244. An Improved Liquid-Phase Synthesis of Simple Alkylpyridines[1])

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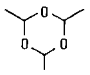
(5.X.84)

Summary

The synthesis of pyridines from mixtures of aldehydes or ketones and NH_3 in the liquid phase has been reinvestigated, using continuous dosage of the carbonyl components to the reaction mixture. The main product from the reaction of acetaldehyde and formaldehyde is 3-methylpyridine (**6**), which is also the main product from the reaction of acrolein or a mixture of crotonaldehyde and formaldehyde under the same conditions. The reaction of other aldehydes with formaldehyde give 3,5-dialkylpyridines, *e.g.* **10**, **16**. Acetone reacts with either formaldehyde or acetaldehyde to give polysubstituted alkylpyridines. A mechanistic pathway is proposed which accounts for the formation of the observed products.

Introduction. – The industrial synthesis of alkylpyridines is usually achieved by the addition-cyclization of aldehyde or ketone mixtures with NH_3[2]). This method is particularly important for pyridine itself, and for 3-methylpyridine (**6**) and 5-ethyl-2-methylpyridine (**2**), which are feedstocks for the vitamins nicotinic acid and nicotinamide. As part of a programme investigating new routes to nicotinic acid, we have developed an improved liquid-phase synthesis of simple alkyl-substituted pyridines.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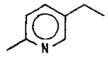
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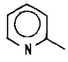
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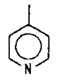
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The self-condensation of paraldehyde[3]) **1** in aq. NH_3 in the presence of an ammonium salt gives a 70% yield of **2** and small amounts of 2-methylpyridine (**3**) and 4-methylpyridine (**4**) [5]. In contrast, the gas-phase reaction of acetaldehyde and NH_3 over a silica/alumina catalyst gives 30–40% yields of **3** and **4** but only 6–7% of **2** [6]. A recent patent, however, described a liquid-phase reaction of acetaldehyde and NH_3, which produced **2** in 77–85% yield [7], a considerable improvement over previous results [8]. The key improvement is the continuous dosage of acetaldehyde throughout the reaction.

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[1]) Parts of this work have already appeared in preliminary form [1].

[2]) For reviews of pyridine synthesis see [2–4].

[3]) Systematic name: 2,4,6-trimethyl-1,3,5-trioxan.

We report here on the reactions of other aldehyde and ketone mixtures under similar conditions, and show that different product mixtures are formed compared with the corresponding gas-phase reaction.

Condensation of Acetaldehyde, Formaldehyde and NH_3. – The reaction of acetaldehyde, formaldehyde and NH_3 in the gas phase has been widely studied [3] [4] and is used commercially for the manufacture of pyridine (**5**) and 3-methylpyridine (**6**). The reaction can be directed to give mainly **5** (in the presence of O_2) [9], or approximately equal amounts of **5** and **6** (in the absence of O_2) [10]. The corresponding liquid-phase reaction has been reported only once, giving a mixture of **2** and **3** [11].

Our first experiments were performed with a 1:1 molar ratio of acetaldehyde and 30% aq. formaldehyde. The precooled (–20°) solution was continuously pumped into a vigorously stirred saturated (3.4M) solution of $(NH_4)_2HPO_4$ maintained at 220° in an autoclave. After cooling and extraction of the products into CH_2Cl_2, the organic extracts were analyzed by GLC using an internal standard. This analysis of the crude products gave results in good agreement with the isolated yields of distilled products and also with test mixtures of known composition. These first experiments showed a product spectrum differing from that observed in the gas phase. The main product (59% yield) was 3-methylpyridine (**6**) while the yield of pyridine was only 1%. Small quantities of other alkylpyridines (**2**, **3**, **7–10**) were also observed[4].


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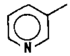
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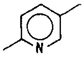
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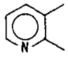
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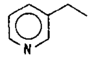
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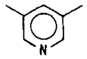
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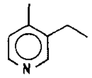
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The product distribution was dependent on the ratio of acetaldehyde to formaldehyde used. The results of a series of experiments using a constant amount of 5 mol aldehyde with the formaldehyde content varying from 0–90 mol-% are shown in *Fig. 1*. To display clearly the change in product composition, the yields of each product are expressed directly in mmol[5]).

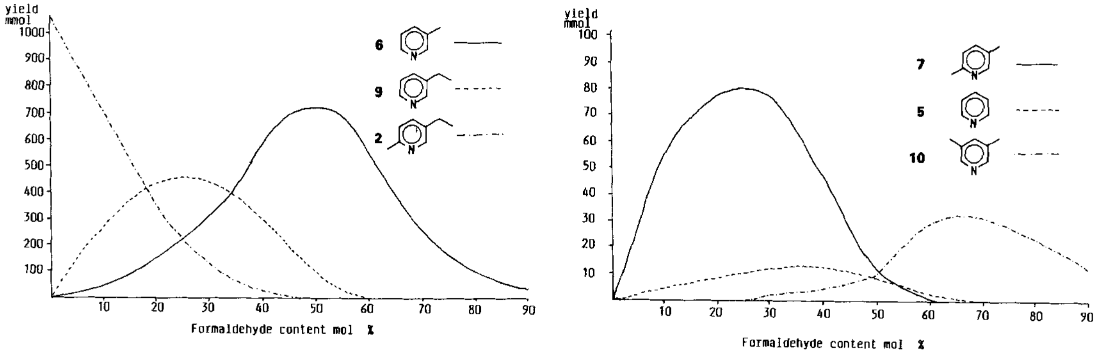

Fig. 1. *Variation of the yields of pyridine bases with the molar ratio of acetaldehyde and formaldehyde*

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[4]) All the products were identified by GLC (coinjection of reference samples) and by GLC/MS. In addition, **5**, **6** and **9** could be isolated from the crude reaction mixture by distillation.

[5]) The yields of **3** and **8** are omitted from *Fig. 1* for clarity. The amounts produced were usually less than 10 mmol. All experiments were performed under standard conditions of temperature (230°) and reaction time (60 min) in 3.4M $(NH_4)_2HPO_4$.

At 50 mol-% formaldehyde the major product is **6**, but with greater acetaldehyde content **7** and **9** are produced in greater quantity, reaching a maximum at 25 mol-% formaldehyde. At this point, the product mixture consists of more than 50% **9**. At even lower formaldehyde concentration, **2** is the major product. Pyridine (**5**) remains a minor product throughout as does 3,5-dimethylpyridine (**10**). All the products, however, reach a maximum yield at ratios of formaldehyde to acetaldehyde corresponding to the stoichiometry shown below. This stoichiometry was used to calculate the percentage yields of the individual products.

$2\ CH_3CHO + HCHO \rightarrow \mathbf{5}$ $3\ CH_3CHO \rightarrow \mathbf{3}$ $4\ CH_3CHO \rightarrow \mathbf{2}$

$2\ CH_3CHO + 2\ HCHO \rightarrow \mathbf{6}$ $3\ CH_3CHO + HCHO \rightarrow \mathbf{7}, \mathbf{8}, \mathbf{9}$

$2\ CH_3CHO + 3\ HCHO \rightarrow \mathbf{10}$

Acetals or polymers of acetaldehyde or formaldehyde can also be allowed to react (see *Table 1* in *Exper. Part*). All materials give practically the same results as acetaldehyde and formaldehyde, except for trioxan, where, because of its relatively slow decomposition under the reaction conditions, products with a higher acetaldehyde content are favoured. The reaction is also not limited to $(NH_4)_2HPO_4$ solution. Many other ammonium salts, or organic amides, or alkali metal salts in the presence of aq. NH_3, give similar results. Some representative examples are given in *Table 2* (see *Exper. Part*).

Acrolein and crotonaldehyde were also investigated as alternative starting materials for this reaction. The only reported successful condensation of acrolein and NH_3 in the liquid phase was performed in aq. propionic acid [12], when **6** could be isolated in 33% yield. Previously, only polymerisation of the acrolein had been reported [8]. On the other hand, the reaction of acrolein with NH_3 in the gas phase to give **5**/**6** mixtures has been widely studied [13]. The addition of acetaldehyde [14] or propionaldehyde [15] to the reaction mixture increases the yield of (**6**).

In contrast to these results, acrolein gave, under our conditions, a relatively high yield of **6** and little polymer formation. The product distribution is the same as that produced by a 1:1 mixture of acetaldehyde and formaldehyde (see *Table 3*). Indeed, mixtures of acrolein, formaldehyde, and acetaldehyde or paraldehyde gave the same results as the equivalent mixture of acetaldehyde and formaldehyde. The reaction of acrolein and propionaldehyde in a 2:1 molar ratio gave, in contrast to the gas-phase reaction [15] a lower yield of **6** and a considerable amount of **10**. As the latter product is formed from propionaldehyde and formaldehyde, this result suggests that acrolein undergoes a very fast *retro*-aldol reaction unter the reaction conditions.

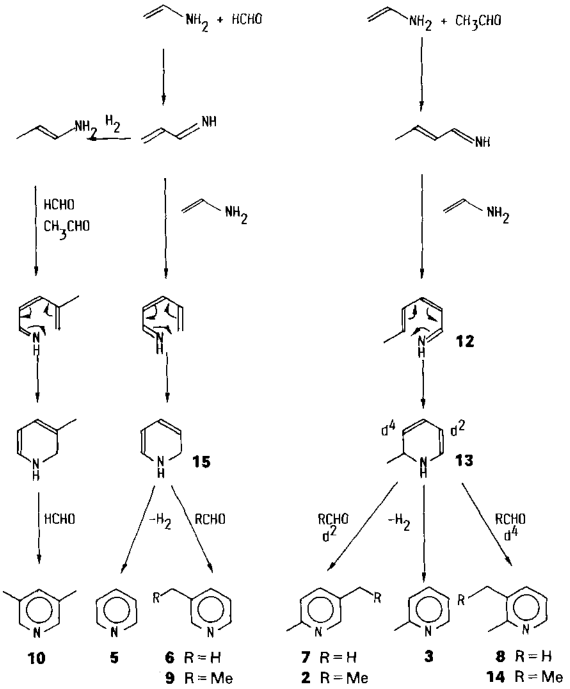
The gas-phase reaction of crotonaldehyde and NH_3 gives mainly 3-ethyl-4-methylpyridine (**11**) [16]. In the liquid phase mainly the pyridine derivative **2** is produced [8]. Both reactions give poor yields. A mixture of crotonaldehyde and formaldehyde in the gas phase gives a high yield of pyridine and very little 3-methylpyridine (**6**) [17]. The corresponding liquid-phase reaction, which has not previously been reported, gave under our conditions similar results to those found for the corresponding mixture of acetaldehyde and formaldehyde. The main product is again **6** (see *Table 3*). Crotonaldehyde alone or together with paraldehyde gives a much higher yield of **2** under these conditions than has previously been reported. A control reaction in which crotonaldehyde and formaldehyde were mixed with $(NH_4)_2HPO_4$ at room temperature and heated to 240° for 1 h gave 2.4% **6** by GLC and only traces of other pyridine derivatives. This shows that the improvement over previous methods lies in the slow dosage of crotonaldehyde at the reaction temperature where the *retro*-aldol reaction is very fast.

From these results it may be concluded that, in contrast to the gas-phase reaction, where acrolein and crotonaldehyde probably react without decomposition, in the liquid phase they react as mixtures of acetaldehyde and formaldehyde.

The mechanism of the formation of pyridines from the aldehyde/NH_3 reaction is not clear. For the specific case of acetaldehyde the proposed mechanisms have been reviewed, covering the literature up to 1974 [18–20]. However, the authors do not distinguish clearly between gas- and liquid-phase reactions, where the reaction pathways are probably different. On the basis of our experimental observations, we propose a mechanistic pathway which accounts for the products formed in the liquid phase.

The suggested pathway for the condensation of acetaldehyde is based in part on that proposed by *Farberov et al.* [20] and consists of 3 steps *(Scheme 1): a)* linear condensation of 3 molecules of acetaldehyde, probably *via* the imines, to give a linear dienal **12**; *b)* electrocyclic ring closure to the dihydropyridine **13**; *c)* either dehydrogenation to **3** or reaction with a fourth molecule of acetaldehyde to give **2**. The addition of the fourth molecule of acetaldehyde may proceed by direct (d^2) or conjugate (d^4) [21] addition of the dienamine to give either **2** or the isomer **14**. The d^2 addition is favoured, but traces of **14** can be detected by GLC in the product mixture (ratio 2:14 = 50:1). The formation of the other minor product **4** can be explained by a conjugate addition

Scheme 1



of the third aldehyde molecule in step *a* leading to an isomeric dihydropyridine and subsequent dehydrogenation.

Scheme 1 also shows how the same 3-step pathway can account for almost all the products from the more complex acetaldehyde/formaldehyde mixture. Here the dihydropyridine **15** formed from two molecules of acetaldehyde and one of formaldehyde is also an intermediate. The final step can be dehydrogenation or addition of a fourth molecule of acetaldehyde or formaldehyde. Products from all three pathways are observed. The major alkylpyridines **6** and **9** are formed *via* **15**, the minor products *via* **13**. Again d^2 rather than d^4 addition of the fourth aldehyde is favoured.

The formation of 3,5-dimethylpyridine (**10**) requires a separate mechanism. It must be formed from 5 aldehyde molecules, and probably involves a hydrogen-transfer step. The hydrogen can be transferred from either of the intermediates **13** or **15** *(Scheme 1)*, or alternatively *via* a *Cannizarro* reaction of the excess formaldehyde. Further addition of formaldehyde and acetaldehyde leads to **10**. The hydrogen-transfer hypothesis for the formation of **10** is supported by a series of experiments in $(NH_4)_2HPO_4$ solution at different pH values. The yields of pyridine and **10** both increase with increasing pH *(Fig. 2)*, suggesting that the mechanisms of their formation are coupled.

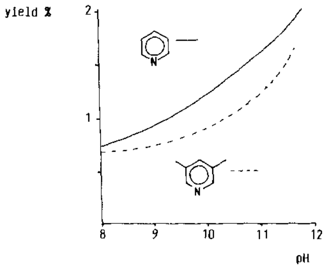
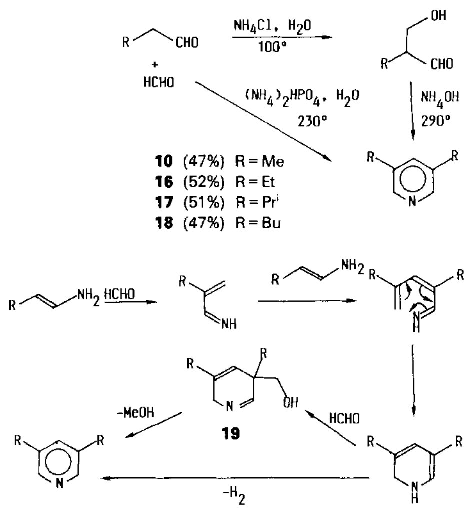


Fig. 2. *Variation of the yield of pyridine and 3,5-dimethylpyridine with the reaction pH*

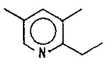
Preparation of 3,5-Dialkylpyridines. – The reaction of higher aldehydes (propionaldehyde, butyraldehyde *etc.*) with formaldehyde and NH_3 is known to give 3,5-dialkylpyridines both in the liquid and in the gas phase. In the gas phase, yields of up to 50% have been reported [22]. In the liquid phase, direct reaction of propionaldehyde and paraformaldehyde in aq. NH_3 at 230° gave only 15% **10** [23], but better results were obtained by heating a pre-formed aldol adduct in aq. NH_3 at higher temperatures [24] [25]. The one-step liquid-phase reaction gave under our conditions the same yields of 3,5-dialkylpyridines as reported for the 2-step reaction *(Scheme 2)*. The pyridines **10** and **16**–**18** were produced with very few by-products and could be easily purified by distillation. Again, the importance of maintaining a low concentration of aldehyde during the reaction was shown by a control experiment, where propionaldehyde and formaldehyde were mixed with aq. $(NH_4)_2HPO_4$ at room temperature and heated to 220° for 1 h. The yield of **10** was only 20%.

A pathway for this reaction analogous to that proposed for the acetaldehyde/formaldehyde reaction is also shown in *Scheme 2*. Here the intermediate **19** cannot aromatize by loss of H_2O as both the 3- and 5-positions are already alkylated. Aromatization thus occurs by loss of MeOH to give the 3,5-dialkylpyridines. Alternatively the dihydropyridine intermediate can be directly dehydrogenated to the aromatic product (*cf.* [25]).

Scheme 2



Propionaldehyde alone, when reacted with $(NH_4)_2HPO_4$ at 230°, gave a 27% yield of the expected alkylpyridine **20** together with an approximately equal amount of a cyclopentenone, which on the basis of the spectroscopic data may be assigned the structure **21**. The latter product is formed by condensation of three molecules of propionaldehyde and cyclization. The pyridine **20** is derived from the condensation of three rather than four molecules of propionaldehyde, the final step being a dehydrogenation. In this case the liquid-phase reaction is inferior to the corresponding gas-phase reaction, where a 65% yield of **20** has been reported [26].



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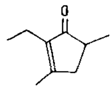

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Reaction of Mixtures of Aldehydes and Ketones with NH_3. – The reactions of mixtures of aldehydes and acetone with NH_3 under the same conditions were also studied. It is known that a mixture of acetone, formaldehyde and NH_3 in the gas phase produces a 36% yield of 2,6-dimethylpyridine (**22**) [27]. Under our conditions in the liquid phase only traces of **22** could be detected. A 4:1 mixture of two trimethylpyridines (90% of the crude product, yields 35% and 8.5%) was produced which could be separated by preparative GLC and were identified as 2,3,4-trimethylpyridine (**23**, major product) and 2,4,5-trimethylpyridine (**24**, minor product)^6). Small amounts of 2,4-dimethylpyridine (**25**) could also be detected (6% of the crude product) (*Scheme 3*). The formation of **23**–**25** may be explained *via* a common intermediate **26**, which may either dehydrogenate or add formaldehyde either d^2 (to give **23**) or d^4 (to give **24**). The preference for d^2 addition is again apparent.

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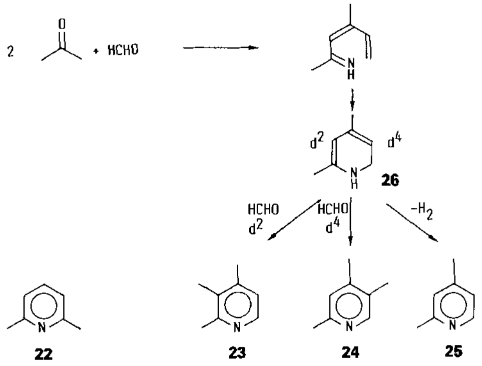
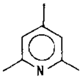
^{6}) Compound **23** has been prepared by the liquid-phase reaction of methyl ethyl ketone and NH_3 (12% yield) [8].

Scheme 3



Acetaldehyde and acetone are reported to give mainly 2,4,6-trimethylpyridine (**27**) in the liquid phase [11]. Our results show a more complex reaction in which the main product (37% yield) is **28**. The other main products were **2**, **27**, **29** and **30**. Traces of **22** and **25** were also found.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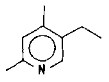
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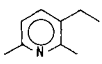
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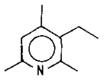
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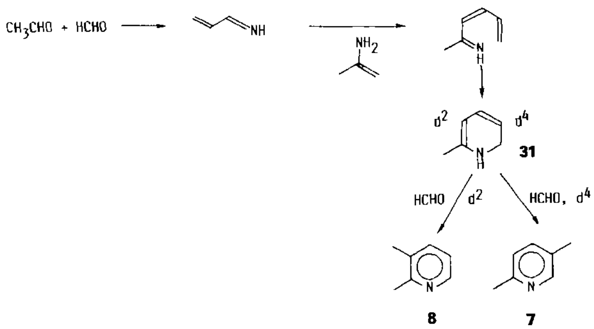
Finally, a three component mixture of acetone, formaldehyde and acetaldehyde (1:2:1) was tested. The main product (34% of the crude mixture, yield 25% based on acetone) is 2,3-dimethylpyridine (**8**), and the other main products are **6** (13% of the mixture) formed from acetaldehyde and formaldehyde, and **23** (10% of the mixture) formed from acetone and formaldehyde *(Scheme 4)*. The isomer **8** is not a major product from the reaction of a combination of any two of the reagents. Its formation may proceed *via* the dihydropyridine **31**. The isomeric dimethylpyridine **7** formed by conjugate addition of the dienamine **31** to formaldehyde is only present to the extent of 4% in the product mixture.

Scheme 4



Conclusion. – From the results presented here the following general conclusions may be drawn: the preferred mode of condensation in the liquid phase is of four molecules of aldehyde or ketone with NH_3, giving the correct oxidation state for the pyridine products without need for oxidation or reduction. In the gas phase, the preferred pathway involves condensation of three molecules of the carbonyl components and subsequent dehydrogenation. The major products in the liquid phase always have a substituent in positions 3 or 5; in the gas phase the products are more often substituted in positions 2 or 4. When the 3- and 5-positions are already substituted after condensation of three aldehyde molecules, then the fourth molecule acts only as the final hydrogen-transfer reagent to give the aromatic products.

Thanks are due to Dr. *A. Gerhard* for preparative GLC and GLC/MS, *J. Jovanovic* for NMR, and *R. Haas* for GLC analyses.

Experimental Part

General. All reactions were carried out in 2-l stainless steel autoclave with magnetically coupled stirrer *(Büchi AG)*. The autoclave was fitted with a dosage pump and an inlet tube, which delivered the reagents into the close vicinity of the stirrer. Melting points (*Tottoli* apparatus) and boiling points are not corrected. IR spectra were recorded on a *Perkin-Elmer 1576* machine using a thin film unless otherwise specified. ^1H-NMR spectra were recorded at 300 MHz on a *Nicolet FT 300* spectrometer or at 200 MHz on a *Bruker 200* machine, ^{13}C-NMR spectra were recorded at 50.29 MHz on a *Bruker 200* machine; solvent $CDCl_3$, standard TMS δ (ppm) = 0. GLC/MS were recorded on a *Finnigan GC-MS 400* machine. Signals are given in *m/z* (rel.%). GLC was performed with a *Hewlett-Packard HP-5880 A* chromatograph, using an *Emulphor 18 M* capillary glass column. Prep. GLC was performed on a *10% OV 101* column.

Alkylpyridines from Acetaldehyde and Formaldehyde. – Reaction of Acetaldehyde and Formaldehyde. A 3.4M aq. $(NH_4)_2HPO_4$ solution (1140 ml) (pH 8.4) was heated to 230° in a 2-l autoclave and vigorously stirred (1500 rpm). A pre-cooled (–20°) solution of acetaldehyde (117.7 g, 2.67 mol) in 213.3 g, 30.0% aq. formaldehyde (2.13 mol) was pumped into the autoclave over 80 min. During the reaction, the pressure rose from 35 to 37 bar. After the addition, the solution was stirred at 230° for a further 10 min, then cooled to r.t. The products were extracted with 3 × 100 ml CH_2Cl_2 and the org. extracts were analyzed by GLC, using pyridazine as an internal standard. The following products were identified: *pyridine* (**5**), 1.0 g (1% yield); *3-methylpyridine* (**6**), 60.6 g (61%); *3-ethylpyridine* (**9**), 21.3 g (22%); *2,5-dimethylpyridine* (**7**), 3.5 g (4%); *3,5-dimethylpyridine* (**10**), 0.6 g (1%) and *5-ethyl-2-methylpyridine* (**2**), 2.0 g (2.5%). Small amounts (< 0.5 g) of *2-methylpyridine* (**3**) and *2,3-dimethylpyridine* (**8**) were also detected. The yields of **6** and **10** are based on formaldehyde consumed, the other yields on acetaldehyde. The GLC analysis method was calibrated with test solutions of the various products in CH_2Cl_2. The crude product from 7 similar experiments was distilled and the fraction b.p. 110–170°/700 Torr collected. GLC analysis of the distillate showed the same product composition as in the crude product. Products **6**, **9**, **7**, and **2** were identified in the ^1H-NMR spectrum of the distillate. Redistillation through a 150-cm column packed with glass rings permitted the isolation of **5** and **6** in ≥ 90% purity, and of **9** in ≥ 80% purity. All the products were identified by GLC (coinjection of reference samples) and by GLC/MS.

Table 1. *Synthesis of Pyridines from Acetaldehyde and Formaldehyde Equivalents*

Formaldehyde equivalent	Acetaldehyde equivalent	Yield of Alkylpyridine [%]					
		5	**6**	**9**	**7**	**10**	**2**
Formaldehyde	Paraldehyde	1	61	21	4	1	2
1,3,5-Trioxan	Acetaldehyde	0.6	17	37	7	0.2	26
1,3,5-Trioxan	Paraldehyde	0.7	16	35	7	0.2	28
Hexamethylenetetramine	Acetaldehyde	1	60	20	4	1	1.5
Hexamethylenetetramine	Paraldehyde	1	66	19	3	1	3
Formaldehydedimethylacetal	Acetaldehyde	1	53	23	4	0.6	3
Formaldehydedimethylacetal	Paraldehyde	1	54	24	4	0.6	2.5
Hexamethylenetetramine	Acetaldehydediethylacetal	1	58	16	3	1	1

Reactions of Acetaldehyde and Formaldehyde Equivalents (Table 1). All the reactions were performed under the same conditions as in the above example so that the calculated molar ratio of acetaldehyde (as its equivalent) to formaldehyde (as its equivalent) was 56:44. The yields of **6** and **10** are based on the formaldehyde equivalent, the other yields are based on the acetaldehyde equivalent. All yields were determined by GLC analysis of the crude product. As an example, a solution of hexamethylenetetramine (1,3,5,7-tetraazatricyclo[3.3.1.1^{3,7}]decane) (49.8 g, 0.36 mol) in 130 ml of H_2O was mixed with a solution of paraldehyde (**1**; *2,4,6-trimethyl-1,3,5-trioxan*) (117.7 g, 0.89 mol) in 100 ml 95% EtOH and pumped over 60 min into 1140 ml 3.4M aq. $(NH_4)_2HPO_4$ at 230°. The reaction was worked up as in the previous example to give a crude product which contained the following products by GLC analysis: **5** (0.9 g, 1%), **6** (63.8 g, 66%), **9** (18.4 g, 19%), **7** (3.2 g, 3%), **10** (0.6 g, 1%), and **2** (2.3 g, 3%).

Effect of the Reaction Medium (Table 2). Aq. solutions of different ammonium salts were used in place of $(NH_4)_2HPO_4$. Alternatively aq. solutions of alkali metal salts or of org. amides served as the reaction medium. In most cases NH_4OH was added to give an initial pH > 7. All reactions were performed with acetaldehyde and formaldehyde (molar ratio 56:44) at 230°. All yields were determined by GLC analysis of the crude product.

Table 2. *Condensation of Acetaldehyde and Formaldehyde in Various NH_3-delivering Systems*

Salt or Amide	Conc. [M]	NH_4OH added [M]	Yield of Alkylpyridine [%]					
			5	**6**	**9**	**7**	**10**	**2**
$(NH_4)_2HPO_4$	3.4	–	1	61	22	4	1	2.5
NH_4Cl	2.0	2.65	2	54	11	5	0.6	1.5
$(NH_4)_2SO_4$	2.0	–	1	50	13	4	1	2
$(NH_4)_2CO_3$	0.88	4.38	1.5	51	15	4	1	1.5
$NH_4O_2CCH_3$	10.0	–	1	44	18	4	0.4	2
NH_4O_2CPh	0.63	2.61	1.5	55	13	5	1	1.5
$NaHSO_4$	1.0	4.38	2	56	14	5	1	1.5
KH_2PO_4	1.0	4.38	1.5	60	16	4	1.5	1
CH_3CONH_2	3.4	–	1.5	53	15	4	1	2
NH_2CONH_2	0.88	4.38	2	52	14	5	1.5	1.5

Table 3. *Synthesis of Pyridines from Acrolein or Crotonaldehyde*

Starting materials and molar ratio	Yield of Alkylpyridine [%]					
	5	**6**	**9**	**7**	**10**	**2**
Acrolein	1	55	8	1	0.7	0.2
Acrolein/Formaldehyde 4:1	0.5	53	2	0.3	1.5	0
Acrolein/Paraldehyde/Formaldehyde 2:3:2	1.5	57	24	4	1	3
Acrolein/Propionaldehyde 2:1	0.6	34	5	1	36	0.4
Crotonaldehyde/Formaldehyde 1:1	1	46	30	9	0.5	11
Crotonaldehyde/Formaldehyde 2:5	0.5	55	3.5	2.5	2	1
Crotonaldehyde	0	0	0.3	0	0	81
Crotonaldehyde/Paraldehyde 3:1	0	0	0.2	0	0	74

Reaction of Acrolein with NH_3. A solution of 115.0 g (2.05 mol) of acrolein in 80 ml 95% EtOH was pumped over 36 min into 1140 ml of an $(NH_4)_2HPO_4$ solution as in the first example. After workup, GLC analysis of the crude product showed the following products: **5** (0.8 g, 1%), **6** (50.0 g, 55%), **9** (5.4 g, 8%), **7** (0.7 g, 1%), **10** (0.5 g, 0.7%), and **2** (0.1 g, 0.2%). *Table 3* shows the results of further experiments using reagent mixtures containing acrolein or crotonaldehyde, performed under the same conditions as in the first example. All yields were determined by GLC analysis of the crude reaction product.

3,5-Dimethylpyridine (**10**). A mixture of a solution of 127.6 g (2.20 mol) propionaldehyde in 40 ml 95% EtOH and 213.3 g 30.2% aq. formaldehyde (2.15 mol) was pumped over 63 min into 1140 ml 3.4M aq. $(NH_4)_2HPO_4$ at 234°. The pressure increased during the reaction from 34 to 47 bar. The reaction was worked up as in the previous examples to give a crude product, which GLC analysis showed to consist of 54.0 g (47%) **10** and 2 g of other alkyl pyridines (**3**, **5** and **6**). Distillation of the crude product gave a 46.7% isolated yield of **10** of 96% purity (GLC), b.p. 165–168°/700 Torr. IR: 3020, 2980, 2870, 1600, 1580, 1460, 1415, 1390, 1320, 1240, 1170, 1140, 1035, 860, 710. ^{1}H-NMR: 2.28 (*s*, 6H); 7.28 (*s*, 1H); 8.25 (*s*, 2H). MS: *107* (100, $C_7H_9N^+$), 92 (24), 79 (40), 77 (20).

3,5-Diethylpyridine (**16**). The reaction of a solution of 148.7 g (2.06 mol) butyraldehyde in 50 ml 95% EtOH with 201.0 g 30.3% aq. formaldehyde (2.03 mol) in 1140 ml $(NH_4)_2HPO_4$ solution at 232° gave 71.7 g (52.3%) **16** by GLC. Distillation of the crude product gave a 51.8% isolated yield of **16** of 95% purity (GLC), b.p. 87–89°/14 Torr ([25]: 98–99°/20 Torr). IR: 3020, 2980, 2960, 2880, 1600, 1575, 1455, 1430, 1380, 1315, 1220, 1155, 1060, 1025, 965, 880, 785, 720, 705. ^{1}H-NMR: 1.25 (*t*, *J* = 7, 6H); 2.62 (*q*, *J* = 7, 4H); 7.30 (*t*, *J* = 2, 1H); 8.28 (*d*, *J* = 2, 2H). MS: 135 (95, $C_9H_{13}N^+$), *120* (100), 106 (24), 91 (15), 77 (16).

3,5-Diisopropylpyridine (**17**). The reaction of a solution of 150.7 g (1.75 mol) 3-methylbutanal in 100 ml 95% EtOH with 174.6 g 30.1% aq. formaldehyde (1.75 mol) in 1140 ml $(NH_4)_2HPO_4$ solution at 232° gave a crude mixture of pyridine derivatives. The combined product from 3 experiments was distilled to give **17** (226.6 g, 51%) of 96% purity (GLC), b.p. 100–102°/14 Torr, which solidified to a white solid, m.p. 37–38°, ([28]: b.p. 223–224°/760 Torr, m.p. 46°). IR (KBr): 2980, 2940, 2880, 1600, 1470, 1430, 1390, 1370, 1215, 1060, 1030, 890, 725. ^{1}H-NMR: 1,28 (*d*, *J* = 7, 12H); 2.90 (*sept.*, *J* = 7, 2H); 7.35 (*t*, *J* = 2, 1H); 8.32 (*d*, *J* = 2, 2H). MS: 163 (43, $C_{11}H_{17}N^+$), *148* (100), 132 (8), 120 (9), 106 (21).

3,5-Dibutylpyridine (**18**). The reaction of a solution of 151.0 g (1.50 mol) hexanal in 100 ml 95% EtOH with 150.0 g 30.1% aq. formaldehyde (1.50 mol) in 1140 ml $(NH_4)_2HPO_4$ solution at 230° gave a crude pyridine base mixture. The combined product from 3 experiments was distilled to give **18** (200.6 g, 47%) of 98% purity (GLC), b.p. 110–112°/4 Torr ([29]: 88–90°/2 Torr). IR: 3020, 2970, 2940, 2880, 2870, 1600, 1580, 1465, 1430, 1380, 1160, 1030, 720. ^{1}H-NMR: 0.95 (*t*, *J* = 7, 6H); 1.35 (*m*, 4H); 1.6 (*m*, 4H); 2.55 (*t*, *J* = 7, 4H); 7.28 (*t*, *J* = 1, 1H); 8.25 (*d*, *J* = 1, 2H). MS: 191 (70, $C_{13}H_{21}N^+$), 162 (16), *149* (100), 106 (82), 77 (21).

Reaction of Proprionaldehyde and NH_3. The condensation of propionaldehyde (150.0 g, 2.58 mol) in 1140 ml $(NH_4)_2HPO_4$ solution at 230° gave a crude product, the GLC of which showed two main components in the ratio 5:3. The crude product from 2 experiments was distilled to give 98.8 g of a mixture of the two products (b.p. 74–80°/14 Torr). The yield of **20** by GLC was 27% and the yield of **21** 18%. 60 g of this mixture was dissolved in 200 ml dil. HCl and extracted with 4 × 100 ml Et_2O. The Et_2O extracts were dried (Na_2SO_4), evaporated and distilled to give 20,4 g *2-ethyl-3,5-dimethylcyclopent-2-enone* (**21**), b.p. 79–81°/20 Torr. IR: 2970, 2940, 2880, 1700, 1645, 1455, 1435, 1385, 1350, 1180, 1055, 930. ^{1}H-NMR: 0.97 (*t*, *J* = 7, 3H); 1.15 (*d*, *J* = 7, 3H); 2.50 (*s*, 3H); 2.10 (*dd*, *J* = 18 and 1, 1H); 2.17 (*q*, *J* = 7, irr. at 0.97→*s*, 2H); 2.35 (*qdd*, *J* = 7.7, and 1, irr. at 2.10→*qd*, *J* = 7 and 7, 1H); 2.70 (*ddd*, *J* = 18, 7 and 1, 1H); ^{13}C-NMR: 12.9 (*q*); 16.4 (*t*); 16.5 (*q*); 16.7 (*q*); 39.7 (*d*); 40.8 (*t*); 140.8 (*s*); 167.2 (*s*); 211.2 (*s*). MS: 138 (63, $C_9H_{14}O^+$), *123* (100), 109 (12), 95 (52), 67 (28).

The aq. solution was made basic with 25% KOH and extracted with 3 × 100 ml $CHCl_3$. The org. extracts were dried (K_2CO_3), evaporated and distilled to give 30.2 g *2-ethyl-3,5-dimethylpyridine* (**20**), b.p. 85–87°/20 Torr ([23]: 85–87°/15 Torr). IR: 2980, 2940, 2880, 1605, 1565, 1470, 1400, 1380, 1230, 1205, 1050, 880, 715. ^{1}H-NMR: 1.25 (*t*, *J* = 7, 3H); 2.25 (*s*, 3H); 2.28 (*s*, 3H); 2.75 (*q*, *J* = 7, 2H); 7.20 (*d*, *J* = 1, 1H); 8.20 (*d*, *J* = 1, 1H). MS: 135 (56, $C_9H_{13}N^+$), *134* (100), 107 (22), 77 (12).

Reaction of Acetone and Formaldehyde. Under the same conditions as the previous examples, a solution of 125.0 g (2.15 mol) acetone in 213.3 g 30.2% aq. formaldehyde (2.15 mol) was added over 65 min to 1140 ml of 3.4M aq. $(NH_4)_2HPO_4$ at 234°. The crude alkylpyridine mixture from 3 experiments was distilled to give 118.9 g of a mixture, b.p. 75–80°/20 Torr, which GLC showed to consist of 73% *2,3,4-trimethylpyridine* (**23**, 35% yield), 18% *2,4,5-trimethylpyridine* (**24**, 8.5% yield), and 6% *2,4-dimethylpyridine* (**25**). The distilled product was separated by preparative GLC to give **23** (major product), ^{1}H-NMR: 2.20 (*s*, 3H); 2.30 (*s*, 3H); 2.55 (*s*, 3H); 6.93 (*d*, *J* = 6, 1H); 8.18 (*d*, *J* = 6, 1H). MS: *121* (100, $C_8H_{11}N^+$), 106 (22), 93 (10), 79 (30), and **24** (minor product), ^{1}H-NMR: 2.18 (*s*, 3H); 2.22 (*s*, 3H); 2.48 (*s*, 3H); 6.92 (*s*, 1H); 8.20 (*s*, 1H). MS *121* (100, $C_8H_{11}N^+$), 106 (25), 93 (8), 91 (7), 79 (23).

Reaction of Acetone and Acetaldehyde. Under the same conditions as the previous examples, a mixture of 116.2 g (2.00 mol) acetone and 88.1 g (2.00 mol) acetaldehyde was added over 64 min to 1140 ml 3.4M aq. $(NH_4)_2HPO_4$ at 234°. The crude alkylpyridine mixture from 2 experiments was distilled to give 148.8 g product mixture, b.p. 63–110°/18 Torr. GLC analysis showed this to consist of 20% *2,4,6-trimethylpyridine* (**27**), 8% **2** and 3 new products with t_R 5.9 min (45%), 7.7 min (7%), and 8.5 min (7%). The distilled products were separated by preparative GLC to yield *3-ethyl-2,6-dimethylpyridine* (**29**, t_R 5.9 min), ^{1}H-NMR: 1.22 (*t*, *J* = 7, 3H); 2.48 (*s*, 3H); 2.50 (*s*, 3H); 2.58 (*q*, *J* = 7, 2H); 6.93 (*d*, *J* = 7, 1H); 7.31 (*d*, *J* = 7, 1H). MS: 135 (64, $C_9H_{13}N^+$), *120* (100), 107 (5), 91 (7), 79 (10), 77 (15), *3-ethyl-2,4-dimethylpyridine* (**29**, t_R 7.7 min), ^{1}H-NMR: 1.20 (*t*, *J* = 7, 3H); 2.27 (*s*, 3H); 2.48 (*s*, 3H); 2.60 (*q*, *J* = 7, 2H); 6.93 (*s*, 1H); 8.20 (*s*, 1H). MS: 135 (57,

$C_9H_{13}N^+$), *120* (100), 107 (4), 93 (7), 91 (10), 77 (10), and *3-ethyl-2,4,6-trimethylpyridine* (**30**, t_R 8.5 min), ^{1}H-NMR: 1.10 (*t*, *J* = 7, 3H); 2.25 (*s*, 3H); 2.43 (*s*, 3H); 2.5 (*s*, 3H); 2.63 (*q*, *J* = 7, 3H); 6.80 (*s*, 1H). MS: 149 (46, $C_{10}H_{15}N^+$), *134* (100), 121 (5), 107 (4), 91 (8), 77 (7).

Reaction of Acetone, Formaldehyde and Acetaldehyde. Under the same conditions as the previous examples, a mixture of 198.9 g 30.2% aq. formaldehyde (2.00 mol), 58.1 g (1.00 mol) acetone, 44.1 g (1.00 mol) acetaldehyde and 15 ml 95% EtOH was added over 60 min to 1140 ml 3.4M aq. $(NH_4)_2HPO_4$ at 234°. After workup, GLC analysis showed the following products: **5** (0.3 g, 0.7%), **6** (10.5 g, 22%), **7** (3.0 g, 3%), **8** (26.9 g, 25% based on acetone), **9** (2.9 g, 8%), **10** (0.3 g, 0.5%), **2** (0.4 g, 1%), and **23** (8.0 g, 13% based on acetone). Distillation of the crude product permitted the isolation of a fraction (b.p. 159–164°/200 Torr) containing 62% **8** by GLC. The identity of **8** was confirmed by NMR and MS.

REFERENCES

[1] *Lonza AG,* Eur. Patent Appl. 40698 (1981), Chem. Abstr. *96,* 104105 (1982), Eur. Patent Appl. 56496 (1982), Chem. Abstr. *97,* 198119 (1982), Eur. Patent Appl. 60551 (1982), Chem. Abstr. *98,* 53705 (1983), Eur. Patent Appl. 70012 (1983), Chem. Abstr. *98,* 198040 (1983), Eur. Patent App. 75727 (1983), Chem. Abstr. *99,* 70570 (1983).

[2] *Kirk-Othmer,* 'Encyclopedia of Chemical Technology', 3rd. edn., Vol. 19, Interscience, New York, 1982, p. 454.

[3] '*Ullmanns* Encyclopädie der Technischen Chemie', 4th edn., Vol. 19, Verlag Chemie, Weinheim, 1980, p. 591.

[4] *F. Brody & P.R. Ruby,* in 'Pyridine and its Derivatives', Part 1, Ed. E. Klingsberg, Interscience, New York, 1960, p. 99; *N.S. Boodman, J.O. Hawthorne, P.X. Masciantonio & W.A. Simon,* in 'Pyridine and its Derivatives', Supplement, Part 1, ed. R.A. Abramovitch, Interscience, New York, 1974, p. 183.

[5] *A. Nenz & M. Pieroni,* Hydrocarbon Process *47,* 139 (1968); *P.L. Frank, J.R. Blegen, R.J. Dearborn, R.L. Meyers & F.E. Woodward,* J. Am. Chem. Soc. *68,* 1368 (1946).

[6] *Nippon Kayaku Co.,* Japanese Patents 71 39873, Chem. Abstr. *76,* 34112 (1972), and 72 44745, Chem. Abstr. *78,* 71926 (1973).

[7] *Merck & Co. Inc.,* United States Patent 3846435, 1974, Chem. Abstr. *80,* 120778 (1974).

[8] *R.L. Frank & R.P. Seven,* J. Am. Chem. Soc. *71,* 2629 (1949).

[9] *Distillers Co.,* German Patent 1670514, 1966, Chem. Abstr. *66,* 18678 (1967).

[10] *Ruetgerswerke AG,* German Patent 2203384, 1973, Chem. Abstr. *79,* 136985 (1973); *ICI Ltd.,* United States Patent 4089863, 1978, Chem. Abstr. *91,* 5117 (1979).

[11] *Farbwerke,* British Patent 147101, 1920, Chem. Abstr. *14,* 3676 (1920).

[12] *ICI Ltd.,* British Patent 1240928 1971, Chem. Abstr. *75,* 98455 (1971).

[13] *H. Beschke & H. Friedrich,* Chem.-Ztg. *101,* 377 (1977).

[14] *Degussa,* German Patent 2703049, 1978, Chem. Abstr. *89,* 146780 (1978).

[15] *Degussa,* German Patent 2703070, 1978, Chem. Abstr. *89,* 179865 (1978).

[16] *A.E. Tschitschibabin & M.P. Oparina,* Ber. Dtsch. Chem. Ges. *60,* 1877 (1927); *J.D. Butler,* J. Catal. *6,* 26 (1966).

[17] *Ruetgerswerke AG,* German Patent 2051316, 1972, Chem. Abstr. *77,* 19545 (1972).

[18] *J. Herzenberg & G. Boccato,* Chem. Ind. (Paris) *80,* 248 (1958).

[19] *J. Gelas,* Bull. Soc. Chim. Fr. *1967,* 3093.

[20] *M.I. Farberov, V.V. Antonova, B.F. Ustavshchikov & N.A. Titova,* Khim. Geterotsikl. Soedin. *1975,* 1587, Chem. Abstr. *84,* 105305 (1976).

[21] *D. Seebach,* Angew. Chem. *91,* 259 (1979).

[22] *Distillers Co.,* French Patent 1332908, 1963, Chem. Abstr. *60,* 509 (1964).

[23] *F. Bohlmann, A. Englisch, J. Politt, H. Sander & W. Weise,* Chem. Ber. *88,* 1831 (1955).

[24] *Bayer AG,* German Patent 2123965, 1972, Chem. Abstr. *78,* 58254 (1973).

[25] *D. Dieterich, H. Reiff, H. Ziemann & R. Braden,* Justus Liebigs Ann. Chem. *1973,* 111.

[26] *C.P. Adams & J. Falke,* Brennstoff. Chem. *47,* 184 (1966).

[27] *Mitsubishi Ltd.,* Japanese Patent 72 46070, Chem. Abstr. *78,* 97495 (1973).

[28] *M.P. Oparina,* J. Russ. Phys. Chem. Soc. *57,* 322 (1925).

[29] *S. Hermanek,* Collect. Czech. Chem. Commun, *24,* 2748 (1959).