Diphenylaminomethyl)benzotriazole (3b) (61%) had m.p. 113—115° (from diethyl ether). Satisfactory analytical data were not obtained. (Dicyclohexylaminomethyl)benzotriazole (3c) (58%) was not obtained sufficiently pure for full characterisation. This compound decomposes with loss of dicyclohexylamine. (*Dimethylaminomethyl*)*benzotriazole methiodide* was prepared from (1c) with methyl iodide in methanol and had m.p. 187° (decomp.); δ (D_2O) 8·3—7·5 (4H, m), 6·3 (2H, s), and 3·3 (9H, s) (Found: C, 37·8; H, 4·6; N, 17·8. $C_{10}H_{15}IN_4$ requires C, 37·7; H, 4·75; N, 17·6%). 1-(Hydroxymethyl)benzotriazole was prepared[13] from

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benzotriazole and formaldehyde. The most pure sample had m.p. 130—142° (from water) (lit.,[13] 148—151°). This compound reverts to benzotriazole and formaldehyde on heating above 100 °C. 1-(Chloromethyl)benzotriazole was prepared [13] from 1-(hydroxymethyl)benzotriazole and had m.p. 135—138° (from methanol) (lit.,[13] 136—138°), $\lambda_{max.}$ (MeOH) 254, 259sh, and 285 (rel. log ε 1·58, 1·43, and 1·00); ($CHCl_3$) 254, 260sh, and 287 nm (1·57, 1·37, and 1·00).

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