

A Novel Reaction of Formaldehyde with Some Diamines

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It has been shown using n.m.r. spectroscopy that formaldehyde reacts with 1,3-diaminopropanes to give 1-formyl-3-methylhexahydropyrimidines.

There have been several reports in the literature on the reaction of formaldehyde with diamines and with β -aminoalcohols under acidic conditions. A recent paper on the reaction of β -mercaptoamine derivatives with formalin and formic acid¹ to give 3-methyl-1,3-thiazolidines has prompted us to communicate our results on the reaction of diamines with formaldehyde under neutral conditions.

The reaction of formaldehyde with propane-1,3-diamine monohydrochloride or acetate was first reported to give a mixture of the salts of hexahydropyrimidine and of its open-chain tautomer, 3-methyleneaminopropylamine.² Later spectroscopic evidence³ showed that the main products of this reaction are hexahydropyrimidine (**1**) and the two crystalline by-products (**2**) and (**3**). On the basis of ¹H n.m.r. studies of a series of substituted hexahydropyrimidines, Evans concluded³ that hexahydropyrimidines bearing two hydrogen atoms at C-2 in the molecule will exist solely as the cyclic form and will exhibit the chemical properties of a cyclic amine.

Hexahydropyrimidine was found to react with formaldehyde³ to form the octa-azacyclo-octacosane (**2**), which was originally obtained from the direct condensation of 1,3-diaminopropane with 2 moles of formaldehyde.⁴ We now

report that (**2**) reacts with a further mole of formaldehyde under neutral conditions to give 1-formyl-3-methylhexahydropyrimidine, (**4**). This can also be obtained as the sole product of the reaction of 1,3-diaminopropane with 3 moles of formaldehyde under neutral aqueous conditions. This compound is a colourless liquid and may be obtained in almost quantitative yield. Satisfactory elemental analysis and molecular weight measurements have been obtained for (**4**).

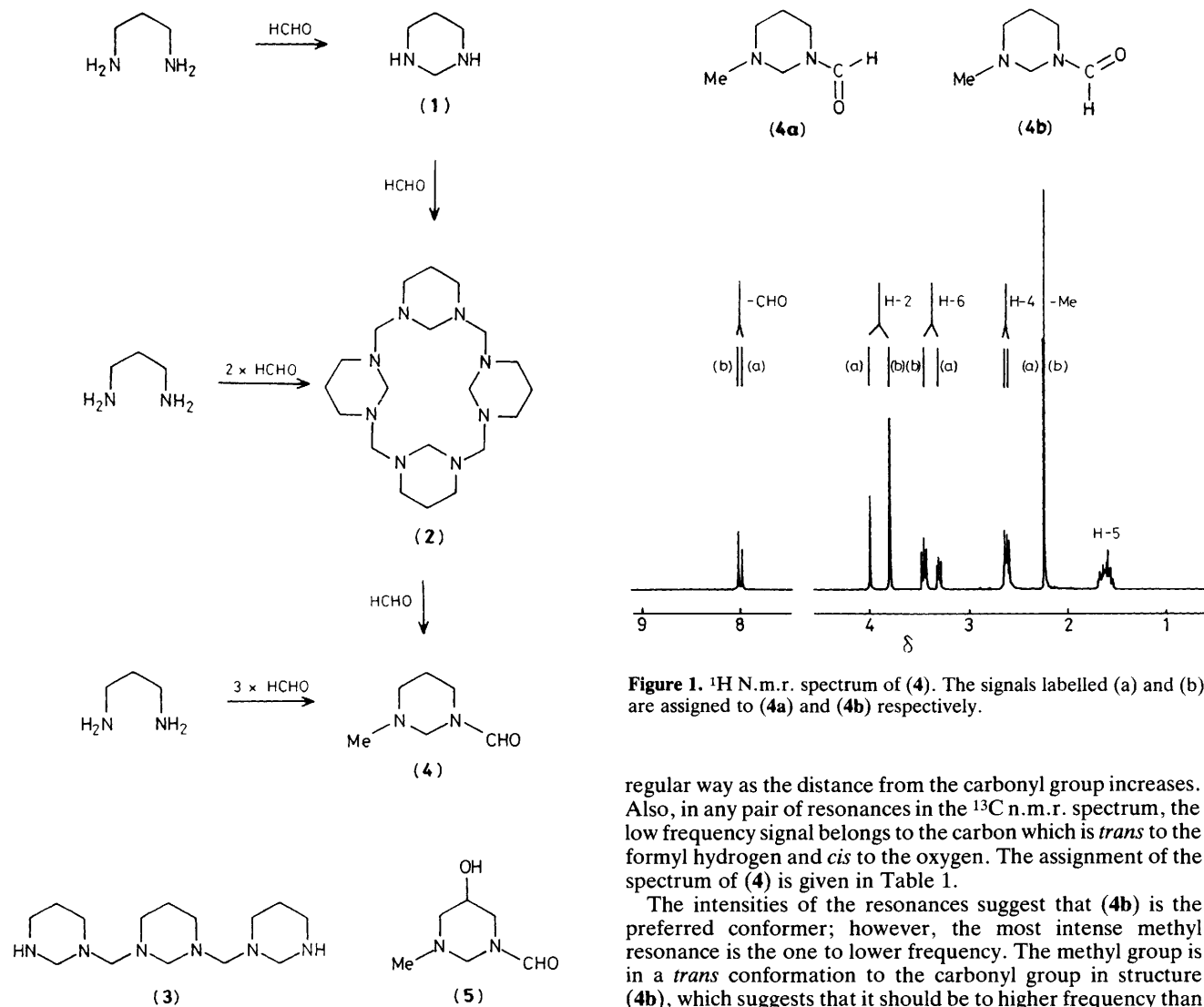
The 250 MHz ¹H n.m.r. spectrum, shown with assignments in Figure 1, suggests that the molecule exists in two conformationally non-equivalent structures as a result of restricted rotation about the N-C(O) bond. The ¹³C n.m.r. spectrum of (**4**) in CDCl₃ solution contains 12 resonances, indicating a doubling of signals caused by the existence of two isomeric forms. If it is assumed that ring inversion is fast on the n.m.r. timescale, the two isomers can be regarded as corresponding to the *s-cis* and *s-trans* structures (**4a**) and (**4b**) respectively.

It has been reported⁵ that for a series of *N,N*-dialkylformamides, lines are observed in the spectra corresponding to *s-cis* and *s-trans* conformations about the amide C-N bond, and that the differences between the carbon chemical shifts for corresponding carbon atoms decrease in a

Table 1. ^{13}C N.m.r. chemical shift data for 1-formyl-3-methylhexahydropyrimidines.

Carbon	Chemical shift ^a					
	(4a)	(4b)	$\Delta\delta^b$	(5a)	(5b)	$\Delta\delta^b$
-CH	160.58	160.72	0.14	164.39	164.56	0.17
<i>trans</i> C-2		68.88	}	}	}	}
<i>cis</i> C-2	62.48					
<i>trans</i> C-4		54.33	}	}	}	}
<i>cis</i> C-4	54.09					
<i>trans</i> C-6	44.66		}	}	}	}
<i>cis</i> C-6		38.91				
<i>trans</i> C-5	24.02		}	}	}	}
<i>cis</i> C-5		22.93				
<i>cis</i> Me	41.39		}	}	}	}
<i>trans</i> Me		41.27				

^a CDCl_3 solution, all shifts referenced to Me_4Si . ^b Chemical shift difference between *trans* and *cis* carbon atoms.



the methyl group of structure (4a). It appears, therefore, that the 'trans rule' does not apply for the *N*-methyl group. Included in Table 1 are the chemical shift data for 1-formyl-5-hydroxy-3-methylhexahydropyrimidine (5) which was obtained from the reaction of 2-hydroxypropane-1,3-diamine with formalin in an analogous manner. The chemical shift changes observed on the introduction of a hydroxy group into the molecule are consistent with the proposed structures.

One possible mechanism for the formation of (4) from propane-1,3-diamine and formaldehyde involves condensation to give (1) initially, followed by substitution at the two secondary amino groups. Loss of the hydroxy group to give the methyleneamino function and subsequent hydride transfer would give the observed product. An intramolecular reaction

mechanism is suggested as piperidine gives only the *N*-hydroxymethyl derivative under these reaction conditions.

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