J. prakt. Chem. 338 (1996) 220–230

Journal für praktische Chemie
Chemiker-Zeitung

Aqueous High-Temperature Chemistry of Carbo- and Heterocycles: Part 24 [1].

First Demonstration of Specific C-C Bond Scission of the Pyridine Ring. Reactions of Piperidine, Pyridine and Some of Their Methyl Derivatives in Aqueous Formic Acid

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Received July 3rd, 1995 respectively November 6th, 1995

Abstract. In its reactions with the title compounds, formic acid variously acts as a formylating, methylating, and reducing agent. Both pyridine and piperidine are converted in significant amounts into 1-methyl-, 1-ethyl-, 1-propyl- and 1-pentyl-piperidines. Of the *N*-alkyl groups, isotopic labeling shows that only *N*-methyl derives from the formic acid, while the *N*-ethyl and *N*-propyl arise from heterocyclic ring C-C bond scission by retro-vinylogous-bis-aza-Aldol reactions. Detailed analysis of the products for pyridine, piperidine, and their 4-methyl derivatives, reacted separately and mixed, supports mechanisms in which a piperidine adds 1,2 to a pyridinium cation, or to a di- or tetra-hydropyridine, to initiate reaction sequences leading to the product slates found.

Introduction

Over the last 50 years, much evidence has accumulated that the common heterocycles can undergo (often reversibly) ring opening under a variety of conditions. However, all examples involve the scission of heteroatom-carbon bonds; the analogy has been made of heterocycles as carbon chains with heteroatoms as padlocks which enable opening by a suitable key. We now disclose the first examples of specific C–C-bond scission in the unactivated heterocyclic system of pyridine, and demonstrate how the long-studied industrially important processes by which pyridine rings are formed from C_1, C_2 and C_3 aldehydes are in principle reversible.

The work to be described had its origin in our extensive studies [1–3] of hydrodenitrogenation of heteroaromatic models of compounds found in fuel resource streams. In the course of this work we recently discovered that at 350 °C, aqueous formic acid induced not only the hydrogenation of the pyridine ring, but its scission [4]. We now report full details of this work and propose appropriate reaction mechanisms.

The gas chromatographic behavior (retention times) of all the compounds employed in this study (starting materials and products) are summarized in Table 1[1]. Tables 2, 3, and 4 contain the compiled mass spectral data for the analysis of the results. Further explanation of the Tables 2–4 is given in the Experimental Section. All the results from the aquathermolyses are collected in Table 5. The product yields (molar %) are represented in the same fashion as described in detail previously [7], and have been corrected with regard to their response factors [8]. Table 6 demonstrates the percentages of the various simple *N*-alkylpiperidines formed from pyridine and their 4-methyl derivatives, singly and admixed. Structures, and proposed mechanistic pathways for the formation of these products (which are justified later in this paper) are given in Schemes 1, and 4–8.

[1] Compounds **1–31** comprise starting materials and identified products and are numbered in order of their GC retention times (see Table 1). Structures numbered **101–147** refer to putative intermediates and generalized structures for the types of reactions postulated.

Table 1 Structure and identification of starting materials and products

no.	$t_{R\,(min)}$	structure	MW	eq wt	basis [a]	factor [b]
1	0.38	pentene	70	70	Table 2	0.97
2	0.40	3-methyl-1-pentene	84	84	Table 2	0.97
3	0.43	pentylamine	87	87	Table 2	0.72
4	0.45	piperidine	85	85	Table 2	0.72
5	0.47	pyridine	79	79	Table 2	0.84
6	0.53	1-(^{13}C)-methylpiperidine	100	100	Table 4	0.72
7	0.53	1-methylpiperidine	99	99	Table 2	0.72
8	0.67	4-methylpiperidine	99	99	Table 2	0.72
9	0.68	*N,N*-dimethylpentylamine	115	115	Table 4	0.38
10	0.72	1,4-dimethylpiperidine	113	113	Table 2	0.71
11	0.79	1-ethylpiperidine	113	113	Table 2	0.71
12	0.82	4-methylpyridine	93	93	Table 2	0.83
13	0.91	*N,N*-dimethyl-2-methylpentylamine	129	129	Table 4	0.71
14	1.05	1-ethyl-4-methylpiperidine	127	127	Table 4	0.71
15	1.22	1-propylpiperidine	127	127	Table 4	0.71
16	1.60	1-propyl-4-methylpiperidine	141	141	Table 4	0.70
17	1.68	1-butylpiperidine	141	141	Table 3	0.70
18	1.95	1-butyl-4-methylpiperidine	155	155	Table 4	0.70
19	2.60	1-(2-methylbutyl)piperidine	155	77.5	Table 4	0.70
20	2.84	1-pentylpiperidine	155	77.5	Table 3	0.70
21	2.95	1-(pent-4-en-yl)piperidine	153	76.5	Table 4	0.70
22	3.10	1-(^{13}C)-formylpiperidine	114	114	Table 4	0.38
23	3.10	1-formylpiperidine	113	113	Table 2	0.38
24	3.17	1-(3-methylpentyl)piperidine	169	84.5	Table 4	0.69
25	3.21	1-pentyl-4-methylpiperidine	169	84.5	Table 4	0.69
26	3.61	1-acetylpiperidine	127	127	Table 2	0.54
27	3.70	1-formyl-4-methylpiperidine	127	127	Table 4	0.38
28	3.76	1-(3-methylpentyl)-4-methylpiperidine	183	91.5	Table 4	0.69
29	4.43	1-(5-aminopentyl)piperidine	170	85	Table 4	0.45
30	4.59	1-acetyl-4-methylpiperidine	141	141	Table 4	0.54
31	5.94	1-(3-methyl-5-aminopentyl)-4-methylpiperidine	198	99	Table 4	0.44

[a] Identification Basis, see appropriate tables. [b] Response Factor, see ref. [8]

Results and Discussion

Piperidine (4). On heating with aqueous 49% HCOOH at 350 °C for 2 h, piperidine (**4**) was completely consumed (Table 5). The major product was 1-formylpiperidine (**23**, 93.9%) together with an appreciable amount of 1-methylpiperidine (**7**, 4.1%). However, 1-ethyl- (**11**, 0.3%), 1-propyl- (**15**, 0.8%) and 1-acetyl-piperidine (**26**, 0.8%) were all detected as minor products along with traces of 1-pentylpiperidine (**20**, 0.1%). After 8 h at 350 °C in 49% HCOOH, the yield of 1-formylpiperidine (**23**) was roughly halved (42.4%) and the aforementioned 1-alkylpiperidines, noticeably 1-pentylpiperidine (**20**, 19.3%) were all formed in larger amounts. It is clear that 1-formylpiperidine (**23**) initially formed is later converted into 1-methylpiperidine (**7**), and *via* deformylation into the other 1-alkylpiperidines.

Piperidine (4) plus 1-Pentene. The same reaction of piperidine was carried out in the presence of 1-pentene (1 equivalent) in 49% HCOOH at 350 °C for 2 h and gave the same slate of products as in the absence of pentene, i.e. 1-methyl-(**7**, 3.9%) and 1-formyl-piperidine (**23**, 94.9%), together with the same minor products. In particular, no significant increase in 1-pentylpiperidine (**20**) was found in this run, suggesting that olefins are not intermediates in these reactions.

1-Methylpiperidine (7). This compound showed a 46.2% conversion after just 0.5 h at 350 °C in 49% HCOOH. The major product was 1-formylpiperidine (**23**, 29.0%). This product is probably formed *via* the *N*-formylation of 1-methylpiperidine with subsequent elimination of a methyl cation probably assisted by the formate ion. Other products included piperidine (**4**, 1.8%), and small quantities of 1-ethyl- (**11**, 1.5%), 1-propyl- (**15**, 0.9%), 1-butyl- (**17**, 1.6%) and 1-pentylpiperidine (**20**, 3.7%). Extending the reaction time to 2 h yielded a similar product slate, although a higher conversion (52.1 %) was observed. The major product was again 1-formylpiperidine (**23**, 28.3%). The *N*-alkylpiperidines observed in the above reaction (350 °C, 0.5 h) were again seen here, but in increased amounts (see Table 5). Extending the reaction time further to 4 h, led to a 48.3% conversion, which is only slightly lower than that observed for the 2 h run. The major product here is again 1-formylpiperidine (**23**, 15.1%). However, it seems likely that during the extended time of this reac-

Table 2 Authentic compounds used as starting materials and for the identification of products

no.	compound	MW	[a]	purity (%)	*m/z* (% relative intensity)	ref [b] spectra #
1	pentene	70	A	100	70 (35); 55 (60);42 (100);41 (45); 39 (35)	331
2	3-methyl-l-pentene	84	A	100	84 (30); 69 (80); 55 (100); 41 (80)	741
3	pentylamine	87	A	99	87 (5); 70 (3); 55 (2); 42 (3); 30 (100)	921
4	piperidine	85	A	99	85 (55); 84 (100); 70 (10); 56 (40); 55 (45)	68011
5	pyridine	79	A	99	79 (60); 55 (20); 52 (100); 50 (60); 44 (70)	67826
7	l-methylpiperidine	99	A	100	99 (35); 98 (100); 84 (10); 70 (30); 58 (10)	68696
8	4-methylpiperidine	99	A	99	99 (60); 98 (95); 84 (40); 70 (10); 56 (100)	68691
9	*N,N*-dimethyl-pentylamine	115	S	100	115 (6); 58 (100); 44 (4); 42 (10)	[c]
10	1,4-dimethylpiperidine	113	A	100	113 (10); 112 (100); 98 (5); 70 (20)	80481
11	l-ethylpiperidine	113	A	99	113 (25); 112 (20); 98 (100); 84 (10)	3071
12	4-methylpyridine	93	A	100	93 (100); 66 (50); 65 (25); 51 (15)	68420
13	*N,N*-dimethyl-2-methylpentylamine	129	S	100	129 (5); 100 (5); 86 (10); 58 (100)	[c]
19	l-(2-methylbutyl)-piperidine	155	S	100	155 (7); 98 (100); 84 (10); 70 (6); 56(10)	[d]
23	l-formylpiperidine	113	A	99	113 (100); 112 (50); 103 (30); 98 (50)	3043
24	l-(3-methylpentyl)-piperidine	169	S	100	169 (3); 154 (9); 98 (100); 84 (5);70 (4)	[d]
26	l-acetylpiperidine	127	A	100	127 (100); 112 (20); 84 (45); 70 (25); 56 (30)	5077

[a]) A = Aldrich, S = synthesized authentic compound (see experimental section). [b]) Spectral numbers of the mass spectral data for the compounds found from a search of the Wiley/NBS Registry of Mass Spectral Data Base: F. W. McLafferty, D. B. Stauffer, 1989. This book is the combination of the revisions of the following two books and their database versions: Registry of Mass Spectra data by E. Stenhagen, S. Abrahamson and F. W. McLafferty and EPA/NIH Database by S. R.Heller, G. W. Milne and its two supplements. [c]) No literature MS data available. [d]) Novel compound.

Table 3 Identification of products by comparison of mass spectral fragmentation with literature data

no.	piperidine	MW	fragmentation found *m/z* (% rel intensity)	ref [a] spectra #	fragmentation reported [b] m/z(% rel intensity)
17	l-butyl-	141	141 (5); 98 (100); 55 (5); 42 (5)	8059	141 (5); 98 (100);55 (5);42 (5)
20	l-pentyl-	155	155 (5); 154 (10); 99 (5); 98 (100)	11568	155 (10); 154 (5); 99 (5); 98 (100)

[a]) Spectral numbers of the mass spectral data for the compounds found from a search of the Wiley/NBS Registry of Mass Spectral Data Base: F.W. McLafferty, D.B. Stauffer, 1989. To this book cp. [b]) in table 2. [b]) Mass spectral data obtained from authentic compound (see experimental section)

Table 4 Identification of products from mass spectral fragmentation patterns

no.	piperidine	MW	fragmentation pattern *m/z* (% rel. intensity, structure of fragment ion)
6	1-(^{13}C)-methyl-	100	100(75, M^+); 99(100, M–H); 71(25, M–Et); 70(10); 58(10, C_3H_8N); 43(30, C_2H_5N)
14	1-ethyl-4-methyl-	127	127(20, M^+); 112(M–CH_3); 84(20, $C_5H_{10}N^+$); 80(15); 70(40); 52(25); 42(60); 33(99)
15	l-propyl-	127	127(5, M^+); 126(20, M–H); 98(100, M–Et); 57(5, C_3H_7N)
16	1-propyl-4-methyl-	141	141(5, M^+); 112(100, M–Et); 70(25); 55(10); 44(30); 42(30)
18	1-butyl-4-methyl-	155	155(10, M^+); 112(100, M–Pr); 84(10); 70(35); 55(20); 44(60); 33(95)
21	1-(pent-4-en-l-yl)-	153	153(1, M^+); 98(100, M–C_4H_7); 84(4); 70(12)
22	1-(^{13}C)-formyl-	114	114(100, M^+); 113(35, M–H); 98(30, M–CH_4); 84(20, M–^{13}CHO); 70(15, M–C_3H_6)
25	1-pentyl-4-methyl-	169	169(5, M^+); 112(100, M–C_4H_9); 84(5); 70(30); 55(5); 44(30)
27	1-formyl-4-methyl-	127	128(100, M^+ + 1); 127(10, M^+); 126(5); 112(25, M–CH_3); 98(10, M–CHO); 84(10, $C_5H_{10}N^+$)
28	1-(3-methylpentyl)-4-methyl-	183	183(5, M^+); 112(100, M–C_5H_{11}); 70(25, M–$C_7H_{15}N$); 55(5); 44(20); 42(10); 41(15)
29	1-(5-aminopentyl)-	170	170(40, M^+); 140(10, M–CH_2=NH_2^+); 112(5); 98(100); 84(10); 70(20); 58(15); 41(15); 42(35)
30	1-acetyl-4-methyl-	141	142(100, M^+ + 1); 141(25, M^+); 140(10, M–H); 126(35, M–CH_3); 98(35, M–$COCH_3$); 84(30)
31	l-(3-methyl-5-amino-pentyl)-4-methyl-	198	198(15, M^+); 197(5); 196(15); 112(100); 70(15); 55(10); 44(20); 42(15); 41(20)

Table 5 Products obtained from 1-Methylpiperidine, 4-Methylpiperidine, 4-Methylpyridine and Pyridine. For names of compounds **1–31** see table 1. For mechanism (mech) see text.

		1-Methylpiperidine				4-Methylpiperidine				4-Methylpyridine			Piperidine			Pyridine		
additive						[a]	[b]			[c]					[d]			[e]
time (h)		0.5	2	4	8	2	2	2	8	2	2	6	2	8	2	2	4	2
no.	mech.																	
1														1.6				
3	iii													2.0				
4		1.8	4.1	5.8				0.4									0.5	
5							(25.6)[f]									84.0	40.3	68.6
6	i																	1.9
7	i	53.8	47.9	51.7	23.4		3.6				3.4		4.1	23.2	3.9	0.9	7.9	
9	iii			2.2	23.1													
10	i					27.5	2.7	13.7	38.0	14.9	0.4	18.2						
11	ii	1.5	4.8	9.0	23.3		0.5				2.4		0.3	0.9	0.6	2.3	2.4	1.5
12										40.4	41.1	35.4						
13	iii			0.4														
14	ii					0.1	1.1	0.4	6.9	1.4	0.4	2.8						
15	ii	0.9	2.1	2.4	14.9		0.7				0.3		0.8	2.4	0.5	3.6	6.6	2.1
16	ii						1.9	0.1	9.3		0.2	1.8						
17	ii	1.6	0.6	1.1	1.3						0.1							
18	ii								0.5	1.6	0.1	0.2						
19	ii						0.3							0.6			1.8	
20	iv	3.7	6.5	5.5	4.8		0.3				0.8		0.1	19.3	0.1	1.2	11.7	6.7
21	iv	6.3	1.2	0.5	0.7													
22	i																	19.2
23	i	29.0	28.3	15.1	2.4		11.9				33.8		93.9	42.4	94.9	8.0	24.6	
24	iv										0.3							
25	ii						2.3		0.6			1.3						
26	i	1.4	4.5	6.3	6.1						12.9		0.8	1.0			2.1	
27	i					70.1	46.5	83.1	33.3	36.5		30.1						
28	ii						0.5		7.0	5.1	3.0	9.7						
29	iii						0.6								0.1		2.1	
30	ii							1.3	3.3		0.8	0.7						
31	iii					2.3	1.5	1.0	1.1									

[a] Pyridine. [b] 3-Methyl-1-pentene. [c] Piperidine. [d] Pentene. [e] 100% $H^{13}COOH$. [f] Residue pyridine from additive

tion, some of the 1-formylpiperidine is reduced by hydride ion from the formic acid to return to 1-methylpiperidine (**7**) in view of the increased amounts of the same higher *N*-alkylpiperidines which were observed (see Table 5). On heating at 350 °C for 8 h with 49% HCOOH, 1-methylpiperidine (**7**) underwent a 76.6% conversion (Table 5). Again, there was a significant increase in the formation of *N*-alkylpiperidines which included 1-ethyl- (**11**, 23.3%), 1-propyl- (**15**, 14.9%), 1-butyl- (**17**, 1.3%), and 1-pentyl-piperidine (**20**, 4.8%). After 8 h, 1-formylpiperidine (**23**) was present only in a small amount (2.4%).

4-Methylpiperidine (8). This compound underwent complete conversion after 2 h (see Table 5) and the major products were 1,4-dimethylpiperidine (**10**, 27.5%), 1-formyl-4-methylpiperidine (**27**, 70.1%) and 1-(3-methyl-5-aminopentyl)-4-methylpiperidine (**31**, 2.3%). A trace amount of 1-ethyl-4-methylpiperidine (**14**, 0.1) was also seen. At 350 °C for 8 h in 49% HCOOH, 4-methylpiperidine (**8**) underwent a complete conversion to give 1,4-dimethylpiperidine (**10**, 38.0%), 1-formyl-4-methylpiperidine (**27**, 33.3%), together with smaller amounts of 1-ethyl-4-methyl- (**14**, 6.9%), 1-propyl-4-methyl- (**16**, 9.3%), 1-butyl-4-methyl- (**18**, 0.5%), 1-pentyl-4-methyl- (**25**, 0.6%) and 1-(3-methylpentyl)-4-methyl-piperidines (**28**, 7.0%). It will be demonstrated that the *N*-alkyl groups on the nitrogen-functionality are now derived from the 4-methylpiperidine (**8**) ring.

4-Methylpiperidine (8) plus 3-Methyl-1-pentene (2). This run was carried out to determine whether or not 3-methyl-1-pentene (**2**) is an intermediate in the formation of **28** from **8**. 4-Methylpiperidine (**8**) on heating with 49% HCOOH at 350 °C for 2 h, in the presence of one equivalent of 3-methyl-1-pentene (**2**), underwent a 100% conversion with the major products being 1,4-dimethylpiperidine (**10**, 13.7%) and 1-formyl-4-methylpiperidine (**27**, 83.1%). The product slate from this run (Table 5) suggests that 3-methyl-1-pentene (**2**) does

not play a significant role in the generation of the products, especially as 1-(3-methylpentyl)-4-methylpiperidine (**28**), was not seen in increased amounts.

Pyridine (5). Pyridine (**5**) on heating with 49% HCOOH at 350 °C for 2 h underwent a 16% conversion into 1-methyl- (**7**, 0.9%), 1-ethyl- (**11**, 2.3%), 1-propyl- (**15**, 3.6%), 1-pentyl- (**20**, 1.2%) and 1-formyl-piperidine (**23**, 8%) (Table 5). Heating in 49% HCOOH at 350 °C for 4 h, increased the conversion from 16% to 59.7% and produced all the foregoing products in much increased quantities, together with 1-acetylpiperidine (**26**, 2.1%), 1-(2-methylbutyl)piperidine (**19**, 1.8%) and 1-(5-aminopentyl)piperidine (**29**, 2.1%).

On heating in 100% $H^{13}COOH$ at 350 °C for 2 h, pyridine (**5**) showed a 31.5% conversion into a similar slate of products (but in increased amounts, probably facilitated by the use of 100% HCOOH – see Table 5) as seen for the run in 49% HCOOH at 350 °C for 2 h. Significantly, only the 1-methylpiperidine (**6**, 1.9%) and the 1-formylpiperidine (**22**, 19.2%) were labeled, and each contained just one ^{13}C label. The fact that 1-ethyl- (**11**, 1.5%), 1-propyl- (**15**, 2.1%), and 1-pentyl-piperidine (**20**, 6.7%) produced simultaneously had no ^{13}C labeled carbons shows conclusively that the ethyl, propyl and pentyl groups in **11**, **15** and **20**, respectively, are all derived completely from pyridine carbon atoms and not from carbons of the formic acid.

4-Methylpyridine (12). 4-Methylpyridine (**12**) on heating in 49% HCOOH at 350 °C for 2 h showed a 59.6% conversion into 1,4-dimethyl- (**10**, 14.9%), 1-formyl-4-methyl- (**27**, 36.5%) and 1-(3-methylpentyl)-4-methyl-piperidine (**28**, 5.1%) together with smaller amounts of 1-ethyl-4-methyl- (**14**, 1.4%) and 1-butyl-4-methyl-piperidine (**18**, 1.6%) (Table 5). Evidently the ethyl and butyl groups required for the *N*-alkylation of 4-methylpiperidine were derived by fragmentation of 4-methylpyridine molecules. 4-Methylpyridine (**12**) on heating in 49% HCOOH at 350 °C for 6 h underwent a 64.6% conversion to 1,4-dimethylpiperidine (**10**, 18.2%), 1-formyl-4-methylpiperidine (**27**, 30.1%), and 1-(3-methylpentyl)-4-methylpiperidine (**28**, 9.7%). Other products included small amounts of 1-ethyl- (**14**), 1-propyl- (**16**), 1-butyl- (**18**), 1-pentyl- (**25**) and 2-acetyl- (**30**) -4-methylpiperidines.

4-Methylpiperidine (8) plus Pyridine (5). To understand the types of intermediates involved in the C–C and C–N bond cleavages, we ran an aquathermolysis of 4-methylpiperidine (**8**) mixed with pyridine (**5**) (1 mole equivalent) in 49% HCOOH at 350 °C for 2 h (Table 5). 4-Methylpiperidine (**8**) underwent a 100% and pyridine a 74.6% conversion under these conditions. Various *N*-substituted piperidines (**7**, **11**, **15**, **19**, **20**, **23** and **29**) were formed together with the following *N*-substituted-4-methylpiperidines: 1,4-dimethyl- (**10**, 2.7%), 1-ethyl-4-methyl- (**14**, 1.1%), 1-propyl-4-methyl- (**16**, 1.9%), 1-pentyl-4-methyl- (**25**, 2.3%), 1-(3-methylpentyl)-4-methyl- (**28**, 0.5%), 1-(3-methyl-5-aminopentyl)-4-methyl- (**31**, 2.3%) and 1-formyl-4-methylpiperidine (**27**, 46.5%).

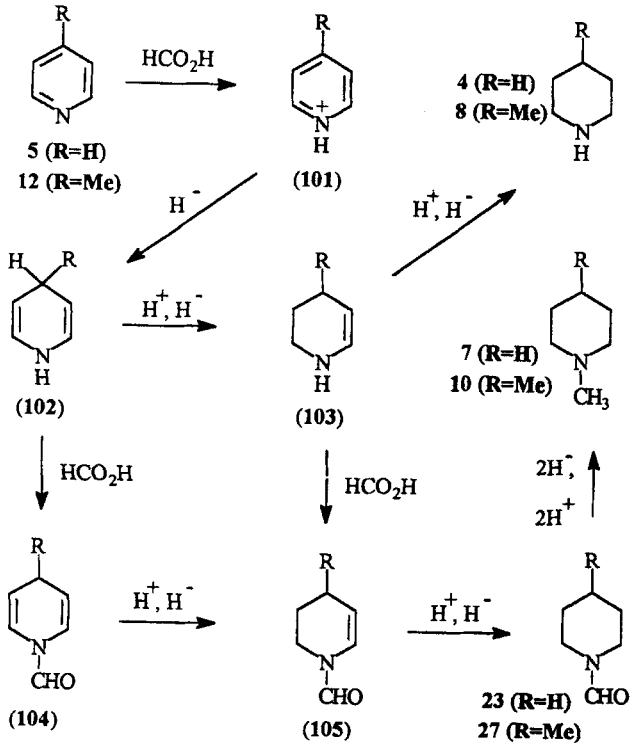
4-Methylpyridine (12) plus Piperidine (4). This reaction was carried out in order to compare the results with those obtained from the 4-methylpiperidine (**8**) plus pyridine (**5**) run. 4-Methylpyridine (**12**) showed a 58.9% conversion with 49% HCOOH at 350 °C for 2 h and the same slate of products was seen as in the case of 4-methylpiperidine (**8**) plus pyridine (**5**) (Table 5). The long list of products can be classified into two groups: (i) *N*-substituted piperidines (**7**, **11**, **15**, **17**, **20**, **23**, **24** and **26**) and (ii) 4-methyl-*N*-substituted piperidines (**10**, **14**, **16**, **18**, **28**, and **30**). No piperidine (**4**) or 4-methylpiperidine (**8**) (reduction product of 4-methylpyridine (**12**)) was left in the reaction mixture which indicates that they were completely consumed in further reactions.

The most striking feature of the results is that the products comprise a relatively small number of specifically *N*-substituted piperidines. The experiment using $H^{13}COOH$ shows conclusively that, apart from the *N*-methyl, all the other *N*-alkyl groups are formed from the ring carbon atoms. The fact that piperidine (**4**) forms a rather similar slate of products to that obtained from pyridine (**5**), indicates that an oxidizing agent is present that could be formic acid or more likely an immonium cation from 1-formylpiperidine (**23**). We believe that most of the products formed can be explained by four types of mechanistic routes:

(i) Conventional reactions where the formic acid is behaving as a hydride ion donor and as a formylating agent.
(ii) Retro-vinylogous-bis-aza-Aldol reactions of products formed by the addition of piperidines to dihydropyridines.
(iii) Simple ring-opening of amidine or aminal type intermediates formed by addition of piperidine to dihydro- or tetrahydropyridines followed by reduction.
(iv) Ring-opening of isomers of products formed by addition of piperidines to a quaternized pyridinium cation.

We now discuss each of these mechanistic pathways in turn.

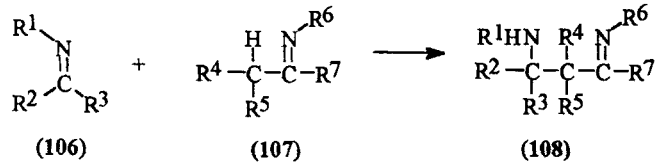
(i) **Conventional Formic Acid Reduction/Formylation.** Formic acid reductions of quaternary salts of pyridine and of 1-methylpyridinium cation to the corresponding fully hydrogenated products, *viz.* piperidine and 1-methylpiperidine (**7**), are well documented [9–12]. The mechanistic pathway [13, 14] to these compounds (Scheme 1) involves formic acid (or formate anion) donating hydride ion to the C-4 of the pyridinium cation **101** resulting in 1,4-dihydropyridine **102**.



Scheme 1

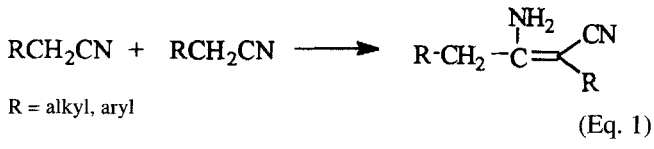
Further successive protonations and attacks of hydride ion at C-6 and C-2 yield piperidines **4** and **8**. Piperidine (**4**) undergoes formylation to 1-formylpiperidine (**23**) which is reduced to 1-methylpiperidine (**7**) in the presence of formic acid as shown in Scheme 1. In the same manner 4-methylpiperidine (**8**), formed from 4-methylpyridine (**12**), is converted successively into 1-formyl-4-methylpiperidine (**27**) and 1,4-dimethylpiperidine (**10**).

(ii) **Retro-vinylogous-bis-aza-Aldol Reaction Route.** The Aldol reaction [15] and its reverse, the retro-Aldol reaction [16], are among the most important reactions in organic chemistry. Mono-aza-Aldol reactions are also well known [17]. Although the self-condensation of nitriles (Equation 1) is a well known "name reaction" (Thorpe-reaction) [18] we have been unable to find any example of the similar self-condensation of imines which would constitute a bis-aza-Aldol reaction, i.e. a transformation of the type **106** → **107** → **108**. The retro-bis-aza-Aldol reaction, which should thus involve



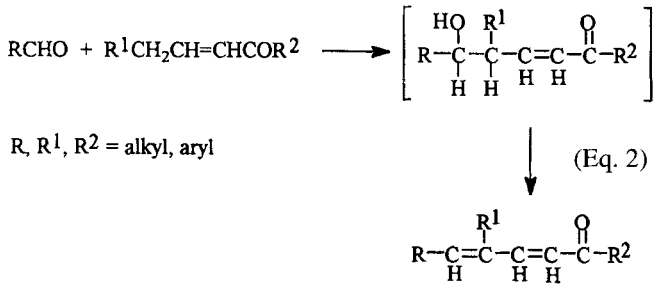
R^1 - R^7 = alkyl, aryl

Scheme 2



R = alkyl, aryl (Eq. 1)

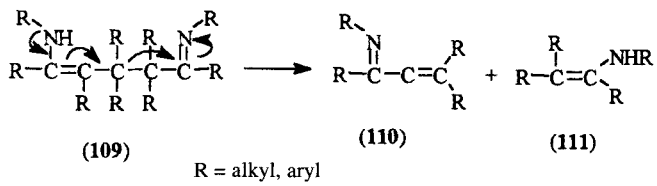
the fragmentation of a β-amino-imine (**108**) into two imines (**106** and **107**) also appears to be unknown (Scheme 2).



R, R^1, R^2 = alkyl, aryl (Eq. 2)

As regards vinylogs of the Aldol reaction, although the reactions of aldehydes at the γ-position of an α,β-unsaturated ketone (Equation 2) is well known [15], we have been unable to find any example when this reaction stops at the intermediate hydroxy compound.

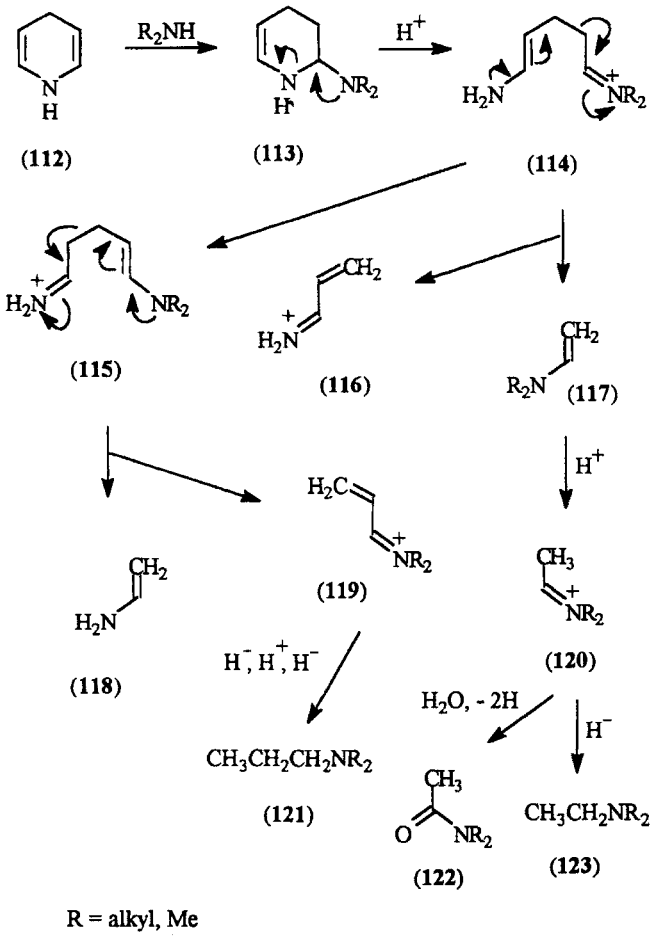
Aza analogs of vinylogous Aldol reactions also appear to be uninvestigated although such reactions are almost certainly involved in the commercially important preparation of pyridines from aliphatic aldehydes and ammonia (see later). Based on the previous arguments, δ-amino-γ,δ-unsaturated imines could be expected to undergo retro-vinylogous-bis-aza-Aldol (RVBAA) reactions *cf* **109** → **110** and **111**.



R = alkyl, aryl

Scheme 3

Compounds of type **109** are tautomers of δ-bis-imines, and the related cations (*cf.* **114**) are capable of formation by ring-opening of the addition products **113** of a secondary amine (R_2NH) to a 1,4-(or 5,6-) dihydropyridine **112**, see Scheme 4. The RVBAA reaction of **114** thus causes scission into protonated acrylaldehyde imine **116** and the *N*-vinyl derivative **117** of the original secondary amine. *N*-Vinyl compound **117** is rapidly converted by successive H^+ and H^- addition (both supplied by formic acid) into the corresponding *N*-ethyl derivative **123**. In addition, intermediate **114** can undergo proton loss and proton addition to give the isomeric δ-amino-γ,δ-unsaturated imine cation **115**. The RVBAA reaction of **115** affords vinylamine **118** and



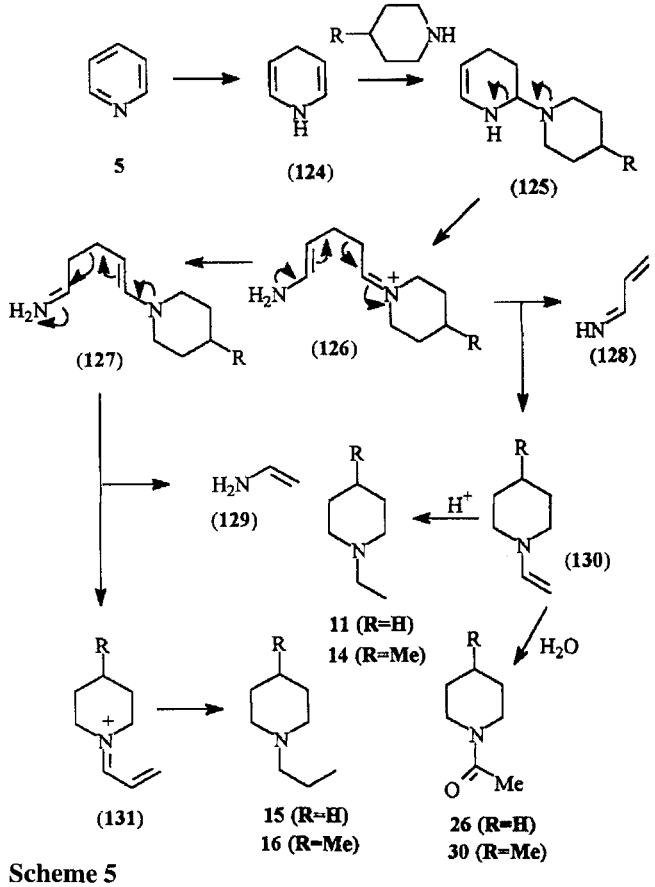
Scheme 4

the unsaturated imine cation **119,** the latter which is converted rapidly, by successive additions of H^-, H^+, and H^-, into the propyl derivative **121** of the original secondary amine. The acetyl derivative **122** can also be formed from **120** by hydration and oxidation and this variation corresponds to the experimentally found products **26** and **30**.

The formation of 1-ethyl- (**11**) and 1-propyl-piperidine (**15**) from the reaction of pyridine (**5**) (and of piperidine (**4**)) with formic acid are thus explained by the transformation of Scheme 5. Moreover, it would be expected that 4-methylpyridine (**12**) (and also 4-methylpiperidine (**8**)) would under similar conditions form 1-alkyl-4-methylpiperidines, as is observed experimentally.

Further evidence for the mechanism proposed can be derived from the selected data of Table 5 which have been abstracted into Table 6. This compares the amounts of the simple *N*-alkylpiperidines formed from piperidine (**4**), 4-methylpiperidine (**8**), pyridine (**5**), and 4-methylpyridine (**12**) alone with those from the two mixed runs. Table 6 demonstrates very clearly that the products expected from the mechanistic routes discussed, and only the expected products are formed in the runs from a single substrate.

Furthermore, Table 6 provides good evidence for the mechanism postulated from the nature, and the proportions of the products formed in the mixed runs. Thus, when 4-methylpiperidine (**8**) and pyridine (**5**) reacted together, the 4-methylpiperidine (**8**) predominately provided the ring component of the piperidines formed (compare 3.5% to 1.5%; Entries xii and xi respectively), whereas pyridine predominately provided the piperidine *N*-alkyl substituent (compare 2.9% to 0.5%; entries xiii and xiv respectively). Conversely, when a mixture of piperidine (**4**) and 4-methylpyridine (**12**) reacted a total of 3.9% of products formed was derived from piperidine (**4**) reacting as the amine HNR_2, compared with 3.7% from the 4-methylpyridine (**12**) reacting as HNR_2. Again, the *N*-alkyl groups of the piperidine products were formed 1.3% from the starting piperidine and 3.5% from the 4-methylpyridine. This is in good agreement with the mechanism proposed in Scheme 5 in which the saturated secondary amine adds to a dihydropyridine in a key step.



Scheme 5

(iii) **Addition to 2,3,4,5-Tetrahydropyridinium Cations.** A simpler sequence of addition of R_2NH to 2,3,4,5-tetrahydropyridinium ring **132** followed by ring-

Table 6 Comparison of the percentages of some of the N-Alkylpiperidines formed from Pyridine (Py) and Piperidine (Pip) and their 4-Methyl derivatives, singly and admixed in 49% HCOOH at 350 °C for 2 h

entry	no.	piperidine product substituent	origin of [a] ring	N-alkyl	4-MePy	Pip	4-MePy + Pip	4-MePip + Py	4-MePip	Py
i	**11**	1-ethyl-	H	Either	—	0.3	2.4	0.5	—	2.3
ii	**14**	1-ethyl-4-methyl-	Me	Either	1.4	—	0.4	1.1	0.1	—
iii	**15**	1-propyl-	H	H	—	0.8	0.3	0.7	—	3.6
iv	**16**	1-propyl-4-methyl-	Me	H	—	—	0.2	1.9	—	—
v	**17**	1-butyl-	H	Me	—	—	0.1	—	—	—
vi	**18**	1-butyl-4-methyl-	Me	Me	1.6	—	0.1	—	—	—
vii	**20**	1-pentyl-	H	H	—	0.1	0.8	0.3	—	1.2
viii	**24**	1-(3-methylpentyl)-	H	Me	—	—	0.3	—	—	—
ix	**25**	*N*-pentyl-4-methyl-	Me	H	—	—	—	2.3	—	—
x	**28**	1-(3-methylpentyl)-4-methyl-	Me	Me	5.1	—	0.3	0.5	—	—
xi	**11, 15, 17, 20, 24** total		H	Either	0	1.2	3.9	1.5	0	7.1
xii	**14, 16, 18, 25, 28** total		Me	Either	8.1	0	3.7	3.5	0.1	0
xiii	**15, 16, 20, 25** total		Either	H	0	0.9	1.3	2.9	0	4.8
xiv	**17, 18, 24, 28** total		Either	Me	6.7	0	3.5	0.5	0	0

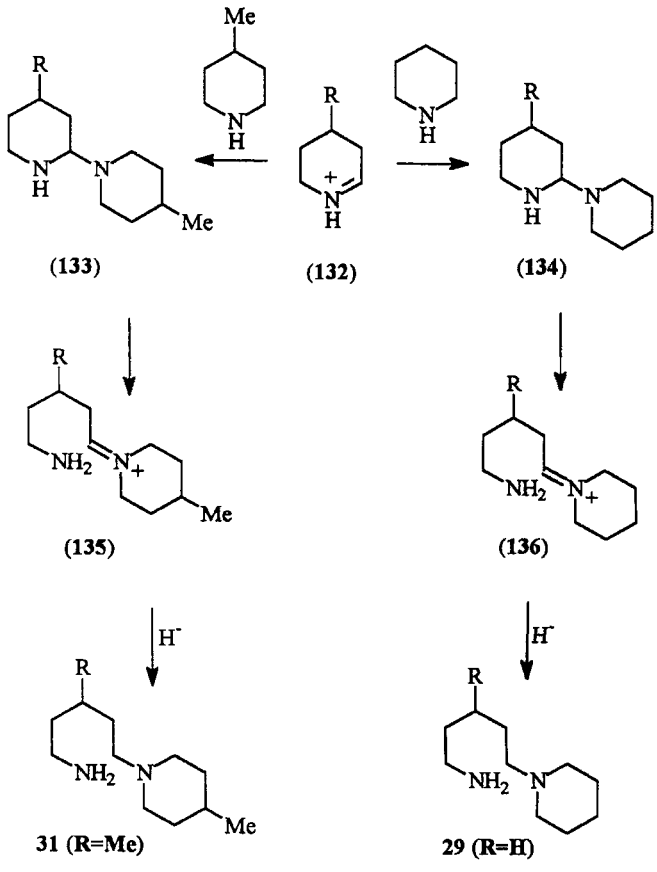
[a]) H is from Py or Pip; Me is from 4-MePy or 4-MePip.

opening and reduction leads to amines of type $R_2N(CH_2)_5NH_2$ and this explains the formation of **29** and **31** (Scheme 6).

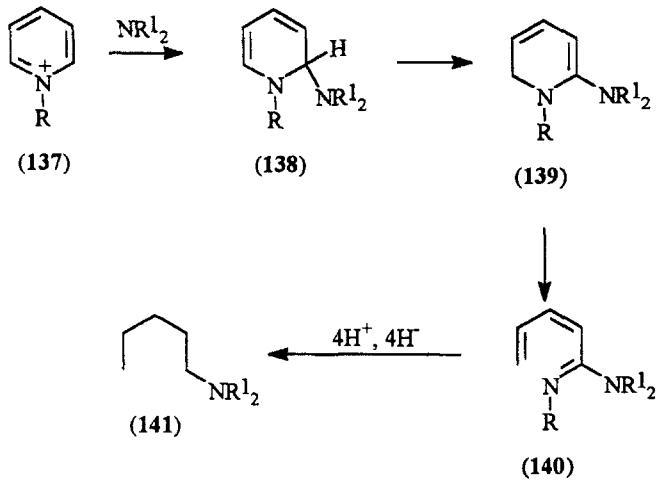
(iv) **Ring Opening of Isomers of Products of Addition of Piperidines to Quaternized Pyridines.** Addition of a secondary amine to quaternized pyridine **137** will give addition product **138** (see Scheme 7). We postulate that a 1,5-hydrogen shift in **138** leads to **139** which can undergo electrocyclic ring-opening to **140**. Next four successive protonations, each followed by a hydride ion addition, converts **140** into the saturated product **141**. We believe mechanisms of these types to be involved in the formation of products **20**, **24**, **25**, **28**, and **29** (Scheme 8).

Conclusions

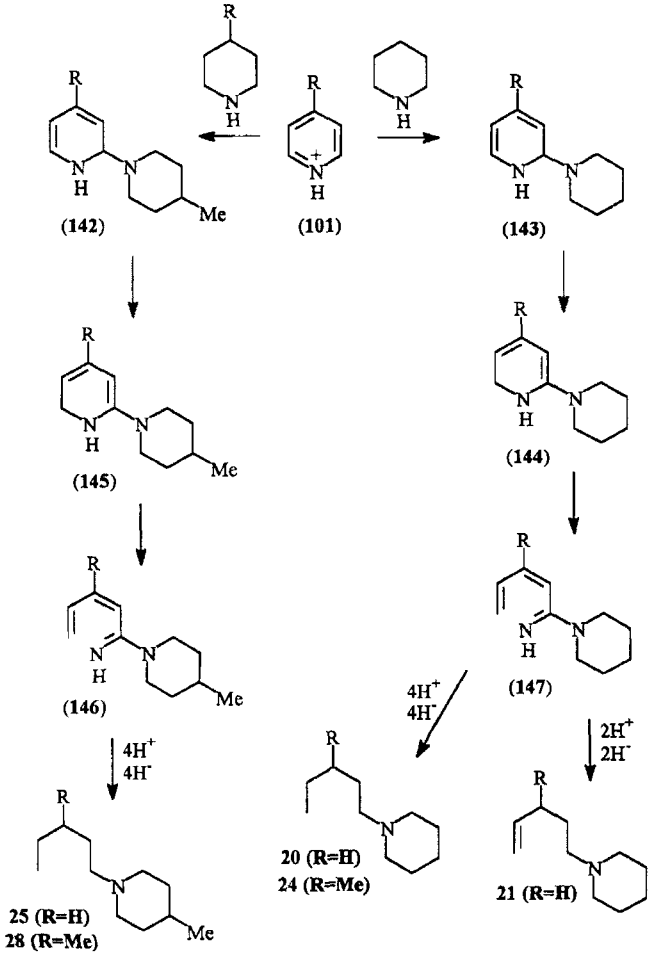
It has been shown that formic acid at 350 °C converts pyridine and piperidine into a well defined mixture of specific *N*-alkylpiperidines. 4-Methylpyridine and 4-methylpiperidine are similarly converted into the corresponding *N*-alkyl-4-methylpiperidines. It has been demonstrated that all the *N*-alkyl groups (except for *N*-methyl) arise from a second molecule of the heterocyclic ring compound and not from the formic acid. The formation of all products can be rationalized by addition of a piperidine molecule to a pyridine or di- or tetra-hydropyridine analog. Evidence is addressed that C–C bond fission occurs by retro-vinylogous-bis-aza-Aldol reactions. These unique C–C bond fissions show for the first time that heterocyclic rings are susceptible to opening other than at the heteroatoms. Many of the reactions proposed in the present work are the reverse of the commercially important pyridine ring-forming reaction from aldehydes and ammonia, and should help in better understanding of the latter.



Scheme 6



Scheme 7



Scheme 8

Experimental

^{1}H-NMR spectra were recorded on a 300 MHz Varian XL300 spectrometer. ^{13}C-NMR spectra were recorded at 75 MHz on the same spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) as the internal standard. Coupling constants (*J* values) are reported in Hz. All Grignard reactions were run under an inert atmosphere using oven dried apparatus. Solvents and anhydrous liquid reagents were dried prior to use: diethyl ether was distilled over sodium benzophenone ketyl. Analytical thin layer chromatography (TLC) was perfomed using pre-coated silica gel 60 F_{254} plastic plates (0.2 mm thick) with iodine as indicator.

1-(Piperidinomethyl)benzotriazole was prepared by applying the literature procedure [5]. The product obtained was washed with EtOH (25 ml) to yield a white solid (8.58 g, 94%) which was pure by ^{1}H-NMR, and used in subsequent reactions: m.p. 88–90 °C (lit [19] m.p. 92.5–93.5 °C).

1-(N,N-Dimethylaminomethyl)benzotriazole was prepared according to the literature procedure [6]. Crystallization of the crude product was induced by cooling the mixture to −18 °C. The crude white solid was filtered and washed with EtOH (20 ml). Recrystallization from ethanol yielded white prisms (14.5 g, 82%), m.p. 95–97 °C (lit [20] m.p. 99–100.5 °C).

General Procedure for the Synthesis of *N*-Alkylpiperidines: Representative Procedure for 1-(2-Methylbutyl)-piperidine (19)

Mg metal (1.66 g, 69.16 mmol) was suspended with an iodine chip in Et_2O (20 ml). 2-Bromobutane (9.5 g, 69.4 mmol) was dissolved in Et_2O (50 ml) and added dropwise to the Mg. After the addition was completed, the mixture was heated under reflux and stirred for 0.5 h. 1-(Piperidinomethyl)benzotriazole (5.0 g, 23.0 mmol) was then added *via* a Soxhlet extractor. The reaction was then stirred and refluxed for 18 h. The reaction was cooled and quenched with a minimal amount of water (2 ml). The bulk of the Et_2O was decanted from the solid and the remainder filtered through celite. The Et_2O was dried ($MgSO_4$) and removed *in vacuo* to yield a crude yellow oil, which was purified by Kugelrohr distillation. A colorless oil (2.20 g, 62%) was isolated, b.p. 65 °C/0.65 mm Hg, ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C, TMS) δ = 0.80 (d, *J* = 8.0 Hz, 3H, CH_3), 0.90 (t, *J* = 8.0 Hz, 3H, CH_3), 1.00–1.10 (m, 1H, CH), 1.30–1.50 (m, 4H, $2CH_2$ [ring]), 1.50–1.60 (quintet, *J* = 8.0 Hz, 4H, CH_2 [ring]), 1.97–2.13 (dd, *J* = 6.0, 8.0 Hz, 2H, CH_2N [aliphatic]), 2.20–2.40 (br m, 4H, CH_2N [ring]); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C, TMS) δ = 11.34, 17.90, 24.63, 26.09, 27.89, 31.98, 55.11, 66.35; HRMS calcd. for $C_{10}H_{21}N$: 155.1674 (M^+), found 155.1666.

1-(3-Methylpentyl)piperidine (24)

This product was obtained as a crude yellow oil and was purified by Kugelrohr distillation to give a colorless oil (3.00 g, 76%), b.p. 75 °C/0.75 mmHg: ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C, TMS) δ = 0.75–0.90 (d + t, *J* = 8.0 Hz, 6H, $2CH_3$), 1.08–1.20 (quintet, *J* = 8.0 Hz, 1H, CH), 1.20–1.35 (m, 4H, $2CH_2$ [aliphatic]), 1.35–1.48 (m, 2H, CH_2 [ring]), 1.5–1.51

(quintet, J = 8.0 Hz, 4H, $2CH_2$ [ring]), 2.20–2.30 (m, 2H, CH_2N [aliphatic]), 2.3–2.4 (br s, 4H, CH_2N [ring]); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C, TMS) δ = 11.24, 19.29, 24.49, 25.96, 29.60, 33.25, 33.53, 54.70; HRMS calcd for $C_{11}H_{23}N$: 169.1830 (M^+), found 169.1827.

General Procedure for the Synthesis of Acyclic Amines: Representative Procedure for *N,N*-Dimethylpentylamine (9)

Butyl bromide (11.68 g, 85.2 mmol) was dissolved in Et_2O (65 ml) and added dropwise to Mg metal (2.05 g, 85.2 mmol) in the presence of an iodine chip. After the addition was complete, the mixture was heated under gentle reflux and stirred for 0.5 h. Then 1-(*N,N*-dimethylaminomethyl)-benzotriazole (5.0 g, 28.4 mmol) was added by Soxhlet extractor. The mixture was stirred and refluxed for 18 h. The reaction mixture was cooled and aqueous NaOH (30 ml) was added. The bulk of the Et_2O was decanted from the solid and the remainder filtered through celite, dried ($MgSO_4$) and concentrated *in vacuo* to give a crude yellow oil – GC yield 79%. The crude product was purified by Kugelrohr distillation to give a colorless oil (27%), b.p. 55 °C/0.9 mm Hg (lit [21] b.p. 122–123 °C/760 mmHg): ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C, TMS) δ = 0.90 (t, J = 6.0 Hz, 3H, CH_3), 1.50–1.60 (m, 6H, $3CH_2$), 2.20 (s, 6H, $2CH_3N$), 2.30 (d, J = 6.0 Hz, 2H, CH_2N); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C, TMS) δ = 13.93, 22.53, 27.11, 29.62, 45.21, 59.76; HRMS calcd. for $C_7H_{17}N$: 115.1361 (M^+), found 115.1364.

N,N-Dimethyl-2-methylpentylamine (13)

This product was obtained crude as a yellow oil which was purified by Kugelrohr distillation to give a colorless oil (1.02 g, 28%), b.p. 75 °C/2 mmHg (lit [22] b.p. 134 °C/760 mmHg). ^{1}H-NMR (300 MHz, $CDCl_3$, 25 °C, TMS) δ = 0.7–0.83 (t, J = 6.0 Hz, 3H, CH_3 [terminal]), 0.88 (d, J = 6.0 Hz, 3H, CH_3), 1.02–1.14 (q, J = 6.0 Hz, 1H, CH_a), 1.22 (d, J = 6.0 Hz, 1H, CH_b), 1.30–1.40 (m, 2H, CH_2), 1.7–1.82 (m, 1H, CH [CH_3]), 2.32–2.38 (dd, J = 6.0, 6.0 Hz, 2H, CH_2N), 2.44 (s, 6H, $2CH_3N$); ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C, TMS) δ = 14.34, 18.19, 20.08, 30.77, 37.77, 45.92, 67.35; HRMS calcd. for $C_8H_{19}N$: 129.1517 (M^+), found 129.1529.

Aquathermolysis: General

All starting materials were checked by GC prior to use; where necessary they were purified to >98%. Aqueous 49% formic acid was deoxygenated with argon for 1 h prior to use. The model compound (0.45 g) and the formic acid (3.16 ml) were charged into a nitrogen-blanketed 1" Swagelok stainless steel bomb (plug and cap) which was then sealed. The reactor was then kept, without agitation, in a fluidized sand bath (model SBS-4) set at 350 °C using a Techne temperature controller (TC-8D) for the specified time period. The temperature profile was measured by a Barnant 115 thermocouple thermometer (type J) placed in the sandbath adjacent to the reaction vessel. After the reaction period, the reactor was immediately cooled with a stream of cold air and then quenched in dry ice. The reaction mixture was then worked up as previously described [7], and subjected to GC analyses on a Hewlett Packard 5890 instrument (flame ionization detector, [FID]) with a 15 m capillary column (SPB-1) and a temperature program of 10 °C/min from 50–250 °C. GC/MS analyses of all compounds were performed on a Varian 3400 gas chromatograph and a Finnigan MAT 700 ion trap detector.

Product Identification

The GC behavior of all the compounds in the present paper (starting material and products) are collated in Table 1 (in the format as explained in earlier papers [8]). Within the reaction mixtures, the identities of all the starting materials and some of their reaction products (**1–5**, **7–13**, **19**, **23**, **24**, **26**) were confirmed by direct comparisons of retention times and mass spectral fragmentation patterns with those of the authentic compounds, under essentially the same mass spectral operating conditions. Table 2 records the major features of the mass spectra together with a literature reference to the MS of the compounds (where available). Table 3 records the mass spectral fragmentation patterns of products **17** and **20** which were identified by comparison with published MS data. In such cases the source of the reference spectrum is always given and the major features of both the experimental and the reference spectrum are recorded. Table 4 records the MS patterns of products **6**, **14–16**, **18**, **21**, **22**, **25**, **27–31** for which no published MS data could be found. These products were assigned from their MS fragmentation patterns, together with a consideration of the reaction conditions, starting materials, and a reasonable mechanistic pathway for their formation from the starting materials. Also, the mass spectral fragmentation patterns for the synthesized compounds (see experimental section) **9**, **13**, **19**, and **24** are represented.

Acknowledgements. We thank Dr. Gopal H. Singhal, Mr. Glenn Brons and Mr. David T. Ferrughelli for their help in the initial phases of this work. We thank Dr. Steven M. Allin and Dr. David H. Powell for helpful discussions.

References

[1] A. R. Katritzky, R. A. Barcock, M. Siskin, W. N. Olmstead, Energy & Fuels **8** (1994) 990

[2] A. R. Katritzky, A. R. Lapucha, M. Siskin, Energy & Fuels **6** (1992) 439

[3] A. R. Katritzky, F. J. Luxem, R. Murugan, J. V. Greenhill, M. Siskin, Energy & Fuels **6** (1992) 450

[4] M. Siskin, A. R. Katritzky, M. Balasubramanian, D. T. Ferrughelli, G. Brons, G. H. Singhal, Tetrahedron Lett. **34** (1993) 4739

[5] A. R. Katritzky, S. Rachwal, B. Rachwal, J. Chem. Soc., Perkin Trans. **1987**, 799

[6] A. R. Katritzky, S. Rachwal, B. Rachwal, P. J. Steel, J. Org. Chem. **57** (1992) 4932

[7] A. R. Katritzky, A. R. Lapucha, R. Murugan, F. J. Luxem, M. Siskin, G. Brons, Energy & Fuels **4** (1990) 493

[8] G. Musumarra, D. Pisano, A. R. Katritzky, A. R. Lapucha, F. J. Luxem, R. Murugan, M. Siskin, G. Brons, Tetrahedron Comp. Method. **2** (1989) 17; A. R. Katritzky, E. S. Ignatchenko, R. A. Barcock, V. S. Lobanow, Anal. Chem. **66** (1994) 1799

[9] A. N. Kost, L. G. Yudin, Zh. Obshch. Khim. **25** (1955) 1947, Chem. Abstr. **50** (1956) 8644
[10] L. G. Yudin, A. N. Kost, Yu. A. Berlin, A. E. Shipov, Zh. Obshch. Khim. **27** (1957) 3021, Chem. Abstr. **52** (1958) 8142
[11] O. Cervinka, O. Kriz, Collect. Czech. Chem. Commun. **30** (1965) 1700, Chem. Abstr. **63** (1965) 1764
[12] O. Cervinka, Chem. Listy **59** (1965) 1058, Chem. Abstr. **63** (1965) 14807
[13] R. Lukes, Collect. Czech. Chem. Commun. **10** (1938) 66, Chem. Abstr. **32** (1938) 3764
[14] R. Lukes, Collect. Czech. Chem. Commun. **12** (1947) 71, Chem. Abstr. **41** (1947) 4150
[15] A. T. Nielsen and W. J. Houlihan in *Organic Reactions*; R. Adams, A. H. Blatt, V. Boekelheide, T. L. Cairns, D.J. Cram, H. O. House, eds; John Wiley and Sons: New York, **16** (1968) 1
[16] C. Thebtaranonth, Y. Thebtaranonth in *The Chemistry of Enones*; S. Patai, Z. Rappoport, eds; John Wiley & Sons: New York, 1989, 99
[17] G. Wittig, H. Reiff, Angew. Chem., Int. Ed. Engl. **7** (1968) 7
[18] E. F. J. Atkinson, J. F. Thorpe, J. Chem. Soc. **89** (1906) 1906
[19] G. B. Bachman, L. V. Heisey, J. Am. Chem. Soc. **68** (1946) 2496
[20] J. H. Burckhalter, V. C. Stephens, L. A. R. Hall, J. Am. Chem. Soc. **74** (1952) 3868
[21] S. Swann Jr., Trans. Electrochem. Soc. **84** (1943) 165
[22] R. Lukes, J. Pliml, Collect. Czech. Chem. Commun. **15** (1950) 512

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