The Preparation of 3*H*-1,2-Diazepine 2-Oxides and their Rearrangement to give 3-Alkenyl-3*H*-pyrazole 2-Oxides

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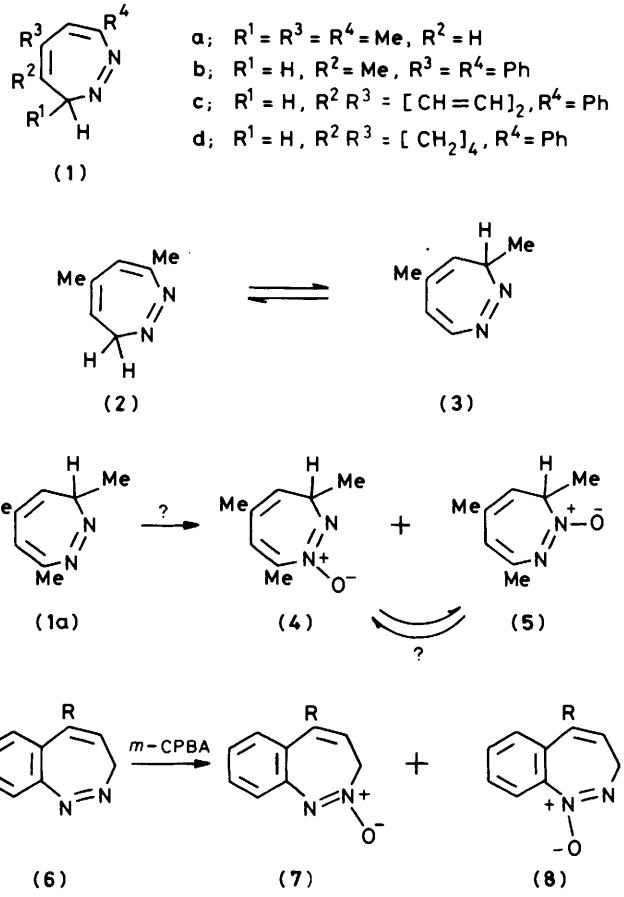
The oxidation of a range of monocyclic and fused 3*H*-1,2-diazepines (**1a**—**d**) with *m*-chloroperbenzoic acid gave the 2-oxides, *e.g.* (**9**)—(**11**). In one case the diazepine 2-oxide (**5**) rearranged readily at room temperature to give the 3-alkenyl-3*H*-pyrazole 2-oxide (**16**) in a *ca.* 1:1 equilibrium mixture with (**5**). The activation energy for ring inversion of the 3*H*-1,2-diazepine 2-oxides, determined by variable-temperature ^{1}H n.m.r. spectroscopy, was *ca.* 12—16 kJ mol^{-1} lower than that for the parent diazepines.

This paper is concerned with the peracid oxidation of 3*H*-1,2-diazepines (**1**). Our interest in the *N*-oxides of this system arose from an earlier observation that [1,5] sigmatropic hydrogen shifts in 3*H*-1,2-diazepines, *e.g.* (**2**)⇌(**3**), are remarkably fast in comparison with those in cycloheptatrienes — the hydrocarbon analogues.[1] We have suggested that this difference is due to the strong electron-withdrawing effect of the azo group and have observed that the hydrogen shift is totally inhibited by complexation of the azo group as its dinuclear di-iron hexacarbonyl derivative.[2] The objective in this work was to enhance the electron-withdrawing effect of the –N=N– moiety by conversion into the *N*-oxide. In particular, we hoped to prepare compounds (**4**) and (**5**) by the oxidation of (**1a**) and to find out how this change affected the rate of the putative hydrogen migration interconverting (**4**) and (**5**). We were encouraged to expect that the oxidation of (**1**) would occur at both nitrogen atoms by the only previous work in this area on the oxidation of the benzo[*c*]-fused system (**6**). This gave the two oxides (**7**) and (**8**) in high yield in a *ca.* 3:1 ratio.[3] In fact the expectation of obtaining the two oxides (**4**) and (**5**) was not realised but the results obtained are of interest.

The initial work was carried out on the benzo[*d*]-fused system (**1c**). On oxidation with *m*-chloroperbenzoic (*m*-CPBA) acid at room temperature it gave only one product, the 2-oxide (**9**) in 81% isolated yield. The oxidation site was deduced from the ^{13}C n.m.r. chemical shifts of C-1 and C-4. It is known[4] that the oxidation of azoalkanes causes deshielding at the carbon atom attached to the oxidised nitrogen atom and shielding at the carbon atom at the other end of the azoxy group. Thus the *N*-oxide, in which C-1 is deshielded by 4.2 p.p.m. and C-4 is shielded by 6.9 p.p.m., compared with (**1c**), must be the 2-oxide as shown, (**9**). The oxidation of the tetrahydrobenzo[*d*]diazepine (**1d**) and the monocyclic system (**1b**) similarly gave only the 2-oxides (**10**) and (**11**) respectively. The structure of compound (**10**) was confirmed by *X*-ray crystallography[5] as shown in the Figure.



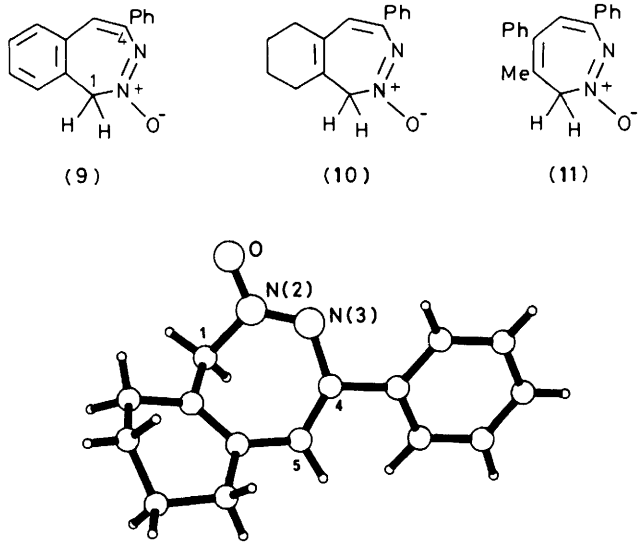
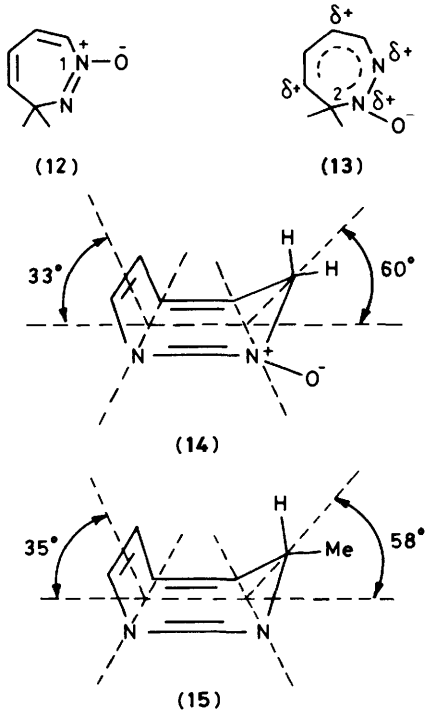


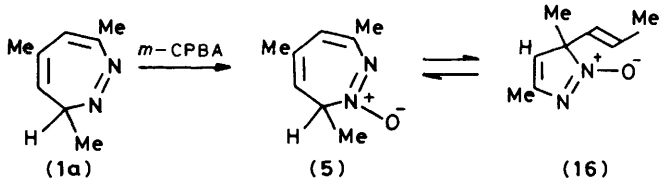
Figure. Structure of the diazepine oxide (**10**)

The selective formation of only the 2-oxides in these reactions is interesting and must reflect their higher thermodynamic stability than the alternative 1-oxides (**12**). This is probably due at least in part to the greater capacity of the former to delocalise the positive charge through the conjugated system as shown in (**13**). However, the degree of delocalisation and hence of

electronic stabilisation will be limited by the non-planarity of the conjugated system as shown in (**14**). A comparison with similar data from the crystal structure of 1-methyl-4-phenyl-1*H*-2,3-benzodiazepine,[6,*] shown in (**15**), shows that the puckering of the diazepine ring has not been much affected by *N*-oxide formation. In this context it is interesting to note that ring inversion of the seven-membered ring in the oxides (**9**)—(**11**) is much easier than in the parent diazepines. Thus, for example, in variable-temperature ^{1}H n.m.r. studies it was found that the coalescence temperature (T_c) for the methylene group at C-1 in the oxide (**9**) was 21 °C ($\Delta G^{\ddagger}$ 59 kJ mol^{-1}) compared with 102 °C ($\Delta G^{\ddagger}$ 72 kJ mol^{-1}) for the parent benzodiazepine (**1c**). The 3*H*-1,2-diazepines which lack benzo annelation, *e.g.* (**1b**) and (**1d**), are much more resistant to ring inversion than is (**1c**) so that, although it is known that T_c is > 130 °C ($\Delta G^{\ddagger}$ > 77 kJ mol^{-1}), it cannot be measured because of thermal decomposition. The corresponding oxides (**11**) and (**10**), however, had, respectively, coalescence temperatures of 54 °C ($\Delta G^{\ddagger}$ 65.0 kJ mol^{-1}) and 31 °C ($\Delta G^{\ddagger}$ 60.9 kJ mol^{-1}). This substantial reduction of the activation energy for ring inversion ($\Delta\Delta G^{\ddagger}$ 12—16 kJ mol^{-1}) is consistent with the stabilisation of the planar transition state by charge declocalisation.



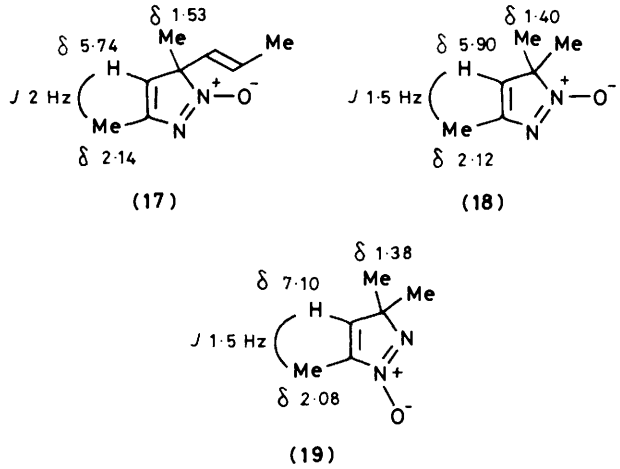
The oxidation of the trimethyl-3*H*-1,2-diazepine (**1a**) did not give the initially expected mixture of the 1- and 2-oxide (**4**) and (**5**). Instead, in this case only, a 3*H*-pyrazole 2-oxide (**16**) was obtained as well as the diazepine oxide (**5**) as shown in Scheme



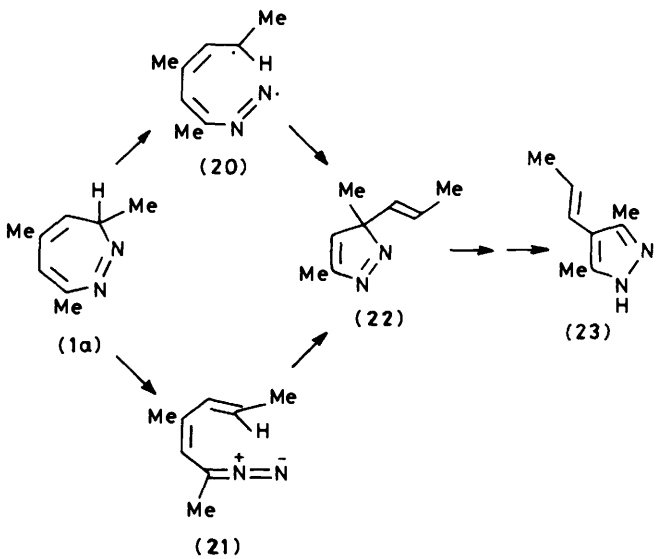
Scheme 1.

* The only 3*H*-1,2-diazepine for which crystal structure data are available.

1. It was found that these compounds could be separated by preparative t.l.c. in >95% isomeric purity and were stable when kept at *ca.* −30 °C. However, each compound isomerised back to a *ca.* 1:1 equilibrium mixture when kept at room temperature overnight. The diazepine oxide (**5**) was identified by the similarity of its ^{1}H and ^{13}C n.m.r. spectra to those of its parent and the oxides (**9**)—(**11**). The other product was formulated as the pyrazole oxide (**16**) on the basis of its ^{1}H n.m.r. spectrum which showed absorptions due to the *E*-propenyl group and the HC=CMe unit of the pyrazole ring. The chemical shifts, shown in structure (**17**), were very similar to those of the oxide (**18**) prepared by Freeman,[7] and the chemical shift of the C-4 proton was quite different from that of the analogous proton in the 1-oxide (**19**). The ^{13}C n.m.r. spectrum of the mixture also contained a peak at δ_C 90.6 p.p.m. which is similar to the chemical shift of C-3 in 3*H*-pyrazoles themselves (94—106 p.p.m.).[8]

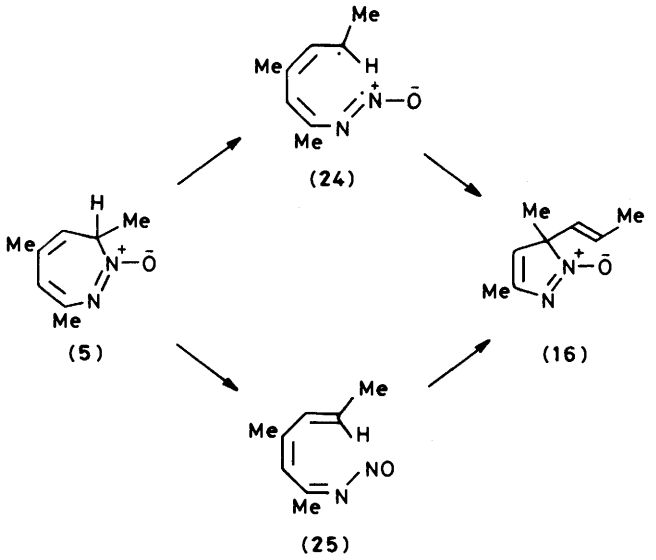


The ring transformation between (**5**) and (**16**) is much like similar conversions between the 3*H*-1,2-diazepines themselves and pyrazoles[9] and between benzodiazepines and indazoles.[10,11] For example the diazepine (**1a**), on being heated at 130 °C, undergoes ring contraction to give the 1*H*-pyrazole (**23**), Scheme 2. The first step giving the 3*H*-pyrazole (**22**) parallels



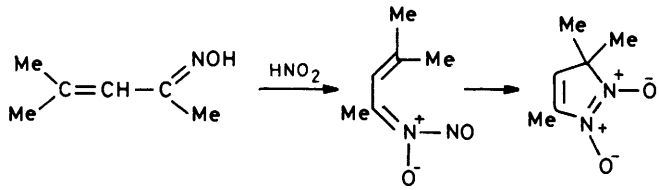
Scheme 2.

the (5)→(16) conversion and is followed by alkenyl group and hydrogen shifts to give (23). The mechanism of the ring contraction is not certain and could involve either a primary homolytic cleavage to give the diradical (20) or electrocyclic ring opening to give the diazo compound (21), followed by 1,5 cyclisation. In the case of the much easier rearrangement of the oxide (5), Scheme 3, it seems very unlikely that the ring cleavage

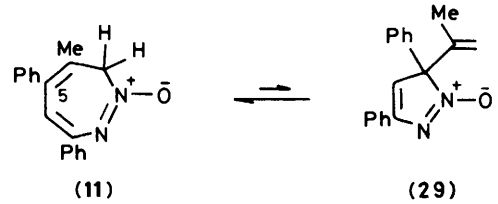


Scheme 3.

is homolytic, *i.e. via* (24), since it is known that homolytic cleavage adjacent to azoxy groups is considerably more difficult than cleavage adjacent to azo groups.[12] It is more likely that electrocyclic ring opening occurs to give the *N*-nitrosoimine (25) as an intermediate. The formation of the pyrazole (16) from (25) by a 1,5-electrocyclisation then parallels the proposed mechanism for the formation of 3,3,5-trimethyl-3*H*-pyrazole 1,2-dioxide (28) from (27) in the nitrosation of mesityl oxide oxime (26).[13]



It is of interest to find an explanation of why the diazepine oxide (5) undergoes an easy ring contraction to give an equilibrium mixture containing a *ca.* 1:1 ratio of (5) and (16) whereas the closely similar oxide (11) does not isomerise to give any detectable amount of (29) even on heating. It seems very likely that the presence of a phenyl group at position 5 in (11) is important in shifting the equilibrium to favour strongly the



diazepine oxide. This phenyl group is conjugated with the diene system in the diazepine oxide and so has a stabilising effect, but loses its conjugation in the hypothetical pyrazole oxide (29).

Experimental

N.m.r. spectra were obtained on Varian HA 100 (^{1}H; 100 MHz) and CFT 20 (^{13}C; 20 MHz), and Bruker WH 360 (^{13}C; 90 MHz) spectrometers. The samples were dissolved in deuteriochloroform unless otherwise stated and the chemical shifts are reported as δ values. Column chromatography was carried out on alumina (Laporte Industries type H; 100—200 mesh; 6% water deactivated) using gravity elution. Light petroleum refers to the fraction of b.p. 40—60 °C. Ether is diethyl ether.

The following diazepines were prepared as described previously: 4-phenyl-1*H*-2,3-benzodiazepine (**1c**),[14] 3,5,7-trimethyl-3*H*-1,2-diazepine (**1a**),[1] 6,7,8,9-tetrahydro-4-phenyl-1*H*-2,3-benzodiazepine (**1d**),[15] and 4-methyl-5,7-diphenyl-3*H*-1,2-diazepine (**1b**).[15]

The oxidation reactions were carried out using equimolar amounts of the diazepine and *m*-CPBA in dichloromethane at room temperature, under nitrogen and in the dark. When the reaction was complete the reaction mixture was washed in turn with aqueous sodium hydrogen carbonate (10% w/v) and water, and dried over anhydrous magnesium sulphate. Evaporation of the solvent under reduced pressure then gave the crude product.

Oxidation of 4-*Phenyl*-1H-2,3-*benzodiazepine* (**1c**).—The diazepine (0.50 g, 2.3 mmol) and *m*-CPBA (85%; 0.42 g, 2.3 mmol) were kept in dichloromethane (40 ml) for 12 h to give a yellow solid after work-up. Chromatography (alumina; 50 vol % ether in light petroleum) gave 4-*phenyl*-1H-2,3-*benzodiazepine* 2-*oxide* (**9**) (0.441 g, 81%) as yellow crystals, m.p. 122—123 °C (from ethanol) (Found: C, 76.3; H, 5.2; N, 11.8. $C_{15}H_{12}N_2O$ requires C, 76.2; H, 5.2; N, 11.9%); δ_H (100 MHz) 4.67 (1 H, d, *J* 6 Hz, 1-H), 5.71 (1 H, d, *J* 6 Hz, 1-H), and 7.2—7.9 (10 H, m, aromatic and 5-H); T_c for the 1-H_2 absorptions = 21 ± 1 °C; δ_C (20 MHz) 73.5 (C-1), 116.0 (C-5), 126.0, 126.2, 127.3, 127.9, 128.3, 128.5, 129.4, 130.3, 134.2 (tert.), 136.8 (tert.), and 145.1 p.p.m. (tert.).

Oxidation of 6,7,8,9-*Tetrahydro*-4-*phenyl*-1H-2,3-*benzodiazepine* (**1d**).—The diazepine (0.165 g, 0.74 mmol) and *m*-CPBA (85%; 0.18 g, 0.88 mmol) were kept in dichloromethane (40 ml) for 2 h to give a yellow solid after work-up. Chromatography (alumina; 30 vol % ether in light petroleum) gave 6,7,8,9-*tetrahydro*-4-*phenyl*-1H-2,3-*benzodiazepine* 2-*oxide* (**10**) (0.125 g, 71%) as a white solid, m.p. 100—101 °C (from ethanol) (Found: C, 74.7; H, 6.9; N, 11.4. $C_{15}H_{16}N_2O$ requires C, 75.0; H, 6.7; N, 11.7%); δ_H (100 MHz; C_2D_6CO; −27 °C) 1.40—1.91 (4 H, m, 2 CH_2), 2.15—2.61 (4 H, m, 2 CH_2), 4.09 (1 H, br d, *J* 11 Hz, 1-H), 5.04 (1 H, d, *J* 11 Hz, 1-H), 6.78 (1 H, s, 5-H), 7.2—7.5 (3 H, m, aromatic), and 7.52—7.77 (2 H, m, aromatic); T_c for the 1-H_2 absorptions = 31 ± 1 °C; δ_C (90 MHz; C_2D_6CO) 21.14 and 21.39 (C-7 and C-8), 27.41 and 28.99 (C-6 and C-9), 73.07 (C-1), 118.54 (C-5), 125.31, 125.51 (tert.), 127.56, 127.63, 134.87 (tert.), 136.70 (tert.), and 144.43 p.p.m. (tert.).

Oxidation of 4-*Methyl*-5,7-*diphenyl*-3H-1,2-*diazepine* (**1b**).—The diazepine (0.091 g, 0.35 mmol) and *m*-CPBA (85%; 0.085 g, 0.42 mmol) were kept in dichloromethane (30 ml) for 5 h to give, after work-up and chromatography (alumina; 30 vol % ether in light petroleum), 4-*methyl*-5,7-*diphenyl*-3H-1,2-*diazepine* 2-*oxide* (**11**) (0.074 g, 77%) as a yellow oil (Found: M^+, 276.124 963. $C_{18}H_{16}N_2O$ requires *M*, 276.126 256); δ_H (100 MHz; −15 °C) 2.10 (3 H, s, Me), 4.08 (1 H, d, *J* 9 Hz, 3-H), 5.33 (1 H, d, *J* 9 Hz, 3-H), 6.84 (1 H, s, 6-H), 7.01—7.50 (8 H, m, aromatic), and 7.52—7.83 (2 H, m, aromatic); T_c for the 3-H_2

absorptions = 54 ± 1 °C; δ_C (20 MHz; C_2D_6CO) 20.46 (Me), 74.92 (C-3), 119.09 (C-6), 124.59 (tert.), 126.49, 128.17, 128.63, 128.74, 129.83, 137.41 (tert.), 138.75 (tert.), 139.96 (tert.), and 146.94 p.p.m. (tert.).

Oxidation of 3,5,7-*Trimethyl*-3H-1,2-*diazepine* (**1a**).—The diazepine (0.50 g, 4.63 mmol) and *m*-CPBA (85%; 0.85 g, 4.63 mmol) were kept in dichloromethane (40 ml) for 12 h to give a yellow oil after work-up. Chromatography (alumina; 50 vol % ether in light petroleum) gave a mixture (0.268 g, 47%) containing 3,5,7-*trimethyl*-3H-1,2-*diazepine* 2-*oxide* (**5**) and 3,5-*dimethyl*-3-*prop*-1-*enyl*-3H-*pyrazole* 2-*oxide* (**16**) in a *ca.* 1:1 ratio, b.p. 80 °C at 0.1 mmHg (Kugelrohr) (Found: M^+, 152.094 738. $C_8H_{12}N_2O$ requires *M*, 152.094 958); δ_C (20 MHz) 14.3, 16.0, 17.7, 20.0, 22.5, 23.8 (6 × Me), 73.1 [C-3 of (**5**)], 90.6 [C-3 of (**16**)], 119.6, 120.0, 120.3, 127.6, 130.0, 139.4, 144.9, and 146.8 p.p.m. Preparative t.l.c. (alumina; 50 vol % ether in light petroleum) gave the isomers in >95% purity. 3,5,7-Trimethyl-3*H*-1,2-diazepine 2-oxide (**5**) had δ_H (100 MHz) 6.08 (1 H, br s, 6-H), 5.05 (1 H, d, *J* 6 Hz, 4-H), 3.76 (1 H, quint., *J* 6 Hz, 3-H), 2.17 (3 H, s, 7-Me), 1.94 (3 H, t, *J* 0.5 Hz, 5-Me), and 1.84 (3 H, d, *J* 6 Hz, 3-Me); 3,5-dimethyl-3-prop-1-enyl-3*H*-pyrazole 2-oxide (**16**) had δ_H (100 MHz) 1.53 (3 H, s, 3-Me), 2.14 (3 H, d, *J* 2 Hz, 5-Me), 2.61 (3 H, d, *J* 6 Hz, CH=CH*Me*), 5.49 (1 H, d, *J* 16 Hz, C*H*=CHMe), 5.74 (1 H, d of q, *J* 16 and 6 Hz, CH=C*H*Me), and 5.88 (1 H, br, 4-H). These samples, in solution in deuteriochloroform, were stable when stored at *ca.* −30 °C but isomerised to give the equilibrium mixture when kept overnight at room temperature.

Acknowledgements

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