Mass Spectrometry in Structural and Stereochemical Problems. CXIII.[1] Specific Hydrogen Rearrangements in the Fragmentations of Hydrazones[2]

DAVID GOLDSMITH[3] AND CARL DJERASSI

Department of Chemistry, Stanford University, Stanford, California

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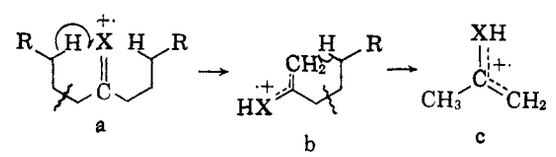
The concept of charge localization in site-specific hydrogen transfer was tested further by examining the mass spectra of N,N-dimethylhydrazones and 2,4-dinitrophenylhydrazones of aldehydes and ketones. Such derivatives possess more than one heteroatom and yet exhibit site-specific hydrogen rearrangements of the McLafferty type. Support for the postulated fragmentation schemes was adduced by deuterium labeling and high-resolution mass spectrometry.

Two of the fundamental processes in the mass spectrometric fragmentations of carbonyl compounds and their derivatives are the "single" and "double" McLafferty rearrangements.[4] The single stage, illustrated formally by the process a → b, involves the transfer of a hydrogen atom and the formation of a neutral olefin and a charged enol. The second stage process, b → c, follows the same basic pathway with



a b c

the hydrogen now being transferred presumably to carbon rather than to oxygen. Two specific structural factors have been found to influence the contributions of ions of these types to the total ionization of carbonyl and related compounds. First, the hydrogen atoms which are transferred in both the single and double stages of the rearrangement are specifically γ hydrogens,[5,6] and second, the rearrangements are much more readily accomplished when the transferred hydrogens originate from a secondary carbon atom (a, R = alkyl) rather than from a primary one (a, R = H).[6] In the recently studied di-*n*-propyl ketone,[6] for example, where only primary γ hydrogens are available, the ion yields of the single and double McLafferty rearrangements are 0.5% Σ_{40} and 3.7% Σ_{40}, respectively. The corresponding fragments in the spectrum of di-*n*-butyl ketone[6] (transfer of secondary hydrogen) contribute 1.8 and 18.1% to the total ionization. The same general relationships are found in the spectra of azomethines[7] and semicarbazones.[8] More strikingly, it has been shown that, whereas the single McLafferty rearrangement peak in the spectrum of valeraldehyde 2,4-dinitrophenylhydrazone constitutes 7.2% of the total ionization, the corresponding fragment in the spectrum of the lower homolog, butyraldehyde 2,4-dinitrophenylhydrazone, is not detected.[9] The latter compound, of course, is one which contains only primary γ hydrogens.

The specificity of the McLafferty rearrangement, in addition to its importance in structure determination, also lends strong support to the general concept of charge localization in mass spectrally produced ions.[10] This is particularly so with simple carbonyl compounds where only one heteroatom is present. In the case of carbonyl derivatives which contain more than one heteroatom the spectra appear to derive from distribution of the charge over much of the heteroatom system. As we have suggested,[11] for example, the fragmentations of oximes are interpretable in terms of charge localization on both nitrogen and oxygen. Similar conclusions have been drawn for the spectra of semicarbazones[8] and 2,4-dinitrophenylhydrazones.[9a] In order to obtain further evidence regarding the specific hydrogen rearrangements as exemplified by the McLafferty process, and the problem of charge localization, we have now investigated the mass spectra of a number of N,N-dimethylhydrazones and 2,4-dinitrophenylhydrazones. The results of this investigation are described in the present communication.

Butyraldehyde and Valeraldehyde N,N-Dimethylhydrazones.—Butyraldehyde N,N-dimethylhydrazone (1) and valeraldehyde N,N-dimethylhydrazone (2) show relatively simple fragmentation patterns. The spectrum (Figure 1) of butyraldehyde dimethylhydrazone shows as the base peak, *m/e* 85 (d), corresponding to β cleavage of the molecular ion with loss of an ethyl radical. The same fragment is responsible for the base peak in the spectrum (Figure 2) of valeraldehyde dimethylhydrazone. Interestingly this type of cleavage appears to be limited to these simple aldehyde dimethylhydrazones, as it is not found as a significant feature of the spectra of the other hydrazones described in this paper, nor of the spectra of the carbonyl compounds themselves,[12] or of their derivatives.[7-9,11] The appearance of these peaks suggests that the charge in the ions produced from aldehyde dimethylhydrazones by electron bombardment may be largely limited to the dimethylamino nitrogen, the more basic of the two nitrogen functions.[13] Thus the observed β cleavage

(1) For paper CXII, see D. S. Weinberg and C. Djerassi, *J. Org. Chem.*, **31**, 3832 (1966).

(2) Financial assistance (Grant No. AM-04257) from the National Institutes of Health is gratefully acknowledged.

(3) National Institutes of Health Special Fellow (1965) while on leave from Emory University, Atlanta, Ga.

(4) F. W. McLafferty, *Anal. Chem.*, **31**, 82 (1959).

(5) For leading references, see C. Djerassi and L. Tökés, *J. Am. Chem. Soc.*, **88**, 536 (1966).

(6) H. Budzikiewicz, C. Fenselau, and C. Djerassi, *Tetrahedron*, **22**, 1391 (1966).

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

(8) D. Becher, S. Sample, and C. Djerassi, *ibid.*, **99**, 2284 (1966).

(9) (a) S. Sample and C. Djerassi, *Nature*, **208**, 1314 (1965); (b) R. J. C. Kleipool and J. T. Heins, *ibid.*, **203**, 1280 (1964).

(10) (a) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Interpretation of Mass Spectra of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1964; (b) for a dissenting point of view, see P. Bommer and K. Biemann, *Ann. Rev. Phys. Chem.*, **16**, 481 (1965).

(11) D. Goldsmith, D. Becher, S. Sample, and C. Djerassi, *Tetrahedron*, in press.

(12) See Chapter 1 in ref 10a.

(13) F. W. McLafferty in "Mass Spectrometry of Organic Ions," F. W. McLafferty, Ed., Academic Press Inc., New York, N. Y., 1963, Chapter 7.

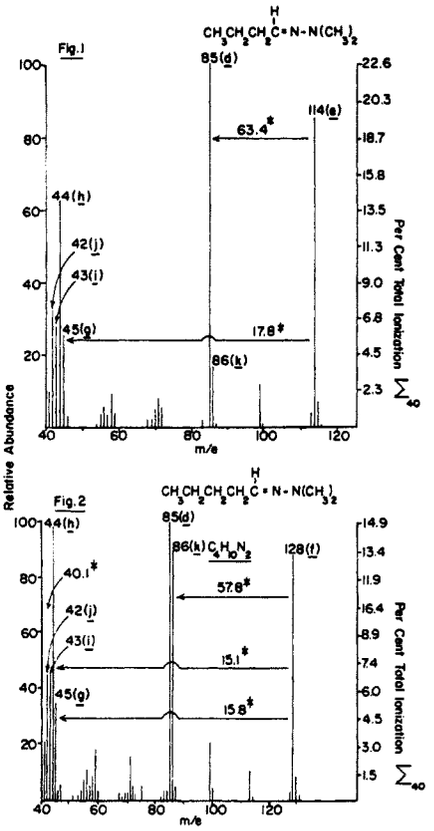
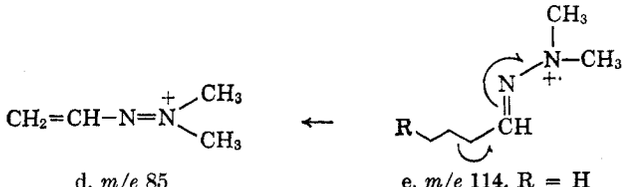


Figure 1.—Mass spectrum of butyraldehyde N,N-dimethylhydrazone. The occurrence of metastable ions is indicated in these spectra by the symbol $\overset{*}{\leftarrow}$, the arrow originating from the parent ion and pointing to the daughter ion involved in the metastable transition. Calculated values for metastable ions are within 0.2 mass units of the observed values.

Figure 2.—Mass spectrum of valeraldehyde N,N-dimethylhydrazone. High-resolution mass measurements are indicated in these spectra by underlined molecular formulas as for instance $C_4H_{10}N_2$ in Figure 2.

may be seen as an allylic cleavage of the molecular ions e and f.



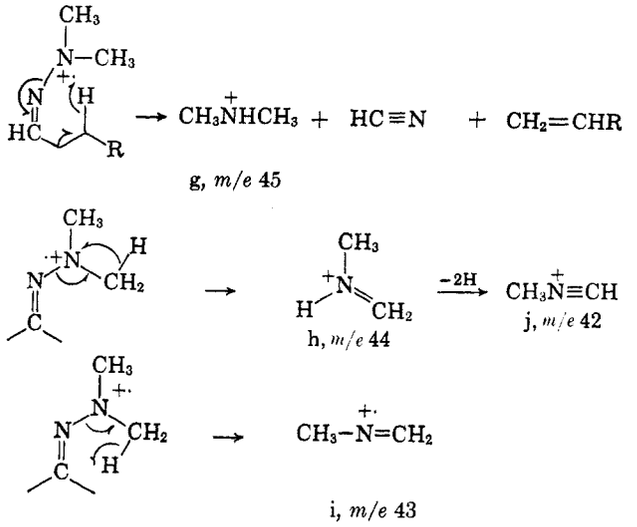
d, *m/e* 85

e, *m/e* 114, R = H
f, *m/e* 128, R = CH_3

Some of the other common features of the spectra of **1** and **2** are the peaks in the region of *m/e* 41 and 45. These species, like the ones described above, also appear to be derived from the molecular ions e and f in which the charge is localized on the saturated nitrogen function. As indicated in Figures 1 and 2, metastable ions (marked with asterisks) are found for the formation of the ions of masses 45 (g), 44 (h), 43 (i), and 42 (j). High-resolution measurements in the spectra of other dimethylhydrazones (see Figures 4 and 6) show that they are derived from the dimethylamino group and possible rationalizations for their formation are given in Chart I.

The most striking difference between the mass spectra of the two aldehyde dimethylhydrazones **1** and **2** is the contribution made to the total ionization in each case by the peak at *m/e* 86. In the spectrum (Figure

CHART I



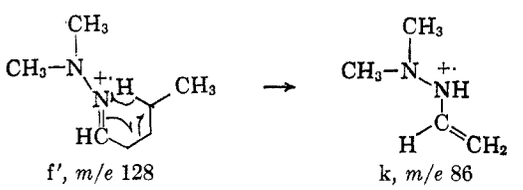
g, *m/e* 45

h, *m/e* 44

j, *m/e* 42

i, *m/e* 43

2) of valeraldehyde N,N-dimethylhydrazone (**2**) this species is present in an ion yield of 12% Σ_{40},[14] while its contribution to the spectrum (Figure 1) of butyraldehyde N,N-dimethylhydrazone (**1**) is only 2.3% Σ_{40}.[14] A high-resolution mass measurement of the composition of the ion of mass 86 in the spectrum of **2** shows it to be $C_4H_{10}N_2$. This species is clearly the result of a McLafferty rearrangement (f′ → k) formulated as resulting from the alternative molecular ion f′ with the *imino* nitrogen being electron deficient.[15] From the intensity relationship of the *m/e* 86 peaks in the spectra of **1** and **2** it is clear that these compounds show a marked preference for the transfer of a secondary hydrogen rather than a primary one. We shall return to a further discussion of this process after consideration of the mass spectra of a number of ketone derivatives.



f′, *m/e* 128

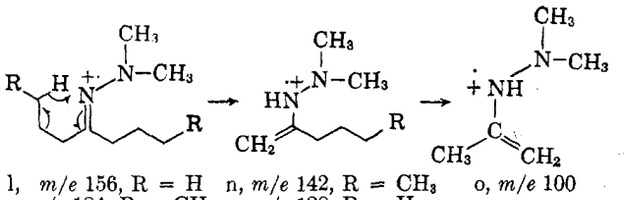
k, *m/e* 86

Di-*n*-propyl Ketone and Di-*n*-butyl Ketone N,N-Dimethylhydrazones.—The mass spectra of di-*n*-propyl ketone N,N-dimethylhydrazone (**3**, Figure 3) and di-*n*-butyl ketone N,N-dimethylhydrazone (**4**, Figure 4) show marked contrasts to the spectra (Figures 1 and 2) of the above-discussed aldehyde derivatives, **1** and **2**. The β cleavage typical of the aldehydic compounds does not occur with **3** and **4**. The fragmentation of the latter substances appears to be largely controlled by localization of charge at the sp^2 nitrogen atom,[15] the molecular ions being represented by l and m. Thus, high-resolution mass measurements (see Figure 4) of significant peaks in the spectrum of the dibutyl compound **4** demonstrate that the dimethyl-

(14) This value is corrected for the contribution of the M + 1 isotope peak of the ion of mass 85.

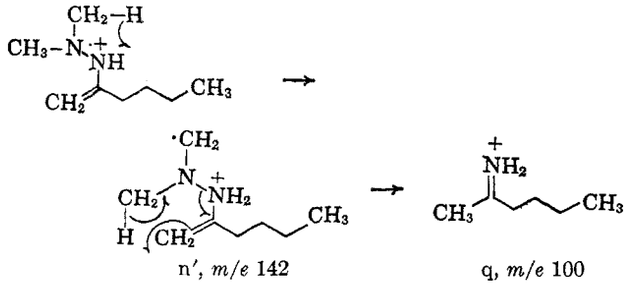
(15) The representations of the molecular ions f and f′ are in a sense only resonance forms since the conversion of $=\dot{N}-\dot{N}<$ to $=\overset{+}{N}-\dot{N}<$ requires merely the transfer of an electron. The hybrid would require the delocalization of three electrons over the two p orbitals of the N–N system thus placing one electron in an antibonding orbital. This excited state resonance hybrid is, however, a not unreasonable species at the relatively high energies encountered in electron-impact phenomena.

amino group is either lost as a neutral fragment in the production of the species of mass 84, 100 (in part), 112, and 140, or is not involved in triggering the fragmentation process. This last suggestion is based on the observation that the ions of masses 142 (n) and 100 (o) correspond to the products of single and double McLafferty rearrangements, m → n → o. Additional evidence for this conclusion comes from the spectrum of γ,γ'-d_4-di-*n*-butyl ketone N,N-dimethylhydrazone which shows a shift of the *m/e* 142 peak to *m/e* 145 and of the *m/e* 100 species to *m/e* 102. These results are in accord with previous demonstrations[6] of the γ-hydrogen specificity of the single and double McLafferty rearrangement. It is also apparent from a comparison of the spectra (Figures 3 and 4) of **3** and **4** that the usual preference for transfer of a hydrogen atom from a substituted carbon atom[6] operates in the quantitative production of the products of the two McLafferty rearrangements. The contribution of the ion o resulting from double rearrangement of m is 7% Σ_{40} while the same ion produced from l, the molecular ion of the dipropyl compound (**3**), occurs in an ion yield of only 0.5% Σ_{40}.



l, *m/e* 156, R = H n, *m/e* 142, R = CH_3 o, *m/e* 100
m, *m/e* 184, R = CH_3 p, *m/e* 128, R = H

Two other aspects of the spectra of compounds **3** and **4** are noteworthy. One is the appearance of the usual series of peaks in the *m/e* 41–45 region, a feature common to all of the dimethylhydrazones that we have examined. The formation of these species presumably follows the same pathways suggested for the fragmentation processes of the aldehyde dimethylhydrazones. The other is the result of the determination of the nature of the minor constituent of the *m/e* 100 peak in the spectrum (Figure 4) of the dibutyl ketone derivative **4**. The composition of this fragment was shown by a high-resolution mass measurement to be $C_6H_{14}N$. In addition the ion is shifted to *m/e* 103 in the spectrum of the corresponding γ,γ'-d_4 compound, a high-resolution mass measurement showing the composition to be now $C_6H_{11}D_3N$. It is clear that two hydrogen transfers from the dimethylamino group to the alkyl chain are required for the production of $C_6H_{14}N$ ion, and a possible path for them is indicated by the sequence n′ → q.



n′, *m/e* 142 q, *m/e* 100

Cyclopentanone and Cyclohexanone N,N-Dimethylhydrazones.—The spectra of cyclopentanone N,N-dimethylhydrazone (**5**) and cyclohexanone N,N-dimethylhydrazone (**6**) are shown in Figures 5 and 6. These compounds show similar spectra characterized by abundant molecular ions[16] and by the appearance of the usual peaks in the *m/e* 41–45 range. Interestingly, these spectra are otherwise very simple. The principal fragmentations of the *acyclic* hydrazones are, of course, not to be expected in the cyclic cases, but neither do we observe to any significant extent the usual modes of decomposition of cyclic ketones[17] and their derivatives. The few cleavages that do occur result in the formation of hydrocarbon fragments or in the loss of groups from the dimethylamino moiety. For example, in the spectrum (Figure 6) of the cyclohexanone derivative **6**, where high-resolution measurements have been made (see Figure 6) peaks are observed at *m/e* 125 (s) for the loss of a methyl group, *m/e* 96

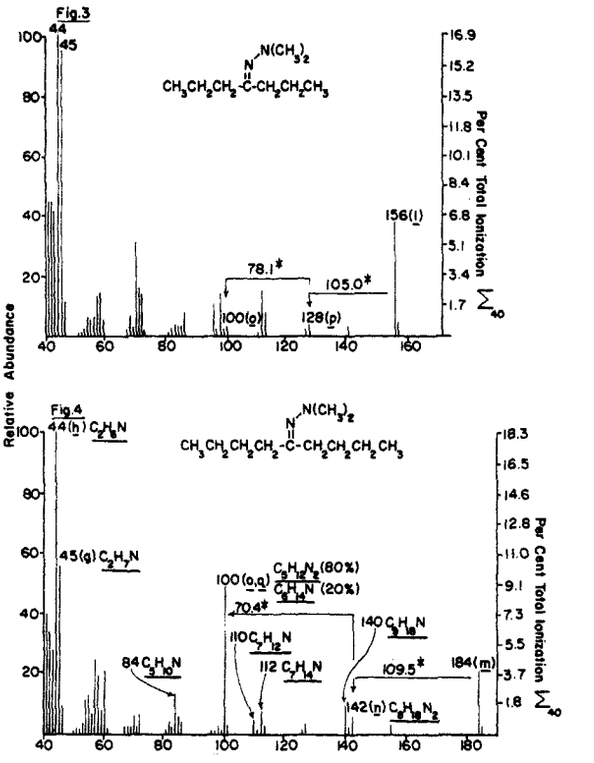
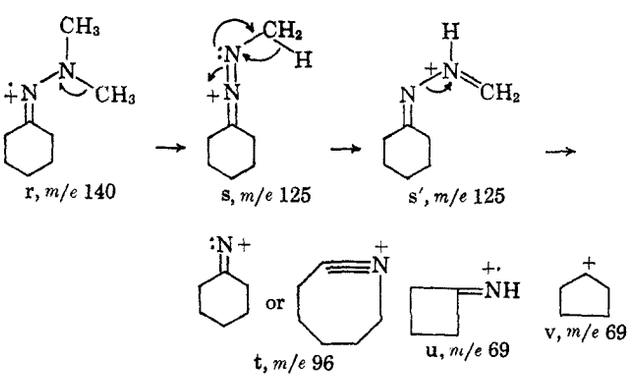


Figure 3.—Mass spectrum of di-*n*-propyl ketone N,N-dimethylhydrazone.
Figure 4.—Mass spectrum of di-*n*-butyl ketone N,N-dimethylhydrazone.

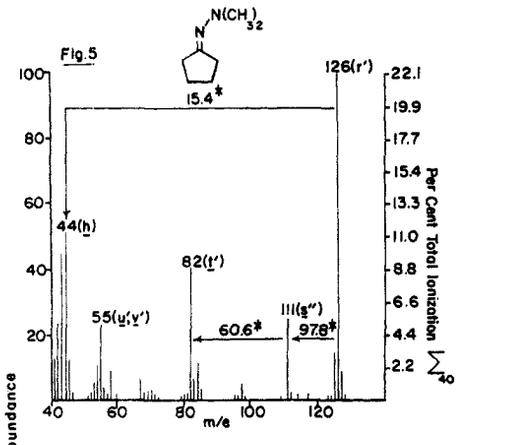


r, *m/e* 140 s, *m/e* 125 s′, *m/e* 125

t, *m/e* 96 u, *m/e* 69 v, *m/e* 69

(16) The spectra of three keto steroid dimethylhydrazones, 5α-cholestan-3-one, 5α-androstan-17-one, and 5α-androstane-3,17-dione N,N-dimethylhydrazones, measured in the laboratory of Professor E. C. Horning, Baylor University, reveal intense peaks for the molecular ions and little significant fragmentation. We wish to thank Professor Horning for providing us with these spectra.

(17) See Chapter 1, section 3 in ref 10a.



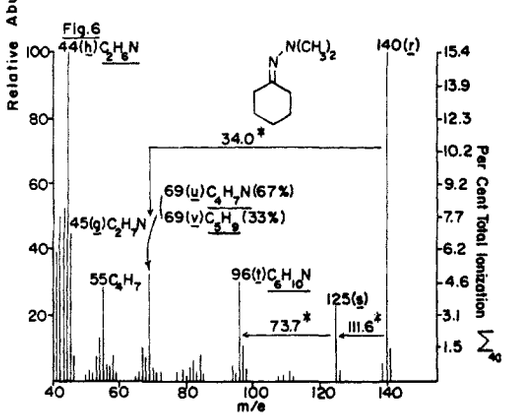
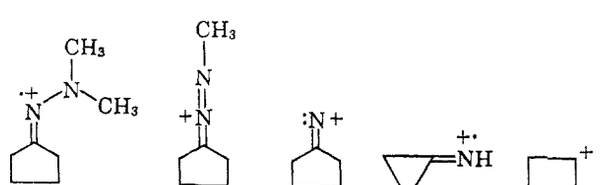


Figure 5.—Mass spectrum of cyclopentanone N,N-dimethylhydrazone.
Figure 6.—Mass spectrum of cyclohexanone N,N-dimethylhydrazone.

(t) for loss of the entire dimethylamino function, and *m/e* 69 (u, v), a doublet resulting from both a cleavage of the ring, and from complete loss of the hydrazone grouping.

Although no high-resolution mass measurements were made with peaks in the spectrum (Figure 5) of cyclopentanone N,N-dimethylhydrazone (**5**) it is clear that the same types of fragmentations occur with **5**. Cleavage products s'', t', u', and v', corresponding to the ones noted above, occur in the spectrum of **5** at positions 14 mass units lower than those in the spectrum of **6**.



r', *m/e* 126 s'', *m/e* 111 t', *m/e* 82 u', *m/e* 55 v', *m/e* 55

The peaks at *m/e* 125 (M − 15) and *m/e* 96 (M − 44) in the spectrum of **6**, and *m/e* 111 (M − 15) and *m/e* 82 (M − 44) in the spectrum of **5**, present an interesting example of a change in fragmentation mechanism with structure. The acyclic ketone dimethylhydrazones **3** and **4** do not show significant peaks in their mass spectra for the loss of methyl groups from the molecular ions. In addition, as indicated by metastable ions shown in Figures 3 and 4, the M − 44 species found in these spectra are formed directly from the molecular ions. In contrast, the mass spectra of both cyclohexanone dimethylhydrazone (**6**) and cyclopentanone dimethylhydrazone (**5**) show relatively intense M − 15 peaks. The methyl group which is lost presumably comes from the dimethylamino function and this contention receives support from the finding that no deuterium is lost in this cleavage in the fragmentation of α,α'-deuterated cyclohexanone N,N-dimethylhydrazone.[18] Remarkably, it is these M − 15 species, as shown by the metastable ions indicated in Figures 5 and 6, which are, at least in part, the precursors of the M − 44 peaks found in the spectra of the cyclic dimethylhydrazones. For the cyclohexanone derivative (**6**) loss of a methyl group from the molecular ion r would lead to the even-electron species s. Rearrangement to s' and cleavage of the N–N bond could then produce t as the M − 44 species. It may be noted that nitrogen species having only an electron sextet appear to be favored intermediates and products in some mass spectral fragmentations, since t and related ions are also found widely in the mass spectra of oximes.[11] In the latter cases, these species are produced by loss of the oxime hydroxyl function.

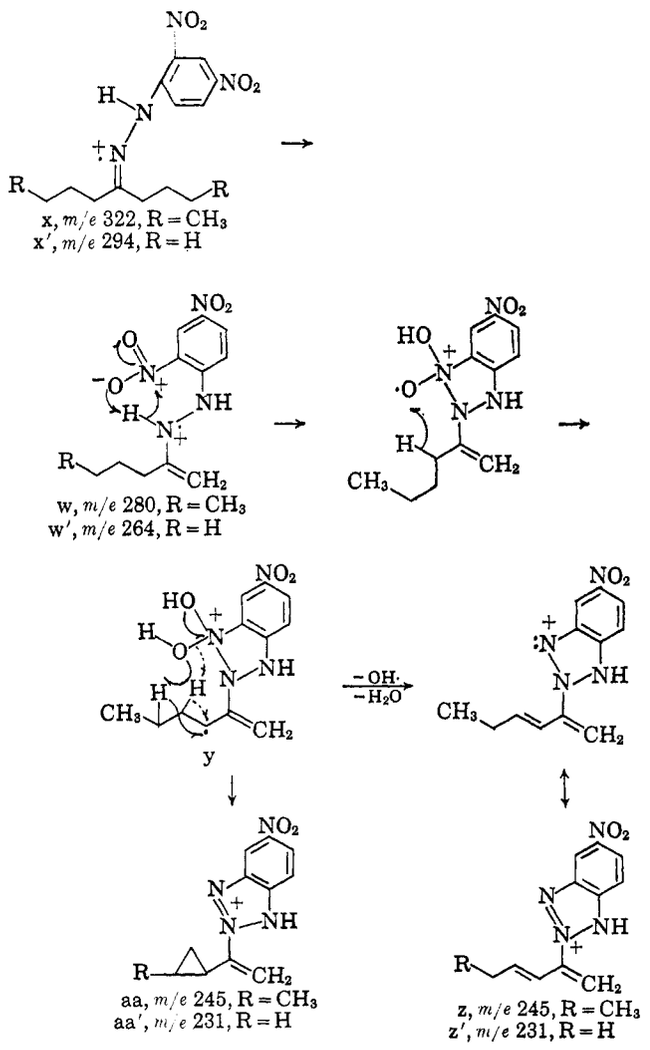
Di-*n*-propyl Ketone and Di-*n*-butyl Ketone 2,4-Dinitrophenylhydrazones.—As noted earlier[9] the 2,4-dinitrophenylhydrazone (DNP) of valeraldehyde shows a peak in its mass spectrum at *m/e* 224 corresponding to a McLafferty rearrangement while the butyraldehyde derivative does not yield an equivalent ion. Extending these observations we have examined the mass spectra of di-*n*-propyl ketone DNP (**7**, Figure 7) and di-*n*-butyl ketone DNP (**8**, Figure 8). We find first that the dibutyl compound shows a relatively strong peak (2.2% Σ_{40}) at *m/e* 280 (w) for the product of a single McLafferty rearrangement. The corresponding fragment (w', *m/e* 266) from **7** while present in the spectrum (Figure 7) is virtually indistinguishable from background. Interestingly, however, neither DNP shows an intense peak at *m/e* 238 for the expected double McLafferty fragment, although in accord with previous observations this species is more abundant in the spectrum of **8** than in that of **7**. On the other hand, both spectra do show peaks (*m/e* 231 and 245) at a position 35 mass units less than the first McLafferty rearrangement species. In the spectrum (Figure 8) of the dibutyl compound **8**, this peak (*m/e* 245, z) is the most intense one in the spectrum.

The loss of 35 mass units has been observed previously in the spectra of 2,4-dinitrophenylhydrazones[9] and in the case of aldehyde DNP's this loss of the elements of H_2O and OH· has been shown to occur from the molecular ion and has been inferred to be a two-stage process. In the present instances the principal loss of 35 mass units occurs from the single McLafferty rearrangement products w and w' and is at least in part a one-step process as shown by the occurrence of the appropriate metastable ions (see Figures 7 and 8). To verify the contention that this seemingly remarkable fragmentation is the result of the combined loss of water and a hydroxyl radical the *m/e* 245 peak in the spectrum of **8** was examined by high-resolution mass

(18) Considerable exchange of the deuterium atoms of 2,2,6,6-d_4-cyclohexanone occurs during the preparation of the dimethylhydrazone. The same ratio, however, of d_0, d_1, d_2, d_3, and d_4 species found in the molecular ion is found in the distribution of the M − 15 peaks indicating that no α hydrogens are lost in the expulsion of a methyl group from **6**.

spectrometry and its composition was confirmed to be $C_{12}H_{13}N_4O_2$. Additional evidence bearing on the formation of this species is available from the spectrum of γ,γ'-d_4-*n*-butyl ketone 2,4-dinitrophenylhydrazone (**9**). The *m/e* 245 peak of the undeuterated compound **8** was found to be shifted in the spectrum of **9** to an approximately equal extent to *m/e* 246 and 247. It is clear, therefore, that at least one and in part two of the three deuterium atoms present in the deuterated equivalent of the ion w must be expelled during this fragmentation and it is reasonable to assume that the one which is lost completely is the deuterium transferred to nitrogen during the course of the rearrangement (x → w) of the molecular ion of **8**.

Another observation pertaining to the mechanism of this fragmentation is that the spectrum (Figure 9) of the *p*-nitrophenylhydrazone of di-*n*-butyl ketone (**10**) reveals both a single (*m/e* 235) and a double McLafferty rearrangement peak (*m/e* 193) with the latter being the base peak of the spectrum. There are not present, however, in this spectrum (Figure 9) any significant peaks at either *m/e* 242 or 200 for the loss of 35 mass units from either the molecular ion or from the first McLafferty rearrangement ion. It is clear then that any mechanism accounting for the formation of the ion of mass 245 in the spectrum (Figure 8) of di-*n*-butyl ketone DNP or of the ion of mass 231 in the spectrum (Figure 7) of the dipropyl compound **7** must account for the following observations. (1) A water molecule



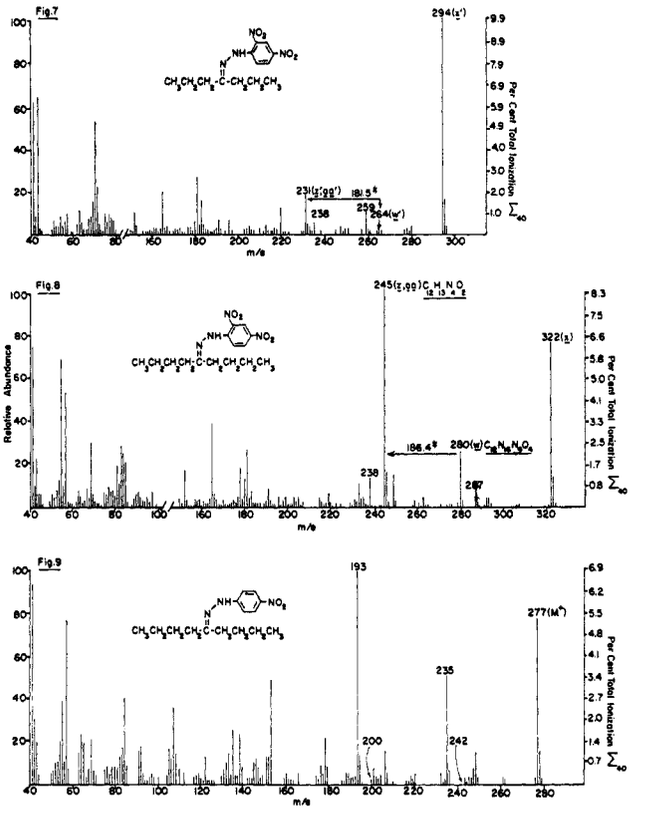


Figure 7.—Mass spectrum of di-*n*-propyl ketone 2,4-dinitrophenylhydrazone.

Figure 8.—Mass spectrum of di-*n*-butyl ketone 2,4-dinitrophenylhydrazone.

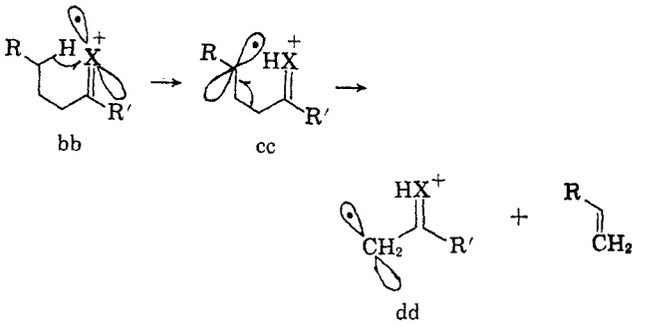
Figure 9.—Mass spectrum of di-*n*-butyl ketone *p*-nitrophenylhydrazone.

and a hydroxyl radical (or their equivalent) are lost in a *single* step. (2) At least one and in large measure two hydrogens originally present in the γ positions of the DNP are lost. (3) The *o*- rather than *p*-nitro group is the source of the two oxygens lost in the neutral fragments. A possible pathway is shown in the sequence x → z. Although the final step, y → z, requires the breaking of two bonds from the same atom, the resulting formation of the highly resonance-stabilized cation z might provide the necessary driving force. The partial loss of the third γ hydrogen (second with respect to w) is accounted for by the loss of either a β hydrogen to give a double bond in the alkyl chain (y → z, dotted arrows) or a γ hydrogen (y → aa, solid arrows) to yield a cyclopropyl system. The corresponding species from the dipropyl ketone DNP (**7**) are represented as z′ and aa′. It may be noted finally that there are also peaks in the spectra of **7** and **8** at *m/e* 259 and 287, respectively, for the loss of 35 mass units from the molecular ions x and x′. The formation of these species is presumably analogous to the process involved in the corresponding fragmentation patterns of aldehyde dinitrophenylhydrazones.[9a]

It has been suggested recently[19] that the site specificity of the McLafferty rearrangement may be viewed as a function of the radical character of the species undergoing this process. That is, the strong directional character of the radical orbital, as in bb, necessitates at least a six-membered transition state for the

(19) (a) C. Djerassi, M. Fischer, and J. B. Thomson, *Chem. Commun.*, 12 (1966); (b) F. W. McLafferty, *ibid.*, 78 (1966).

transfer of a hydrogen atom. In addition it has been suggested[19b] that mass spectrometric reactions occurring *via* radical intermediates will be characterized by *site-specific* transfer reactions to form new bonds to the original radical site, and on this basis the McLafferty rearrangement might be written as the stepwise process bb → dd. This mechanism clearly suggests that the nature of the radical species produced at the γ carbon (as in cc) will strongly influence the feasibility of this fragmentation mode; *i.e.*, the more stabilized a radical can be at the γ position the more easily will the rearrangement occur, and the more abundant will be the fragment resulting from such a process. The clear prediction is then that a hydrogen atom on a secondary atom will be transferred more readily than one on a primary carbon atom since the usual order of radical stabilities is 3° > 2° > 1°.[20] As noted earlier, ketones,[6] aldehydes,[12] esters,[12] azomethines,[7] semicarbazones,[8] aldehyde DNP's,[9] and oximes[11] show γ-hydrogen specificity and with the exception of only the last class of compounds they all show in their mass spectra a striking preference for transfer of a secondary hydrogen. We have shown in this paper that the same specific hydrogen transfers occur with ketone dimethylhydrazones and dinitrophenylhydrazones. It seems, therefore, that the trigger for the type of fragmentation exemplified by the McLafferty rearrangement may be the localization of both charge and radical



character at specific atomic sites in ions produced by electron impact.

(20) See, for example, J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 422.

Experimental Section

The mass spectra and the high-resolution mass measurements were determined with an AEI MS-9 mass spectrometer operating with an ionizing voltage of 70 ev and with a source temperature of 200°. The samples were admitted into the ion source through an all-glass heated inlet system operating at 80°.

The dimethylhydrazones were prepared according to a modification of a published procedure[21,22] using commercially available aldehydes or ketones and N,N-dimethylhydrazine. In a typical preparation the carbonyl compound was dissolved in a large excess of dimethylhydrazine and the solution was heated under reflux for 2 hr. After cooling, the excess reagent was removed *in vacuo* and ice and saturated salt solution were added to the residue. The organic phase was isolated and purified by gas liquid partition chromatograph on an Apiezon L column operating at 150° and 15 psi of helium.

(21) R. H. Wiley, S. C. Slaymaker, and H. Krauss, *J. Org. Chem.*, **22**, 204 (1957).

(22) See also G. R. Newkome and D. L. Fishel, *ibid.*, **31**, 677 (1966).

Selective Mono-O-alkylation of 2,6-Dibromohydroquinone

LINNEAUS C. DORMAN

Edgar C. Britton Research Laboratory, The Dow Chemical Company, Midland, Michigan

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It was demonstrated that 2,6-dibromohydroquinone can be selectively mono-O-alkylated at either the 1 or 4 oxygen depending on whether the monoanion or dianion is being alkylated. The monoanion alkylates preferentially at the 1 oxygen and the dianion at the 4 oxygen. The selectivity in each case is increased on changing from water to dimethyl sulfoxide and this difference in selectivity is attributed mainly to solvation effects. 2,6- and 3,5-dibromophenols were employed as model compounds and their relative rates of methylation provide support for the rationalization of the 2,6-dibromohydroquinone O-alkylation reactions.

In connection with some work in this laboratory, it was of interest to prepare several 3,5-dibromo-4-alkoxyphenols (II). 2,6-Dibromohydroquinone appeared to be a suitable intermediate for this purpose. At first inspection, it appeared that this hydroquinone would preferentially mono-O-alkylate at the unhindered 4 oxygen. Therefore, the projected synthetic route to II (Scheme I) was first to alkylate the 4 oxygen with a benzyl group, followed by an alkylation of the 1 oxygen with the desired R group, and finally removal of the benzyl group by hydrogenolysis.

Proceeding in this manner, 2,6-dibromohydroquinone was alkylated with benzyl bromide in dimethyl sulfoxide (DMSO) with potassium carbonate as base. Near-equimolar quantities of each reagent were used. The mono-O-alkylated product, isolated in 62% yield, had ν_{OH} (0.5% CCl_4) at 3430 (broad) and 3610 (sharp) cm^{-1} characteristic of intermolecularly hydrogen bonded and free phenolic absorptions, respectively.[1,2] This product was, therefore, 3,5-dibromo-4-benzyloxyphenol (III) and not the anticipated isomer, 2,6-dibromo-4-benzyloxyphenol (I).[3,4] In order to clarify the factors which lead to this result, the mono-O-alkylation reactions of 2,6-dibromohydroquinone monoanion and dianion and of model compounds, 2,6- and 3,5-dibromophenoxides, were studied.

(1) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen and Co. Ltd., London, 1962, p 96.

(2) Note that intramolecular hydrogen bonding of phenolic OH by two *ortho* bromine atoms as in structure I gives rise to a single, sharp absorption band near 3515 cm^{-1}: I. Brown, G. Eglinton, and M. Martin-Smith, *Spectrochim. Acta*, **18**, 1593 (1962).

(3) During the course of this work, it was learned that A. W. Baker, H. O. Kerlinger, and A. T. Shulgin [*ibid.*, **20**, 1467 (1964)] had found similar results in the methylation of 2,6-dichlorohydroquinone and 2,6-dibromohydroquinone. The author wishes to take this opportunity to express his appreciation to these authors for communicating their results.

(4) H. E. Ungnade and K. T. Zilch [*J. Org. Chem.*, **16**, 64 (1951); *Chem. Abstr.*, **45**, 6600 (1951)] monomethylated 2,6-dibromohydroquinone in methanol using sodium methoxide and methyl iodide. It remains questionable, however, whether they assigned the correct structure to the major product. The product they reported was "2,6-dibromo-1-methoxyphenol," mp 139.5–140.2°. The correct structure was found to be 3,5-dibromo-4-methoxyphenol (see the Experimental Section).