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SLOW INVERSION IN 1,2,3,4-TETRAHYDRO-s-TETRAZINES (LEUCOVERDAZYLS)

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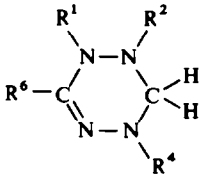
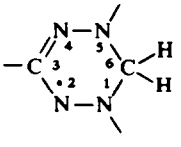
Abstract—The proton NMR spectra of several hitherto unknown, substituted 2,4-diphenyl-1,2,3,4-tetrahydro-s-tetrazines were measured and studied as a function of temperature. The slow inversion process observed is an N-2 inversion.

1,2,3,4-TETRAHYDRO-s-TETRAZINES (I) (leucoverdazyls) frequently show a broad ^{1}H NMR absorption at room temperature which stems from the ring methylene protons. At lower temperatures this resonance appears as an AB quartet, while the other signals remain unchanged. These spectral changes indicate a slow inversion process, which results in the exchange of the two diastereotopic hydrogens of the methylene bridge. ^{1}H NMR studies of verdazyls (II)[1] revealed a ring inversion in these free radicals. The close relationship between verdazyls and 1,2,3,4-tetrahydro-s-tetrazines prompted us to study a series of these compounds in order to obtain information on the conformational mobility in I.



I 1,2,3,4-tetrahydro-s-tetrazine†



II verdazyl†

The compounds summarized in Table 1 have been prepared *via* the following reactions:

Alkylation[2] of 1,2,3,4-tetrahydro-s-tetrazines (III), obtained by hydrogenation of the parent verdazyls (II) with Pd/$BaSO_4$[3] as catalyst, yielded VI, IX, X, XII, XIII, XIV, XVI, and XVII.

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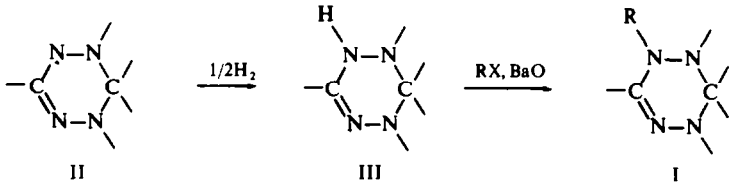
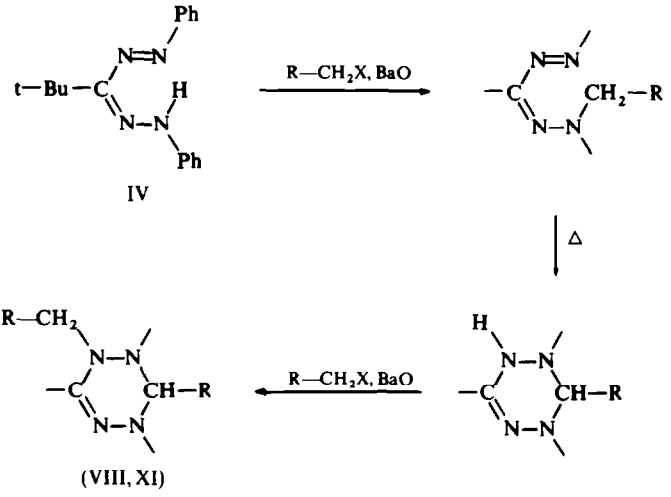
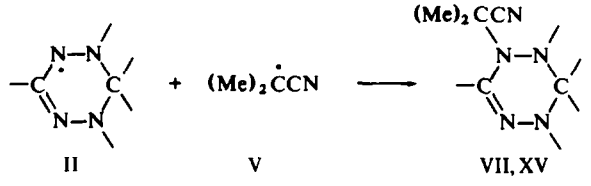
† Verdazyls (II) are also referred to as 3,4-dihydro-s-tetrazine-1(2H)yl free radicals. Since the free valence and the CN double bond are not localized in the ring system, the name "verdazyl" for this special class of nitrogen radicals[2] is advantageous. For leucoverdazyls (I) and derivatives with localized bonds we employ the tetrazine nomenclature, i.e. 1,3,5-triphenylleucoverdazyl is named 2,4,6-triphenyl-1,2,3,4-tetrahydro-s-tetrazine.



Combined alkylation[4] of 3-t-butyl-1,5-diphenylformazan (IV) gave VIII and XI directly.



1[2-Cyano-propyl-(2)]-tetrahydro-s-tetrazines (VII and XV) were obtained by coupling the verdazyls (II) with the cyano-propyl radical V.[5]

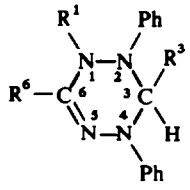


Considering the possible conformations of tetrahydro-s-tetrazines such as IX, we have to discuss four inversion processes, each of which might possibly yield the observed results.

(1) The tetrahydro-s-tetrazine ring corresponds to a cyclohexene system. In cyclohexenes the barrier of the half chair ring inversion has been found to be about 6 kcal/mole.[6] Therefore we assume that the ring inversion in tetrahydro-s-tetrazines is also fast on the NMR time scale within the temperature range studied, and is not the slow inversion process observed.

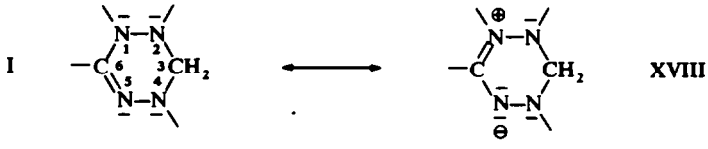
(2) Furthermore we assume that the inversion process at N-4 is fast compared to the inversion process of the hydrazine nitrogens N-1 and N-2. We know of no example

TABLE 1. 2,4-DIPHENYL-1,2,3,4-TETRAHYDRO-S-TETRAZINES PREPARED



Compound	R^1	R^3	R^6	m.p.
VI	Bz	H	H	145–147°
VII	$C(Me)_2CN$	H	H	164–165° (dec)
VIII	Me	H	t-Bu	85– 86°[4]
IX	Bz	H	t-Bu	100–101°
X	Bz	Me	t-Bu	128–129°
XI	Bz	Ph	t-Bu	136–137°
XII	Me	H	Ph	138–139°[2]
XIII	Bz	H	Ph	169–171°
XIV	i-Pr	H	Ph	124–125°
XV	$C(Me)_2CN$	H	Ph	149–150° (dec)[5]
XVI	Bz	H	Bz	117–118°
XVII	i-Pr	H	Bz	85– 86°

of a hydrazone in the literature in which an inversion of the sp^3 nitrogen atom of a hydrazone has been observed to be slow on the NMR time scale.



I XVIII

(3) Resonance structures such as XVIII must be considered for the ground state of tetrahydro-s-tetrazines. Therefore the barrier of the inversion process at N-1 depends on the contribution of XVIII to the system. Corresponding to results obtained in other amidine systems[7] we assume that the inversion process at N-1 is considerably faster than the inversion at N-2.

(4) The remaining possibility is a slow inversion at N-2. Such a process at N-2 should yield AB spectra and equal free energies of activation for both the $>N^1—CH_2—C_6H_5$ and the $>N^2—C^3H_2—N^4<$ signals.

The measured chemical shifts of the significant protons in VI–XV are summarized in Table 2. These data show that AB spectra are observed for methylene ring protons as well as for the methylene protons in the benzyl substituent. Table 3 gives the free energies of activation for the inversion process in VI, VIII, IX, and XIV. Within error limits, equal free energies of activation are obtained from both the ring and the benzyl methylene proton signals. Additionally one finds that the barrier increases significantly with the size of the N-1 substituent (VIII < IX < XIV < XV). In XV the bond from N-1 to the substituent cleaves at higher temperatures, yielding free

TABLE 2. PROTON CHEMICAL SHIFTS OF 2,4-DIPHENYL-1,2,3,4-TETRAHYDRO-S-TETRAZINES (VI–XV)

Compd.	[°C]	$>N^2—C^3H_AH_B\ \ N^4<$			$>N^1—CH_{A'}H_{B'}—Ph$			$>N^1—CCH_{3A''}CH_{3B''}—R$		Solvent
		τ_A	τ_B	$\lvert J_{AB}\rvert$ [Hz]	$\tau_{A'}$	$\tau_{B'}$	$\lvert J_{A'B'}\rvert$ [Hz]	$\tau_{A''}$	$\tau_{B''}$	
VI	−40	4·36	6·72	12	5·33	5·80	14	—	—	d_6-acetone/$CDCl_3$ (1:1)
VII	+25	4·65	5·73	12	—	—	—	8·20	8·43	$CDCl_3$
VIII	−50	4·14	5·84	12·5	—	—	—	—	—	d_6-acetone/$CDCl_3$ (1:1)
IX	0	4·23	5·68	12	5·33	5·89	15	—	—	cyclohexanone
X	+25	—		—	5·15	5·37	14	—	—	$CDCl_3$
XI	+25	—	—	—	5·60	6·79	14·5	—	—	$CDCl_3$
XII	−20	4·12	5·58	12·5	—	—	—	—	—	d_6-acetone/$CDCl_3$ (1:1)
XIII	−10	4·08	5·83	12		[a]				cyclohexanone
	0	4·26	5·87	12		[b]				d_6-acetone/$CDCl_3$ (1:1)
XIV	+25	4·19	5·71	12	—	—	—	8·83	8·88[c]	d_6-acetone/$CDCl_3$ (1:1)
XV	+25	4·31	4·84	13	—	—	—	8·27	8·61	$CDCl_3$

[a] Broad absorption ($\bar{\tau} \approx 5{\cdot}7$).

[b] A'B' spectrum ($\bar{\tau} = 5{\cdot}69$) the outer satellites of which were invisible.

[c] $J_{A''B''} = J_{B''B''} = 6$ [Hz].

radicals[5] before the coalescence of the AB quartets is reached. All these results agree well with the interpretation that the inversion at N-2 is the slow inversion process observed. The barrier of the N-2 inversion depends strongly on the size of the N-1 substituent. Attempts to detect the lower barriers of the N-1, N-4 or ring inversion failed. One does not find an additional line broadening or splitting of the AB quartets at lower temperatures, i.e. in VII at $-40°$.

TABLE 3. FREE ENERGIES OF ACTIVATION $\Delta G_c^{\ddagger}$ FOR INVERSION PROCESSES IN 2,4-DIPHENYL-1,2,3,4-TETRAHYDRO-S-TETRAZINES (60 MHz)

Compd.	Signal	T_c [°C]	$\Delta G_c^{\ddagger}$ [kcal/mole]	Solvent
VI	$>N^1-CH_2-Ph$	−20	12·4	d_6-acetone/$CDCl_3$ (1:1)
	$>N^2-C^3H_2-N^4<$	0	12·5	d_6-acetone/$CDCl_3$ (1:1)
VIII	$>N^2-C^3H_2-N^4<$	+27	14·3	d_6-acetone/$CDCl_3$ (1:1)
IX	$>N^1-CH_2-Ph$	+59	16·4	cyclohexanone
	$>N^2-C^3H_2-N^4<$	+72	16·6	cyclohexanone
XIV	$>N^2-C^3H_2-N^4<$	+145	20·4	diphenylether
	$-CH(CH_3)_2$	+97	19·5	diphenylether

In conclusion, the slow inversion process observed in tetrahydro-s-tetrazines can be explained by an N-2 inversion.

EXPERIMENTAL

The NMR spectra were recorded on a Varian A-60 spectrometer equipped with a variable temperature unit.[7] Free energies of activation were calculated in the usual way[7] from the coalescence of signals. Because of the large chemical shift differences between coalescing A and B proton absorptions the errors of $\Delta G_c^{\ddagger}$-values may range from $\pm 0{\cdot}2$ to $\pm 0{\cdot}5$ kcal/mole.

2,4-Diphenyl-1-benzyl-1,2,3,4-tetrahydro-s-tetrazine (VI). 2,4-Diphenyl-1,2,3,4-tetrahydro-s-tetrazine[2] (3 g) in DMF (50 ml), BaO (10 g), $Ba(OH)_2 \cdot 8\,H_2O$ (1g), and benzyl bromide (3 ml) were stirred for 24 hr in a N_2 atmosphere. The mixture was partitioned between benzene and H_2O, the benzene layer was washed 3 times with H_2O and evaporated in vacuum. The residue yielded from EtOH colourless crystals (2·9 g), m.p. 145–147°. (Found: C, 76·77; H, 6·42; N, 17·29. $C_{21}H_{20}N_4$ requires: C, 76·80; H, 6·14; N, 17·06%).

1-[2-Cyano-propyl-(2)]-2,4-diphenyl-1,2,3,4-tetrahydro-s-tetrazine (VII). 2,4-Diphenyl-1,2,3,4-tetrahydro-s-tetrazine[2] (4 g) in benzene (200 ml) and 2,2'-azodi(isobutyronitril) (1 g) were refluxed, while air was vigorously bubbled through the mixture and a soln of 2,2'-azido(isobutyronitril) (3 g) in benzene (100 ml) was added dropwise within 3 hr. The green colour of the mixture changed to yellow. The mixture was evaporated in vacuum and the residue chromatographed on Al_2O_3 (Brockmann) to give upon elution with benzene 2,2-azodi(isobutyronitril) (1·7 g). Further elution with benzene-CH_2Cl_2 (4:1) yielded a fraction, which gave colourless crystals from EtOH (2·6 g). m.p. 164–165° (dec.). (Found: C, 70·55; H, 6·55; N, 23·25. $C_{18}H_{19}N_5$ requires: C, 70·79; H, 6·27; N, 22·94%).

6-t-Butyl-2,4-diphenyl-1-benzyl-1,2,3,4-tetrahydro-s-tetrazine (IX). 3-t-Butyl-1,5-diphenylverdazyl[4] (5·8 g) in DMF (100 ml) was hydrogenated on 5% $Pd/BaSO_4$[3] (0·5 g) until the soln was colourless (10 mmole H_2), then BaO (10 g), $Ba(OH)_2 \cdot 8\,H_2O$ (1 g), and BzBr (5 ml) were added while N_2 was bubbled through the mixture. The mixture was stirred for 16 hr in a N_2 atmosphere and treated as above (VI): from EtOH

colourless crystals (5·9 g), m.p. 100–101°. (Found: C, 77·89; H, 7·40; N, 14·80. $C_{25}H_{28}N_4$ requires: C, 78·09; H, 7·34; N, 14·57%).

3-*Methyl*-6-*t*-*butyl*-2,4-*diphenyl*-1-*benzyl*-1,2,3,4-*tetrahydro*-s-*tetrazine* (X). 6-Methyl-3-t-butyl-1,5-diphenylverdazyl[1] (2 g) in DMF (100 ml), 5% $Pd/BaSO_4$[3] (0·3 g), BaO (10 g), $Ba(OH)_2 \cdot 8\,H_2O$, (1 g), and BzBr (3 ml) were treated as above (IX). The residue was chromatographed on Al_2O_3 (Brockmann) to give upon elution with cyclohexane nearly colourless fractions preceeding the green zone. Colourless crystals (1·4 g) from EtOH, m.p. 128–129°. (Found: C, 78·09, H, 7·35; N, 14·15. $C_{26}H_{30}N_4$ requires: C, 78·35; H, 7·59; N, 14·06%).

6-*t*-*Butyl*-2,3,4-*triphenyl*-1-*benzyl*-1,2,3,4-*tetrahydro*-s-*tetrazine* (XI). 3-t-Butyl-1,5-diphenylformazan[4] (5·6 g) in DMF (100 ml), BaO (15 g), $Ba(OH)_2 \cdot 8\,H_2O$ (1·5 g), and BzBr (15 ml) were treated as in the preparation of VI: from benzene/ligroine colourless crystals (6·8 g), m.p. 136–137°. (Found: C, 80·71: H, 7·12; N, 12·42. $C_{31}H_{32}N_4$ requires: C, 80·83; H, 7·00; N, 12·17%).

2,4,6-*Triphenyl*-1-*benzyl*-1,2,3,4-*tetrahydro*-s-*tetrazine* (XIII). 1,3,5-Triphenylverdazyl[2] (1 g) in DMF (50 ml), 5% $Pd/BaSO_4$[3] (0·1 g), BaO (5 g), $Ba(OH)_2 \cdot 8\,H_2O$ (0·5 g), and BzBr (2 ml) were treated as above (IX): from benzene/ligroine colourless crystals (0·8 g), m.p. 169–171°. (Found: C, 80·33; H, 5·68; N, 13·88. $C_{27}H_{24}N_4$ requires: C, 80·17; H, 5·98; N, 13·85%).

1-*i*-*Propyl*-2,4,6-*triphenyl*-1,2,3,4-*tetrahydro*-s-*tetrazine* (XIV). 1,3,5-Triphenylverdazyl[2] (2 g) in DMF (100 ml), 5% $Pd/BaSO_4$[3] (0·1 g), BaO (10 g), $Ba(OH) \cdot 8\,H_2O$ (1 g), and i-PrI (5 ml) were treated as above (IX). The residue was chromatographed on Al_2O_3 (Brockmann) to give upon elution with cyclohexane a colourless fraction following the brown zone. Colourless crystals (1·1 g) from MeOH, m.p. 124–125°. (Found: C, 77·21; H, 6·78; N, 16·01. $C_{23}H_{24}N_4$ requires: C, 77·49; H, 6·79; N, 15·72%).

1,5-*Diphenyl*-3-*benzylverdazyl*. Paraformaldehyde (1 g) in $CHCl_3$ (20 ml) and BF_3-Et_2O (10 ml) were stirred for 5 min; a soln of 1,5-diphenyl-3-benzylformazan[8] (5 g) in $CHCl_3$ (150 ml) was added and the mixture stirred for 30 min. After addition of $CHCl_3$ (200 ml), ice (200 g), 2 N NaOH (250 ml), and 38% aqueous formaldehyde (20 ml) the mixture was vigorously shaken in a separating funnel. The $CHCl_3$ layer was twice washed with H_2O and evaporated in vacuum. The residue was chromatographed on Al_2O_3 (Brockmann) to give upon elution with benzene green fractions, which yielded from acetone/MeOH dark green crystals (3·1 g), m.p. 116–117° (dec.). (Found: C, 76·89; H, 5·98; N, 17·19. $C_{21}H_{19}N_4$ requires: C, 77·04; H, 5·85; N, 17·11%).

2,4-*Diphenyl*-1,6-*dibenzyl*-1,2,3,4-*tetrahydro*-s-*tetrazine* (XVI). 1,5-Diphenyl-3-benzylverdazyl (2 g) in DMF (100 ml), 5% $Pd/BaSO_4$[3] (0·2 g), BaO (10 g), $Ba(OH)_2 \cdot 8\,H_2O$ (1 g), and BzBr (3 ml) were treated as above (IX). The residue was chromatographed on Al_2O_3 (Brockmann) to give upon elution with cyclohexane/benzene (1:1) a colourless fraction preceeding the green zone. Colourless crystals (0·9 g) from EtOH, m.p. 117–118°. (Found: C, 80·24; H, 6·02; N, 13·65. $C_{28}H_{26}N_4$ requires: C, 80·36; H, 6.26; N, 13·39%).

1-*i*-*Propyl*-2,4-*diphenyl*-6-*benzyl*-1,2,3,4-*tetrahydro*-s-*tetrazine* (XVII). 1,5-Diphenyl-3-benzylverdazyl (2 g) in DMF (100 ml), 5% $Pd/BaSO_4$[3] (0·2 g), BaO (10 g), $Ba(OH)_2 \cdot 8\,H_2O$ (1 g), and i-PrI (5 ml) were treated as above (IX). The residue was chromatographed on Al_2O_3 (Brockmann) to give upon elution with cyclohexane/benzene (2:1) a colourless fraction preceeding the green zone. Colourless crystals (1 g) from MeOH, m.p. 85·86°. (Found: C, 78·14; H, 6·85; N, 15·25. $C_{24}H_{26}N_4$ requires: C, 77·80; H, 7·07; N, 15·12%).

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