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

I. The Preparation and Characterization of Methyl- and Phenyl-substituted Hexahydro-1,2,4,5-tetrazines

KAI ARNE JENSEN and STEEN HAMMERUM

Chemical Laboratory II (General and Organic Chemistry), The H. C. Ørsted Institute, University of Copenhagen, Universitetsparken 5, DK-2100 Copenhagen, Denmark

Some new methods for preparation of methyl- and phenyl-substituted hexahydro-1,2,4,5-tetrazines are described, and these are compared with known methods. The reactions of 1,4-di-substituted hexahydro-1,2,4,5-tetrazines with acyl halides, anhydrides, isocyanates, and isothiocyanates have been shown to lead to acyl, carbamoyl, and thiocarbamoyl derivatives, respectively. On acid hydrolysis the latter form thiosemicarbazides or thiosemicarbazones. The centro-symmetrical structure of hexahydro-1,2,4,5-tetrazines unsubstituted in the 3- and 6-positions is confirmed by ^{1}H nuclear magnetic resonance spectroscopy.

A number of hexahydro-1,2,4,5-tetrazines have been prepared by condensation of hydrazines with aldehydes,[1] but the structures of several of these compounds were not established with certainty.[2] Recently, Dorn and Dilcher [3] have employed ^{1}H nuclear magnetic resonance to show the centro-symmetrical nature of 1,4-dibenzyl- and 1,4-dimethylhexahydro-1,2,4,5-tetrazines. The constitution of the latter has later been definitively established by Ansell and coworkers [4] by an X-ray examination. As part of our current investigation into hexahydrotetrazine chemistry [5,6] we have had occasion to prepare several differently substituted hexahydro-1,2,4,5-tetrazines, and in view of the current interest in the physical properties of these compounds [4,7,8] we wish to report here the results of an examination of some useful methods for the preparation of methyl- and phenyl-substituted hexahydro-1,2,4,5-tetrazines (*cf.* Fig. 1).

Hexahydro-1,2,4,5-tetrazines unsubstituted in the 3- and 6-positions have previously been prepared by condensation of aqueous formaldehyde with mono- or 1,2-disubstituted hydrazines.[3,6,9–16] The reaction of methyllithium with azomethane [9] and thermolysis of the sodium salt of 1,1-dimethyl-2-benzenesulfonylhydrazine in di-ethylene glycol [17] have given rise to 1,4-dimethylhexahydro-1,2,4,5-tetrazine (Ia), and oxidation of 1,1-dimethyl-4-phenylse-

	R^1	R^2	R^3
Ia	CH_3	H	H
IIa	C_6H_5	H	H
IIIa	CH_3	C_6H_5	H
IVa	$(CH_3)_2CH$	C_6H_5	H
Va	H	H	CH_3
VIa	CH_3	H	CH_3
VIIa	CH_3	CH_3	H
VIIIa	C_6H_5	C_6H_5	H

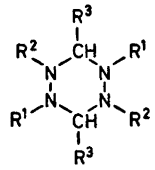


Fig. 1.

micarbazide with lead tetraacetate has been reported [18] to lead to a derivative of Ia, 1,4-dimethyl-2,5-di(*N*-phenyl-carbamoyl)hexahydro-1,2,4,5-tetrazine. Hunt and Hough [19] have obtained some 1,4-dialkylhexahydro-1,2,4,5-tetrazines from the reaction of alkylhydrazines with methylene halides. 1,4-Dimethyl-2,5-diphenylhexahydrotetrazine has been prepared from dimethylnitrosamine and phenyllithium.[20] The preparation of 3,6-dialkylhexahydro-1,2,4,5-tetrazines from hydrazine and aliphatic aldehydes has recently been examined very thoroughly.[21–23]

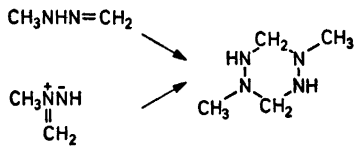


Fig. 2.

These reactions proceed either through a formaldehyde hydrazone, which subsequently undergoes head-to-tail dimerization, or through an azomethine imine type of dipolar intermediate, which also dimerizes head to tail. The observations by Dorn and Dilcher [3] and by Hammerum [6] on the reactions of alkylhydrazines with formaldehyde and by Ioffe and Stopskii [24] and by Schmidt [25] on the dimerization of formaldehyde phenylhydrazone support the assumption of a hydrazone intermediate in the direct condensations.

We have reinvestigated the various procedures given in the literature for the preparation of compounds Ia-VIIIa and found the formation of hexahydro-1,2,4,5-tetrazines from aqueous formaldehyde and the appropriate hydrazine to be a generally applicable method, since it proceeds in good yield and presents no experimental difficulties. Various formaldehyde derivatives have been investigated as possible sources of formaldehyde *in situ*. Among these methylene bromide has proven useful for the preparation of Ia and VIIa under anhydrous conditions.

Preparation. To find a useful preparative method for Ia from easily accessible starting materials we have examined the reactions between equimolar amounts of methylhydrazine and (1) aqueous formaldehyde, (2) methylene chloride, (3) methylene bromide, (4) chloromethyl methyl ether, (5) formalde-

hyde diethyl acetal, (6) paraformaldehyde, and (7) gaseous formaldehyde under a variety of reaction conditions. Among these the reaction with aqueous formaldehyde at 0°C is preferable, since it gives good yields and presents no experimental difficulties. The reaction between methylhydrazine and chloromethyl methyl ether gave irreproducible yields, regardless of whether it was carried out with KOH, K_2CO_3, $(C_2H_5)_3N$, or excess methylhydrazine to trap the liberated HCl. The use of methylene halides gave consistently low yields when carried out in inert solvents.[19] However, better results were obtained by mixing the reactants neat in the presence of Na_2CO_3. Paraformaldehyde reacts with methylhydrazine to give Ia in low yield, whereas Ia was not observed from methylhydrazine and reagents (5) or (7).

The preparation of 1,4-diphenylhexahydro-1,2,4,5-tetrazine (IIa) was also investigated. Schmitz and Ohme [12] reported the condensation of excess phenylhydrazine with aqueous formaldehyde in glacial acetic acid to give IIa. We have found the yield to be improved by using equimolar amounts of the two reactants in acetic acid-water mixtures. Best results are obtained in 50 % acetic acid. Low yields were experienced using ethanol or water as solvents, with or without hydrochloric acid in catalytic amounts. Preparations from chloromethyl methyl ether and phenylhydrazine were also carried out, but with extremely low yields. Reaction of phenylhydrazine with methylene bromide did not lead to IIa in observable amounts.

The preparation of 3,6-dimethylhexahydro-1,2,4,5-tetrazine (Va) and 1,3,4,6-tetramethylhexahydro-1,2,4,5-tetrazine (VIa) from acetaldehyde and hydrazine or methylhydrazine in ethanol has been studied recently by Skorianetz and Kováts.[21–23] Omission of solvent results in lower yields and less pure products.

Treatment of 1,2-dimethylhydrazine with methylene bromide in the presence of Na_2CO_3 leads to 1,2,4,5-tetramethylhexahydro-1,2,4,5-tetrazine (VIIa). This procedure is as convenient as the preparation from aqueous formaldehyde.

Chemical properties. Phenylhexahydrotetrazines are stable compounds under normal conditions. Conversely, alkylhexahydrotetrazines are quite sensitive to hydrolysis and oxidation; they should be stored in the cold, preferably under nitrogen. Ia decomposes to yellow substances upon prolonged standing, even at +4°C, as do Va and VIa. The last two also undergo conversion to hydrazones when traces of moisture are present.[22]

Hexahydrotetrazines with free NH groups undergo reactions typical of substituted hydrazines and may be characterized as such by their conversion to hydrazides by acylating agents and to thiosemicarbazides by isothiocyanates. A number of such derivatives have been prepared (*cf.* Table 2). Introduction of bulky carbonyl and thiocarbonyl substituents has proven difficult, probably for steric reasons. Thus, Ia reacts sluggishly and incompletely with *tert*-butyl isothiocyanate. IIa reacts slowly with isopropyl isothiocyanate, forcing conditions being necessary to introduce two thiocarbonyl substituents, and will not add more than one molecule of *tert*-butyl isothiocyanate. Attempts to introduce *tert*-butylcarbonyl groups into IIa by the action of pivaloyl chloride met with no success at all; instead reaction products corresponding to secondary reactions were isolated.

Table 1. Alkyl- and arylsubstituted hexahydro-1,2,4,5-tetrazines.

Compound	R^1 [a]	R^2 [a]	R^3 [a]	Lit.	M.p.	Yield, %	Formula	Analyses: C, H, N		
Ia	CH_3	H	H	9	123–125	70	$C_4H_{12}N_4$	Found: 41.07;	10.18;	48.10
								Calc: 41.33;	10.42;	48.25
IIa	C_6H_5	H	H	12	220–221	85	$C_{14}H_{16}N_4$	Found: 69.75;	6.92;	23.50
								Calc:. 69.95;	6.72;	23.33
IIIa	C_6H_5	CH_3	H	13	148–149	85	$C_{16}H_{20}N_4$	Found: 71.55;	7.54;	20.96
								Calc.: 71.62;	7.51;	20.88
IVa	C_6H_5	i-C_3H_7	H	14	160–162	50	$C_{20}H_{28}N_4$	Found: 74.30;	8.72;	17.40
								Calc.: 74.02;	8.70;	17.28
Va	H	H	CH_3	22	100–104 [d]	85	$C_4H_{12}N_4$	Found: 41.00;	10.34;	48.05
								Calc.: 41.33;	10.42;	48.25
VIa	CH_3	H	CH_3	22	70–80 [e]	70	$C_6H_{16}N_4$	Found: [b] 47.75;	11.00;	37.65
								Calc.: 49.97;	11.18;	38.85
VIIa	CH_3	CH_3	H	15	b.p. 60–62/12 mm	70	$C_6H_{16}N_4$	Found: 49.69;	10.93;	39.12
								Calc.: 49.97;	11.18;	38.85
VIIIa	C_6H_5	C_6H_5	H	16	198–199	55	$C_{26}H_{24}N_4$	Found: 79.75;	6.29;	14.35
								Calc.: 79.56;	6.16;	14.28
VIIIb	BrC_6H_4	BrC_6H_4	H	–	249–250 dec.	95	$C_{26}H_{20}N_4Br_4$	Found: [c] 44.29;	2.92;	7.92
								Calc.: 44.10;	2.85;	7.91

[a] *Cf.* Figure 1. [b] Discrepancy between calculated and found values indicates incomplete removal of water of crystallization. [c] Bromine, found: 45.19; calc.: 45.14. [d] Sealed capillary. [e] Deliquescent.

Table 2. Acyl- and thiocarbamoylsubstituted hexahydro-1,2,4,5-tetrazines.

Compound	R^1 [a]	R^2 [a]	R^3 [a]	M.p.	Yield, %	Formula	Analyses: C, H, N, S
Ib	CH_3	CH_3CO	H	219 – 220[g]	65	$C_6H_{16}N_4O_2$	Found: 47.95; 8.12; 28.21 Calc.: 47.96; 8.06; 27.98
Ic	CH_3	CH_3NHCS	H	284 – 286 dec.[d]	90	$C_8H_{18}N_6S_2$	Found: 36.72; 7.02; 32.13; 24.51 Calc.: 36.63; 6.92; 32.05; 24.40
Id	CH_3	$(CH_3)_3CNHCS$	H	248 – 249	10	$C_{14}H_{30}N_6S_2$	Found: 48.76; 8.77; 24.18; 18.45 Calc.: 48.52; 8.73; 24.25; 18.50
IIb	C_6H_5	CH_3CO	H	257 – 258	90	$C_{18}H_{20}N_4O_2$	Found: 66.45: 6.24; 17,32 Calc.: 66.59; 6.21; 17.27
IIc	BrC_6H_4	CH_3CO	H	[h]	95	$C_{18}H_{18}N_4O_2Br_2$	Found: 44.83; 3.83; 11.63; 33.15[f] Calc.: 44.82; 3.76; 11.62; 33.16
IId	C_6H_5	C_2H_5CO	H	219 – 220	60	$C_{20}H_{24}N_4O_2$	Found: 68.10; 7.00; 15.77 Calc.: 68.14; 6.86; 15.91
IIe	C_6H_5	$i\text{-}C_3H_7CO$	H	242 – 244	35	$C_{22}H_{28}N_4O_2$	Found: 69.60; 7.46; 14.88 Calc.: 69.44; 7.42; 14.73
IIf	C_6H_5	C_6H_5CO	H	257.5 – 258.5[c]	35	$C_{28}H_{24}N_4O_2$	Found: 75.03; 5.46; 12.77 Calc.: 74.99; 5.38; 12.49
IIg	BrC_6H_4	C_6H_5CO	H	252 – 253 dec.	95	$C_{28}H_{22}N_4O_2Br_2$	Found: 55.65; 3.78; 9.26; 26.38[f] Calc.: 55.47; 3.66; 9.24; 26.36
IIh	C_6H_5	C_2H_5NHCO	H	300 – 302	90	$C_{20}H_{26}N_6O_2$	Found: 62.79; 6.82; 22.00 Calc.: 62.80; 6.85; 21.98
IIi	C_6H_5	C_6H_5NHCO	H	301 – 304	80	$C_{28}H_{26}N_6O_2$	Found: 70.30; 5.60; 17.56 Calc.: 70.27; 5.48; 17.56
IIj	BrC_6H_4	BrC_6H_4NHCO	H	298 dec.	95	$C_{28}H_{22}N_6O_2Br_4$	Found: 42.35; 3.06; 10.72 Calc.: 42.35; 2.79; 10.58

Table 2. Continued.

IIk	C_6H_5	CH_3NHCS	H	313 – 314[d]	60	$C_{18}H_{22}N_6S_2$	Found: 56.10; 5.64; 21.60; 16.49 Calc.: 55.87; 5.74; 21.72; 16.59
IIl	C_6H_5	C_2H_5NHCS	H	295 – 296[d]	70	$C_{20}H_{26}N_6S_2$	Found: 58.01; 6.40; 20.23; 15.29 Calc.: 57.96; 6.32; 20.28; 15.44
IIm	C_6H_5	*i*-C_3H_7NHCS	H	315.5 – 316.5	75	$C_{22}H_{30}N_6S_2$	Found: 59.99; 6.94; 18.99; 14.43 Calc.: 59.71; 6.83; 18.99; 14.46
IIn	C_6H_5	*i*-C_3H_7NHCS[b]	H	215 – 217	25	$C_{18}H_{23}N_5S$	Found: 63.50; 6.84; 20.62; 9.39 Calc.: 63.32; 6.79; 20.52; 9.37
IIo	C_6H_5	*t*-C_4H_9NHCS[b]	H	189 – 190	25	$C_{19}H_{25}N_5S$	Found: 63.95; 7.36; 19.72; 8.99 Calc.: 64.20; 7.09; 19.71; 9.00
IIp	C_6H_5	C_6H_5NHCS	H	299 – 303 dec.	90	$C_{28}H_{26}N_6S_2$	Found: 65.70; 5.21; 16.61; 12.44 Calc:. 65.87; 5.13; 16.46; 12.54
Vb	CH_3CO	H	CH_3	260 – 270[e]	65	$C_8H_{16}N_4O_2$	Found: 48.10; 8.08; 28.02 Calc.: 47.96; 8.06; 27.98
Vc	C_3H_7CO	H	CH_3	218 – 220	60	$C_{12}H_{24}N_4O_2$	Found: 56.27; 9.48; 21.92 Calc.: 56.20; 9.44; 21.87
Vd	*i*-C_3H_7CO	H	CH_3	270 – 275[e]	50	$C_{12}H_{24}N_4O_2$	Found: 55.93; 9.57; 21.80 Calc.: 56.20; 9.44; 21.87
Ve	C_6H_5CO	H	CH_3	252 – 254[d]	15	$C_{18}H_{20}N_4O_2$	Found: 66.35; 6.20; 17.16 Calc.: 66.65; 6.22; 17.27
Vf	CH_3NHCS	H	CH_3	240 – 241	75	$C_8H_{18}N_6S_2$	Found: 36.60; 7.00; 31.75; 24.20 Calc.: 36.63; 6.92; 32.05; 24.40
Vg	*i*-C_3H_7NHCS	H	CH_3	250 – 251 dec.[d]	90	$C_{12}H_{26}N_6S_2$	Found: 45.26; 8.23; 26.50: 20.39 Calc.: 45.27; 8.23; 26.40; 20.10
Vh	*t*-C_4H_9NHCS	H	CH_3	250 – 252	45	$C_{14}H_{30}N_6S_2$	Found: 48.70; 8.75; 24.42; 18.22 Calc.: 48.54; 8.73; 24.26; 18.47
Vi	$C_6H_5CH_2NHCS$	H	CH_3	233 – 234[d]	80	$C_{20}H_{26}N_6S_2$	Found: 57.80; 6.43; 20.19; 15.23 Calc.: 57.96 6.32; 20.28; 15.44

[a] *Cf.* Fig. 1. [b] Only one thiocarbamoyl group, *cf.* p. 1267. [c] Lit. value 243.[12] [d] Strongly dependent upon rate of heating. [e] Sublimation. [f] Analytical figures for bromine. [g] Lit. value 218 – 220.[3] [h] Decomposes slowly at 260 – 330 without melting.

Characterization of compounds Va and VIa is complicated by the facile bisection of the molecules to yield hydrazones. However, under suitable conditions Va may be converted to acyl and thiocarbamoyl derivatives, whereas VIa yields only derivatives of acetaldehyde methylhydrazone.

Acyl and thioacyl derivatives of Ia, IIa, and Va are quite stable compounds. They are recovered unchanged after prolonged heating at 200°C (*e.g.* refluxing in ethylene glycol or benzonitrile). Acyl derivatives of Ia are unaffected by mild oxidizing agents such as bromine, whereas phenyl compounds undergo *p*-substitution.

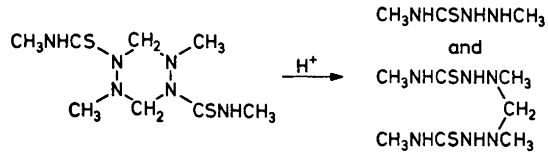


Fig. 3.

Irrespective of substituents, hexahydrotetrazines are hydrolyzed by the action of dilute mineral acids to aldehydes and hydrazines. This provides a facile route to the hitherto difficultly accessible 1-methylthiosemicarbazides;[26] *e.g.* 1,4-dimethylthiosemicarbazide is formed by heating Ic in aqueous hydrochloric acid. 1,1′-Methylenedithiosemicarbazides are also found in the reaction mixture. Since incomplete hydrolysis will lead to 1,2′-methylenedithiosemicarbazides, these products must arise from partial recombination of thiosemicarbazide and formaldehyde; *cf.* Jensen *et al.*[26] Hydrolysis of thiocarbamoyl derivatives of Va leads to thiosemicarbazones.

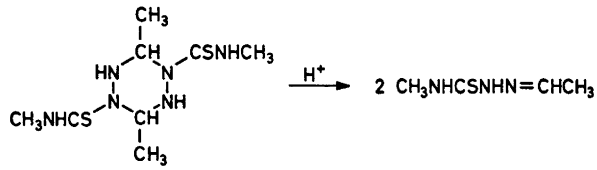
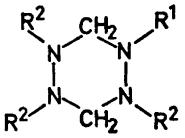


Fig. 4.

The centrosymmetrical substitution pattern of the hexahydrotetrazines Ia, IIa, IIIa, IVa and their acyl and thioacyl derivatives is unambiguously demonstrated by the occurrence in the NMR spectra of one singlet or AB system due to the methylene groups (*cf.* Table 3). It is interesting to note that the upfield doublet of the AB system of the acyl and thioacyl substituted hexahydrotetrazines is always observed at τ 5.60 ± 0.18 ppm, whereas the chemical shift of the low field proton is dependent upon the nature of the neighbouring *N*-substituents; in some cases it is observed more than 2.6 ppm downfield, which is a surprisingly large difference for geminal protons. The position of the upfield doublet of the derivatives of IIa agrees well with what

Table 3. NMR chemical shifts of ring methylene protons in substituted hexahydro-1,2,4,5-tetrazines at 40°C, in ppm relative to TMS (τ).



R^1	R^2	H_α[a]	H_β[a]	J_{HH}(Hz)	Solvent
CH_3	H	6.37		singlet	$CDCl_3$
		6.57		singlet	CCl_4
CH_3	CH_3CO	5.04	5.58	13	$CDCl_3$
CH_3	CF_3CO[b]	5.16	5.32	14	$CDCl_3$
CH_3	C_6H_5NHCO[c]	5.01	5.41	13	$CDCl_3$
CH_3	CH_3NHCS	4.04	5.42	14	$CDCl_3$
CH_3	$(CH_3)_3CNHCS$	3.76	5.52	13.5	$CDCl_3$
CH_3	CH_3[d]	6.43		singlet	$CDCl_3$
		6.68		singlet	CCl_4
C_6H_5	H	5.58		singlet[i]	DMSO-d_6
C_6H_5	CH_3CO	3.69	5.59	14	$CDCl_3$
C_6H_5	C_2H_5CO	3.68	5.60	14	$CDCl_3$
C_6H_5	$(CH_3)_2CHCO$	3.74	5.62	13.5	$CDCl_3$
C_6H_5	C_6H_5NHCO	3.82	5.44	14	DMSO-d_6
C_6H_5	CH_3NHCS	2.76 ± 0.12[f]	5.54[g]	14	DMSO-d_6
C_6H_5	C_2H_5NHCS	2.82 ± 0.28[f]	5.51[g]	14	DMSO-d_6
C_6H_5	$(CH_3)_3CNHCS$[e]	5.09	5.47	14	$CDCl_3$
		2.85 ± 0.35[f]	5.76[g]	12	$CDCl_3$
C_6H_5	CH_3	5.47		singlet[h]	$CDCl_3$
		5.42		singlet	CCl_4
C_6H_5	$(CH_3)_2CH$	5.25		singlet	$CDCl_3$
C_6H_5	C_6H_5	4.61		singlet	$CDCl_3$
		4.42		singlet	DMSO-d_6

[a] Values obtained using the relationship $\delta_A - \delta_B = \sqrt{(\nu_1 - \nu_4)(\nu_2 - \nu_3)}$. [b] Values taken from Ref. 3. [c] Values taken from Ref. 18. [d] See also Ref. 7. [e] Only one thiocarbonyl group, CH_3 groups therefore distinct. [f] Absorption hidden in aromatic multiplet, outer limits given. [g] Obtained (see footnote *a*) using any value in the interval for H_α. [h] Coalesces to AB quartet below 0°C. [i] Coupling to NH eliminated by addition of D_2O.

is found for acyl and thioacyl derivatives of alkylhexahydrotetrazines,[6] suggesting that only one of the two methylene protons is subjected to significant deshielding by the phenyl groups.

EXPERIMENTAL

Elemental analyses were carried out in the microanalytical department of this laboratory by Mr. Preben Hansen and his staff.

NMR spectra were recorded on a Varian A-60A spectrometer.

1,4-Dimethylhexahydro-1,2,4,5-tetrazine (*Ia*). a. From formaldehyde. Methylhydrazine (0.2 mol) and 40 % aqueous formaldehyde (0.2 mol) were cautiously mixed with vigorous

stirring at −10°C. The reaction mixture was left overnight at +4°C. and then the volume of the solution was reduced by passing a slow stream of nitrogen over it. The precipitated crystals were collected, washed with ice-cold methanol-ether (1 : 1), and recrystallized from diethyl ether. The methanol-ether wash was added to the mother liquor, from which a second crop could be isolated by repetition of the slow evaporation of solvent. Total yield 8.0 g (70 %). Physical data in Table 1.

b. From chloromethyl methyl ether. Methylhydrazine (0.2 mol) and KOH (0.2 mol) were dissolved in methanol (30 ml). Chloromethyl methyl ether (0.2 mol) in ether (30 ml) was added slowly with stirring and cooling. Upon completion of the addition the reaction mixture was freed from ether and refluxed for 2 h. The precipitated KCl was removed by filtration and the solvent evaporated under vacuum. The white crystalline material was recrystallized from ether. Yield 2.0 g (17 %).

c. From methylene bromide. Methylene bromide (0.2 mol) was added dropwise to a mixture of methylhydrazine (0.2 mol) and anhydrous Na_2CO_3 (0.2 mol). After 8 h the reaction mixture was extracted several times with warm ether, which was evaporated. Yield 3.5 g (30 %).

1,4-Diphenylhexahydro-1,2,4,5-tetrazine (IIa). To a cooled solution of phenylhydrazine (0.1 mol) in 50 ml of 50 % aqueous acetic acid was added 40 % aqueous formaldehyde (0.1 mol) with stirring and cooling. After 2 h the precipitated material was collected, washed thoroughly with water and methanol and dried over KOH pellets. Yield 10.2 g (85 %). This material may be recrystallized, with about a 15 % loss, from boiling dimethylformamide or boiling pyridine and washed with ether to give the colourless crystalline compound.

1,4-Dimethyl-2,5-diphenylhexahydro-1,2,4,5-tetrazine (IIIa) was prepared according to Knorr and Weidel.[13]

1,4-Diisopropyl-2,5-diphenylhexahydro-1,2,4,5-tetrazine (IVa) was prepared according to Goodwin and Bailey.[14]

3,6-Dimethylhexahydro-1,2,4,5-tetrazine (Va) and *1,3,4,6-tetramethylhexahydrotetrazine (VIa)* were prepared according to Skorianetz and Kováts.[22]

1,2,4,5-Tetramethylhexahydrotetrazine (VIIa). a. From aqueous formaldehyde. Aqueous formaldehyde (0.1 mol) was slowly added with stirring and cooling to 1,2-dimethylhydrazine (0.1 mol). The reaction mixture was left for 24 h at 4°C and then extracted several times with ether. The ether solution was dried over Na_2CO_3, the solvent stripped in vacuum and the residue distilled at reduced pressure. Yield 5.1 g (70 %), b.p. 60 – 62/12 mm, 84 – 85/35 mm.

b. From methylene bromide. 1,2-Dimethylhydrazine (0.1 mol) was mixed with methylene bromide (0.1 mol) and Na_2CO_3 (0.1 mol) in 20 ml of 50 % ethanol and refluxed for 3 h. The solution was then extracted with three 30 ml portions of methylene chloride and dried over Na_2CO_3, the solvent stripped in vacuum and the residue distilled as above. Yield 3.6 g (50 %).

1,2,4,5-Tetraphenylhexahydrotetrazine (VIIIa) was prepared according to Bischoff.[16]

1,5-Diacetyl-1,4-dimethylhexahydro-1,2,4,5-tetrazine (Ib). To a cold solution of Ia (0.01 mol) in 15 ml of ether and 5 ml of ethanol was added acetic anhydride (0.03 mol) in 10 ml of ether. Colourless crystals precipitated upon leaving the solution in the refrigerator overnight. Yield 1.3 g (65 %). Physical data are listed in Table 2.

1,4-Dimethyl-2,5-bis(N-*methylthiocarbamoyl*)*hexahydro-1,2,4,5-tetrazine (Ic)*. To a solution of Ia (0.02 mol) in 10 ml of ethanol was added a solution of methyl isothiocyanate (0.05 mol) in 60 ml of ether. After 20 h at room temperature 20 ml of light petroleum (b.p. 40 – 60°C) was added and the solution left in the refrigerator overnight. The precipitated material was filtered off and recrystallized from ethanol. Yield 4.7 g (90 %).

2,5-Bis(N-tert-*butylthiocarbamoyl*)*-1,4-dimethylhexahydro-1,2,4,5-tetrazine (Id)*. To a solution of Ia (0.02 mol) in 5 ml of pyridine was added *tert*-butyl isothiocyanate (0.08 mol), and the mixture was refluxed for 3 h and left standing overnight. The precipitated material was recrystallized from methanol. Yield 0.7 g (10 %).

2,5-Diacyl-1,4-diphenylhexahydro-1,2,4,5-tetrazines were prepared by adding a slight excess of acid chloride to a pyridine solution of IIa and refluxing for 1 h. Crystallization was induced by addition of water and cooling. They were recrystallized from ethanol (the dibenzoyl compound from pyridine). Physical data are listed in Table 2.

2,5-Bis(N-*alkylthiocarbamoyl*)*-1,4-diphenylhexahydro-1,2,4,5-tetrazines* were prepared by adding an excess of alkyl isothiocyanate to a pyridine solution of IIa and refluxing for

2–4 h. They crystallized upon partial evaporation of the solvent, addition of ether and cooling. They could be recrystallized from aqueous pyridine. Physical data in Table 2.

2-(N-tert-Butylthiocarbamoyl)-1,4-diphenylhexahydro-1,2,4,5-tetrazine (IIo). To 2.4 g (0.01 mol) of IIa were added 9.2 g (0.08 mol) *tert*-butyl isothiocyanate and 5 ml of pyridine. The mixture was heated to 100°C for 3 h; pyridine and remaining isothiocyanate were then removed in vacuum and the residue freed from unreacted IIa by fractional crystallization from aqueous pyridine. Yield 850 mg (25 %).

1,4-Diphenyl-2,5-bis(N-phenylthiocarbamoyl)hexahydro-1,2,4,5-tetrazine (IIp), 1,4-diphenyl-2,5-bis(N-phenylcarbamoyl)hexahydro-1,2,4,5-tetrazine (IIi), and *1,4-diphenyl-2,5-bis(N-ethylcarbamoyl)-hexahydro-1,2,4,5-tetrazine (IIh)* were prepared in the same manner as were the *N*-alkylthiocarbamoyl derivatives of IIa.

1,4'-Diacyl-3,6-dimethylhexahydro-1,2,4,5-tetrazines. To a stirred and cooled suspension of 0.01 mol Va (as tetrahydrate) in 20 ml of ether and 10 ml of ethanol was added 0.03 mol of acid anhydride in 50 ml of ether. After 2 h at room temperature the reaction mixture was cooled to −20°C and the solid material collected and recrystallized from ethanol.

From the reaction of Va with isobutyric anhydride 1,2-diisobutyrylhydrazine was isolated as a byproduct in 23 % yield, apparently formed after acid-induced decomposition of Va into acetaldehyde and hydrazine. From the reaction of Va with benzoic anhydride 1,2-dibenzoylhydrazine (16 %) was likewise isolated.

1,4'-Bis(N-alkylthiocarbamoyl)-3,6-dimethylhexahydro-1,2,4,5-tetrazines. Va (0.01 mol, as tetrahydrate) was dissolved in 30 ml of cold ethanol, and 0.04 mol of alkyl isothiocyanate in 30 ml of ether was added slowly with stirring and cooling. The reaction mixture was left overnight at room temperature, and the precipitated material was freed from solvent, washed twice with ethanol and recrystallized from pyridine or dimethyl sulfoxide. Physical data are listed in Table 2.

The products obtained in this manner from Va and methyl, isopropyl, *tert*-butyl, and benzyl isothiocyanates were shown to be different from the corresponding acetaldehyde 4-alkylthiosemicarbazones (see below) – of which they may be regarded as dimers – by m.p. and infrared spectra (*cf.* Ref. 26, p. 30). In some cases thiosemicarbazones could be isolated as by-products from the above reaction (in less than 5 % yield), illustrating that Va under these conditions is slowly converted either to acetaldehyde and hydrazine or to acetaldehyde hydrazone, compounds that may subsequently react with methyl isothiocyanate to give the thiosemicarbazone as the end product. The thiocarbamoyl hexahydrotetrazines are not converted into thiosemicarbazones, and thiosemicarbazones do not dimerize under the reaction conditions employed.

Acetaldehyde thiosemicarbazones were prepared from acetaldehyde and the corresponding thiosemicarbazides according to Jensen *et al.*[26] when not described in the literature:

Acetaldehyde 4-isopropylthiosemicarbazone, m.p. 110–111°C. (Found: C 45.01; H 8.30; N 26.23; S 20.06. Calc. for $C_6H_{13}N_3S$: C 45.27; H 8.23; N 26.40; S 20.10.)

Acetaldehyde 4-tert-butylthiosemicarbazone, m.p. 125–126.5°C. (Found: C 48.68; H 9.76; N 24.30; S 18.53. Calc. for $C_7H_{15}N_3S$: C 48.54; H 8.73; N 24.26; S 18.47.)

Acetaldehyde 4-benzylthiosemicarbazone, m.p. 112–113°C. (Found: C 57.84; H 6.28; N 20.29; S 15.63. Calc. for $C_{10}H_{13}N_3S$: C 57.96; H 6.32; N 20.28; S 15.44.)

Acetaldehyde 2,4-dimethylthiosemicarbazone, m.p. 58.5–59.5°C. (Found: C 41.55; H 7.56; N 29.00; S 21.75. Calc. for $C_5H_{11}N_3S$: C 41.37; H 7.64; N 28.95; S 22.04.)

Attempts to prepare derivatives of VIa through reactions with acetic anhydride or methyl isothiocyanate met with no success. Acetylations in the manner indicated for Va resulted in oils, believed to be impure acetaldehyde 1-methylacethydrazone. Reactions with methyl isothiocyanate invariably yielded acetaldehyde 2,4-dimethylthiosemicarbazone, irrespective of reaction conditions. These results are believed to find their explanation in the circumstance that the conversion of VIa into acetaldehyde methylhydrazone is much faster than the conversion of Va, and much faster than acetylation or thiocarbamoylation under the reaction conditions employed. This is in accordance with the fact that trisubstituted hydrazines react only slowly with isothiocyanates.[26]

1,4-Di(p-bromophenyl)-2,5-diacetylhexahydro-1,2,4,5-tetrazine (IIc). Bromine (0.006 mol) in chloroform (10 ml) was added dropwise to a stirred pyridine solution (50 ml) of IIb (0.001 mol) at room temperature. After 2 h the pyridine was removed at reduced pressure and the residue washed with methanol and recrystallized from dimethylformamide-methanol. Physical data are listed in Table 2.

The *p*-bromophenyl hexahydrotetrazines VIIIb, IIg, and IIj were prepared similarly from VIIIa, IIf, and IIi.

Acid hydrolysis of thiocarbamoyl hexahydro-1,2,4,5-tetrazines. Ic (0.004 mol) was hydrolyzed by 90 min reflux in 10 ml of 12 M HCl and 5 ml of methanol. The solution was cooled and neutralized with aqueous ammonia and evaporated to dryness. The organic material was taken up in chloroform, and 1,4-dimethylthiosemicarbazide and 1,1'-methylene-1,4-dimethylthiosemicarbazide were isolated by fractional crystallization. IIk was hydrolyzed in a similar manner to yield 1-phenyl-4-methylthiosemicarbazide (no recombination with formaldehyde). Vf yielded acetaldehyde 4-methylthiosemicarbazone upon hydrolysis as above; this compound separated upon addition of ammonia. The hydrolysis products were shown to be identical with authentic samples by m.p. and infrared spectra.

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