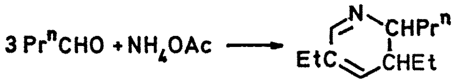
Condensation of Aldehydes with Ammonium Salts to give Substituted Pyridines

By H. B. CHARMAN* and J. M. ROWE

(*Imperial Chemical Industries Ltd., Heavy Organic Chemicals Division, Research and Development Department, Billingham, Teesside*)

Summary Treatment of n-butanal with ammonium acetate in acetic acid gave 3,5-diethyl-2,3-dihydro-2-n-propylpyridine, or, by oxidation, 3,5-diethyl-2-n-propylpyridine; similarly, acetaldehyde on oxidation gave 2-picoline.

THE reaction of aldehydes and ammonia to give substituted pyridines has received much attention, predominantly at 150—250° under pressure in the liquid phase and at higher temperatures in the vapour phase.[1] We now report conditions under which the condensation proceeds at near-ambient temperatures to give initially a substituted dihydropyridine, or, by copper(II)-catalysed oxidation with molecular oxygen, a substituted pyridine.



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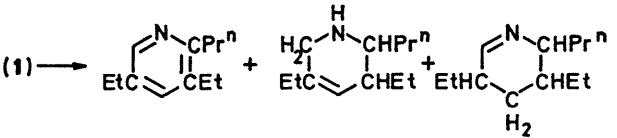

(2)

(2) **(3)** **(4)**

The reaction of n-butanal (1·6M) and ammonium acetate (0·8M) in deuterioacetic acid was studied at 35° for 1 h and subsequently at room temperature by n.m.r. spectroscopy. Initially, 3,5-diethyl-2,3-dihydro-2-n-propylpyridine (**1**) was formed (equation 1), with its concentration reaching a maximum after 45 min and then diminishing as 3,5-diethyl-2-n-propylpyridine (**2**), its 1,2,3,6-tetrahydro-derivative (**3**), and a small proportion of the 2,3,4,5-tetrahydro-derivative (**4**) were formed by disproportionation (equation 2.) No other products were detected (n.m.r.) apart from the crotoner,† 2-ethylhex-2-enal. From n.m.r. spectra peak areas, after 45 min, about 90% of the aldehyde had reacted, and the molar ratio (**1**) : 2-ethylhex-2-enal was 6 : 1. After 9 days the products were (with molar ratios in parentheses) (**1**) (2), (**2**) (4), (**3**) and (**4**) (4), and 2-ethylhex-2-enal (1).

The products were identified by their n.m.r. spectra and by i.r., n.m.r., and high resolution mass spectroscopy of the basic products separated by ether extraction. The assignment of n.m.r. peaks to (**2**) was confirmed by comparison with a reference spectrum of an authentic sample.

The effect of oxygen on the reaction was examined to see if (**1**) or intermediates in its formation could be oxidised to give (**2**), using copper(II) acetate as catalyst. Oxygen was passed through a solution of n-butanal (0·9M), ammonium acetate (0·52M), and copper(II) acetate (0·022M) in acetic acid at 65° for 105 min. Oxygen [0·14 mol l^{-1} (of solution)] was absorbed, and ether extraction of the basic product yielded (**2**) (60% based on aldehyde added) containing less than 1% hydropyridines (n.m.r.). The % yields of other products were n-butyric acid, 4, carbon dioxide, 0·5, and carbon monoxide, $< 0\cdot1$.

TABLE. *Oxidation of acetaldehyde in the presence of ammonium salts; copper*(II) *acetate,* 0·022M; *ammonium acetate,* 0·52M; *acetaldehyde,* 0·73 mol l^{-1} (*of reaction solution*) *added continuously over the time indicated as an equivolume mixture with the carboxylic acid solvent*

T, °C	Solvent acid	Duration of acetaldehyde addition, min	Oxygen absorbed, mol l^{-1} (of solution)	Yield of 2-picoline based on acetaldehyde added, %
70	Acetic	60	0·08	10
90	Acetic	60	0·14	29
100	Propionic	60	0·17	40
110	Propionic	35	0·18	52

The substituted pyridine (**2**) was separated by ether extraction of the combined products from a series of oxidation experiments and distillation (139—140°/35 mm), and was characterised by preparation of the picrate, m.p. 122°; lit[2] m.p. 122° and chloroplatinate, m.p. 165—6°, lit[2] m.p. 166—7°. The distillate contained a trace of (**3**) (n.m.r.)

The reaction of acetaldehyde (1·4M) and ammonium acetate (0·9M) in deuterioacetic acid was also examined by n.m.r. spectroscopy at 35°. Most of the aldehyde had

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† From n-butanal by aldol condensation and dehydration.

reacted within 45 min to give what appeared to be a polymeric product; substituted pyridines were not detected. However, with oxygen and copper(II) acetate as catalyst 2-picoline was formed and was estimated by v.p.c. (see Table). 5-Ethyl-2-methyl-pyridine, which is normally the principal product from acetaldehyde and ammonia at higher temperatures,[1] was not detected.

It is suggested that acetaldehyde reacts with ammonium acetate to give a dihydro-2-picoline, and that this can then undergo further condensation reactions. Dihydropyridine readily decomposes;[3] oxidation of the dihydro-2-picoline to 2-picoline could compete with the condensation reactions, oxidation being favoured at higher temperatures (see Table).

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[1] 'Pyridine and its Derivatives, Pt 1,, ed. E. Klingsberg, Interscience, New York, 1960, p. 474.

[2] M. Tracy and J. Patrick, *J. Amer. Chem. Soc.*, 1952, **74**, 2984.

[3] N. Cook and J. Lyon, *J. Amer. Chem. Soc.*, 1965, **87**, 3283.