Mass Spectrometry in Structural and Stereochemical Problems. CXX.[1] Electron-Impact-Induced Fragmentation Processes of Methoxycarbonylhydrazones[2]

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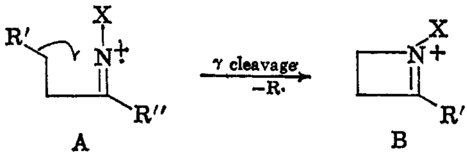
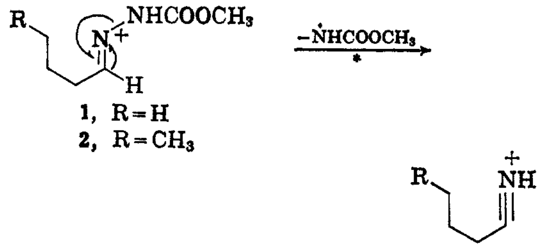
As an extension of the study of possible charge localization in carbonyl group derivatives, the methoxycarbonyl- and some ethoxycarbonylhydrazones of a series of simple aldehydes and ketones were prepared and investigated mass spectrometrically. The marked correlation between these spectral fragmentation patterns and those of previously examined carbonyl group derivatives allows certain generalizations about cleavage processes to be made based on the concept of charge localization at the imino nitrogen.

Apart from Woodward's classical resolution of *dl*-camphor through its diastereoisomeric 1-menthoxycarbonylhydrazones[4] and an attempted revival of interest by Rabjohn[5] in 1953, little use has been made of the alkoxycarbonylhydrazones as a carbonyl group derivative. Interest in this functionality stemmed from our continuing study of the effect of possible charge localization on the mass spectrometric fragmentation pattern in derivatives of aldehydes and ketones. Previous publications from this laboratory have outlined plausible modes of electron-impact cleavage in the oximes,[6] azomethines,[7] semicarbazones,[8] dimethylhydrazones,[9] and 2,4-dinitrophenylhydrazones[9,10] of simple aldehydes and ketones, all of which show several features in common. The well-known McLafferty rearrangement[11] is present to a greater or less degree in all the aliphatic acyclic derivatives containing a γ-hydrogen atom (with the sole exception of *n*-butyraldehyde 2,4-dinitrophenylhydrazone[10]) while γ cleavage[12] with apparent formation of an even-electron, four-membered nitrogen heterocyclic species (B) seems to be another electron-impact-promoted process indifferent to the functionality (X) on the *imino* nitrogen.



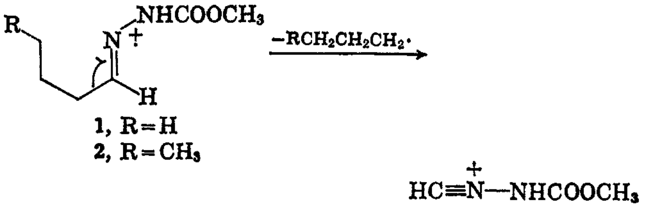
It seems likely that in both these cleavage reactions and indeed, generally, charge localization at this *imino* nitrogen directs the fragmentation of these compounds and only in isolated instances, *e.g.*, in the mass spectra of *n*-butyraldehyde and *n*-valeraldehyde dimethylhydrazones,[9] need one postulate retention of charge elsewhere in the molecule to account for the presence of well-documented fragment ions. It is precisely for this reason that we undertook the present investigation of N-methoxycarbonylhydrazones since the basicity of the *amino* nitrogen should differ in this type of derivative. If charge localization at the sp^2 nitrogen is indeed the most important feature then this structural change should have little effect on the principal fragmentation modes.

n-Butyraldehyde and n-Valeraldehyde N-Methoxycarbonylhydrazones.[13]—With few exceptions the major fragment ions in the mass spectra (Figures 1 and 2) of these compounds could be predicted from the results of the previous work[6–10] on the electron-impact-induced cleavages of carbonyl group derivatives. This was gratifying since it demonstrated that certain broad generalizations on the fragmentation of related functionalities were possible. Thus, α fission with hydrogen transfer to produce the even-electron species a of mass 70 accounts for the base peak of the *n*-butyraldehyde derivative while homolysis on the alternate side of the carbon–nitrogen double bond can give rise to the peak at *m/e* 101 (b).



1, R = H
2, R = CH$_3$

a, R = H, *m/e* 70
a′, R = CH$_3$, *m/e* 84
(25% by high resolution)



1, R = H
2, R = CH$_3$

$HC\equiv\overset{+}{N}-NHCOOCH_3$

b, *m/e* 101

There is a contribution from the McLafferty rearrangement ion c at mass 116 which by loss of methanol can form the resonance stabilized isocyanate ion d. This species was also encountered in the sequential breakdown of the semicarbazones of di-*n*-propyl and di-*n*-butyl ketone[8] under electron bombardment, in-

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[1] Paper CXIX: M. M. Green, D. S. Weinberg, and C. Djerassi, *J. Am. Chem. Soc.*, **88**, 3883 (1966).

[2] Financial assistance from the National Institutes of Health (Grants No. AM-04257 and CA-07195) is gratefully acknowledged.

[3] NATO Postdoctoral Fellow, 1965–1966.

[4] R. B. Woodward, T. P. Kolman, and G. C. Harris, *J. Am. Chem. Soc.*, **63**, 120 (1941).

[5] N. Rabjohn and H. D. Barnstorff, *ibid.*, **75**, 2259 (1953).

[6] D. Goldsmith, D. Becher, S. Sample, and C. Djerassi, *Tetrahedron*, in press.

[7] M. Fischer and C. Djerassi, *Chem. Ber.*, **99**, 1541 (1966).

[8] D. Becher, S. Sample, and C. Djerassi, *ibid.*, in press.

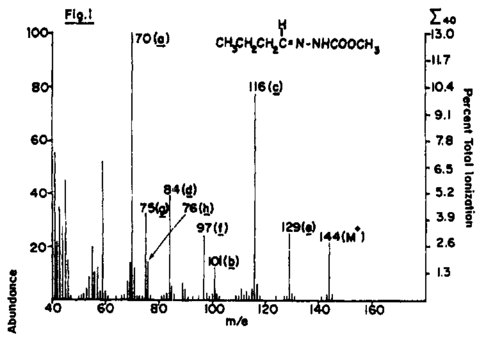
[9] D. Goldsmith and C. Djerassi, *J. Org. Chem.*, in press.

[10] S. Sample and C. Djerassi, *Nature*, **208**, 1314 (1965); see also R. J. C. Kleipool and J. T. Heins, *ibid.*, **203**, 1280 (1964).

[11] F. W. McLafferty, *Anal. Chem.*, **31**, 82 (1959).

[12] J. B. Thomson and C. Djerassi, *Chem. Commun.*, in press.

[13] Throughout this paper the use of the fishhook arrow denotes a proposed one-electron shift, while observed metastable transitions are marked by an asterisk (*). High-resolution mass measurements were carried out whenever there was any doubt as to the composition or homogeneity of a peak.



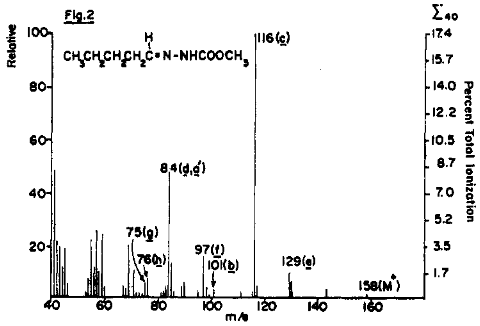
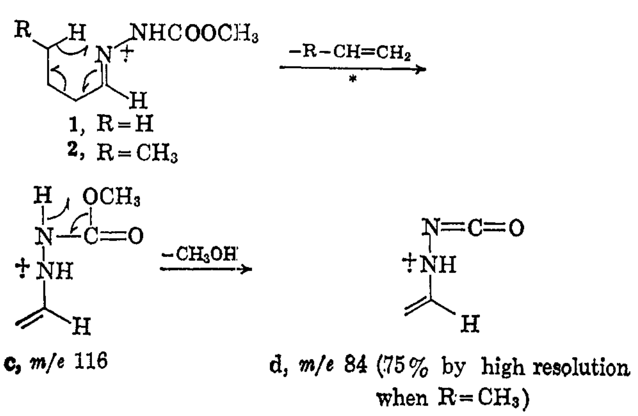


Figure 1.—Mass spectrum of *n*-butyraldehyde N-methoxycarbonylhydrazone.

Figure 2.—Mass spectrum of *n*-valeraldehyde N-methoxycarbonylhydrazone.

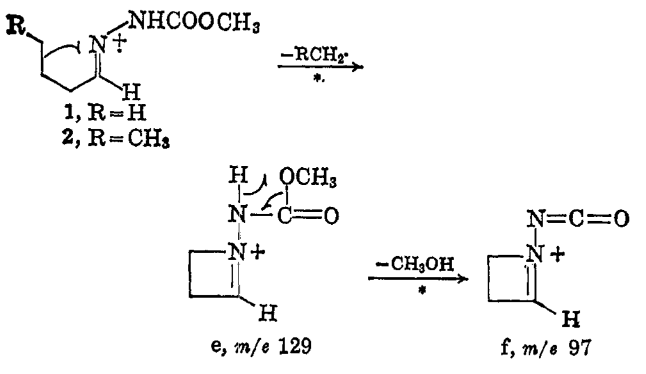
volving expulsion of a molecule of ammonia through a four-membered cyclic transition process. Loss of methanol (e → f) from the even-electron species e following γ cleavage (1 → e) also occurs presumably by the same pathway.



1, R=H
2, R=CH3

c, *m/e* 116

d, *m/e* 84 (75% by high resolution when R=CH3)

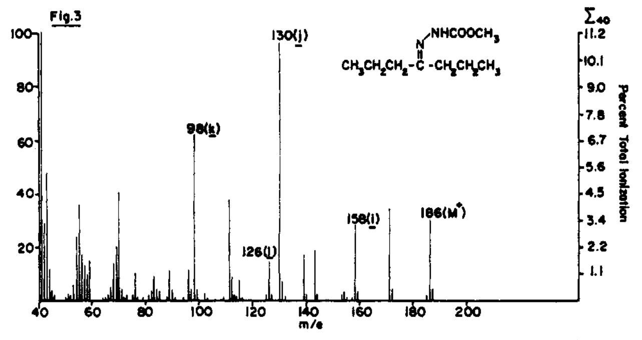


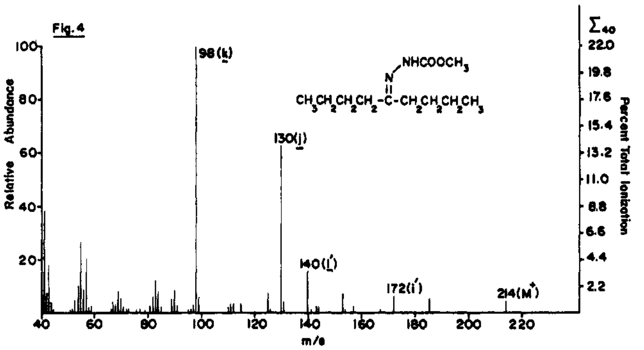
1, R=H
2, R=CH3

e, *m/e* 129

f, *m/e* 97

The above fragmentations have been interpreted on the basis of charge localization at the doubly bonded nitrogen atom, but in the case of the peaks at *m/e* 75 and 76, shown by high-resolution measurements to have the compositions $C_2H_5NO_2$ and $C_2H_6NO_2$, respectively, localization of the charge radical at the carbonyl oxygen atom offers a more plausible rationale for the presence of these ions g and h.





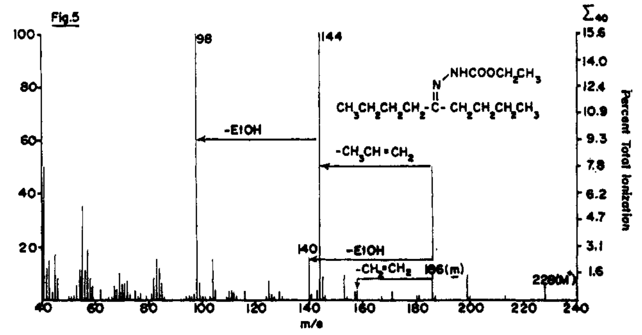
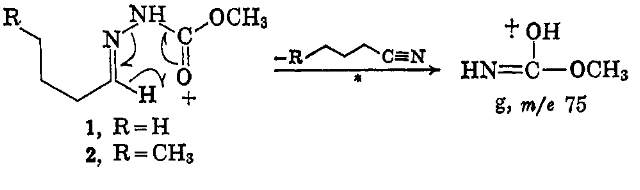


Figure 3.—Mass spectrum of di-*n*-propyl ketone N-methoxycarbonylhydrazone.

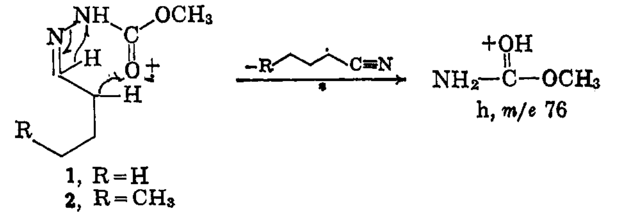
Figure 4.—Mass spectrum of di-*n*-butyl ketone N-methoxycarbonylhydrazone.

Figure 5.—Mass spectrum of di-*n*-butyl ketone N-ethoxycarbonylhydrazone.



1, R=H
2, R=CH3

g, *m/e* 75



1, R=H
2, R=CH3

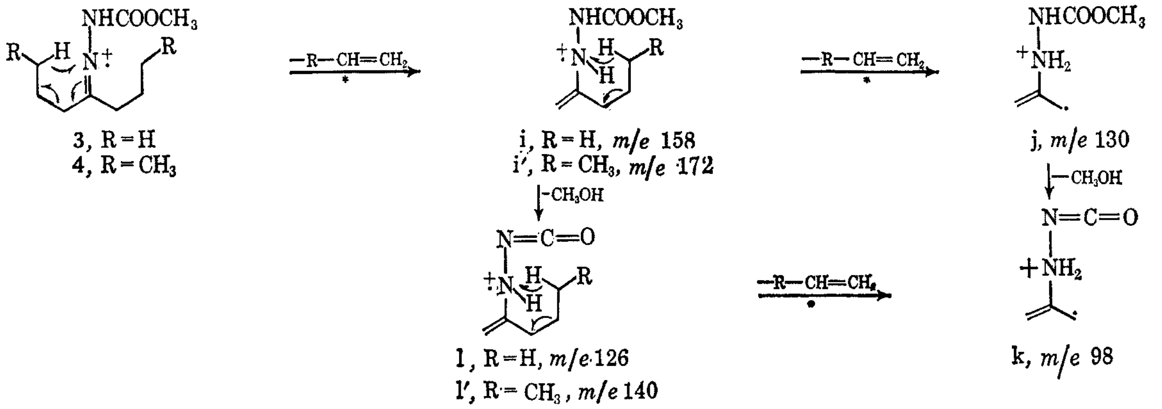
h, *m/e* 76

Qualitatively the mass spectrum of valeraldehyde N-methoxycarbonylhydrazone (2) resembles that of its lower homolog (1) but the base peak (at *m/e* 116) in the spectrum (Figure 2) is that of the McLafferty rearrangement species c. This is in accordance with the general observation in the series of carbonyl group derivatives so far investigated, that a primary γ-

Table I

			Found,%			Calcd,%		
Carbonyl compd	Mp, °C	Formula	C	H	N	C	H	N
			Methoxycarbonylhydrazones					
n-Valeraldehyde	50–51	$C_7H_{14}N_2O_2$	53.1	8.7	17.6	53.2	8.9	17.7
Di-*n*-propyl ketone	89–90	$C_9H_{18}N_2O_2$	58.2	9.8	15.0	58.0	9.7	15.0
Di-*n*-butyl ketone	64–65	$C_{11}H_{22}N_2O_2$	61.5	10.3	13.0	61.6	10.3	13.1
			Ethoxycarbonylhydrazones					
n-Valeraldehyde	Oil	$C_8H_{16}N_2O_2$	55.8	9.2	16.4	55.8	9.4	16.3
Di-*n*-propyl ketone	Oil	$C_{10}H_{20}N_2O_2$	59.9	10.1	14.2	60.0	10.1	14.0
Di-*n*-butyl ketone	Oil	$C_{12}H_{24}N_2O_2$	63.3	10.6	12.4	63.1	10.6	12.3

Scheme I

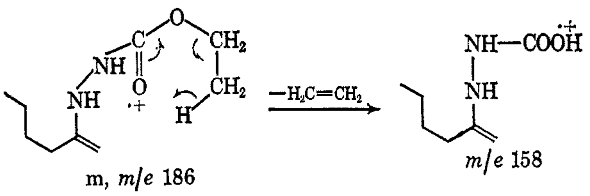


hydrogen atom is transferred less readily than a secondary one[14] in this site-specific six-membered hydrogen rearrangement process. The determination of γ specificity in the present series of compounds will be discussed in the following section.

Di-*n*-propyl and Di-*n*-butyl Ketone N-Methoxycarbonylhydrazones.—As in the case of the aldehyde derivatives, the mass spectra of both these compounds (Figures 3 and 4) were largely predictable and showed no deviation from the anticipated fragmentation modes. There were, however, the usual quantitative differences between the two spectra; in terms of per cent total ionization, the single and double McLafferty rearrangement ions i and j and their corresponding isocyanate species k provided 3.1% Σ_{40}, 11.3% Σ_{40}, and 7.0% Σ_{40} in the spectrum of the di-*n*-propyl ketone derivative, while in the mass spectrum of the di-*n*-butyl ketone N-methoxycarbonylhydrazone these ions constituted 1.3, 13.6, and 22%, respectively, of the total ionization (Σ_{40}). (See Scheme I.)

In addition, the single McLafferty rearrangement species i and i′ can lose methanol prior to the second rearrangement to furnish ions l and l′ (1.9% Σ_{40} and 3.5% Σ_{40}, respectively). As the spectrum of γ,γ'-d_4-di-*n*-butyl ketone methoxycarbonylhydrazone showed complete specificity of the single McLafferty rearrangement and 87% specificity of the second hydrogen transfer, the larger total contribution of the four ions i′, j, k, and l′ from the di-*n*-butyl ketone derivative can therefore be attributed to the proven ease of transfer of a secondary over a primary hydrogen.[14]

A comparison of the mass spectra (Figures 4 and 5) of the methoxycarbonyl- and ethoxycarbonylhydrazones of di-*n*-butyl ketone indicates that in the latter case there is little or no McLafferty rearrangement at the ester function, *i.e.*, there is no M − 28 peak, but there is a small M − (42 + 28) representing loss of ethylene from the single McLafferty rearrangement ion m. This may be compared with the double McLafferty transfer to nitrogen and its corresponding isocyanate species (at masses 144 and 98, respectively) which both represent the base peak in the spectrum of the ethyl ester. This evidence reinforces the previously stated argument about the likeliness of charge localization in the molecular ion at the doubly bonded nitrogen to direct fragmentation almost exclusively, even when the same energetically favorable processes can occur to doubly bonded oxygen elsewhere in the molecule. (Although it must be added that in this particular case the competition is between the less favorable transfer of a primary hydrogen to oxygen and that of a secondary one to nitrogen.)



Cyclopentanone and Cyclohexanone N-Methoxycarbonylhydrazones.—Few of the fragmentations in the mass spectra (Figures 6 and 7) of the methoxycarbonylhydrazones of cyclopentanone and cyclohexanone appear to be influenced by the nature of the alkoxycarbonyl grouping. The spectrum of the ethoxycarbonyl derivative of cyclopentanone, with the exception of a small McLafferty rearrangement ion at *m/e* 142 involving the ethoxycarbonyl group is virtually identical with that of its lower homolog. In both cases the base peak of the cyclopentanone derivatives is at *m/e* 67 shown by high-resolution measurements to be C_5H_7 (n or n′). The genesis of this ion is obscure as it has been established in related compounds that it is a β rather than the expected α hydrogen that is lost from the ring.[8]

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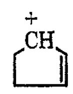
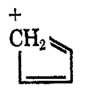
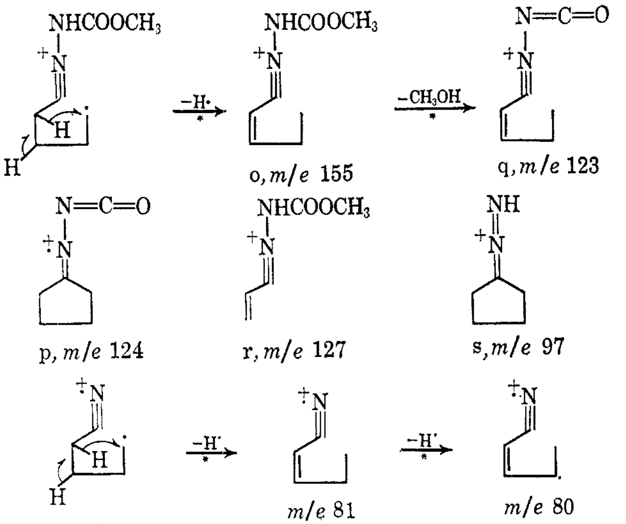
[14] H. Budzikiewicz, C. Fenselau, and C. Djerassi, *Tetrahedron*, **22**, 1391 (1966), and references therein.


n

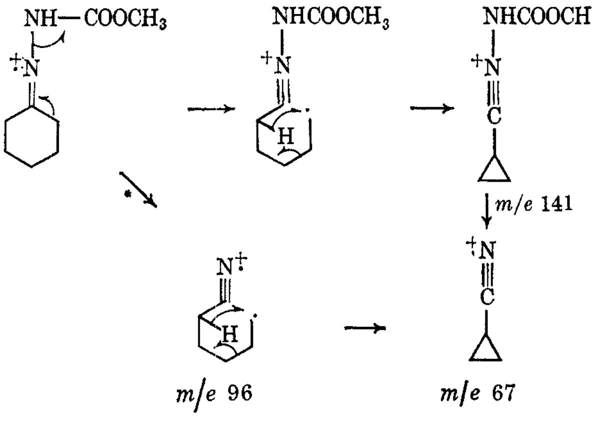

n′

Prominent ions also appear at M − 1 (o), M − 32 (p), M − (1 + 32) (q), M − 29 (r), at *m/e* 97 (s), 82 (t), 81, 80, and 59 ($COOCH_3^+$) together with several strong peaks at lower *m/e* values which were not fully investigated. However, the origin of each of the above ions has an analogy in either the oxime[6] or the semicarbazone[8] series and it is not unreasonable to expect that the lower *m/e* fragments also correspond to those observed in the spectra of other cyclopentanone derivatives.

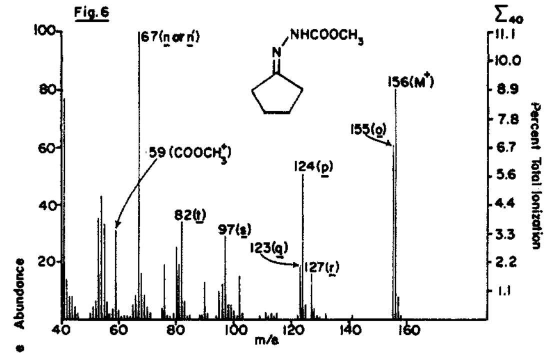


t, *m/e* 82

As in the case of its semicarbazone derivative,[8] the base peak in the mass spectrum of the methoxycarbonylhydrazone of cyclohexanone is at *m/e* 67. As shown by high-resolution mass spectrometry, this is a mixture of two isomers C_5H_7 and C_4H_5N the latter of which can be derived in a number of ways but probably follows one or both of the fragmentation pathways shown. The derivation of the hydrocarbon ion is less predictable but obviously involves several hydrogen transfers, generating either n or n′.



Other fragmentations of the molecular ion include the loss of a hydrogen radical, loss of ethylene to give a *m/e* 142 peak (u), loss of methanol (v), loss of a propyl radical generating species w at mass 127, a double α cleavage with hydrogen transfer to furnish ion (x), and scission of the functional group producing an ion at mass 81 (y), the homolog of the base peak at *m/e* 67 in the cyclopentanone derivative.



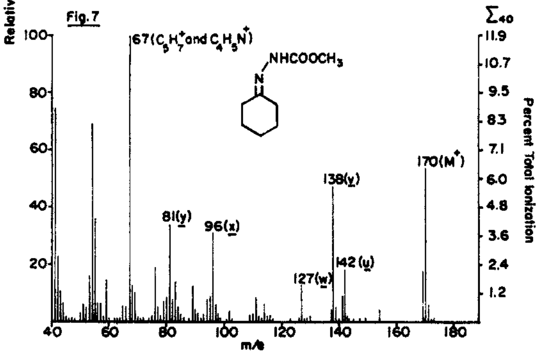
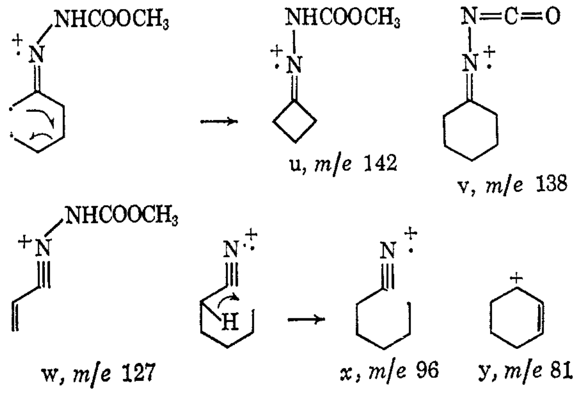


Figure 6.—Mass spectrum of cyclopentanone N-methoxycarbonylhydrazone.

Figure 7.—Mass spectrum of cyclohexanone N-methoxycarbonylhydrazone.



Although no labeling experiments were carried out for the derivatives of the cyclic ketones, we feel justified in making the above assignments because of the close similarity in fragmentation patterns between the alkoxycarbonylhydrazones and their corresponding semicarbazone and oxime derivatives for which labeled compounds were prepared and investigated mass spectrometrically.[6,8]

Experimental Section

The mass spectra and high-resolution mass measurements were recorded on an A.E.I. MS-9 mass spectrometer by Mr. R. Ross, using the direct inlet system and an ionizing voltage of 70 ev.

The alkoxycarbonylhydrazones were prepared by the method of Rabjohn[5] and purified either by crystallization from aqueous ethanol; or by preparative thin layer chromatography on silica gel G in chloroform–methanol (95:5); or by high-vacuum fractionation. All compounds ran as a single spot on tlc plates. Methoxycarbonylhydrazine (methyl carbazate) was synthesized according to the method of Diels[15] while ethyl carbazate was generously provided by Dr. O. Halpern of the Syntex Research Center, Palo Alto, Calif. Melting points and analyses of derivatives not previously described are tabulated in Table I.

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[15] O. Diels, *Ber.*, **47**, 2186 (1914).

The Anodic Oxidation of Organic Compounds. I. The Electrochemical Methoxylation of 2,6-Dimethoxypyridine and N-Methylpyrrole

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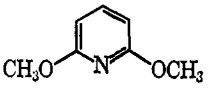
The first examples of nitrogen heterocycles, 2,6-dimethoxypyridine and N-methylpyrrole, have been anodically methoxylated. The dimethoxypyridine afforded a bisketal and a tetramethoxypyridine believed to be 2,3,3,6,6-pentamethoxy-1,4-azacyclohexadiene and 2,3,5,6-tetramethoxypyridine, respectively. N-Methylpyrrole gave 1-methyl-2,2,5,5-tetramethoxypyrroline. The ketal groups of these products were successfully hydrolyzed either partially or totally depending on the concentration of acid. Possible mechanisms for these novel reactions are discussed.

Anodic alkoxylations of organic compounds have been described in the furan,[1] thiophene,[2] benzenoid aromatic,[3] and olefinic series.[4] The products observed in these reactions are usually cyclic acetals, bisquinone ketals, ortho esters, and ethers, which are derived from the over-all addition of at least two alkoxy groups to the reductant. The electrochemical alkoxylation of nitrogen heterocycles has not, to our knowledge, been previously reported.

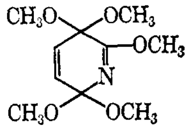
The anodic oxidation of 2,6-dimethoxypyridine I in methanol gave a mixture of at least five components as determined by vpc analysis (Figure 1). The crude electrolysate afforded four fractions on distillation and a considerable quantity of tarry residue. The lowest boiling fraction consisted of starting material (Figure 1, peak A). The second fraction (peak B) could not be isolated in sufficient quantity and purity for a positive identification; however, spectral data (ultraviolet and infrared) indicated that this oil was aromatic.

The third fraction (peak D) was obtained as a colorless oil, possessing no characteristic aromatic absorption, but a very strong ketal region in its infrared spectrum. The elemental analysis and the nmr spectrum showed an over-all addition of three methoxy groups to I. There are two possible structures that may be accommodated by these observations: the *p*-azaquinone ketal II and the *o*-azaquinone ketal III. By spectroscopic comparison with similar compounds it may be demonstrated that the *p*-azaquinone ketal II is the more probable structure. Thus the nmr spectrum[3] of 2,3,3,6,6-pentamethoxy-1,4-cyclohexadiene (IV) had bands at τ 6.80 and 6.38 and a group of eight peaks (ABX system) extending from 5.12 to 3.93 with $J_{AB} = 10.0$ cps, while the spectrum of the product exhibited peaks at τ 6.75 and 6.25, and a quartet (AB system) extending from τ 4.23 to 3.75 with $J_{AB} = 10.0$ cps. In addition the ultraviolet spectrum of 3,3,6,6-tetramethoxy-1,4-cyclohexadiene (V) with λ_{max} 215 mμ (ϵ 1000) was almost identical with that of the product, with λ_{max} 213 mμ (ϵ 1100).

The last fraction obtained from the electrolysate solidified on standing and was identified (peak C) as a tetramethoxypyridine from its nmr spectrum and elemental analysis. Two isomers are possible: the 2,3,5,6- and the 2,3,4,6-tetramethoxypyridine (VI and VII). However, the symmetry of that portion of the nmr spectrum characteristic of methoxy groups (a doublet of equal intensity at τ 6.32 and 6.20) is consistent with structure VI.



I



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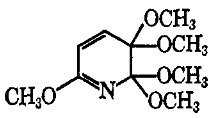

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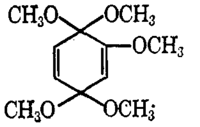
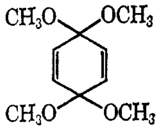
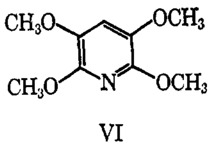


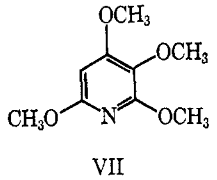
IV



V



VI



VII

The chemistry of the azaquinone ketal II (or III) was briefly explored. Hydrolysis in aqueous acetic acid gave two compounds, dimethyl 4,4-dimethoxyglutaconate (VIII) and 4,4-dimethoxyglutaconimide (IX). The major product in 10 to 25% acetic acid was VIII, while in 0.5% acetic acid, almost pure IX could be isolated. The glutaconate VIII, a mixture of *cis* and *trans* isomers, was converted to dimethyl α-oxoglutarate 2,4-dinitrophenylhydrazone.

The glutaconimide IX had an nmr spectrum with peaks at τ 6.65 and 6.70 (doublet of equal intensity for

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[1] N. Elming in "Advances in Organic Chemistry: Methods and Results," Vol. 2, R. A. Raphael, E. C. Taylor, and H. Wynberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1960, p 67.

[2] K. E. Kolb, Ph.D. Thesis, The Ohio State University, 1953.

[3] N. L. Weinberg and B. Belleau, *J. Am. Chem. Soc.*, **85**, 2525 (1963).

[4] T. Inoue, K. Koyama, T. Matsuoka, K. Matsuoka, and S. Tsutsumi, *Tetrahedron Letters*, 1409 (1963).