127. Alkylaminopyridines and some Analogues as Derivatives for the Structure Elucidation of Long Aliphatic Chains by Mass Spectrometry

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Dedicated to Professor *Edgar Lederer*, Gif-sur-Yvette, on the occasion of his 70th birthday

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Summary

Several long chain primary alcohols (saturated, monoolefinic and methyl branched) have been converted *via* their mesylates into various long chain alkylated aromatic compounds with basic character, and their mass spectra compared. The spectra of 2-alkylaminopyridines and to some extent those of 3-alkylaminopyridines exhibit most clearly the structure of the aliphatic chain, allowing the localization of branchings and double bonds.

In the mass spectra of long chain primary alcohols the structural features of the chain, *e.g.* branching points and positions of double bonds, are poorly exhibited [1]. With their common derivatives as for example acetates, trifluoroacetates or trimethylsilyl ethers the situation is similar [1]. In the fragmentation of their molecular ions, two types of reactions prevail, one occurs within the functional group, *e.g.* the loss of a methyl group from the trimethylsilyl residue, and the other is an elimination leading to an olefinic chain, known to undergo extensive rearrangements before secondary fragmentations occur [2].

In view of the fact that long chain primary alcohols are common constituents of natural products, *e.g.* waxes, it appeared interesting to search for derivatives whose mass spectra would represent more clearly the structure of the chain. Attempts in this direction have been made by using methyl ethers [3] and dimethylsilyl ethers [4], which did improve the exhibition of certain features of the chain structure, but did not alter the general picture. In order to achieve a more fundamental change in the behaviour of the aliphatic chains, it was felt that the hydroxyl group should be replaced by some other functional group, suitable for inducing a specific fragmentation of the chain.

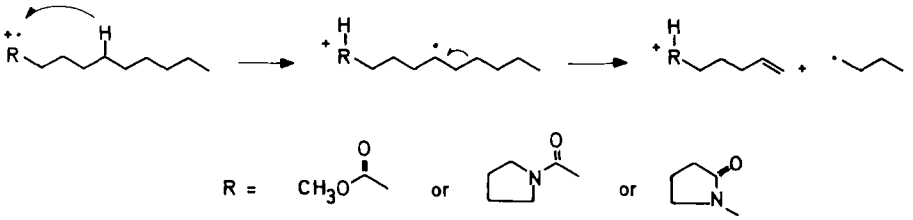
The chain structure is fairly well exhibited in fatty acids and their methyl esters [5], and in fact, long chain alcohols isolated from waxes, have been oxidized to the corresponding acids for elucidation of the chain structure [6]. Amides, particularly pyrrolidides give an even better picture of the chains than methyl esters, allowing, for example, the location of a double bond [7].

The hydroxyl group in a series of long chain alcohols was therefore replaced, *via* the mesylate, by the 1-pyrrolidinonyl group [8]. A much more characteristic

fragmentation of the chain could be obtained than from the corresponding alcohols. However, a clearcut exhibition of the double bond position was not achieved with this derivative, so a search for other groups with fragmentation-directing properties was initiated.

The mechanism of the chain fragmentation originally proposed for the fragmentation of esters [9] and adapted for the amides [10], consists essentially of an H-rearrangement from the chain to the functional group producing a radical on the chain. The radical triggers a chain cleavage leading to a relatively stable, nonradical cation *(Scheme 1)*.

Scheme 1



Although there exists no proof for such a mechanism [11] and its details are not known, it serves very well for heuristic purposes [10]. Thus any functional groups, which favour random H-abstractions over all other fragmentations, particularly cleavages and *McLafferty*-rearrangements, appear to be suitable for our purposes. Aromatic nuclei with basic character appeared to be promising candidates.

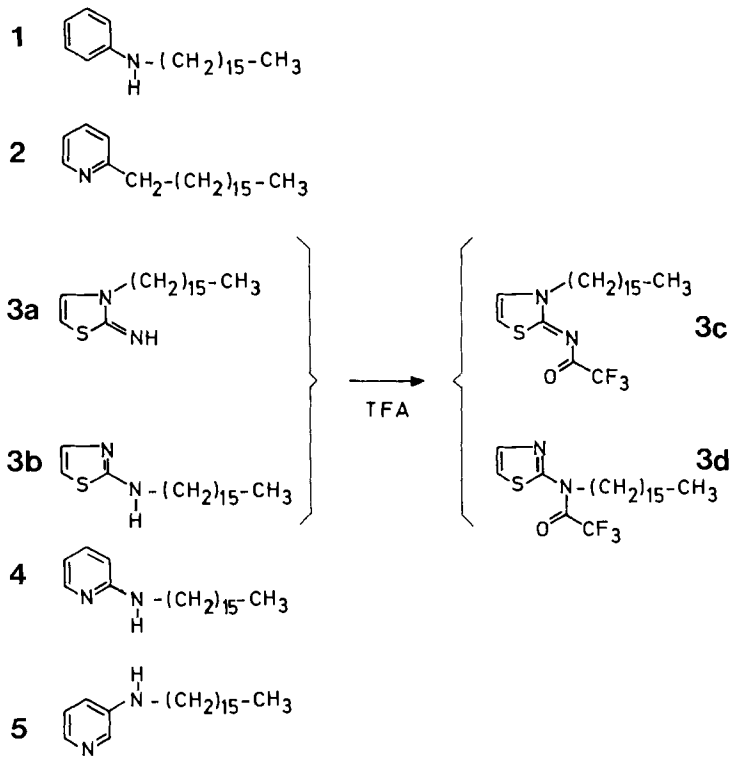
A number of common aromatic nuclei were therefore chosen as possibly useful substituents of long chains. Aniline, picoline, 2-aminothiazole, 2-aminopyridine and 3-aminopyridine reacted with hexadecyl bromide to give compounds **1** to **5**, including the trifluoroacetyl (TFA) derivatives **3c** and **3d** *(Scheme 2)*, and the mass spectra of the resulting derivatives were recorded *(Fig. 1* to *8)*.

The ideal result of such a study would be a series of peaks of comparable intensity generated by cleavage of every C,C-bond in the chain and no other fragmentation. It is obvious *(Fig. 1* to *8)* that we are still far from this achievement, but the desired series of peaks is nevertheless seen in some of the spectra in acceptable relative intensity. Significant peaks of these series are marked by mass numbers in the *Figures 1* to *8*. Other peaks in the spectra, which arise from fragmentations unrelated to the mechanism of *Scheme 1, e.g.* α-cleavage, *McLafferty* rearrangement or loss of NH_2 or SH, are only referred to by remarks in the figure captions or on the formulae. Since these ions are not relevant in the present context, they will not be discussed in further detail.

The worst representation of the structure of the chain is found, not unexpectedly, in the aniline derivative *(Fig. 1)*. Although the desired series of peaks is present, the relative intensity of the peaks, compared with the α-cleavage, is so small that this derivative is probably of no analytical value.

Pyridine shows a much better result *(Fig. 2)*, but the intensity of the desired peaks is still quite low in comparison with the dominating peak 93, the product of a *McLafferty* reaction (note the intensity enhancement factor 10 in *Fig. 1* and *2*).

Scheme 2



The reaction of hexadecyl bromide with 2-aminothiazole yielded two isomeric products **3a** and **3b** *(Fig. 3* and *4)*. Obviously a fairly intense series of the desired peaks is obtained, but the pattern at the low mass end, between *m/e* 113 and 155, is disturbingly irregular. The reason for the intensity variations in this mass range of both spectra is not well understood.

Spectra of the TFA derivatives exhibit the chain structure poorly *(Fig. 5* and *6)*. Loss of the CF_3-group and other reactions dominate, so this type of derivative was not investigated further.

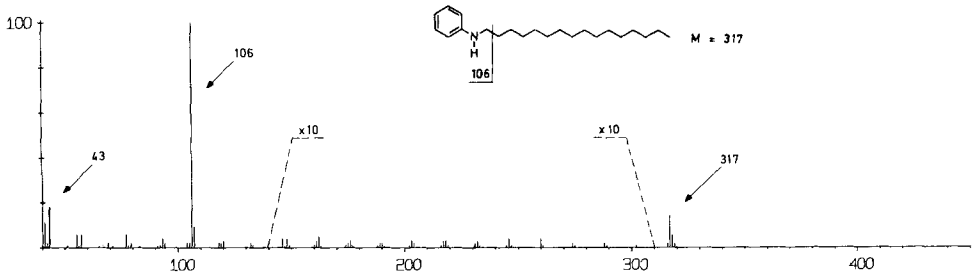


Fig. 1. *Mass spectrum of* N-*hexadecylaniline* (**1**)

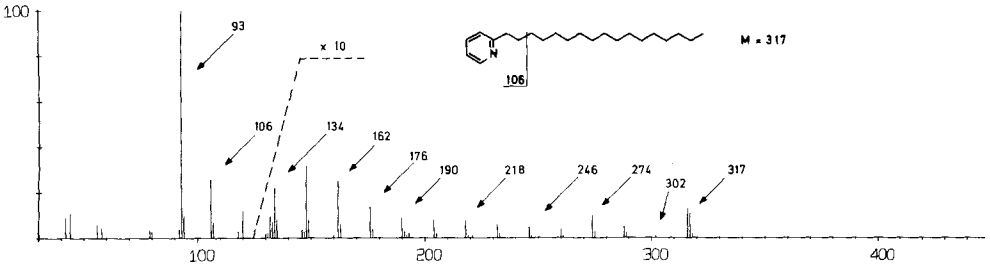


Fig. 2. *Mass spectrum of 2-heptadecylpyridine* (**2**)

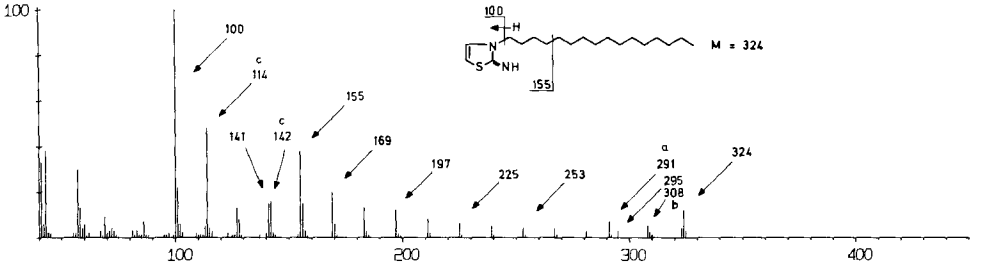


Fig. 3. *Mass spectrum of 3-hexadecyl-2-imino-4-thiazoline* (**3a**) (a: $M-SH$, b: $M-NH_2$, c: unexplained)

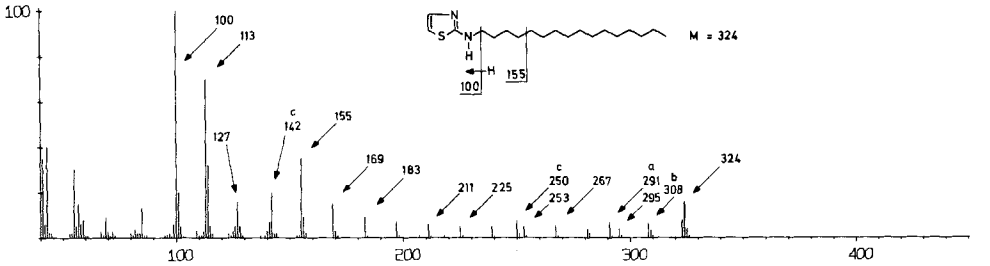


Fig. 4. *Mass spectrum of 2-(hexadecylamino)thiazole* (**3b**) (a: $M-SH$, b: $M-NH_2$, c: unexplained)

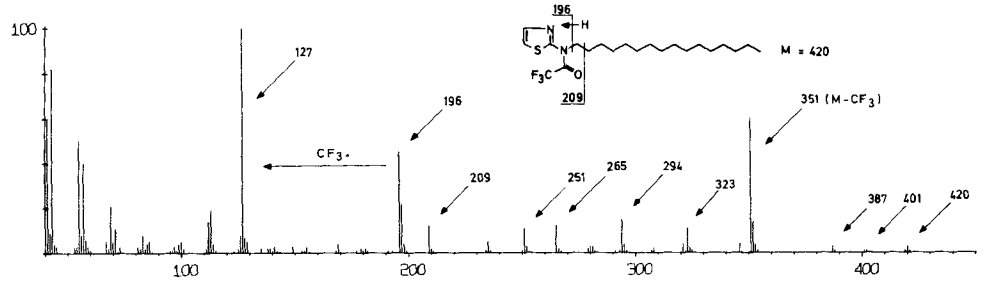


Fig. 5. *Mass spectrum of 2-(N-hexadecyltrifluoroacetamido)thiazole* (**3c**)

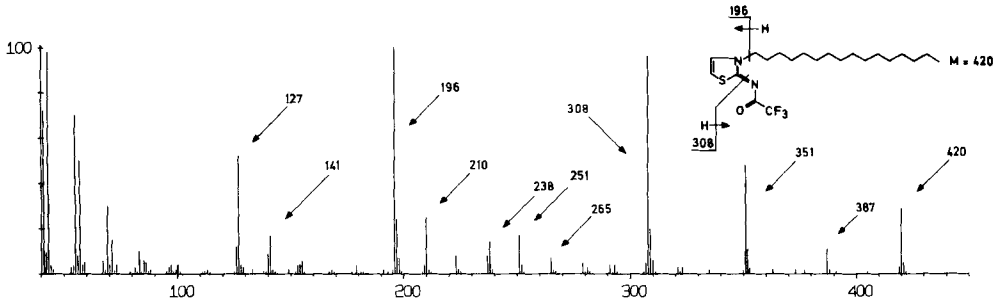


Fig. 6. *Mass spectrum of 3-hexadecyl-2-[(trifluoroacetyl)imino]-4-thiazoline* (**3d**)

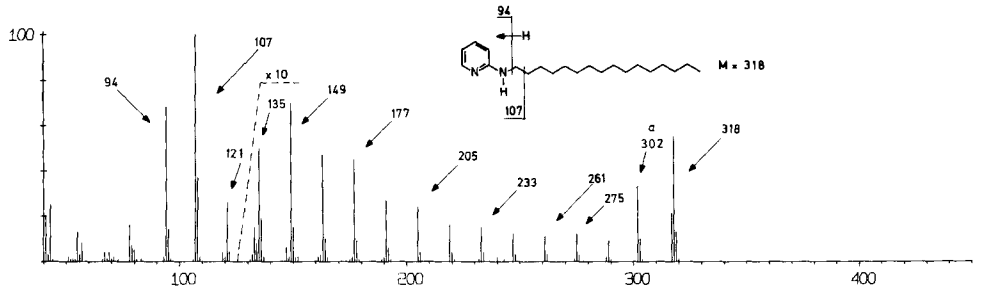


Fig. 7. *Mass spectrum of 2-(hexadecylamino)pyridine* (**4**) (a: $M-NH_2$)

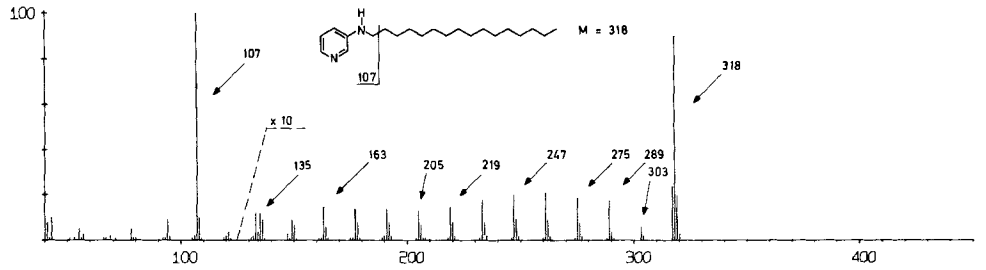
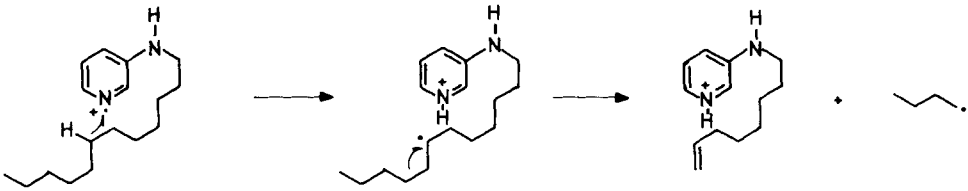


Fig. 8. *Mass spectrum of 3-(hexadecylamino)pyridine* (**5**)

The most promising results were achieved with 2- and 3-aminopyridines **4** and **5** *(Fig. 7* and *8)*. Although the intensity of the peaks in question is not very great relative to the base peak *m/e* 107 generated by an *α*-cleavage (note the enhancement factor 10 in the *Figures*), the intensity pattern is very regular in both cases. While in the 2-aminopyridine derivative the peak intensities fall in the usual way, going from low to high mass, the intensity distribution is quite remarkable in the 3-aminopyridine derivative **5**. Here the intensities increase slightly with increasing mass. The reason for this behaviour appears to be that the H-abstraction from the chain is mainly accomplished by the pyridine nitrogen. This process requires a larger ring size in the transition state of the *meta*-substituted pyridine, changing the statistical distribution of the radical in favour of more distant sites [12] *(Scheme 3)*.

Another remarkable, though undesired feature of this spectrum is the occurrence of a series of satellite peaks one mass unit above the desired series of peaks. These

Scheme 3



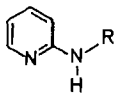
ions must arise through the loss of olefins from the molecular ion, requiring a H-rearrangement. A discussion of possible mechanisms must await results with deuterated compounds.

Based on these results both aminopyridines were selected for further investigation. It was hoped that the 2-aminopyridine derivative would possibly represent favourably structural features close to the heterocyclic ring, with the 3-aminoderivative representing the more distant features in contrast. To examine the possible exhibition of structural features of the chain, both aminopyridines were attached to 3 different chains, by treating them with the mesylates of (*Z*)-9-octadecen-1-ol, (*Z*)-6-octadecen-1-ol and 3,7,11,15-tetramethylhexadecan-1-ol respectively, to yield **6** to **11** *(Scheme 4)*.

The results obtained with **2-aminopyridine** are shown in *Figures 9, 10* and *11*.

Taking the mechanism of *Scheme 1*, and considering qualitatively the usual order for H-abstraction and cleavage reactions (allylic > vinylic, tertiary > secondary > primary) the spectra can be quite readily interpreted. The position of the double bond is clearly defined by the lack of intensity of the peaks between the allylic positions. According to these simple rules, there should be no peaks present at mass numbers which correspond to cleavage across a double bond. There are however peaks of relatively low intensity found, which correspond to such a cleavage accompanied by H-rearrangements, *e.g. m/e* 217 in *Figure 9* or 175 in *Figure 10*. Probably these peaks arise by the same mechanism as the other peaks, but from parent ions which have undergone previous double bond rearrangements [2].

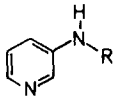
Scheme 4



6 R = $(CH_2)_8 - CH = CH - (CH_2)_7 - CH_3$

7 R = $(CH_2)_5 - CH = CH - (CH_2)_{10} - CH_3$

8 R = $\left(CH_2 - CH_2 - \underset{\displaystyle CH_3}{\underset{|}{CH}} - CH_2\right)_4 - H$



9 R = $(CH_2)_8 - CH = CH - (CH_2)_7 - CH_3$

10 R = $(CH_2)_5 - CH = CH - (CH_2)_{10} - CH_3$

11 R = $\left(CH_2 - CH_2 - \underset{\displaystyle CH_3}{\underset{|}{CH}} - CH_2\right)_4 - H$

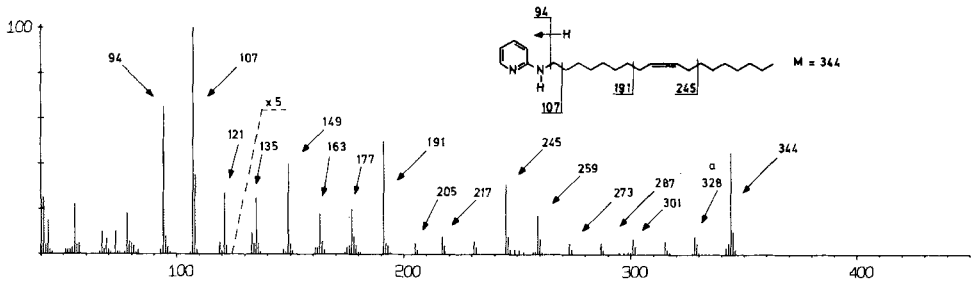


Fig. 9. *Mass spectrum of 2-[(Z)-9-octadecenylamino]pyridine* (**6**) (a: $M - NH_2$)

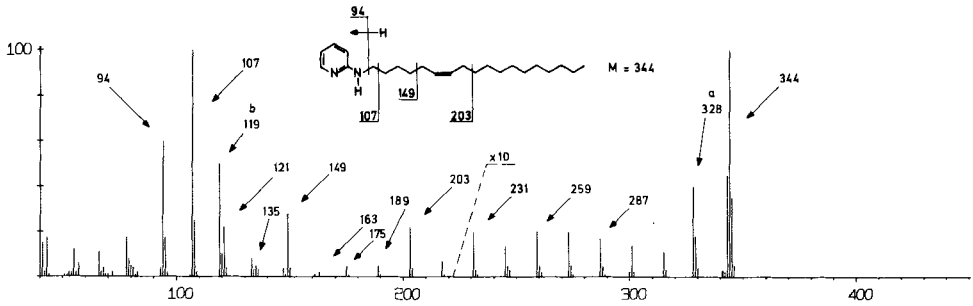


Fig. 10. *Mass spectrum of 2-[(Z)-6-octadecenylamino]pyridine* (**7**) (a: $M - NH_2$, b: unexplained)

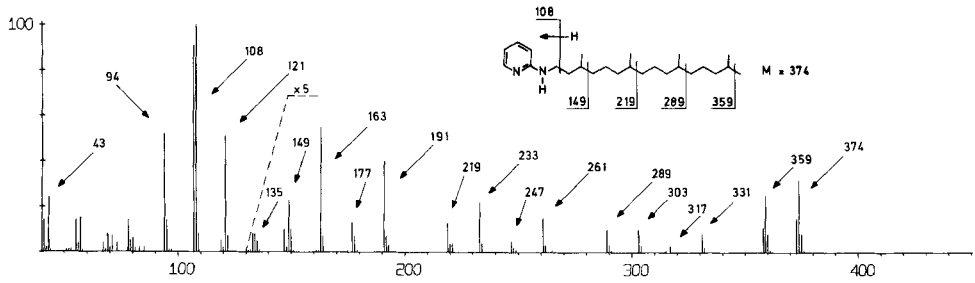


Fig. 11. *Mass spectrum of 2-[(3,7,11,15-tetramethylhexadecyl)amino]pyridine* (**8**)

In contrast to other classes of compounds, *e.g.* unsubstituted olefins, this reaction appears to play a minor role in the present derivatives. The branching points in the methylated compound **8** *(Fig. 11)* can also be clearly recognized by the absence (or at least very low intensity, *e.g.* at *m/e* 135) of the peaks at the corresponding positions. Thus this derivative is fairly well suited for the exhibition of at least such simple features of a chain and further studies appear justified.

The spectra of the olefinic and the tetramethylated **3-aminopyridine** derivatives **9**, **10** and **11** *(Scheme 4)* are shown in *Figures 12, 13* and *14*. Although the double bond positions and also most of the branchings can be recognized basically in the same way as with the 2-alkylaminopyridine the picture appears more complicated. This is particularly true in the region near the functional group. In the Δ^6-derivative *(Fig. 13)* the chain pattern nearer than the double bond position has practically

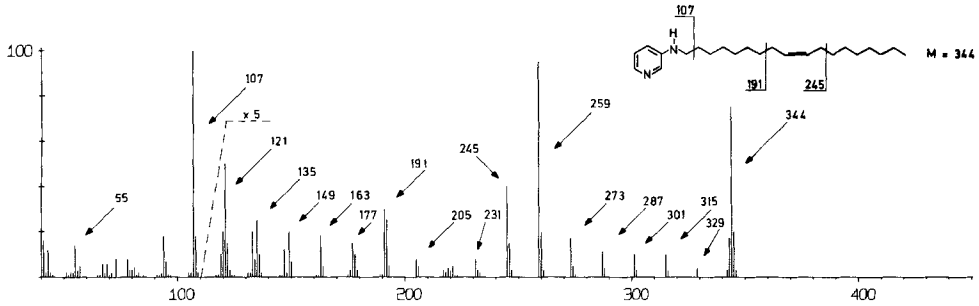


Fig. 12. *Mass spectrum of 3-[(Z)-9-octadecenylamino]pyridine* (**9**)

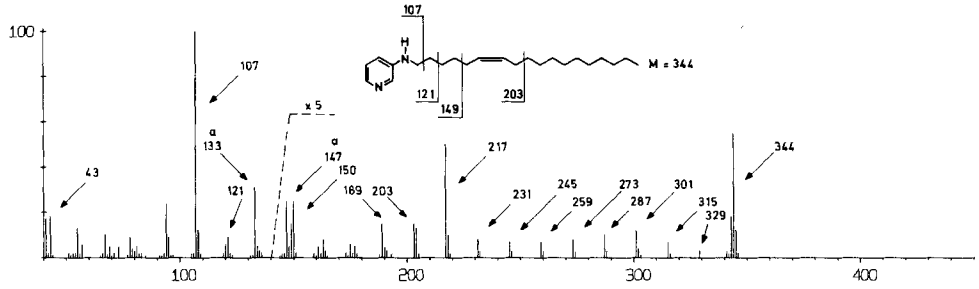


Fig. 13. *Mass spectrum of 3-[(Z)-6-octadecenylamino]pyridine* (**10**) (a: unexplained)

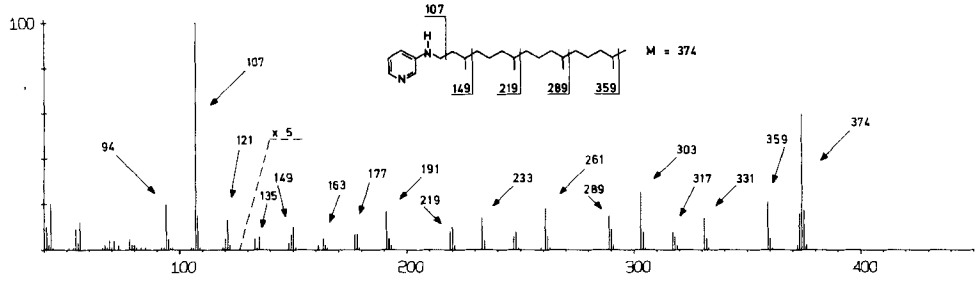


Fig. 14. *Mass spectrum of 3-[(3,7,11,15-tetramethylhexadecyl)amino]pyridine* (**11**)

vanished and in **11**, for example, the first methyl group is not clearly indicated by the pattern (peak 135 in *Fig. 14* not absent). In the olefinic derivatives the remarkably intense peaks from the homoallylic cleavage are noteworthy. No proven explanation is available, but it may be surmised that for steric reasons the H-abstraction in the more distant allylic position which precedes the homoallylic cleavage is particularly favoured. Although in these cases the region close to the heterocyclic ring is not well depicted, and the satellite peaks one mass unit above the desired peaks are of disturbing intensities in some instances, a good representation of the more distant features of the chain structure by the 3-aminopyridine derivatives appears established by the experiment. No olefinic compounds with *E*-configuration were available. It appears difficult to predict intensity differences between the spectra of *E*- and *Z*-isomers, particularly in the 3-aminopyridine derivatives.

Conclusion. – From the results obtained so far, it appears likely that 2-alkylamino-, and in special cases also 3-alkylaminopyridines are analytically useful derivatives for the elucidation of structural features of long chain primary alcohols (and halides). Both derivatives are superior in their fragmentation-directing ability to the pyrrolidinones investigated earlier, and similar to the pyrrolidides used for improving the chain fragmentation in fatty acids [7].

Experimental Part

The derivatives were prepared by classical methods on a 0.5 mg scale. Compounds **1**, **3a**, **3b**, **5**, **9**, **10** and **11** were obtained by heating mesylates or bromides with excess of the amine to 100° for 1 h in DMSO. Compound **2** was prepared by treating 1-hexadecyl bromide with a reagent obtained from α-picolin and BuLi in THF at $-50°$. Compounds **3c** and **3d** were obtained by treating a mixture of **3a** and **3b** with trifluoroacetic anhydride in ethyl acetate for 2 h at RT. Compounds **4**, **6**, **7** and **8** were obtained by treating the mesylate or the bromide with a reagent prepared from excess of 2-aminopyridine and *t*BuOK in dry (CaH_2-distilled) DMSO [10].

No effort was made to optimize the preparation procedures.

Work-up was always done by distributing the reaction products between hexane and water. The dried hexane solution was concentrated and used for analysis by gas chromatography/mass spectrometry (GC./MS.).

GC./MS.-analysis: *Varian* 1740 gas chromatograph coupled *via* a frit separator to a *Varian*-MAT CH7 mass spectrometer. GC.: 3% OV-17 on Gaschrom Q, 150–300° 8°/min. MS.: EI, 70 eV, 250°.

The starting materials 1-hexadecyl bromide, (*Z*)-9-octadecen-1-ol and (*Z*)-6-octadecen-1-ol are commercially available (*Fluka*, Buchs, Switzerland); 3,7,11,15-tetramethylhexadecan-1-ol was prepared by hydrogenation of phytol with Pd/C in ethyl acetate.

The structures of compounds **3a** and **3b** were assigned on the basis of the mass spectra of their CF_3CO derivatives **3c** and **3d**. The mass spectrum of the CF_3CO derivative of **3d** showed, in addition to the peaks also shown by the isomeric compound **3c** *(Fig. 5* and *6)* a signal of 97% relative intensity at *m/e* 308, corresponding to the loss of CF_3CONH from the molecular ion. Since this structural element can only be eliminated from the TFA derivative of structure **3d**, all structures can be assigned as given in **3a** to **3d**.

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