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Structural Studies by Nuclear Magnetic Resonance. VIII. Ring-Substituted Phenylhydrazones, Semicarbazones, and Thiosemicarbazones

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RECEIVED MARCH 28, 1964

The n.m.r. spectra of ring-substituted phenylhydrazones, thiosemicarbazones, and semicarbazones were examined in various solvents at 60 Mc. Hydrogens *cis* or *trans* to Z resonate at higher magnetic fields in benzene than in aliphatic solvents. Because of stereospecific association between benzene and substrate the upfield shift of *cis*-hydrogens is two to six times larger than that of *trans*-, and this inequality is a reliable criterion of assigning configurations to compounds of structure $R_1R_2C{=}NNHX$. All these compounds, neat or in solution, are in the *imino* form with no detectable amounts of either *azo* or *enamine* forms. The products isolated from the reactions of carbonyl compounds with 2,4-dinitrophenylhydrazine, semicarbazide, and thiosemicarbazide are generally the thermodynamically more stable isomers. In most cases the initially isolated products reflect kinetic control of product formation rather than fast configurational isomerization and isomer solubility. From chemical shifts and spin–spin coupling in various solvents information was obtained that is pertinent to conformational assignments, solvent–solute interactions, and mechanisms of configurational isomerization. The acid-catalyzed isomerization of thiosemicarbazones involves nucleophilic participation of sulfur; that of semicarbazones and 2,4-dinitrophenylhydrazones attack by solvent. In trifluoroacetic acid these compounds are protonated appreciably at the *imino* nitrogen. The magnetic anisotropies of the aromatic ring and the carbonyl and the thiocarbonyl groups are not the main contributors to the magnetic nonequivalence between *cis*- and *trans*-hydrogens.

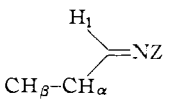
From n.m.r. studies on compounds of structure I information can be elicited that is pertinent to *syn*

$$R_1R_2X{=}YZ$$
I

and *anti* configurational assignments, kinetic or thermodynamic control of product formation, solvent–solute interactions, equilibrium constants, activation parameters for configurational isomerization, and conformations of R_1, R_2, and Z. Such information in turn can be used to probe into the factors affecting spin–spin coupling and to determine empirical anisotropic effects of X = YZ on their environment. This paper deals with ring-substituted phenylhydrazones, semicarbazones, and thiosemicarbazones.

Results and Discussion

Chemical Shifts.—Tables I–III summarize the chemical shifts of several representative compounds in various solvents.[2] The values are accurate to ±0.05 p.p.m.; relative values between *cis*- and *trans*-hydrogens are accurate to ±0.008 p.p.m. The notation used to distinguish the various protons on the R groups is shown in II, each proton being referred to as *cis* or *trans* with respect to Z. For unsymmetrical com-



II

pounds assignments of hydrogens as *cis* or *trans* are based on arguments given previously.[3] The assignments for symmetrical compounds were made to conform to those of unsymmetrical ones. All spectra were taken at 60 Mc. with the temperature probe maintained at about 36°.

(1) Fellow of the Alfred P. Sloan Foundation.

(2) For data on other compounds and more extensive solvent studies see F. M. Vane, Ph.D. Thesis, Michigan State University, 1963; R. A. Taller, M.S. Thesis, Michigan State University, 1963.

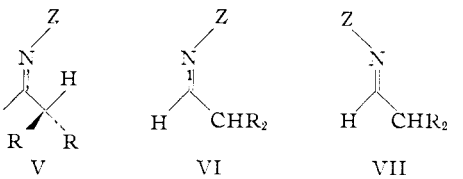
(3) (a) G. J. Karabatsos, J. D. Graham, and F. M. Vane, *J. Am. Chem. Soc.*, **84**, 733 (1962); (b) G. J. Karabatsos, B. L. Shapiro, F. M. Vane, J. S. Fleming, and J. S. Ratka, *ibid.*, **85**, 2784 (1963); (c) G. J. Karabatsos, R. A. Taller, and F. M. Vane, *ibid.*, **85**, 2326, 2327 (1963); (d) G. J. Karabatsos and R. A. Taller, *ibid.*, **85**, 3624 (1963).

Solvent Effects.—From the data we draw several conclusions that are pertinent to structural and configurational assignments. (a) All compounds examined, neat or in solution, are in the *imine* (II) form. We were unable to detect any *azo* (III) or *enamine* (IV) forms. (b) H_1, regardless of solvent, resonates at lower magnetic fields when *cis* to Z than when *trans* ($\Delta\nu \sim 30$–40 c.p.s.) and can be used to assign con-

$$R_1R_2CH{-}N{=}NX \qquad C{=}CNHNHX$$
III IV

figurations. (c) Generally, $H_\alpha(CH_3)$ resonates at higher magnetic fields when *cis* to Z than when *trans*. In dimethyl sulfoxide, acetone, methanol, nitrobenzene, tetramethylurea, and dimethylformamide, $\Delta\nu$ ($\nu_{cis} - \nu_{trans}$) is usually small, about 2–3 c.p.s., and for several acetaldehyde derivatives the resonances of *cis*- and *trans*-hydrogens are reversed in these solvents; *e.g.*, H_α of acetaldehyde 2,4-dinitrophenylhydrazone resonates at lower magnetic fields when *cis* to the dinitroanilino group than when *trans* in solutions of acetone, dimethyl sulfoxide, dimethylformamide, and tetramethylurea. H_α of acetaldehyde *o*-nitrophenylhydrazone and thiosemicarbazone behaves similarly in dimethyl sulfoxide and tetramethylurea. (d) $H_\alpha(CH_2)$ again resonates (generally) at higher magnetic fields when *cis* to Z than when *trans*. $\Delta\nu$ values, however, are smaller than those for $H_\alpha(CH_3)$, they are often zero, and for derivatives of phenylacetone they are negative (reversal of *cis* and *trans* resonances). (e) $H_\alpha(CH)$ always resonates at *lower* magnetic fields ($\Delta\nu \sim 20$ c.p.s.) when *cis* to Z than when *trans* and can be confidently used for configurational assignments. (f) $\nu_{H\beta}$ is very sensitive to Z and solvent.

The inconsistent behavior of H_α, although limiting its usefulness in assigning configurations, is instructive in conformational assignments. The change from α-methyl (shielded) to α-methine (deshielded) implies



V VI VII

TABLE I

CHEMICAL SHIFTS (τ-VALUES) OF NITROPHENYLHYDRAZONES

$R_1R_2C{=}NNHC_6H_4NO_2(o)$			H_1		$H_\alpha(CH)$		$H_\alpha(CH_2)$		$H_\alpha(CH_3)$		$H_\beta(CH_3)$		
R_1	R_2	Solvent	*cis*	*trans*	*cis*	*trans*	*cis*	*trans*	*cis*	*trans*	*cis*	*trans*	NH
H	CH_3	CH_2Br_2							7.98	7.94			−0.67
CH_3	CH_3	CH_2Br_2							7.97	7.87			− .53
CH_3	CH_2CH_3	CH_2Br_2					7.62	7.62	8.03	7.93	8.85	8.79	− .50
CH_3	CH_2CH_3	C_6H_6							8.62	8.28	9.23	9.03	
CH_3	$CH(CH_3)_2$	CH_2Br_2			[a]	7.40			7.98	7.96	[a]	8.82	−0.40
CH_3	$CH_2C_6H_5$	CH_2Br_2					6.27	6.31	8.17	8.09			−0.63
CH_3	$CH_2C_6H_5$	C_6H_6					6.73	6.40	8.75	8.40			
CH_2CH_3	CH_2CH_3	CH_2Br_2					7.54	7.54			8.80	8.77	−0.83
CH_2CH_3	CH_2CH_3	$(CH_3)_2SO$					[b]				8.85	8.83	− .70
CH_2CH_3	CH_2CH_3	$(CH_3)_2CO$					[b]				8.82	8.77	− .81
$R_1R_2C{=}NNHC_6H_4NO_2(m)$													
H	CH_3	CH_2Br_2							8.04	7.95			
CH_3	CH_3	CH_2Br_2							8.07	7.93			
CH_3	CH_3	C_6H_6							8.85	8.18			
CH_3	CH_2CH_3	CH_2Br_2					7.70	7.65	8.11	7.97	8.87	8.87	
CH_3	CH_2CH_3	C_6H_6							8.75	8.23	9.27	9.00	
CH_3	$CH(CH_3)_2$	CH_2Br_2			[a]	7.38			8.11	7.68	8.88	8.88	
CH_3	$CH_2C_6H_5$	CH_2Br_2					6.27	6.31	8.17	8.09			
$R_1R_2C{=}NNHC_6H_4NO_2(p)$													
H	CH_3	CH_2Br_2							8.04	7.96			
CH_3	CH_3	CH_2Br_2							8.05	7.92			2.48
CH_3	CH_3	C_6H_6							8.97	8.30			
CH_3	CH_2CH_3	CH_2Br_2					7.67	7.63	8.07	7.96	8.87	8.87	2.37
CH_3	CH_2CH_3	C_6H_6						7.93	8.83	8.25	9.33	9.03	
CH_3	$CH(CH_3)_2$	CH_2Br_2			[a]	7.42			8.10	8.03	[a]	8.87	2.27
CH_3	$CH_2C_6H_5$	CH_2Br_2					6.33	6.38	8.17	7.95			2.35
CH_3	$CH_2C_6H_5$	C_6H_6					6.78	6.63	8.88	8.22			
CH_2CH_3	CH_2CH_3	CH_2Br_2					7.65	7.61			8.83	8.83	2.20
CH_2CH_3	CH_2CH_3	$(CH_3)_2CO$					[b]				8.90	8.85	0.83
CH_2CH_3	CH_2CH_3	$(CH_3)_2SO$					7.64	7.58			8.92	8.88	0.15
$CH(CH_3)_2$	$CH(CH_3)_2$	CH_2Br_2			7.02	7.31					8.85	8.83	2.07
$R_1R_2C{=}NNHC_6H_3(NO_2)_2$													
H	H	CH_2Br_2	2.73	3.23									
H	H	CF_3CO_2H	3.07										
H	CH_3	CH_2Br_2	2.35	2.85					7.85	7.82			
H	CH_3	$(CD_3)_2CO$							7.86	7.88			
H	CH_3	$(CD_3)_2SO$							7.93	7.95			
H	CH_3	C_6H_6							8.85	8.46			
H	CH_3	CF_3CO_2H	1.80						7.48				
H	$CH_2C(CH_3)_2$	CH_2Br_2	2.50	3.00			7.71	7.68			8.90[c]	8.97[c]	
H	$CH_2C(CH_3)_3$	C_6H_6					8.18	8.02			9.21[c]	9.18[c]	
H	$CH_2C(CH_3)_3$	CF_3CO_2H	2.03				7.37				8.84[c]		
CH_3	CH_2CH_3	CH_2Br_2					7.50	7.50	7.87	7.82	8.72	8.78	
CH_3	CH_2CH_3	$C_6H_5NO_2$					7.55	7.55	7.97	7.88	8.75	8.80	
CH_3	CH_2CH_3	$(CD_3)_2CO$					7.46	7.46	7.85	7.82	8.72	8.79	
CH_3	CH_2CH_3	C_5H_5N					7.57	7.57	8.08	7.93	[a]	8.87	
CH_3	CH_2CH_3	CF_3CO_2H					6.67	6.67	7.11	7.05	8.65	8.58	
CH_3	$CH_2C_6H_5$	CH_2Br_2					6.19	6.25	7.97	7.81			−0.95
CH_3	$CH_2C_6H_5$	C_6H_6					6.82	6.67	8.72	8.21			
CH_3	$CH(CH_3)_2$	CH_2Br_2			[d]	7.27			7.91	[d]	[d]	8.97	
CH_2CH_3	CH_2CH_3	CH_2Br_2					7.50	7.50			8.75	8.79	
CH_2CH_3	CH_2CH_3	CF_3CO_2H					6.76	6.72			8.50	8.41	
CH_2CH_3	$CH_2C_6H_5$	CH_2Br_2					6.13	6.21			8.86	8.75	−1.15
							(7.54)[e]	(7.42)[e]					
CH_2CH_3	$CH_2C_6H_5$	C_6H_6					6.63	6.50			9.28	8.97	
							(8.12)[e]	(7.82)[e]					

[a] Peaks were not detected because of small concentrations of the *anti* isomers. [b] Solvent interference. [c] *t*-Butyl group (γ-CH_3) [d] Only one isomer. [e] Methylene of the ethyl group.

that the conformation of groups having a methine hydrogen is V. In such a conformation the methine hydrogen is in the CCN=Z plane and should behave, as it does, similarly to H_1. The finding that J_{HH} is larger in VI, 7.5 c.p.s., than in VII, 5 c.p.s., supports this conclusion further.[4]

(4) See ref. 3c. A detailed discussion on the conformations of R_1 and R_2 (1) from spin-spin coupling studies will appear elsewhere.

As with phenylhydrazones[3d] *cis*- and *trans*-hydrogens resonate at higher magnetic fields in benzene than in aliphatic solvents. The upfield shift of *cis*-hydrogens is generally two to six times larger than that of the corresponding *trans* (Table V), and this inequality is a convenient and reliable criterion for assigning configurations to compounds of structure $R_1R_2C{=}NNHX$. A hydrogen-bonded complex of conformation VIII

TABLE II

CHEMICAL SHIFTS (τ-VALUES) OF $R_1R_2C{=}NNHC_6H_4X$

$R_1R_2C{=}NNHC_6H_4CH_3(p)$			H_1		$H_\alpha(CH_2)$		$H_\alpha(CH_3)$		$H_\beta(CH_3)$		
R_1	R_2	Solvent	*cis*	*trans*	*cis*	*trans*	*cis*	*trans*	*cis*	*trans*	NH
H	CH_3	CH_2Br_2	[a]	3.43			8.22	8.09			
H	CH_3	$(CH_3)_2CO$	2.90	3.50			8.17	8.13			
H	CH_3	$(CH_3)_2SO$	2.87	3.52			8.17	8.13			
H	CH_3	C_6H_6	[a]	3.70			8.85	8.30			
CH_3	CH_3	CH_2Br_2					8.22	8.02			
CH_3	CH_3	C_6H_6					8.75	8.18			3.50
CH_3	CH_2CH_3	Neat			[b]	7.88	8.58	8.22	9.18	9.00	3.37
CH_3	CH_2CH_3	CH_2Br_2			[b]	7.75	8.25	8.07	8.95	8.92	3.43
CH_3	CH_2CH_3	C_6H_6			[b]	7.87	8.70	8.18	9.26	8.97	
$R_1R_2C{=}NNHC_6H_4Cl(p)$											
H	CH_3	CH_2Br_2	[a]	3.28			8.17	8.07			
H	CH_3	C_6H_6	[a]	3.85			8.93	8.38			
CH_3	CH_3	CH_2Br_2					8.17	8.00			
CH_3	CH_3	C_6H_6					8.88	8.25			
CH_3	CH_2CH_3	CH_2Br_2			[b]	7.75	8.23	8.02	8.92	8.92	
CH_3	CH_2CH_3	C_6H_6			[b]	7.91	8.72	8.22	9.24	9.00	
$R_1R_2C{=}NNHC_6H_4CO_2H(o)$											
H	CH_3	CH_2Br_2					8.05	7.98			
H	CH_3	C_6H_6					8.59	8.42			
CH_3	CH_3	CH_2Br_2					8.05	7.92			
CH_3	CH_3	C_6H_6					8.50	8.18			
CH_3	CH_2CH_3	CH_2Br_2			[b]	7.63	8.07	7.94		8.85	−1.40
CH_3	CH_2CH_3	C_6H_6			[b]	7.87	8.47	8.15		8.95	−2.08
$R_1R_2C{=}NNHC_6H_4CO_2H(p)$											
H	CH_3	CH_2Br_2					8.05	7.98			
CH_3	CH_3	CH_2Br_2					8.08	7.93			
CH_3	CH_2CH_3	CH_2Br_2			[b]	7.65	8.10	7.96		8.87	
CH_3	CH_2CH_3	C_6H_6			[b]	7.97	8.92	8.24		9.02	

[a] Interference by aromatic protons. [b] Exact resonance absorption could not be determined.

TABLE III

CHEMICAL SHIFTS (τ-VALUES) OF SEMICARBAZONES AND THIOSEMICARBAZONES

$R_1R_2C{=}NNHCONH_2$			H_1		$H_\alpha(CH)$		$H\alpha(CH_2)$		$H_\alpha(CH_3)$		$H_\beta(CH_3)$	
R_1	R_2	Solvent	*cis*	*trans*	*cis*	*trans*	*cis*	*trans*	*cis*	*trans*	*cis*	*trans*
H	CH_3	CH_2Br_2	3.00	3.53					8.12	8.07		
CH_3	CH_3	$CHCl_3$							8.15	8.00		
CH_3	CH_3	CF_3CO_2H							7.32	7.23		
CH_3	CH_2CH_3	$CHCl_3$					7.71	7.71	8.12	8.03	8.90	8.90
CH_3	CH_2CH_3	CF_3CO_2H					7.00	6.95	7.33	7.27	8.56	8.56
CH_3	$(CH_2)_2CH_3$	$CHCl_3$						7.77	8.15	8.04		
CH_3	$(CH_2)_2CH_3$	CF_3CO_2H						7.03	7.35	7.27		
CH_3	$CH_2C_6H_5$	CF_3CO_2H					5.69	5.67	7.33	7.40		
CH_3	$CH(CH_3)_2$	$CHCl_3$			[a]	7.50			8.15	[a]	[a]	8.92
CH_3	$CH(CH_3)_2$	CF_3CO_2H				6.67			7.37	7.33	8.58	8.55
CH_2CH_3	CH_2CH_3	$CHCl_3$					7.72	7.72			8.92	8.92
CH_2CH_3	CH_2CH_3	CF_3CO_2H					6.99	6.92			8.57	8.55
$CH(CH_3)_2$	$CH(CH_3)_2$	$CHCl_3$			7.02	7.35					8.89	8.87
$CH(CH_3)_2$	$CH(CH_3)_2$	C_6H_6			8.00	7.70					9.16	9.06
$CH(CH_3)_2$	$CH(CH_3)_2$	CF_3CO_2H			6.42	6.72					8.54	8.50
$R_1R_2C{=}NNHCSNH_2$												
H	CH_3	$(CH_3)_2SO$	2.52	3.23					8.05	8.08		
CH_3	CH_3	$CHCl_3$							8.05	7.96		
CH_3	CH_3	CH_2Br_2							8.01	7.94		
CH_3	CH_3	$CH_2Br_2 + CF_3CO_2H$							7.96			
CH_3	CH_3	CF_3CO_2H							8.22			
CH_3	CH_3	C_5H_5N							8.16	8.12		
CH_3	CH_3	$C_6H_5NO_2$							8.09	8.01		
CH_3	CH_2CH_3	$CHCl_3$					7.65	7.65	8.04	7.98	8.85	8.88
CH_3	CH_2CH_3	C_6H_6					8.83	8.25	8.75	8.46	9.48	9.22
CH_3	CH_2CH_3	CF_3CO_2H					7.80		8.12		8.83	
CH_2CH_3	CH_2CH_3	$CHCl_3$					7.65	7.65			8.86	8.88
CH_2CH_3	CH_2CH_3	CF_3CO_2H					7.78				8.87	

[a] Only one isomer.

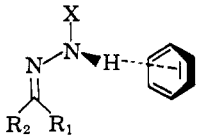
TABLE IV

COMPARISON OF CHEMICAL SHIFTS IN BENZENE AND METHYLENE BROMIDE

$R_1R_2C{=}NNHX$			$-\Delta\nu^a$ (α-CH_3)		$-\Delta\nu^a$ (α-CH_2)		$-\Delta\nu^a$ (α-CH)		$-\Delta\nu^a$ (β-CH_2)	
R_1	R_2	X	*cis*	*trans*	*cis*	*trans*	*cis*	*trans*	*cis*	*trans*
H	CH_3	$C_6H_4CH_3(p)$	37.8	12.6						
H	CH_3	$C_6H_4Cl(p)$	45.6	18.6						
H	CH_3	$C_6H_4CO_2H(o)$	32.4	26.4						
H	CH_3	$C_6H_3(NO_2)_2$	60.0	38.4						
H	$CH_2C(CH_3)_3$	$C_6H_3(NO_2)_2$			28.2	20.4			18.6[b]	12.6[b]
CH_3	CH_3	$C_6H_4CH_3(p)$	31.8	9.6						
CH_3	CH_3	$C_6H_4Cl(p)$	42.6	15.0						
CH_3	CH_3	$C_6H_4NO_2(m)$	46.8	15.0						
CH_3	CH_3	$C_6H_4NO_2(p)$	55.2	22.8						
CH_3	CH_3	$C_6H_4CO_2H(o)$	27.0	15.6						
CH_3	CH_3	$C_6H_3(NO_2)_2$	51.6	32.4						
CH_3	CH_2CH_3	$C_6H_4CH_3(p)$	27.0	6.6		7.2			18.6	3.0
CH_3	CH_2CH_3	$C_6H_4Cl(p)$	29.4	12.0		9.6			19.2	4.8
CH_3	CH_2CH_3	$C_6H_4NO_2(o)$	35.9	21.0					22.8	14.4
CH_3	CH_2CH_3	$C_6H_4NO_2(m)$	38.4	15.6					24.0	7.8
CH_3	CH_2CH_3	$C_6H_4NO_2(p)$	45.6	17.4		18.0			27.6	9.6
CH_3	CH_2CH_3	$C_6H_4CO_2H(o)$	24.0	11.4						
CH_3	CH_2CH_3	$C_6H_4CO_2H(p)$	38.8	8.4						
CH_3	CH_2CH_3	$CSNH_2$	42.6	29.4		36.0			37.2	21.0
CH_3	CH_2CH_3	$C_6H_3(NO_2)_2$	51.6	29.4		33.0			36.0	18.6
CH_3	$CH_2C_6H_5$	$C_6H_4NO_2(o)$	27.6	5.4	34.8	18.6				
CH_3	$CH_2C_6H_5$	$C_6H_4NO_2(p)$	42.6	16.2	27.0	15.0				
CH_3	$CH_2C_6H_5$	$C_6H_3(NO_2)_2$	45.0	24.0	37.8	25.2				
CH_3	$CH(CH_3)_2$	$C_6H_4NO_2(o)$	38.4							12.6
CH_3	$CH(CH_3)_2$	$C_6H_3(NO_2)_2$	48.6							17.4
CH_3	$C(CH_3)_3$	$C_6H_3(NO_2)_2$	37.8							14.4
CH_2CH_3	$CH_2C_6H_5$	$C_6H_3(NO_2)_2$			30.0 (34.8)[c]	17.4 (24.0)[c]			25.2	13.2
$CH(CH_3)_2$	$CH(CH_3)_2$	$CONH_2$					58.8	21.6	15.6	12.0

[a] $\Delta\nu = \nu_{\text{in benzene}} - \nu_{\text{in methylene bromide}}$; for semicarbazones and thiosemicarbazones it is the difference in benzene and chloroform. For convenience the differences are expressed in c.p.s. [b] *t*-Butyl group. [c] Methylene of the ethyl group.

accounts for this inequality and adequately accommodates all other data.[5] It is expected that increase in the acidity of the NH should increase the equi-



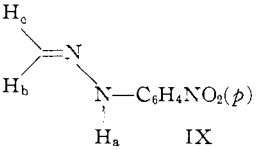
VIII

librium constant of reaction 1, and consequently lead to higher $\Delta\nu$ values ($\Delta\nu = \nu_{\text{in benzene}} - \nu_{\text{in aliphatic solvent}}$). The data agree fairly well with this suggestion, especially whenever conformational and steric

$$R_1R_2C{=}N{-}NHX + C_6H_6 \rightleftarrows \underset{\text{VIII}}{R_1R_2C{=}N{-}NHX\cdot C_6H_6} \quad (1)$$

effects are similar; *e.g.*, *cis*-α-methyl protons of *p*-substituted phenylhydrazones. By the same arguments used in the discussion of phenylhydrazones we conclude that nitrobenzene, pyridine, and halobenzenes hydrogen bond through the lone pairs of electrons on the heteroatoms.[5]

The NH of *o*-nitrophenylhydrazones and *o*-carboxyphenylhydrazones is strongly intramolecularly hydrogen bonded as evidenced from its low resonance value ($\tau = -0.5$ to -0.8 for *o*-nitrophenylhydrazones and -1.4 to -2.1 for *o*-carboxyphenylhdrazones) and the insensitivity of this resonance to solvent changes. In contrast, the NH of *p*-nitrophenylhydrazones resonates at higher magnetic fields and its resonance is strongly solvent dependent (Table I). Exchange of this NH with strong hydrogen-bonding solvents is apparently slow as evidenced from the persistence of $J_{H_aH_b}$ of formaldehyde *p*-nitrophenylhydrazone even in dimethyl sulfoxide (IX).



IX

$J_{H_aH_b} = 0.7$ c.p.s., $J_{H_aH_c} = 0$, $J_{bc} = 11.6$ c.p.s.

syn-anti **Isomers.**—Table V summarizes *syn/anti* ratios in several solvents. The values were determined by integration of peak areas and are accurate to $\pm 5\%$. "Initial" ratios refer to ratios obtained immediately after solution of the compounds.

Because in solution isomers interconvert rapidly, it is often difficult to decide whether the initially isolated solids are single isomers or mixtures of *syn* and *anti*. The usually sharp melting points favor single isomers; so do the following observations: (a) In cases where isomerization is slow enough to be followed by n.m.r., a single isomer is detected in freshly prepared solutions; *e.g.*, aldehyde 2,4-dinitrophenylhydrazones (thermodynamically more stable isomers),[3b] methyl benzyl and ethyl benzyl 2,4-dinitrophenylhydrazones (Fig. 1 shows the spectrum of a freshly prepared solution of ethyl benzyl ketone DNP and of one at equilibrium), acetaldehyde phenylhydrazone[3d] and *p*-chlorophenylhydrazone (thermodynamically less stable isomers). (b) In several cases where isomerization is rapid, different *syn/anti* ratios were calculated from

(5) Since these compounds behave similarly to phenylhydrazones, the reader should see ref. 3d for a detailed discussion on this and related points.

TABLE V

syn/anti[i] RATIOS OF $R_1R_2C{=}NNHX$ IN SOLUTION

$R_1R_2C{=}NNHX$ R_1	R_2	X	% *syn/anti* (init.)	% *syn/anti* (equil.)
H	CH_3	$C_6H_4CH_3(p)$		58/42[a]; 63/27[b]; 57/43[c]
H	CH_3	$C_6H_4Cl(p)$	0/100[a-e]	68/32[a]; 66/34[b-d]; 70/30[e]
H	CH_3	$C_6H_4NO_2(o)$	75/25[a]	56/44[a]
H	CH_3	$C_6H_4NO_2(m)$	80/20[a]	60/40[a]
H	CH_3	$C_6H_4NO_2(p)$		65/35[a]
H	CH_3	$C_6H_4CO_2H(o)$		50/50[a,b]
H	CH_3	$CONH_2$		57/43[f]
H	CH_3	$CSNH_2$		74/26[g]
H	$CH_2C(CH_3)_3$	$C_6H_3(NO_2)_2$		86/14[a]; 88/12[b]
H	$CH_2C_6H_5$	$C_6H_3(NO_2)_2$		~90/10[b]
CH_3	CH_2CH_3	$C_6H_4CH_3(p)$		83/17[a]; 80/20[b]; 70/30[c] 78/28[h]
CH_3	CH_2CH_3	$C_6H_4Cl(p)$		84/16[a-c]; 86/14[d] 89/11[e]
CH_3	CH_2CH_3	$C_6H_4NO_2(o)$	95/5[a]	85/15[a]
CH_3	CH_2CH_3	$C_6H_4NO_2(m)$		87/13[a]
CH_3	CH_2CH_3	$C_6H_4NO_2(p)$	95/5[a]	81/19[a]
CH_3	CH_2CH_3	$C_6H_4CO_2H(o)$		85/15[a]; 83/17[b]
CH_3	CH_2CH_3	$C_6H_4CO_2H(p)$		86/14[a]; 85/15[b]
CH_3	CH_2CH_3	$CONH_2$	95/5[g]	85/15[g]
CH_3	CH_2CH_3	$CSNH_2$		83/17[g]
CH_3	CH_2CH_3	$C_6H_3(NO_2)_2$		83/17[a]
CH_3	$CH_2C_6H_5$	$C_6H_4NO_2(o)$		86/14[a]
CH_3	$CH_2C_6H_5$	$C_6H_4NO_2(m)$		86/14[a]
CH_3	$CH_2C_6H_5$	$C_6H_4NO_2(p)$		84/16[a]
CH_3	$CH_2C_6H_5$	$CONH_2$		84/16[i]
CH_3	$CH_2C_6H_5$	$C_6H_3(NO_2)_2$	100/0[a]	85/15[a]
CH_3	$(CH_2)_2CH_3$	$CONH_2$		86/14[g]; 71/29[i]
CH_3	$(CH_2)_2CH_3$	$CSNH_2$		80/20[g]
CH_3	$(CH_2)_2CH_3$	$C_6H_3(NO_2)_2$		86/14[a]
CH_3	$(CH_2)_2C_6H_5$	$C_6H_3(NO_2)_2$		85/15[f]
CH_3	$CH(CH_3)_2$	$C_6H_4NO_2(o)$		92/8[a]
CH_3	$CH(CH_3)_2$	$C_6H_4NO_2(m)$		97/3[a]
CH_3	$CH(CH_3)_2$	$C_6H_4NO_2(p)$	100/0[a]	100/0[a]
CH_3	$CH(CH_3)_2$	$CONH_2$	100/0[g]	100/0[g]
CH_3	$CH(CH_3)_2$	$C_6H_3(NO_2)_2$	100/0[a]	100/0[a]
CH_3	$C(C_3H)_3$	$C_6H_3(NO_2)_2$	100/0[a,b]	100/0[a,b]
CH_2CH_3	$CH_2C_6H_5$	$C_6H_3(NO_2)_2$	100/0[a]	45/55[a]
CH_2CH_3	$CH(CH_3)_2$	$C_6H_3(NO_2)_2$		~80/20[a,b]
$CH_2C_6H_5$	$CH(CH_3)_2$	$CONH_2$		~80/20[e]
$CH_2C_6H_5$	$CH(CH_3)_2$	$C_6H_3(NO_2)_2$		82/18[a]; 90/10[b]

[a] Methylene bromide. [b] Benzene. [c] Carbon tetrachloride. [d] Methanol. [e] Dimethyl sulfoxide. [f] Nitrobenzene. [g] Chloroform. [h] Neat. [i] Trifluoroacetic acid. [j] *syn* is the isomer having R_1 and NHX *cis*.

spectra obtained immediately upon solution and after a few minutes (equilibrium). In all such cases the initial values gave higher concentrations of the thermodynamically more stable isomers. (c) Mixtures of *syn* and *anti* isomers that were prepared by evaporation of solvent from equilibrated solutions melted over wide ranges and at temperatures lower than those of the original compounds.

Isolation of a single isomer implies either kinetically controlled formation of only one isomer, or rapid isomer equilibration and precipitation of the less soluble one. In the case of aldehyde 2,4-dinitrophenylhydrazones where isomer equilibration is slow, it was demonstrated that product formation (thermodynamically more stable isomers) was kinetically controlled.[3b] The isolation of generally the more stable isomers favors the first possibility. In terms of steric interactions in the transition state[6] it is only reasonable to expect formation of the thermodynamically more stable isomers; *e.g.*, reaction 2 should be favored over 3. In the two cases where we isolated the less stable isomers the initial product formed was a gummy oil that crystallized only after standing for several hours. It is conceivable therefore that the initially formed more stable isomer equilibrated and the less stable one crystallized. That solubility might be important in determining which isomer is initially isolated is shown by the following: The reaction of 2,4-dinitrophenylhydrazine

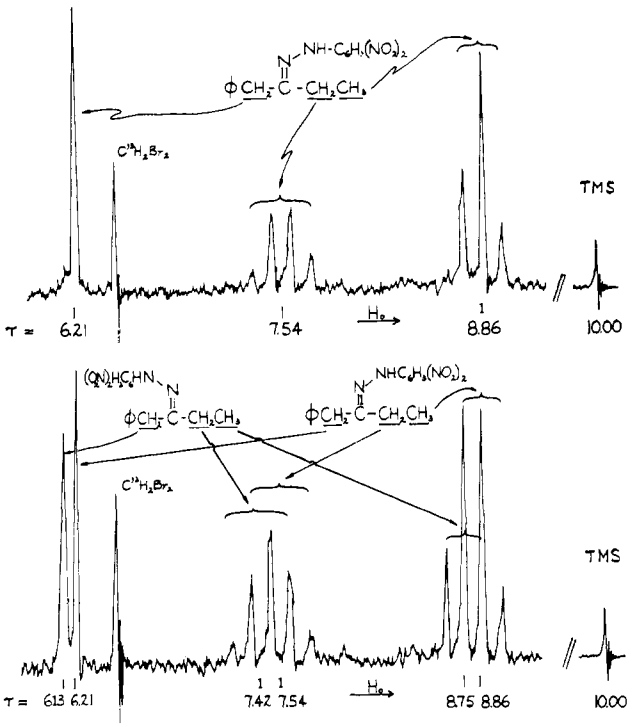
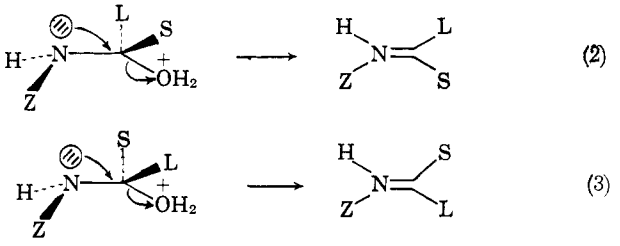


Fig. 1.—60-Mc. n.m.r. spectrum of benzyl ethyl ketone 2,4-dinitrophenylhydrazone: bottom, freshly prepared solution; top, at equilibrium.



with ethyl benzyl ketone leads to the isomer (m.p. 145°) having the ethyl and the 2,4-dinitroanilino groups *cis* to each other, although the two isomers are of comparable thermodynamic stability. When a 1:1 mixture of the two isomers is recrystallized from methanol, the first precipitate is pure *cis*-ethyl isomer. Subsequent partial evaporation of solvent leads to darker crystals, m.p. 112–114°, that have a composition 30% *cis*-ethyl and 70% *cis*-benzyl.

Configurational Isomerization.—Configurational isomerization is strongly acid catalyzed and depends upon the nature of R_1, R_2, and Z. In the absence of acid, ketone derivatives isomerize faster than aldehyde derivatives; in its presence the reverse is true.

Configurational isomerization of thiosemicarbazones about the C=N bond is extremely acid sensitive; *e.g.*, when a trace of trifluoroacetic acid is added to a methylene chloride solution of acetone thiosemicarbazone the methyl doublet, τ = 7.94, 8.01, collapses to a singlet, τ = 7.96. Acetic acid also causes collapse of the doublet, but in this case larger amounts of acid are needed. The doublet is present in solutions of freshly

(6) For the mechanism of formation of semicarbazones and related compounds see W. P. Jencks, *J. Am. Chem. Soc.*, **81**, 475 (1959); B. M. Anderson and W. P. Jencks, *ibid.*, **82**, 1773 (1960).

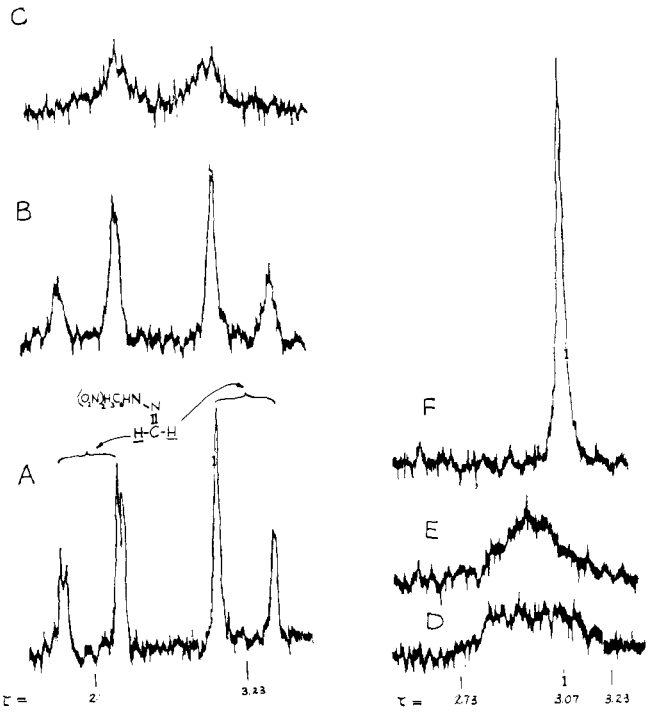
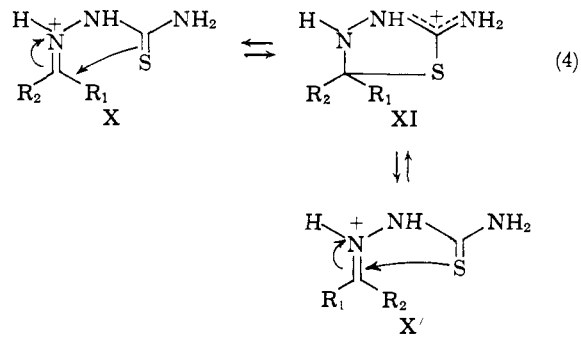


Fig. 2.—60-Mc. n.m.r. spectrum of formaldehyde 2,4-dinitrophenylhydrazone: A, in methylene bromide; B, after addition of 2 drops of trifluoroacetic acid; C, after addition of 4 drops of trifluoroacetic acid; D, after addition of 6 drops of trifluoroacetic acid; E, after addition of 10 drops of trifluoroacetic acid; F, in trifluoroacetic acid.

purified chloroform, but collapses to a singlet if the chloroform used has developed slight acidity on standing. The doublet does not collapse upon addition of pyridine or in pure pyridine. All other thiosemicarbazones behave similarly. A most pertinent observation is the upfield shift of α-hydrogens, but not of β, on addition of excess trifluoroacetic acid; *e.g.*, in pure trifluoroacetic acid the methyl resonance of acetone thiosemicarbazone occurs at $\tau = 8.22$. That nothing has happened to the structure of thiosemicarbazones is attested by their recovery upon addition of aqueous base to the acid solutions.

Acid affects semicarbazones and 2,4-dinitrophenylhydrazones differently from thiosemicarbazones. (a) Ketone derivatives show two isomers in trifluoroacetic acid. The line widths are broader than they are in other solvents and the separations between *cis*- and *trans*-hydrogens are slightly smaller than they are in methylene bromide. (b) Aldehyde derivatives show only a single isomer that results from rapid isomer equilibration; *e.g.*, when trifluoroacetic acid is added to a methylene bromide solution of formaldehyde 2,4-dinitrophenylhydrazone the A spectrum (CH_2=NZ) broadens and eventually collapses to a singlet (Fig. 2). (c) In acetic acid configurational isomerization of aldehyde derivatives is slow enough to permit detection of both isomers. (d) In trifluoroacetic acid the resonances of H_1 and H_α are shifted to lower fields by about 0.8 p.p.m. while those of H_β and H_γ are affected only slightly.

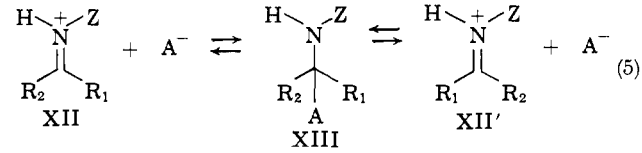
The above observations suggest several conclusions with respect to the mechanisms of configurational isomerization and site of protonation in trifluoroacetic acid. Configurational isomerization of thiosemicarbazones must occur according to (4). In view of the high



(4)

nucleophilicity of sulfur and the appreciable degree of single bond character of the C=S bond, the intermediacy of XI seems quite reasonable. Judging from the magnitude of the upfield shift of α-hydrogens, 0.25 p.p.m., the concentration of XI in trifluoroacetic acid must be appreciable and those of X and X′ negligible; *e.g.*, for propene $\tau_{(CH_3)} = 8.30$ and for CH_3C–S compounds $\tau_{(CH_3)} = 8.55$. From the strengths of the bonds involved—disregarding resonance contributions—XI should be favored over X by about 40–50 kcal./mole.

Semicarbazones and 2,4-dinitrophenylhydrazones most likely isomerize according to (5). The inclusion of the nucleophile (trifluoroacetate ion) in the isomerization step is suggested by the faster isomerization of aldehyde than ketone derivatives (steric effect).



(5)

Judging from the appreciable downfield shift of H_1 and H_α the concentrations of XII and XII′ must be larger than that of XIII. In the case of formaldehyde 2,4-dinitrophenylhydrazones where H_1 is not shifted downfield it is conceivable that the concentration of XIII is appreciable. This is reasonable in view of the decreased nonbonded interactions in XIII when both R_1 and R_2 are hydrogen.

The data have been interpreted in terms of protonation at the imino nitrogen. Unfortunately, they do not indicate if any of the other basic sites in these molecules is protonated and what the extent of protonation is at each site.

Anisotropic Effects.—The difference in chemical shift between *cis*- and *trans*-hydrogens arises—beside specific solvent anisotropic effects—from the anisotropy of C=NZ, which is composed of the anisotropies of various groups, bonds, and lone electron pairs. The magnitude of this effect in turn depends upon the conformations of R_1, R_2, and Z. Although not explicitly stated, it was implied[3a] that the magnetic nonequivalence between *cis*- and *trans*-hydrogens of 2,4-dinitrophenylhydrazones and semicarbazones arose from the anisotropic effects of the aromatic ring and the carbonyl group. We shall show that such is not the case.

The relative effect on *cis*- and *trans*-hydrogens of the ring anisotropy can be estimated if the conformation of Z is known. Of the several conformations that result from rotation about the N–N and C–N bonds—in the examined *ortho*-substituted phenylhydrazones rotation about the C–N bond is inhibited by intra-

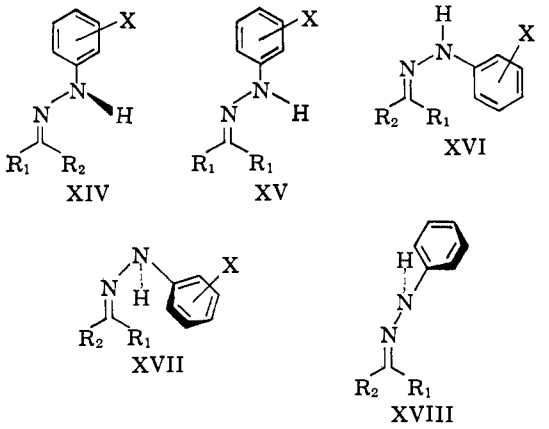
TABLE VI

CALCULATED EFFECTS OF RING ANISOTROPY ON *cis*- AND *trans*-HYDROGENS

	H_1 (*cis*)	H_1 (*trans*)	α-CH_3 (*cis*)[a]	α-CH_3 (*trans*)[a]
Conf. XV				
ρ	3.69	4.19	4.0	4.7
z	0	0	0	0
P.p.m.	−0.218	−0.318	−0.159	−0.087
$\nu_{cis} - \nu_{trans}$	−0.08		−0.072	
Conf. XVI				
ρ	2.04	3.12	1.53	3.84
z	0	0	0	0
P.p.m.	−1.159	−0.340	−1.744	−0.186
$\nu_{cis} - \nu_{trans}$	−0.819		−1.558	
Conf. XVII				
ρ	1.8	2.4	1.8	2.6
z	1.6	2.3	1.7	2.8
P.p.m.	+0.272	+0.127	+0.313	+0.114
$\nu_{cis} - \nu_{trans}$	+0.145		+0.199	
Conf. XVIII				
ρ	2.6	3.7	2.3	4.2
z	1.45	0.9	1.9	1.0
P.p.m.	−0.120	−0.154	−0.091	−0.110
$\nu_{cis} - \nu_{trans}$	+0.034		+0.201	
$\nu_{cis} - \nu_{trans}$ (exp)	−0.5 to −0.7		+0.05 to +0.2 (α-CH_3)	
			−0.3 (α-methine)	

[a] The (averaged) position of the methyl hydrogens was taken to be the center of the triangle formed by the three hydrogens.

molecular hydrogen bonding—conformations XIV (pyramided nitrogen) and XV (planar nitrogen)[7] are the only ones that are consonant with the results; *e.g.*, solvent effects, and do not suffer from severe nonbonded interactions and loss of π–sp^3 overlap. Using Johnson and Bovey's nuclear shielding values[8] we have calculated for conformations XV–XVIII the effect of a benzene ring on various hydrogens. Table VI summarizes the results. It is clear from a comparison of the calculated and experimental values that the anisotropy of the ring is not the dominant contributor to the magnetic nonequivalence between *cis*- and *trans*-hydrogens. This conclusion is further supported by the fact that hydrazones and N-methylhydrazones show effects analogous to those observed with phenyl- and ring-substituted phenylhydrazones.



Experimental

Preparation of Carbonyl Derivatives.—All carbonyl derivatives are known compounds and were prepared by usual procedures.

N.m.r. Spectra.—All n.m.r. spectra were determined at 60 Mc. on a Model A-60 spectrometer (Varian Associates, Palo Alto, Calif.), at about 36°. Undegassed solutions were used with tetramethylsilane as internal reference.

Acknowledgment.—We thank the United States Atomic Energy Commission for financial support, Grant AT(11-1)-1189.

(7) Evidence favors a pyramidal configuration for the nitrogen of aniline and N-substituted anilines; *e.g.*, J. C. Evans, *Spectrochim. Acta*, **16**, 428 (1960); A. T. Bottini and C. P. Nash, *J. Am. Chem. Soc.*, **84**, 734 (1962).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF OREGON, EUGENE, OREGON]

Calabash Curare Alkaloids. Specific Deuterium Labeling and Nuclear Magnetic Resonance Studies[1-3]

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RECEIVED APRIL 3, 1964

The important calabash curare alkaloids—dihydrotoxiferine, curarine-I, calebassine, toxiferine-I, C-alkaloid-A, and C-alkaloid-E—have been synthesized with specific deuterium labeling at the 17- and 17′-positions. Through comparative n.m.r. studies of these derivatives and by the use of spin decoupling experiments, confirming evidence has been obtained for the structural assignments and spectral interpretations of these alkaloids.

Of the various contributions made to the chemistry of calabash curare since the first isolation studies of Wieland,[5] undoubtedly the most significant of which was the linking of the important alkaloids of this group with Wieland–Gumlich aldehyde and thus, in turn, with the strychnine family.[6-10] The identity of Wieland–Gumlich aldehyde with caracurine VII and 18-desoxy Wieland–Gumlich aldehyde with hemidihydrotoxiferine made possible the direct syntheses of dihydrotoxiferine,[7] toxiferine-I,[7,8,10] curarine-I,[11] cale-

(1) This investigation was supported in part by a research grant (B-671) from the National Institute of Neurological Diseases and Blindness of the National Institutes of Health, Public Health Service.

(2) For the preceding communication, see V. Boekelheide, O. Ceder, T. Crabb, Y. Kawazoe, and R. N. Knowles, *Tetrahedron Letters*, **26**, 1 (1960).

(3) Preliminary presentation of this work was made at the Second International Symposium on Natural Products at Prague, Aug. 29, 1962.

(4) (a) Research Associate, National Institutes of Health, 1960–1963; (b) Roche Anniversary Foundation Postdoctoral Fellow, 1963.

(5) H. Wieland, W. Konz, and R. Sonderhoff, *Ann.*, **527**, 160 (1937).

(6) K. Bernauer, S. K. Pavanaram, W. von Philipsborn, H. Schmid, and P. Karrer, *Helv. Chim. Acta*, **41**, 1405 (1958).

(7) K. Bernauer, F. Berlage, W. von Philipsborn, H. Schmid, and P. Karrer, *ibid.*, **41**, 2293 (1958).

(8) F. Berlage, K. Bernauer, W. von Philipsborn, P. Waser, H. Schmid, and P. Karrer, *ibid.*, **42**, 394 (1959).

(9) A. R. Batters-By and H. F. Hodson, *Proc. Chem. Soc.*, 126 (1959).

(10) A. R. Batters-By and H. F. Hodson, *J. Chem. Soc.*, 736 (1960).

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