Preparation of *N*-Hydroxyazoles by Oxidation of Azoles

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Azoles without *N*-substituents are oxidized with per-acids or perborate to the corresponding *N*-hydroxy substituted azoles. 1,2,4-Triazole and tetrazole produce two isomers separated through their *O*-benzyl derivatives. Imidazole and 1,2,3- and 1,2,4-triazole can be di-oxygenated in low yields. *N*-Hydroxypyrazole is deoxygenated by per-acid.

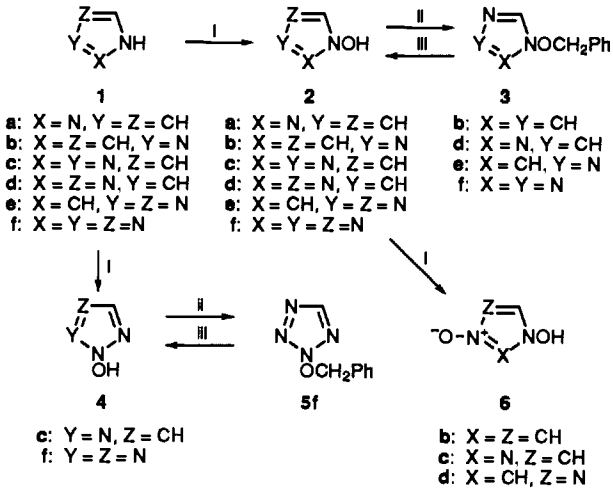
Few syntheses of unannulated *N*-hydroxy substituted 5-membered nitrogen heteroaromatics have been reported. 1-Hydroxypyrroles,[1] 1-hydroxypyrazoles,[2–6] 1-hydroxyimidazoles,[7] 1-hydroxy-1,2,3-triazoles,[8] 1-hydroxy-1,2,4-triazoles[9] and 4-hydroxy-1,2,4-triazoles[10] have been obtained by cyclization of oximes or dioximes followed by partial reduction. 1-Hydroxypyrazole[11] and 1-hydroxy-4-pivaloyl-1,2,3-triazole,[12] have been obtained by rearrangements whereas 5-substituted 1-hydroxytetrazoles were prepared by cyclization of azidoximes.[13–15] However, direct oxidation of N–H azoles to *N*-hydroxyazoles seems only reported in patents describing oxidation with peroxyphthalic acid of pyrazole **1a**,[16–18] imidazole **1b**[19] and 1,2,4-triazole **1d**[20] to give the corresponding 1-hydroxy derivatives **2a**, **2b** and **2d**. With respect to the other parent azoles, details on the preparation of 1-hydroxy-1,2,3-triazole **2c** have not been given,[21] 1-hydroxytetrazole **2f** was obtained by reaction of nitrolic acid with hydrazoic acid[22] whereas 2-hydroxytetrazole **4f** has not been described previously.

N-Hydroxyazoles are, however, of great interest as possible metabolites from the biological degradation of azoles, as intermediates in the synthesis of substituted azoles, and as auxiliaries in condensations catalysed by mixed anhydrides in the same way as *N*-hydroxybenzotriazole has been used in, for example, peptide and nucleoside synthesis.[23–25]

It was found that the *N*-hydroxyazoles **2a–f** and **4f** are formed by oxidation of the parent azoles **1a–f** (Scheme 1). Yields are modest or low, but unchanged starting material can usually be recovered. The separation of the azole from its *N*-hydroxy derivative, both polar compounds, were effected either by partition between organic and aqueous solutions at different pH, the *N*-hydroxyazoles being more acidic than their progenitors, or by separation of the *O*-benzyl derivatives followed by debenzylation of the benzyloxyazole.

Several oxidation procedures were attempted as shown in Table 1. 3-Chloroperbenzoic acid, hydrogen peroxide plus formic acid and sodium perborate plus pivalic acid were most effective. 3-Chloroperbenzoic acid gave highest yields for the oxidation of pyrazole **1a**, imidazole **1b**, 1,2,3-triazole **1c** and 1,2,4-triazole **1d** while the perborate reagent was superior for the oxidation of the tetrazole **1f**.

1,2,3-Triazole gave only one mono-oxidation product **2c**; the isomer **4c** was not observed. In contrast, 1,2,4-triazole **1d** produced a mixture of two isomeric *N*-hydroxy derivatives **2d**, **e** corresponding to the two N–H tautomers **1d** and **1e** of the parent azole. Similarly, the tetrazole **1f** gave a mixture of **2f** and **4f**. Although direct separation of the isomers **2f** and **4f** failed, the corresponding *O*-benzyl derivatives **3f** and **5f** could be separated. The *O*-benzyl derivatives were formed as the sole products (no *N*-benzylation was detected) when the sodium salts of the *N*-hydroxytetrazoles were benzylated with benzyl bromide in DMF. That the benzylation takes place at oxygen



Scheme 1 *Reagents and conditions:* i, see text; ii, NaH, $PhCH_2Br$, DMF, 20 °C, 24 h; iii, 47% aq. HBr

was revealed by the position of the ^{13}C NMR signals of the CH_2 group at *ca.* 83 ppm. Chromatographic separation of the isomeric benzyloxytetrazoles gave **3f** and **5f** which were differentiated by the position of the ^{13}C NMR signal from C-5 at 136.9 and 149.9 ppm. These positions are characteristic of 1- and 2-substituted tetrazoles, respectively.[26] Subsequent debenzylation through heating with aqueous hydrogen bromide gave the individual *N*-hydroxytetrazoles **2f** and **4f**. The isomeric benzyloxy-1,2,4-triazoles **3d**, **e** could be prepared and separated in the same way.

The oxidation of the imidazole **1b**, 1,2,3-triazole **1c** and 1,2,4-triazole **1d** gave rise to small amounts of the highly polar di-oxygenated products **6b**, **6c** and **6d**. Compound **6b** is well known and was not isolated because of the low yield.[7] Under optimized reaction conditions 1-hydroxy-1,2,3-triazole 3-oxide **6c** and 4-hydroxy-4*H*-1,2,4-triazole 1-oxide **6d** could be isolated in 7 and 5% yield, respectively.

The low yield of the oxidation products is attributed to deoxygenation of the *N*-hydroxyazoles effected by the oxidants used. Such an oxidative degradation was observed when pure 1-hydroxypyrazole **2a** was converted into the pyrazole **1a** to an extent of *ca.* 40% when treated with hydrogen peroxide in formic acid under the conditions for oxidation of **1a** to **2a**. Two possible mechanisms for the degradation are shown in Scheme 2.

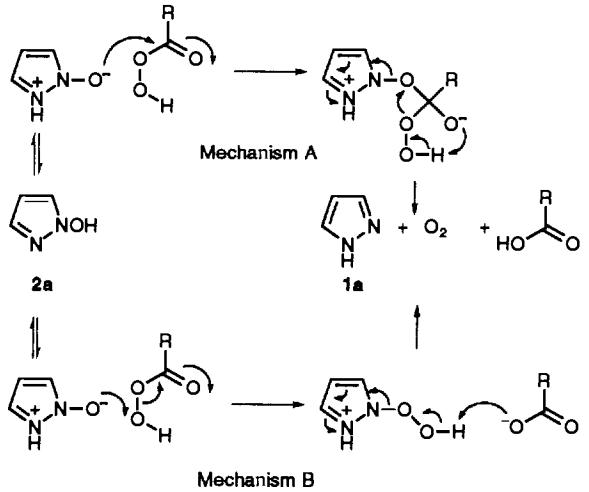
Therefore, in the oxidation processes the oxidant is consumed during competing oxidation and deoxygenation and the reaction invariably ends up with a mixture of starting material and product.

Similar competing processes limit the yield by the oxidation of 1-substituted pyrazoles to their *N*-oxides.[27] Competition of

Table 1 Oxidation of azoles with different oxidation agents[a]

Azole	Oxidation agent[b]	Solvent	Temp. (°C)	Reaction time (h)	Product(s)	Yield (%)	Unchanged starting material (%)
1a	60% H_2O_2[c]	HCO_2H	20	48	**2a**	15[d]	63[d]
1b			20	18		0[e]	100[e]
1c			20	64	**2c**	39[d]	47[d]
1d			20	18		0[e]	100[e]
1f			20	21		0[e]	100[e]
1a	3-Chloroperbenzoic acid (1.2 equiv.)	EtAc	20	168	**2a**	50[d]	36[d]
1b			20	24	**2b**	32[e]	66[e]
					6b	2[e]	
1c			20	168	**2c**	39[d]	47[d]
					6c	7[d]	
1d			20	120	**2d**	8[d]	78[e]
					3d	5[d]	
					6d	5[d]	
1f			20		**2f**	1[e]	98[e]
					4f	1[e]	
1a	$NaBO_3$ (2 equiv.)	*tert*-$BuCO_2H$	100	15		0[e]	100[e]
1b			100	3	**2b**	12[e]	88[e]
1c			100	15	**2c**	5[e]	94[e]
					6c	1[e]	
1d			100	6	**2d**	0[e]	100[e]
1f			100	3	**2f**	33[d]	40[d]
					4f	17[d]	

[a] Optimized procedures are described in detail in the Experimental section. [b] The following oxidation reagents were tried but gave substantially lower yields or no *N*-oxidation at all: 35% H_2O_2 in HCO_2H, 60% H_2O_2 in $MeCO_2H$, 60% H_2O_2 in CF_3CO_2H and urea·H_2O_2 in CF_3CO_2H. [c] Extended reaction times did not increase the yield. Addition of H_2O_2 in portions at intervals may give slightly higher yields. [d] Yield of isolated, pure compound. [e] Yield determined by ^1H NMR.



Scheme 2

this kind also explains why the yield of the *N*-hydroxyazoles was sensitive to the concentration of the reactants.

Because of the reciprocal nature of the oxidation, yields are fair to low despite many attempts of optimization. Nonetheless, the optimized procedures are quite efficient for preparation of the *N*-hydroxyazoles since unchanged starting material is recovered and can be recycled.

Experimental

General.—All solvents and reagents were obtained from Fluka or Aldrich and used without further purification unless otherwise stated. *N*,*N*-Dimethylformamide (DMF) was distilled from phosphorus pentoxide.[28] For the drying of solutions, magnesium sulfate was used unless otherwise stated. Solvents were removed under reduced pressure by rotary evaporation. Filtration through silica gel was performed using silica gel Merck 60 (70–230 mesh). All new compounds were colourless, unless otherwise stated. The purity of all compounds was confirmed from their melting points and by thin layer chromatography and NMR spectroscopy. ^1H NMR spectra (Table 2) were recorded at 200 MHz on a Bruker AC-200 instrument with tetramethylsilane as an internal standard. ^{13}C NMR spectra (Table 3) were obtained at 50.32 MHz with the solvent peak at [δ 76.90 ppm for $CDCl_3$, 47.07 ppm for CD_3OD, 28.05 ppm for $(CD_3)_2CO$ and 67.40 ppm for dioxane in D_2O] as an internal standard.

Warning: in large scale experiments using hydrogen peroxide and formic acid excess of peroxide should be reduced with sodium sulfite prior to extraction with diethyl ether.

Oxidation of Pyrazoles.—(a) A mixture of the pyrazole **1a** (1.00 g), formic acid (1.4 cm^3) and hydrogen peroxide (60%; 2.0 cm^3) was stirred at 0 °C for 1 h and then at 20 °C for 19 h. After this, further formic acid (0.7 cm^3) and hydrogen peroxide (1.0 cm^3) were added to the mixture and stirring continued for 9 h. The addition of further formic acid and hydrogen peroxide was repeated after which the mixture was stirred for 20 h. Phosphate buffer (1.9 mol dm^{-3}, pH 5.0; 10 cm^3) was then added to the reaction mixture followed by 33% aqueous sodium hydroxide to bring it to pH 10.5. Continuous extraction [dichloromethane–diethyl ether (1:1), 2 h] and removal of the organic solvents gave unchanged starting material **1a** (0.63 g, 63%). The aqueous solution was acidified to pH 3.5 with conc. hydrochloric acid and extracted with dichloromethane–diethyl ether (1:1) for 2.5 h. Removal of the solvents from the extract produced 1-hydroxypyrazole **2a** (0.18 g, 15%), m.p. 54–60 °C. Ball-tube distillation (100 °C, 0.5 mmHg) gave the product, m.p. 72 °C (lit.,[11] m.p. 75 °C).

Table 2 ^{1}H NMR data of *N*-hydroxyazoles and *N*-benzyloxyazoles

Compound	Solvent	δ/ppm (*J*/Hz)[a] 2-H	3-H	4-H	5-H	Ph	CH_2
2a	$CDCl_3$		7.19 (4-H, 2.62) (5-H, 1.05)	6.20 (3-H, 2.62) (5-H, 2.36)	7.38 (3-H, 1.05) (4-H, 2.36)		
2b·HBr	D_2O	8.78 (4-H, 1.6) (5-H, 1.6)		7.53[b] (2-H, 1.6) (5-H, 2.2)	7.35[b] (2-H, 1.6) (4-H, 2.2)		
3b	$CDCl_3$	7.37 (4-H, 1.3) (5-H, 1.3)		6.92[b] (2-H, 1.3) (5-H, 1.3)	6.88[b] (2-H, 1.3) (4-H, 1.3)	7.40–7.26	5.10
2c	$(CD_3)_2CO$			7.89[b] (5-H, 1.06)	7.82[b] (4-H, 1.06)		
6c	D_2O			7.63	7.63		
2d·HBr	D_2O		8.45[b]		9.23[b]		
3d	$CDCl_3$		7.76[b]		7.57[b]	7.38–7.23	5.28
2e·HBr	D_2O		9.29		9.29		
3e	$CDCl_3$		8.07		8.07	3 H, 7.41–7.37 2 H, 7.29–7.26	5.14
6d	CD_3OD		8.94[b] (5-H, 0.9)		8.31[b] (3-H, 0.9)		
2f	D_2O				9.06		
3f	$CDCl_3$				8.10	3 H, 7.45–7.35 2 H, 7.31–7.26	5.45
4f	D_2O				8.67		
5f	$CDCl_3$				8.35	7.40	5.57

[a] The proton to which coupling takes place is given. [b] The assignments may have to be interchanged.

Table 3 ^{13}C NMR data of *N*-hydroxyazoles and *N*-benzyloxyazoles

Compound	Solvent	δ_C/ppm C-2 (C-1')	C-3 (C-2')	C-4 (C-3')	C-5 (C-4') [CH_2]	*J*/Hz[a] C-2	C-3	C-4	C-5
2a	$CDCl_3$		131.5	103.2	122.6		189.2 4-H, 4.8 5-H, 8.7	179.7 3-H, 8.3 5-H, 8.3	193.2 3-H, 4.1 4-H, 8.7
2b·HBr	D_2O	131.0		120.6[b]	118.2[b]	225.2		206.7 5-H, 11.8 2-H, 4.3	205.1 4-H, 10.5 2-H, 6.3
3b	$CDCl_3$	133.3	(129.3)[b]	115.2[b] (128.5)[b]	120.2[b] (131.4) [82.2]				
2c	$(CD_3)_2CO$			129.8	118.0			197.3 5-H, 10.9	202.5 4-H, 14.7
6c	D_2O			121.3	121.3				
2d·HBr	D_2O		139.8[b]		131.5 (br)[b]		225.2 5-H, 7.8		228.4
3d	$CDCl_3$	(132.5)	146.8 (129.5)	(128.7)	135.7 (br) (129.6) [81.0]		213.2 5-H, 11.5		218.3
2e·HBr	D_2O		140.9		140.9		228.6 5-H, 3.8		228.6 3-H, 3.8
3e	$CDCl_3$	(131.9)	138.9 (br) (129.9)	(129.2)	138.9 (br) (130.4) [83.8]		216.8		216.8
6d	CD_3OD		132.9[a]		123.8 (br)[b]				
2f	D_2O				138.5				225.8
3f	$CDCl_3$	(131.3)	(129.9)	(129.1)	136.9 (130.4) [83.4]				223.5
4f	D_2O				146.5				220.5
5f	$CDCl_3$	(131.3)	(129.5)	(128.6)	149.9 (129.8) [83.0]				216.9

[a] Long range couplings are given indicating the hydrogen atom to which the coupling takes place. [b] The assignments may have to be interchanged.

(b) A mixture of the pyrazole **1a** (15.0 g), ethyl acetate (900 cm^3) and 3-chloroperbenzoic acid (55%; 66 g) was stirred for 7 d, after which the ethyl acetate was removed and the residue extracted with water (6 × 100 cm^3). Trace amounts of 3-chlorobenzoic acid were removed by extraction of the aqueous phase with dichloromethane (2 × 100 cm^3), which also

removed minor amounts of the pyrazole **1a** and the 1-hydroxypyrazole **2a**. These were recovered by reducing the volume of the organic phase to *ca.* 50 cm^3 followed by extraction with conc. hydrochloric acid (20 cm^3). The acidic aqueous phase was washed with dichloromethane (2 × 50 cm^3) and added to the original aqueous phase. Addition of trisodium phosphate dodecahydrate (115 g) was followed by 33% aqueous sodium hydroxide to adjust the pH to 10.5. Continuous extraction with dichloromethane–diethyl ether (2:3) for 16 h. Evaporation of the extract gave starting material (5.4 g, 36%). The aqueous solution was adjusted to pH 2 by addition of conc. hydrochloric acid and extracted [dichloromethane–diethyl ether (2:3)] for 6 h. Evaporation of the extract gave the 1-hydroxypyrazole **2a** (9.25 g, 50%) which, after low temperature recrystallization from heptane–ethyl acetate (4:1) had m.p. 70 °C (Found: C, 42.8; H, 4.8; N, 33.6. $C_3H_4N_2O$ requires C, 42.86; H, 4.80; N, 33.32%).

Oxidation of Imidazoles.—A mixture of the imidazole **1b** (0.51 g), ethyl acetate (100 cm^3) and 3-chloroperbenzoic acid (55%; 2.80 g) was stirred at 20 °C for 24 h and then evaporated to dryness to give a mixture of 1-hydroxyimidazole **2b**, 1-hydroxyimidazole 3-oxide **6b** and unchanged starting material **1b** in the ratio 16:1:33 (^1H NMR). Water (20 cm^3) was added to the mixture which was then continuously extracted with diethyl ether for 3 h to remove 3-chlorobenzoic acid and some imidazole. 33% Aqueous sodium hydroxide (0.330 g) was added to the aqueous phase which was then subjected to continuous extraction with diethyl ether for 5 h in order to remove most of the imidazole. To complete deprotonation a second amount of 33% aqueous sodium hydroxide (0.170 g) was added to the aqueous phase which was then evaporated to dryness and dried (100 °C, 0.1 mmHg). Dimethylformamide (2.0 cm^3) and benzyl chloride (0.49 cm^3) were added to the residue and the mixture stirred for 24 h. The DMF was removed and the residue was ball-tube distilled (105–150 °C, 0.3 mmHg) to give crude **3b** (0.29 g); this was purified by preparative TLC (dichloromethane–diethyl ether [1:1]) to afford 1-benzyloxyimidazole **3b** (0.23 g, 18%) (R_F 0.65) identical with the material described previously.[7] The 1-benzyloxyimidazole **3b** (61 mg) was heated with 47% aqueous hydrogen bromide (0.5 cm^3) at 100 °C for 6 h to induce debenzylation. The mixture was washed with dichloromethane (5 × 3 cm^3), evaporated to dryness, treated with methanol (5 cm^3) and toluene (5 cm^3), evaporated to dryness and treated again with methanol and toluene. Evaporation of the reaction mixture afforded 1-hydroxyimidazolium bromide **2b**·HBr (57 mg, 99%), m.p. 119–122 °C (methanol–diethyl ether) (Found: C, 21.7; H, 3.0; N, 16.75. $C_3H_5BrN_2O$ requires C, 21.84; H, 3.05; N, 16.98%).

Oxidation of 1,2,3-Triazole.—(a) A mixture of the 1,2,3-triazole **1c** (0.51 g), formic acid (0.7 cm^3) and hydrogen peroxide (60%; 1.0 cm^3) were stirred at 0 °C for 1 h and then at 20 °C for 50 h. Further formic acid (0.35 cm^3) and hydrogen peroxide (0.5 cm^3) were added to the mixture and stirring was continued for 24 h. The addition of further formic acid and hydrogen peroxide was repeated and the mixture finally stirred for 48 h. Phosphate buffer (1.9 mol dm^{-3}, pH 5.0; 5.0 cm^3) was added to the reaction mixture which was then adjusted to pH 9.0 by the addition of 33% aqueous sodium hydroxide and continuously extracted [dichloromethane–diethyl ether (1:1)] for 6 h. The extract was dried ($MgSO_4$) and evaporated to give unchanged starting material **1c** (0.24 g, 47%). The aqueous solution was adjusted to pH 2.0 by the addition of conc. hydrochloric acid and then continuously extracted as above for 23 h. Evaporation of the extract gave 1-hydroxy-1,2,3-triazole **2c** (0.25 g, 39%), m.p. 93 °C (acetone) (Found: C, 28.25; H, 3.6; N, 49.1. $C_2H_3N_3O$ requires C, 28.24; H, 3.55; N, 49.40%).

(b) A mixture of the 1,2,3-triazole **1c** (0.83 g), ethyl acetate (10 cm^3) and 3-chloroperbenzoic acid (55%, 4.4 g) was stirred for 7 d and then evaporated and the residue extracted with water (6 × 5 cm^3). The combined extracts were continuously extracted with dichloromethane–diethyl ether (1:2) for 18 h and the aqueous phase evaporated to dryness to give 1-hydroxy-1,2,3-triazole 3-oxide **6c** (86 mg, 7%), m.p. 215 °C (methanol) (Found: C, 23.7; H, 3.0; N, 41.3. $C_2H_3N_3O_2$ requires C, 23.77; H, 2.99; N, 41.58%). The organic extract was evaporated and the residue dissolved in phosphate buffer (1.9 mol dm^{-3}, pH 5.0; 20 cm^3) and the solution washed with dichloromethane (3 × 5 cm^3). 33% Aqueous sodium hydroxide was then added to it to bring it to pH 9.0 when work-up as described in the previous experiment gave 1-hydroxy-1,2,3-triazole **2c** (0.40 g, 39%), m.p. 92–93 °C together with 47% of unchanged starting material.

Oxidation of 1,2,4-Triazole.—(a) A mixture of the 1,2,4-triazole **1d** (0.22 g), ethyl acetate (5 cm^3) and 3-chloroperbenzoic acid (55%; 1.22 g) was stirred at 20 °C for 5 d and then evaporated and extracted with water (6 × 5 cm^3). The combined extracts were washed with dichloromethane (3 × 10 cm^3), treated with 33% aqueous sodium hydroxide (1.1 equiv.) and evaporated. The residue was dried (100 °C, 0.1 mmHg) and then stirred with DMF (2 cm^3) and benzyl bromide (0.46 cm^3) for 18 h after which it was evaporated to dryness and the residue extracted with dichloromethane (4 × 5 cm^3). Evaporation of combined extracts and preparative TLC [dichloromethane–diethyl ether (1:1)] of the residue gave 1-benzyloxy-1,2,4-triazole **3d** (46 mg, 8.1%) R_F 0.59, m.p. 28 °C (ethyl acetate–hexane) (Found: C, 61.5; H, 5.2; N, 23.9. $C_9H_9N_3O$ requires C, 61.70; H, 5.18; N, 23.99%). The next fraction contained 26 mg 4-benzyloxy-1,2,4-triazole **3e** (26 mg, 4.5%) R_F 0.09, m.p. 91 °C (ethyl acetate) (Found: C, 61.6; H, 5.2; N, 23.8%).

1-Benzyloxy-1,2,4-triazole **3d** (145 mg) was heated with 47% aq. HBr (1.5 cm^3) at 60 °C for 4 h to induce debenzylation. The mixture was washed with dichloromethane (5 × 3 cm^3) and the aqueous phase was evaporated to dryness. The residue was treated with methanol (5 cm^3) and toluene (5 cm^3) and the mixture evaporated to dryness; this was repeated to afford 1-hydroxy-1,2,4-triazolium bromide **2d**·HBr (134 mg, 98%), m.p. 127–129 °C (precipitated from ethyl acetate–methanol with diethyl ether) (Found: C, 15.2; H, 2.6; N, 25.2. $C_2H_4BrN_3O$ requires C, 14.47; H, 2.43; N, 25.32%).

Similar debenzylation of 4-benzyloxy-1,2,4-triazole **3e** gave 4-hydroxy-1,2,4-triazolium bromide **2e**·HBr (99%), m.p. 130–132 °C (precipitated from ethyl acetate–methanol with diethyl ether) (Found: C, 14.1; H, 3.0; N, 24.5. $C_2H_4BrN_3O$·20 mol% H_2O requires C, 14.17; H, 2.62; N, 24.78%).

(b) A mixture of the 1,2,4-triazole **1d** (0.66 g), ethyl acetate (45 cm^3) and 3-chloroperbenzoic acid (55%; 3.60 g) was stirred at 20 °C for 7 d. The resulting precipitate was filtered off and washed at 0 °C with ethyl acetate (2 × 5 cm^3) and recrystallized from aqueous methanol to give 1-hydroxy-1,2,4-triazole 3-oxide **6d** (46 mg, 4.7%); repeated recrystallization of this from methanol gave m.p. 183–185 °C (Found: C, 23.55; H, 2.9; N, 41.4. $C_2H_3N_3O_2$ requires C, 23.77; H, 2.99; N, 41.58%).

Oxidation of Tetrazole.—A mixture of the tetrazole **1f** (1.72 g), sodium perborate trihydrate (7.5 g) and pivalic acid (15 g) were stirred at 100 °C for 3 h, after which some of the pivalic acid was removed at 70 °C and 4 mmHg. The mixture was then diluted with water (30 cm^3), washed with dichloromethane (5 × 30 cm^3), treated with hydrochloric acid to bring it to pH 1, diluted with methanol (50 cm^3) and evaporated to dryness. Hydrochloric acid and methanol were added to the residue after which the mixture was evaporated and treated with phosphate buffer (1.9 mol dm^{-3}, pH 5.0; 5.0 cm^3) followed by

aqueous sodium hydroxide to bring the mixture to pH 4.3. It was then extracted with dichloromethane–diethyl ether (2:3) for 18 h. Evaporation of the extract gave starting material (0.69 g, 40%). The aqueous solution was adjusted to pH 1 with conc. hydrochloric acid and extracted [dichloromethane–diethyl ether (1:1), 24 h]. Evaporation of the extract gave a 1.9:1 mixture of 2-hydroxytetrazole **4f** and 1-hydroxytetrazole **2f** (1.27 g, 60%). 33% Aqueous sodium hydroxide (1.1 equiv.) was added to the mixture which was then evaporated and the residue dried (100 °C, 0.01 mmHg). DMF (9.4 cm^3) and benzyl bromide (2.10 cm^3) were added to the residue at 0 °C and the mixture was then stirred at 20 °C for 3 h. After this the DMF was evaporated from the mixture and preparative TLC [dichloromethane–diethyl ether–hexane (1:1:2)] of the residue afforded 2-benzyloxytetrazole **5f** (1.58 g, 37%), R_F 0.71, m.p. 38–40 °C (ethyl acetate–hexane) (Found: C, 54.2; H, 4.5; N, 31.7. $C_8H_9N_4O$ requires C, 54.54; H, 4.58; N, 31.80%). The next fraction contained 1-benzyloxytetrazole **3f** (0.79 g, 18%), R_F 0.31, m.p. 47 °C (ethyl acetate–hexane) (Found: C, 54.5; H, 4.5; N, 31.7%).

A mixture of 1-benzyloxytetrazole **3f** (92 mg) and aqueous hydrogen bromide (47%; 0.50 cm^3) was stirred for 16 h after which it was diluted with water (1 cm^3), washed with dichloromethane (5 × 3 cm^3), treated with phosphate buffer (1.9 mol dm^{-3}, pH 5.0; 5 cm^3) and adjusted to pH 2 with conc. HCl. Extraction [dichloromethane–diethyl ether (1:1), 3 h] of the mixture followed by removal of the solvents gave 1-hydroxytetrazole **2f** (42 mg, 33% total yield), m.p. 151–153 °C (ethyl acetate) (lit.,[22] m.p. 153 °C) (Found: C, 13.75; H, 2.3; N, 64.8. CH_2N_4O requires C, 13.96; H, 2.34; N, 65.11%).

Debenzylation of 2-benzyloxytetrazole **5f** gave 2-hydroxytetrazole **4f** (17%), m.p. 143–146 °C (ethyl acetate) [Found: C, 14.0; H, 2.3; N, 65.1 (exploded)].

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