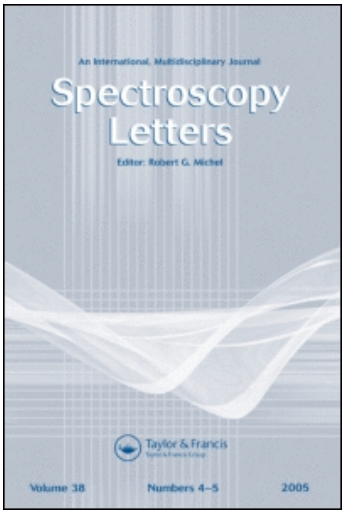

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Mass Spectral Studies of Biheteroaryls: Part 3. Identification of Dimeric Products Obtained from the Homolytic Methylation of the Lutidines

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MASS SPECTRAL STUDIES OF BIHETEROARYLS.
Part 3. IDENTIFICATION OF DIMERIC PRODUCTS OBTAINED FROM THE HOMOLYTIC METHYLATION OF THE LUTIDINES.[1]

KEY WORDS : Gas chromatography - mass spectrometry, homolytic methylation, dipyridylethanes, fragmentation.

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Abstract : The dimeric products formed during the homolytic methylation of the lutidines with t-butyl peroxide at 135° have been identified by gas chromatography - mass spectrometry. The 2,6- and 3,5- lutidines gave the corresponding dimethyldipyridylethanes whilst the 2,4-, 2,5- and 3,4- lutidines gave both the normal and crossed products.

In part 2,[1] the mass spectral fragmentation patterns of a series of dipyridylalkanes were studied as a pre-requisite for the utilisation of the gas chromatography - mass spectrometry (GC-MS) technique for the identification of the dimeric products obtained from the homolytic methylation of the lutidines.

During the homolytic methylation of an alkylated heteroaromatic compound, abstraction of a hydrogen from the methyl group can also occur to give a heteroaralkyl radical which may then dimerise to produce a diheteroarylalkane. Johnston and Williams[2] used reactions of t-butoxy and methyl radicals, generated from t-butyl peroxide to prepare the dipyridylethane dimers (2) and (3) from 3- and 4- picoline in good yield.

 0038-7010/85/1801-0035$3.50/0

$$Het - CH_2 - CH_2 - Het'$$

(1) Het = Het' = 2-Py

(2) Het = Het' = 3-Py

(3) Het = Het' = 4-Py

(4) Het = Het' = 6-Me-2-Py

(5) Het = Het' = 5-Me-3-Py

(6) Het = Het' = 4-Me-2-Py

(7) Het = Het' = 2-Me-4-Py

(8) Het = 4-Me-2-Py, Het' = 2-Me-4-Py

(9) Het = Het' = 5-Me-2-Py

(10) Het = Het' = 6-Me-3-Py

(11) Het = 5-Me-2-Py, Het' = 6-Me-3-Py

(12) Het = Het' = 4-Me-3-Py

(13) Het = Het' = 3-Me-4-Py

(14) Het = 4-Me-3-Py, Het' = 3-Me-4-Py

(15) Het = Het' = 2-quinolyl

(16) Het = 2-Py, Het' = 3-Py

(17) Het = 2-Py, Het' = 4-Py

Py = pyridyl (C_5H_4N)

Subsequently, Abramovich and Kenaschuk[3] also identified (3) from the methylation of 4-picoline with acetyl peroxide. Bass and Nababsing[4,5] later studied the homolytic methylation of the picolines with t-butyl peroxide and obtained the appropriate 1,2-dipyridylethanes in each case; (1) - (3) were also produced, together with the respective phenylethylpyridines, during the homolytic benzylation of the picolines with dibenzylmercury in non-acidic solution.

Much less attention has been focused upon the lutidine series; only those dimeric products from the symmetrical compounds have been charact-

erised to date. Bonnier, Court and Gelus[6] have undertaken a thorough examination of the homolytic phenylation of all the lutidine derivatives. In a subsequent paper,[7] the products from the reaction with 2,6-lutidine were separated by GC and amongst the dimeric compounds identified was 1,2-bis(6-methyl-2-pyridyl)ethane (4). Siv, Vernin and Metzger[8] studied the thermal decomposition of 3-(p-tolyl)-1-(3,4-dimethylisooxazol-5-yl)triazene in 3,5-lutidine and identified the dimer, 1,2-bis(5-methyl-3-pyridyl)ethane (5) as a product. Earlier Dou et al.[9] had noted that secondary products were formed during the homolytic benzylation of 3,5-lutidine in acidic solution, which were not investigated.

With an asymmetric lutidine more dimeric products of this type become possible. For example, in the reaction with 2,4-lutidine hydrogen abstraction would produce both the 4-methyl-2-pyridyl and 2-methyl-4-pyridyl radicals which may dimerise to give the "normal" dipyridylethanes (6) and (7) respectively. Furthermore, these radicals may also combine to produce the "crossed" product (8).

In the present work upon the identification of such dimeric compounds the products have been separated by GC and characterised by coupled MS. In our preliminary mass spectral study[1] it was shown that (1) fragmented through asymmetric cleavage whilst (2) and (3) exhibited symmetrical rupture. Before the detailed studies were started, pure synthesised samples of the known dipyridylethane dimers (4) and (5) obtained from the homolytic methylation of 2,6- and 3,5- lutidine were first examined to confirm that the above fragmentation rules functioned satisfactorily in the lutidine series. The identity of each dimer was initially verified by ^{1}H NMR spectroscopy.

Siv, Vernin and Metzger[8] have previously studied (5) in $CDCl_3$ solution at 90 MHz and reported the presence of five singlet signals. The compound has now been examined at 360 MHz ; at this higher field the aromatic signals appeared as a broadened triplet (actually a broadened doublet of doublets)

Table 1

Mass Spectral Results

m/z	A	B	C	D	E	F	G	H	J
39	6	4	9	8	10	11	7	6	6
41	3			5	13	20			
42					6	8			
43				12	15	18	10	10	
44				6	5	64	36	38	
45		6		16	5	60		22	8
46		3							
47		4							
49		12							
50		6							
51		3		5		6			
52					5				
53		4		6			5		
55					5	7			
56					5	9			
57					13	20			
58				8	7	12	6	6	
59				8	8	11	5	6	
65	8		11		8	6	8		
66	4		8		5		5		
67					7	8			
72						6			
73				12	12	16		8	
75						6			
77	7		8	20	11	11	18	29	14
78		3		6	5	7	6	6	7
79	3	10	5	13	10	12	9	8	17
81						7			
82		7							
86					6	10			
87				10	12	15		5	
88				7	6	8			
89				12	14	20		6	6

Table 1 (continued)

m/z	A	B	C	D	E	F	G	H	J
91		3			7	10			
92	8		11	5	7	6	5		
93	6		11		15	6	11		
94	5		5						
102				7	5	6			
103					6	11			
105	5		6		5	5			
106	5	100	9	100	10	40	22	100	100
107		10	13	13	7	13	6	21	23
108						6			
117		3				6			
118		7	5						
119	4	3	5	13	6	6			
120	100	7	100	5	80	12	40	6	
121	12		13		11				
131					5				
133					5	7			
147						6			
183					5				
196	4								
197	5		8	5	7	12	14		14
198					5				
209					5				
211	27		21	11	100	27	100	12	9
212	56	68	40	63	72	100	34	28	61
213	10	9	7	10	13	21	5	6	11

Compounds

A : (4)
B : (5)
C : GC peak 1
D : GC peak 2
E : GC peak 3
F : GC peak 4
G : GC peak 5
H : GC peak 6
J : GC peak 7

assigned to H-4 and as two broadened doublets for H-2/H-6. Definitive assignments were made by selective removal of long range benzylic couplings[10] by irradiation at the CH_2 and CH_3 frequencies respectively, to leave the signals as sharp doublets (J_{24} 2.2 Hz, J_{46} 2.0 Hz).

The NMR of (4) has previously been measured by Bonnier and Court[7] in acetone-d_6 solution, frequency not given but assumed to be 60 MHz. The H-3, H-4 and H-5 protons formed an AB_2 spin system similar to that observed for 2,6-lutidine.[11] Examination of this compound at 360 MHz in $CDCl_3$ solution produced a first order spectrum with a low field broadened triplet (J 7.7 Hz) for H-4. The H-3 and H-5 protons each appeared as broadened doublets which were coincident at 100 MHz and just separated (Δ = 0.02 p.p.m.) at 360 MHz. Attempts to make individual assignments by selective removal of benzylic couplings, however, were unsuccessful.

The MS of (4) and (5) are given in Table 1. Rupture of the central alkyl bridge by the two distinctive pathways previously demonstrated[1] was still the dominant pathway leading to the base peak in each case. These pathways were therefore independent of the additional methyl groups introduced ; indeed, loss of a methyl radical only occurred to a very limited extent. Such ejections took place from the main rupture fragments to give the ions at m/z 105 (5%) for (4) and at m/z 91 (3%) for (5). Loss of a methyl radical from the molecular ion of (4) also occurred to a small extent.

The homolytic methylation reactions of the lutidine derivatives were conducted by heating with t-butyl peroxide for 48 hours at 135° under nitrogen. The dimeric products were separated by GC on a Carbowax column temperature programmed between 140° and 235°, and then identified by coupled GC-MS. The reactions with 2,6- and 3,5- lutidine gave only a single dimeric product in each case, identified as (4) and (5) respectively by comparison with the MS of the synthesised samples. Since the dimeric products were eluted at the extreme end of the chromatograms (see Table 2) the intensity

Table 2

GC relative retention times and peak identifications (a)

Compound(s)	Relative retention time (b)	Peak Number
(1)	1.48	
(2)	2.08	
(3)	2.35	
(4)	1.44	1
(5)	2.29	2
(6) & (8)	1.92	3
(7)	2.12	4
(9) & (11)	2.02	5
(10)	2.17	6
(12),(13),(14)	2.60	7

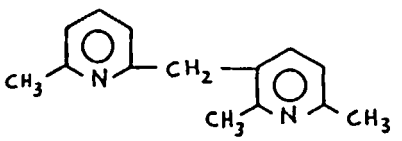
NOTES

(a) - 12.5% Carbowax 20M on Celite (72-85 mesh) temperature programmed between 140° and 235° at 3° per minute.

(b) - Relative to bibenzyl = 1.00. Bibenzyl elution time, ca. 20 minutes.

of the background signals was increased due to a degree of column bleed. (see Table 1, peaks 1 and 2)

Previously Bonnier and Court[7] identified the dimeric product (18) from the homolytic phenylation of 2,6-lutidine with benzoyl peroxide. The compound was separated by preparative GC on an asphalt column operated


(18)

isothermally at 260°. This product was not detected in the homolytic methylation of 2,6-lutidine with the chromatographic conditions used in the present work. It should perhaps be mentioned that certain features of the ^{1}H NMR spectral evidence[7] for this compound appears rather suspect, since two singlets for H-4 and H-4' were reported at 7.1 - 7.5 δ. It would be expected, however, that these protons should appear as a doublet (J 7 Hz), and as either a triplet (J 7 Hz) or as the A portion of an AB_2 spin system. The chemical shifts and integrals for the remaining protons were all in accordance with the proposed structure (18).[7]

From the reaction with 2,4-lutidine, two GC peaks attributable to dimeric products were obtained (see Table 2). The smaller peak (no. 4) has been identified as due to (7). (see Table 1) The molecular weight was 212, and symmetrical rupture of the alkyl bridge was consistent with a "normal" di-4-pyridylethane. The MS from the larger GC peak (no. 3) suggested the presence of (6), since there were large α-cleavage peaks at m/z 211 and m/z 120 present. Further inspection of the spectrum indicated that the $(M - 1)^+$ peak was considerably more intense than expected, as shown by the comparison of the respective intensities of the M^+ and $(M - 1)^+$ ions for various dipyridylalkanes given in Table 3. For the di-2-pyridylethane series the values of $\frac{M - 1}{M}$ were in the range 0.31 - 0.58 whilst for peak no. 3 the value was 1.39. This enhanced intensity suggests that a second component, whose MS has a prominent $(M - 1)^+$ fragment ion, must be present. Such large $(M - 1)^+$ ions has previously been shown[1] to be characteristic of "crossed" dipyridylethanes and dipyridylmethanes (see Table 3). Differentiation between these two classes of compound is possible by MS.[1] The dipyridylmethanes are particularly stable to electron impact and their secondary fragmentation processes involve the loss of the

Table 3

Relative intensities of M^+ and $(M - 1)^+$ ions
for some dipyridylalkanes and related compounds

Compound	Structural type (a)	$\frac{M-1}{M}$ (b)
(1)	2s	0.58 (c)
(15)	2s	0.31 (c)
(4)	2s	0.48
2-phenylethylpyridine	2s	1.16 (c)
GC peak no. 3 (d)	2s + 2as	1.39
GC peak no. 5 (d)	2s + 2as	2.94
2-benzylpyridine	1	4.35 (c)
(16)	2as	3.13 (c)

NOTES

(a) - 1 = methane, 2 = ethane
as = asymmetric ("crossed")
s = symmetric ("normal")

(b) - $\frac{M-1}{M} = \frac{\text{Intensity of } (M-1)^+ \text{ ion}}{\text{Intensity of } M^+ \text{ ion}}$

(c) - Data from reference 1.

(d) - See Table 2.

elements of HCN. In contrast, the "crossed" di-2,x-pyridylethanes do not suffer any initial loss of HCN but instead exhibit slight rupture of the central alkyl bridge to give small, but detectable, peaks for both the $PyCH_2^+$ and $PyCH_2CH_2^+$ ions. Inspection of the MS of GC peak no. 3 indicated that both β - and γ-cleavage ions were present but there was no evidence to indicate any significant loss of HCN from either the M^+ or $(M - 1)^+$ ion. The second component would therefore appear to be the "crossed" dimer (8).

Some evidence for the formation of "crossed" dipyridylalkanes is already available. From the photoalkylation of a mixture of 2- and 4-(hydroxymethyl)pyridine in acidic methanol solution, Stenberg and Travecedo[12] obtained (1), (3) and (17), the structure of the "crossed" product (17) was inferred by IR and NMR comparison with the other two isomeric dipyridylethanes.

The results from the reaction with 2,5-lutidine paralleled those from the 2,4-isomer. The larger GC peak (no. 5) represented a mixture of compounds (9) and (11). The smaller GC peak (no. 6) was due to compound (10), in this case the m/z 106 ion was of greater intensity than that for GC peak no. 4 (compound (7)) due to the enhanced stability of the appropriate azabenzyl cation.[13] The rest of the fragmentation patterns (see Table 1) of the peaks were generally quite similar except for variable contributions from background column bleed.

The final reaction studied was that with 3,4-lutidine. Despite various chromatographic conditions being attempted only one GC peak (no. 7) could be obtained in the dipyridylethane elution region. It is known that 3-alkyl- and 4-alkyl- pyridine derivatives are often difficult to separate.[14] GC peak no. 7 was considerably distorted which suggested that multiple components were present. Accordingly several MS were taken during elution of the peak, all of which were quite similar ; that given in Table 1 is for the scan made at the centre of the peak. The MS and GC peak shape is consistent with the probable presence of all possible dimers since both the "normal" compounds (12) and (13) and the "crossed" product (14) would all favour symmetric cleavage to produce the observed base peak at m/z 106. The very low intensity of the $(M - 1)^+$ ion ($\frac{M - 1}{M} = 0.15$) is also of interest. As already mentioned, such an ion would not be favoured by the "crossed" dimer (14), however, it should be a very prominent peak in the MS of any possible dipyridylmethane product, which shows these types of products to be absent.

The present work has shown that homolytic methylation of asymmetric lutidine derivatives additionally gives both "normal" and "crossed" dimethyldipyridylethanes as products. Final confirmation of certain individual compounds must wait until improved separation techniques become available.

EXPERIMENTAL

1,2-bis(6-methyl-2-pyridyl)ethane (4)

A solution of t-butyl peroxide (6 g.) in 2,6-lutidine (100 g.), under nitrogen, was heated under reflux in a xylene vapour bath for 72 hours. The low boiling products and the excess of 2,6-lutidine were removed by distillation through a fractionating column. The residue was distilled under reduced pressure to give (4) (3.2 g., 37%), b.p. 150-60°/5 mm. Recrystallisation from light petroleum gave colourless needles, m.p. 49-50°, lit.[15] m.p. 48-9°.

^{1}H NMR (360 MHz, $CDCl_3$, p.p.m. δ) : 2.50 (6H, s, CH_3); 3.12 (4H, s, CH_2); 6.89/6.91 (2H, 2H, bd, bd, J = 7.7 Hz, 7.7 Hz, H-3/H-5); 7.39 (2H, t, J = 7.7 Hz, H-4).

1,2-bis(5-methyl-3-pyridyl)ethane (5)

The procedure employed for the synthesis of (4) was used. Distillation of the residue gave (5) (4.0 g., 46%), b.p. 165-70°/1 mm. Recrystallisation from light petroleum gave colourless plates, m.p. 85-6°, lit.[8] m.p. 80°.

^{1}H NMR (360 MHz, $CDCl_3$, p.p.m. δ) : 2.26 (6H, s, CH_3); 2.83 (4H, s, CH_2); 7.20 (2H, dd, J_{24} = 2.2 Hz, J_{46} = 2.0 Hz, H-4), 8.18 (2H, d, J_{24} = 2.2 Hz, H-2), 8.24 (2H, d, J_{46} = 2.0 Hz, H-6).

Homolytic methylations of the lutidines

Solutions of t-butyl peroxide (0.365 g., 0.0025 mole) in the appropriate lutidine (5.35 g., 0.05 mole) were heated in an oil bath at 135° for 48 hours. The resultant solutions were analysed by GC (Pye 104 chromatograph, 5' column of 12.5% Carbowax 20M on Celite (72-85 mesh), temperature programmed from 140° to 235° at 3°/minute, nitrogen carrier gas flow rate

45 ml./minute) coupled to the MS (A.E.I. model MS902). All GC-MS measurements were performed by the Physico Chemical Measurements Unit, Harwell to whom we are indebted. Mass spectra are given in Table 1, intensities of ions above 3% of the base peak (5% for GC-MS determinations) only are shown, ions below m/z 39 are not included. GC relative retention times and peak identifications are shown in Table 2.

The ^{1}H NMR spectra were determined at the University of Edinburgh, courtesy of Dr. I. H. Sadler.

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