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FORMATION OF DIHYDROPYRAZOLES BY FRAGMENTATION OF A STRAINED BISHYDRAZONE

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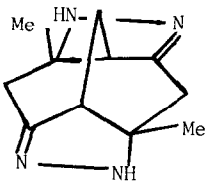
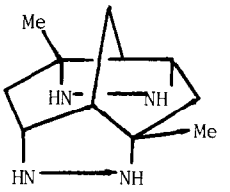
Aluminium chloride induced cleavage of the tetracyclic bishydrazone (1) gives a tricyclic pyrazole characterised as the bisamide (5). Similarly lithium aluminium hydride reduces the bishydrazone (1) with cleavage of a strained ring to give a dihydropyrazole characterised as the bisamide (10).

The preceding communication[1] describes the reduction using lithium aluminium hydride and aluminium chloride (mole ratio 1:1) of the bishydrazone (1) to give the bishydrazine (2). We describe the different behaviour of (1) which with either lithium aluminium hydride acting as a base, or with aluminium chloride acting as an acid, undergoes carbon-carbon bond cleavage to give dihydropyrazole products.



(1)



(2)

Reaction of (1) with aluminium chloride in ether induces rearrangement with formation in 83% yield of an equilibrium mixture of the pyrazoles (3) and (4). Acetylation of this mixture with acetic anhydride in pyridine gives a single crystalline diamide (5)[2] and acetylation with acetic anhydride in acetic acid gives a mixture of diamides (5) and (6).

The establishment of the structure of the crystalline diamide as either (5) or (6) is based on the following evidence:

i) mass spectral and microanalytical data establish the molecular formula $C_{15}H_{20}N_4O_2$;

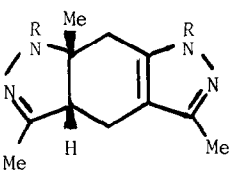
ii) observation of five methyl groups in the ^1H n.m.r. spectrum at 7.40, 7.76, 7.82, 8.02 and 8.32 τ associated with two acetyl groups, two methyl groups attached to sp^2 carbon centres and a quaternary methyl group, and observation of two imine carbons in the ^{13}C n.m.r. spectrum at 149.21 and 155.95 p.p.m. together with two further resonances at 117.53 and 141.99 p.p.m. associated with vinylic carbon centres establish that tetracyclic (1) has undergone fragmentation to give a tricyclic system with creation of a quaternary methyl group;

iii) comparison of the u.v. spectrum (λ_{max} 242nm) with that of 1-acetyl-3,5-dimethyl-1H-pyrazole[3] (7) (λ_{max} 241nm) suggests the presence of a pyrazole moiety;

iv) fragmentation of a six-membered ring in (1) would lead to a tricyclic system, which with incorporation of a pyrazole moiety and a residual dihydropyrazole moiety would require a six-membered carbocyclic ring. Resonances observed at 5.90 (doublet J 18 Hz), 6.71 (doublet J 18Hz), 6.88 (triplet J 6Hz) and 7.33 τ (multiplet) associated with H-8, H-8, H-3a and H-4 respectively accord with this requirement. This evidence is supported by the ^{13}C n.m.r. data.

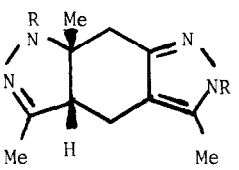
Distinction between the alternative structures (5) and (6) can be made by comparison of the spectra of the isomers observed by acetylation under the different conditions with the model pyrazoles (7) and (8) (obtained via reaction of 2-acetylcyclohexanone with hydrazine). Assignments are based on chemical shift differences of (a) the methyl group attached to the pyrazole moiety and (b) the methylene groups. Deshielding by the anisotropic effect of the carbonyl group in acetylated methyl pyrazoles is well documented,[4] and accounts for the observed[5] chemical shifts in (7). Similarly, isolation of (8) rather than the alternative possibility (9) is proved[6] by observation of the methyl resonance at 7.82τ. In (9) a value of ~7.5τ would be expected. Further support for (8) comes from the relative chemical shifts of the methylene protons at 7.04 and 7.63τ which again shows the deshielding influence of the acyl group. Comparison of the spectral data of (8) with those of (5) and (6) permits straightforward assignments based on chemical shift differences of both methyl and methylene groups.

Reduction of (1) with lithium aluminium hydride in ether followed by acetylation of the product with acetic anhydride in either pyridine or acetic acid gives a single crystalline product[7] in 43% yield. Observation of a quaternary methyl group at 8.61τ suggested the close structural relationship of this product with (5) and (6). Determination of the molecular



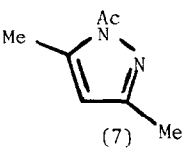
(3) R=H

(5) R=Ac

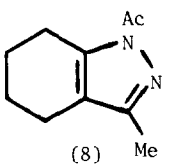


(4) R=H

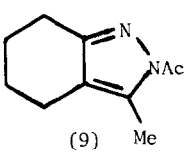
(6) R=Ac



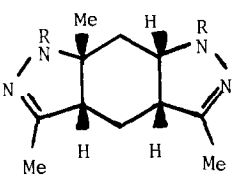
(7)



(8)



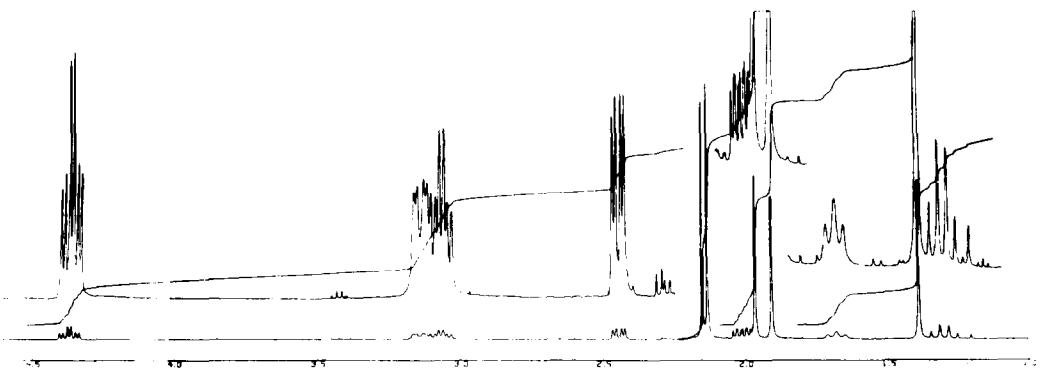
(9)



(10) R=Ac

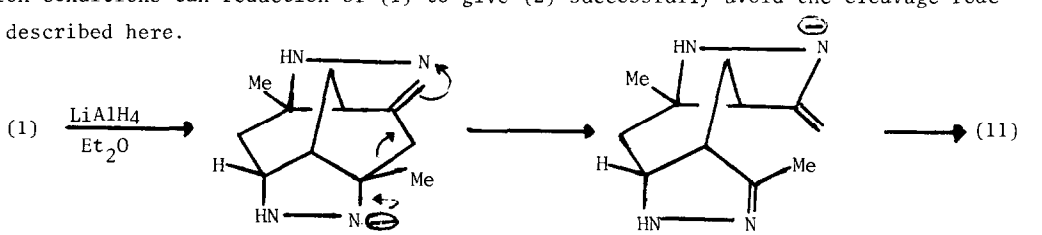
(11) R=H

formula ($C_{15}H_{22}N_4O_2$) by mass spectral and microanalytical data and absence of a pyrazole chromophore in the u.v. spectrum suggested the presence of two dihydropyrazole moieties and hence formation of (10) or an isomer differing only in the stereochemistry at a ring junction position. Structure (10) is established by analysis of the ^{1}H n.m.r. spectrum (400MHz) (see Figure) using coupling constant data and NoE experiments. A *cis* relationship between the quaternary methyl group and H-9 and a *syn* relationship between the quaternary methyl group and H-3 are proved by analysis of NoE. Similarly a *cis* relationship between H-3 and H-7 and a *syn* relationship between H-7 and H-9 is established. Hence a *cis-syn-cis* stereochemistry is suggested by NoE experiments, and is confirmed by observation of the following coupling constants J_{23} = 12 and 4Hz; J_{37} = 12Hz; J_{78} = 12 and 6Hz; and J_{89} = 12 and 4Hz. These results require a *cis-syn-cis* structure for (10) which adopts a non-chair conformation.



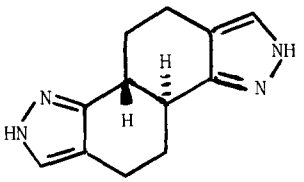
^{1}H n.m.r. spectrum (400 Mhz) of (10)

Although the reductive Grob type fragmentation of substituted alcohols is well known[8] formation of (11) from (1) requires a reduction step and an unusual carbon-carbon cleavage of a β-hydrazohydrazone. The base catalysed cleavage (see Scheme) is analogous to a base catalysed retro aldol reaction. Cleavage permits the relief of strain associated with an anti-Bredt hydrazone. Similarly cleavage of (1) promoted by aluminium chloride has analogy with an acid catalysed retro-aldol reaction. Only by avoidance of the more acidic or basic reaction conditions can reduction of (1) to give (2) successfully avoid the cleavage reactions described here.



SCHEME

These cleavage reactions permit the easy synthesis of either the pyrazoles (3) and (4), or the dihydropyrazole (11). Such compounds are structurally closely related to pyrazoles having antiallergic activity and in particular to the recently prepared (12), which as a mixture of tautomers shows[9] significant and prolonged anti-allergic activity.



(12)

References and Notes

1) J.M. Mellor, R.N. Pathirana and J.H.A. Stibbard, Tetrahedron Lett., 1982, preceding paper.

2) Data for (5): m.p. 147-149°C; ^{1}H n.m.r. ($CDCl_3$) (τ) 5.90 (1H,d,J 18Hz), 6.71 (1H,d,J 18Hz) 6.88 (1H,t,J 6Hz), 7.33 (2H,m), 7.40 (3H,s), 7.76 (3H,s), 7.82 (3H,s), 8.02 (3H,s) and 8.32 (3H,s); ^{13}C n.m.r. ($CDCl_3$) (p.p.m.) 11.87, 14.08, 19.45, 22.94, 23.22, 26.39, 31.71, 57.11, 66.69, 117.53, 142.00, 149.21, 155.95, 169.10 and 170.48.

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5) Data for (7): m.p. 105-106°C; ^{1}H n.m.r. ($CDCl_3$) (τ) 4.08 (1H,s), 7.38 (3H,s), 7.50 (3H,s) and 7.79 (3H,s).

6) Data for (8): m.p. 41-42°C; ^{1}H n.m.r. ($CDCl_3$) (τ) 7.04 (2H,m), 7.38 (3H,s), 7.63 (2H,m), 7.82 (3H,s) and 8.26 (4H,m); ^{13}C n.m.r. ($CDCl_3$) (p.p.m.) 12.01, 20.16, 22.38, 22.54, 24.76, 120.06, 142.26, 151.10 and 170.81.

7) Data for (10): m.p. 145-148°C; ^{1}H n.m.r. ($CDCl_3$) (τ) 5.60 (1H,dt J12 and 4Hz), 6.85 (1H,dd J13 and 4Hz), 6.92 (1H,dt J12, 12 and 6Hz), 7.55 (1H, dd J12 and 4Hz), 7.85 (3H,s), 7.86 (3H,s), 8.00 (1H,m), 8.04 (3H,s), 8.10 (3H,s), 8.32 (1H,t J13 and 12Hz), 8.61 (3H,s) and 8.70 (1H,q J 12Hz); ^{13}C n.m.r. (p.p.m.) 14.08, 14.55, 21.78, 22.73, 23.10, 24.23, 30.60, 45.96, 53.13, 55.36, 62.49, 155.23, 156.97, 168.02 and 168.60.

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