

THE CHEMISTRY OF HEXAHYDRO-1,2,4,5-TETRAZINES - III.
FORMATION AND DIMERIZATION OF FORMALDEHYDE ALKYLHYDRAZONES¹

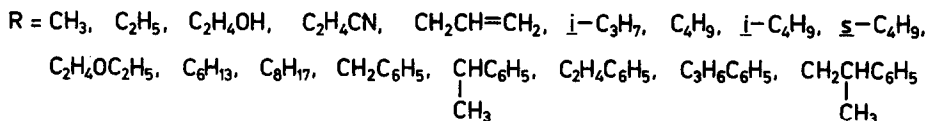
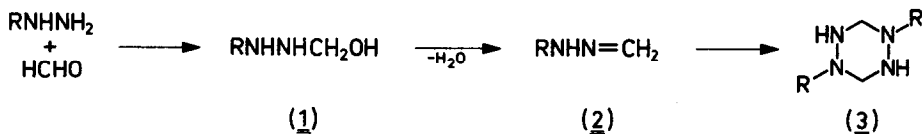
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The reactions of aliphatic aldehydes with hydrazine and alkylhydrazines have recently been thoroughly examined.^{2,3} Only very little is known, however, of the reactions of the simplest possible aldehyde, formaldehyde, with alkylhydrazines. One formaldehyde hydrazone (of isopropylhydrazine, (2), R = *i*-C₃H₇) has been described,⁴ and 1,4-dialkylhexahydro-1,2,4,5-tetrazines (3) have been reported to arise from 1:1 condensations of methyl- and benzylhydrazine with formaldehyde.^{5,6} We now report the results of an investigation of the condensation reactions of 16 alkylhydrazines with formaldehyde.

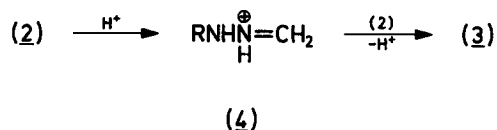
The initial reaction products of 1:1 condensations of alkylhydrazines with formaldehyde under neutral or weakly alkaline conditions are formaldehyde alkylhydrazones (2). These may subsequently dimerize in an acid catalysed reaction to give the corresponding head-to-tail dimers (3).



In a typical experiment aqueous formaldehyde was added slowly to the equimolar amount of benzylhydrazine, with stirring and external cooling. After an hour formaldehyde benzylhydrazone (2, R = CH₂C₆H₅) was taken up in CHCl₃,

dried and distilled in vacuum. It is fairly stable at -30°C , and may be stored under these conditions for periods up to a week without significant dimerization.

The liquid hydrazone is slowly transformed into the solid 1,4-dibenzyl-hexahydro-1,2,4,5-tetrazine (III, $\text{R} = \text{CH}_2\text{C}_6\text{H}_5$) if left at room temperature. Addition of acetic acid/acetate buffer (pH 5.5) to the hydrazone causes almost instantaneous conversion to the hexahydro-tetrazine. Likewise, the hexahydro-1,2,4,5-tetrazine separates immediately from the reaction mixture if the condensation is carried out in buffer solution. This acceleration of the rate of dimerization suggests the intermediacy of a protonated hydrazone (4) in the conversion of (2) to (3).



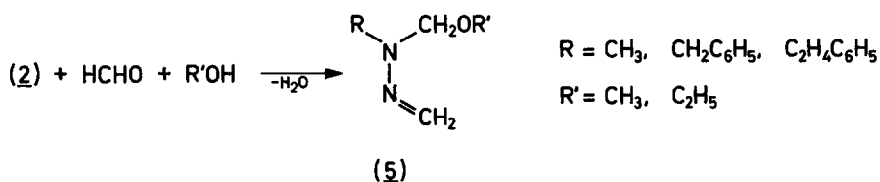
The rate of hydrazone dimerization in the absence of acid varies inversely with the length of the alkyl group; similarly, the presence of bulky substituents and chain branching retard the rate of formation of (3). Typically, the formaldehyde hydrazones of lower alkyl hydrazines may be detected (by ^1H nuclear magnetic resonance spectroscopy) only in the reaction mixture, but dimerize upon removal of solvent. Hydrazones with branched alkyl or aralkyl groups may be distilled in vacuum without decomposition and dimerize only slowly at $+4^{\circ}\text{C}$. An extreme example is formaldehyde (α -methylbenzyl)hydrazone, where dimerization is only 75% complete after 24 months in the refrigerator.

NMR spectroscopy provides a convenient method for distinguishing between (2) and (3), since the methine protons of the former give rise to an AB system centered at τ 3.7, whereas the methylene protons of (3) appear as a broad singlet at τ 6.4 (cf. table 1). On cooling this part of the spectrum becomes a multiplet, which is simplified to an AB quartet ($J = 11$ Hz) upon substitution of deuterium on the nitrogen. The coalescence temperatures are usually slightly below room temperature. These results imply that the com-

pounds undergo slow nitrogen inversion with simultaneous fast ring inversion, by analogy with 1,2,4,5-tetramethylhexahydro-1,2,4,5-tetrazine.⁷

The 1,4-dialkylhexahydro-1,2,4,5-tetrazines have been characterized as the corresponding 2,5-diacyl- and 2,5-bis(*N*-alkylthiocarbonyl)-derivatives through the action of acid anhydrides or alkyl isothiocyanates. The NMR spectra of these exhibit one AB-system corresponding to the ring methylene groups, confirming the centrosymmetrical nature of (3).

Condensation reactions carried out with excess formaldehyde in water or without solvent produce complicated reaction mixtures, from which 3:2 and 4:2 condensation products may be isolated (cf. ref 5). However, the reactions of alkyldiazines with excess alcoholic formaldehyde lead to the formation of formaldehyde *N*-alkyl-*N*-alkoxymethylhydrazones (5). Compounds of this nature have previously only been isolated from reactions of aromatic aldehydes with alkyldiazines in methanol/HCl.^{8,9}



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Table 1. Formaldehyde alkylhydrazones (2) and 1,4-dialkylhexahydro-1,2,4,5-tetrazines (3).^a

R	(2)		(3)	
	b.p. °C/mm Hg	NMR (CH ₂ =N) d,e	m.p. °C	NMR (N-CH ₂ -N) d,f
CH ₃	- ^b	3.55 3.85 11½ Hz	123-25	6.37
C ₂ H ₅	-	-	139-40	6.35
C ₂ H ₄ OH	- ^b	3.47 4.00 11½ Hz	146-48	6.44 ^g
C ₂ H ₄ CN	- ^b	3.30 3.75 11½ Hz	122-23	6.30
CH ₂ CH=CH ₂	- ^b	3.50 3.90 11½ Hz	103-04	6.35
C ₄ H ₉	- ^b	3.40 3.88 11½ Hz	135-36	6.38
<i>i</i> -C ₄ H ₉	35-38/12	3.50 3.90 11½ Hz	109-10	6.45
<i>s</i> -C ₄ H ₉	42-45/12	3.47 3.98 11½ Hz	-	-
C ₂ H ₄ OC ₂ H ₅	- ^b	3.42 3.83 11½ Hz	93-101 ^c	6.27
C ₆ H ₁₃	-	3.43 3.85 11½ Hz	128-30	6.38
C ₈ H ₁₇	70-74/0.5	3.57 3.98 11½ Hz	125-27	6.39
CH ₂ C ₆ H ₅	53-56/0.5	3.52 3.88 11½ Hz	165-67	6.32
CH(CH ₃)C ₆ H ₅	ca. 60/0.4	3.68 4.02 11½ Hz	102-07 ^c	6.42
C ₂ H ₄ C ₆ H ₅	- ^b	3.47 3.82 11½ Hz	151-53	6.30
C ₃ H ₆ C ₆ H ₅	80-85/0.5	3.62 3.97 11½ Hz	75-77	6.40
CH ₂ CH(CH ₃)C ₆ H ₅	- ^b	3.55 3.90 11½ Hz	137-38	6.40 6.52 ^h

a. All new compounds described in this paper showed satisfactory elemental analyses.

b. Detected in spectrum of reaction mixture.

c. Possibly accompanied by dissociation, (3) → (2).

d. 60 MHz (Varian A-60A), CDCl₃, 40°C.

e. One AB pair of doublets; doublet centers given in τ-values.

f. Broadened singlet, τ-values.

g. DMSO-*d*₆ solution.

h. AB pair of doublets, J = 11 Hz.