The Nuclear Magnetic Resonance Spectra and Structure of Aliphatic Azoxy Compounds[1]

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The structure of unsymmetrical aliphatic azoxy compounds may be determined by the chemical shifts of the groups attached to the nitrogen atoms. The application of this technique to the structure of nitroso dimers and the cupferron alkylation products confirm previous assignments. The potential utility of nuclear magnetic resonance for the determination of the stereochemistry of aliphatic azoxy compounds is indicated.

While the structures of unsymmetrical aromatic azoxy compounds may be determined by reference to their ultraviolet spectra and by competitive electrophilic substitution reactions,[2] efforts to assign structures to unsymmetrical aliphatic azoxy compounds by chemical means have been frustrated because the reactions themselves depend upon the attached groups.[3] Nuclear magnetic resonance spectroscopy should be a unique tool for solving this problem since the groups attached to the two nitrogen atoms should differ greatly in their chemical shifts. The structures of the thiolsulfonates resulting from oxidation of unsymmetrical disulfides have been determined in this way.[4] It was presumed that the group attached to the oxidized nitrogen would appear at lower field, as was found to be true of the thiolsulfonates. From the data summarized in Table I, it can be seen that these

TABLE I

Compound		Chemical shift, τ[a]
$(CH_3)_3C-N(\rightarrow O)=N-C(CH_3)_3$[b]	(I)	8.72, 8.52
$(CH_3)_3C-N(\rightarrow O)=CHC_6H_5$[c]	(II)	8.50
$(CH_3)_3C-N=CHC_6H_5$[c]	(III)	8.75
$CH_3N(\rightarrow O)=NCH_3$[d]	(IV)	6.93, 5.95
$CH_3N(\rightarrow O)=NOSO_2C_7H_7$[e]	(V)	6.00
$C_6H_5CH_2N(\rightarrow O)=NCH_2C_6H_5$[b]	(VI)	5.65, 4.98
$C_6H_5CH_2N(\rightarrow O)=NOSO_2C_7H_7$[e]	(VII)	4.80

[a] The spectra were measured on 10% solutions in carbon tetrachloride containing tetramethylsilane, using a Varian Associates V-4300B 40-Mc. n.m.r. spectrometer. [b] Experimental section. [c] W. D. Emmons, *J. Am. Chem. Soc.*, **79**, 5739 (1957). [d] B. W. Langley, B. Lythgoe, and L. S. Rayner, *J. Chem. Soc.*, 4191 (1952). [e] Ref. 12.

basic assumptions necessary for structure assignment are correct; *i.e.*, the shifts of the two groups are different and the group attached to the quaternary nitrogen is found at lower field. The application of these data to the products of several reactions follows.

1. Condensation of Hydroxylamines and Nitroso Compounds.—In the aromatic series the synthesis of unsymmetrical azoxy compounds by the condensation of an aryl nitroso compound with another arylhydroxylamine is not practical because disproportionation occurs and generally leads to a mixture of the two symmetrical azoxy compounds.[5] However, one report of such a reaction in the aliphatic series indicated that unsymmetrical azoxy compounds could be obtained.[6] Since new efficient routes to aliphatic nitroso compounds[7] and hydroxylamines[8] have become available recently, their reaction would provide a route to a variety of unsymmetrical aliphatic azoxy compounds if this preliminary report[6] were correct. However, it also has been reported that the condensation of benzylhydroxylamine with nitrosobenzene yields a mixture of ω-azoxytoluene (monomer[9] or dimer[10]) and azoxybenzene,[9] the products of disproportionation.

From the limited data presented it seemed that Aston and Jenkins had obtained an unsymmetrical azoxy compound from the reaction of N-methylhydroxylamine with 1-nitroso-1,1,3,3-tetramethylbutane; the position of the oxygen was not determined rigorously, but the structure of the compound was suggested to be N-*t*-octyl-N′-methyldiazine N′-oxide (VIII).[6]

$$CH_3NHOH + (CH_3)_3CCH_2C(CH_3)_2NO \longrightarrow CH_3N(\rightarrow O)=NC(CH_3)_2CH_2C(CH_3)_3$$

VIII

This reaction was re-examined using 2-nitroso-2-methylpropane.[7] The product isolated was a mixed azoxy compound whose n.m.r. spectrum consisted of two sharp singlets at 8.47 and 6.90 τ. Based on the chemical shift data of compounds I–V in Table I, the correct structure of the condensation product must be N-methyl-N′-*t*-butyldiazine N′-oxide (IX). The spec-

$$CH_3NHOH + (CH_3)_3CNO \longrightarrow CH_3N=N(\rightarrow O)C(CH_3)_3$$

IX

(1) This research was carried out under Army Ordnance contract DA-01-021 ORD-11878.

(2) A. Angeli and B. Valori, *Atti Accad. Naz. Lincei*, **21**, 155 (1912).

(3) B. T. Gillis and K. F. Schimmel, *J. Org. Chem.*, **27**, 413 (1962).

(4) P. Allen, Jr., D. J. Berner, and E. R. Malinowski, *Chem. Ind.*, 1164 (1961).

(5) E. Bamberger, *Ber.*, **33**, 1941, 1953 (1900).

(6) J. G. Aston and D. M. Jenkins, *Nature*, **167**, 863 (1951).

(7) W. D. Emmons, *J. Am. Chem. Soc.*, **79**, 6522 (1957).

(8) H. Feuer and B. F. Vincent, Jr., *ibid.*, **84**, 3771 (1962).

(9) B. M. Lynch and K. H. Pausacker, *J. Chem. Soc.*, 3340 (1954).

(10) E. Bamberger and E. Renauld, *Ber.*, **30**, 2278 (1897).

trum of the crude reaction product revealed weak signals at 8.72 and 6.02 τ indicating traces of the other isomer, but it could not be isolated. By analogy it is suggested that the nitrosooctane product also has the structure, with the oxygen attached to the nitrogen bearing the octyl group, rather than structure VIII.

The condensation of methylhydroxylamine and nitrosobenzene occurred in the same way yielding N-methyl-N′-phenyldiazine N′-oxide (X). This azoxy compound

$$CH_3NHOH + C_6H_5NO \longrightarrow CH_3N{=}\overset{\overset{O}{\uparrow}}{N}C_6H_5$$

X

pound previously was prepared by the action of the methyl Grignard reagent on methyl phenylnitrosohydroxylamate.[11,12] The methyl proton resonance of compound X was found at 6.60 τ.[13]

When the reaction of benzylhydroxylamine with nitrosobenzene was repeated using the method empolyed for the *t*-nitrosobutane–methylhydroxylamine condensation, a high-melting (190°), insoluble product similar to that previously described[9,10] was obtained, but it proved to be identical, by comparison of infrared spectra, with N-benzyl-N′-phenyldiazine N′-oxide (XI)

$$C_6H_5CH_2NHOH + C_6H_5N{=}O \longrightarrow$$

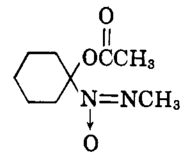
$$C_6H_5CH_2N{=}\overset{\overset{O}{\uparrow}}{N}C_6H_5 \xleftarrow{CH_3CO_3H} C_6H_5CH{=}NNHC_6H_5$$

XI

prepared by the action of peracetic acid on benzaldehyde phenylhydrazone.[3] The variable melting point behavior of this compound[3] and its insolubility cast considerable doubt on previous attempts at structure elucidation by mixture melting points[9] and molecular weight determinations.[10]

Based upon the few examples reported here, it appears that the condensation of aliphatic hydroxylamines and aryl or alkyl nitroso compounds does yield unsymmetrical azoxy compounds, and that the nitroso group is the source of the oxygen atom in the derived azoxy group.

2. Oxidation of Azo Compounds.—Treatment of cyclohexanone methylhydrazone and other ketone methylhydrazones with peracetic acid or with lead tetraacetate followed by peracetic acid, yields α-acetoxyazoxy compounds.[14] The n.m.r. spectrum of the cyclohexanone product consisted of two sharp singlets due to the methyl groups at 7.93 τ (CH_3CO_2–) and 6.85 τ (N–CH_3) and two broad bands due to the ring protons. The position of the N-methyl resonance indicates that the methyl group is attached to the unoxidized nitrogen, and that the structure of the oxidation product is XII. Additional evidence for this structure comes from the separation of the ring protons into two groups of six and four, with the group of four appearing at lower field. The four protons of the α-positions of the cyclohexane ring are in the same relation to the oxidized nitrogen as those of the methyl groups of azoxyisobutane (I), and would be expected to be found at lower field than the other protons. (In the corresponding azo compound all the ring protons have the same chemical shift; see section 5.)



XII

In a similar manner, the products from the oxidation of phenylacetone and acetophenone methylhydrazones[14] may be assigned analogous structures with oxidation occurring preferentially at the alkyl-substituted rather than methyl-substituted nitrogens. The N-methyl proton resonances of these compounds were found at 6.93 and 6.80 τ, respectively.

This preference for oxidation at the nitrogen not substituted with a methyl group was also shown by benzeneazomethane, which was converted by perbenzoic acid predominantly to the azoxy compound X. However, a trace of the isomeric oxidation product Xa was isolated by vapor chromatography. Its

$$C_6H_5N{=}NCH_3 \xrightarrow{CH_3CO_3H} C_6H_5N{=}\overset{\overset{O}{\uparrow}}{N}CH_3 + X$$

Xa

methyl proton resonance was found at 5.85 τ. The selectivity of these oxidations seems remarkable and no simple explanation suggests itself.

3. Structure of Nitroso Dimers.—The formulation of nitroso dimers as diazine dioxides[15] recently has been attacked.[11] If the diazine dioxide structure is correct, the chemical shift of the groups attached to the nitrogen atoms ought to be similar to that of the same groups attached to the oxidized nitrogen of azoxy compounds and nitrones. Four nitroso dimers were examined: *cis*- and *trans*-nitrosomethane dimers,[16] *t*-nitrosobutane dimer,[7] and α-nitrosotoluene dimer.[7]

α-Nitrosotoluene dimer showed one methylene signal, indicating a symmetrical structure, at 4.62 τ, which is compatible with the methylene group being attached to an oxidized nitrogen rather than to a nonoxidized nitrogen (*cf.* compounds VI and VII, Table I).

cis-Nitrosomethane dimer showed a single signal at 5.80 τ while *trans*-nitrosomethane dimer showed its singlet at 6.00 τ. Again the position of the signals indicates the methyl groups are attached to oxidized nitrogens and the presence of only one signal indicates symmetrical structures. A possible reason for the *trans*-dimer having higher field shift is discussed in section 5.

The n.m.r. spectrum of *t*-nitrosobutane dimer consisted of two signals at 8.75 and 8.40 τ, whose ratio

(11) M. V. George, R. W. Kierstead, and G. F Wright, *Can. J. Chem.*, **37**, 679 (1959).

(12) Mixed azoxy compounds of type X also are available from the reaction of Grignard reagents with phenylnitrosohydroxylamine tosylates (T. E. Stevens, to be published).

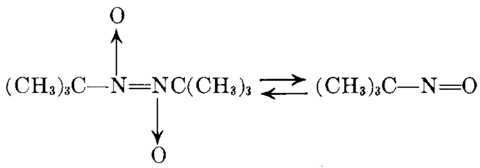
(13) Conjugation of the phenyl group with the nitrone or azoxy function led to paramagnetic shifts of the alkyl group proton resonance compared to that of the corresponding dialkyl compound; *e.g.*, $C_6H_5N{=}NCH_3$, 6.10 τ; X, 6.60 τ; $C_6H_5CH{=}\underset{\downarrow}{N}CH_3$ (O), 6.65 τ (doublet, J = 2 c.p.s.); $C_6H_5N{=}\underset{\downarrow}{N}CH_3$ (O), 5.85 τ; $C_6H_5CH{=}\overset{\overset{O}{\uparrow}}{N}CH_3$, 6.25 τ; $C_6H_5CH{=}\overset{\overset{O}{\uparrow}}{N}CH_2C_6H_5$, 5.13 τ.

(14) B. T. Gillis, Duquesne University, private communication. We are indebted to Dr. Gillis for examples of these compounds.

(15) B. G. Gowenlock and W. Lüttke, *Quart. Rev.*, **12**, 321 (1958).

(16) T. Emery and J. B. Neilands, *J. Am. Chem. Soc.*, **82**, 4903 (1960).

was temperature dependent. As the temperature was lowered, the area of the higher field band decreased, and as the temperature was increased this band area increased. The position of these bands is consistent with their assignment to the monomer and dimer, respectively, dissociation being accompanied by the change of a charged nitrogen to an uncharged nitrogen (Table I, compounds I–III). The presence of dimer in

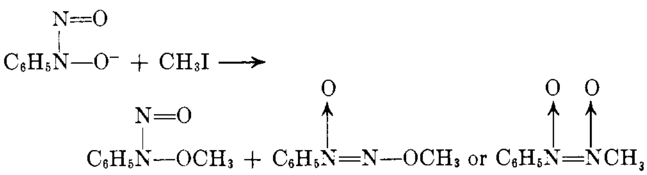


8.40 τ 8.75 τ

solution at room temperature is at some variance with a previous report[17] on the dissociation of nitroso dimers which indicated that *t*-nitrosobutane was completely dissociated in solution at room temperature.

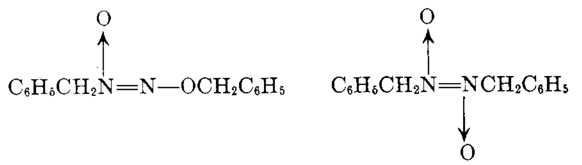
All these data strongly suggest that the diazine dioxide structure[15] is the correct structure for nitroso dimers.

4. Alkylation of Nitrosohydroxylamines.—When cupferron is alkylated with methyl iodide, two isomers are obtained. The so-called β isomer is N-nitroso-N-methoxyaniline (XIII), while the α isomer has been suggested variously to be N-methoxy-N′-phenyldiazine N′-oxide (XIV)[18] or N-methyl-N′-phenyldiazine



XIII XIV XV

dioxide (XV).[11] It was thought that n.m.r. analysis of XIV/XV would provide evidence of the correct structure. The n.m.r. spectrum of the α isomer showed a sharp singlet at 5.85 τ compatible with a methyl group attached to an oxidized nitrogen. However, a review of the literature indicated the O-methyl groups are found in the same region; O-methylacetophenone oxime, for example, has a signal at 6.07 τ. Because of this ambiguity it was not possible to establish the structure of the α isomer directly by n.m.r. analysis. However, another similar product was available from the benzylation of N-nitrosobenzylhydroxylamine[19]; in this case the two alternative structures would be XVI and XVII. Compound XVI should display two methylene signals, while XVII should display only one.



XVI XVII

Structure XVII has been assigned to the α-nitrosotoluene dimer,[15] and it is known that this material and the benzylation product are different compounds.[19] As mentioned, the α-nitrosotoluene dimer showed only one methylene signal consistent with structure XVII while the benzylation product showed two signals at 5.00 and 4.80 τ indicating structure XVI for this product. By analogy structure XIV should be the correct one for the cupferron methylation product.[20]

5. Stereochemistry of Azoxy Compounds.—In the course of examining the n.m.r. spectra of azoxymethane (IV), ω-azoxytoluene (VI), and azoxyisobutane (I), the spectra of the corresponding azo compounds were also determined. It had been anticipated that upon oxidation of the azo linkage both alkyl groups would undergo a downfield shift due to a reduction of electron density at both nitrogens with the group attached directly to the oxidized nitrogen suffering the larger shift. Indeed, upon oxidation of disulfides to thiosulfonates, the alkyl groups attached to both sulfurs undergo a downfield shift.[4]

Azoisobutane was examined first. The methyl resonance consisted of a sharp singlet at 8.87 τ. Upon oxidation the anticipated shifts were found. Azoxyisobutane (Table I) has two singlets at 8.72 and 8.52 τ. Rather different results were obtained with other azo–azoxy pairs. ω-Azotoluene showed a sharp singlet due to the methylene group at 5.15 τ. Upon careful oxidation with perbenzoic acid, the azoxy compound VI, m.p. 42–43°, was obtained. It showed two signals as expected, but as shown in Table I, whereas one was at lower field, the other was at much higher field than in the azo compound. Since this azoxy compound could be isomerized by base to a high-melting isomer identical to the oxidation product of benzaldehyde benzylhydrazone,[9] it is assumed to be the *trans* isomer[21]; the high-melting compound is the *cis* isomer.[21]

Similarly the proton resonance of azomethane appears at 6.32 τ, between the signals for the methyl groups of azoxymethane (IV, Table I), and those of 1-acetoxy-1-methaneazocyclohexane (6.37 τ), 2-acetoxy-2-methaneazo-1-phenylpropane (6.23 τ), 1-acetoxy-1-methaneazo-1-phenylethane (6.32 τ), and benzeneazomethane (6.10 τ) appear at lower field than the proton resonances of the corresponding azoxy compounds (section 2).

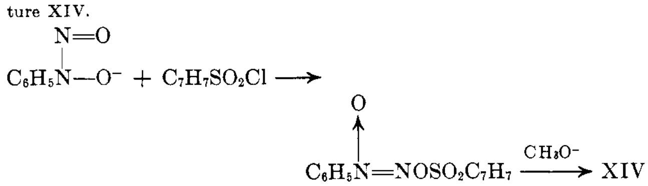
Based upon this series of compounds it is apparent that it is the group attached to the unoxidized nitrogen which is undergoing the upfield shift upon oxidation of azo to azoxy compounds. The upfield shift is most probably due to diamagnetic shielding associated with the conical region above the plane of the nitrogen–oxygen bond.[22,23] This shielding should be most effective when the alkyl group and the oxygen atom are *cis* to each other. It is reasonable to assume that the azo

(17) J. R. Schwartz, *J. Am. Chem. Soc.*, **79**, 4353 (1957).

(18) E. Bamberger and T. Ekecrantz, *Ber.*, **29**, 2412 (1896).

(19) R. Behrend and E. Konig, *Ann.*, **263**, 218 (1891).

(20) In a contemporary study[12] it was shown that cupferron reacts with *p*-toluenesulfonyl chloride to produce a tosylate which, upon treatment with sodium methoxide, yields this same methylation product thus proving structure XIV.



(21) J. N. Brough, B. Lythgoe, and P. Waterhouse, *J. Chem. Soc.*, 4069 (1954).

(22) For similar shielding due to other unsaturated functions, see L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, p. 112.

(23) For an example of paramagnetic shielding due to the nitrogen–oxygen bond, see A. Huitric and W. F. Trager, *J. Org. Chem.*, **27**, 1926 (1962).

compounds have the *trans* configuration (azomethane is known to be *trans*[24]) and that no isomerization occurred in the oxidation step.[21] Thus all these azoxy compounds would have the required *trans* configuration. In order to complete this picture it would be desirable to have the spectra of *cis* azoxy compounds which are known.[3] Unfortunately, all the *cis* compounds are characterized by extremely low solubility in organic solvents, and it has not yet been possible to obtain n.m.r. spectra of any of them. It is anticipated that if the suggestions about the shielding of the groups in *trans* azoxy compounds are correct, that in the *cis* isomer both alkyl groups would be found at lower field than in the corresponding azo compound.[25]

Differences in the chemical shifts of *cis*- and *trans*-nitrosomethane dimers (section 3) appear to be attributable to similar differences in shielding. In the *trans* isomer both methyl groups are *cis* to an oxygen atom and thus shielded, while in the *cis* isomer both are *trans* to the oxygens and are not shielded. As would be predicted on this basis, the *trans* dimer resonates at higher field than the *cis* dimer.

Experimental

Azoxyisobutane.—To a solution of 5.0 g. (0.035 mole) of azoisobutane[26] in 15 ml. of methylene chloride was added 15 ml. of 40% peracetic acid at 5–10° over a 15-min. period. The mixture was stirred an additional 15 min. at 10°, at 25° for 15 min., at 40° for 30 min., and at reflux for 30 min. The mixture was diluted with water and extracted with methylene chloride. These extracts were washed with water, sodium carbonate solution, sodium bisulfate solution, and water and then dried. The solvent was removed and the residue distilled in a Holzman column. Azoxyisobutane was obtained as a colorless liquid, b.p. 50° (20 mm.); $n^{20}D$ 1.4208.

Anal. Calcd. for $C_8H_{18}N_2O$: C, 60.72; H, 11.46; N, 17.71. Found: C, 61.00; H, 11.40; N, 17.52.

***trans*-ω-Azoxytoluene.**—A solution containing 2.67 g. of perbenzoic acid in 50 ml. of chloroform was stirred at 0° while a solution of 4.2 g. (0.02 mole) of ω-azotoluene[27] was added over a 30-min. period. The resulting mixture was stirred at 0–5° overnight. It was then treated with excess 10% potassium iodide solution followed immediately by excess sodium thiosulfate solution. The organic layer was separated and washed successively with ice water, cold 1 *N* sodium hydroxide solution, and water, dried, and concentrated. The oily residue crystallized from ethanol; m.p. 42–43°; yield, 3 g. (67%).

***cis*-ω-Azoxytoluene.**—One gram of *trans*-ω-azoxytoluene, m.p. 42–43°, was dissolved in 10 ml. of 10% sodium methoxide solution. When this mixture was stirred for a short time, a white solid separated. Recrystallization from toluene–ethanol yielded white crystals, m.p. 190–192°. This material is presumably the same as that obtained by Lynch and Pausacker,[9] m.p. 209°. The stereochemistry of this material was not determined but, based on later work,[21] is certainly the *cis* isomer.

N-Methyl-N′-phenyldiazine N′-Oxide. A.—To a solution of 2.59 g. of perbenzoic acid in 70 ml. of methylene chloride was added 2.4 g. (0.02 mole) of benzeneazomethane[28] in 25 ml. of methylene chloride at 0–5°. The mixture was stirred at ice-bath temperature overnight, then worked up as for *trans*-ω-azoxytoluene. The desired azoxy compound was obtained by distillation, b.p. 78° (3.5 mm.). Vapor chromatography of this material on a Dow 710 silicone oil on Chromosorb column revealed the presence of a small amount of more highly absorbed material which was collected. Its infrared, ultraviolet, and n.m.r. spectra were measured on the same dilute carbon tetrachloride solution. Because of the small amount of material, no elementary analyses could be obtained. Its infrared spectrum has a band at 1495 cm.$^{-1}$ almost identical to that in N-methyl-N′-phenyldiazine N′-oxide (X). Its ultraviolet spectrum shows intense absorption at 290 mμ. The position of this maximum is that expected of an azoxy compound with the partial structure $ArN{=}\underset{\overset{\downarrow}{O}}{N}—$.[29] The structure of this material is proposed to be **N-methyl-N′-phenyldiazine N-oxide (Xa).**

The main product had an infrared spectrum identical to that of authentic N-methyl-N′-phenyldiazine N′-oxide (X).[11]

B.—To a solution of 9.5 g. (0.09 mole) of nitrosobenzene in 50 ml. of absolute ethanol was added with cooling 2.8 g. (0.06 mole) of N-methylhydroxylamine. The resulting mixture was heated under reflux overnight and then distilled to yield 5.6 g. (68%) of the azoxy compound. The infrared spectrum of this material corresponded to that reported[11] and its ultraviolet spectrum (λ_{max} 245 mμ, ϵ_{max} 10,300) is consistent with the assigned structure.

N-Methyl-N′-*t*-butyldiazine N′-Oxide.—The directions of Aston and Jenkins[6] were followed using 2.4 g. (0.03 mole) of *t*-nitrosobutane,[7] 2.6 g. (0.03 mole) of N-methylhydroxylamine hydrochloride, and 1.9 g. (0.033 mole) of potassium hydroxide. The azoxy compound was isolated as a colorless liquid, b.p. 60–62° (110 mm.); $n^{20}D$ 1.4265; yield, 2.2 g. (63%).

Anal. Calcd. for $C_5H_{12}N_2O$: C, 51.69; H, 10.42; N, 24.12. Found: C, 51.36; H, 10.50; N, 24.19.

N-Benzyl-N′-Phenyldiazine N′-Oxide.—To a solution of 9.5 g. (0.09 mole) of nitrosobenzene in 50 ml. of absolute ethanol was added all at once 7.3 g. (0.06 mole) of benzylhydroxylamine[30] at 0–5°. The mixture was stirred at room temperature overnight. Upon cooling the mixture a white solid separated (9.8 g.); upon crystallization from xylene it melted at 186–190°. Its infrared and ultraviolet spectra were identical with those of an authentic sample.[3]

Acknowledgment.—We are indebted to Mrs. Carolyn Haney for measurement of the n.m.r. spectra and to Mrs. Inella Shepard for other technical assistance.

(24) H. Boersch, *Monatsch.*, **65**, 327 (1935).

(25) Similar diamagnetic shielding has been proposed to account for shifts encountered upon oxidation of furazans to furoxans. Since back polarization effects are difficult to assess in these highly conjugated materials, it is not known whether they are directly comparable to aliphatic azoxy compounds. For leading references, see R. K. Harris, A. R. Katritzky, S. Øksne, A. S. Bailey, and W. C. Patterson, *J. Chem. Soc.*, 197 (1963).

(26) T. E. Stevens, *J. Org. Chem.*, **26**, 2351 (1961).

(27) A. F. Bickel and W. A. Waters, *Rec. trav. chim.*, **69**, 312 (1950).

(28) E. Tafel, *Ber.*, **18**, 1742 (1885).

(29) C. L. Stevens, B. T. Gillis, J. C. French, and T. H. Haskell, *J. Am. Chem. Soc.*, **80**, 6088 (1958).

(30) L. W. Jones and M. C. Sneed, *ibid.*, **39**, 674 (1917).