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Preparation and Spectral Studies of Heterocyclic Hydrazone Analogs

Michael McAneny

PREPARATION AND SPECTRAL STUDIES OF HETEROCYCLIC HYDRAZONE ANALOGS

by

Michael McAneny

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Michael McAneny

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INTRODUCTION

Considerable attention has been given to the problem of correlating the ultraviolet spectra and structure of hydrazones and a review of the subject has been completed recently by Weber.[4,10,11] Weber collected the spectra of several compounds having either three or four alkyl or aryl substituents on the hydrazone chromophore, $\rangle C = N - N \langle$. He found marked differences in the spectra for these two structural types. All of these compounds exhibited a long wavelength absorption with the wavelength depending upon the degree of aryl substitution. However, a distinct difference was noted in the molar extinction coefficients for the spectra of the two types of compounds depending upon the degree of substitution. The absorbance of the trisubstituted compounds was usually as much as five times as great as that of the analogous tetrasubstituted compound. He concluded that this difference was related to significant steric hindrance present in the tetrasubstituted hydrazones and absent or less severe in the trisubstituted compounds. It was interpreted that this steric hindrance prevented the molecule from assuming conformations which allow high probability for the interactions necessary to produce the high intensity long wavelength absorption. As a means of further investigating this steric effect, a study of the ultraviolet spectra of heterocyclic hydrazone analogs was proposed where the steric hindrance would be controlled by ring structure. Thus, it would be expected that the five or six atom heterocyclic compounds which are analogous

to tetrasubstituted hydrazones would have ultraviolet spectra which are closely related to the spectra of trisubstituted hydrazones.

The preparation and spectral examination of such compounds and the correlation of their spectra with those of related hydrazones was the objective of the work described here.

EXPERIMENTAL

Preparation of Compounds

General procedure

The pyrazolines and tetrahydropyridazines were prepared by condensing an appropriately substituted hydrazine with the required aldehydes or ketones to form the desired heterocyclic compounds. In order to effect the cyclization, the carbonyl compound contained a leaving group on either the β or γ carbon atom, e.g. -Cl, $-N^{+}(CH_3)_3$. In one case an α, β unsaturated or terminally unsaturated compound was used.

The organic starting materials were obtained from Distillation Products Inc. or Aldrich Chemical Co. and all analyses were completed by Galbraith Microanalytical Laboratories.

Preparation of 1-Methylpyrazoline. Following the method of Ioffe and Zelenin[6] methylhydrazine (23 g, 0.5 mole) and monosodium phosphate monohydrate (70 g, 0.5 mole) were dissolved in water (150 ml) and acrolein (28 g, 0.5 mole) was added dropwise while the mixture was cooled in an ice-salt bath. After 0.5 hr potassium hydroxide (50 g) was added. The reaction mixture was then allowed to come to room temperature and, after separation, the organic layer was distilled. The oil collected was again treated successively with potassium hydroxide and with potassium carbonate. Redistillation of the organic material provided 3.0 g of 1-methylpyrazoline, b.p. 109°, n_D^{20} 1.4544. Lit. values:[6] b.p. 109.0-109.4°; n_D^{20} 1.4548.

Preparation of 1-Phenylpyrazoline. A method similar to that above was used for the preparation of 1-phenylpyrazoline; phenylhydrazine (30.0 g, 0.28 mole) and monosodium phosphate monohydrate (35.0 g, 0.25 mole) were combined in water (75 ml) to form a paste-like mixture. Acrolein (14 g, 0.25 mole) was added in portions with constant mixing followed by addition of aqueous sulfuric acid (2%) solution (300 ml). The 1-phenylpyrazoline was separated from the hydrazine salts by steam distillation. The yellow oil which collected solidified and after crystallization from 60-110° petroleum ether gave 2.6 g, of pure 1-phenylpyrazoline: m.p. 51-52°. Lit. value:[3] m.p. 51-52°C.

Preparation of 1-Phenyl-3-methylpyrazoline. Following the procedure reported by Nazarov, Matsoyan, and Vartanyan[9], γ-ketobutylacetate (13.7 g, 0.08 mole) was added to a solution of sodium acetate trihydrate (6.8 g, 0.05 mole) dissolved in 80 ml of a 3:1 ethanol-water mixture. Phenylhydrazine (8.7 g, 0.08 mole) was added from a dropping funnel and the solution was stirred. This mixture was allowed to stand for 0.25 hr and then refluxed for 8 hr. The solvent was decanted from the solid product and the 1-phenyl-3-methylpyrazoline was purified by recrystallization from ethanol to provide 1.4 g of white needles, m.p. 73-76°C. Lit. value[9]: b.p. 76-77°C.

Preparation of 1,3-Diphenylpyrazoline. Phenylhydrazine hydrochloride (7.25 g, 0.05 mole), β-dimethylaminopropiophenone hydrochloride (10.65 g, 0.05 mole), 10 ml 10% aqueous sodium solution and

15 ml acetic acid were dissolved in 250 ml ethanol and the mixture refluxed for 45 minutes. At the end of this time the solution was neutralized with 125 ml of 10% aqueous sodium hydroxide and extracted with ethyl ether. The ether solution was dried over magnesium sulfate, and the solvent removed by vacuum evaporation to produce a yellow solid. Recrystallization from ethanol produced 2.5 g of pure 1,3-diphenyl-pyrazoline, yellow needles, m.p. 154°. Lit. value[8]: m.p. 152.5-153°C.

Preparation of 1,3-Diphenyl-1,4,5,6-tetrahydropyridazine. γ-Chlorobutyrophenone (9.1 g, 0.05 mole) and phenylhydrazine (5.4 g, 0.05 mole) were dissolved in 50 ml of absolute ethanol and then refluxed for 2.5 hr. After cooling the alcohol solution the precipitated solid was washed with 10% aqueous sodium hydroxide solution (250 ml). The yellow solid was dissolved in benzene and the solution dried over magnesium sulfate. Concentration produced a pale yellow solid. The solid was recrystallized from ethanol and dried in vacuo to yield 1.6 g pale yellow leaflets of 1,3-diphenyl-1,4,5,6-tetrahydropyridazine: m.p. 138-139°C.

The n.m.r. spectrum in deuterochloroform showed absorption at δ 2.1 (2H, triplet, J = 5.5 cps); δ 2.6 (2H, triplet, J = 5.5 cps); δ 3.6 (2H, triplet, J = 5.5 cps) and a complex aromatic multiplet δ 6.85-7.9 (10 H).

Anal. Calcd. for $C_{16}H_{16}N_2$: C, 81.31; H, 6.82; N, 11.85. Found: C, 81.34; H, 6.85; N, 11.71.

Preparation of 3-Phenylpyrazoline. β-Trimethylaminopropiophenone iodide (15.4 g, 0.05 mole) and 100 ml absolute ethanol were combined

and heated at reflux to effect solution of the quaternary ammonium salt. Hydrazine (1.6 g, 0.05 mole) was added dropwise to the hot ethanol solution and reflux was continued for 3 hr. After cooling to room temperature the ethanol solution was combined with 10% aqueous sodium hydroxide solution (200 ml) and water (100 ml). Cooling in a refrigerator caused the formation of a precipitate which after recrystallization from ethanol gave 1.6 g of pure 3-phenylpyrazoline m.p. 107-108°. Lit. value[2]: m.p. 44-45°.

The n.m.r. spectrum in deuterochloroform showed a complex collection of signals at δ 2.9-3.2 (4 H), a singlet at δ 5.95 (1 H broad) and a multiplet δ 7.2-7.9 (5 H).

Anal. Calcd. for $C_9H_{10}N_2$: C, 73.94; H, 6.90; N, 19.16. Found: C, 73.77; H, 7.12; N, 18.9.

Preparation of 1-Methyl-3-Phenyl-1,4,5,6-Tetrahydropyridazine. Following a method similar to that of Grandberg, Kost, and Terent'ev[5], a solution of γ-chlorobutyrophenone (5.5 g, 0.03 mole) in 3 ml absolute ethanol was added dropwise to methylhydrazine (1.3 g, 0.03 mole) dissolved in 3 ml absolute ethanol. The resulting solution was then refluxed on a steam bath for 1.75 hr. The reaction solution was allowed to cool, neutralized with aqueous ammonia, and extracted with ether. The ether solution was dried over magnesium sulfate, decanted, and the ether removed by vacuum evaporation. The resulting yellow oil was vacuum distilled to produce 0.7 g 1-methyl-3-phenyl-1,4,5,6-tetrahydropyridazine: b.p. 119°, $n_D^{25°}$ 1.5906. The compound, decomposed with the development of a dark coloration when exposed to

light or air, and no satisfactory elemental analysis was obtained. Analysis performed on a sample sealed under nitrogen and sent by airmail to the analyst gave the results indicated below. The above properties were observed after repeated vacuum distillation.

Anal. Calcd. for $C_{11}H_{14}N_2$: C, 75.82; H, 8.09; N, 16.08. Found: C, 75.32; H, 8.04; N, 14.32.

The n.m.r. spectrum was consistent with the assigned structure. Three complex triplets at δ 1.9, 2.3, and 2.7 (2 H each multiplet), a singlet at δ 2.85 (3 H), and a complex multiplet at δ 7.1-7.7 (5 H).

The ultraviolet absorption spectra of the above compounds dissolved in 95% ethanol or 6N ethanolic hydrogen chloride were measured between the wavelengths 200 and 400 mμ using a Cary Model 14 spectrophotometer. The n.m.r. spectra were obtained with a Varian A-60 spectrometer. The following table summarizes the ultraviolet spectra. Summaries of spectra for analogous hydrazones have been taken from the literature and are also presented in the table.

TABLE I

Ultraviolet Spectra of Substituted
Hydrazones and Related Heterocyclic Compounds

Compound	Solvent	λ(mμ)	ε	λ(mμ)	ε	λ(mμ)	ε	λ(mμ)	ε
1,3-Diphenylpyrazoline	Ethanol	243	13,300	303 sh	7,500	356	19,400		
	Alc. HCl	254	14,850	315 sh	2,500	365	1,930		
1,3-Diphenyl-1,4,5,6-tetrahydropyridazine	Ethanol	233	13,080	310 sh	11,300	340	18,600		
1-Phenyl-3-methyl-pyrazoline	Ethanol	244 sh	5,500	276	12,000				
	Alc. HCl			282	900				
1-Methyl-3-phenyl-1,4,5,6-tetrahydropyridazine	Ethanol	224	7,436	292	9,912				
3-Phenylpyrazoline	Ethanol	220	8,180	283	8,260				
1-Phenylpyrazoline	Ethanol	240 sh	5,800	280	12,800				
1-Methylpyrazoline	Ethanol	236	3,600						

TABLE I (cont.)

Ultraviolet Spectra of Substituted
Hydrazones and Related Heterocyclic Compounds

Compound	Solvent	λ (mμ)	ε	λ (mμ)	ε	λ(mμ)	ε	λ(mμ)	ε
Acetophenonephenyl-hydrazone[a]	Ethanol	232	12,850	244 sh	11,500	302 sh	13,750	330	19,900
Acetophenonemethylphenyl-hydrazone[a]	Ethanol			250	20,900	288	2,650	347	3,850
	Alc. HCl			244	14,450	278	2,000	358	195
Acetonemethylphenyl-hydrazone[a]	Ethanol			249	10,900	283	3,350		
	Alc. HCl	229	6,550			270	710		
Acetonephenylhydrazone[a]	Ethanol	End Absorption				270	16,800		
	Alc. HCl	222	14,450			273	3,050		
Acetophenonemethyl-hydrazone[b]	Methanol	206	12,050	218 sh	7,950	278	9,980		
Acetophenonedimethyl-hydrazone[b]	Methanol	206	11,200	234	11,200	308	2,160		

a. See Reference 11. b. See Reference 1.

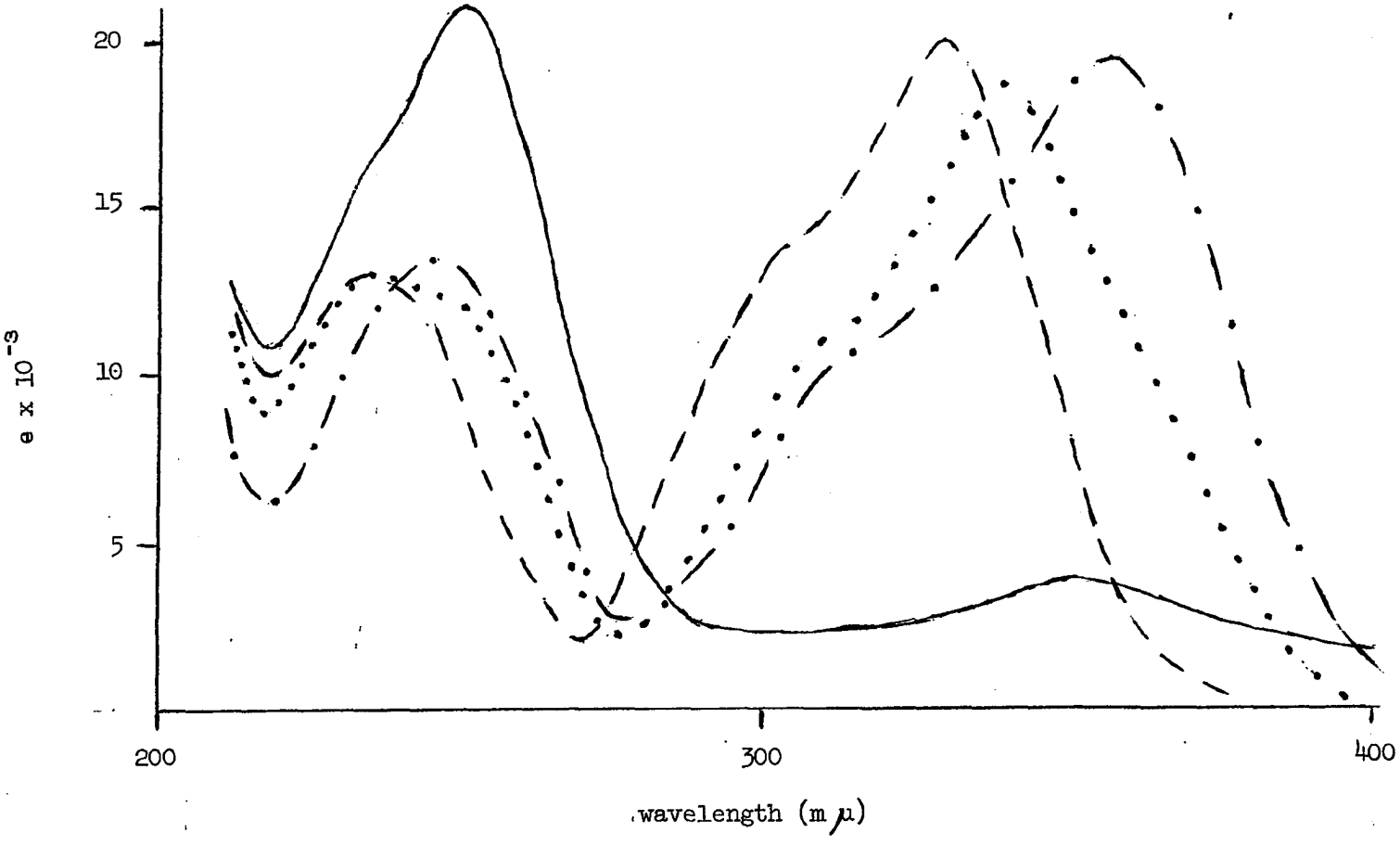

Figure 1. Selected Spectra of Hydrazones and Related Heterocyclic Compounds

—·—· 1,3-Diphenylpyrazoline

····· 1,3-Diphenyl-1,4,5,6-tetrahydropyridazine

- - - - Acetophenonephenylhydrazone

——— Acetophenonemethylphenylhydrazone

DISCUSSION OF EXPERIMENTAL RESULTS

A comparison of the ultraviolet spectra of acetonephenylhydrazone, acetonementhylphenylhydrazone, and 1-phenyl-3-methylpyrazoline reveals the following relationship. The ultraviolet spectra of acetone-methylphenylhydrazone and acetonephenylhydrazone differ greatly in the intensity of the long wavelength absorption at 270-290 mμ. The molar extinction coefficient for the trisubstituted hydrazone is approximately five times as large as the value for the tetrasubstituted compound while it is only 1.4 times as large as the value measured for analogous five atom ring heterocyclic compound. Because the difference in the electron releasing capabilities of an alkyl group substituent and a hydrogen atom is not large in organic molecules, it is reasonable to conclude that the same electronic interactions are involved in the absorptions of all three compounds. That is, the same chromophore is in operation in all three compounds. Thus, the major differnece observed (extinction value) is related to the probability of achieving similar excited states.

The spectral variations are more striking for a second group of compounds including acetophenonemethylhydrazone, acetophenonedimethyl-hydrazone, 1-methyl-3-phenyl-1,4,5,6-tetrahydropyridazine, and 3-phenyl-pyrazoline. In this series of compounds the extinction coefficient for the trisubstituted compound is again in the order of five times greater than that of the tetrasubstituted hydrazone; while it is only six per-cent greater than the value obtained for the corresponding six membered

ring heterocyclic compound. In addition to this the extinction coefficient value for 3-phenylpyrazoline, while being smaller than the value for acetophenonemethylhydrazone, is nevertheless of the same order indicating that the effect of replacing the amino hydrogen atom with a methyl group is small.

A similar relationship is observed for the series of compounds which includes acetophenonemethylphenylhydrazone, acetophenonephenylhydrazone, 1,3-diphenylpyrazoline, and 1,3-diphenyl-1,4,5,6-tetrahydropyridazine. In this case a long wavelength absorption occurs between 340 and 365 mμ. The molar extinction coefficient for the trisubstituted compound is again five times as large as that of the tetrasubstituted compound; while it is only three percent larger than the extinction coefficient for the five atom ring heterocyclic analog, 1,3-diphenylpyrazoline, and six percent larger than that of 1,3-diphenyl-1,4,5,6-tetrahydropyridazine, the six atom heterocyclic compound. In order to illustrate these features more clearly, the spectra of these four compounds having phenyl substitution on the carbon and nitrogen atoms are reproduced in Figure 1. Since the only substituent change in the two series described is replacement of a hydrogen atom with a methyl group, it is again concluded that the absorption spectra are due to the same chromophore in all four compounds.

When the ultraviolet spectra for the trisubstituted hydrazone and heterocyclic compound in the two series was obtained in 6N ethanolic hydrogen chloride the intensity of the long wavelength absorption was

found to be greatly diminished. In strong acid the amino nitrogen atom, which is more basic than the imino nitrogen atom is protonated. This prevents the delocalization of the extra pair of electrons thus prohibiting their excitation to higher energy states by the absorption of low energy (long wavelength) ultraviolet light.

Both the amino and imino nitrogen atoms in these molecules have a non-bonding pair of electrons which influence the ultraviolet spectra. These non-bonding electrons at the amino nitrogen atom are probably in an sp^3 hybridized atomic orbital, and those of the imino nitrogen are in an sp^2 orbital. For interaction to occur between these electrons and the electrons of the carbon-nitrogen pi bond the molecule must assume a conformation which will permit the axis of the non-bonding orbital of the amino nitrogen atom to become coplanar with the axis of the p orbital of the imino nitrogen atom which is part of the carbon-nitrogen pi system. According to Weber and examples cited by Wepster,

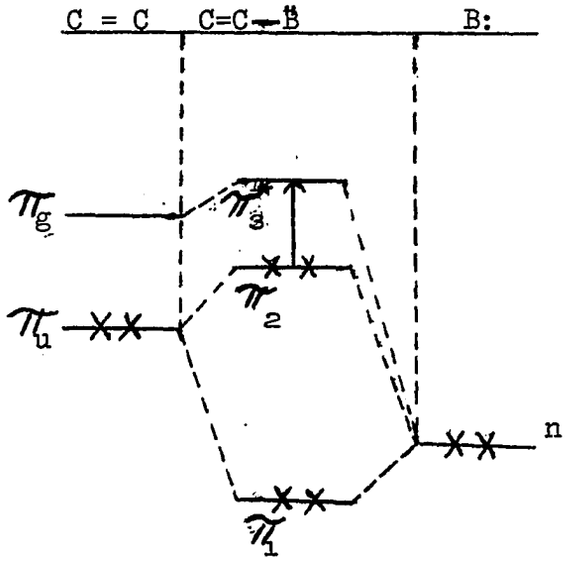

Fig. 2.[7] Energy levels for a substituted ethylene, C=C—B:.

this overlap can result in the formation of a non-linear, non-localized pi bond which is important in describing the ground state for unhindered hydrazones but not significant for hindered hydrazones in which orbital overlap is reduced.

Jaffe and Orchin discuss in molecular orbital terminology an analogous situation of an atom having a non-bonding pair of electrons adjacent to one of a pair of pi bonded carbon atoms. The ground state is described by two pi molecular orbitals, π_1 and π_2, and excitation may occur by a $\pi_2 \longrightarrow \pi^*_3$ transition. The π_2 energy level is higher than the n or π_u energy levels which results in a low energy (long wavelength) transition to the π^*_3 level (see Fig. 2).

The pyrazolines and 1,4,5,6-tetrahydropyridazines are structurally similar to tetrasubstituted hydrazones. However, where the open chain molecule is sterically hindered in assuming conformations allowing effective orbital overlap, the heterocyclic molecule is forced into a planar or near-planar conformation by ring structure and thereby allows orbital overlap as in the trisubstituted chromophore. On the basis of the small difference between the long wavelength extinction values for trisubstituted hydrazones and pyrazolines, the ring confines the amino nitrogen in essentially the same conformations it assumes in the non-cyclic derivatives.

The observed ultraviolet spectra of the tri and tetrasubstituted hydrazones presented earlier may be interpreted, in part, as follows: The effect of strong acid in reducing the intensity of the long wavelength band confirms the involvement of the non-bonding electrons of the terminal nitrogen atom in this electron excitation. The intensity of the

absorption related to this transition is a function of the concentration of the molecules possessing the necessary ground state for this excitation. This concentration will be proportional to the population of conformers possessing the necessary geometry to provide these ground and excited states. These states require coplanar or near coplanar geometry for the planes which include the carbon and terminal nitrogen atoms of the chromophore and their attached atoms or groups. The concentration of conformers possessing this geometry and related electronic states is high for those molecules having only three substituents on the chromophore. Accordingly, the molar extinction coefficient is large. However, the presence of four substituents modifies the conformation composition. As a result of the steric factor proposed by Weber the concentration of conformers having the coplanar or near coplanar geometry described above is less when four substituents are attached to the chromophore. Correspondingly, the number of molecules possessing the necessary electronic states for the long wavelength absorption will be reduced and the absorption intensity is also reduced. In this case the spectra now include absorptions resulting from excitations occurring in the "isolated" chromophore portions i.e. $\rangle C = N -$ and $-\overset{\cdot\cdot}{N}-Ar$.

The effect of the five or six atom ring in the heterocyclic analogs is to minimize the concentration of conformers having a large twist angle at the nitrogen-nitrogen atom band. Consequently, the concentration of conformers having the coplanar or near coplanar geometry at the carbon and terminal nitrogen atoms is high.

The observation that the molar extinction coefficients for these heterocyclic compounds (substituted pyrazolines and tetrahydropyridazines) is comparable to that of the trisubstituted hydrazones indicates that the conformer populations (with respect to the nitrogen-nitrogen atom bond) in these two groups of compounds is similar. Thus, as observed, the ultraviolet spectra of the substituted pyrazolines and tetrahydropyridazines is similar (high intensity long wavelength band) to the spectra of related trisubstituted hydrazones. This similarity exists for the 1- or 3-monosubstituted heterocyclic compounds or the 1,3-disubstituted compounds. This observation necessitates the incorporation of the steric effect in the partial interpretation of the ultraviolet spectra of the tri and tetrasubstituted hydrazone chromophores as first proposed by Weber.

SUMMARY

A number of alkyl and aryl substituted pyrazolines and 1,4,5,6-tetrahydropyridazines have been prepared and their ultraviolet spectra obtained. 1,3-Diphenyl-1,4,5,6-tetrahydropyridazine and 1-phenyl-3-methyl-1,4,5,6-tetrahydropyridazine have not been previously described. Although they are structurally similar to tetrasubstituted hydrazones their spectra are similar to trisubstituted hydrazones. This substantiates previous evidence that the spectral differences between trisubstituted and tetrasubstituted hydrazones are a consequence of steric hindrance in the tetrasubstituted compounds.

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VITA

The author was born November 29, 1943, in Johnstown, Pennsylvania. He attended Bishop McCort High School in that city graduating in 1961. In June, 1965 he received the degree of Bachelor of Science from John Carroll University, Cleveland; and entered the graduate school at Western Michigan University in August of that year.