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STRUCTURAL STUDIES BY NUCLEAR MAGNETIC RESONANCE—XII

CONFORMATIONS AND CONFIGURATIONS OF N-METHYLPHENYLHYDRAZONES

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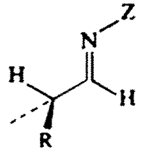
Abstract—Conformations and configurations were assigned to several aldehyde and ketone N-methylphenylhydrazones from analysis of their 60-Mc NMR spectra. Whereas ketone N-methylphenylhydrazones show detectable configurational isomerism about the C=N double bond, aldehyde N-methylphenylhydrazones exist solely as the *syn* isomers. This observation is rationalized in terms of conformational isomerism about the N—N single bond.

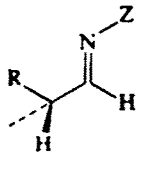
Interpretation of the spin–spin coupling constants of aldehyde N-methylphenylhydrazones in terms of rotamers I and II, whereby a single bond eclipses the double bond, leads to the following results: For α-monosubstituted derivatives when R is Me, Et, i-Pr, or Ph, ΔF_{34}° for I → II is +60, +300, +600 and +700 cal/mole, respectively. When R is *t*-Bu ΔF_{34}° is +2,500 cal/mole. For α,α-disubstituted derivatives when R is Me, Et or i-Pr, ΔF_{34}° for I → II is +100, +350 and +700 cal/mole, respectively. For cyclohexanecarboxaldehyde N-methylphenylhydrazone ΔF_{34}° for I → II is +50 cal/mole.

Some stereospecific spin-spin coupling constants between protons separated by five and six bonds are listed and compared with analogous couplings.

THE relative stabilities of I and II were evaluated when Z is methoxy[2] and compared to those of aliphatic aldehydes.[3] We have extended our NMR studies to N-methylphenylhydrazones, Z = N-methylanilino, as part of a program designed to probe further into the nature of the factors influencing rotamer stability and configurational isomerism about C=N double bonds.



I



II

RESULTS

The chemical shifts, whose accuracy is ±0·03 ppm, and the *syn*/*anti* ratios of representative N-methylphenylhydrazones are summarized in Table 1. The notation

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[1] Fellow of the Alfred P. Sloan Foundation.

[2] G. J. Karabatsos and N. Hsi, *Tetrahedron* **23**, 1079 (1967).

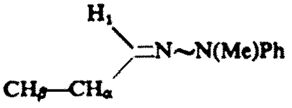
[3] G. J. Karabatsos and N. Hsi, *J. Amer. Chem. Soc.* **87**, 2864 (1965).

TABLE 1. CHEMICAL SHIFTS (τ-VALUES) OF N-METHYLPHENYLHYDRAZONES

$R_1R_2C{=}NN(Me)Ph$			H_1	$H_\alpha(CH)$	$H_\alpha(CH_2)$	$H_\alpha(CH_3)$		$H_\beta(CH_3)$			%	$\Delta F_{38}°$(Kcal/mole)
R_1	R_2	Solvent[a]	*cis*	*trans*	*trans*	*cis*	*trans*	*cis*	*trans*	NCH_3	*syn*[b]/*anti*	(*syn* → *anti*)
H	H	CCl_4	3·68							6·82		
			(3·83)[c]									
H	H	C_6H_6	3·90							7·37		
			(4·04)[c]									
H	Me	Neat	3·41				8·21			7·17	100/0	
H	Me	CCl_4	3·11				7·95			6·75	100/0	
H	Me	C_6H_6	3·48				8·14			7·25	100/0	
H	Et	CCl_4	3·06		7·55				8·82	6·75	100/0	
H	Et	C_6H_6	3·38		7·68				8·92	7·22	100/0	
H	Neopentyl	Neat	3·48		7·86					7·20	100/0	
H	Neopentyl	CCl_4	3·34		7·78					6·84	100/0	
H	Neopentyl	C_6H_6	3·48		7·78					7·30	100/0	
H	Benzyl	CCl_4	3·20		6·34					6·82	100/0	
H	Benzyl	C_6H_6	3·55		6·37					7·37	100/0	
H	i-Pr	CCl_4	3·37						8·85	6·86	100/0	
H	i-Pr	C_6H_6	3·58						8·92	7·32	100/0	
Me	Me	Neat				8·33	8·13			7·22		
Me	Me	CCl_4				8·15	7·97			7·05		
Me	Me	C_6H_6				8·42	8·20			7·17		
Me	Et	CCl_4			7·64	8·13	7·93	8·99	8·80	7·02	86/14	+1·2
Me	Et	C_6H_6			7·85	8·38	8·13	9·27	8·95	7·16	86/14	+1·2
Me	Neopentyl	CCl_4			7·71	8·07	7·87	8·95[d]	9·03[d]	7·00	93/7	+1·7
Me	Neopentyl	C_6H_6			7·82	8·27	8·00	9·02[d]	9·15[d]	7·15	93/7	+1·7
Me	Benzyl	Neat			6·45	8·37	8·17			7·10	80/20	+0·93
					(6·88)[e]					(7·16)[f]		
Me	i-Pr	CCl_4		7·35		8·17	8·00	9·00	8·82	7·02	94/6	+1·8
Me	i-Pr	C_6H_6		7·52		8·37	8·17	9·25	8·93	7·15	94/6	+1·8
Me	t-Bu	CCl_4				8·15			8·80	7·08	100/0	
Me	t-Bu	C_6H_6				8·32			8·87	7·20	100/0	
Me	Ph	CCl_4				7·64				6·82	100/0	

[a] About 10% (v/v) concentrations. [b] *Syn* is the isomer having R_1 *cis* to N-methylanilino group. [c] Resonance of *trans*-H_1. [d] Resonance of γ-protons. [e] Resonance of *cis*-CH_2. The resonance of the *cis*-CH_2 groups of the other compounds listed could not be established. [f] Resonance of NCH_3 *cis* to benzyl.

used to distinguish the various protons is shown in III, each proton being referred to as *cis* or *trans*



III

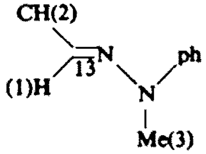
with respect to the N-methylanilino group. Assignment of peaks to *syn* and *anti* isomers is based on previously presented arguments.[4] The *syn*/*anti* ratios were determined by integration of peak areas and are accurate to ±5%.

The absence of detectable configurational isomerism, even after heating or acid treatment, about the C=N double bond of all aldehyde N-methylphenylhydrazones is the most notable feature of the data. We have assigned the *syn* configuration to these isomers for reasons that will be discussed later.

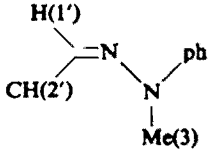
Figures 1 and 2 show the effect of dilution on the chemical shifts of representative N-methylphenylhydrazones. Whereas dilution with benzene shifts the N-methyl proton resonance of acetaldehyde and other aldehyde N-methylphenylhydrazones upfield, it shifts the corresponding resonance of acetone and other ketone N-methylphenylhydrazones downfield.

The UV spectra in Table 2 show additional differences between aldehyde and ketone N-methylphenylhydrazones. Whereas the maximum absorption of the aldehyde derivatives occurs about 278 mμ, that of the ketone derivatives occurs lower and is similar to those of 1-methyl-1-phenylhydrazine and N,N-dimethylaniline.

In Table 3 we have summarized the spin-spin coupling constants between various nuclei, whose notation appears in IV and V.



IV



V

The proton-^{13}C coupling constants, $J_{1-^{13}C}$, whose accuracy is ±2 c/s, were determined from natural abundance spectra and are typical couplings involving sp^2-hybridized carbon atoms. In accord with previously reported[5] J_{HH} values of CH_2=N-systems J_{11} is unusually large.[6]

Another difference between aldehyde and ketone N-methylphenylhydrazones is manifested in J_{23}. The former have finite J_{23} values, whose trend is opposite to that of J_{12}, the latter zero. The J_{12}, with accuracy of ±0·05 c/s, is the coupling pertinent to the problem of rotational isomerism about the single bonds joining the sp^2 to the sp^3 hybridized carbon atoms. In Table 4 we have summarized the effect of temperature on a few of these constants. Their overall correspondence to the analogous couplings of aldehydes[3] and *syn*, but not *anti*, isomers of oxime O-methyl ethers[2] is one indication

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[4] G. J. Karabatsos, R. A. Taller and F. M. Vane, *J. Amer. Chem. Soc.* **85**, 2326 (1963).

[5] B. L. Shapiro, S. J. Ebersole, G. J. Karabatsos, F. M. Vane and S. L. Manatt, *J. Amer. Chem. Soc.* **85**, 4041 (1963).

[6] For an explanation see J. A. Pople and A. A. Bothner-By, *J. Chem. Phys.* **42**, 1339 (1965).

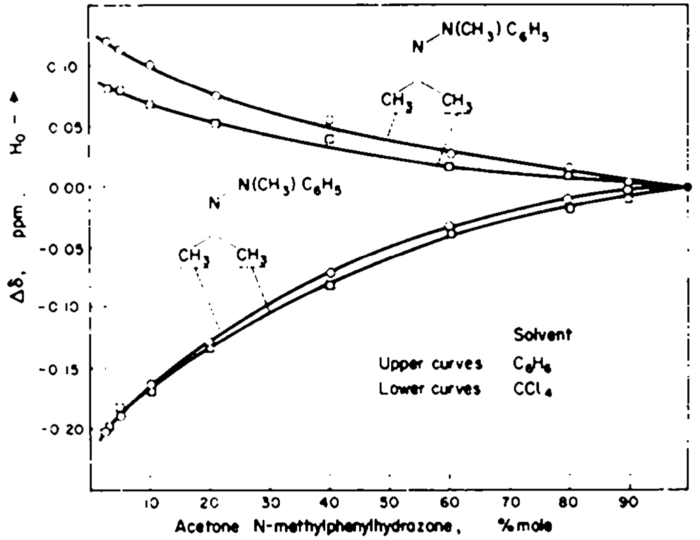


FIG. 1

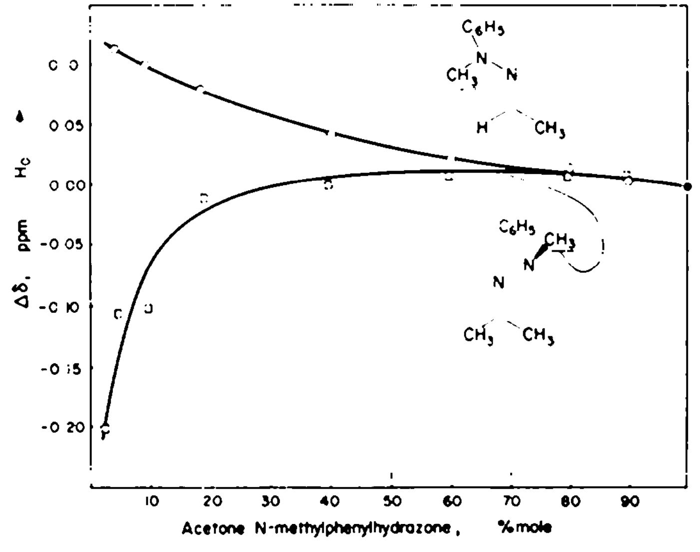


FIG. 2

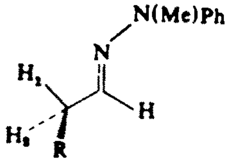
that we have correctly assigned the *syn* configuration to the aldehyde N-methylphenylhydrazone isomers.

DISCUSSION

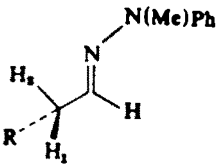
Rotational isomerism. Making the reasonable assumption[2,3] that I and II are the stable rotamers of aldehyde N-methylphenylhydrazones, the relative populations of VI and VII are related to $J_{obs.}$ by Eq. (1), where p is the fractional population of VI, (1-p) that of VII, J_t is the *trans* coupling, and J_g is

$$J_{obs.} = p(J_t + J_g)/2 + (1 - p)J_g \qquad (1)$$

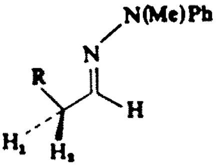
$$J_{obs.} = pJ_t + (1 - p)J_g \qquad (2)$$



VIa



VIb



VII

TABLE 2. UV SPECTRA OF N-METHYLPHENYLHYDRAZONES

$R_1R_2C{=}NN(Me)Ph$ R_1	R_2	Solvent	λ_{max}(mμ)	$\varepsilon \times 10^4$	Plateau^a λ_{max}	Plateau^a $\varepsilon \times 10^3$
H	Me	95% EtOH	278	1·84		
H	Me	cyclohex.	277	1·31		
H	Et	95% EtOH	278	1·84		
H	Et	cyclohex.	277	1·40		
H	*n*-Pr	95% EtOH	279	2·23		
H	3-Pentyl	95% EtOH	279	2·21		
Me	Me	95% EtOH	250	0·95	~288	~3·0
Me	Me	cyclohex.	249	0·59	~280	~1·0
Me	Et	95% EtOH	250	1·03	~277	~3·5
Me	Et	cyclohex.	250	0·45		
$PhN(Me)NH_2$		95% EtOH	247	1·0		
$PhN(Me)_2$		95% EtOH	251	1·5		

[a] In addition to the main peak at 250 mμ the ketone derivatives show this broad and flat shoulder.

TABLE 3. SPIN-SPIN COUPLING CONSTANTS (c/s) OF NEAT N-METHYLPHENYLHYDRAZONES

$R_1R_2C{=}NN(CH_3)C_6H_5$ R_1	R_2	$J_{11'}$	J_{12}	J_{13}	$J_{1'3}$	J_{23}	$J_{2'3}$	$J_{1^{13}C}$
H	H	12·0^a		0·80^a	<0·4^{a,b}			
H	Me		5·06	0·77		0·40		162
H	Et		4·76	0·76		~0·4		154
H	*n*-Pr		5·10	0·66		~0·4		157
H	i-Bu		5·33	0·70		0·3		156
H	Neopentyl		5·98	0·76		<0·2		
H	Benzyl		5·40	0·79		0·3		
H	i-Pr		4·60	0·80		0·3		156
H	sec-Bu		5·24	0·71		~0·2		153
H	3-Pentyl		5·91	0·67		<0·1		155
H	$CH(Et)(CH_2)_3Me$		5·97	0·70		<0·1		
H	$CH(CHMe_2)_2$		6·39	0·71		<0·1		
H			4·48	0·72		<0·2		158
Me	Me					0^c	0	
Me	Et					0	0	
Me	Neopentyl					0	0	
Me	i-Pr					0	0	
Me	t-Bu						0	
Et	Et					0	0	

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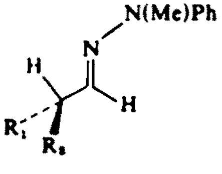
[a] Values from 10% CCl_4 sol. [b] Estimated from the half-width, about 1·8 c/s, of H(1'). [c] All values reported as zero are estimated from the half-widths of the appropriate H(2), H(2') and H(3). These half-widths are about 0·5 c/s, as compared with a 0·4 c/s half-width of the TMS signal.

Table 4. Effect of temperature on $J_{H_\alpha H_1}(J_{12})$ of some N-methylphenylhydrazones

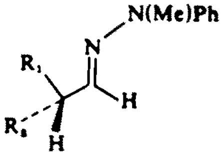
$R_1R_2CH_2CH_1{=}NN(Me)Ph$		$J_{H_\alpha H_1}$ (c/s)*			
R_1	R_2	0°	36°	65°	95°
H	H	5·06	5·06	5·10	5·08
H	Me	4·78	4·76	4·71	
H	t-Bu		5·98	5·90	5·60
Et	Et		5·91	5·83	5·60
			4·41		4·43

* These values, accurate to ±0·05 c/s, are from neat solns.

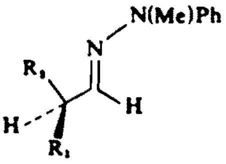
the *gauche*. Equation (2) relates the populations of VIII and IX to $J_{obs.}$, where p is



VIII



IXa



IXb

the fractional population of VIII and (1 − p) that of IX. The free energy differences for $VI_a \rightarrow VII$ and $VIII \rightarrow IX_a$ are expressed by Eqs. (3) and (4), respectively.

$$\Delta F^\circ_{VI_a \rightarrow VII} = -RT \ln (J_t + J_g - 2J_{obs.})/(J_{obs.} - J_g) \quad (3)$$

$$\Delta F^\circ_{VIII \rightarrow IX_a} = -RT \ln \tfrac{1}{2}(J_t - J_{obs.})/(J_{obs.} - J_g) \quad (4)$$

The J_t and J_g needed for calculation of p and ΔF° can be calculated from Eqs. (5) and (6), by assuming that

$$J_{obs.}\ (\text{acetaldehyde deriv.}) = \tfrac{1}{3}(J_t + 2J_g) \quad (5)$$

$$J_{obs.}\ (t\text{-butylacetaldehyde deriv.}) = \tfrac{1}{2}(J_t + J_g) \quad (6)$$

t-butylacetaldehyde N-methylphenylhydrazone exists exclusively in VI. In view of our previous results[2,3] such an assumption is reasonable. As mentioned,[2,3] however, an error would be introduced in p and ΔF°, because of the incorrect assumption that J_t and J_g are independent of the α-carbon substituents. This error can be diminished by applying a 0·4 c/s correction for each alkyl or aryl α-substituent, i.e. by increasing $J_{obs.}$ of each monosubstituted derivative by 0·4 c/s and of each disubstituted by 0·8 c/s.[7] We have thus calculated $J_t = 10{\cdot}3$ c/s, $J_g = 2{\cdot}4$ c/s, and the p and ΔF° values reported in Table 5. For reasons previously discussed[2,3] the ΔF° values are probably reliable to ±30%.

Since ΔH° and $\Delta F_{36}{}^\circ$ values between I and II are comparable in magnitude,[2,3] it is interesting to compare now the relative stabilities of I and II as a function of Z. Although any firm conclusions at this stage will be premature and must await further experimentation, apparently increase in the electronegativity of Z decreases the ratio

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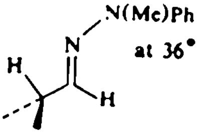
[7] The correctness of our choice of 0·4 c/s is supported further by the temperature variation of $J_{obs.}$ of propionaldehyde and cyclopropanecarboxaldehyde N-methylphenylhydrazones (Table 4).

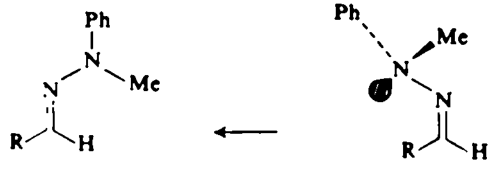
TABLE 5. ROTAMER POPULATIONS AND $\Delta F°$ VALUES OF N-METHYLPHENYLHYDRAZONES

$R_1R_2CHCH{=}NN(Me)Ph$		%  at 36°	$\Delta F_{36}°$ for $VI_a \to VII$ (cal/mole)
R_1	R_2		
H	Me	69	+60
H	Et	78	+300
H	i-Pr	84	+600
H	Ph	86	+700
H	t-Bu	99[a]	+2,500[a]
			$\Delta F_{36}°$ for $VIII \to IX_a$
Me	Me	38	+100
Et	Et	46	+350
i-Pr	i-Pr	59	+700
		35	+50

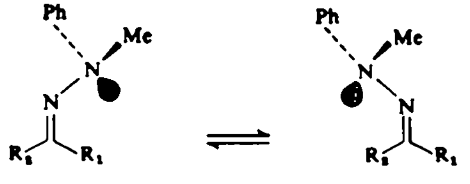
[a] Values at 65°.

II|I. For example, whereas $\Delta F_{36}°$ for I → II of propionaldehyde oxime O-methyl ether is about +300 cal/mole, the corresponding value of propionaldehyde N-methylphenylhydrazone is only +60 cal/mole.

Conformations of the N-*methylanilino group*. The absence of detectable configurational isomerism about the C=N double bond of the aldehyde, but not of the ketone, N-methylphenylhydrazones may be rationalized in terms of rotational isomerism about the N—N single bond. For example, whereas in isomer X the unshared electron pair orbital on the anilino nitrogen is parallel to and overlaps with the π-orbitals of the C=N double bond, in isomer XI, as a result of nonbonded repulsions between R and N-methylanilino, it would be orthogonal to the π-orbitals. The ensuing loss of resonance stabilization in IX might therefore be responsible for the presence of



X XI

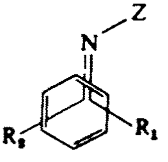


XII XIII

only X isomers. In contrast to the aldehyde N-methylphenylhydrazone isomers, both isomers of the ketone N-methylphenylhydrazones would suffer loss of overlap (XII and XIII), and their relative stabilities would therefore be primarily a function of the nonbonded interactions between R_1, R_2 and N-methylanilino. The correctness of this explanation is supported by the following:

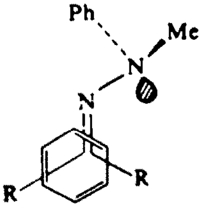
(a) *UV Spectra.* Conformations XII and XIII require that the ultraviolet spectra of ketone N-methylhydrazones be similar to those of N,N-disubstituted anilines. Indeed, their 250 mμ maximum absorption is similar to the 247 mμ absorption of 1-methyl-1-phenylhydrazine and to the 251 mμ absorption of N,N-dimethylaniline. In contrast, the λ_{max} of X should be bathochromically shifted, as is the case, on account of conjugation between the carbon-nitrogen double bond and the N-anilino group.

(b) *Solvent effects on chemical shifts.* Orientation of benzene by interaction with the C=N double bond (XIV) is a common and important feature of compounds having C=N double bonds. In the present case, judging by the larger upfield shift of the *trans*-α-methyl over the *cis*-α-methyl protons (Fig. 1) on dilution with benzene, the benzene is probably closer to R_2 than R_1.

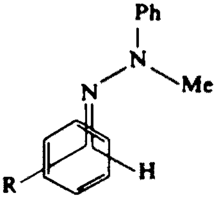


XIV

If our assumptions on the conformations of the N-methylanilino groups are correct, then, on the basis of XV and XVI, the N-methyl protons of the aldehyde N-methylhydrazones should be shifted upfield on dilution with benzene, whereas the corresponding protons of the ketone N-methylphenylhydrazones should be shifted downfield. The results (Fig. 2) cogently support this argument.



XV



XVI

Long range couplings. Like all long range spin–spin couplings[8] the five bond, J_{13} and $J_{1'3}$, and six bond, J_{23} and $J_{23'}$, couplings observed in the present work are stereospecific. As might have been anticipated, the stereochemical dependence of the five bond coupling (XVII) is similar to that of the analogous four bond (XVIII).[9]

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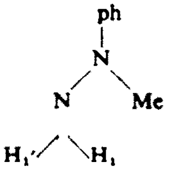
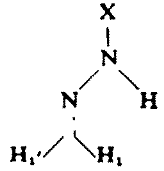
[8] For a review on long range coupling see S. Sternhell, *Revs. Pure Appl. Chem.* **14**, 15 (1964).

[9] G. J. Karabatsos, B. L. Shapiro, F. M. Vane, J. S. Fleming and J. S. Ratka, *J. Amer. Chem. Soc.* **85**, 2784 (1963).

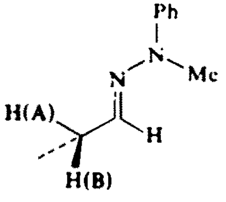


XVII $J_{H_1Me} = 0{\cdot}7$–$0{\cdot}8$ c/s.
$J_{H_1Me} < 0{\cdot}4$ c/s

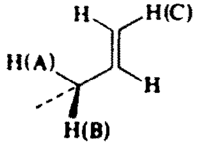


XVIII $J_{H_1H} = 0{\cdot}7$–$0{\cdot}8$ c/s
$J_{H_1,H} < 0{\cdot}1$ c/s

The stereospecificity of the six bond coupling, J_{23}, is borne out by its decrease on increase of the populations of VI and VIII. Disregarding the sign of the coupling, J_{B-CH_3} is therefore greater than J_{A-CH_3} (XIX). A similar trend was observed[10] with

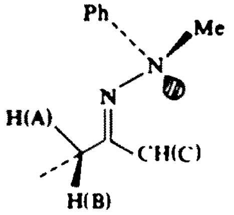


XIX



XX

the four bond coupling (XX) involving A, B and C. The further dependence of J_{23} on the conformation of the N-methylanilino group is summarized under XXI.



XXI $J_{A-Me} = J_{B-Me} = J_{C-Me} = 0$

EXPERIMENTAL

Preparation of N-methylphenylhydrazones. To 0·05 mole 1-methyl-1-phenylhydrazine in 10 ml water, after addition of sufficient glacial AcOH to dissolve the hydrazine, was added dropwise 0·05 moles of the appropriate aldehyde or ketone. After stirring the mixture for 30 min at room temp, the organic layer was separated, dried over K_2CO_3, and fractionated under reduced press. All products were oils. Di-t-butylacetaldehyde did not form the corresponding N-methylphenylhydrazone even under reflux conditions.

NMR spectra were determined at 60-Mc on a Model A-60 spectrometer (Varian Associates, Palo Alto, Calif.). Undegassed sol were used with TMS as internal reference.

UV spectra were taken at 25° with a Beckman D.B. spectrophotometer.

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[10] A. A. Bothner-By, C. Naar-Colin and H. Günther, *J. Amer. Chem. Soc.* **84**, 2748 (1962).