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Reactions of Piperidine with Aldehydes over Alumina: A Facile Route to 3-Alkylpyridines

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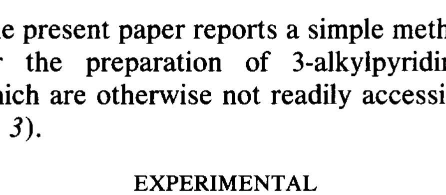
A mixture of an aldehyde and piperidine dissolved in benzene or a benzene solution of the corresponding alkylidene bis-1-piperidine, when passed over alumina at 420°C gave, among other products, 3-alkylpyridine in 20–40% yield. Possible mechanism of the reaction is discussed.

INTRODUCTION

In continuation of earlier studies on the reactions of benzyl alcohol (*1*) over alumina, the reaction of benzaldehyde with piperidine on alumina was carried out at 420°C. Interestingly the reaction led to the formation of 3-benzylpyridine. The reaction was found to be general for other aldehydes too giving the corresponding 3-alkylpyridines.



SCHEME 1

The present paper reports a simple method for the preparation of 3-alkylpyridines which are otherwise not readily accessible (*2, 3*).

EXPERIMENTAL

Alumina was prepared by the controlled hydrolysis of aluminum isopropoxide by the moisture present in the atmosphere as reported elsewhere (*1*).

Reagents. Piperidine, pyridine, benzyl chloride, benzaldehyde, *p*-methoxybenzaldehyde, *p*-methylbenzaldehyde, mercuric acetate, and pyridine-3-carboxylic acid used were of Analytical Grade. Butanal, ethanal, 2-methylpropanal, pentanal, and propanal were prepared by the dehydrogenation of corresponding alcohols over copper–chromium oxide catalyst at about 350°C (*4*).

Apparatus and experimental techniques. The catalytic flow-reactor and the general experimental techniques had been described previously (*5*). All the reactions were carried out at atmospheric pressure without carrier gas. Products were analyzed by gas chromatography using SE-30 (5% on 60–80 mesh Chromosorb-G, acid-washed white, $\frac{1}{8}$-diam. 6-foot length) column and FI-detector. Identification and quantitative estimations were made by comparison of retention time and peak areas, calibrated with the help of authentic samples. Further, the structures were confirmed by analyzing and comparing spectral data of pure compounds isolated from the reaction mixture with those of authentic ones.

Preparation and isolation of 3-benzylpyridine. A mixture of 2.12 g (0.02 mol) of benzaldehyde and 3.36 g (0.04 mol) of piperidine was made up to 20 ml in benzene. Condensation takes place with the separation of water. After 15 min the mixture was dried with anhydrous sodium sulfate. The solution was then passed over alumina at 420°C at 20 ml/h rate. Products were collected in a water-cooled receiver. Gas chromatographic analysis of this crude reaction

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products showed the presence of toluene (40%), *N*-benzylpiperidine (15%), 3-benzylpyridine (35%), and trace amounts of benzyl alcohol, benzoic acid, stilbene, and benzoylpiperidide. Benzene was distilled off and the residue was diluted with chloroform. The basic compounds were extracted with dil. HCl 2 or 3 times. Then the extract was made alkaline by dil. sodium hydroxide and extracted thrice with benzene. Evaporation of the benzene gave a residue which was chromatographed over 40 g silica gel (60–120 mesh) using chloroform as eluant. Removal of chloroform yielded 1 g (30%) of 3-benzylpyridine. Further elution with chloroform and 5% methanol and removal of solvent gave 0.33 g N-benzylpiperidine (10%).

The reactions of other aldehydes with piperidine were carried out and the products were analyzed/isolated in a similar manner.

Authentic 3-benzylpyridine was prepared by the reaction of lithium aluminum hydride and piperidine with benzyl chloride as reported in the literature (*6*). *N*-Alkylpiperidines were prepared by standard procedures (*7*). 3-Benzylpyridine as well as 3-butylpyridine obtained from the reaction of corresponding aldehydes with piperidine over alumina were oxidized by $KMnO_4$ to pyridine-3-carboxylic acid (*8*).

Benzylidine bis-1-piperidine **1** (*9*) was prepared by stirring 1:2 molar solution of benzaldehyde and piperidine in benzene for 1 h. Water formed in the reaction was removed by the addition of anhydrous Na_2SO_4. Evaporation of benzene gave the solid benzylidene bis-1-piperidine **1**. This was further purified by crystallization from hexane m.p. 94°C. A mixture of *N*-benzylpiperidine and *N*-benzyl-2,3-dehydropiperidine **2** was prepared by treating the former with mercuric acetate (*10*).

RESULTS AND DISCUSSION

Reactions of piperidine with aldehydes such as benzaldehyde, ethanal, propanal, butanal, 2-methylpropanal, and pentanal were carried out on alumina at 420°C. The results are summarized in Table 1. In the reaction of benzaldehyde with piperidine, toluene, *N*-benzylpiperidine, and 3-benzylpyridine were formed in major amount in addition to small amounts of benzyl alcohol, benzoic acid, benzyl benzoate, stilbene, and *N*-benzoylpiperidide. Simi-

TABLE 1

Reactions of Aldehyde with Piperidine on Alumina

Substance No.	Aldehyde	Product	Yield[a]	Picrate m.p.[b] (Ref. (*11*)) (°C)
1	Ethanal	3-Ethylpyridine	25	127.5–128 (128.1–128.5)
2	Propanal	3-Propylpyridine	35	98–99 (99.8–100.2)
3	Butanal	3-Butylpyridine	37	90 (90–90.5)
4	Pentanal	3-Pentylpyridine	36	78 (78.8–79)
5	2-Methylpropanal	3-Isobutylpyridine[e]	20	112.5–113 (113–114)
6	Benzaldehyde	3-Benzylpyridine	30	118.5 (119)
7	*p*-Methylbenzaldehyde	3-[4-methyl]Benzylpyridine [12]	19	89[c]
8	*p*-Methoxybenzaldehyde	3-[4-methoxy]Benzylpyridine[d]	18	117

Note. Weight of alumina 3 g, reactant: a mixture of 0.02 mol of the aldehyde and 0.04 mol of piperidine in 20 ml of benzene. Temp. 420°C, flow rate 20 ml/h.

[a] Yield isolated by column chromatography and based on aldehyde taken initially.

[b] Picrate m.p. are uncorrected.

[c] Picrate m.p. is not reported in literature.

[d] Not known in literature. High resolution mass spectrum, M^+ Calcd. 199.09971, Found 199.09732.

[e] Could not be isolated in pure form.

larly 3-alkylpyridines and *N*-alkylpiperidines were formed in major amounts in the reactions of other aldehydes with piperidine. *N*-Alkylpiperidines (not shown in Table 1) were identified by comparing their gas chromatographic retention times and NMR spectra with those of authentic samples prepared by the reaction of piperidine with alkyl chloride (*7*). The structure of 3-benzylpyridine was confirmed by analyzing and comparing spectral data (ir, NMR, and MS) of this sample with those of an authentic sample prepared by the reaction of benzyl chloride with pyridine and lithium aluminum hydride (*6*). Authentic samples of the other 3-alkylpyridines were not available. Their identity has been established from NMR spectra (Table 2) and the m.p. of the picrates (Table 1). Further 3-benzylpyridine isolated from the reaction mixture have been oxidized to pyridine-3-carboxylic acid by aqueous potassium permanganate. The structure of the resulting acid has been confirmed by comparing ir, NMR, m.p., and mixed m.p. of this sample with that of authentic pyridine-3-carboxylic acid.

Benzylidine bis-1-piperidine **1** crystallized out when a mixture of piperidine and benzaldehyde in hexane was kept for 15 min. The structure of this compound has been established by comparing its m.p. with the reported value (*9*) and analyzing the NMR spectrum. The pure benzylidene bis-1-piperidine **1** when passed over alumina gave toluene, piperidine, *N*-benzylpiperidine, and 3-benzylpyridine. The reaction between piperidine and the aldehyde is uncatalyzed. For the catalytic reaction one can use the purified alkyldine bis-1-piperidine or simply use a mixture of the aldehyde and piperidine in benzene. Such a solution contains the condensation product along with small quantities of the aldehyde and piperidine, exact composition of which was not derived. The yields are the same whether one uses a solution of the prepared condensation product or a mixture of the aldehyde and piperidine.

N-Benzylpiperidine passed over alumina was recovered unchanged. However, 3-benzylpyridine was obtained when *N*-benzyl-2,3-dehydropiperidine (obtained as a mixture with *N*-benzylpiperidine by the ox-

TABLE 2

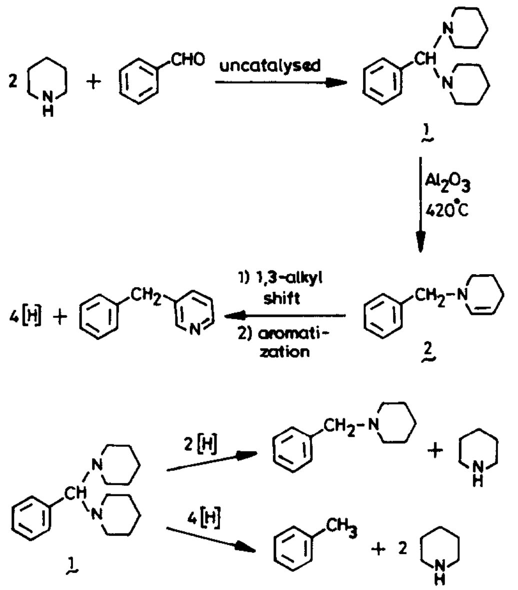
NMR Data of 3-Alkylpyridines[a,b]

1	3-Ethylpyridine	∂ 1.22 (3*H*,*t*), 2.52 (2*H*,*q*), 6.7–7.25 (2*H*,*m*), 8.05 (2*H*,*m*)
2	3-Propylpyridine	∂ 0.9 (3*H*,*t*), 1.5 (2*H*,*m*), 2.55 (2*H*,*t*), 7.2 (1*H*,*m*), 7.4 (1*H*,*m*), 7.45 (1*H*,*m*), 8.5 (2*H*,*m*)
3	3-Butylpyridine	∂ 0.9 (3*H*,*t*), 1.2–1.8 (4*H*,*m*), 2.65 (2*H*,*t*), 7.2 (1*H*,*m*), 7.45 (1*H*,*m*), 8.5 (2*H*,*m*)
4	3-Isobutylpyridine	∂ 0.95 (6*H*,*d*), 1.8 (1*H*,*m*), 2.45 (2*H*,*d*), 7 (1*H*,*m*), 7.2 (1*H*,*m*), 8.2 (2*H*,*m*)
5	3-Pentylpyridine	∂ 0.9 (3*H*,*t*), 1.2–1.8 (6*H*,*m*), 2.5 (2*H*,*t*), 6.8 (1*H*,*m*), 7.15 (1*H*,*m*), 8.1 (2*H*,*m*)
6	3-Benzylpyridine	∂ 3.7 (2*H*,*s*), 6.8 (7*H*,*m*), 8.2 (2*H*,*m*)
7	3-[4-methoxy]Benzylpyridine	∂ 3.5 (3*H*,*s*), 3.65 (2*H*,*s*), 6.4–6.8 (5*H*,*m*), 7.1 (1*H*,*m*), 8.1 (2*H*,*m*)
8	3-[4-methyl]Benzylpyridine	∂ 2.21 (3*H*,*s*), 3.75 (2*H*,*s*), 6.8 (6*H*,*m*), 7.1 (1*H*,*m*), 8.15 (2*H*,*m*)[c]

[a] All the NMR were recorded in EM-390, 90 MHz, $CDCl_3/CCl_4$–TMS–solvent.

[b] In general signal at ∂ 8.15 ascribed to C_2 and C_6 protons of pyridine, was solvent dependent. It appeared as a broad peak in $CDCl_3$ and a sharp peak in CCl_4. In mixture of $CDCl_3$ and CCl_4, the peak broadened as the concentration of $CDCl_3$ increased.

[c] In one particular sample of $CDCl_3$ the peak disappeared completely.



SCHEME 2

idation of the latter with mercuric acetate (*10*)) was passed over alumina. In none of the above reactions was pyridine detected. All these results suggest that the reaction may be going through benzylidene bis-1-piperidine and *N*-benzyl-2,3-dehydropiperidine as shown by the Scheme 2.

The formation of *N*-benzylpiperidine and toluene could be due to the hydrogenolysis of one or both of C–N bonds of benzylidine bis-1-piperidine by the hydrogen liberated during the aromatization of *N*-benzyl-2,3-dehydropiperidine (Scheme 2). No isomerization of the alkyl group has been observed in these reactions. The exact nature of the 1,3 shift of alkyl group during the aromatization of *N*-alkyl-2,3-dehydropiperidine is not known. Reactions of piperidine with acrolein and crotonaldehyde resulted in a complex mixture of pyridine compounds which could not be analyzed.

The reaction reported here is a simple route for 3-alkylpyridines which are otherwise difficult to prepare.

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REFERENCES

1. Jayamani, M., and Pillai, C. N., *J. Catal.* **82,** 485 (1983).
2. Abramovitch, R. A., and Saha, J. G., *Advan. Heterocycl. Chem.* **6,** 229 (1966).
3. Schoefield, K., "Hetero-Aromatic Nitrogen Compounds," p. 163. Plenum, New York, 1967.
4. Vogel, A. I., "A Textbook of Practical Organic Chemistry," 3rd ed. p. 320. Longmans, Green, London, 1956.
5. Kannan, S. V., and Pillai, C. N., *Indian J. Chem.* **8,** 1144 (1970).
6. Giam, C. S., and Abbott, S. D., *J. Amer. Chem. Soc.* **93,** 1294 (1971).
7. Moore, M. L., Organic Reactions, **5,** 301 (1949).
8. "Practical Handbook of Organic Chemistry" (P. A. Ongloy, Ed.), p. 363. Pergamon, Elmsford, N.Y., 1973 (English).
9. Cook, A. H., and Cox, S. F., *J. Chem. Soc.* 2342 (1949).
10. Leenard, N. J., and Hank, Jr., F. P., *J. Amer. Chem. Soc.* **79,** 5279 (1957).
11. "The Chemistry of Heterocyclic Compounds," Part 2: Pyridine and its derivatives, (Klinsberg, Ed.), p. 155. Interscience, London, 1961.
12. Lewis, A. W., Wei, K. C., McGlotten, J., and Robert, F., *J. Heterocycl. Chem.* **14(1),** 47 (1977).