MASS SPECTROSCOPIC STUDY OF 2,5-DIMETHYL-4-BENZOYL- AND 2,5-DIMETHYL-4-BENZYLPYRIDINE DERIVATIVES

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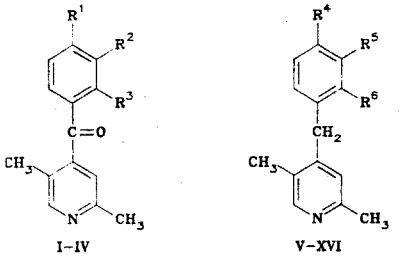
The dissociative ionization of sixteen 4-benzoyl- and 4-benzylpyridine derivatives and their deuteroanalogs has been studied. An ortho effect, due to the benzoyl and benzyl radicals in the methyl group in the 5-position of the pyridine ring, has been detected. It has also been established that fragmentation of 4-benzoylpyridines substituted with a nitro group in the benzene ring leads to $[M - OH]^+$ ions, due to the ortho effect, whereas fragmentation of 4-benzylpyridines leads to $[M - C_6H_5R]^+$ ions. The probability of a given process depends on the position and nature of any substituent in the benzene ring; this makes it possible to identify different isomers in a given series of compounds.

Functionally substituted γ-benzoyl- and γ-benzylpyridines [1-4] have recently become accessible, due to the development of new methods for the synthesis of pure pyridine bases. These compounds are important as starting materials in the synthesis of previously unknown pyridinium ylides, indolizines, and other nitrogen-containing heterocycles [4-6]. These compounds are also of practical importance in their own right, due to the existence of compounds in these series which possess nonlinear optical and photochromic properties, as well as biological activity [7, 5].

Based on these considerations, it was of interest to us to investigate the dissociative ionization pathways of 4-benzoyl- and 4-benzylpyridines, in order to determine the structural and analytical possibilities of mass spectroscopy for these series of compounds. The mass spectra behavior of only two of the representatives of pyridine derivatives which are the subject of this study has been reported previously in the literature; they are 2,5-dimethyl-4-benzyl- and 2,5-dimethyl-4-p-tolylpyridine [8].

In the present paper we have examined the fragmentation patterns of sixteen 2,5-dimethyl-4-benzoyl- and 2,5-dimethyl-4-benzylpyridine derivatives and their deuteroanalogs (I-XVI):



I-IV V-XVI

I $R^1=R^2=R^3=H$ (if not noted further $R=H$); II $R^1=NO_2$; III $R^2=NO_2$; IV $R^3=NO_2$; V $R^5=CH_3$; VI $R^6=CH_3$; VII $R^4=NH_2$; VIII $R^4=ND_2$; IX $R^4=OH$; X $R^4=OD$; XI $R^4=Cl$; XII $R^4=NHCOCH_3$; XIII $R^4=NDCOCH_3$; XIV $R^4=NO_2$; XV $R^5=NO_2$; XVI $R^6=NO_2$

In the mass spectra of compounds I-XVI (Table 1), the molecular ion peaks (M^+) are either high or average intensity. In the case of benzoyl derivatives I-IV, the intensities of the M^+ peaks (W_M values) are 2-4 times lower than those of the benzyl derivatives V-XVI (Table 2). The presence of a nitro group in the ortho position of the benzoyl substituent (compound IV) decreases the value of W_M 1.5-2 times, compared to the W_M values for the para- and meta-nitro-substituted 4-benzoylpyridines II and III. The value of W_M in the mass spectra of 4-benzyl-

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TABLE 1. Mass Spectra of 2,5-Dimethyl-4-benzoyl- and 2,5-Dimethyl-4-benzylpyridines*

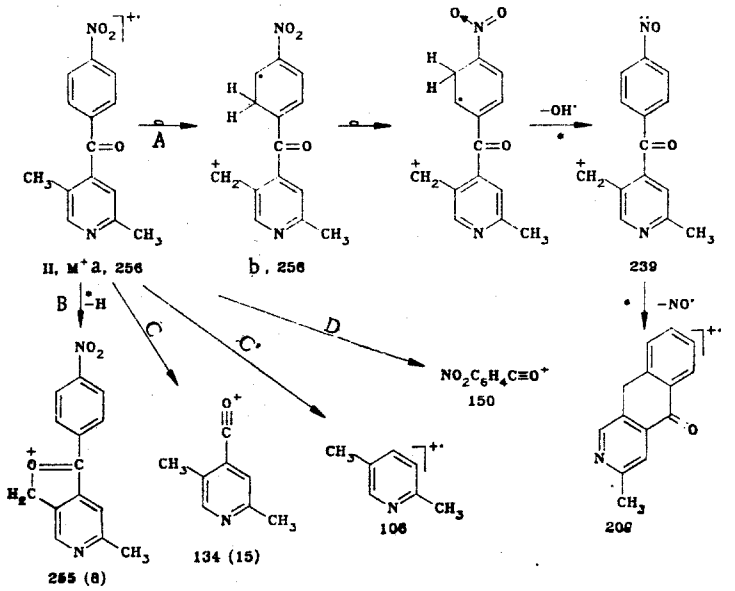
Compound	m/z Values (relative intensities of ion peaks as % of maximum)
I	211 (M^+, 42), 210 (48), 196 (12), 193 (12), 182 (14), 106 (22), 105 (86), 79 (14), 78 (16), 77 (100). $W_M=6$
II	256 (M^+, 40), 239 (81), 210 (56), 209 (100), 150 (40), 106 (38), 104 (45), 92 (21), 79 (31), 77 (46). $W_M=6$
III	256 (M^+, 55), 240 (19), 239 (100), 210 (60), 150 (57), 134 (24), 106 (53), 104 (42), 79 (33), 77 (42). $W_M=8$
IV	256 (M^+, 45), 239 (50), 211 (52), 210 (59), 209 (100), 181 (42), 180 (36), 150 (42), 106 (50), 77 (46). $W_M=4$
V	212 (16), 211 (M^+, 100), 210 (96), 196 (65), 195 (18), 194 (18), 181 (20), 105 (56), 91 (17), 77 (24). $W_M=16$
VI	211 (M^+, 70), 210 (34), 196 (100), 194 (20), 181 (38), 119 (20), 105 (80), 91 (26), 77 (27), 65 (22). $W_M=10$
VII	213 (14), 212 (M^+, 100), 211 (17), 197 (9), 195 (6), 120 (24), 119 (43), 106 (40), 93 (40), 77 (9). $W_M=32$
VIII	214 ($M_{D_2}^+$, 33), 213 (M_D^+, 92), 212 (M^+, 100), 120 (46), 119 (92), 108 (28), 107 (98), 106 (93), 94 (60), 93 (56). $W_M=20$
IX	214 (11), 213 (M^+, 75), 212 (16), 198 (15), 141 (8), 120 (14), 119 (100), 107 (36), 77 (14), 69 (15). $W_M=14$
X	214 (M_D^+, 43), 213 (M^+, 59), 212 (12), 199 (9), 198 (12), 120 (13), 119 (100), 108 (14), 107 (22), 69 (11). $W_M=16$
XI	231 (M^+, 30), 196 (22), 119 (100), 91 (20), 89 (21), 77 (55), 75 (21), 69 (27), 65 (30), 63 (59). $W_M=5$
XII	255 (14), 254 (M^+, 100), 212 (62), 211 (16), 195 (10), 120 (11), 119 (14), 106 (26), 93 (17), 77 (10). $W_M=21$
XIII	255 (M^+, 100), 254 (M^+, 57), 213 (68), 212 (45), 120 (26), 119 (40), 107 (38), 106 (22), 94 (35), 93 (20). $W_M=17$
XIV	243 (14), 242 (M^+, 100), 196 (26), 195 (15), 194 (12), 181 (13), 180 (10), 119 (19), 106 (12), 77 (10). $W_M=25$
XV	243 (15), 242 (M^+, 100), 225 (24), 209 (18), 196 (24), 195 (31), 194 (40), 180 (23), 106 (20), 77 (31). $W_M=15$
XVI	242 (M^+, 59), 225 (100), 210 (26), 195 (28), 194 (31), 152 (28), 106 (30), 92 (25), 77 (50), 65 (33). $W_M=5$

*The ten most intense ion peaks are given.

pyridines is a function of the character and position of functional groups located on the benzene ring. The value of W_M is 2-3 times greater for compounds containing NO_2, NH_2, and $NHCOCH_3$ substituents in the para-position of the benzene ring, relative to compounds which contain CH_3, OH, and Cl substituents in this position. In the transition from para- to meta- and ortho-nitrosubstituted 4-benzylpyridines, the stability of the molecular ion is lowered 1.7 and 7 times, respectively; this is due to the increased probability of loss of an OH radical from the molecular ion.

The formation of the main fragment peaks in the mass spectra of 4-benzoylpyridine derivatives I-IV is illustrated in Scheme 1 using compound II as an example. The most noticeable characteristic of the dissociative ionization of nitro derivatives II-IV is the elimination of an OH group from the M^+ molecular ion (Scheme 1, path A, Table 2). The appearance of intense $[M - OH]^+$ fragment ion peaks is unexpected in these compounds, since molecules of II-IV do not contain a substituent in the ortho position relative to the nitro group, which would be capable of exerting an ortho effect [9]. Loss of an OH radical therefore probably takes place via transfer of a hydrogen atom from the methyl group, found in position 5 of the pyridine ring, to the phenyl ring, followed by subsequent migration to the ortho position relative to the nitro group. An analogous mechanism for the appearance of $[M - OH]^+$ ion peaks has been observed previously in the dissociative ionization of nitrofluorenes [10], nitro-2(4)-azafluorenes [11], and nitrodiphenylmethanes [12]. The transfer of a hydrogen atom from the methyl group to the benzoyl fragment is thus based on their mutual ortho-orientation on the pyridine ring, and may be considered as an example of the ortho effect of these structural elements in the fragmentation of 2,5-dimethyl-4-benzoylpyridines.

The formation of $[M - H]^+$ fragments in the case of compounds I-IV probably occurs from both forms of the molecular ions, M^+,a and M^+,b (Scheme 1, path B). The loss of a hydrogen atom via path B is apparently accompanied by ring closure involving the resulting methylene group in position 5 and the oxygen atom of the benzoyl group. This type of mechanism for the elimination of a hydrogen atom is consistent with the sharp decrease in the intensity of the $[M - H]^+$ fragment peaks in the mass spectra of nitro-substituted derivatives II-IV; this is

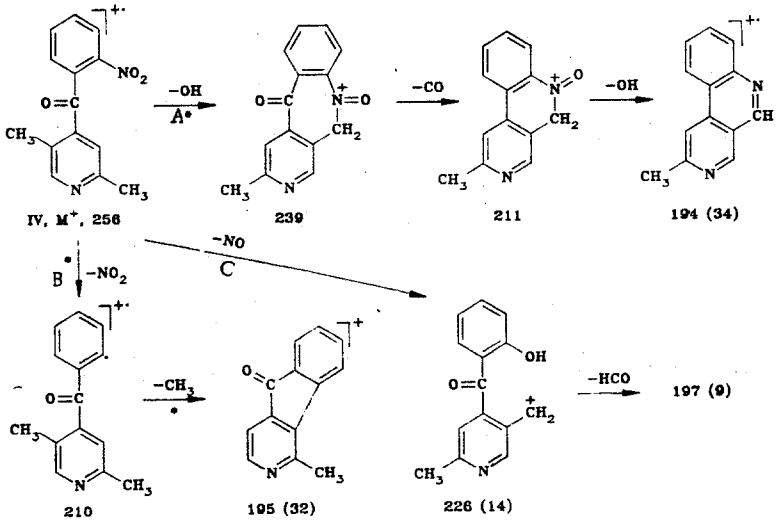


Scheme 1

*The intensities of fragment peaks (in % of maximum), which were not included in Table 1, are given in parentheses.

due to the competing fragmentation pathway involving ion M^+,b and loss of a hydrogen atom from it in the form of the OH radical (Scheme 1, path A).

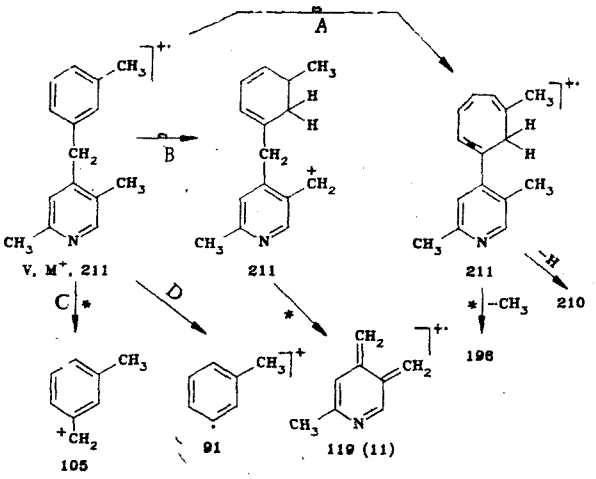
The presence of a nitro group in compound IV which is ortho to the carbonyl group is associated with the appearance of new paths for the fragmentation of M^+. The mass spectrum of IV exhibits successive cleavage of a CO molecule and OH radical from the $[M - OH]^+$ fragment ion (Scheme 2, path A). The $[M - NO_2]^+$ fragment at m/e 210 precedes, and seems to expose, cleavage of a CH_3 radical, which may be explained in terms of the formation of a bond between the pyridine $C_{(5)}$ and benzoyl $C_{(2)}$ carbon atoms (Scheme 2, path B); this is also associated with the ortho-orientation of the nitro group in the benzoyl substituent in compound IV. This structural factor probably also explains the formation of the $[M - NO, - HCO]^+$ ion at m/z 197; the latter is apparently formed as a result of loss of an HCO· particle from a phenolic hydroxyl group (Scheme 2, path C).



Scheme 2

Dissociative ionization of 4-benzoylpyridines I-IV also occurs via cleavage of the C–C bond between the carbonyl group and either the pyridine or benzene ring (Scheme 1, paths B,

B', and D); this is characteristic of the decomposition of other aromatic and heteroaromatic ketones as well [13, 14]. Cleavage of the bond between the carbonyl group and the pyridine ring appears to be the main fragmentation pathway for compound I, whereas for the nitro derivatives II-IV, elimination of an OH radical and subsequent loss of a molecule of NO is the dominant pathway for dissociative ionization. It should be emphasized that the probability of the formation of the $[M - OH]^+$ ion is the same for all three nitro isomers II-IV, although the stability of this ion differs for the three compounds, as evidenced by the ratio of $I_{[M - OH]^+}/I_{[M - OH, - NO]^+}$, which is equal to 0.8, 1.1, and 0.5 for compounds II, III, and IV, respectively. This difference may be exploited for the identification of different isomers.



Scheme 3

The appearance of the main fragment peaks in the mass spectra of the 4-benzylpyridine derivatives V-XVI can be explained based on the pathways shown in Scheme 3 using compound V as an example. The formation of intense peaks due to $[M - H]^+$ and $[M - CH_3]^+$ ions appears to be characteristic of the decomposition of methyl-substituted (on the benzene ring) benzylpyridines V and VI. These are probably formed as a result of expansion of either the benzene or pyridine rings to tropylium or azatropylium rings, respectively, which, in turn, is due to incorporation of the CH_2 group of the benzyl substituent fragment (Scheme 3, path A). This hypothesis is supported by the relatively large intensity of the $[M - H]^+$ ion peak in the mass spectrum of 4-benzylpyridine [15], compared to its intensity in 2,5-dimethyl-4-phenylpyridine [16], and also by the sharp decrease in the intensity of the $[M - H]^+$ and $[M - CH_3]^+$ fragment peaks in the presence of heteroatom-containing substituents on the benzene ring, such as in compounds VII-XVI.

2,5-Dimethyl-4-benzylpyridines V-XVI also exhibit an ortho effect between the benzyl functional group and a CH_3 radical located in the ortho position relative to the pyridine ring (Scheme 3, path B). In contrast to the decomposition of 2,5-dimethyl-4-benzoylpyridines I-IV, the effect leads to the appearance of rearranged fragment ions $[M - C_6H_5R]^+$ at m/z 119, rather than $[M - H]^+$ or $M - OH]^+$ fragments. The first observation of the formation of an analogous fragment ion was made by Meyerson in his study of the dissociative ionization of o-methyldiphenylmethane [17]. The probability of this type of fragmentation process is determined by the position and nature of the substituent attached to the benzyl functional group. The most intense $[M - C_6H_5R]^+$ ion peaks are observed in the mass spectra of compounds VII, IX, and XI (corresponding to 24, 16, and 11%, respectively, of the total ion current), which contain NH_2, OH, and Cl substituent groups, respectively, attached to the para position of the benzyl radical. The positive charge is always maintained on the pyridine fragment in this process. The amino derivative VII appears to be an exception to this trend. For the nitro derivatives XIV-XVI, the intensity of the peak due to the rearranged $[M - C_6H_5R]^+$ ion is equal to 4.6, 2, and 0.5% (relative to the total ion current), respectively, i.e., the intensity decreases in the order para > meta > ortho-isomer. In the case of methyl-substituted derivatives, the corresponding intensity for the para isomer [8] is 13.8%, and 1.8 (V) and 2.6% (VI) for the meta- and ortho-isomers. These observations reveal, therefore, that the most pronounced ortho effect is operative in the decomposition of para-substituted (on the benzene ring) derivatives.

TABLE 2. Intensities of Characteristic Ion Peaks (as % of total ion current) in the Mass Spectra of Compounds I-XVI*

Compound	M^+	$[M-H]^+$	$[M-CH_3]^+$	$[M-OH]^+$	$[M-NO_2]^+$	$[M-C_6H_5R]^+$	$[M-Ar]^+$	$[M-ArX]^+$	$[ArX]^+$
I	6	7,0	2,0	1,0	—	—	1,0	3,0	12,0
II	6	1,0	0.5	12,0	8,0	—	2,0	6,0	6,0
III	8	1,6	0,9	14,5	8,7	—	3,5	7,7	8,3
IV	4	0,8	0,6	4,4	5,2	—	1,6	4,4	3,7
V	16	15,4	10,4	—	—	1,8	—	1,8	9,0
VI	10	4,9	14,3	—	—	2,9	—	2,3	11,4
VII	32	5,4	2,9	—	—	13,7	7,7	12,7	12,7
VIII	20	3,4	1,8	—	—	8,6	5,8	8,0	8,0
IX	14	3	2,8	0,9	—	18,6	2,6	1,1	6,4
X	16	2,6	2,6	0,9	—	21,3	2,8	1,1	3,0
XI	5	0,8	0,5	—	$[M-Cl]^+$ 3,7	16,7	2,7	2,3	5,0
XII	21	0,6	0,6	—	—	2,9	2,3	5,5	—
XIII	17	0,5	0,3	—	—	6,8	4,4	3,7	—
XIV	25	2,3	1,0	0,5	6,5	4,8	1,5	3,0	—
XV	15	0,7	0,7	3,6	3,6	2,2	1,5	3,0	—
XVI	5	—	1,8	8,5	1,7	0,6	0,8	2,5	—

*X = CO for compounds I-IV, and X = CH_2 for compounds V-XVI.

In contrast to the mass spectra of the nitrobenzoylpyridines II-IV, the mass spectra of the nitrobenzylpyridine derivatives XIV-XVI exhibit large differences in the intensity of the $[M - OH]^+$ peaks for the para-, meta, and ortho-isomers (Table 2). One factor contributing to this may be the ease of cleavage of the Ar–CH_2 bond (Scheme 3, path B), which can occur either in synchrony with or following transfer of a hydrogen atom from the ortho-methyl group to the benzyl radical. This hypothesis is consistent with the observation that the intensity of the $[M - OH]^+$ ion peak is eight times greater in the mass spectrum of the meta-nitro isomer XV than in the mass spectrum of the para-nitro isomer XIV. The maximum intensity of the $[M - OH]^+$ fragment peak is found for the dissociative ionization of the ortho-nitro isomer XVI; this is readily explained in terms of the ortho effect of the methylene group of the benzyl radical and the NO_2 substituent, and is analogous to the fragmentation of o-nitrotoluene [18].

The fragmentation process of 4-benzylpyridines V-XVI also involves the appearance of ions corresponding to cleavage of the C–C bond between the benzyl radical and the pyridine ring (Scheme 3, path C), with the positive charge localized on the benzyl fragment. The chloro derivative XI is an exception to this observation; its mass spectrum shows the positive charge localized on both molecular fragments. Cleavage of the C–C bond between the benzene ring and the methylene group (Scheme 3, path D) takes place in the decomposition of the methyl derivatives V and VI. For this process, the positive charge is localized on the hydrocarbon fragment in the case of the methyl derivatives V and VI, and on the pyridinium portion of the molecule in the case of the amino derivative VII. Subsequent to cleavage of a ketene molecule, compound XII, which contains an acetylamino functional group, fragments along a pathway analogous to that of its synthetic precursor, compound VII. However, the relative intensities of the peaks due to the characteristic ions, at m/z 119, 106, and 93, are different in the mass spectra of these two compounds, which makes it easy to identify derivative XII, not only on the basis of the molecular ion peaks, but also using these fragment peaks. The mass spectra of the deuterated analogs VIII, X, and XIII confirm the existence of the decomposition pathways C and D.

Studies of the fragmentation of 2,5-dimethyl-4-benzoyl- and 2,5-dimethyl-4-benzylpyridines have demonstrated that the mass spectroscopic method permits the reliable differentiation of benzoyl and benzyl derivatives in these series of compounds, based on the characteristic appearance of the ortho effect between the CH_3 group in position 5 of the pyridine ring and the benzoyl or benzyl substituent in position 4. This method also permits the identification of methyl- and nitro-substituted isomers in this group of compounds, and can establish the presence of NH_2, OH, $NHCOCH_3$, Cl, and NO_2 substituents on the benzene ring.

EXPERIMENTAL

Mass spectra of compounds I-XVI were recorded on an MX-1303 serial apparatus, fitted with a system for direct introduction of the sample in an ion stream, at an ionizing energy

of 70 eV, and inlet temperatures of 70°C (V-XVI) and 80°C (I-IV). Compounds I-XVI were synthesized according to previously described methods [1-4]. Their purities were assessed by TLC, GLC, IR, PMR, and mass spectroscopy. Mass spectra of the deuteroanalogs VIII, X, and XIII were obtained under conditions of spontaneous deuterium exchange between compounds VII, IX, and XII in the vapor phase with CD_3OH vapor in the ionizing chamber of the mass spectrometer.

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QUATERNIZATION OF PYRIDINES WITH HALOADAMANTANES

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The quaternization of pyridine and its 3- and 4-derivatives with 1-haloadamantanes has been carried out in the presence of a small quantity of water in the pyridines.

The quaternization reaction of pyridines with alkyl halides is well known [1]. However, its use for quaternization of compounds with a halogen atom at the bridgehead has received virtually no study. It is known that under severe conditions 1-bromoadamantane reacts with pyridine [2], 4-methylpyridine and isoquinoline [3].

We have previously obtained adamantylpyridinium salts by a conjugated haloamination reaction of 1,3-dehydroadamantane and 3,7-dimethylenebicyclo[3.3.1]nonane [4, 5] and also by interaction of 3,7-dimethylenebicyclo[3.3.1]nonane with pyridine hydrochloride [6].

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