TABLE I

CONDITIONS AND RESULTS OF THE HYDROXIDE ION CATALYZED HYDROLYSIS OF META AND PARA N-SUBSTITUTED ESTERS IN WATER AT 25.0° AND 0.5 *M* IONIC STRENGTH[a]

G	Registry no.	pH	k_2, M^{-1} min^{-1}	k_{rel}	$k_{\mathrm{p}}/k_{\mathrm{m}}$
p-O^-	3783-38-8	9.7–10.1	5.8×10^2	1.0	0.67
m-O^-	15905-18-7	9.7–10.0	8.6×10^2	1.5	
p-CH_3	7630-02-6	7.5–8.4	3.2×10^4	55.0	9.1
m-CH_3	4685-10-3	9.1–9.3	3.5×10^3	6.0	
p-CH_3O	32812-78-5	8.0–8.4	4.2×10^4	72.0	4.5
m-CH_3O	32785-04-9	8.7–9.0	9.4×10^3	16.0	
b	2459-09-8	10.4–10.5	2.2×10^2	0.38	4.5
c	93-60-7	10.9–11.0	4.9×10^1	0.084	

[a] pOH = 14.30 − pH. [b] Methyl 4-pyridinecarboxylate. [c] Methyl 3-pyridinecarboxylate.

by $k/[OH^-]$, where k is the observed pseudo-first-order constant. This means that the hydrolysis of the ester is catalyzed only by hydroxide ion under the conditions employed.[6] The k_2 values given in Table I represent the average of two experiments at the indicated pH; the average deviation is <10%. Nmr experiments employing a phosphate buffer solution of the para *N*-methoxy ester showed that only ester hydrolysis takes place; no side products were detected.[7]

In order to obtain a measure of the activating effect of the positive charge in I, the hydrolysis of meta and para methyl pyridinecarboxylates (III) also was studied (Table I).[4] Comparison with the results for the *N*-methyl esters indicates that the positive charge increases reactivity by a factor of about 100. The para ester is more reactive than the meta ester in both types of compounds, suggesting activation of the para positions by a resonance effect.

The results for I indicate that there is a 72-fold spread in reactivity with the para *N*-oxide ester being the least and the para *N*-methoxy compound being the most reactive. The nature of the electronic effects of the N substituents is revealed by a comparison of the positional rate constants. It is assumed that the electronic effects of the substituents are superimposed on the effects of the annular nitrogen atom and the positive charge. Relative to the *N*-methyl compound, the methoxy group activates while the oxide substituent deactivates meta positions in both I and II, indicating the presence of inductive effects. A methoxy group is activating relative to a methyl group in para positions of I but the opposite order is found in II. This result clearly indicates that the resonance effect of the methoxy group is less important in the heterocyclic series. A similar conclusion has been advanced concerning the importance of resonance effects in *N*-alkoxypyridinium ions on the basis of ground state infrared studies.[8] That resonance effects do operate in I is seen by the para/meta ratio which decreases in the order CH_3, CH_3O, and O^-. A reduced resonance effect for an uncharged group on a positively charged annular nitrogen atom is readily understandable. Electron delocalization by such a process places a positive charge on the group and this is inhibited electrostatically by the adjacent positive charge on the nitrogen atom.

It is clear that the electronic effects of substituents on a positively charged annular nitrogen atom can be quite different from those on an annular carbon atom.

Experimental Section

Compounds.—*N*-methyl esters were prepared from the esters and methyl iodide in methanol and were recrystallized from ethanol: 1-methyl-3-carboxymethylpyridinium iodide, mp 130° (lit.[9] mp 129.5–130.2°); 1-methyl-4-carboxymethylpyridinium iodide, mp 180–181° (lit.[10] mp 179°). *N*-oxide esters were prepared by N oxidation of the esters using H_2O_2–CH_3CO_2H: 3-carboxymethylpyridine 1-oxide, mp 101–102° (lit.[10] mp 101–102°); 4-carboxymethylpyridine 1-oxide, mp 115–117° (lit.[10] mp 118–119°). *N*-methoxy esters were prepared from the *N*-oxide esters using dimethyl sulfate by minor variations of a method used to prepare similar compounds.[7] These compounds were isolated as perchlorate salts. Ether aided precipitation of the perchlorate salts, though initial precipitation was induced only at −70° in the case of 1-methoxy-4-carboxymethylpyridinium perchlorate, mp 71–72° (ethanol). *Anal.* Calcd for $C_8H_{10}ClNO_7$: C, 35.9; H, 3.7; O, 41.9. Found: C, 35.8; H, 3.8; O, 41.6. 1-Methoxy-3-carboxymethylpyridinium perchlorate had mp 88–89° (ethanol). *Anal.* Found: C, 36.1; H, 3.8; O, 41.7.

Rates of Ester Hydrolysis.—Reactions were followed using a Radiometer TTT-1c titrator operating in the pH-Stat mode. Reaction mixtures consisted of ester and 0.5 *M* KCl. Complete reaction represented the addition of ~0.45 ml of 0.1 *M* KOH to 25 ml (initial) of the reaction mixture. Constant temperature (25.0°) was maintained by circulation of water about the titration cell. Pseudo-first-order rate plots were obtained by the Guggenheim method;[11] they were linear over 2–3 half-lives.

Acknowledgment.—This work was supported in part by the National Science Foundation (GP 25500).

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(6) M. L. Bender, *Chem. Rev.*, **60**, 53 (1960).

(7) R. Eisenthal and A. R. Katritzky, *Tetrahedron*, **21**, 2205 (1965).

(8) A. R. Katritzky, C. R. Palmer, F. J. Swinbourne, T. T. Tidwell, and R. D. Topsom, *J. Amer. Chem. Soc.*, **91**, 636 (1969).

(9) H. L. Bradlow and C. A. VanderWerf, *J. Org. Chem.*, **16**, 1143 (1951).

(10) "Dictionary of Organic Compounds," 4th ed, Oxford University Press, New York, N. Y., 1965.

(11) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, Wiley, New York, N. Y., 1961.

Organic Mass Spectrometry. I. Retro-1,3-dipolar Cycloaddition Reaction Induced by Electron Impact

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The mechanistic interrelation between the two important electrocyclic reactions, Diels–Alder and the 1,3-dipolar cycloaddition, is of current interest.[1] Although it is well established that both reactions are

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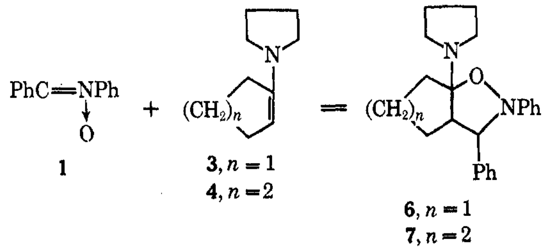
(1) A. Firestone, *J. Org. Chem.*, **33**, 2285 (1968); R. Huisgen, *ibid.*, **33**, 2291 (1968).

thermally and photochemically reversible[2] and that the Diels–Alder reaction can also be reversed by electron impact,[3] little has been reported on the possible retro-1,3-dipolar cycloaddition induced by electron impact. Here we report an example of such a reaction.

We determined the mass spectra of the isoxazolidines **6** and **7**,[4] the dipolar cycloadducts between α,*N*-diphenylnitrone (**1**) and 1-pyrrolidino-1-cyclopenene (**3**) or 1-pyrrolidino-1-cyclohexene (**4**).



1

3, $n = 1$
4, $n = 2$

6, $n = 1$
7, $n = 2$

If the thermal retro-1,3-dipolar cycloaddition takes place prior to ionization, the mass spectra of **6** and **7** should be superimposable on those of **1**[5] and **3** or **4**.[6] Indeed the mass spectrum of the 1:1 mixture of **1** and **3**, determined under the same operating condition, was explainable in terms of the additivity principle.

The peaks in the spectra of **6** and **7** were summarized in Table I. The pattern is substantially different from that of the mixture. Thus, there are strong peaks at *m/e* 334 or 348 (M^+) and at *m/e* 227 or 241 (M^+ − PhNO). The base peak is the respective enamine molecular ion (*m/e* 137 or 151) while the nitrone molecular ion peak is rather weak. Moreover, the ratio of the relative abundance of *m/e* 197 and of *m/e* 91 is 0.05 and 0.07 for **6** and **7**, respectively, while the same ratio was 0.38 for **1** itself.[5] This strongly indicates that the thermal retrocycloaddition prior to electron impact is highly unlikely.

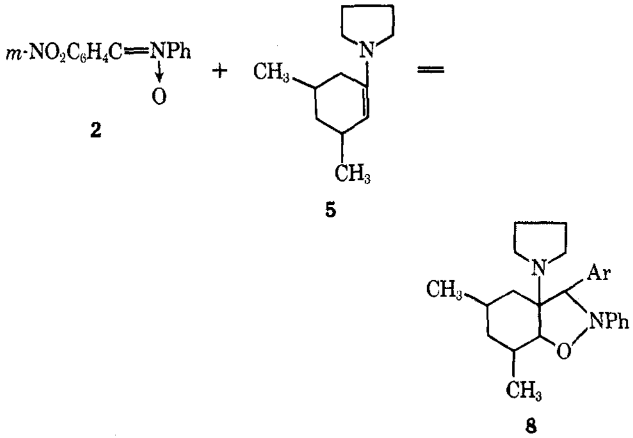
TABLE I
MASS SPECTRA OF NITRONE–ENAMINE CYCLOADDUCTS (IONIZATION VOLTAGE 70 eV)

	m/e[a]		
Compd, ion	**6**	**7**	**8**
M^+	334 (6)	348 (8)	411 (10)
$M^+ - C_4H_8N$	264 (1)	278 (1)	351 (1)
M^+ − nitrosobenzene	227 (9)	241 (3)	314 (3)
Nitrone$^+$	197 (2)	197 (2)	242 (4)
Schiff base$^+$	181 (6)	181 (5)	226 (7)
Enamine$^+$	137 (100)	151 (100)	179 (100)[b]
Enamine$^+$ − H	136 (53)	150 (39)	178 (49)
$C_6H_5N^+$	91 (39)	91 (28)	91 (31)
$C_6H_5^+$	77 (35)	77 (23)	77 (30)
Metastable	56.2	63.5	76.1

[a] Values in parentheses are intensities relative to enamine$^+$. [b] The base peak is enamine$^+$ − Me (113).

An alternative explanation which can account for all these observations is that (at least most of) the cycloadducts cleave upon electron impact into enamine molecular ion and nitrone molecule. That this type of fragmentation does in fact occur is supported by the position of the metastable peaks, *i.e.*, *m/e* 56.2 ($= 137^2/334$) and 63.5 ($= 151^2/348$), respectively.

We have shown that a sterically crowded enamine **5**, derived from *cis*-3,5-dimethylcyclohexanone, and **1** or α-*m*-nitrophenyl-*N*-phenylnitrone (**2**) gave the "reverse oriented" cycloadduct **8**.[7] It was expected that **8** should show much the same fragmentation pattern upon electron impact if the retrodipolar cycloaddition mechanism is applicable to this compound since the difference in the structure between **6** or **7** and **8** is merely the location of pyrrolidine ring which should have little effect if any on the cleavage pattern of this type.



2

5

8

The peaks observed for **8** are also included in Table I. The base peak is not the enamine molecular ion, but (enamine$^+$ − Me) peak although the former is next to the strongest. Otherwise the fragmentation pattern is consistent with the retrocycloaddition mechanism. The nitrone peak is again weak and the metastable peak was observed at the expected position, *i.e.*, at *m/e* 76.1 ($= 179^2/421$). The *m/e* 91 peak is as strong as the *m/e* 77 peak, as was observed for **6** and **7**. Thus the former peak in **6** and **7** is now assignable to $C_6H_5N^+$ rather than $C_7H_7^+$.

We suspected that this type of cleavage might be common to all 1,3-dipolar cycloadducts. It was reported, for instance, that 3,5-diphenyl-1,2,4-oxadiazole (**9**), formally a cycloadduct between benzonitrile oxide and benzonitrile, gave peaks at *m/e* (rel intensity) 222 (48), 119 (100), and 103 (61).[8] Thus, contrary to our results, the 1,3 dipole, not the dipolarophile, gave the base peak. The original author[8] claimed that the electron impact causes the migration of phenyl group from C(5) to N(4), followed by the cleavage at O(1)–N(2) and C(3)–N(4) bonds to give

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(2) H. Kwart and K. King, *Chem. Rev.*, **68**, 415 (1968); R. Huisgen, H. Hauck, R. Grashey, and H. Seidl, *Chem. Ber.*, **101**, 2568 (1968); *ibid.*, **102**, 736 (1969).

(3) K. Biemann, "Mass Spectrometry," McGraw-Hill, New York, N. Y., 1962, p 103; H. Nozaki, H. Kato, and R. Noyori, *Tetrahedron*, **25**, 166 (1969).

(4) Y. Nomura, F. Furusaki, and Y. Takeuchi, *Bull. Chem. Soc. Jap.*, **40**, 1740 (1967).

(5) T. H. Kinstle and J. G. Stam, *Chem. Commun.*, 185 (1968); B. S. Larson, G. Schroll, S.-O. Lawesson, J. H. Bowie, and R. G. Cooks, *Tetrahedron*, **24**, 5193 (1968).

(6) H. J. Jakobsen, S.-O. Lawesson, J. T. B. Marshall, G. Schroll, and D. H. Williams, *J. Chem. Soc. B*, 940 (1966).

(7) Y. Nomura, F. Furusaki, and Y. Takeuchi, *Bull. Chem. Soc. Jap.*, **43**, 1913 (1970).

(8) J. L. Cotter, *J. Chem. Soc.*, 5491 (1964).

PhNCO$^+$ and PhCN. We are continuing efforts to delineate the scope of retro-1,3-dipolar cycloaddition reaction induced by electron impact.

Experimental Section

The preparation of the cycloadducts **6**, **7**,[4] and **8**[7] was previously described. The mass spectra were determined with Hitachi RMU-6D mass spectrometer at the ionization voltage 70-eV. The temperature of the sample heater and the ionization chamber was 100 and 250°, respectively.

Registry No.—**1**, 1137-96-8; **3**, 7148-07-4; **4**, 1125-99-1; **6**, 29068-11-9; **7**, 16361-46-9; **8**, 29348-00-3.

Conjugative and Steric Factors Affecting the Conformational Preference of Some Aromatic Sulfides

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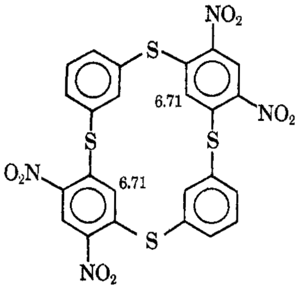
We have had for some time evidence that the conformational preference of diphenyl sulfides and analogs could be detected by nmr, based on the fact that the diamagnetic shielding[1] of one ring on the ortho positions of the adjacent nucleus is a function of the molecular conformation.

As is already well known,[2] an interesting property of the aromatic sulfides arises from the fact that unshared electrons of the bridged heteroatom may develop a resonance interaction with the π electrons of the aromatic ring.[2]

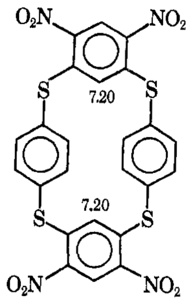
The intensity of this resonance effect and the extent to which it would affect the conformational preference of these molecules seemed to us an interesting subject of investigation. This paper is concerned with the results obtained in the case of some open-chain and cyclic aromatic sulfides bearing electron-attracting groups (nitro) eventually capable of inducing conformational preferences in these molecules.

Results and Discussion

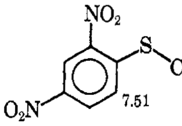
The nmr spectra of the two novel cyclic sulfides I and II show that the protons evaluated resonate at somewhat higher field with respect to the corresponding proton in compound III (chemical shift values in parts per million). This suggests that, due to the specific conformation assumed by the cyclic structures, the protons concerned experience the diamagnetic shielding of the adjacent aromatic rings.



I

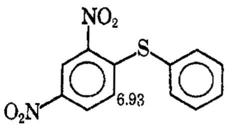


II

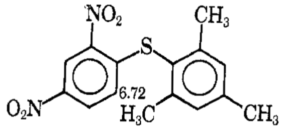


III

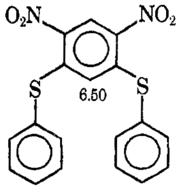
Furthermore, comparatively higher shieldings are found for pertinent protons in the open-chain aromatic sulfides IV–VII for which, contrary to the case of cyclic molecules I and II, there are no steric restraints posed on the possible molecular conformations (see below).



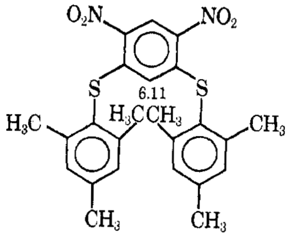
IV



V

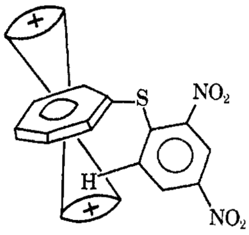


VI



VII

A satisfactory rationalization of these data is obtained considering that, due to the proximity of the aromatic rings in these molecules, the shielding of the ring current[1] of the adjacent nucleus on the ortho positions of the other ring is a function of the molecular conformation. In aromatic sulfides the possibility arises for the unshared electrons of the bridged heteroatom to develop a resonance interaction with the π electrons of the aromatic ring.[2] Here in particular, because of the concerted effect of the two strong electron-attracting groups, a partial bonding arises between π electrons localized on the bridgehead carbon atoms and the unshared electron pairs of the sulfur atom. The percentage of double bond character induced in the C_{Ar}–S bond is here high enough to cause the aromatic ring bearing the two nitro groups to lie in the C_{Ar}–S–C_{Ar} plane. Steric repulsion forces the adjacent ring out of this plane, so that the molecule assumes conformation VIII, where the ortho aromatic hydrogen lies below the



VIII

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[1] C. E. Johnson and F. A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958).

[2] C. C. Price and S. Oae in "Sulphur Bonding," Ronald Press, New York, N. Y., 1962, and references cited therein.