prepared by recrystallization from chloroform–methanol (2:3), mp 227–229°.

Anal. Calcd for $C_{26}H_{34}N_2O_4S_2$: C, 62.12; H, 6.82; N, 5.57; S, 12.76; mol wt, 502.7. Found: C, 62.48; H, 6.90; N, 5.86; S, 13.06; mol wt, 493.

Infrared absorptions (Nujol) were at 6.61 (>C=C<), 7.58, and 8.72 (SO_2) μ. The nmr spectrum ($CDCl_3$) showed broad singlets at δ 1.58 and 3.13 (piperidine groups), a singlet at 4.66 (four benzylic protons), and a multiplet at 7.40 (aromatic protons).

Method B.—Employing procedures as described above, 1,1-di(1-piperidino)ethylene (13.0 g, 0.067 mole) was treated with excess phenylmethanesulfonyl chloride (25.6 g, 0.134 mole) in the presence of triethylamine (15.2 g, 0.150 mole). After the usual work-up, 2.2 g of **20b** was isolated from the filtered solid. The major portion of the desired product, however, was obtained from the mother liquor after removal of the benzene giving rise to a brown semisolid. Recrystallization from methanol–chloroform afforded **20b**. A total of 10.0 g (29.7% yield) was isolated. The mixture melting point with an authentic sample showed no depression.

In addition there was obtained 2.3 g of brown oil which resisted characterization. Its infrared spectrum (neat) showed bands at 5.76, 6.10, 6.24, 6.70, 6.93, 7.60, 8.03, 8.45, 8.61, 8.80, and 9.65 μ.

1,1-Di(1-piperidino)-2-(methanesulfonyl)-2-phenyl(methanesulfonyl)ethylene (20c). Method A.—Employing similar procedures as described above, methanesulfonyl chloride (4.93 g, 0.043 mole) was treated with **19b** (15.1 g, 0.043 mole) in benzene in the presence of triethylamine (5.06 g, 0.05 mole). After the usual work-up, benzene was removed from the mother liquor to leave a yellow solid which was recrystallized from ethyl acetate–methanol (trace) to give 12.3 g (67.2% yield) of crude **20c**. An analytical sample was prepared by recrystallizations (thrice) from methanol and chloroform, mp 176.5–178.5°.

Anal. Calcd for $C_{20}H_{30}N_2O_4S_2$: C, 56.31; H, 7.09; N, 6.57; S, 15.03, mol wt, 426.6. Found: C, 56.22; H, 7.32; N, 6.81; S, 14.90; mol wt, 426.

The infrared spectrum (Nujol) had bands at 6.53 (s), 7.60 (s), 7.76 (s), 8.60 (m), and 8.76 (s) μ. The nmr spectrum ($CDCl_3$) showed a broad singlet and a broad doublet at δ 1.63 and 3.30 (piperidino groups), a multiplet at 7.25 (aromatic protons), and two singlets at 3.20 (methyl protons) and 4.63 (benzylic protons).

Method B.—In a 50-ml erlenmeyer flask were placed 0.54 g (2 mmoles) of **18** and 0.22 g (2.2 mmoles) of triethylamine in 25 ml of benzene. To the above stirred mixture was slowly added 0.38 g (2 mmoles) of phenylmethanesulfonyl chloride in 15 ml of benzene over a 10-min period. The mixture was stirred overnight and filtered. Benzene was removed from the filtrate leaving a yellow oil which solidified after cooling. Recrystallizations from ethyl acetate and then from methanol afforded 0.29 g (34.1% yield) of white, crystalline material, mp 176.5–178.0°. The mixture melting point with **20c** showed no depression. Its infrared spectrum (Nujol) was identical with that of **20c**.

1,1-Di(1-piperidino)-2,2-di(methanesulfonyl)ethylene (20d).—Following the method described above, methanesulfonyl chloride (0.28 g, 2.4 mmoles) was treated with **18** (0.65 g, 2.4 mmoles) in the presence of triethylamine (0.26 g, 2.6 mmoles). After the usual work-up benzene was evaporated from the filtrate to a yellow oil. Work-up with solvents such as ethyl acetate, ethanol, methanol, and hexane followed by cooling gave a yellow solid. Two recrystallizations from ethyl acetate–methanol (trace) afforded 0.32 g (38.1% yield) of **20d**, mp 196.0–197.5°.

Anal. Calcd for $C_{14}H_{26}N_2O_4S_2$: C, 47.97; H, 7.48; N, 7.99; S, 18.30. Found: C, 48.04; H, 7.75; N, 7.93; S, 18.06.

The infrared spectrum (Nujol) showed bands at 6.62 (s), 7.56 (s), 7.77 (s), 8.56 (w), and 8.74 (m) μ. The nmr spectrum ($CDCl_3$) revealed a broad singlet and a broad doublet at δ 1.75 and 3.50 (piperidine groups), a singlet at 3.22 (six methyl protons).

Registry No.—**1a**, 1950-82-9; **1b**, 10099-00-0; **1c**, 10099-01-1; **1d**, 10099-02-2; **1e**, 10099-03-3; **1f**, 10099-04-4; **1g**, 10099-05-5; **1h**, 10099-06-6; **1i**, 10099-07-7; bromomethanesulfonyl chloride, 10099-08-8; **2**, 10099-10-2; **3**, 10099-11-3; **4**, 10099-13-5; **5**, 10099-12-4; **6**, 10099-14-6; **7**, 10084-33-0; **8a**, 1433-29-0; hydrochloride of **8b**, 10099-16-8; **11**, 10099-09-9; **17**, 1623-62-7; **18**, 10076-45-6; **19a**, 1599-17-3; **19b**, 10099-19-1; **20a**, 10084-34-1; **20b**, 10099-20-4; **20c**, 10099-21-5; **20d**, 10076-46-7; benzylsulfonyl-N-acetylmorpholine, 1709-88-2.

Acknowledgment.—This investigation was supported by Public Health Service Grant No. CA-04536-08 from the National Cancer Institute and by Contract No. DA-49-193-MD-2949 from the U. S. Army Medical Research and Development Command.

Mass Spectrometry in Structural and Stereochemical Problems. CXXIV.[1] Mass Spectral Fragmentation of Alkylquinolines and Isoquinolines[2]

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Received October 7, 1966

The mass spectra of alkylquinolines and isoquinolines were examined. Evidence was obtained for an azatropylium ion intermediate in the pathway leading to the M − (H + HCN) ion from methylquinolines and isoquinolines. The predominant fragmentation modes of alkylquinolines and isoquinolines having more than three carbon atoms in the chain are β cleavage and McLafferty rearrangement. The relative amounts of these cleavages can be correlated with the electron density at the position of substitution. Alkyl chains at C-4 and C-8 undergo facile γ and δ cleavage, probably because the resulting radicals can be stabilized by cyclization to the *peri* position.

Compounds containing quinoline and isoquinoline ring systems are prevalent in nature. Since structure elucidation of such compounds may be limited by the small quantities of material available, application of mass spectrometry to these systems is frequently required. However, aside from Clugston and McLean's[5] study of the behavior of oxygenated quinolines upon electron impact, no systematic investigation of the characteristic cleavages of substituted quinolines or isoquinolines has been undertaken.

The only important fragment in the mass spectra of quinoline (Σ_{40} = 9.2%) and isoquinoline (Σ_{40} = 9.1%)

(1) For paper CXXII, see S. Huneck, C. Djerassi, D. Becher, M. Barber, M. v. Ardenne, K. Steinfelder, and R. Tümmler, *Tetrahedron*, in press.

(2) We are indebted to the National Institutes of Health for financial aid (Grants No. AM-04257 and GM-11309).

(3) (a) Recipient of National Science Foundation (1963–1965) and National Institutes of Health (1965–1966) Predoctoral Fellowships; (b) recipient of National Science Foundation Postdoctoral Fellowship (1963–1964).

(4) H. C. Ørsted Institute, University of Copenhagen, Denmark.

(5) D. M. Clugston and D. B. McLean, *Can. J. Chem.*, **44**, 781 (1966).

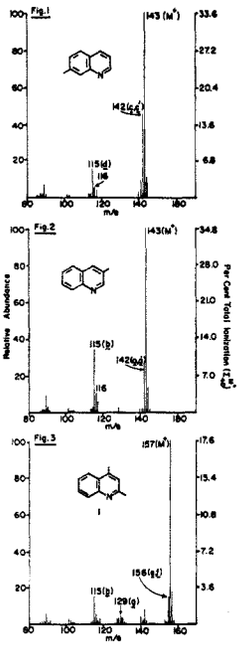


Figure 1.—Mass spectrum of 7-methylquinoline.
Figure 2.—Mass spectrum of 3-methylquinoline.
Figure 3.—Mass spectrum of 2,4-dimethylquinoline.

arises by expulsion of hydrogen cyanide from the molecular ion.[6] Introduction of a methyl substituent (see Figures 1 and 2) decreases the importance of this process [*m/e* 116 in Figure 1 (Σ_{40} = 1.0%) and Figure 2 (Σ_{40} = 2.1%)] but favors two new modes of cleavage.

The first is loss of a hydrogen radical from the molecular ion. Hydrogen cyanide is then expelled from this M − H species to give an M − (H + HCN) fragment (d or b). It can be seen from Table I that,

TABLE I

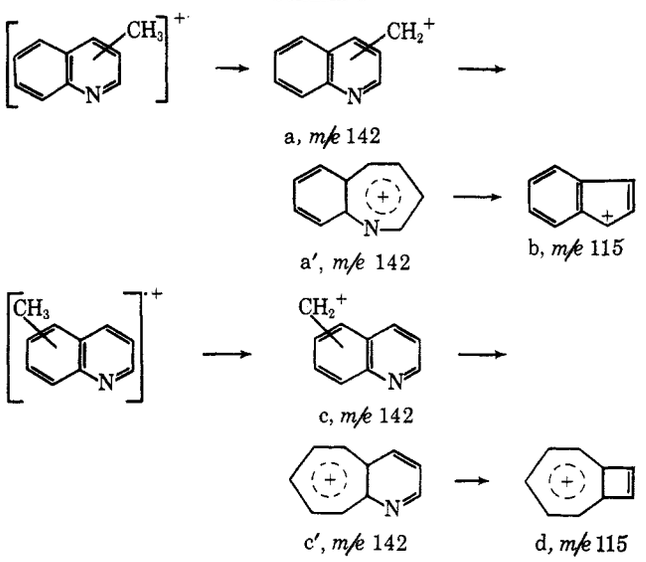
INTENSITIES (Σ_{40}) OF PEAKS CAUSED BY M − H AND M − (H + HCN) FRAGMENTS OF METHYLQUINOLINES AND ISOQUINOLINES

Position of methyl substituent	Registry no.	M − H	M − (H + HCN)	[M − (H + HCN)]/(M − H)
	I. Monomethylquinolines			
2	91-63-4	3.9	5.0	1.28
3		9.0	11.8	1.32
4	491-35-0	6.5	9.3	1.32
5	7761-55-4	16.5	5.7	0.34
6	91-62-3	14.7	4.8	0.32
7		13.4	4.0	0.31
8	611-32-5	13.4	4.2	0.31
	II. Monomethylisoquinolines			
1	1721-93-3	4.9	10.1	2.04
3	1125-80-0	5.5	11.1	2.08
Position of methyl substituents	Registry no.	M − H	M − (H + HCN)	M − (H + CH_3CN)
	III. Dimethylquinolines			
2, 4		5.3	0.9	2.7
2, 3	1721-89-7	8.0	2.3	8.4

if the methyl substituent is in the heterocyclic ring, the ratio of peak intensities [M − (H + HCN)]/(M − H) is nearly constant. This suggests that before further decomposition, each of the M − H fragments rearranges to an intermediate in which the carbon of the original methyl group is equivalent to the ring carbon atoms. Since hydrogen cyanide is then expelled from a common M − H intermediate, the extent of formation of the M − (H + HCN) fragment should not depend upon the position of the original substituent. The intermediate in question may be written as the azatropylium ion a′. The rearrangement process is then analogous to the conversion of benzyl cations to tropylium ions.[7] The relative abundance of the *m/e* 115 peak from 2-, 3-, and 4-methylquinoline can be rationalized either in terms of formation of the azatropylium ion a′ directly from the molecular ion or by rearrangement of an initially formed benzyl carbonium ion a. In the latter case, the relative intensity of the peak would be determined by the known[8] order of stability (3 > 4 > 2) of a carbonium ion at the various positions on the quinoline nucleus. Direct azatropylium ion formation, as noted in alkylbenzenes,[7] should yield similar results since in such an event the abundance of ion a′ should vary as the inverse of the order of molecular ion stability, namely, 2 > 4 > 3.

If the ring-expanded ion a′ is produced directly, the ejected hydrogen atom presumably stems from the ring as well as from the methyl substituent.[7] Since no deuterated methylquinolines were available, this point could not be substantiated. So for the sake of brevity, we are arbitrarily depicting all M − 1 species as the initially produced benzyl ions (Scheme I).

SCHEME I



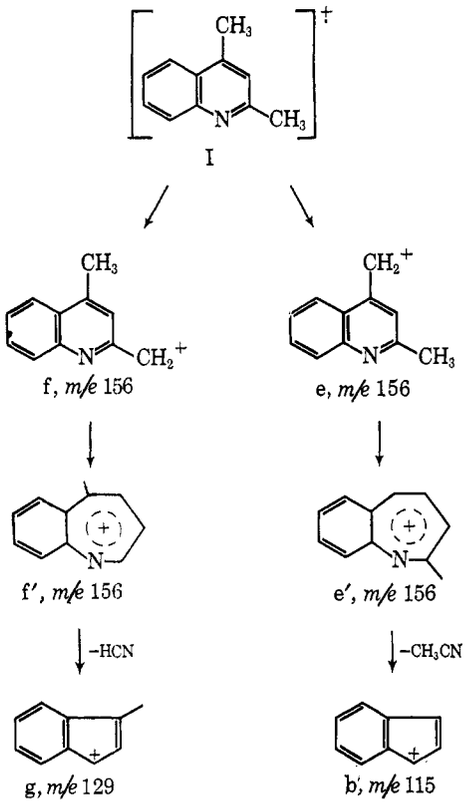
The relative amounts of M − (H + CH_3CN) (b) and M − (H + HCN) (g) peaks in the spectrum (see Figure 3) of 2,4-dimethylquinoline (I) further indicate the importance of stability of the carbonium ion intermediate. The fragment arising by loss of acetonitrile (e′ → b) from M − H is three times as abundant as that formed by loss of hydrogen cyanide (f′ → g) from M − H, probably because the former process occurs through the ring-expanded form (e′) of the more stable[8] carbonium ion (e). Since the difference in stability[8] of the two possible benzyl ions from 2,3-di-

(6) Catalog of Mass Spectral Data, American Petroleum Institute Research Project 44, Carnegie Institute of Technology, Pittsburgh, Pa., Spectra No. 625 and 626.

(7) H. M. Grubb and S. Meyerson in "Mass Spectrometry of Organic Ions," Academic Press Inc., F. McLafferty, Ed., New York, N. Y., 1963, Chapter 10; see also S. Meyerson, *Rec. Chem. Prog.*, **26**, 257 (1965).

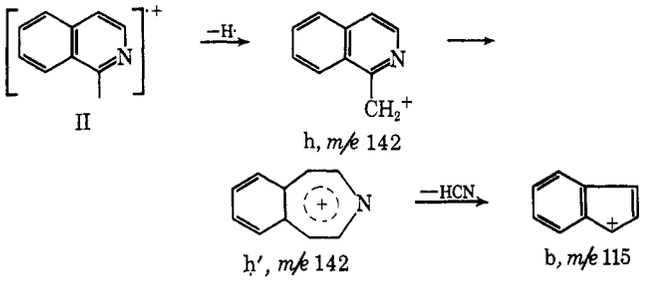
(8) H. C. Longuet-Higgins and C. Coulson, *Trans. Faraday Soc.*, **43**, 87 (1947).

SCHEME II



methylquinoline is even greater, the ratio [M − (H + CH_3CN)]/[M − (H + HCN)] increases from 3.0 to 3.6 (see Table I and Scheme II).

The spectra of 1- (II) and 3-methylisoquinoline also show peaks for M − (H + HCN) fragments (see Table I). Since hydrogen cyanide can be lost in two different ways from the azatropylium ion h′, the ratio [M − (H + HCN)]/(M − H) is nearly twice as high for both 1- and 3-methylisoquinoline as it was for 2-methylquinoline (see Table I).



The [M − (H + HCN)]/(M − H) ratio for quinolines having methyl substituents in the benzene (see Figure 1 and Table I) is much lower than that observed for 2-, 3-, and 4-methylquinoline (see Table I) indicating that decomposition of these M − H fragments (c′ → d) is a much less important process. Inasmuch as loss of a hydrogen atom from a methyl substituent in the benzene ring does not lead to a tropylium ion intermediate from which loss of hydrogen cyanide would be particularly favored, it might be anticipated that the M − HCN peaks (known[6] to be abundant in the spectrum of quinoline itself) would be more intense than the M − (H + HCN) peaks in the spectra of these methylquinolines. In fact, the reverse was observed. Since formation of a tropylium ion in the benzene ring would not be expected to enhance loss of hydrogen

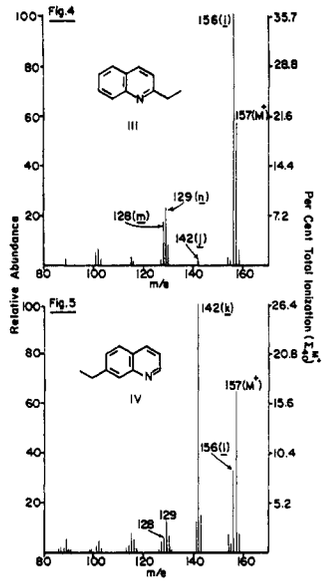


Figure 4.—Mass spectrum of 2-ethylquinoline.
Figure 5.—Mass spectrum of 7-ethylquinoline.

cyanide from the heterocyclic ring, it might be postulated that the benztropylium ion c′ rearranges to an azatropylium ion c″ before further decomposition.

The most important fragmentation of ethylquinolines and isoquinolines (see Figures 4 and 5 and Table II) is loss of a hydrogen or methyl group. The relative favorability of these processes varies with the position of the ethyl group relative to the heterocyclic nitrogen. For example, in the spectra of 2-ethylquinoline (III,

TABLE II

INTENSITIES (Σ_{40}) OF PEAKS ARISING FROM β-CLEAVAGE WITH AND WITHOUT HYDROGEN REARRANGEMENT IN ALKYLQUINOLINES AND ISOQUINOLINES

Compd	Registry no.	β cleavage	Hydrogen rearrangement and β cleavage
Quinoline			
2-Ethyl		Of H 35.7	
		Of CH_3 0.7	
7-Ethyl		Of H 8.7	
		Of CH_3 26.4	
2-*n*-Propyl	1613-32-7	1.5	33.3
2-*n*-Butyl		0.8	40.3
2-Isobutyl	93-19-6	2.6	40.6
2-Neopentyl	7661-57-6	3.0	47.0
4-Isobutyl		7.8	1.4
6-*n*-Butyl		21.9	29.8
6-*n*-Propyl	7761-58-7	29.6	5.1
7-*n*-Butyl		28.5	21.4
7-*n*-Propyl	7761-59-8	33.8	8.5
Isoquinoline			
1-Ethyl	7761-60-1	Of H 27.5	
		Of CH_3 0.3	
1-*n*-Propyl	7761-37-2	1.2	28.0
1-*n*-Butyl		1.0	36.6
1-Isobutyl	7761-40-7	1.7	34.7
3-*n*-Butyl		3.3	32.6
3-*n*-Butyl-4-methyl	7761-45-2	6.9	30.0

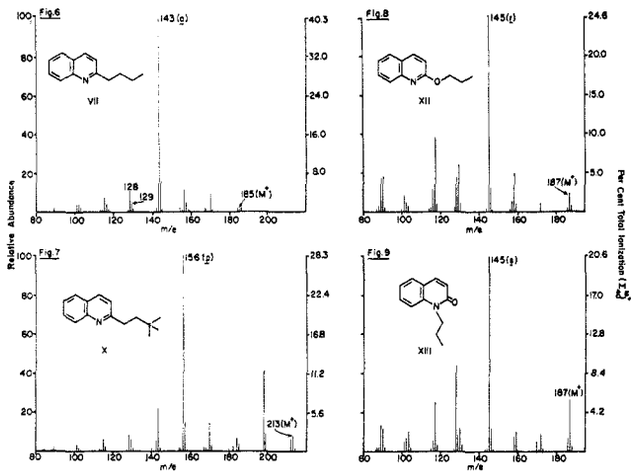
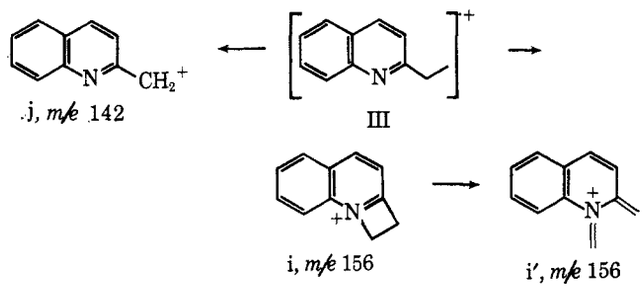


Figure 6.—Mass spectrum of 2-*n*-butylquinoline.
Figure 7.—Mass spectrum of 2-(3,3-dimethyl-*n*-butyl)quinoline.
Figure 8.—Mass spectrum of 2-*n*-propyloxyquinoline.
Figure 9.—Mass spectrum of 1-*n*-propylcarbostyril.

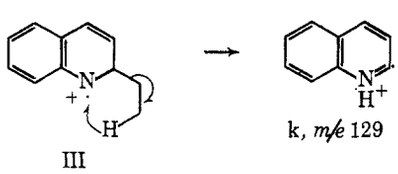
see Figure 4) and 1-ethylisoquinoline (see Table II), the peak for hydrogen atom elimination (*m/e* 156, fragment i) is more intense than the one for β cleavage of a methyl group (*m/e* 142, fragment j).

Although the pertinent deuterium-labeling experiment has not been performed, studies of the corresponding pyridines[9] indicate that the hydrogen lost in formation of i most likely originates from the methyl group. The immonium ion i may then further rearrange to i'.



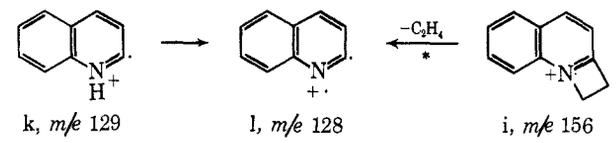
j, *m/e* 142 III i, *m/e* 156 i', *m/e* 156

According to Spiteller,[9] α cleavage with hydrogen rearrangement is particularly favored in pyridines having a two-carbon chain at position 2. An analogous ion (k) of mass 129 is present in the spectrum of 2-ethylquinoline (III, see Figure 4) and 1-ethylisoquinoline.



III k, *m/e* 129

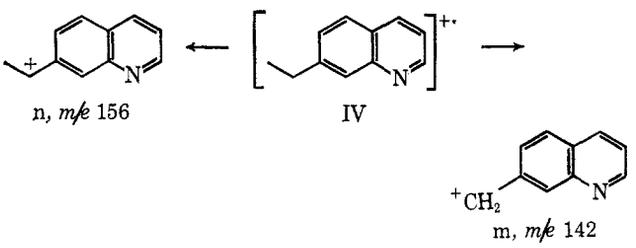
The adjacent peak at *m/e* 128 (1) can be formed either by expulsion of a hydrogen atom from k (*m/e* 129) or by decomposition of *m/e* 156 with loss of ethylene. The rapid diminution of the *m/e* 128 peak with respect to both the *m/e* 129 and 156 peaks at low voltage (12 ev) could be consistent with either pathway. While both may be operating, a metastable ion was observed (*m/e* 105) only for the transition *m/e* 156 → *m/e* 128. If the carbon chain is longer (see Figure 6, *m/e* 128 and



k, *m/e* 129 l, *m/e* 128 i, *m/e* 156

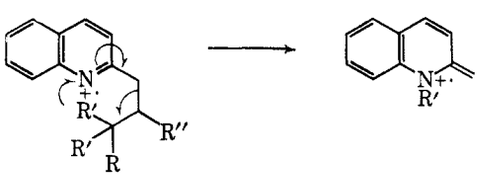
129) or if the ethyl substituent is in the benzene ring (see Figure 5, *m/e* 128 and 129), these cleavages are not as prevalent.

The spectrum of 7-ethylquinoline (IV, see Figure 5) is analogous to that of ethylbenzene[7] in that the M − CH_3 ion (m) is more abundant than its M − H counterpart (n).



n, *m/e* 156 IV m, *m/e* 142

When the length of the alkyl chain is increased to three carbon atoms, β cleavage accompanied by hydrogen rearrangement (hereafter referred to as a McLafferty rearrangement) becomes an important fragmentation pathway, *e.g.*, V → o. This cleavage is analogous to that observed[10] in the spectrum of 2-(3-heptyl)pyridine.



	o,
V, R = R′ = R″ = H	V, *m/e* 143
VI, R = R′ = D; R″ = H	VI, *m/e* 144
VII, R′ = R′ = H; R = CH_3	VII, *m/e* 143
VIII, R′ = D; R″ = H; R = CH_3	VIII, *m/e* 144
IX, R = R′ = H; R′ = CH_3	IX, *m/e* 143

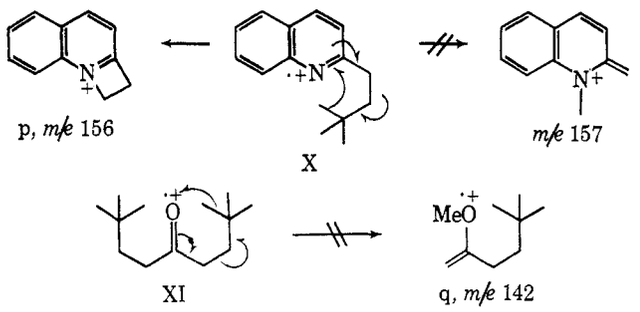
The rearrangement ion dominates the spectrum of 2-*n*-propyl (V, see Table II), 2-*n*-butyl (VII, see Table 2) and 2-isobutylquinoline (IX, see Table II). The *m/e* 143 peak is shifted completely to *m/e* 144 in the spectra of the deuterium-labeled compounds VI and VIII establishing that the hydrogen is transferred specifically from the γ position as had been observed earlier[7] in alkylbenzenes.

This cleavage is blocked by tetrasubstitution at the γ-carbon atom. The most important fragment ion in the spectrum (Figure 7) of 1-(3,3-dimethyl-*n*-butyl)-quinoline (X) is the result of γ cleavage of the *t*-butyl radical (X → p) rather than a methyl migration (X → *m/e* 157) corresponding to the hydrogen migration observed above. This result was expected as there is no peak in the spectrum[11] of 2,2,8,8-tetramethyl-5-nonanone (XI) which corresponds to an ion resulting from the methyl migration XI → q.

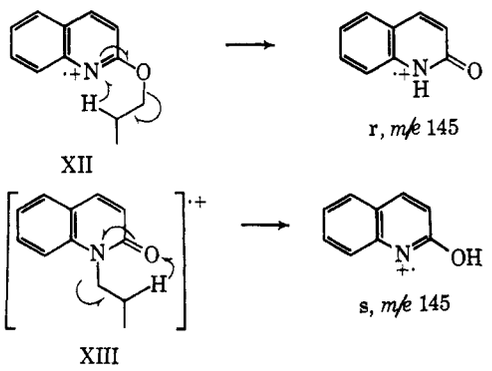
(9) G. Spiteller, "Massenspectrometrische Strukturanalyse Organischer Verbindungen," Verlag Chemie, Weinheim, 1966, p 172.

(10) K. Biemann, "Mass Spectrometry, Organic Chemical Applications," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 130.

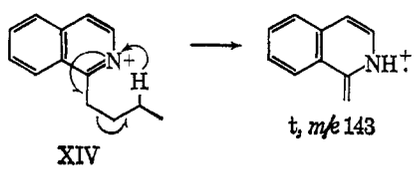
(11) R. Arndt and C. Djerassi, *Chem. Commun.*, 578 (1966).



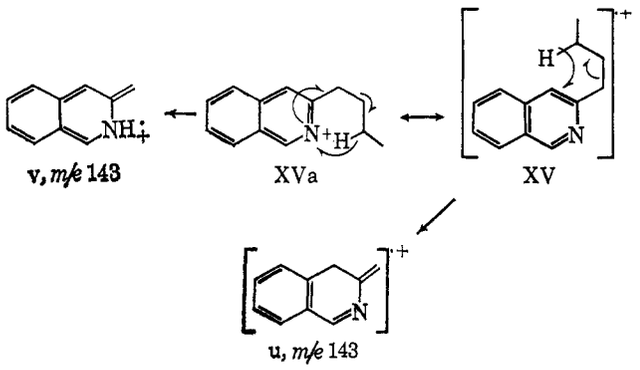
A rearrangement ion r is also observed if one carbon atom of the alkyl chain is replaced by oxygen. In fact, *m/e* 145 (r) is the most intense peak in the spectrum (Figure 8) of 2-*n*-propyloxyquinoline (XII).[12] The reverse process may also be operative; for the most abundant fragment in the spectrum (Figure 9) of 1-*n*-propylcarbostyril (XIII, see Figure 9) is the tautomeric species (s).



Since the reactivity of substituents at C-1 of isoquinoline and C-2 of quinoline are similar,[13] the fragmentation of alkyl substituents at these positions might be expected to be comparable. Indeed, the spectra (*e.g.*, Figure 10) of 1-alkylisoquinolines are very similar to those of the corresponding 2-alkylquinolines (*e.g.*, Figure 6) in that the McLafferty rearrangement is the dominant cleavage (*e.g.*, XIV → t). The rearrangement was again shown to be a site-specific γ-hydrogen transfer by appropriate deuterium-labeling experiments.



The rearrangement ion in the spectrum (Figure 11) of 3-*n*-butylisoquinoline (XV) was of particular interest. Hydrogen may be transferred during the McLafferty rearrangement of an alkyl group at this position to



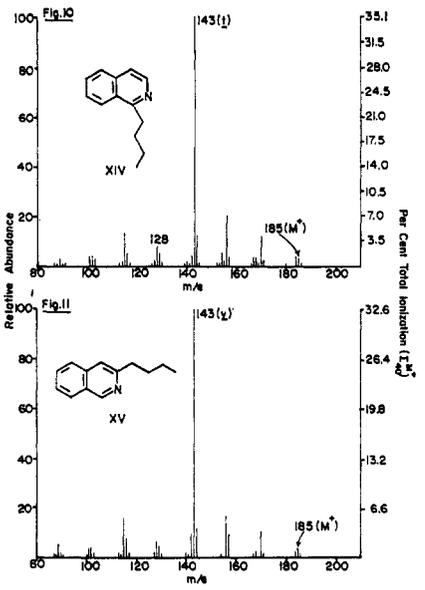


Figure 10.—Mass spectrum of 1-*n*-butylisoquinoline.
Figure 11.—Mass spectrum of 3-*n*-butylisoquinoline.

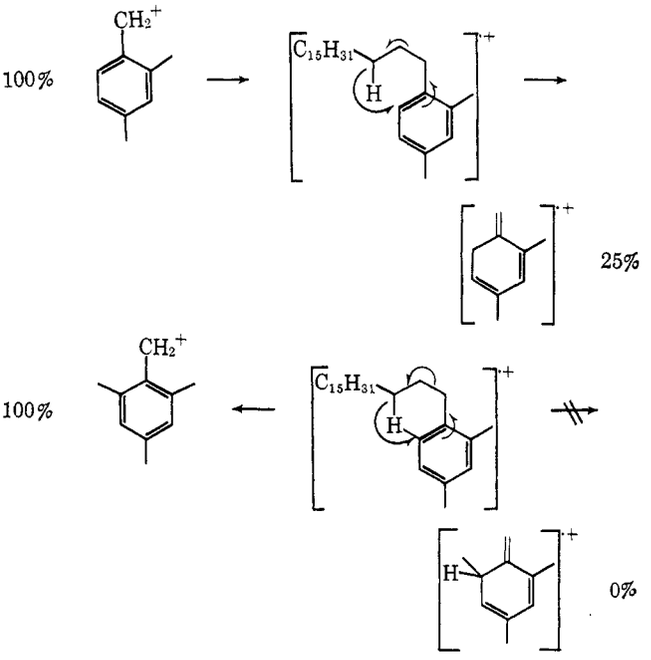
either the adjacent aromatic carbon (C-4, XV → u) or to the heterocyclic nitrogen (XVa → v).

In order to establish the preferred direction of the transfer, the spectrum (see Table II) of 4-methyl-3-*n*-butylisoquinoline was examined. If significant amounts of transfer to carbon were occurring, the intensity of the peak resulting from the rearrangement ion should be diminished in the presence of a C-4 methyl group.[14] Since the abundance of the rearrangement ion was nearly the same in the substituted and unsubstituted compounds (see Table II) it may be concluded that the rearrangement is probably initiated

(12) The hydrogen transfer may not proceed in the specific manner drawn, for J. MacLeod and C. Djerassi [*J. Am. Chem. Soc.*, **88**, 1840 (1966)] have shown that the analogous cleavage of phenyl *n*-butyl ether does not involve a site-specific hydrogen transfer.

(13) "Heterocyclic Compounds," Vol. 4, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1952, pp 246 ff and 475 ff.

(14) The spectrum of 1,3,5-trimethyl-2-octadecylbenzene shows no fragment resulting from a McLafferty rearrangement, whereas the spectrum of 1,4-dimethyl-2-octadecylbenzene shows a rearrangement ion of intensity given below: ref 6, Spectrum No. 1573 and 1515.



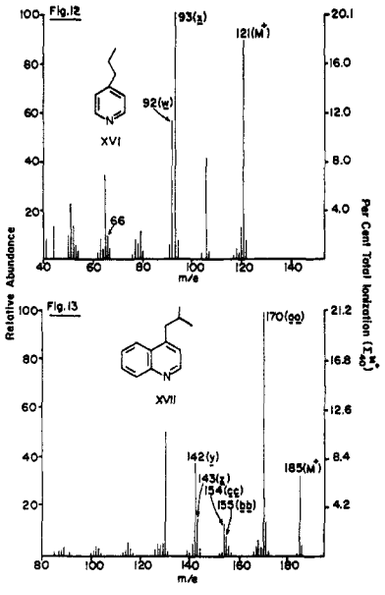


Figure 12.—Mass spectrum of 4-*n*-propylpyridine.
Figure 13.—Mass spectrum of 4-isobutylquinoline.

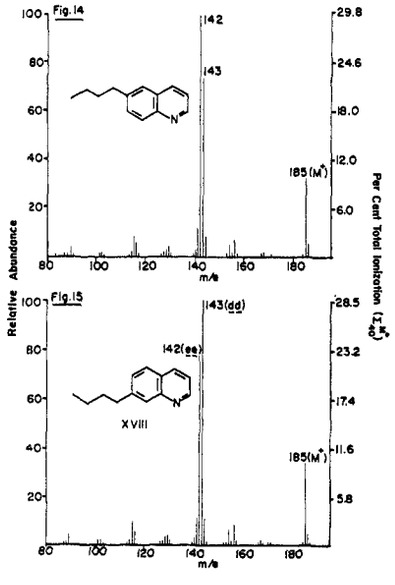


Figure 14.—Mass spectrum of 6-*n*-butylquinoline.
Figure 15.—Mass spectrum of 7-*n*-butylquinoline.

by hydrogen transfer to nitrogen (XVa → v) in accordance with the expected increased "positive charge density" on nitrogen relative to C-3.

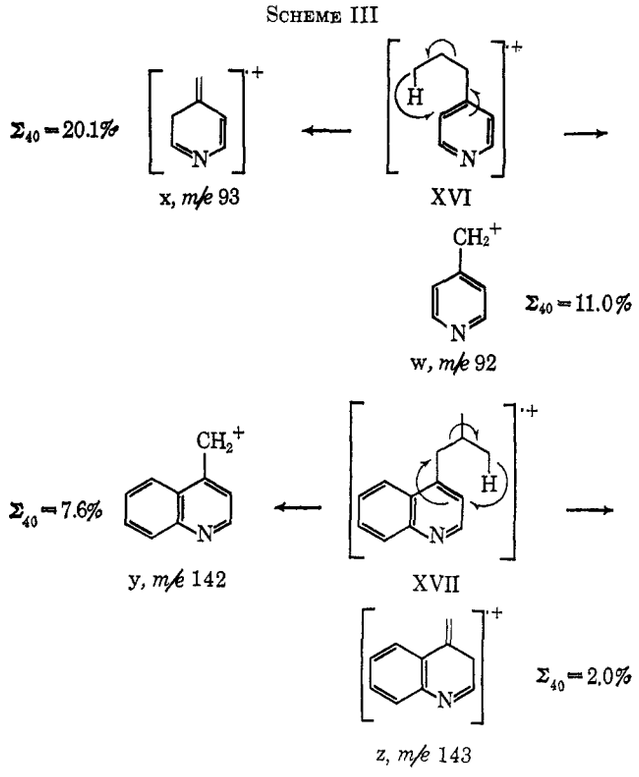
Although the spectrum (Figure 12) of 4-*n*-propylpyridine (XVI) is dominated by peaks arising from β cleavage (w) and McLafferty rearrangement (x), ions (y and z) arising in this way are unimportant in the spectrum (Figure 13) of 4-isobutylquinoline (XVII) (Scheme III).

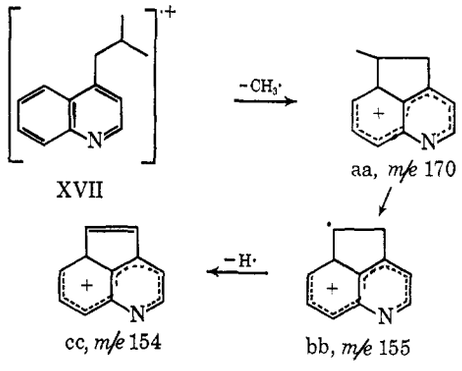
Instead, the dominant fragmentation is γ cleavage of a methyl group to produce a radical which is presumably stabilized by cyclization to the *peri*-carbon atom (giving fragment aa).

As shown by the appropriate metastable peaks[15] at *m/e* 141.2 and 153.9, the cyclized fragment aa loses another methyl group (calcd for $170^2/155 = 141.2$) forming ion bb. Expulsion of a hydrogen atom from bb (calcd for $155^2/154 = 153.9$) forms ion cc. No deuterium labeling experiments were performed to determine the exact origin of the ejected hydrogen.

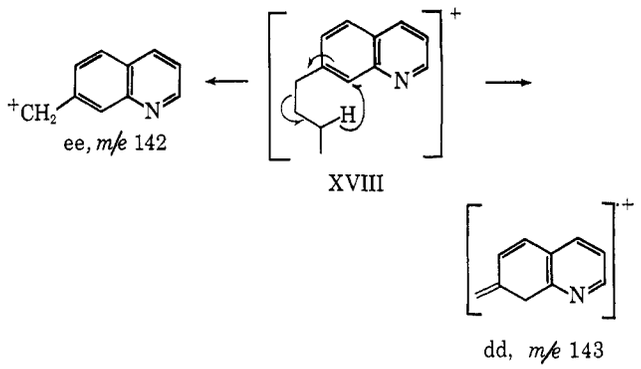
(15) All metastable peaks were determined by means of a logarithmic transfer recorder developed recently in these laboratories: R. T. Aplin, H. Budzikiewicz, H. S. Horn, and J. Lederberg, *Anal. Chem.*, **37**, 776 (1965).

SCHEME III



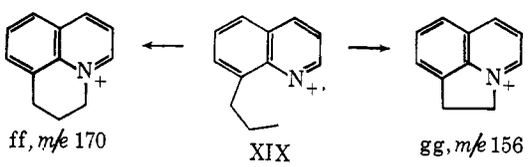


A 6- or 7-alkylquinoline (see Figures 14 and 15) exhibit a fragmentation pattern much like that of the corresponding alkyl benzene.[7] When the hydrogen transferred is secondary as in 6- (see Figure 14 and Table II) and 7-*n*-butylquinoline (XVIII, see Figure 15 and Table II), the peaks for ions resulting from McLafferty rearrangement (dd) and β cleavage (ee) are of nearly equal intensities. It is important to note that the relative abundance of the rearrangement (dd, *m/e* 143) and β-cleavage fragments (ee, *m/e* 142) in the spectrum of 7-*n*-butylquinoline (XVIII) is reversed in the spectrum (Figure 14) of 6-*n*-butylquinoline. This is presumably a reflection of the stability of the two benzyl carbonium ions; for ee is destabilized relative to the benzyl ion at C-6 by virtue of the fact that C-7 has a lower electron density than C-6.[8] Alternatively, it may reflect differences in "positive charge densities" at the various ring carbons to which hydrogen is transferred.

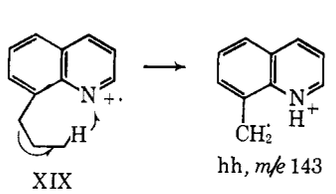


The mass spectrum (Figure 16) of 8-*n*-propylquinoline (XIX) shows intense peaks corresponding to loss of hydrogen (ff, *m/e* 170), methyl (gg, *m/e* 156), and ethylene (hh, *m/e* 143). The spectra of 8-*n*-pentyl-3,6-di-*n*-propylquinoline (see Figure 18) and 6-*n*-pentyl-3,8-di-*n*-propylquinoline (see Figure 17) were helpful in elucidating the nature of these fragments. Despite the presence of other alkyl groups in the molecule capable of McLafferty rearrangement and β cleavage, only ions analogous to those formed (see Figure 16) from 8-*n*-propylquinoline (XIX) were observed in Figure 17. Also, the major fragments arising from the 8-*n*-pentylquinoline correspond to M − (H + C_2H_4), M − (CH_3 + C_2H_4), and M − (C_2H_4 + C_2H_4). On this basis we conclude that the heterocyclic nitrogen is involved in the fragmentation of the C-8 alkyl chain.

Since the M − H peak in the spectra of the 8-*n*-propylquinolines (see Figures 16 and 17) is superseded by an M − C_2H_5 ion (*m/e* 254) in the spectrum (Figure 18) of the 8-*n*-pentylquinoline, the ejected hydrogen atom probably comes from the γ-carbon atom. Such a cleavage would be expected to be favored since the resulting radical can be stabilized by cyclization to the heterocyclic nitrogen (see ff).



The *m/e* 143 ion in the spectrum of 8-*n*-propylquinoline probably arises from β cleavage accompanied by seven-centered transfer of hydrogen to the heterocyclic nitrogen. Such seven-centered McLafferty rearrangements have precedent in the work of Rol.[16]



In summary, it can be seen that the cleavages observed are quite dependent upon the size and position of the alkyl group. This feature should make mass spectrometry a valuable adjunct to structure elucidation of alkylated quinolines and isoquinolines.

(16) N. C. Rol, *Rec. Trav. Chim.*, **84**, 413 (1965).

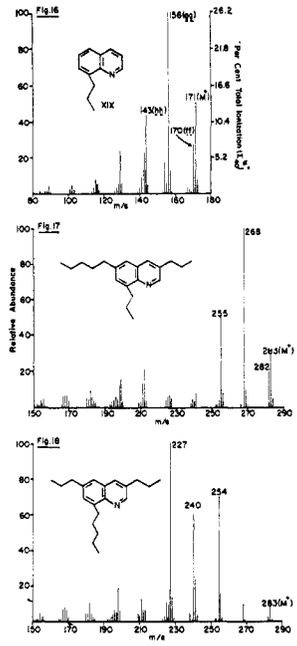


Figure 16.—Mass spectrum of 8-*n*-propylquinoline.
Figure 17.—Mass spectrum of 6-*n*-pentyl-3,8-di-*n*-propylquinoline.
Figure 18.—Mass spectrum of 8-*n*-pentyl-3,6-di-*n*-propylquinoline.

Experimental Section[17]

Labeled Alkyl Halides.—The method of Duffield[18] was used to convert 2,2,2-d_3-ethyl bromide[19] to 3,3,3-d_3-*n*-propyl bromide while 2,2-d_2-*n*-propyl bromide[20] was converted to 3,3-d_2-*n*-butyl bromide according to the literature directions.[20]

Labeled 2-Alkylquinolines (VI and VIII).—Using the method of Cervinka and co-workers,[21] N-ethoxyquinolinium iodide was added to the Grignard reagent of 3,3-d_2-*n*-butyl or 3,3,3-d_3-*n*-propyl bromide to give the labeled 2-alkylquinolines. The corresponding unlabeled compounds prepared in this way exhibited the same mass spectrometric fragmentation pattern as the analytically pure samples described below.

2-Alkylquinolines (V, VII, and IX) and 1-Alkylisoquinolines (XIV).—N-Butyllithium (1 ml of a 1.6 *N* hexane solution; Foote, Exton, Pa.) was added to a solution of 1-methylisoquinoline or 2-methylquinoline (0.1 g, 0.7 mmole) in tetrahydrofuran in a current of nitrogen. After stirring this mixture for 1.5 hr, an alkyl bromide solution (*n*-propyl, 2,2-d_2-*n*-propyl, ethyl, 2,2,2-d_3-ethyl or isopropyl; 0.92 mmole) was added. After further stirring overnight, the reaction was quenched by pouring the mixture into water. The product was extracted with ether. After the ether extract had been dried over magnesium sulfate, the solvent was removed by distillation. The crude quinoline or isoquinoline (0.6 mmole) was purified by gas chromatography (20% Apiezon L, 175°).

The following compounds were prepared by use of an appropriate modification of the above procedure: (1) **1-*n*-propylisoquinoline and 1-(3,3,3-d_3-*n*-propyl)isoquinoline** (*Anal.* Calcd for $C_{12}H_{13}N$: C, 84.21; H, 7.60; N, 8.19; mol wt, 171. Found:

(17) All preparative gas chromatography was performed on an Aerograph instrument equipped with the various columns noted in this section. Nmr spectra were measured by Dr. Lois J. Durham on a Varian A-60 instrument. Microanalyses were performed by Messrs. J. Consul and E. Meier. Melting points are uncorrected and were determined on a Kofler hot stage. All mass spectra were measured on a Consolidated Electrodynamics Corp. mass spectrometer No. 21-103C by Mr. Nelson Garcia or one of the authors (D. A. L.). The all-glass inlet system was heated to 200° and, the isatron temperature was maintained at 250°. The ionizing energy was 70 ev, and the ionizing current was 50 μa.

(18) A. M. Duffield, H. Budzikiewicz, and C. Djerassi, *J. Am. Chem. Soc.*, **87**, 2913 (1965).

(19) C. Djerassi and C. Fenselau, *ibid.*, **87**, 5747 (1965).

(20) A. M. Duffield, R. Beugelmans, H. Budzikiewicz, D. H. Williams, D. Lightner, and C. Djerassi, *ibid.*, **87**, 2920 (1965).

(21) O. Cervinka, A. Fabryova, and L. Matouchova, *Collection Czech. Chem. Commun.*, **28**, 535 (1963).

C, 84.21; H, 7.64; N, 8.12; mol ion, 171), (2) **1-*n*-butylisoquinoline and 1-(3,3-d_2-*n*-butyl)isoquinoline** (*Anal* Calcd for $C_{13}H_{15}N$: C, 84.32; H, 8.11; N, 7.67; mol wt, 185. Found: C, 84.33; H, 8.33; N, 7.80; mol ion, 185.), (3) **2-*n*-propylquinoline** (*Anal.* Calcd for $C_{12}H_{13}N$: C, 84.21; H, 7.60; N, 8.19; mol wt, 171. Found: C, 84.42; H, 7.68; N, 8.06; mol ion, 171.), (4) **2-*n*-butylquinoline** (*Anal.* Calcd for $C_{13}H_{15}N$: C, 84.32; H, 8.11; H, 7.67; mol wt, 185. Found: C, 84.10; H, 8.37; N, 7.39; mol ion, 185.), (5) **1-isobutylisoquinoline** (*Anal.* Calcd for $C_{13}H_{15}N$: C, 84.32; H, 8.11; N, 7.67; mol wt, 185. Found: C, 84.11; H, 8.11; N, 7.44; mol ion, 185.)

3-*n*-Butylisoquinoline (XV).—A solution of 3-isoquinoline carbonitrile[22] (0.125 g, 0.8 mmole) in 25 ml of ether was added to *n*-propylmagnesium bromide (prepared from 0.5 g of *n*-propyl bromide). The mixture was heated under reflux for 3 hr. After water was added to decompose excess Grignard reagent, the solution was made acidic with 30% sulfuric acid. The aqueous acidic extracts were heated on a steam bath for 20 min. After neutralization with sodium bicarbonate, the ketone was extracted into chloroform. The chloroform extracts were dried over magnesium sulfate, and the solvent was evaporated. Recrystallization of the residue from methanol–water gave 75 mg of 3-butyrylisoquinoline melting at 73–74°; ν_{max} 1600 cm^{-1} (C=O).

Anal. Calcd for $C_{13}H_{13}NO$: C, 78.39; H, 6.53; N, 7.03; mol wt, 199. Found: C, 78.18; H, 6.84; N, 6.72; mol ion, 199.

A solution of 3-butyrylisoquinoline (0.075 mg, 0.038 mmole) and 95% hydrazine hydrate (0.25 ml) in 1 ml of ethanol and 2.5 ml of diethylene glycol was heated under reflux for 1 hr. Potassium hydroxide (0.25 g) was added, and the heating was continued for an additional 0.5 hr. The condensor was then removed, and the temperature of the bath was raised to 210°. After maintaining this temperature for 3 hr, the mixture was cooled, water was added, and the product was extracted with ether. After the extract was dried over magnesium sulfate, the solvent was removed by distillation. The resulting 3-*n*-butylisoquinoline (30 mg) was homogeneous by gas chromatography on 20% Apiezon L at 175°.

Anal. Calcd for $C_{13}H_{15}N$: mol wt, 185. Found: mol ion, 185.

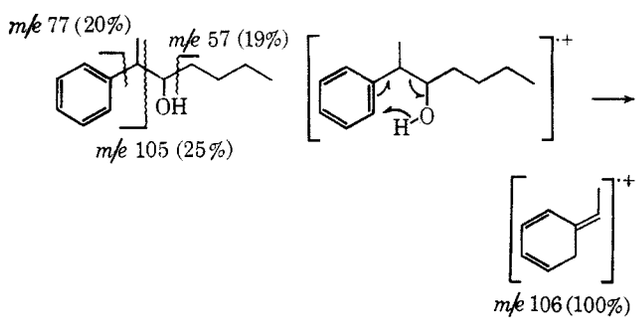
2-Phenyl-3-heptanol.—An ethereal solution of α-phenylpropionaldehyde (5 g, 0.04 mole; K & K Laboratories, Plainview, N. Y.) was added dropwise to the Grignard reagent prepared from 10 g of *n*-butyl bromide and 5.0 g of magnesium. After the reaction was heated under reflux for 4 hr, water was added to decompose the excess reagent. The carbinol was then extracted with ether, the ether extract was dried over magnesium sulfate and the solvent was removed by distillation. Distillation of the alcohol [bp 110° (2 mm)] gave a product (3.3 g, 0.0175 mole) which was homogeneous by gas chromatography (20% Apiezon L, 175°): ν_{max} 3320 cm^{-1} (OH).

Anal. Calcd for $C_{13}H_{20}O$: mol wt, 192. Found: mol ion, 192.

For the mass spectral fragmentation, see Chart I.

CHART I

MASS SPECTRAL FRAGMENTATION



2-Phenyl-3-heptanone.—The carbinol prepared above (3.3 g, 0.0175 mole) was dissolved in 150 ml of 50% acetone–glacial acetic acid. A stoichiometric amount of chromium trioxide in 8 *N* sulfuric acid was added dropwise while cooling the reaction mixture to keep the temperature below 20°. After pouring the solution into water, the ketone was extracted with ether. The extract was dried over magnesium sulfate, and the ether was removed by distillation to give 2.8 g of 2-phenyl-3-heptanone[23] homogeneous by gas chromatography (Apiezon L, 175°) and thin layer chromatography (using benzene as eluent): bp 93–94° (2 mm); ν_{max} 1690 cm^{-1} (C=O).

Anal. Calcd for $C_{13}H_{18}O$: C, 82.10; H, 9.47. Found: C, 81.73; H, 9.54.

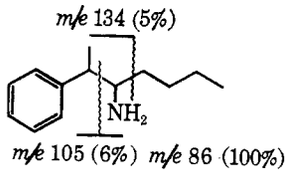
Preparation of 2-Phenyl-3-aminoheptane.—Hydroxylamine hydrochloride (3 g) and 2-phenyl-3-heptanone (3 g, 0.016 mole) were dissolved in 5 ml of absolute ethanol and 5 ml of anhydrous pyridine. The mixture was heated under reflux overnight and then poured into water. The oxime was extracted with ether, the ether extract was washed three times with water and dried over magnesium sulfate, and the ether and any remaining pyridine were removed by distillation. Distillation of the crude material from a hot box [(bath temperature 120–160° at (2 mm)] resulted in 2 g of 2-phenyl-3-heptanone oxime; ν_{max} 3230 (OH), 1610 cm^{-1} (C=N). Sodium (3 g, 0.13 mole) was added in small portions to a solution of the above oxime (1.2 g, 5.0 mmoles) in 28 ml of "super-dry" ethanol. After the mixture was heated under reflux for 0.5 hr, it was acidified with dilute hydrochloric acid, the nonbasic material was taken up in ether, the aqueous phase was neutralized with sodium bicarbonate, and the amine was extracted with ether. The ether extract was dried over magnesium sulfate, and the solvent was removed by distillation. The amine (0.7 g, 3.6 mmoles) was homogeneous by gas chromatography on 20% Apiezon L at 175°: ν_{max} 3300 (NH), 1575 cm^{-1} (CN).

Anal. Calcd for $C_{13}H_{21}N$: C, 81.67; H, 10.99; N, 7.32; mol, 191. Found: C, 81.32; H, 10.97; N, 7.12; mol ion, 191.

For the mass spectral fragmentation, see Chart II.

CHART II

MASS SPECTRAL FRAGMENTATION



Preparation of 4-Methyl-3-*n*-butylisoquinoline.—2-Phenyl-2-aminoheptane (1.0 g, 5.3 mmoles) was heated under reflux with 2 ml of 95% formic acid for 48 hr. The reaction was quenched by pouring the mixture into water. After extracting the formyl derivative with ether, the ether was washed with water and sodium bicarbonate solution. The extract was dried over magnesium sulfate and the solvent was removed by distillation. The amide (0.6 g, 2.7 mmoles) was distilled from a hot box [bath temperature 170–180° (2 mm)]: ν_{max} 3300 (NH), 1670 cm^{-1} (C=O). Unreacted starting material could be recovered by neutralization of the original aqueous layer and extraction with ether.

The N-formylamine (0.6 g, 2.7 mmole) was dissolved in 3 ml of anhydrous xylene. Phosphorus pentoxide (0.75 g) was added, and the mixture was heated under reflux for 6 hr. After the excess phosphorus pentoxide was decomposed with water, the solution was made basic with sodium bicarbonate, and the dihydroisoquinoline was extracted with chloroform. The material was not further purified but immediately dehydrogenated by heating for 2 hr at 200° with 100 mg of 10% palladium on carbon. Ether was added and the resulting solution was then extracted with 10% hydrochloric acid. The acid extracts were neutralized with sodium bicarbonate and the amine was extracted with ether. After the extract was dried over magnesium sulfate, the solvent was removed by distillation to give 100 mg of 3-*n*-butyl-4-methylisoquinoline (90% pure by gas chromatography on Apiezon L at 175°).

Anal. Calcd for $C_{14}H_{17}N$; C, 84.44; H, 8.58; N, 7.03; mol wt, 199. Found: C, 83.92; H, 8.64; N, 7.24; mol ion, 199.

The nmr spectrum (CCl_4 solution with TMS as internal standard) showed a singlet at δ 2.52 (three protons of the 4-methyl group), a triplet centered at 0.95 (methyl protons of *n*-butyl group), a multiplet centered at 1.55 (five β and γ hydrogens of

(22) G. A. Swan, *J. Chem. Soc.*, 2038 (1958).

(23) A. K. Mills and A. E. Wilder Smith, *Helv. Chim. Acta*, **43**, 1915 (1960).

the *n*-butyl group), a triplet at 2.9 (benzylic hydrogens of *n*-butyl group), and singlet at 8.38 (proton on C-1 of isoquinoline nucleus).

Registry No.—1-*n*-Propylisoquinoline, 7661-37-2; 1-*n*-butylisoquinoline, 7661-38-3; 2-*n*-propylquinoline, 1613-32-7; 2-*n*-butylquinoline, 7661-39-4; 1-isobutylisoquinoline, 7661-40-7; 3-butyrylisoquinoline, 7661-41-8; 3-*n*-butylisoquinoline, 7661-42-9; 2-phenyl-3-heptanol, 7661-43-0; 2-phenyl-3-heptanone, 7661-44-1; 2-phenyl-3-aminoheptane, 7634-70-0; 3-*n*-butyl-4-methylisoquinoline, 7661-45-2; 1-(3,3,3-d_3-*n*-propyl)isoquinoline, 7661-46-3; 1-(3,3-d_2-*n*-butyl)isoquinoline, 7634-71-1; 7-methylquinoline, 612-60-2; 3-methylquinoline, 612-58-8; 2,4-dimethylquinoline, 1198-37-4; 2-ethylquinoline, 1613-34-9; 7-ethylquinoline, 7661-47-4; 2-(3,3-dimethyl-*n*-butyl)quinoline, 7661-48-5; 2-*n*-propyloxyquinoline, 945-83-5; 1-*n*-propylcarbostyril, 944-70-7; 4-*n*-propylpyridine, 1122-81-2; 4-isobutylquinoline, 7661-51-0; 6-*n*-butylquinoline, 7634-74-4; 7-*n*-butylquinoline, 7661-52-1; 8-*n*-propylquinoline, 7661-53-2; 6-*n*-pentyl-3,8-di-*n*-propylquinoline, 7661-54-3; 8-*n*-pentyl-3,6-di-*n*-propylquinoline, 7634-75-5.

Acknowledgment.—Dr. Wai H. Hui (on leave from the University of Hong Kong) synthesized 2-neopentyl-,[24] 2-isobutyl-,[24] and 2-ethylquinoline,[24] and Mr. Roger Kornberg (undergraduate summer research assistant) synthesized 1-ethylisoquinoline.[24] Dr. Z. Velenta[25] (University of New Brunswick, Fredericton, New Brunswick, Canada) provided 6-*n*-pentyl-3,8-di-*n*-propyl- and 8-*n*-pentyl-3,6-di-*n*-propylquinoline. Dr. Yasuo Makisumi[26] (Shionogi and Co., Osaka, Japan) provided 1-*n*-propylcarbostyril and 2-*n*-propyloxyquinoline, while Dr. K. Schofield (University of Exeter, Exeter, England) donated 6-*n*-propyl-, and *n*-butylquinoline as well as 7-ethyl-, 7-*n*-propyl-, and 7-*n*-butylquinoline.

(24) W. Bradley and S. Jeffrey, *J. Chem. Soc.*, 2770 (1954).
(25) Z. Valenta, H. Rashid, R. Wightman, and J. Wilson, *Tetrahedron Letters*, No. 23, 1559 (1963).
(26) Y. Makisumi, *ibid.*, **39**, 2833 (1964).

Mass Spectrometry in Structural and Stereochemical Problems. CXXV.[1] Mass Spectrometry of Some Steroid Trimethylsilyl Ethers[2]

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Received October 18, 1966

Using deuterium and substituent labeling as well as high-resolution mass measurements, plausible assignments could be made for the diagnostically most significant peaks in the mass spectra of some steroid trimethylsilyl ethers which have been used in the past for structural purposes. The variations in these spectra, which are shown to be strongly dependent upon experimental conditions, are commented upon as are other features of the mass spectra. Charge retention in the silicon-containing moiety does not compete very effectively with the more favored hydrocarbon carbonium ions produced when methyl groups are substituted at C-4.

In recent years, trimethylsilyl ether derivatives have been used extensively in the purification and identification of nonvolatile materials, especially in connection with a technique combining gas–liquid partition chromatography and mass spectrometry.[4] This method has found application in a variety of fields[5-8] but has been particularly relevant to steroid metabolites.[5,9,10] Aside from the fact that trimethylsilyl ether derivatives greatly facilitate gas–liquid partition chromatographic separation in comparison with the parent steroids,[11] they also appear to direct mass spectrometric fragmentation in a manner characteristic of particular groups of steroids. In order to acquire information other than empirical formula determinations from a mass spectrum, it is most important that some insight be gained into such electron-impact-induced fragmentation patterns. Ryhage[4] and his collaborators have pointed out that there is a particularly characteristic fragmentation sequence for trimethylsilyl ethers of Δ^5-3-hydroxy steroids, and, in fact, the existence of an intense peak at m/e 129 has been used by them as practically conclusive evidence for the identification of the trimethylsilyl derivative of this type of sterol. Sjövall and Vihko[5] have found this same diagnostically useful peak, but with reduced intensity, in the mass spectrum of the trimethylsilyl ethers of 3-hydroxy 5α-steroids. Ryhage[4] has attributed the composition of this molecular fragment to the trimethylsiloxy group, carbon atoms 2, 3, and 4 of ring A, and a loss of a hydrogen atom from the charge-retaining species (see wavy line in I), and Sjövall and Vihko[5] state that the exact composition of this frag-

(1) Paper CXXIV: S. D. Sample, D. A. Lightner, O. Buchardt, and C. Djerassi, *J. Org. Chem.*, **32**, 997 (1967).
(2) Financial assistance by the National Institutes of Health (Grants No. CA 07195 and AM 04257) is gratefully acknowledged. The purchase of the Atlas CH-4 mass spectrometer was made possible by NASA Grant Gs 81-60.
(3) National Science Foundation Predoctorate Fellow, 1966–1967.
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