ml of methanol was added 0.22 g (0.0054 mol) of sodium hydroxide dissolved in a small amount of water. To the resulting solution was added 0.8 g (0.0027 mol) of **14** and the mixture was then stirred at 30–40° for 2 days. After being acidified with dilute H_2SO_4, the mixture was extracted with ether. The ethereal solution was washed with saturated sodium bicarbonate and then with water, and dried over Na_2SO_4. Removal of the solvent left 0.5 g of a light yellow oil which, on tlc analysis,[12] showed two spots at the R_f values of 0.36 and 0.58, in a ratio of 3:2. A compound with the R_f value of 0.36 was collected by preparative tlc[13] and identified as **16**: yield 50%; mp 83–84° (ether); ir (Nujol) 3320 (OH), 1760 (lactone C═O), 1598 cm^{-1} (benzene ring); nmr (CCl_4) δ 0.86 (s, 3, cis CH_3 to $C_6H_5CH_2$–), 1.01 (s, 3, trans CH_3 to $C_6H_5CH_2$–), 2.50–3.30 (m, 3, mixture of α-H and benzyl methylene), 4.60 (broad s, 1, OH), 5.18 (s, 1, γ-H), 7.19 (s, 5, $C_6H_5CH_2$–).

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 71.06; H, 7.00.

The aqueous layer was acidified with silute H_2SO_4 to give 0.3 g (42%) of **15**.

α-Benzyl-α-carboxy-β,β-dimethyl-γ-hydroxy-γ-butyrolactone (15) showed mp 135–137° (benzene); ir (Nujol) 3400 (OH), 2800–2500 (COOH), 1763 (lactone C═O), 1695 (acid C═O), 1600 cm^{-1} (benzene ring); nmr [$(CD_3)_2CO$] δ 1.22 (s, 6, 2 CH_3), 3.33 (s, 2, $C_6H_5CH_2$–), 5.48 (s, 2, COOH and OH), 5.60 (s, 1, γ-H).

Anal. Calcd for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 64.00; H, 6.25.

Registry No.—**1**, 917-93-1; **2a**, 42203-05-4; **2b**, 42203-07-6; **3**, 42203-06-5; **4**, 42203-08-7; *cis*-**5**, 42203-09-8; *trans*-**5**, 42203-10-1; **6**, 42203-11-2; **10a**, 42203-12-3; **10b**, 42203-13-4; **11**, 42203-14-5; **12**, 116-51-8; **14**, 42203-16-7; **15**, 42203-17-8; **16**, 42203-18-9; dimethyl malonate, 108-59-8; diethyl malonate, 105-53-3; dimethyl sodiomalonate, 18424-76-5; diethyl sodiomalonate, 996-82-7; 2-bromo-2-methylpropanal, 13206-46-7.

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[12] Conditions of tlc: support, silica gel G (E. Merck AG, Darmstadt), 0.1 mm; developer, *n*-hexane–chloroform–acetone (3:2:1 v/v); spray reagent, H_2SO_4–$KMnO_4$ (7:3 w/w). The spot of **14** on tlc appeared at R_f 0.58.

[13] Conditions of preparative tlc: support, silica gel G (E. Merck AG; Darmstadt), 0.8 mm; developer, *n*-hexane–chloroform–acetone (3:2:1 v/v); eluent, acetone.

Mass Spectrometry in Structural and Stereochemical Problems. CCXXXIV.[1] Alkyl Pyridyl Ketones

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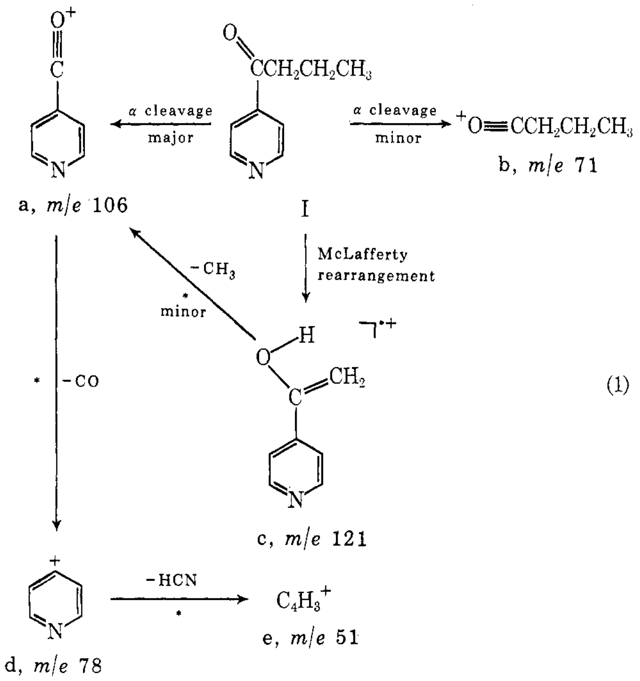
The mass spectra of the three isomeric propyl pyridyl ketones are reported. Negligible influence by the ring nitrogen was observed in the 3 and 4 isomers. Fragmentation of the McLafferty rearrangement ion is observed to occur without prior ketonization. The mass spectrum of propyl 2-pyridyl ketone is markedly different owing to interactions of the side chain with the ring nitrogen. A similar behavior is noted in the higher homologs.

Although the mass spectra of alkyl phenyl ketones have been extensively studied,[2] very little attention has been directed toward the unimolecular decomposition of alkyl pyridyl ketones upon electron impact. This is somewhat surprising in view of much other work on the significant influence of heteroatoms on the fragmentation pattern of many substituted pyridine ions.[3] In light of this and our interest in the electron impact induced fragmentations of ketones,[4] we considered it informative to examine the electron impact induced fragmentations of alkyl pyridyl ketones, specifically the three isomeric propyl pyridyl ketones (I, II, III) and some of their labeled analogs.

Propyl 4-Pyridyl Ketone (I).—The mass spectrum of propyl 4-pyridyl ketone (I) is shown in Figure 1. The major fragmentation pathways are illustrated in eq 1. The elemental composition of the ions was substantiated by high-resolution mass measurements. Its behavior is quite similar to that of butyrophenone with the two major fragmentation pathways being simple cleavage α to the carbonyl group, yielding ions a (*m/e* 106) and b (*m/e* 71) and a McLafferty rearrangement to form the ion c of mass 121. Exact mass measurements showed that the expulsion of CO from the molecular ion makes only a 3% contribution to the *m/e* 121 peak. Specific labeling of the three propyl carbons with deuterium also confirms the fragmentation scheme. The McLafferty rearrangement ion c fragments by loss of CH_3 as verified by the observation of the appropriate metastable peak. Examination of the metastable



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[1] For the previous paper, see S. Hammerum and C. Djerassi, *J. Amer. Chem. Soc.*, submitted for publication.

[2] H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967.

[3] (a) E. V. Brown and M. B. Shambhu, *Org. Mass. Spectrom.*, **6**, 479 (1972); (b) C. S. Barnes, R. J. G. Goldrach, J. Halbert, J. G. Wilson, R. J. Lyall, and S. Middleton, *Tetrahedron Lett.*, 705 (1973); (c) R. G. Cooks, R. N. McDonald, P. T. Cranor, H. E. Petty, and N. L. Wolfe, *J. Org. Chem.*, **38**, 1114 (1973); (d) G. H. Kellen, L. Bauer, and L. L. Bell, *J. Heterocycl. Chem.*, **5**, 647 (1968); (e) R. J. Moser and E. V. Brown, *Org. Mass Spectrom.*, **4**, 555 (1970); (f) C. P. Whittle, *Tetrahedron Lett.*, 3689 (1968); (g) E. V. Brown and R. J. Moser, *J. Heterocycl. Chem.*, **8**, 189 (1971).

[4] K. B. Tomer and C. Djerassi, *Org. Mass Spectrom.*, **6**, 1285 (1972).

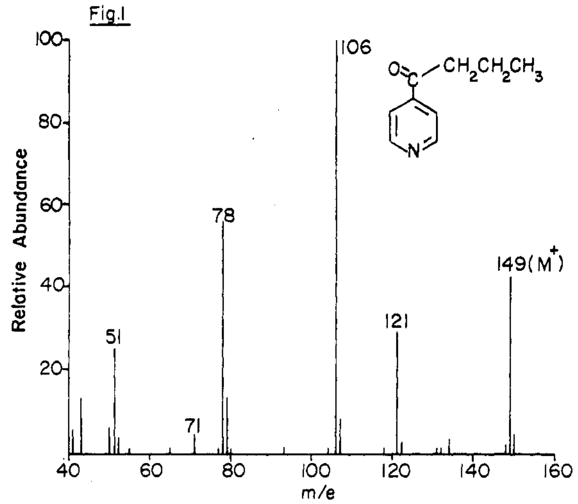


Figure 1.—70-eV mass spectrum of propyl 4-pyridyl ketone (I).

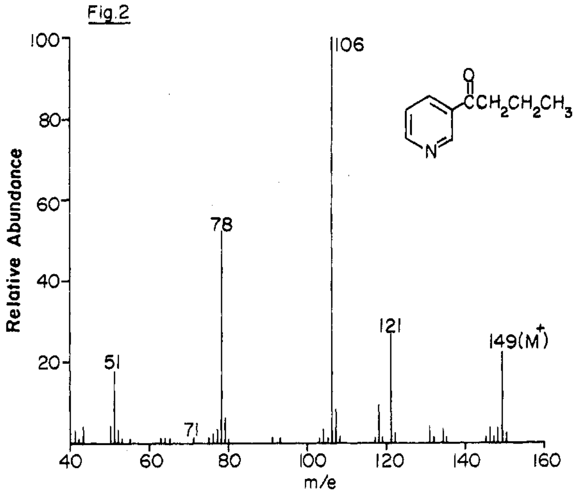
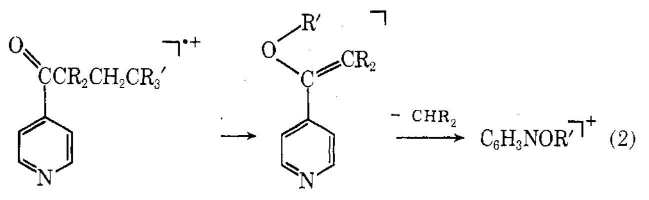


Figure 2.—70-eV mass spectrum of propyl 3-pyridyl ketone (II).

peaks for this process in the mass spectra of the labeled ketones showed that the loss of CH_3 does not involve the itinerant hydrogen (eq 2). Thus, this ion does

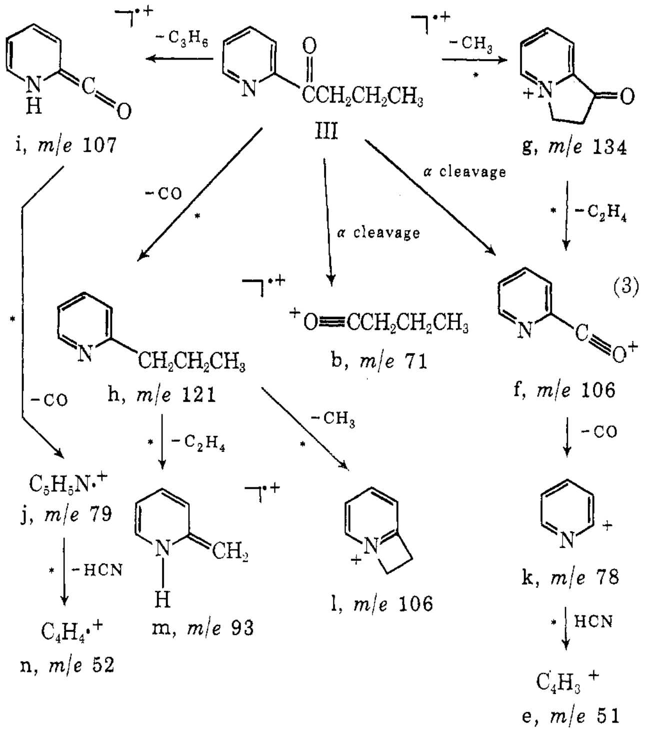


I' , R = D; R' = H   c', R = D; R' = H
I'', R = H; R' = D   c'', R = H; R' = D

not reketonize prior to CH_3 expulsion, but must lose a ring hydrogen in this process. Identical results were observed for the expulsion of CH_3 from the McLafferty rearrangement ion of butyrophenone.[4] The deuterium labeling also show that this methyl loss is a minor process in the formation of the $C_6H_4NO^+$ ion a in the 70-eV spectrum (~1%).

Propyl 3-Pyridyl Ketone (II).—The mass spectrum of propyl 3-pyridyl ketone (II) is shown in Figure 2. A comparison of Figures 1 and 2 as well as the behavior of the deuterium-labeled analogs show that the mass spectra exhibit only minor differences. The major fragmentation pathways are, therefore, the same as those for the 4 isomer (eq 1). High-resolution mass measurements indicate no contribution from CO loss to the *m/e* 121 peak.

Propyl 2-Pyridyl Ketone (III).—The mass spectrum (Figure 3a and 3b) of propyl 2-pyridyl ketone (III) shows striking differences from those (Figures 1 and 2) of the 3 and 4 isomers. High-resolution mass measurements show that, in this compound, the *m/e* 121 peak results from CO expulsion ($C_8H_{11}N$; 94%) rather than from a McLafferty rearrangement (C_7H_7NO; 6%). The *m/e* 106 peak, much reduced in importance in comparison to that found in the spectra of the 3 and 4 isomers, is also revealed to be a doublet [51% C_6H_4NO (f); 49% C_7H_8N (l)]. With the aid of deuterium labeling (Table I), high-resolution mass measurements, and the presence of metastable ions, the fragmentation pattern in eq 3 is proposed which encompasses several fragmentations attributable to involvement of the pyridyl nitrogen.



[M − CH_3]·+.—The loss of methyl (unimportant in I and II) is shown by deuterium labeling to involve only the terminal methyl group of the propyl chain. This peak increases in importance as the ionizing energy is decreased and the reaction is marked by an abundant (70 eV) metastable peak (*m/e* 120.8).

Thus a cyclization reaction is implicated rather than a simple cleavage. This ion is not observed in the mass spectrum (Figure 4) of ethyl 2-pyridyl ketone (IV) (Figure 4) but loss of hydrogen in IV is more important than in III. In accordance with these observations, butyl 2-pyridyl ketone (V) and pentyl 2-pyridyl ketone (VI) lose ethyl (Figure 5) and propyl (Figure 6) fragments. Thus cyclization to form a five-membered ring is preferred over other ring sizes (eq 4). This is in contrast to the observation of preferential four-membered ring formation in simple 2-alkyl pyridines and quinolines.[2,5] Since this cyclization process is not important in the 3 and 4 isomers, interaction of the ring

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[5] S. D. Sample, D. A. Lightner, O. Buchardt, and C. Djerassi, *J. Org. Chem.*, **32**, 997 (1967).

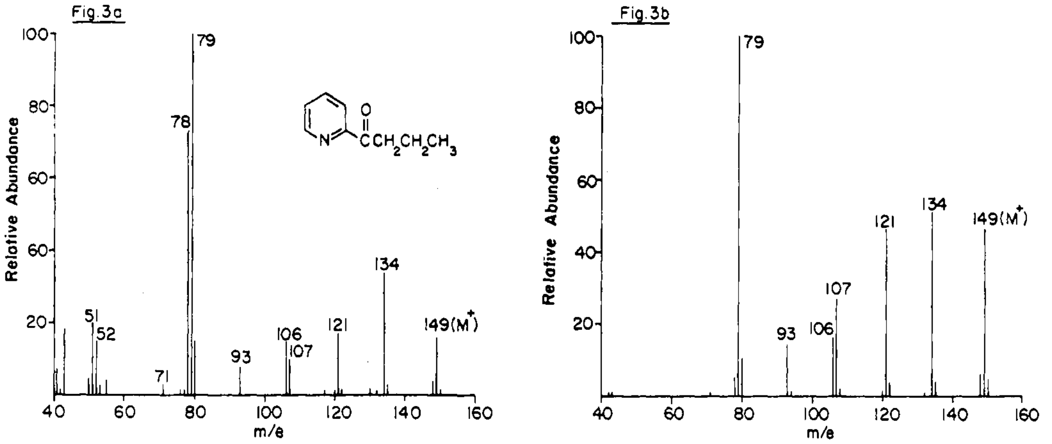


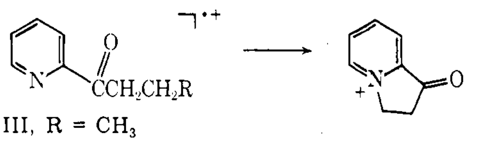
Figure 3.—(a) 70-eV mass spectrum of 2-pyridyl ketone (III); (b) 12-eV mass spectrum of 2-pyridyl ketone (III).

TABLE I

COMPARISON OF MASS SHIFTS ENCOUNTERED IN THE MAIN PEAKS OF THE SPECTRA OF LABELED PROPYL 2-PYRIDYL KETONES AT 70 AND 12 eV[a]

		% *m/e* 134 which shifts to[b]			% *m/e* 121 which shifts to[b]			% *m/e* 107 which shifts to[b]			% *m/e* 106 which shifts to[b]			% *m/e* 93 which shifts to[b]			% *m/e* 79 which shifts to[b]			% *m/e* 78 which shifts to[b]		
eV		135	136	137	122	123	124	108	109	110	107	108	109	94	95	96	80	81	82	79	80	81
70	α-d_2	0	100	0	0	100	0	0	0	0	0	55	0	0	83	0	15	0	0	0	0	0
	β-d_2	0	100	0	4	96	0	100	0	0	0	20	0	20	0	0	60	0	0	0	0	0
	γ-d_3	0	0	0	5	0	95	0	0	0	0	0	0	100	0	0	0	0	0	0	0	0
12	α-d_2	0	100	0	0	100	0	0	0	0	0	84	0	0	90	0	7	0	0	0	0	0
	β-d_2	0	100	0	0	94	0	100	0	0	12	62	0	16	0	0	90	0	0	0	0	0
	γ-d_3	0	0	0	2	0	98	0	0	0	0	0	0	100	0	0	0	0	0	0	0	0

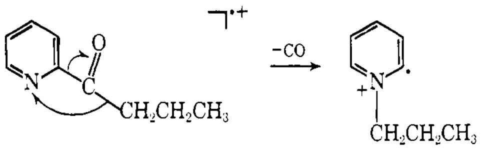
[a] All compounds have been corrected to 100% isotopic purity. [b] ±5%.



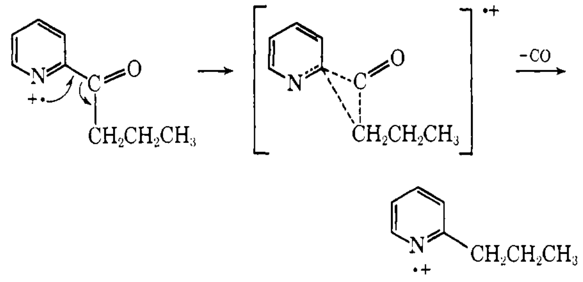
(4)

III, R = CH_3
IV, R = H
V, R = CH_2CH_3
VI, R = $CH_2CH_2CH_3$

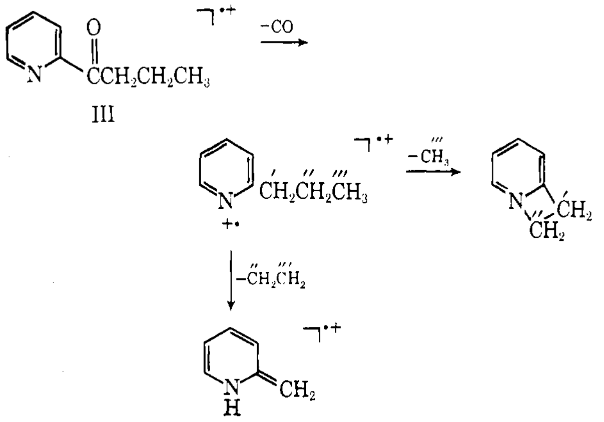
g



(5)



(6)



(7)

nitrogen with the side chain is invoked to initiate this reaction.

[M − CO]·+.—Brown and Shambhu[3a] and Barnes and coworkers[3b] have observed the expulsion of CO from phenyl 2-pyridyl ketones but not from the 3 and 4 isomers. The mass spectrum of 2-acetylpyridine has been reported[6] and a peak corresponding to loss of 28 mass units observed (Figure 7). The occurrence of this fragmentation in 2-acetylpyridine (VII) and ethyl 2-pyridyl ketone (IV) (Figure 4) in addition to the higher homologs (Figure 5 and 6) demonstrates that chain length is not a significant factor in the reaction. Two mechanisms can be drawn for this reaction involving either propyl migration to nitrogen (eq 5) or extrusion of CO with bonding between the 2 position and the propyl moiety (eq 6).

The [M − CO] ion fragments further by loss of CH_3 or C_2H_4. The deuterium labeling results (Table I) show that the loss of CH_3 involves the terminal CH_3 group of the propyl chain and the C_2H_4 loss involves hydrogen transfer from C-3 of the propyl group with loss of C-2 and C-3 (eq 7). The appropriate metastable peaks for these reactions were observed. The fragmentation pattern of 2-propylpyridine[2] is similar and on this basis the mechanism in eq 6 is assigned to this reaction.

[M − C_3H_6]·+.—The deuterium-labeling results (Table I) show that expulsion of C_3H_6 occurs with site-specific hydrogen transfer from the β carbon of the

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(6) A. Ferretti and V. P. Flanagan, *J. Agr. Food Chem.*, **19**, 245 (1971).

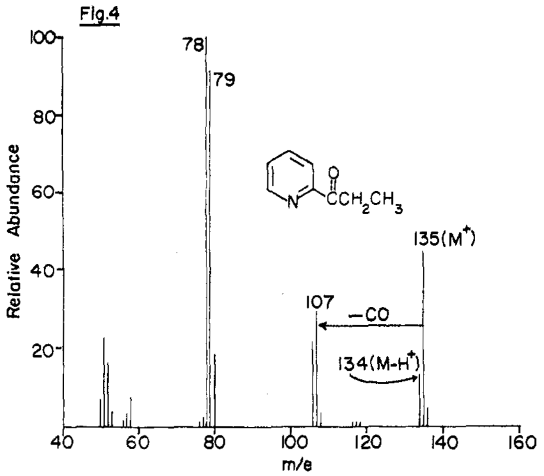

Figure 4.—70-eV mass spectrum of ethyl 2-pyridyl ketone (IV).

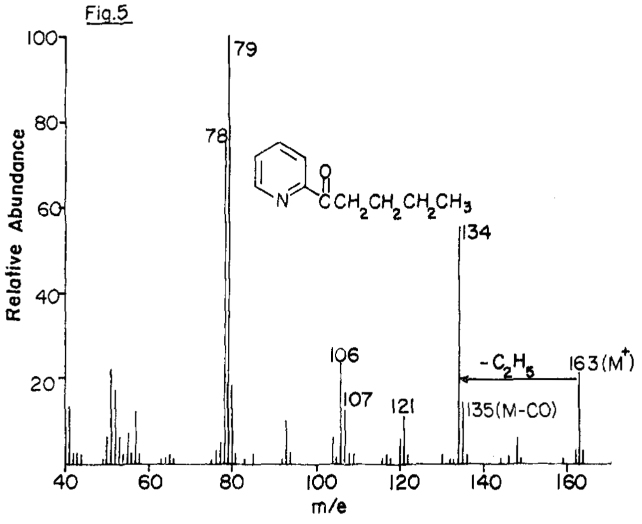

Figure 5.—70-eV mass spectrum of butyl 2-pyridyl ketone (V).

propyl group. On this basis, the structure i in scheme 3 is assigned to this ion. Fragmentation of this ion occurs by CO expulsion giving rise to an ion of composition $C_5H_5N\cdot^+$. This then expels HCN as expected for pyridine ions. When the itinerant hydrogen is replaced by deuterium, much greater HCN loss than DCN loss occurs in the second field-free region. This is consistent with the observation of Williams and Ronayne[7] that the hydrogens in the pyridine molecular ion become scrambled prior to HCN expulsion. The deuterium-labeling results (Table I) also show that the hydrogen transferred from the propyl chain to eventually form the $C_5H_5N\cdot^+$ ion arises largely from the β carbon. Thus, the expulsion of C_3H_6 initiates the major fragmentation pathway in propyl 2-pyridyl ketone.

The mass spectrum of butyl 2-pyridyl ketone (Figure 5) shows that when the McLafferty rearrangement to oxygen (*m/e* 121) involves transfer of a secondary hydrogen, it can compete with the McLafferty rearrangement to nitrogen (*m/e* 107). Although the *m/e* 121 and *m/e* 107 peaks are of similar intensity, the evidence for extensive further fragmentation of these ions (scheme 3) makes further comparisons of the two pathways dangerous.

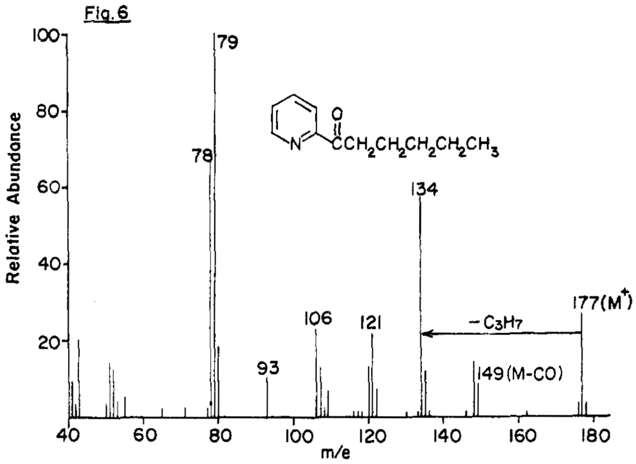

Figure 6.—70-eV mass spectrum of pentyl 2-pyridyl ketone (VI).

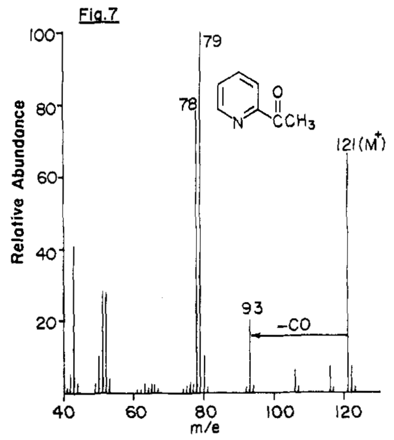

Figure 7.—70-eV mass spectrum of 2-acetylpyridine (VII).

In conclusion, propyl 2-pyridyl ketone exhibits fragmentation patterns strikingly different from those of the 3 and 4 isomers. These differences are attributable to interaction between the substituent and ring nitrogen.

Experimental Section

Low-resolution mass spectra were run on an AEI MS-9 spectrometer using a heated inlet system. High-resolution mass spectra were run on a Varian MAT 711 instrument. Technical assistance was provided by Mr. R. Ross and Miss A. Wegmann. All ionizing voltages are nominal.

The alkyl pyridyl ketones[8a,b] were prepared by reaction of the appropriate alkylmagnesium bromide with the appropriate cyanopyridine (Aldrich Chemical Co.) followed by acidic hydrolysis.[8b,9] The ketones were purified by glc.

The α-d_2 propyl pyridyl ketones were prepared by exchange of the unlabeled ketones on a 10% KOD/10% carbowax 6000 glc column.[10] β-d_2 and γ-d_3 propyl pyridyl ketones were prepared by reaction of the appropriate labeled propylmagnesium bromide and the appropriate cyanopyridine. After acidic hydrolysis, the ketones were purified by glc.

Acknowledgment.—Financial support from the National Institutes of Health (Grants No. AM 04257 and RR 612) is gratefully acknowledged.

Registry No.—I, 1701-71-9; II, 1701-70-8; III, 22971-32-0; IV, 3238-55-9; V, 7137-97-5; VI, 42203-03-2; VII, 1122-62-9.

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[7] D. H. Williams and J. Ronayne, *Chem. Commun.*, 1129 (1967).

[8] (a) *Beilstein*, XXI, pp 280–282; (b) J. F. Geldard and F. Lions, *Inorg. Chem.*, **2**, 270 (1963).

[9] (a) F. B. LaForge, *J. Amer. Chem. Soc.*, **50**, 2477 (1928); (b) C.-C. Chu and P. C. Teague, *J. Org. Chem.*, **23**, 1578 (1958); (c) I. Suzuki, *Chem. Pharm. Bull.*, **4**, 1479 (1956).

[10] M. Senn, W. J. Richter, and A. I. Burlingame, *J. Amer. Chem. Soc.*, **87**, 680 (1965).