# The Chemistry of Benzotriazole. Part 3.[1] The Aminoalkylation of Benzotriazole

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1-(1-Hydroxyalkyl)benzotriazoles convert a wide variety of aromatic and heteroaromatic primary amines into their mono *N*-[1-(benzotriazol-1-yl)alkyl] derivatives in high yield. Aliphatic primary amines frequently give bis-derivatives. Product structure is established by $^{13}C$ n.m.r.; dangers in the use of $^{1}H$ n.m.r. to distinguish 1- and 2-substituted benzotriazoles are pointed out.

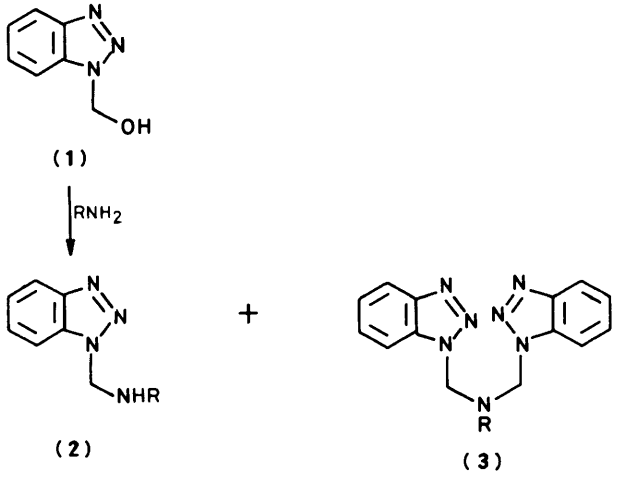
Aminomethylation (or Mannich reaction) of benzotriazole with formaldehyde and dialkylamines[2–9] or arylamines[10–12] is a well known process. Urea, thiourea and substituted thioureas gave Mannich bases with benzotriazole in the presence of cuprous chloride.[13] 5-Chlorobenzotriazole,[6,8] 5-methylbenzotriazole[14] and 5-nitrobenzotriazole[8,15] were also aminomethylated by formaldehyde and amines. The reaction of *N*,*N*-dimethylbenzylamine with 1-chlorobenzotriazole[16] also gave a product of this type: 1-[benzyl(methyl)aminomethyl]-benzotriazole.

Aminomethylbenzotriazoles possess interesting biological activity,[4,6,8,9,11,12] act as corrosion inhibitors,[3,17,18] are additives for insulating and lubricating oils[7,19–21] and adhesion improving agents for photopolymerizable paints.[22]

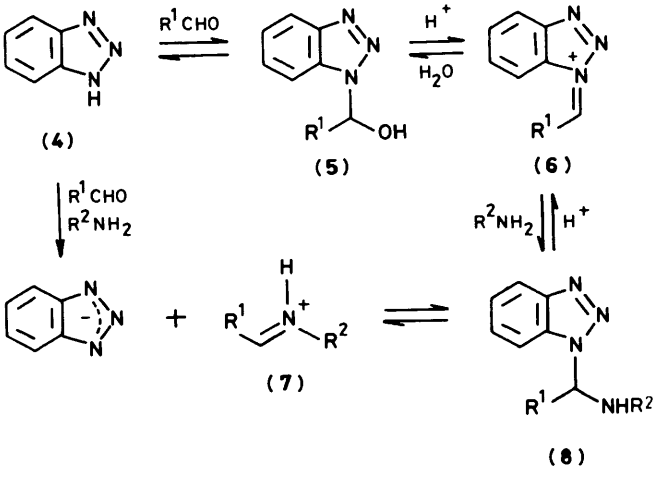
We now report that 1-hydroxymethylbenzotriazole (**1**) when used as starting material instead of benzotriazole and formaldehyde in reactions with amines produces the corresponding aminomethylbenzotriazoles (**2**) (Scheme 1) in almost quantitative yields. This technique has apparently only been reported once before.[10] Special attention has been paid to the preparation of derivatives of electron-deficient heterocyclic amines, a type not previously investigated and with potential biological activity (Table 1). Thus, 1-(2-pyridylaminomethyl)-benzotriazole, its derivatives with chloro, bromo, or methyl substituents on the pyridine ring, and *N*-benzotriazol-1-ylmethyl derivatives of 4-aminopyridine (**2m**), 2-aminothiazole (**2n**), and 2-amino-5,7-dimethyl-1,8-naphthyridine (**2g**) were obtained just as readily as the analogous (**2a—e**) were prepared from ring substituted anilines. The use of amines as acidic as 2-aminopyrimidine [$pK_a$ = 23.5 in water[23,24] or 25.9 in dimethyl sulphoxide (DMSO)[25]], 2-aminopyrazine ($pK_a$ = 25.8 in DMSO[26]) or even 5-nitro-2-aminopyridine ($pK_a$ = 15.8 in water[23,24]) did not complicate the reaction. Difficulties encountered with adenine were connected with its low solubility in the solvents used rather than its high acidity[27] ($pK_a$ = 9.8). Amides can also be used successfully: benzamide and methylurea reacted with 1-hydroxymethylbenzotriazole to give (**2s**) and (**2t**), respectively.

Primary aliphatic amines react very readily with 1-hydroxymethylbenzotriazole but as shown by elemental analyses and n.m.r. spectra, two molecules of benzotriazole are generally incorporated to give products (**3**). A similar composition was found for the product from hydroxylamine. However, the reaction of 1-hydroxymethylbenzotriazole with aliphatic amines is not so clearcut as for that with aromatic amines. The product composition depends to some extent on the proportion of starting materials used. This is well illustrated by the reaction with benzylamine. Product (**2u**) was obtained from the reaction carried out under conditions analogous to those applied for aromatic amines but tertiary amine (**3j**) was isolated in good yield when the proportion of starting 1-hydroxymethylbenzotriazole to benzylamine was changed from 1:1 to 2:1. In most cases the major products obtained from aliphatic amines are the tertiary amines (**3**), but they were usually contaminated with the corresponding monobenzotriazol-1-ylmethylamines (**2**) (detected by n.m.r. and t.l.c., although not isolated) which made their crystallization difficult.

Aldehydes other than formaldehyde can also be used successfully as starting materials for the condensation with benzotriazole and aromatic amines (Scheme 2): the compounds (**8**), with $R^1$ = alkyl or aryl and $R^2$ = 2-pyridyl, 2-pyrimidyl or other aromatic system, were obtained in high yields by mild heating of equimolar mixtures of the appropriate aldehyde, benzotriazole and amine (Table 3). The purity of the crude




Scheme 1.




Scheme 2.

**Table 1.** 1-Arylaminomethylbenzotriazoles (**2**)

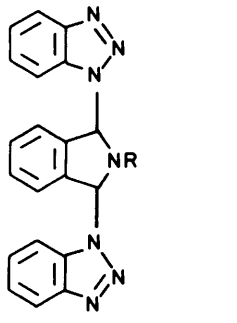
| Cpd. No. | R | Formula | Yield (%) | Recryst. Solvent | M.p. (°C) (lit. m.p.) | Found (Required) (%) C | H | N | $\nu_{max.}$[N–H] $cm^{-1}$ | δ[N–$CH_2$–N] p.p.m. (*J*/Hz) |
|---|---|---|---|---|---|---|---|---|---|---|
| (**2a**) | 4-Chlorophenyl | $C_{13}H_{11}ClN_4$ | 91 | EtOH | 165—167 (164[a]) | 60.6 (60.4) | 4.3 (4.3) | 21.7 (21.7) | 3 309 | 6.16 (d, *J* 7.2) |
| (**2b**) | 4-Nitrophenyl | $C_{13}H_{11}N_5O_2$ | 99 | MeOH–AcOH (1:1) | 210—213 (208—209[a]) | 58.0 (58.0) | 4.1 (4.1) | 26.2 (26.0) | 3 341 | 6.31 (d, *J* 7.2) |
| (**2c**) | 2-Benzoylphenyl | $C_{20}H_{16}N_4O$ | 96 | EtOH | 102—103 | 72.9 (73.2) | 5.1 (4.9) | 16.8 (17.1) | 3 392 | 6.31 (d, *J* 7.0) |
| (**2d**) | 2-Carboxyphenyl | $C_{14}H_{12}N_4O$ | 99 | EtOH–AcOH (1:1) | 189—191 (176[a]) | 62.4 (62.7) | 4.5 (4.5) | 20.6 (20.9) | 3 313 | 6.49 (d, *J* 7.3) |
| (**2e**) | 4-Carboxyphenyl | $C_{14}H_{12}N_4O_2$ | 98 | EtOH–AcOH (1:1) | 224—226 (203—205[a]) (204—205[b]) | 62.6 (62.7) | 4.7 (4.5) | 20.7 (20.9) | 3 335 | 6.31[c] (d, *J* 7.0) |
| (**2f**) | 2-Pyridyl | $C_{12}H_{11}N_5$ | 98 | Toluene | 137—138 | 64.0 (64.0) | 5.0 (4.9) | 31.3 (31.1) | 3 315 | 6.37 (d)[d] |
| (**2g**) | 4-Methyl-2-pyridyl | $C_{13}H_{13}N_5$ | 96 | EtOH | 157—158 | 65.4 (65.3) | 5.6 (5.5) | 29.6 (29.3) | 3 305 | 6.40 (d)[d] |
| (**2h**) | 6-Methyl-2-pyridyl | $C_{13}H_{13}N_5$ | 95 | EtOH | 138—139 | 65.2 (65.3) | 5.7 (5.5) | 29.5 (29.3) | 3 262 | 6.40 (d)[d] |
| (**2i**) | 4,6-Dimethyl-2-pyridyl | $C_{14}H_{15}N_5$ | 97 | MeOH–AcOH (1:1) | 154—156 | 66.3 (66.4) | 6.2 (6.0) | 27.6 (27.6) | 3 353 | 6.33 (d)[d] |
| (**2j**) | 5-Chloro-2-pyridyl | $C_{12}H_{10}ClN_5$ | 94 | MeOH | 171—172 | 55.3 (55.5) | 3.7 (3.9) | 27.0 (27.0) | 3 295 | 6.35 (d, *J* 7.0) |
| (**2k**) | 5-Bromo-2-pyridyl | $C_{12}H_{10}BrN_5$ | 99 | MeOH–AcOH (1:1) | 173—174 | 47.3 (47.4) | 3.2 (3.3) | 22.9 (23.0) | 3 270 | 6.36 (d, *J* 7.2) |
| (**2l**) | 5-Nitro-2-pyridyl | $C_{12}H_{10}N_6O_2$ | 94 | MeOH | 228—230 | 53.1 (53.3) | 3.7 (3.7) | 30.8 (31.1) | 3 245 | 6.53[c] (d, *J* 7.0) |
| (**2m**) | 4-Pyridyl | $C_{12}H_{11}N_5$ | 85 | Toluene | 200—201 | 63.8 (64.0) | 4.9 (4.9) | 31.3 (31.1) | 3 270 | 6.18[c] (d, *J* 7.1) |
| (**2n**) | 2-Thiazolyl | $C_{10}H_9N_5S$ | 95 | MeOH–AcOH (1:1) | 149—151 | 51.9 (51.9) | 3.9 (3.9) | 30.2 (30.3) | 3 297 | 6.32 (s) |
| (**2o**) | 2-Pyrimidyl | $C_{11}H_{10}N_6$ | 91 | MeOH | 147—148 | 58.7 (58.4) | 4.5 (4.5) | 37.4 (37.1) | 3 255 | 6.46 (d, *J* 7.1) |
| (**2p**) | Pyrazinyl | $C_{11}H_{10}N_6$ | 88 | MeOH–AcOH (1:1) | 150—152 | 58.3 (58.4) | 4.3 (4.5) | 37.4 (37.1) | 3 258 | 6.43 (d, *J* 7.0) |
| (**2q**) | 5,7-Dimethyl-1,8-naphthyridin-2-yl | $C_{17}H_{16}N_6$ | 86 | PhMe–AcOH (1:1) | 255—157 | 67.0 (67.1) | 5.3 (5.3) | 27.5 (27.6) | 3 193 | 6.70[c] (d, *J* 6.9) |
| (**2r**) | 6-Purinyl | $C_{12}H_{10}N_8$ | 95 | $H_2O$–AcOH (4:1) | 245—250 (decomp.) | 53.7 (54.1) | 3.7 (3.8) | 42.8 (42.1) | 3 200 | 6.9[e] (6 s) |
| (**2s**) | Benzoyl | $C_{14}H_{12}N_4O$ | 77 | MeOH | 175—176 | 66.5 (66.7) | 4.7 (4.8) | 22.2 (22.2) | 3 321 | 6.40 (d, *J* 7.0) |
| (**2t**) | Methylcarbamoyl | $C_9H_{11}N_5O$ | 75 | MeOH | 206—208 | 52.6 (52.7) | 5.5 (5.4) | 34.2 (34.1) | 3 280 | 6.21 (d, *J* 6.8) |
| (**2u**) | Benzyl | $C_{14}H_{14}N_4$ | 45 | Toluene | 136—138 | 70.8 (70.6) | 5.6 (5.9) | 23.2 (23.5) | 3 400 | 5.76 (d, *J* 6.7) |

[a] Ref. 10; [b] J. J. Licari, L. W. Harzel, G. Dougherty, and F. R. Benson, *J. Am. Chem. Soc.*, 1955, **77**, 5386. [c] Spectrum in [$^2H_6$]-DMSO; [d] Coupling pattern complex because of partial coupling with the aromatic protons; [e] Spectrum in $CF_3CO_2OH$. Other n.m.r. spectra in $CDCl_3$

products depends on the quality of the starting aldehydes used and reached 95% (according to n.m.r.) when the aldehydes were redistilled through a column before reaction, with collection of a narrow boiling point fraction. However, the attempted synthesis of tertiary amines [*cf* (**3**)] derived from aldehydes other than formaldehyde did not succeed. Complex mixtures were formed when benzotriazole was heated with aliphatic aldehydes and aliphatic amines.

Phthalaldehyde condensed with two molecules of benzotriazole and one molecule of amine affording *N*-substituted 1,3-di(benzotriazol-1-yl)-1,3-dihydroisoindoles (**9**). α-β-Unsaturated aldehydes undergo the same reaction with benzotriazole and aromatic amines at the carbonyl group as do other aldehydes but a second molecule of benzotriazole adds to the double bond. Thus, crotonaldehyde gives 2-[1,3-di(benzotriazol-1-yl)butylamino]pyridine (**10**). A similar addition of benzotriazole to the double bond of crotonaldehyde was observed earlier when the third reagent involved was an alcohol[1] instead of an amine. The carbonyl groups of ketones are generally not reactive enough to undergo condensation with benzotriazole and amines similarly to aldehydes. Cyclohexanone, however, heated at 120 °C with benzotriazole and aromatic amines gave the products (**11**) in fair yield.

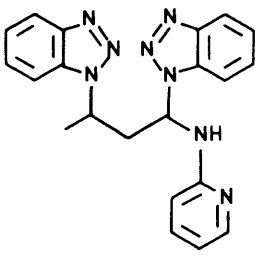
Possible routes leading to (**8**) are depicted in Scheme 2. The reaction of benzotriazole with an aliphatic aldehyde is very rapid and an equilibrium between (**5**) and (**4**) and strongly favouring (**5**) is rapidly established.[1] Because of the acidic reaction conditions (added acetic acid or benzotriazole itself serving as an acid), an equilibrium between (**5**) and (**6**) is also expected. The iminium form (**6**) can act as an electrophile in the reaction with amines to produce (**8**). Protonations to the amino group may cause reversible decomposition of product (**8**) to



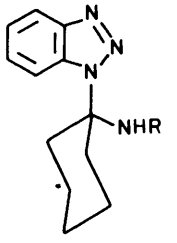
(9)

a; R = Ph

b; R = 2-pyridyl



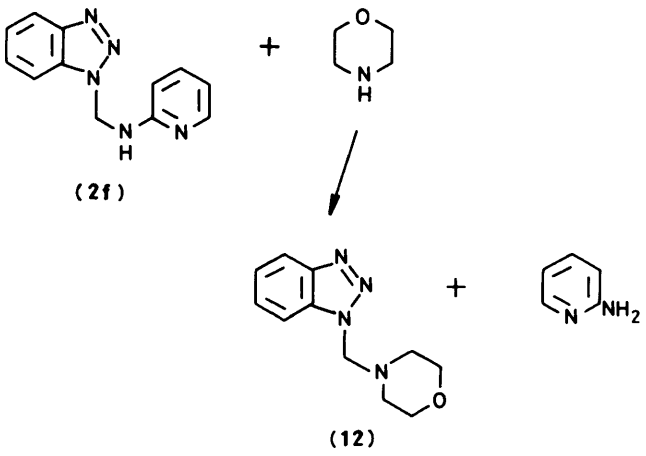
(10).



(11)

a; R = $C_6H_4Cl$-4

b; R = 2-pyridyl



(2f)

(12)

Scheme 3.

iminium ion (**6**), however, the 1-(aminoalkyl)benzotriazole (**8**) separates, because its solubility in the solvents used is lower than that of the starting materials.

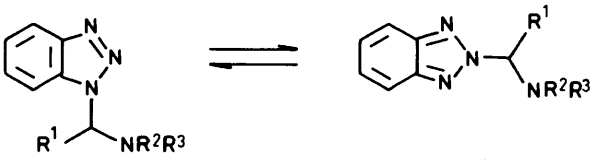
An alternative route *via* (**7**) seems less probable for three reasons. First, the reaction between isobutyraldehyde and 2-aminopyridine to give a Schiff base is slow: when 1M solutions in $CDCl_3$ were mixed, no evidence of reaction was observed by n.m.r. after 48 h. The aldehyde signal disappeared only very slowly (more than a half of the starting material remained after 48 h) when the reaction was repeated in the presence of phenol ($pK_a = 9.97$[28]) or acetic acid ($pK_a = 4.76$[29]) to get similar conditions of acidity as in the presence of benzotriazole ($pK_a = 8.2$[30]). On the other hand, when 1M solutions of isobutyraldehyde, 2-aminopyridine, and benzotriazole were mixed in proportions 1:1:1, the aldehyde signal disappeared completely after 6 h.

Second, benzotriazole is rather a poor nucleophile in comparison to an amine used in the reaction, so step (**6**) ⟶ (**8**) should be preferred over that (**7**) ⟶ (**8**). Third, evidence for reversibility of step (**6**) ⟶ (**8**) indicates a low barrier for this transformation. Thus, crystallization of 1-(2-pyridylaminomethyl)benzotriazole (**2f**) in the presence of morpholine afforded the new product (**12**) in which the 2-aminopyridine moiety was displaced (Scheme 3).

The last reaction suggests the possibility of the application of 1-hydroxymethylbenzotriazole or, more generally, 1-(α-hydroxyalkyl)benzotriazoles as blocking reagents for aromatic amino groups in synthesis.

The difference in the reactivity of aromatic and aliphatic amines may be due to their differing nucleophilicity. The considerable electron withdrawing ability of the benzotriazolylmethyl substituent decreases still further the nucleophilicity of electron poor aromatic amino groups. Product (**2**) derived from an aromatic amine is therefore unable to react with another molecule of 1-hydroxymethylbenzotriazole at a rate comparable to that of the starting amine. This strongly increases the concentration of (**2**) in the solution and results in its precipitation. Product (**2**) derived from an aliphatic amine still reacts fast enough to compete with the starting amine in the reaction with 1-hydroxymethylbenzotriazole to give the di(benzotriazolylmethyl) derivative (**3**). Product (**3**) is usually the least soluble in the protic solvent used. The above reasoning requires that the reactions leading to (**2**) and (**3**) are reversible. As an additional argument for this reversibility, products (**3**) were also obtained from reactions carried out with large excesses of aliphatic amines. Steric hindrance is of minor importance: thus cyclohexylamine gives product (**3**) just as does methylamine.

A further important structural point needs explanation. Starting from benzotriazol-1-ylmethanol one could expect that the product after reaction with an amine should be the corresponding benzotriazol-1-ylmethylamine as shown in Scheme 1, and in the preceding discussion this has been implicitly assumed. However, it is known from the literature[5] that benzotriazol-1-ylmethylamines derived from dialkylamines exist in solution in an equilibrium between forms (**13**) and (**14**) (Scheme 4, $R^1 = H$, $R^2 = R^3 =$ alkyl), although form (**13**) dominates (Scheme 4).



(13) (14)

Scheme 4.

The simplest method for distinguishing 1-benzotriazole and 2-benzotriazole derivatives is based on $^1H$ n.m.r. spectroscopy. The more symmetrical molecules of (**14**) give simple AA'BB' splitting pattern in the $^1H$ spectra with signals from protons at C-4 and C-7 deshielded by electron pairs on N-1 and N-3, shifted to about 8 p.p.m. In a molecule of (**13**), only one proton at C-4 is deshielded in a similar manner. Therefore, the proportion of intensities of signals occurring at *ca.* 8 p.p.m. to those at *ca.* 7.5 p.p.m. may be used as a measure for the equilibration, although some exceptions from this rule have been found.[5]

We have applied this criterion to our new compounds. In the case of the tertiary amines (**3**), the much longer intensity for the higher field peak below 7.8 p.p.m. than the peaks at >8.1 p.p.m. indicates that the 1-benzotriazole compound dominates strongly. The eleven signals in the spectrum of *N,N*-dibenzotriazol-1-ylmethylaminocyclohexane (**3h**) confirmed its exclusive

**Table 2.** Dibenzotriazol-1-ylmethylamines (3)

| Compd. | R | Formula | Yield (%) | Recryst. solvent | M.p. (°C) | Found (%) (Required) C | H | N | δ (p.p.m.) ($CDCl_3$) ($N-CH_2-N$) | ($N-CHR^1_2$) |
|---|---|---|---|---|---|---|---|---|---|---|
| (3a) | H | $C_{14}H_{13}N_7$ | 65 | EtOH | 177—178 | 60.2 (60.2) | 4.7 (4.7) | 35.0 (35.1) | 5.69 (d) | — |
| (3b) | OH | $C_{14}H_{13}N_7O$ | 44 | Ether–THF | 173—174 | 57.0 (56.9) | 4.3 (4.4) | 33.5 (33.2) | 5.85 (s) | — |
| (3c) | Me | $C_{15}H_{15}N_7$ | 76 | Ether–pentane | 88—90 | 61.2 (61.4) | 5.3 (5.2) | 33.4 (33.4) | 5.74 (s) | 2.61 (s) |
| (3d) | Et | $C_{16}H_{17}N_7$ | 84 | EtOH | 82—84 | 62.2 (62.5) | 5.4 (5.6) | 32.3 (31.9) | 5.73 (s) | 2.98 (q) |
| (3e) | Pr | $C_{17}H_{19}N_7$ | 62 | THF | 106—108 | 63.3 (63.5) | 6.1 (6.0) | 30.4 (30.5) | 5.74 (s) | 2.87 (t) |
| (3f) | $Pr^i$ | $C_{17}H_{19}N_7$ | 80 | Ether–pentane | 78—79 | 63.3 (63.5) | 6.0 (6.0) | 30.7 (30.5) | 5.78 (s) | 3.48 (m) |
| (3g) | $CH_2CH_2Ph$ | $C_{22}H_{21}N_7$ | 87 | EtOH | 122—124 | 68.9 (68.9) | 5.6 (5.5) | 25.6 (25.6) | 5.71 (s) | 3.15 (t) |
| (3h) | Cyclohexyl | $C_{20}H_{23}N_7$ | 85 | Ether | 118—119 | 66.3 (66.5) | 6.5 (6.4) | 27.2 (27.1) | 5.85 (s) | 3.01 (m) |
| (3i) | $CH_2(CH_2)_6Me$ | $C_{22}H_{29}N_7$ | 89 | EtOH | 88—89 | 67.6 (67.5) | 7.7 (7.5) | 25.3 (25.0) | 5.73 (s) | — |
| (3j) | $CH_2Ph$ | $C_{21}H_{19}N_7$ | 98 | Toluene | 108—109 | 68.6 (68.3) | 5.2 (5.2) | 26.2 (26.5) | 5.75 (s) | 4.00 (s) |

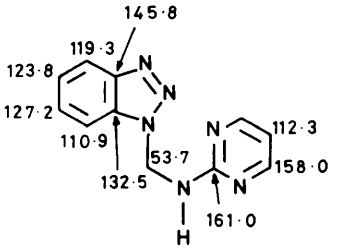
**Table 3.** 1-(Arylaminoalkyl)benzotriazoles (8)

| Compd. | $R^1$ | $R^2$ | Formula | Yield (%) | Recryst. Solvent | M.p. (°C) | Found (Required) (%) C | H | N | $\nu_{max.}$(N–H) $cm^{-1}$ | δ p.p.m. (J/Hz) $CDCl_3$ [α CH of $R^1$][a] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| (8a) | Pr | $C_6H_3Cl_2$-3,5 | $C_{16}H_{16}Cl_2N_4$ | 82 | EtOH | 113—114 | 57.1 (57.3) | 4.8 (4.8) | 16.6 (16.7) | 3 297 | 2.36 (q, *J* 7.3) |
| (8b) | Pr | $C_6H_4CO_2H$-4 | $C_{17}H_{18}N_4O_2$ | 90 | EtOH | 151—152 | 65.6 (65.8) | 6.0 (5.8) | 17.8 (18.1) | 3 304 | 2.34 (q, *J* 7.2)[b] |
| (8c) | Me | 2-Pyridyl | $C_{13}H_{13}N_5$ | 98 | EtOH | 126—128 | 65.2 (65.2) | 5.6 (5.5) | 29.3 (29.3) | 3 289 | 2.06 (d, *J* 6.4) |
| (8d) | Et | 2-Pyridyl | $C_{14}H_{15}N_5$ | 87 | EtOH | 118—120 | 66.4 (66.4) | 6.0 (6.0) | 27.5 (27.6) | 3 307 | 2.45 (q, *J* 7.3) |
| (8e) | Pr | 2-Pyridyl | $C_{15}H_{17}N_5$ | 82 | EtOH | 126—128 | 67.7 (67.4) | 6.6 (6.4) | 26.4 (26.2) | 3 305 | 2.43 (q, *J* 7.2) |
| (8f) | $Pr^i$ | 2-Pyridyl | $C_{15}H_{17}N_5$ | 98 | EtOH | 160—162 | 67.3 (67.4) | 6.6 (6.4) | 26.3 (26.2) | 3 309 | 2.80 (m) |
| (8g) | $Bu^t$ | 2-Pyridyl | $C_{16}H_{19}N_5$ | 85 | EtOH–DMSO (3:1) | 189—190 | 68.1 (68.3) | 7.0 (6.8) | 24.7 (24.9) | 3 326 | — |
| (8h) | $C_6H_4Cl$-4 | 2-Pyridyl | $C_{18}H_{14}ClN_5$ | 85 | MeOH | 132—134 | 64.5 (64.4) | 4.2 (4.2) | 20.7 (20.8) | 3 307 | — |
| (8i) | $Pr^i$ | 5-Bromo-2-pyridyl | $C_{15}H_{16}BrN_5$ | 83 | EtOH–AcOH (1:1) | 159—160 | 51.9 (52.0) | 4.7 (4.7) | 20.3 (20.2) | 3 294 | 2.73 (m) |
| (8j) | Me | 4-Pyridyl | $C_{13}H_{13}N_5$ | 85 | Toluene | 71—72 | 65.3 (65.2) | 5.7 (5.5) | 29.3 (29.3) | 3 261 | 2.01 (d, *J* 6.6) |
| (8k) | Pr | Pyrimidin-2-yl | $C_{14}H_{16}N_6$ | 86 | EtOH | 73—74 | 62.6 (62.6) | 6.0 (6.0) | 31.3 (31.3) | 3 238 | 2.47 (q, *J* 7.2) |
| (8l) | $C_6H_4Me$-4 | Pyrimidin-2-yl | $C_{18}H_{16}N_6$ | 76 | EtOH | 175—176 | 68.0 (68.3) | 5.0 (5.1) | 26.7 (26.6) | 3 243 | — |

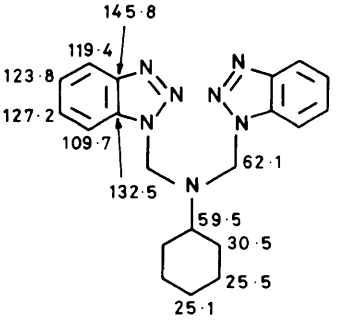
[a] Signals derived from N–CH–N overlap with those from aromatic protons; [b] Spectrum in $CDCl_3$–[$^2H_6$]-DMSO (3:1)

existence in form (**13**), as was expected from the $^1H$ n.m.r. spectrum of (**3h**).

However, for the secondary amines, the two multiplets in their n.m.r. spectra, one centred at 7.5 and the second at about 8.15 p.p.m., are of equal intensities, whether or not $R^1$ = proton or an alkyl substitutent [compounds (**2**) and (**8**), respectively]. Although the $^1H$ n.m.r. spectrum thus suggested that the secondary amines (**2**) and (**8**) existed mainly as form (**14**), $^{13}C$ n.m.r. did not confirm this. There are, 10 signals in the $^{13}C$ n.m.r. spectrum of 2-(benzotriazol-1-yl)methylaminopyrimidine (**2o**) in deuteriochloroform indicating that it is correctly formulated as (**13**). This conclusion is the opposite to that from the $^1H$ n.m.r spectrum: clearly the $^1H$ n.m.r. criterion is not trustworthy. The benzotriazole carbon atom chemical shifts are similar for (**2o**) and (**3h**) [see diagrams (**15**) and (**16**)] both cases supporting the conclusions drawn from $^{13}C$ n.m.r. and illustrating the limitations of $^1H$ n.m.r. as a tool for investigating the equilibrium between forms (**13**) and (**14**).




(15)




(16)

It is interesting that no equilibration between the appropriate forms (**13**) and (**14**) was observed. To explain these facts, we believe it is insufficient to consider only steric hindrance, as previously done,[4] the electronic influence donating and electron withdrawing substituents on the stabilization of 1- and 2-substituted benzotriazole moieties should be taken into account. Hydrogen bonding between molecules of products may also play an important part, and we plan to further investigate these matters.

## Experimental

For general experimental details, see Part 1 of this series.

*Reactions of 1-Hydroxymethylbenzotriazole with Aromatic Amines: General Procedure.*—1-Hydroxymethylbenzotriazole (1.49 g, 10 mmol) and the amine (10 mmol) were dissolved under reflux in ethanol (as little as possible), kept at room temperature for 5 h, and then at −5 °C for 12 h; most of the product (**2**) was precipitated. The solid was filtered off, washed with cold ethanol (5 ml) and dried *in vacuo* (60 °C/30 mmHg). When the hydroxymethylbenzotriazole and amines used were pure, the 1-arylaminomethylbenzotriazoles (**2**) frequently gave correct CHN analysis without further purification. Analytical samples, however, were usually recrystallized from solvents given in Table 1.

*Reactions of 1-Hydroxymethylbenzotriazole with Aromatic Amines: Special Procedure for Arylaminomethylbenzotriazoles* (**2b**), (**2e**), (**2l**), (**2r**), *and* (**2s**) *of Low Solubility in Ethanol.*—To a stirred boiling saturated solution of appropriate arylamine (10 mmol) in water/ethanol/acetic acid (1:1:1) was added a concentrated hot solution of 1-hydroxymethylbenzotriazole (10 mmol) in the same solvent. In the case of adenine (**2s**), water/acetic acid (4:1) was used as a solvent. The mixture was left at 25 °C for 3 h. The precipitate was washed with methanol and dried in a vacuum oven at 60 °C. Analytical samples were recrystallized from the solvents given in Table 1.

*Reaction of 1-Hydroxymethylbenzotriazole with Ammonia: Product* (**3a**).—2% Aqueous ammonia (21.2 ml, 25 mmol) was neutralized with acetic acid (phenolphthalein). 1-Hydroxymethylbenzotriazole (5.96 g, 40 mmol) in methanol was then added (50 ml) and the mixture was kept at 25 °C for 5 h and then at −5 °C for 16 h. The obtained precipitate was filtered off, washed with water, and recrystallized from ethanol to give analytically pure (**3a**) (Table 2).

*Reaction of 1-Hydroxymethylbenzotriazole with Hydroxylamine: Product* (**3b**).—Hydroxylamine hydrochloride (0.69 g, 10 mmol) in water (10 ml) was neutralized with 2% sodium hydrogen carbonate. 1-Hydroxymethylbenzotriazole (2.98 g, 20 mmol), dissolved in methanol (20 ml), was added. The mixture was kept at 25 °C for 5 h and at −5 °C overnight. The precipitate was washed with cold water (10 ml) and dried *in vacuo* (60 °C/30 mmHg) to give crude (**3b**). An analytical sample was obtained by dissolving the crude material in tetrahydrofuran (THF), dilution with the same amount of diethyl ether, and cooling to −5 °C for 16 h.

*Reactions of 1-Hydroxymethylbenzotriazole with Aliphatic Amines: General Procedure for the Preparation of* (**3c**—**j**).—1-Hydroxymethylbenzotriazole (2.98 g, 20 mmol), acetic acid (0.57 ml, 10 mmol) and ethanol (30 ml) and an aliphatic amine (12 mmol) were refluxed for 2 min and poured into ice–water. The mixture was extracted with chloroform (50 ml) and the extracts washed with water and dried ($MgSO_4$). Evaporation afforded the crude oily tertiary amine (**3**). It was dried *in vacuo* (60 °C/30 mmHg). The solid product was recrystallized from the appropriate solvent (Table 2).

*Reaction of Benzotriazole with Aldehydes and Aromatic Amines: General Procedure.*—Benzotriazole (1.19 g, 10 mmol), aldehyde (12 mmol), and amine (10 mmol) were refluxed in ethanol (minimum needed for complete solution) for 10 min. The mixture was kept at 25 °C for 5 h and −5 °C for 16 h. The resulting precipitate was filtered off, washed with diethyl ether and dried *in vacuo* to give the crude *N*-[1-(benzotriazol-1-yl)alkyl]arylamine (**8**). Analytical samples of (**8**) were prepared by recrystallization of the crude products from the solvents mentioned in Table 3.

*Preparation of the Derivatives of Acetaldehyde: General procedure for* (**8d**) *and* (**8j**).—A mixture of 1-hydroxymethylbenzotriazole (**5**; $R^1$ = Me) (1.63 g, 10 mmol) and 2- or 4-aminopyridine (0.94 g, 10 mmol) was heated gently until all solid melted. The mixture kept at room temperature solidified into a crude product. Analytical samples of (**8d**) and (**8j**) were obtained by recrystallization of the crude materials from the solvents given in Table 3.

*Reaction of Phthalaldehyde with Aniline: Product* (**9a**).—A mixture of phthalaldehyde (0.67 g, 5 mmol), benzotriazole (1.19 g, 10 mmol), and aniline (0.46 ml, 5 mmol) was heated at 120 °C under nitrogen for 15 min. The mixture was cooled to room temperature and triturated with diethyl ether. The precipitate was washed with ether and dried under vacuum to give crude 1,3-*di*(*benzotriazol*-1-*yl*)-2-*phenyl*-2,3-*dihydroisoindole* (**9a**) (1.67 g, 78%) which recrystallized from ethanol as prisms, m.p. 158—160 °C (Found: C, 72.4; H, 4.4; N, 22.7. $C_{26}H_{19}N_7$ requires C, 72.7; H, 4.5; N, 22.8%); δ($CDCl_3$/[$^2H_6$]-DMSO, 3:1) 7.20 (3 H, m), 7.45 (5 H, s), 7.52 (6 H, m), and 8.00 (5 H, m); $\nu_{max.}$ 1 610, 1 503, 1 442, 1 368, 1 313, 1 272, 1 236, 1 087, 927, 810, 737, and 688 $cm^{-1}$.

*Reaction of Phthalaldehyde with 2-Aminopyridine: Product* (**9b**).—Reaction of phthalaldehyde (0.67 g, 5 mmol), benzotriazole (1.19 g, 10 mmol), and 2-aminopyridine (0.47 g, 5 mmol), as described for aniline, gave crude 1,3-*di*(*benzotriazol*-1-*yl*)-2-(2-*pyridyl*)-2,3-*dihydroisoindole* (**9b**) (1.72 g, 80%) crystallized from DMSO as prisms, m.p. 217—218 °C (Found: C,

69.7; H, 4.2; N, 26.0. $C_{25}H_{18}N_8$ requires C, 69.7; H, 4.2; N, 26.0%); δ([$^2H_6$]-DMSO) 7.25 (4 H, m), 7.58 (7 H, m), 8.03 (4 H, m), and 8.34 (3 H, m); $\nu_{max.}$ 1 646, 1 588, 1 478, 1 440, 1 385, 1 322, 1 093, 778, 742, and 723 $cm^{-1}$.

*Synthesis of* 2-[1,3-*Di*(*benzotriazol*-1-*yl*)*butylamino*]*pyridine* (**10**).—Benzotriazole (2.97 g, 25 mmol) and crotonaldehyde (0.83 ml, 10 mmol) in ethanol (10 ml) were heated under reflux for 30 min. 2-Aminopyridine (0.94 g, 10 mmol) was added and the refluxing continued for an additional 15 min. The mixture was kept at 25 °C for 5 h and at −5 °C overnight. The precipitate recrystallized from ethanol to give the title compound (**10**) (3.22 g, 84%) as grains, m.p. 174—176 °C (Found: C, 65.8; H, 5.4; N, 29.3. $C_{21}H_{20}N_8$ requires C, 65.6; H, 5.2; N, 29.2%); δ($CDCl_3$/[$^2H_6$]-DMSO, 2:1) 1.62 (3 H, d, *J* 6.8 Hz), 3.37 (2 H, m), 4.82 (1 H, m), 6.60 (2 H, m), 7.43 (8 H, m), and 8.03 (4 H, m); $\nu_{max.}$ 3 328, 1 608, 1 392, 1 376, 1 160, 1 102, 1 097, 979, 781, 771, and 745 $cm^{-1}$.

*Reaction of Benzotriazole with Cyclohexanone and* 4-*Chloroaniline:* 1-(*Benzotriazol*-1-*yl*)-1-(4-*chlorophenylamino*)*cyclohexane* (**11a**).—Benzotriazole (1.19 g, 10 mmol), 4-chloroaniline (1.27 g, 10 mmol), and cyclohexanone (0.98 g, 10 mmol) were heated at 120 °C for 30 min under nitrogen. The cooled mixture was triturated with diethyl ether–pentane (1:1) and the precipitate washed with hexane, and recrystallized from ethanol to give 1-(*benzotriazol*-1-*yl*)-1-(4-*chlorophenylamino*)*cyclohexane* (**11a**) (2.65 g, 81%) as prisms, m.p. 85—87 °C (Found: C, 65.9; H, 5.9; N, 17.1. $C_{18}H_{19}ClN_4$ requires C, 66.1; H, 5.9; N, 17.1%); δ($CDCl_3$) 1.80 (6 H, m), 2.40 (4 H, m), 6.78 (2 H, d, *J* 9.0 Hz), 7.27 (2 H, d, *J* 9.0 Hz), 7.60 (2 H, m), 8.10 (2 H, m), and 8.27 (1 H, 6 s); $\nu_{max.}$ 3 335, 2 940, 2 860, 1 652, 1 595, 1 485, 1 447, 1 390, 1 312, 1 160, 1 095, 1 010, 838, 822, and 740 $cm^{-1}$.

*Reaction of Benzotriazole with Cyclohexane and* 2-*Aminopyridine:* 1-(*Benzotriazol*-1-*yl*)-1-(2-*pyridylamino*)*cyclohexane* (**11b**).—Benzotriazole (1.19 g, 10 mmol), 2-aminopyridine (0.94 g, 10 mmol), and cyclohexanone (0.98 g, 10 mmol) by the procedure given for (**11a**), gave 1-(*benzotriazol*-1-*yl*)-1-(2-*pyridylamino*)*cyclohexane* (**11b**) (2.64 g, 90%) as prisms, m.p. 122—123 °C (Found: C, 69.2; H, 6.5; N, 24.0. $C_{17}H_{19}N_5$ requires C, 69.6; H, 6.5; N, 23.9%); δ 1.77 (6 H, m), 2.38 (2 H, m), 2.77 (2 H, m), and 8.07 (3 H, m); $\nu_{max.}$ 3 295, 2 942, 2 925, 1 594, 1 523, 1 479, 1 416, 1 302, 1 172, 1 053, 774, and 738 $cm^{-1}$.

*Reaction of* 2-(*Benzotriazol*-1-*yl*)*methylamino*-4-*methylpyridine* (**2g**) *with Morpholine.*—Compound (**2g**) (1.20 g, 5 mmol) and morpholine (0.87 ml, 10 mmol) were heated at 100 °C for 30 min. The mixture was diluted with water (5 ml) and kept at 0 °C overnight to give analytically pure N-(*benzotriazol*-1-*yl*)*methylmorpholine* (**12**) (0.87 g, 80%), m.p. 103—105 °C (Found: C, 60.7; H, 6.6; N, 25.9%); δ 2.68 (4 H, t, *J* 5.58 Hz), 3.77 (4 H, t, *J* 5.4 Hz), 5.58 (2 H, s), 7.55 (1 H, 7.73 (2 H, m), and 8.23 (1 H, m).

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*Received* 10*th February* 1986; *Paper* 6/281