Synthesis and Properties of 2,5-Dihydro-3,6-dimethylpyrazine[1]

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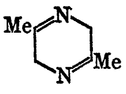
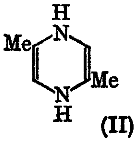
Summary The structure of the self-condensation product of α-aminoacetone has been shown by n.m.r. spectroscopy to be 2,5-dihydro-3,6-dimethylpyrazine (I); the thermal instability of this dihydropyrazine is shown to be due to its dimerization.

Reaction of aminoacetone hydrochloride with potassium hydroxide gives an unstable liquid base, $C_6H_{10}N_2$. The structure of this substance, which was first obtained by Gabriel and Colman in 1902,[2] has not been unequivocally established to date. The structure (I) is generally *assumed* to be correct.[3] However, the structure (II) has also been assumed.[4] In the most recent study of the compound, Cornforth[5] concluded that its properties, particularly its i.r. spectrum, were most consistent with a mixture of (I) and (II), or with (III) alone.[6]

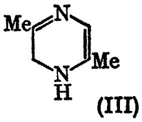
The liquid base, b.p. 43—45° (0·6—0·8 mm Hg), $\nu_{C=N}$ 1665 cm^{-1} (neat), has now been prepared in 36% yield by reaction in a two-phase (water–ether) system with all operations carried out with exclusion of air. The key result which permits unequivocal assignment of structure (I) to this highly unstable liquid is the n.m.r. spectrum (60 MHz, neat liquid, internal Me_4Si reference) which shows as its main features two singlets, δ 1·90 (3H), and 3·86 (2H) p.p.m., respectively. The two peaks exhibit long-range coupling. This coupling, easily discernible at 100 Hz sweep width (not fully resolved), is most reasonably assigned principally to "five-bond" coupling between the methyl protons and the protons of the non-adjacent methylene group.[7]



(I)



(II)



(III)

Minor peaks at δ 2·41 and 8·29 p.p.m. (3 : 1) in the spectrum are due to 2,5-dimethylpyrazine, the principal oxidation product of (I). Small peaks at δ 1·63 and 5·61 p.p.m. (3 : 1) are assigned tentatively to either (II) or (III).‡

2,5-Dihydro-3,6-dimethylpyrazine, (I), is the simplest unconjugated dihydropyrazine not incorporating stabilizing groups such as phenyl[8] or hydroxyphenyl[9] whose structure is certain. It is highly reactive towards metals, *e.g.* steel. This reactivity is evidently responsible in part for decomposition observed during g.l.c. The compound could, however, be recovered after passage through the chromatograph. Its mass spectrum (70 ev, heated inlet) is essentially that of the oxidation product, 2,5-dimethylpyrazine (M^+ 108).

On heating to 80°, the dihydropyrazine (I) surprisingly loses its sensitivity to air. On further standing, at room

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‡ Typically, distillates have consisted of *ca.* 86% (I) and 7% (II) [or *ca.* 79% (I) and 14% (III), if the latter is assumed], the remainder being 2,5-dimethylpyrazine.

temperature, it is slowly converted, in part, into an air-stable solid dimer, $C_{12}H_{20}N_4$ (M^+ 220) The thermal instability of (I), and its instability to storage,§ is thus due to slow reaction of (I) with itself or with one of its tautomers That the latter is the more likely explanation is suggested by the observation that this dimer is the same¶ as the *solid* "$C_6H_{10}N_2$" previously obtained by Gabriel and Colman[2] by reaction of the oxalate salt of (I) with potassium hydroxide and for which a dimeric structure has been postulated by Cornforth [5] The potassium hydroxide evidently speeds up equilibration of (I) with a tautomer The presence of such an isomer in minor amounts is suggested by the n m r spectrum of (I) (see above)

Dimer formation by another dihydropyrazine, 2,3-dihydro-5,6-diphenylpyrazine, in boiling alcoholic potassium hydroxide, has been reported[10] and recently corroborated by Mager and Berends [11]

I thank Professor Hans Wynberg and members of his group for their interest and valuable discussions I also thank Mrs K S Rozema-Meyer for numerous spectra and Dr W D Weringa and Mr P J M Wakkers for mass spectra.

(*Received, October 31st, 1969, Com* 1651)

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§ This point is presumed since slow leakage of oxygen in stored samples cannot be rigorously excluded

¶ By spectroscopic comparison with a sample prepared according to Gabriel and Colman [2] The exact mass of the molecular ion of this sample was determined mass spectrometrically Calc for $C_{12}H_{20}N_4$ 220 169 Found 220 168 Reversibility of dimerization, noted by Gabriel and Colman,[2] is also evident mass spectrometrically at 210°

[1] Presented at the Second International Congress of Heterocyclic Chemistry, Montpellier, France, July 10, 1969

[2] S Gabriel and J Colman *Ber* , 1902 **35** 3805

[3] *e g* , G R Ramage and J K Landquist in "Chemistry of Carbon Compounds," ed E H Rodd, vol 4B, Elsevier, Amsterdam, 1959, pp 1319 1333—1336, L A Paquette, ' Principles of Modern Heterocyclic Chemistry," Benjamin, New York, 1968, pp 316—317.

[4] L P Ellinger and A A Goldberg, *J Chem Soc* , 1949, 263

[5] J W Cornforth, *J Chem Soc* , 1958, 1174

[6] The strong band at 3260 cm^{-1} (associated NH) forced the conclusion given While I have also observed this band, it is evidently spurious and due to the difficulty in completely drying the compound Other workers have reported similar difficulties in the synthesis of imines, *e g* D A Nelson and J J Worman, *Chem Comm* , 1966, 487, W H Bell, G B Carter, and J Dewing *J Chem Soc.* (*C*), 1969, 352

[7] Similar "five-bond" coupling has been reported recently for the conjugated dihydropyrazine, 2,3-dihydro-2,2,5,6-tetramethylpyrazine by J M Kliegman and R K Barnes, *Tetrahedron Letters*, 1969, 1953 I have also observed such coupling in 2,3-dihydro-5,6-dimethylpyrazine

[8] S Gabriel, *Ber* , 1908, **41**, 1127, L Horner, A Christmann, and A Gross, *Chem Ber* , 1963, **96**, 399

[9] Th Kappe, K Burdeska, and E Ziegler, *Monatsh* , 1966, **97**, 77

[10] A T Mason and L A. Dryfoos, *J Chem Soc* , 1893, **63**, 1293

[11] H I X Mager and W. Berends, *Rec Trav chim* , 1965, **84**, 314