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The Chemistry of Hexahydro-1,2,4,5-tetrazines

IV. The Reactions of Alkylhydrazines with Formaldehyde*

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The condensation reactions of alkylhydrazines with formaldehyde are shown to lead to formaldehyde alkylhydrazones. These dimerize in an acid-catalyzed reaction to yield 1,4-dialkylhexahydro-1,2,4,5-tetrazines. With straight-chain alkyl groups the dimerization process is too rapid to allow isolation of the hydrazones in a pure state. A stepwise ionic mechanism for the dimerization process rather than dimerization of 1,3-dipolar azomethine imines is suggested. Condensations with alcoholic formaldehyde in excess lead to formaldehyde *N*-alkyl-*N*-alkoxymethylhydrazones. The reaction course is not significantly influenced by the inclusion of functional groups in the alkyl moieties of the hydrazines. The hexahydro-1,2,4,5-tetrazines are characterized as diacyl and bis(thiocarbamoyl)derivatives. NMR spectra of 1,4-dialkylhexahydro-1,2,4,5-tetrazines give evidence of hindered nitrogen inversion, the barrier to which is increased upon acyl substitution.

In a recent communication [1] we reviewed the formation of 1,4-dimethyl and 1,4-diphenyl hexahydro-1,2,4,5-tetrazines by condensation of formaldehyde and formaldehyde derivatives with methyl- and phenylhydrazine. Only a very few reactions of alkylhydrazines with formaldehyde have been reported in the literature: Müller and Rundel [2] prepared 1,4-dimethylhexahydro-1,2,4,5-tetrazine (III*a*) from methylhydrazine and aqueous formaldehyde, and Schmitz and Ohme [3] further described the isolation of the 3:2 and 4:2 condensation products VI and IX from methylhydrazine with excess formaldehyde. Dorn and Dilcher [4] have reported the preparation of hexahydro-1,2,4,5-tetrazines (III) by reaction of substituted benzylhydrazines with weakly alkaline aqueous formaldehyde, and Zurini and Rosicky [5] reported the formation of 1,4-bis(2-phenylethyl)hexahydro-1,2,4,5-tetrazine (III*o*) from aqueous formaldehyde and phenethylhydrazine. None of these authors mention the intermediate formation of formaldehyde alkylhydrazones. Ioffe,[6] however,

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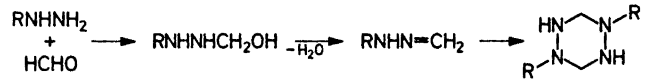
has isolated the isopropylhydrazone of formaldehyde (II*f*), which dimerized upon standing. The only other formaldehyde monoalkylhydrazone that has been reported in the literature is the methylhydrazone (II*a*), which was detected by Hutton and Steel [7] in solution after base-catalyzed isomerization of azomethane. In a preliminary report Block and Young [8] recently noted the apparent failure of β-hydroxyethylhydrazine to react with formaldehyde.

We now report the results of an investigation of the reaction of formaldehyde with a series of alkylhydrazines (*cf.* Fig. 1) in various media. The product distribution has been found to be dependent on the molar ratio of the reactants, since the initial reaction products, formaldehyde alkylhydrazones, may react further with formaldehyde, and on the nature of the alkyl group, since the reactivity of the hydrazones has been found to depend upon chain length and branching.

RESULTS

The addition of aqueous formaldehyde to an equimolar amount of an alkylhydrazine produces an alkylhydroxymethylhydrazine (I), which subsequently eliminates water with formation of a formaldehyde alkylhydrazone (II).



I II III

a: R = CH_3 g: R = C_4H_9 n: R = $CH_2C_6H_5$

b: R = C_2H_5 h: R = i-C_4H_9 o: R = $CH_2CH_2C_6H_5$

c: R = C_2H_4OH i: R = sec.-C_4H_9 p: R = CHC_6H_5 (CH_3)

d: R = C_2H_4CN j: R = $C_2H_4OC_2H_5$

e: R = $CH_2CH{=}CH_2$ k: R = cyclo-C_6H_{11} q: R = $CH_2CH_2CH_2C_6H_5$

f: R = i-C_3H_7 l: R = C_6H_{13} r: R = $CH_2CHC_6H_5$ (CH_3)

m: R = C_8H_{17}

Fig. 1

Only hydrazones derived from hydrazines with branched alkyl groups or from aralkylhydrazines have been isolated in a pure state, whereas straight-chain aliphatic formaldehyde hydrazones dimerize *in situ* or upon attempted purification (distillation) to give 1,4-dialkylhexahydro-1,2,4,5-tetrazines (III). The rate of dimerization varies inversely with the length of the n-alkyl group. Lower alkylhydrazones have been detected (by NMR spectroscopy) only in chloroform extracts of the reaction mixtures, since dimerization takes place upon evaporation of solvent. Hydrazones with higher alkyl substituents (*e.g.* octyl) may be distilled in vacuum after removal of solvent, but the distillates

Table 1. 1,4-Dialkylhexahydro-1,2,4,5-tetrazines (III).

	Alkyl	M.p.	Yield %	Formula		Analyses (C, H, N)		
a	CH_3	123–125[a]	70	$C_4H_{12}N_4$	Found	41.07	10.18	48.10
					Calc.	41.33	10.42	48.25
b	C_2H_5	139–140	25	$C_6H_{16}N_4$	Found	49.64	11.11	38.61
					Calc.	49.97	11.18	38.85
c	C_2H_4OH	146½–148	70	$C_6H_{16}N_4O_2$	Found	41.02	9.14	31.78
					Calc.	40.89	9.15	31.80
d	C_2H_4CN	122–123	40	$C_8H_{14}N_6$	Found	49.20	7.30	43.28
					Calc.	49.46	7.27	43.27
e	$CH_2CH=CH_2$	103–104	40	$C_8H_{16}N_4$	Found	57.00	9.61	33.48
					Calc.	57.11	9.59	33.30
g	C_4H_9	135–135½	70	$C_{10}H_{24}N_4$	Found	59.80	12.05	27.88
					Calc.	59.95	12.08	27.97
h	*i*-C_4H_9	109–110	65	$C_{10}H_{24}N_4$	Found	60.34	12.24	28.22
					Calc.	59.95	12.08	27.97
j	$C_2H_4OC_2H_5$	93–101[b]	20	$C_{10}H_{24}N_4O_2$	Found	51.65	10.25	24.02
					Calc.	51.70	10.41	24.12
l	C_6H_{13}	128½–130	45	$C_{14}H_{32}N_4$	Found	65.60	12.62	21.50
					Calc.	65.57	12.58	21.85
m	C_8H_{17}	125–127	70	$C_{18}H_{40}N_4$	Found	69.30	12.82	17.98
					Calc.	69.17	12.90	17.93
n	$C_6H_5CH_2$	165–167[c]	90	$C_{16}H_{20}N_4$	Found	71.65	7.80	20.72
					Calc.	71.61	7.51	20.88
o	$C_6H_5CH_2CH_2$	151–153[d]	40	$C_{18}H_{24}N_4$	Found	73.08	8.20	18.73
					Calc.	72.94	8.16	18.90
p	$C_6H_5CH(CH_3)$	102–107[b]	–[e]	$C_{18}H_{24}N_4$	Found	72.84	8.22	18.98
					Calc.	72.94	8.16	18.90
q	$C_6H_5CH_2CH_2CH_2$	75–77½	25	$C_{20}H_{28}N_4$	Found	74.10	8.72	17.26
					Calc.	74.03	8.70	17.27
r	$C_6H_5CHCH_2(CH_3)$	137–138	45	$C_{20}H_{28}N_4$	Found	73.75	8.82	16.97
					Calc.	74.03	8.70	17.27

[a] Lit.[2] 121–123°C. [b] Possibly accompanied by dissociation. [c] Lit.[4] 158–160°C. [d] Lit.[5] 143–145°C. [e] Not determined.

partially solidify in the receiver as the dimers. The dimerization of these hydrazones has been monitored by NMR spectroscopy and is essentially complete in nonaqueous solvents within a few hours. Addition of water to the samples causes weak signals (< 10 %) corresponding to the methylene protons of the hydrazones to reappear, indicating that the dimerization process is reversible and to some degree solvent-dependent.

The reactions of aralkylhydrazines are sufficiently slow to allow the various steps of the reaction sequence to be observed separately. Addition of aqueous formaldehyde to benzylhydrazine in the presence of Na_2CO_3 produces II*n* as a clear viscous liquid. This can be vacuum-distilled without significant dimerization, and can be stored unchanged in a closed vessel at low temperatures for periods of up to a week. The dimerization process is, however, fairly rapid in

solution, especially in the presence of acid. Addition of acetate buffer (pH 5.5) in aqueous methanol to the liquid hydrazone causes almost instantaneous solidification. Likewise, addition of formaldehyde to benzylhydrazine in acetate buffer (pH 5.5) causes the hexahydro-1,2,4,5-tetrazine III*n* to precipitate immediately from the reaction mixture.

Formaldehyde alkylhydrazones with secondary alkyl groups (II*f*, II*i*, II*p*) are stable compounds that dimerize only slowly in solution or neat, an extreme example being II*p*, where the dimerization process is only 75 % complete after 24 months at +4°C. Hydrazones where the chain branching is once removed from the nitrogen atom (*e.g.* isobutyl, II*h*) also undergo dimerization at a slower rate than the corresponding hydrazones with unbranched alkyl groups and may be distilled without appreciable dimer formation. This stability is assumed to reflect steric hindrance in the transition state leading to the hexahydro-1,2,4,5-tetrazine.

The inclusion of unsaturation or of functional groups such as C–C double bonds or hydroxyl, alkoxyl, or cyano groups in the alkyl moieties (*cf.* Fig. 1) does not appreciably influence the reaction course, since hexahydro-1,2,4,5-tetrazines have been isolated in all cases in fair to good yields. It is of interest to note that tetrahydro-1,3,4-oxadiazine is not formed in detectable amounts in the condensation of formaldehyde with β-hydroxyethylhydrazine, in contrast to what has been reported for the reactions of other aldehydes with hydrazines of this kind.[8–12]

The condensation reactions have been carried out with aqueous formaldehyde or paraformaldehyde, neat or in aqueous or alcoholic solutions, at temperatures ranging from −10°C to reflux, with no significant variation in product distribution. Hexahydro-1,2,4,5-tetrazines are likewise formed in fair to good yields in reactions of alkylhydrazines with methylene bromide in the presence of Na_2CO_3. Formaldehyde hydrazones are assumed to be intermediates in this reaction also.

The earlier proposal by Ioffe [6] that the dimer of formaldehyde isopropylhydrazone should have an open-chain structure (deprotonated XIII) is believed to be erroneous in view of these results. The assignment was made on the basis of signals in the NMR spectrum corresponding to an equal number of $CH_2{=}N$ and $N{-}CH_2{-}N$ protons. These probably arise from an approx-

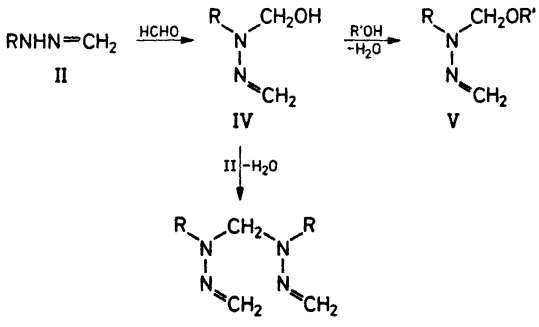


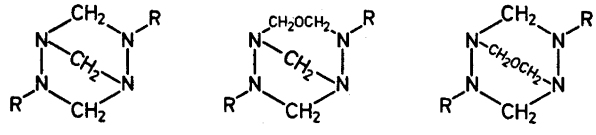
Fig. 2

imately 2:1 mixture of II*f* and III*f*; the τ-value quoted for the $N-CH_2-N$ protons (6.37) agrees well with the average value found in this study for the ring methylene protons of the 1,4-dialkylhexahydro-1,2,4,5-tetrazines (*cf.* Table 5). We have obtained similar misleading results from the NMR spectra of, *e.g.*, III*p*, which also dissociates very easily in solution to give the hydrazone II*p*.

Condensations with formaldehyde in excess produce formaldehyde *N*-alkyl-*N*-alkoxymethylhydrazones (V) when performed in alcoholic solution, probably *via* IV. Similar compounds have been isolated by Howard *et al.*[13] and by Dorn *et al.*[14] from acid-catalysed reactions of aromatic aldehydes with alkylhydrazines in methanol. The reaction of cyclohexylhydrazine and excess formaldehyde is an exception, producing 1,4-dicyclohexyl-1,2,4,5-tetraazabicyclo[2,2,1]heptane (VII*k*), as has also been reported by Schmitz and Ohme.[3] Their identification was based mainly on elemental analysis and infrared evidence. We have examined the NMR and mass spectra of this compound, and found excellent agreement with the proposed structure. Bicyclic compounds of this nature have been observed by Schmitz and Ohme[15] and by Karabatsos and Taller[16] to arise from condensations of phenylhydrazine with excess formaldehyde; their formation appears to be quite general for arylhydrazines.[17,18] We have, however, not found definitive evidence for the formation of VII in reactions of other alkylhydrazines with formaldehyde. Recently, Nelsen and Hintz[19] reported that compounds of this kind may be formed in reactions of 1,4-dialkylhexahydro-1,2,4,5-tetrazines with formaldehyde, but experimental conditions were not given.

Reactions with excess formaldehyde carried out in aqueous solutions give rise to complicated reaction mixtures, apparently arising from condensation in a variety of molar ratios. In a few instances, 3:2 condensation products, methylene-*bis*-alkylhydrazones of formaldehyde (VI), have been isolated in agreement with the report by Schmitz and Ohme.[3] Rabjohn and Sloan[20] have shown that condensations of methylhydrazine with aliphatic aldehydes also lead to compounds of this nature. We have found that reactions of other alkylhydrazines with acetaldehyde proceed in a similar manner.[21]

A 4:2 condensation product has been isolated from the reaction of methylhydrazine with formaldehyde. The structure suggested earlier[3] for this compound (IX) is probably incorrect, since NMR spectra obtained at several temperatures indicate that the two methyl groups are situated permanently in magnetically different positions. A possible structure is VIII. Johns *et al.*[18] have shown that the reactions of phenylhydrazine and *p*-nitrophenylhydrazine with excess formaldehyde also produce compounds similar to VIII and IX.



VII VIII IX

Fig. 3

DISCUSSION

Dorn and Dilcher [4] have suggested that the formation of hexahydro-1,2,4,5-tetrazines by condensation of aliphatic hydrazines with formaldehyde occurs *via* azomethine imines (X or XI), which were assumed to undergo 1,3-dipolar cyclodimerization.

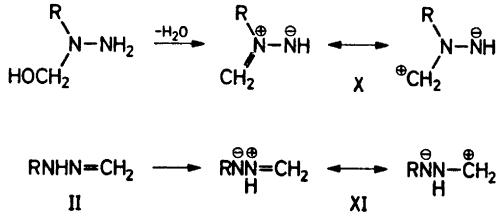


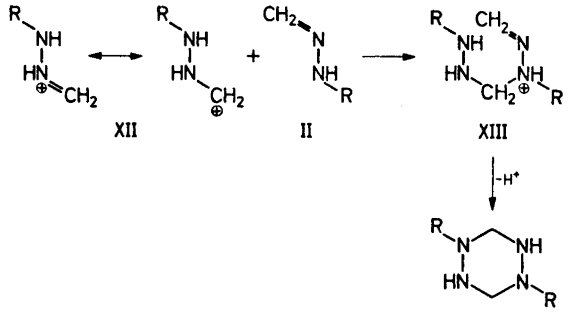
Fig. 4

Similar 1,3-dipolar species have been suggested by Grashey and coworkers [22] to be intermediates in the formation of 3,6-diarylhexahydro-1,2,4,5-tetrazines from aromatic aldehydes and 1,2-dialkylhydrazines, and by Zinner and collaborators [23] in the condensations of di- and trisubstituted hydrazines with aldehydes. However, Zwanenburg *et al.*,[24] have argued that the formation of 1,3-dipolar intermediates will be unfavourable in purely aliphatic systems of this kind. The evidence presented here strongly suggests that 1,3-dipolar intermediates are not important in the formation of 1,4-dialkylhexahydro-1,2,4,5-tetrazines. It should also be noted that a concerted dimerization of 1,3-dipolar species such as these would be a disallowed reaction under the Woodward-Hoffman rules.

The formation of species such as X would require formaldehyde to add to the substituted nitrogen atom of the hydrazine, with subsequent elimination of water. The polarographic evidence presented by Dorn and Dilcher [4] appears, however, to establish that the attack takes place at the unsubstituted nitrogen atom. Possible 1,3-dipolar species involved in the dimerization process will consequently be of structure XI. This molecule is a tautomer of the hydrazone II, but the equilibrium concentration of XI will probably be exceedingly small, which then requires that the subsequent dimerization should occur very rapidly. This, in turn, demands that XI be very reactive, but attempts to "trap it" have proved unsuccessful. It would be expected to add to the CN double bond of formaldehyde hydrazones, forming *N*-aminotriazolidines,[25] but these have not been observed to be formed in the reactions examined, nor were they observed by Schmitz [26] in condensations of formaldehyde with mixtures of 1,1- and 1,2-dialkylhydrazines. Furthermore, the condensations of butyl- and benzylhydrazine with formaldehyde are unaffected by added dipolarophiles such as diphenylacetylene or norbornene, and no adducts are observed. 1,3-Dipolar cycloadditions are usually reversible, but 1,4-dialkylhexahydro-1,2,4,5-tetrazines are not observed to react with dipolarophiles at elevated temperatures (*e.g.* reflux in xylene for 24 h). Similar

results have been reported by Oppolzer,[27] who has shown that 1,3-dipolar species are not present in significant amounts in the formation of 1,2,4,5-tetraalkylhexahydro-1,2,4,5-tetrazines from formaldehyde, in contrast to what was observed [27] in the reactions of 1-acyl-2-alkylhydrazines and 1-alkyl-2-arylhydrazines with formaldehyde.

The catalytic effect of acid on the dimerization of the formaldehyde hydrazones described above indicates that a protonated hydrazone (XII) is involved in the dimer formation. Addition of XII to the hydrazone produces XIII, which by deprotonation would yield the open-chain dimer claimed by Ioffe [6] to be formed from formaldehyde isopropylhydrazone. Intramolecular addition in XIII across the CN double bond produces the hexahydro-1,2,4,5-tetrazine.



XII II XIII III

Fig. 5

Skorianetz and Kováts [28] have found that the dimerization of acetaldehyde hydrazone also is subject to acid catalysis; they suggest a mechanism of dimerization similar to ours. The acid-catalyzed reductive dimerization of formaldehyde dialkylhydrazones has likewise been suggested to occur *via* protonated hydrazone intermediates.[29,30]

CHEMICAL PROPERTIES

The alkylhydrazine derivatives of formaldehyde described in the present study are all hydrolyzed rapidly by aqueous mineral acid with regeneration of the starting materials. The (alkoxyalkyl)alkylhydrazones, V, and methylenebis(alkylhydrazones), VI, should be kept in closed vessels, since even atmospheric moisture causes partial hydrolysis with liberation of formaldehyde, which in some cases recondenses to give other products. The formaldehyde hydrazones, II, are quite stable compounds but for the dimerization reactions described above. Compounds II, V, and VI are mostly colourless liquids that rapidly acquire a slight yellow tint upon contact with air, probably due to oxidation.[28]

1,4-Dialkylhexahydro-1,2,4,5-tetrazines are likewise stable compounds, though the lower members of the series examined are somewhat sensitive to hydrolysis and oxidation. They may form yellow, oily substances upon

prolonged standing in open vessels and should be stored at low temperatures, preferably under nitrogen.

1,4-Dialkylhexahydro-1,2,4,5-tetrazines dissociate slowly to formaldehyde alkylhydrazones upon heating. They undergo reactions typical of substituted hydrazines, and have been characterized as diacyl derivatives (XIV) by the action of acetic or propionic anhydride (*cf.* Table 3) and as bis-thiosemicarbazides (XV) by addition of isothiocyanates (*cf.* Table 4).

Table 2. Formaldehyde alkylhydrazones (II).

	Alkyl	B.p. (°C/mmHg)	Yield (%)	Formula	Analyses (C, H, N)			
h	i-C_4H_9	35 – 38/12	75	$C_5H_{12}N_2$	Found	60.21	11.91	27.69
					Calc.	59.95	12.08	27.97
i	*sec*-C_4H_9	42 – 45/12	55	$C_5H_{12}N_2$	Found	60.21	11.89	27.89
					Calc.	59.95	12.08	27.97
m	C_8H_{17}	70 – 74/0.5	[a]		Found [a]			
					Calc.			
n	$CH_2C_6H_5$	53 – 56/0.5	40	$C_8H_{10}N_2$	Found	71.65	7.54	21.13
					Calc.	71.61	7.51	20.86
p	CHC_6H_5 | CH_3	*ca.* 60/0.4	45	$C_9H_{12}N_2$	Found	73.50	8.37	18.02
					Calc.	72.94	8.16	18.90
q	$CH_2CH_2CH_2C_6H_5$	80 – 85/0.5	45	$C_{10}H_{14}N_2$	Found	74.25	8.68	16.75
					Calc.	74.03	8.70	17.27

[a] Dimerizes; *cf.* Table 1 for yield and analysis of dimer.

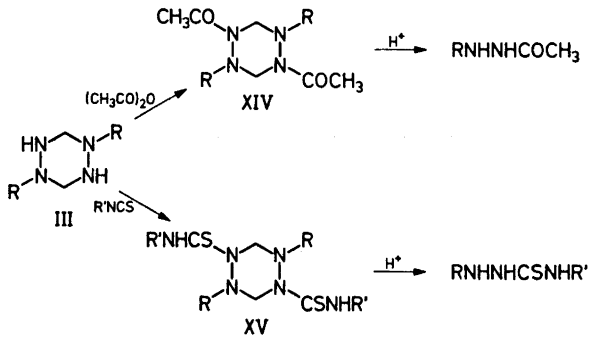


Fig. 6

These derivatives are thermally very stable, for they may be recovered unchanged in more than 80 % yield after 4 h reflux in inert solvents at 200°C. Hydrolysis in dilute mineral acids proceeds only slowly and takes place at the aminal bonds (ring cleavage) with formation of formaldehyde and hydrazides or 1,4-disubstituted thiosemicarbazides.

Table 3. 1,4-Dialkyl-2,5-diacylhexahydro-1,2,4,5-tetrazines (XIV).

	Alkyl	Acyl	M.p.	Yield %	Formula	Analyses (C, H, N)			
b	C_2H_5	CH_3CO	169–171	55	$C_{10}H_{20}N_4O_2$	Found	52.37	8.82	24.46
						Calc.	52.61	8.83	24.54
d	C_2H_4CN	CH_3CO	286–289	75	$C_{12}H_{18}N_6O_2$	Found	51.62	6.54	30.04
						Calc.	51.78	6.52	30.20
g	$CH_2CH=CH_2$	CH_3CO	184–185	95	$C_{12}H_{20}N_4O_2$	Found	57.20	8.08	22.15
						Calc.	57.10	7.99	22.22
j	C_4H_9	CH_3CO	103–105	60	$C_{14}H_{28}N_4O_2$	Found	59.10	9.96	19.64
						Calc.	59.12	9.92	19.70
j[1]	C_4H_9	C_2H_5CO	83–85	65	$C_{16}H_{32}N_4O_2$	Found	61.62	10.32	18.09
						Calc.	61.50	10.32	17.93
i	i-C_4H_9	CH_3CO	139–140	40	$C_{14}H_{28}N_4O_2$	Found	59.25	10.02	19.69
						Calc.	59.12	9.92	19.70
k	$C_2H_4OOCCH_3$	CH_3CO	164–168	80	$C_{14}H_{24}N_4O_6$	Found	48.88	7.32	16.28
						Calc.	48.83	7.03	16.27
	$C_2H_4OC_2H_5$	CH_3CO	128–131	85	$C_{14}H_{28}N_4O_4$	Found	53.20	8.96	17.42
						Calc.	53.14	8.92	17.71
	C_6H_{13}	CH_3CO	91–93	70	$C_{18}H_{36}N_4O_2$	Found	63.50	10.65	16.44
						Calc.	63.49	10.65	16.46
n	C_8H_{17}	CH_3CO	97–99	70	$C_{22}H_{44}N_4O_2$	Found	66.35	11.07	14.05
						Calc.	66.62	11.18	14.13
a	$C_6H_5CH_2$	CH_3CO	221–222[a]	95	$C_{20}H_{24}N_4O_2$	Found	68.38	6.92	15.92
						Calc.	68.16	6.86	15.90
l	$C_6H_5CH_2$	C_2H_5CO	207–211	65	$C_{22}H_{28}N_4O_2$	Found	69.20	7.61	14.48
						Calc.	69.44	7.42	14.73
	$C_6H_5CH_2CH_2$	CH_3CO	152–154	45	$C_{22}H_{28}N_4O_2$	Found	69.21	7.45	14.78
						Calc.	69.44	7.42	14.73
	$C_6H_5CH(CH_3)$	CH_3CO	267–268[b]	45	$C_{22}H_{28}N_4O_2$	Found	69.50	7.47	14.68
						Calc.	69.44	7.42	14.73
	$C_6H_5CH_2CH_2CH_2$	CH_3CO	110½–111½	50	$C_{24}H_{32}N_4O_2$	Found	70.40	7.84	13.62
						Calc.	70.56	7.90	13.72
	$C_6H_5CHCH_2(CH_3)$	CH_3CO	160–162	60	$C_{24}H_{32}N_4O_2$	Found	70.40	7.94	13.67
						Calc.	70.56	7.90	13.72

[a] Lit.[4] 222–223°C. [b] With concurrent sublimation.

SPECTROSCOPIC PROPERTIES

Infrared and ^1H nuclear magnetic resonance (NMR) spectra of all compounds described have been recorded and found to be in agreement with the proposed structures. The mass spectra of the 1,4-dialkylhexahydro-1,2,4,5-tetrazines and their acyl derivatives have been published elsewhere.[31]

The NMR spectra of 1,4-dialkylhexahydro-1,2,4,5-tetrazines formed in the condensation reactions described above confirm that these compounds are all centrosymmetrically substituted. The alkyl substituents give rise to one set of lines, and the ring methylene protons give rise to a broad singlet at τ 6.37 ± 0.10 (*cf.* Table 5), which splits upon cooling to give a multiplet. This becomes

Table 4. 1,4-Dialkyl-2,5-bis(thiocarbamoyl)-1,2,4,5-tetrazines (XV).

	R	R¹	M.p.[a]	Yield %	Formula	Analyses (C, H, N, S)				
b	C_2H_5	CH_3NHCS	225–226	65	$C_{10}H_{22}N_6S_2$	Found	41.57	7.79	29.15	22.17
						Calc.	41.37	7.64	28.95	22.04
c	C_2H_4OH	CH_3NHCS	247–248½	75	$C_{10}H_{22}N_6O_2S_2$	Found	37.55	6.97	26.05	19.98
						Calc.	37.25	6.88	26.06	19.89
e	$CH_2CH=CH_2$	CH_3NHCS	195–210[b]	85	$C_{12}H_{22}N_6S_2$	Found	45.80	7.06	26.65	20.13
						Calc.	45.85	7.05	26.74	20.36
g	C_4H_9	CH_3NHCS	178–180	95	$C_{14}H_{30}N_6S_2$	Found	48.75	8.76	24.48	18.75
						Calc.	48.54	8.73	24.26	18.47
*g*¹	C_4H_9	C_6H_5NHCS	215–217	95	$C_{24}N_{34}N_6S_2$	Found	61.10	7.22	17.81	13.79
						Calc.	61.24	7.28	17.85	13.62
h	i-C_4H_9	CH_3NHCS	255–257	40	$C_{14}H_{30}N_6S_2$	Found	48.64	8.71	24.12	18.47
						Calc.	48.54	8.73	24.26	18.47
j	$C_2H_4OC_2H_5$	CH_3NHCS	200–203[b]	80	$C_{14}H_{30}N_6O_2S_2$	Found	44.49	8.11	22.13	–[c]
						Calc.	44.43	7.99	22.21	–
n	$C_6H_5CH_2$	CH_3NHCS	291–292[b]	80	$C_{20}H_{26}N_6S_2$	Found	57.90	6.47	20.20	15.71
						Calc.	57.96	6.32	20.28	15.44
o	$C_6H_5CH_2CH_2$	CH_3NHCS	261–263	20	$C_{22}H_{30}N_6S_2$	Found	59.59	6.85	18.70	14.56
						Calc.	59.71	6.83	18.99	14.46

[a] Several compounds give off liquid before melting; the figure listed is the apparent m.p. of the main portion. [b] Strongly dependent upon rate of heating. [c] Analytical figures for S not reproducible.

Table 5. Chemical shifts of ring methylene protons in 1,4-dialkylhexahydro-1,2,4,5-tetrazines (III).

Alkyl	Chemical shift[c]	Solvent	Coalescence[e] temp., °C
CH_3[a]	6.37	$CDCl_3$	10[f,g]
–[a]	6.57	CCl_4	–
C_2H_5	6.35	$CDCl_3$	–
C_2H_4OH	6.44	DMSO-d_6	–[h]
C_2H_4CN[b]	6.30	$CDCl_3$	–[i]
$CH_2CH=CH_2$	6.35	$CDCl_3$	20[f]
C_4H_9	6.38	$CDCl_3$	25[f]
i-C_4H_9	6.45	$CDCl_3$	15[f]
$C_2H_4OC_2H_5$	6.27	$CDCl_3$	–
C_6H_{13}	6.38	$CDCl_3$	–[h]
C_8H_{17}	6.39	$CDCl_3$	–
$CH_2C_6H_5$	6.32	$CDCl_3$	15[f]
$C_2H_4C_6H_5$	6.30	$CDCl_3$	10[f]
$CH(CH_3)C_6H_5$	6.42	$CDCl_3$	–
$C_3H_6C_6H_5$	6.40	$CDCl_3$	15[f]
$CH_2CH(CH_3)C_6H_5$	6.40[d] 6.52[d]	$CDCl_3$	–

[a] Taken from Ref. 1. [b] The chemical shifts of all exocyclic protons coincide. [c] τ-values. [d] AB-quartet at 40°C, J_{HH} = 11 Hz; doublet centers given. [e] Approximate, ±5°C. [f] J_{HH} = 11 Hz. [g] *Cf.* Ref. 31. [h] Above 0°C. [i] Below 0°C.

one AB pair of doublets when the amino hydrogen atoms are replaced by deuterium, showing that the two CH_2-groups are magnetically equivalent. Also, the ring methylene protons of the acyl and thiocarbamoyl derivatives (XIV and XV) give rise to only one AB system, and the acyl (thioacyl) groups appear as one set of lines at all temperatures examined.

Dorn and Dilcher [4] have previously employed similar NMR data for acyl derivatives of III*a* and III*n* to show the centrosymmetric nature of these compounds; the structure of III*a* has since been conclusively confirmed by an X-ray examination.[32]

Table 6. Chemical shift of ring methylene protons in 1,4-dialkyl-2,5-diacylhexahydro-1,2,4,5-tetrazines (XIV).

Alkyl	Acyl	Chemical shift [h]		J_{HH}(Hz)	Solvent	Temp. °C
CH_3	CH_3CO	5.02	5.58	13½	$CDCl_3$	40
–	–	4.87	5.42	13½	$CDCl_3$	−50
–	–	5.22	5.53	13½	DMSO-d_6	40
–	–	5.32		–	DMSO-d_6	80
C_2H_5	CH_3CO	4.85	5.70	13½	$CDCl_3$	40
– [a]	–	4.80	5.60	13½	$CDCl_3$	−50
$CH_2CH=CH_2$	CH_3CO	4.88	5.77	13½	$CDCl_3$	40
C_4H_9 [a]	CH_3CO	4.94	5.77	13½	$CDCl_3$	40
C_4H_9 [a]	CH_3CH_2CO [g]	4.90	5.75	13½	$CDCl_3$	40
– [a]	– [g]	5.12	5.67	13½	DMSO-d_6	40
– [a]	– [g]	5.12	5.70	13½	DMSO-d_6	100
i-C_4H_9 [b,c]	CH_3CO	4.93	5.74	13½	$CDCl_3$	40
– [a,c]	–	5.17	5.62	13½	DMSO-d_6	40
– [a]	–	5.15	5.67	13½	DMSO-d_6	100
–	–	5.25 [i]	5.57 [j]	–	DMSO-d_6	120
–	–	5.42 [k]		–	DMSO-d_6	140
$C_2H_4OC_2H_5$ [d]	CH_3CO	4.90	5.72	13½	$CDCl_3$	40
$C_2H_4OOCCH_3$ [d]	CH_3CO	4.81	5.73	13½	$CDCl_3$	40
C_6H_{13} [a]	CH_3CO	4.95	5.78	13½	$CDCl_3$	40
C_8H_{17} [a]	CH_3CO	4.93	5.75	13½	$CDCl_3$	40
$CH_2C_6H_5$ [e]	CH_3CO	4.85	5.63	13½	$CDCl_3$	40
– [a]	–	4.79	5.56	13½	DMSO-d_6	40
$CH_2C_6H_5$ [f]	CH_3CH_2CO [g]	4.80	5.60	13½	$CDCl_3$	40
$C_2H_4C_6H_5$ [d]	CH_3CO	4.80	5.73	13½	$CDCl_3$	40
$CH(CH_3)C_6H_5$	CH_3CO	5.02	6.00	13½	$CDCl_3$	40
$C_3H_6C_6H_5$ [d]	CH_3CO	4.92	5.78	13½	$CDCl_3$	40
$CH_2CH(CH_3)C_6H_5$ [d]	CH_3CO	4.85	5.78 [i] 5.85	13½	$CDCl_3$	40
– [d]	–	5.04	5.62 [i] 5.74	13½	DMSO-d_6	40

[a] α-Methylene protons magnetically non-equivalent. [b] α-Methylene protons magnetically non-equivalent; ABC-system observed. [c] Methyl groups also magnetically non-equivalent. [d] α-Methylene protons appear as part of multiplet due also to other protons. [e] α-Methylene protons magnetically non-equivalent; AB-system observed with $\Delta\nu_{AB}=0.25$ ppm, $J_{AB}=12\frac{1}{2}$ Hz. [f] α-Methylene protons magnetically non-equivalent; AB-system observed with $\Delta\nu_{AB}=0.28$ ppm, $J_{AB}=12\frac{1}{2}$ Hz. [g] CH_2-protons magnetically non-equivalent. [h] AB pair of doublets; doublet centers given in τ-values, calculated according to $\delta_A-\delta_B=\sqrt{(\nu_1-\nu_4)(\nu_2-\nu_3)}$. [i] High-field doublet appears as pair of doublets, both given. [j] Two broad singlets. [k] Very broad singlet.

Table 7. Chemical shifts of ring methylene protons in 1,4-dialkyl-2,5-bis(thiocarbamoyl)-hexahydro-1,2,4,5-tetrazines (XV).

Alkyl	Thiocarbamoyl	Chemical shift		J_{HH}(Hz)	Solvent
CH_3 [a]	CH_3NHCS	4.04	5.42	14	$CDCl_3$
CH_3 [a]	t-C_4H_9NHCS	3.76	5.52	13½	$CDCl_3$
C_2H_5 [b]	CH_3NHCS	3.92	5.60	13½	$CDCl_3$
C_2H_4OH [c]	CH_3NHCS	4.05	5.42	14	DMSO-d_6
$CH_2CH=CH_2$	CH_3NHCS	4.15	5.50	13½	DMSO-d_6
C_4H_9 [b]	CH_3NHCS	3.96	5.60	13½	$CDCl_3$
C_4H_9 [b]	C_6H_5NHCS	3.70	5.43	13½	$CDCl_3$
i-C_4H_9 [d,e]	CH_3NHCS	3.93	5.55	13½	$CDCl_3$
$C_2H_4OC_2H_5$ [c]	CH_3NHCS	3.95	5.62	13½	$CDCl_3$
$CH_2C_6H_5$ [f]	CH_3NHCS	3.71	5.38	13½	DMSO-d_6
$C_2H_4C_6H_5$ [c]	CH_3NHCS	3.74	5.61	13½	DMSO-d_6

[a] Taken from Ref. 1. [b] α-Methylene protons magnetically non-equivalent; pattern and coupling constants obscured by overlapping CH_3NH signal. [c] α-Methylene protons resonance lines appear as part of multiplet due to other protons. [d] α-Methylene protons magnetically non-equivalent; ABC-system observed. [e] Methyl groups magnetically non-equivalent. [f] α-Methylene protons magnetically non-equivalent; AB-system observed with $\Delta\nu_{AB}=0.39$ ppm, $J_{AB}=12\frac{1}{2}$ Hz.

The appearance of an AB pair of doublets in the NMR spectra of III upon cooling must be due to the onset either of slow ring inversion or slow nitrogen inversion. Anderson and Roberts [33] have shown that in 1,2,4,5-tetramethyl-hexahydro-1,2,4,5-tetrazine the barrier to nitrogen-inversion, though here unobservable by the NMR method, is at least as high as the observable barrier to ring inversion. By analogy we assume that the AB systems observed in the spectra of III are due to a relatively high barrier to inversion at the nitrogen atoms. The approximate coalescence temperatures have been determined for a number of compounds and are usually slightly below room temperature (*cf.* Table 5). In spectra of several of the compounds below the coalescence temperature the protons of the α-methylene groups of the alkyl substituents also are magnetically nonequivalent. This effect is another consequence of slow inversion; the resulting multiplets coalesce at approximately the same temperature as the AB-system of the endocyclic methylene protons.

Introduction of acyl or thiocarbamoyl substituents causes a considerably increase in the difference in chemical shift between the axial and equatorial protons of the ring methylene groups (*cf.* Tables 6 and 7), and raises the coalescence temperatures of the AB-system. In general, introduction of *N*-acyl substituents in saturated nitrogen heterocycles of cyclohexane-like structure such as these is expected to lower the barrier to ring inversion by making the nitrogen atom nearly planar.[34] At the same time the acyl (or thioacyl) groups will exert an electron-withdrawing effect, which will increase the electronegativity of the amide nitrogen atoms and in consequence raise the barrier to inversion at the adjacent nitrogen. The increase in energy barrier to inversion observed in XIV and XV relative to III is therefore consistent with the assumption that restricted inversion of the nitrogen atoms is responsible

for the magnetic non-equivalence of the ring methylene protons in III as well as in XIV and XV. The coalescence temperatures of the AB-systems due to the endocyclic CH_2-groups of XIV and XV are very dependent upon the nature of the alkyl substituents. The two doublets in the spectrum of the diacetyl derivative of III*a* collapse to give a singlet between 60 and 80°C, whereas the non-equivalence for most of the other compounds persists above 120°C. Magnetic non-equivalence is also observed for exocyclic groups; the α-methylene protons of the alkyl substituents generally give rise to multiplets (*cf.* Tables 6 and 7), and also groups further removed from the ring may exhibit nonequivalence, *e.g.* the CH_2-groups of propionyl substituents and the CH_3-groups in derivatives of III*h*. These may, however, collapse to identical peaks at temperatures lower than those required for coalescence of the AB-system due to the ring methylene groups.

The preferred conformation of the acyl and thiocarbamoyl derivatives is belived to be as shown in Fig. 7 for the diacetyl derivative of III*a*, with the

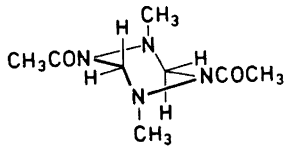


Fig. 7

alkyl substituents axial. This conformation will minimize the steric repulsion of the alkyl and acyl substituents in the same manner as has been found for *N*-acetyl piperidines, in which alkyl substituents at the 2-carbon atoms have been shown to be axial.[35] Simultaneously, this conformation will reduce the interaction of lone-pairs on neighbouring nitrogen atoms.

It is evident from this model that the equatorial proton of the ring CH_2-group will be much more strongly influenced by the anisotropy of the neighbouring carbonyl group than the axial proton. This is borne out by the difference between the chemical shifts of H_a and H_e, which in XIV is 0.8 ppm (average value for $CDCl_3$ solution, slightly less in DMSO-d_6). The corresponding difference in XV is 1.8 ppm, in good agreement with the results obtained by Walter and coworkers [36] for the relative anisotropy of C=O and C=S groups. The average chemical shift of the axial protons in XIV is nearly the same as in XV (τ 5.71 ± 0.15 and 5.52 ± 0.11), confirming that these protons are not subjected very much to the deshielding effects of the acyl or thioacyl groups. Similar values have been found [1] for the axial protons of the ring methylene groups in acyl and thiocarbamoyl 1,4-diphenylhexahydro-1,2,4,5-tetrazines (τ 5.60 ± 0.16), which indicates that the magnetic environment of these protons in acylated hexahydro-1,2,4,5-tetrazines is not affected very much by the substituents on the 1 and 4 nitrogen atoms.

EXPERIMENTAL

Elemental analyses were carried out in the microanalytical department of this laboratory. The NMR spectra were recorded on a Varian A-60A spectrometer, and the mass spectra on an AEI MS-902 mass spectrometer.

Starting materials. The alkylhydrazines employed in the present study were commercial products where available (methylhydrazine, β-hydroxyethylhydrazine, ethylhydrazine oxalate, butylhydrazine oxalate, cyclohexylhydrazine hydrogenoxalate, benzylhydrazine oxalate) or prepared by modified versions of reported procedurs.[37,38] The formaldehyde, unless otherwise noted, was used as a *ca.* 40 % aqueous solution, the formaldehyde content of which was determined before use by titration according to Walker.[39]

Reaction between equimolar amounts of alkylhydrazine and formaldehyde

The 1,4-dialkylhexahydro-1,2,4,5-tetrazines and formaldehyde alkylhydrazones described were prepared by one or more of the procedures *a* – *e*. Physical constants for these compounds are found in Tables 1 and 2; the yields given were not optimized. The identities of the reaction products were ascertained by mass spectrometry,[31] NMR spectroscopy, and elemental analyses.

a. Formaldehyde (0.1 mol) was added slowly with stirring to the alkylhydrazine (0.1 mol), care being taken to keep the temperature of the reaction mixture below 5°C. After 2 h, Na_2CO_3 (2 g) was added and the mixture extracted with 3 × 25 ml chloroform. The organic phase was dried over Na_2SO_4 and the solvent removed *in vacuo*. The residue, which was an oil (formaldehyde alkylhydrazone) or a solid (1,4-dialkylhexahydro-1,2,4,5-tetrazine), was purified by vacuum distillation or recrystallization.

b. Methylene bromide (0.1 mol) was added dropwise to a stirred suspension of Na_2CO_3 (0.1 mol) in alkylhydrazine (0.1 mol). After 8 h the reaction mixture was extracted several times with warm diethyl ether, which was subsequently evaporated to dryness, leaving the solid hexahydrotetrazine.

c. Paraformaldehyde (0.1 mol) was added slowly to a stirred and cooled solution of alkylhydrazine (0.1 mol) in methanol (10 ml). After 2 h at room temperature the reaction mixture was warmed gently for 15 min and Na_2CO_3 (2 g) was added. The solution was extracted with 3 × 25 ml chloroform and worked up as in *a*.

d. To a stirred and cooled suspension of alkylhydrazine oxalate (0.1 mol) and NaOH (0.2 mol) in methanol (100 ml) was added formaldehyde (0.1 mol). The mixture was left overnight, decanted from solid material and the solvent evaporated *in vacuo*; the residue was purified as given under *a*.

e. Formaldehyde (0.1 mol) was added dropwise to a refluxing solution of alkylhydrazine (0.1 mol) in methanol or ethanol (50 ml). After 1 h the reaction mixture was cooled to −30°C, and the precipitated material (III) collected by filtration. The mother liquor was evaporated to half the original volume and extracted with chloroform after addition of Na_2CO_3 (2 g). The organic phase was then worked up as given under *a* to give a second crop of III.

1,4-Dimethylhexahydro-1,2,4,5-tetrazine (III*a*) was prepared as described in the literature and by procedure *c* in 40 % yield. It is best purified by vacuum sublimation (60°C/12 mmHg).

1,4-Diethylhexahydro-1,2,4,5-tetrazine (III*b*) was prepared by procedure *d* and recrystallized from diethyl ether.

1,4-Bis(β-hydroxyethyl)hexahydro-1,2,4,5-tetrazine (III*c*) was prepared by procedure *e* and recrystallized from 2-propanol.

1,4-Bis(β-cyanoethyl)hexahydro-1,2,4,5-tetrazine (III*d*) was prepared by procedure *a*; the precipitated crystals were sufficiently pure after washing with ice cold methanol and diethyl ether.

1,4-Diallylhexahydro-1,2,4,5-tetrazine (III*e*) was prepared according to procedure *a* and recrystallized from diethyl ether. The NMR spectrum of a chloroform extract shows that this contains II*e* as well as III*e*. The relative concentration of these was not determined due to interference from overlapping peaks.

1,4-Dibutylhexahydro-1,2,4,5-tetrazine (III*g*) was prepared by procedure *a* (yields 45–70 %), *b* (yield 40 %), *c* (yield 55 %), *d* (yield 25 %), and *e* (yield 60 %). Preparation according to procedure *e* but run at room temperature gave similar results, as did preparation with 1 ml 4 M aqueous HCl added (procedure *e*). NMR spectra of extracts of the reaction mixture (procedure *a*) after 2 h showed II*g* and III*g* to be present in a ratio of *ca.* 1:3.

Formaldehyde isobutylhydrazone (II*h*) and *1,4-diisobutylhexahydro-1,2,4,5-tetrazine* (III*h*). Procedure *a* was followed, and the reaction mixture was extracted with 4 × 25 ml ether. Removal of the ether and distillation gave II*h* in 75 % yield. This dimerized with formation of III*h* upon standing in a closed vessel at room temperature for a week. Yield 65 % (based on isobutylhydrazine), recrystallized from hexane.

Formaldehyde sec-*butylhydrazone* (II*i*) was prepared as was II*h*, in 55 % yield. Dimerization was not observed but may take place under suitable conditions.

1,4-Bis(β-ethoxyethyl)hexahydro-1,2,4,5-tetrazine (III*j*) was prepared according to procedure *a* and recrystallized from ether.

1,4-Dihexylhexahydro-1,2,4,5-tetrazine (III*l*) was prepared according to procedure *a*. Extraction with chloroform was unnecessary, since III*l* precipitated from the reaction mixture after two days at 4°C. Recrystallized from ether.

Formaldehyde octylhydrazone (II*m*) *and 1,4-dioctylhexahydro-1,2,4,5-tetrazine* (III*m*). Procedure *a* was employed, with methanol (5 ml) added to the reaction mixture to break the emulsion formed. Distillation of the residue after removal of chloroform afforded II*m*, which partly solidified in the receiver as III*m*. NMR spectra of the distillate immediately after distillation showed the ratio II*m*:III*m* to be 1:2; after 2 h at room temperature the ratio was found to be 1:7. III*m* was recrystallized from hexane.

Formaldehyde benzylhydrazone (II*n*) *and 1,4-dibenzylhexahydro-1,2,4,5-tetrazine* (III*n*). Reaction of benzylhydrazine with formaldehyde according to procedure *a* yielded an oil from which crystalline material slowly deposited at room temperature (III*n* in 25 % yield). The liquid was filtered and distilled to give II*n* in 40 % yield. This compound is fairly stable towards dimerization when kept at −30°C (no precipitation of III*n*; NMR spectra taken at frequent intervals showed only slight appearance of III*n* after a week).

Procedure *b*, *c*, and *d* afforded III*n* in yields of 10 %, 45 %, and 10 %, respectively.

An improved procedure for the preparation of III*n* based on the observation that the dimerization of formaldehyde alkylhydrazones is promoted by acid is given below. It is expected that similar procedures for the preparation of other water-insoluble hexahydro-1,2,4,5-tetrazines (C_4 and up) will lead to improved yields.

Benzylhydrazine (0.1 mol) was dissolved in methanol (20 ml) and added to 150 ml aqueous acetic acid/acetate buffer (pH = 5.5, 0.5 mol CH_3COOH per l). Formaldehyde (0.1 mol) was added slowly, with almost instantaneous precipitation of solid material. This was collected by filtration after an hour, dissolved in chloroform and dried over Na_2SO_4. The solvent was removed *in vacuo* and the solid residue was washed with cold ether to give III*n* in 90 % yield.

Acid catalyzed dimerization of II*n*. A methanolic solution of II*n* in methanol (1g in 2 ml) was added slowly to 5 ml aqueous acetic acid/acetate buffer (pH = 5.5), which caused immediate solidification (precipitation) of the organic material. The NMR-spectrum of the solid showed this to be III*n*. Similar addition of II*n* in methanol to water or 0.5 M NaCl was without effect, and the hydrazone was recovered almost quantitatively.

Preparation of III*n in the presence of dipolarophiles*. Benzylhydrazine (0.1 mol) and norbornene (0.1 mol) were dissolved in methanol (20 ml) and cooled to 0°C. Formaldehyde (0.1 mol) was then added slowly and the reaction mixture was left for 4 h, and extracted with chloroform. The solvent was removed *in vacuo* after drying over Na_2SO_4 and the residue taken up in ether. III*n* precipitated overnight at 4°C in 55 % yield.

Similar results were obtained with diphenylacetylene added instead of norbornene.

1,4-Bis(2-phenylethyl)hexahydro-1,2,4,5-tetrazine (III*o*) was prepared by procedure *a*; the reaction mixture was not extracted but left at 4°C for a week. The precipitated material (III*o*) was collected and recrystallized from 2-propanol. NMR spectra of CCl_4 extracts of the mother liquor showed the presence of II*o*, which was not isolated.

Formaldehyde (1-phenylethyl)hydrazone (II*p*) and *1,4-bis-(1-phenylethyl)hexahydro-1,2,4,5-tetrazine* (III*p*). Reaction of (1-phenylethyl)hydrazine with aqueous formaldehyde according to procedure *a* yielded a clear oil, which was distilled to give II*p* in 45 % yield.

NMR spectra of the reaction mixture and of the distillate did not show any III*p* to be present. After one year at 4°C no solid material had precipitated, while after two years nearly complete crystallization had occurred. NMR spectra of the solid showed this to consist of at least 75 % III*p* (the rest being unchanged II*p*). An exact determination of the degree of dimerization was rendered impossible by dissociation III*p*→2II*p* taking place in solution.

Formaldehyde (3-phenylpropyl)hydrazone (II*q*) and *1,4-bis-(3-phenylpropyl)-hexahydro-1,2,4,5-tetrazine* (III*q*). Formaldehyde and (3-phenylpropyl)hydrazine were reacted according to procedure *a*. The reaction mixture was extracted with ether. The extracts were dried over Na_2SO_4 and distilled to give II*q*. This dimerized within five days nearly completely (> 85 % on NMR) when left at 4°C; the resulting III*q* was recrystallized from hexane.

1,4-Bis(2-phenylpropyl)hexahydro-1,2,4,5-tetrazine (III*r*) was prepared according to procedure *a*. III*r* precipitated from the reaction mixture when kept at 4°C for four days. Recrystallized from hexane.

2,5-Diacyl-1,4-dialkylhexahydro-1,2,4,5-tetrazines (XIV*a*–*r*) were prepared by treating an ethereal solution of the appropriate 1,4-dialkylhexahydro-1,2,4,5-tetrazine with excess acetic anhydride and recrystallized from methanol or ethanol. Physical constants for these derivatives are listed in Table 3.

According to Dorn and Dilcher [4] XIV may also be prepared from the crude dialkylhexahydro-1,2,4,5-tetrazine without prior purification. We have found this to be generally true, even though the yields are lower and the purity of the diacylated derivative less satisfactory. In a few instances we have found acetylation with acetic anhydride of the mother liquors from the preparation of III (procedure *a*) to result in formation of isomers of the desired diacyl derivatives (XIV). The identity of these products is not yet clear.

Isomer of XIV*h*. The mother liquor from the preparation of III*h* (procedure *a*, reaction mixture not extracted with chloroform but left at 4°C for a week, when the precipitated III*h* was removed by filtration) was treated with excess acetic anhydride and a catalytic amount of pyridine. The precipitated material was removed after a day and recrystallized from methanol. M.p. 115–116°C. (Found: C 59.30; H 9.90; N 19.78. Calc. for $C_{14}H_{28}N_4O_2$: C 59.12; H 9.92; N 19.70.) The mass spectrum was quite similar to that of XIV*h*,[31] showing the molecular ion at *m/e* 284(4 %) and major fragment ions at *m/e* 241(23 %), *m/e* 143(100 %), *m/e* 142(33 %), *m/e* 141(17 %), *m/e* 113(72 %), *m/e* 99(48 %), *m/e* 87(23 %), *m/e* 86(17 %), *m/e* 85(10 %), *m/e* 84(28 %), *m/e* 57(60 %). The NMR-spectrum ($CDCl_3$) showed four broad peaks at τ 5.6, 5.9, 6.1, 6.3 (total 4H), and peaks at 7.1 (broad d, $J = 7$ Hz, 4H), 7.9 (s, 6H), 8.1–8.7 (m, 2H), 9.0 (d, $J = 6$ Hz, 6H), 9.1 (d, $J = 6$ Hz, 6H).

Isomer of XIV*c*. This compound was prepared in a similar manner. M.p. 133–134°C. (Found: C 48.81; H 7.28; N 16.36. Calc. for $C_{14}H_{24}N_4O_6$: C 48.83; H 7.03; N 16.27.) The NMR-spectrum ($CDCl_3$) showed peaks at τ 5.5–6.1 (broad, 6H), 6.4–6.8 (broad, 4H), 7.8 (s, 6H), 7.9 (s, 6H).

Isomer of XIV*n*. This compound was prepared in a similar manner. M.p. 180–181°C. (Found: C 68.15; H 7.04; N 15.97. Calc. for $C_{20}H_{24}N_4O_2$: C 68.16; H 6.86; N 15.98.) The NMR-spectrum ($CDCl_3$) showed peaks at τ 2.6 (s, 10H), 5.6, 5.8, 6.0 (three broad peaks, total 8H), 8.2 (broad s, 6H).

1,4-Dialkyl-2,5-bis(thiocarbamoyl)hexahydro-1,2,4,5-tetrazines (XV) were prepared by treating the appropriate 1,4-dialkylhexahydro-1,2,4,5-tetrazine in ether or pyridine with an excess of methyl or phenyl isothiocyanate and recrystallized from ethanol. Physical constants for these compounds are given in Table 4.

Thermal stability of XIV and XV. Benzonitrile solutions of the derivatives XIV*a*, *g*, and *n*, or XV*g* and *n* (0.5 g in 10 ml) were heated under reflux for 4 h. Cooling and removal of solvent left unchanged starting material in 80–90 % yield. Similar results were obtained in refluxing nitrobenzene and ethylene glycol.

Reaction between alkylhydrazines and excess formaldehyde

Formaldehyde N-*ethoxymethyl*-N-*methylhydrazone* (V, $R = CH_3$, $R' = C_2H_5$). Formaldehyde (0.3 mol) was added dropwise and with stirring to a solution of methylhydrazine

(0.1 mol) in ethanol (50 ml). After 1 h the reaction mixture was saturated with Na_2CO_3 and extracted with $CHCl_3$. The resulting solution was dried over Na_2SO_4 and distilled to give a clear liquid, b.p. 42–45°C/15 mmHg. (Found: C 51.68; H 10.27; N 23.16. Calc. for $C_5H_{12}N_2O$: C 51.70; H 10.41; N 24.12.) NMR spectrum ($CDCl_3$): τ 3.9 (d, $J=11$ Hz, 1H), 4.1 (d, $J=11$ Hz, 1 H), 5.3 (s, 2H), 6.6 (q, $J=7$ Hz, 2H), 7.2 (s, 3H), 8.9 (t, $J=7$ Hz, 3H).

Formaldehyde N-*methoxymethyl*-N-*benzylhydrazone* (V, $R=C_6H_5CH_2$, $R'=CH_3$) was prepared in a similar manner from formaldehyde (0.3 mol) and benzylhydrazine (0.1 mol) in methanol. B.p. 70–72°C/0.5 mmHg. (Found: C 67.54; H 8.11; N 15.44. Calc. for $C_{10}H_{14}N_2O$: C 67.39; H 7.92; N 15.72.) NMR spectrum ($CDCl_3$): τ 2.8 (s, 5H), 3.9 (d, $J=11$ Hz, 1H), 4.1 (d, $J=11$ Hz, 1H), 5.3 (s, 2 H), 5.6 (s, 2H), 6.8 (s, 3H).

Formaldehyde N-*ethoxymethyl*-N-*benzylhydrazone* (V, $R=C_6H_5CH_2$, $R'=C_2H_5$) was prepared from formaldehyde (0.3 mol) and benzylhydrazine (0.1 mol) in ethanol, as given for the methyl analog (above). B.p. 72–75°C/0.5 mmHg. (Found: C 68.59; H 8.60; N 14.47. Calc. for $C_{11}H_{16}N_2O$: C 68.72; H 8.39; N 14.57.) NMR spectrum ($CDCl_3$): τ 2.9 (s, 5H), 4.0 (d, $J=11$ Hz, 1H), 4.2 (d, $J=11$ Hz, 1H), 5.3 (s, 2H), 5.7 (s, 2H), 6.6 (q, $J=7$ Hz, 2H), 8.9 (t, $J=7$ Hz, 3H). In addition small peaks were observed corresponding to the methoxy analog (see above), which was formed from traces of methanol in the aqueous formaldehyde.

Formaldehyde N-*methoxymethyl*-N-*(2-phenylethyl)hydrazone* (V, $R=C_6H_5CH_2CH_2$, $R'=CH_3$) was formed from (2-phenylethyl)hydrazine (0.1 mol) and formaldehyde (0.3 mol) in methanol. B.p. 77–78°C/0.4 mmHg. (Found: C 69.02; H 8.40; N 14.04. Calc. for $C_{11}H_{16}N_2O$: C 68.72; H 8.39; N 14.57.) NMR spectrum ($CDCl_3$): τ 2.8 (s, 5H), 3.7 (d, $J=11$ Hz, 1H), 4.0 (d, $J=11$ Hz, 1H), 5.5 (s, 2H), 6.4–6.7 (m, 2H), 7.0–7.4 (m, 2H).

*Methylene bis(*N-*methyl*-N′-*methylenehydrazine)* (VI, $R=CH_3$). Methylhydrazine (0.1 mol) was mixed with solid paraformaldehyde (0.2 mol) without a solvent; the reaction mixture was kept at room temperature after the initial exothermic reaction for 10 h, and then made strongly basic with NaOH (pH = 11), saturated with NaCl and extracted several times with ether. The ethereal solution was dried over Na_2SO_4 and distilled. The fraction boiling 60–70°C/11 mmHg was taken and redistilled to produce a clear, slightly yellow liquid, b.p. 65–68°C/11 mmHg (lit.[3] 68–69°C/13 mmHg). (Found: C 46.52; H 9.36; N 43.57. Calc. for $C_5H_{12}N_4$: C 46.85; H 9.44; N 43.71.) NMR spectrum ($CDCl_3$): τ 4.0 (d, $J=11$ Hz, 2H), 4.1 (d, $J=11$ Hz, 2H), 5.3 (s, 2H), 7.3 (s, 6H.)

A higher boiling fraction was collected at 85–90°C/12 mmHg and redistilled to give a clear liquid, b.p. 95–97°C/16 mmHg (lit.[3] 79–80°C/13 mmHg). (Found: C 45.75; H 9.08; N 35.66. Calc. for $C_{16}H_{14}N_4O$: C 45.55; H 8.92; N 35.41.) The NMR spectrum ($CDCl_3$) showed a series of multiplets in the region τ 5.1–6.7 (total 8H), and two sharp singlets at τ 7.4 and 7.6 (each 3H). The latter do not coalesce upon heating to 100°C (in DMSO-d_6). These results are compatible with the structure *5,8-dimethyl-3-oxa-1,5,6,8-tetraazabicyclo[4,2,1]nonane*, (VIII, $R=CH_3$).

Reaction of benzylhydrazine and excess aqueous formaldehyde. Formaldehyde (0.15 mol) was added slowly with stirring and cooling to a mixture of benzylhydrazine (0.1 mol), acetic acid (0.11 mol), and sodium acetate (0.01 mol) in water (10 ml). During the addition III*n* separated as a white solid, which liquefied as more formaldehyde was added. The reaction mixture was left overnight, extracted with chloroform, dried over Na_2SO_4, and evaporated *in vacuo*. The remainder was then taken up in ether, filtered from solid III*n*, and, after removal of solvent, distilled at 190–210°C/2 mmHg. The product became semi-solid when kept at 4°C. (Found: C 72.82; H 7.33; N 19.70. Calc. for $C_{17}H_{20}N_4$: C 72.83; H 7.19; N 19.98.) The NMR spectrum ($CDCl_3$) suggests the product to be a mixture of *methylene bis(*N-*benzyl*-N′-*methylenehydrazine)*, (VI, $R=C_6H_5CH_2$) and *1,4-dibenzyl-1,2,4,5-tetraazabicyclo[2,2,1]heptane*, (VII, $R=C_6H_5CH_2$).

1,4-Dicyclohexyl-1,2,4,5-tetraazabicyclo[2,2,1]heptane, (VII, R = cyclo-C_6H_{11}). Cyclohexyl hydrogenoxalate (0.1 mol) was mixed with formaldehyde (0.16 mol) in 10 ml 50 % methanol. The stirred reaction mixture became nearly homogeneous over 5 min, when a slightly yellow solid precipitated. The reaction mixture was made slightly basic with Na_2CO_3 and then extracted with chloroform. Evaporation of the solvent after drying over Na_2SO_4 left a colorless product, m.p. 138–139°C in 70 % yield. (Found: C 68.20; H 10.65; N 21.13. Calc. for $C_{15}H_{28}N_4$: C 68.13; H 10.67; N 21.19.) NMR spectrum ($CDCl_3$):

τ 6.4 (d, $J = 7.5$ Hz, 2H), 6.7 (s, 2H), 6.8 (d, $J = 7.5$ Hz, 2H), 7.5 – 9.2 (m, 22H). Mass spectrum: *m/e* 264 (3 %, M^+), *m/e* 153 (11 %), *m/e* 139 (92 %), *m/e* 126 (27 %), *m/e* 97 (11 %), *m/e* 83 (100 %), *m/e* 70 (25 %), *m/e* 69 (13 %), *m/e* 68 (25 %), *m/e* 67 (31 %).

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