Tetrahedron Letters No. 25, pp 2217 - 2220, 1978.
Pergamon Press Ltd. Printed in Great Britain.
0040-4039/78/0615-2217$02.00/0

NITROENAMINES - 7[1]. SYNTHESIS OF 2,5-BIS-ω-AMINOALKYL PYRAZINES THROUGH A NOVEL REDUCTIVE CYCLODIMERIZATION

S. Rajappa* and R. Sreenivasan
CIBA-GEIGY Research Centre, Goregaon, Bombay 400 063, India.

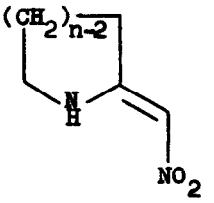
(Received in UK 10 April 1978; accepted for publication 27 April 1978)

Catalytic reduction of the nitroenamines 1 under neutral conditions to the aminomethyl derivatives 2 is well-known[2]. We now wish to report the unexpected formation of the symmetrically substituted pyrazines 3 during catalytic reduction of 1 under acidic conditions.

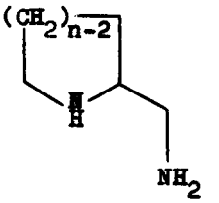
Thus, hydrogenation of 2-nitromethylene-hexahydroazepine[3] (1c) in methanol containing acetic acid at 45° in an Ente apparatus in presence of 10% Pd/C catalyst resulted in an uptake of 2.5 moles of hydrogen. Addition of the calculated amount of alcoholic HCl and evaporation of the solvent, followed by crystallization of the residue from methanol/isopropanol gave a 67% yield of the dihydrochloride of 2,5-bis(5-aminopentyl)pyrazine (3c), m.p. 305° (d). The structure of the compound rests on the following evidence[4]. There are only three bands in the ^{1}H NMR spectrum of the dihydrochloride in D_2O, with the intensity ratio 1:4:6 at 8.33 (sharp singlet), 2.50 - 3.17 (m) and 1.17 - 2.00 ppm (m). The free base (3c), liberated by NaOH, and crystallised from hexane, had m.p. 58-61°. Its ^{1}H NMR spectrum in $CDCl_3$ likewise showed a sharp singlet at 8.38 ppm, multiplets at 2.5 - 3.0 and 1.4 - 2.0 ppm, and a singlet at 1.33 ppm (NH_2; vanishing on deuteration); these four bands had the intensity ratio 1:4:6:2. The acetyl derivative[5] also exhibited a low-field singlet in its ^{1}H NMR spectrum. This was seen at 8.33 ppm in $CDCl_3$ + DMSO-d_6. In TFA, this was shifted further downfield, to 9.05 ppm; in this solvent, the other bands were at 3.09 - 3.70 (m), 2.50 (s; $NCOCH_3$) and 1.33 - 2.17 (m), the intensity of the four bands being in the ratio 1:4:3:6.

The mass spectrum of the base 3c showed the molecular ion at m/e 250, corresponding to the molecular formula $C_{14}H_{26}N_4$. The mass spectral fragmentation pattern of the acetyl derivative indicated the presence of two side-chains of the structure $-(CH_2)_5-NH-Ac$: molecular ion at m/e 334 (100%), peaks at m/e 221 (90%; loss of CH_2=CH-CH_2-CH_2-NHAc) and 108 (loss of a second molecule of CH_2=CH-CH_2-CH_2-NHAc). This leaves a nucleus represented by $C_4H_2N_2$.

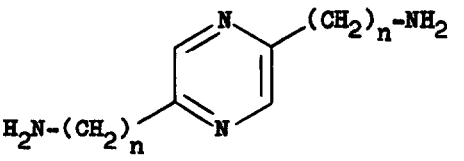
The nucleus must evidently be aromatic, and the two protons attached to it



1

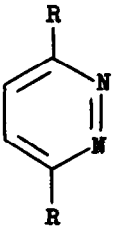


2

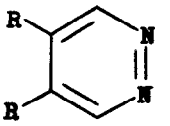


3

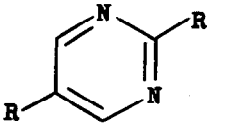
a: n = 3
b: n = 4
c: n = 5
d: n = 6



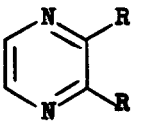
A



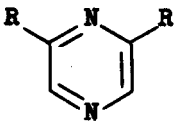
B



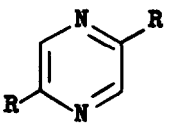
C



D



E



F

R = $-(CH_2)_5-NH_2$

must be situated in identical environments in order to give rise to the sharp singlet at low field in the ^1H NMR spectra described above.

Of the six possible structures (A - F) possessing an aromatic $C_4H_2N_2$ nucleus with the required symmetry, C and D could be straightaway ruled out by the further topological requirement that two chains of seven continuous carbon atoms each should be present in the molecule[6]. A choice between the pyridazines (A, B), and the pyrazines (E, F) could be easily made on the basis of the U.V. and

^{1}H NMR spectra. Thus the acetyl derivative had λ_{max} (EtOH): 275 (log ε 3.87) and 300 nm (sh) (log ε 3.12); λ_{max} (EtOH-HCl): 278 nm (log ε 3.87). This was comparable to the U.V. spectrum of methylpyrazine[7]: λ_{max} (pH 7): 271 (log ε 3.77) and 295 nm (sh) (log ε 3.05); λ_{max} (2N H_2SO_4): 276 nm (log ε 3.82). In contrast, 4-methylpyridazine is reported to have the following U.V. spectrum[8]: λ_{max} (pH 7): 247 (log ε 3.16) and 292 nm (log ε 2.57); λ_{max} (pH 0.7): 221 nm (log ε 3.78). A comparison of the chemical shift of the nuclear proton confirms this deduction. The α-protons of pyridazine resonate at 9.21 ppm and the β-protons at 7.50 ppm[9]. The nuclear protons of 2,5-dimethylpyrazine are seen at 8.35 ppm[10]; this tallies well with the chemical shift of the low-field singlet in the base 3c and its acetyl derivative, as reported above.

The final choice between the pyrazines E and F could be made by taking recourse to classical organic chemistry. Drastic alkaline potassium permanganate oxidation of 3c gave a dicarboxylic acid, $C_6H_4N_2O_4$ (Mass spectrum: m/e 168 → 124 → 80), identical (m.p., mixed m.p., I.R., paper chromatogram) with authentic pyrazine-2,5-dicarboxylic acid. Structure F is thus established.

The yields of the homologous pyrazines as a function of the ring-size of the starting nitroenamine are listed in the Table. In the case of the 5 and 6-membered rings (1a, 1b) (n = 3,4), the reduction product was a mixture of 2 and 3; the former had to be removed by vacuum distillation before the pyrazines 3a and 3b could be obtained pure.

Table

n	% yield of pyrazine
3	26
4	8
5	67
6	58

α-Aminoketones are known to cyclodimerize to pyrazines[11]. We believe that in our reaction, an α-aminoketimine may be the intermediate which dimerizes to a dihydropyrazine; subsequent oxidation, perhaps during work-up, would lead to the fully aromatic pyrazines.

Synthetic procedures leading directly to symmetrically substituted pyrazines bearing functional groups in the side-chains are extremely rare[11,12]. It is in this context that the present method assumes significance. The diamine 3c, for instance, is now easily accessible from caprolactam in three simple

steps, via the iminoether and the nitromethylene derivative 1c.

Acknowledgements

We thank Dr. S. Selvavinayakam and his associates for the analytical and spectral data.

References and Notes

1. Part 6: S. Rajappa and K. Nagarajan, J. Chem. Soc., Perkin Trans. II, in press.

2. (a) S. Rajappa and R. Sreenivasan, Indian J. Chem., 14B, 400 (1976); (b) Hungarian Pat. 156,590; Chem. Abstr., 72, 43497 (1970); I. Beck and J. Rakoczi, Acta Chim. Acad. Sci. Hung., 77, 199 (1973).

3. R.G. Glushkov and O. Yu Magidson, Zhur. Obshchei Khim., 30, 1855 (1960); Chem. Abstr., 55, 7430 (1961).

4. Satisfactory elemental analyses have been obtained for all compounds reported in this communication.

5. Prepared from the dihydrochloride by treatment with acetic anhydride in pyridine at room temperature for 16 h; m.p. 154-156°; $C_{18}H_{30}N_4O_2$.

6. The starting material has one such chain; it is difficult to conceive of fragmentation - recombination of this carbon framework during catalytic hydrogenation.

7. Physical methods in Heterocyclic Chemistry, Vol. III, Ed. A.R. Katritzky, Academic Press, 1971, p. 92.

8. ibid., p. 88.

9. High Resolution NMR Spectra Catalog, Varian Associates, Vol. 2, No. 398.

10. ibid., No. 459.

11. G.W.H. Cheeseman and E.S.G. Werstiuk, in Advances in Heterocyclic Chemistry, Vol. 14, Ed. A.R. Katritzky and A.J. Boulton, Academic Press, Inc., New York, N.Y., 1972, p. 99.

12. H. Iida, K. Hayashida, M. Yamada, K. Takahashi and K. Yamada, Synthetic Communications, 3, 225 (1973).