3,4-Diethylpyridine

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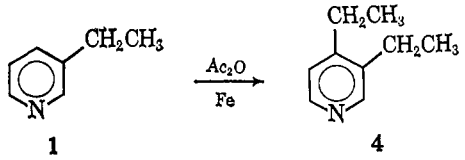
The role played by 3,4-diethylpyridine as a degradation product in the structure elucidation of various alkaloid groups is well documented.[1] More recently this compound has provided the starting point for the synthesis of an important group of benzomorphan analgesics.[2] Despite the repeated utilization of 3,4-diethylpyridine, however, no adequate synthesis of this compound has been recorded heretofore. The only synthesis reported in fact is that of Koenigs[3] whereby 3-ethyl-4-methylpyridine (β-collidine) is converted by formaldehyde to 3-ethyl-4-(β-hydroxyethyl)-pyridine and the latter is successively reduced with phosphorous–hydriodic acid and finally zinc in an overall yield of 8% or less. We wish to report two methods for synthesizing 3,4-diethylpyridine which afford this substance in 55–60% isolated yield.

The first approach is based on the method of Arens and Wibaut[4] for preparing 4-ethylpyridine by reductive alkylation of pyridine with acetic anhydride and zinc dust. By employing a modification[5] of this method in which iron powder is substituted for zinc, 3-ethylpyridine could be converted in 55% yield to 3,4-diethylpyridine. The intermediate formation of the species **2**[4b] and **3**[6] enroute to **4** in the unsubstituted pyridine series (R = H) has been well established.



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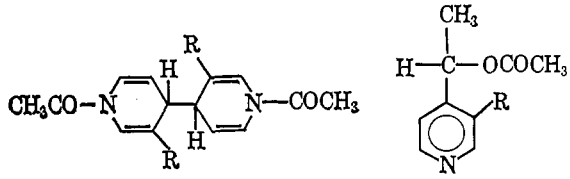
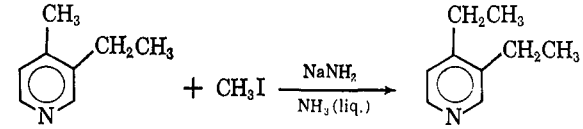


2 **3**

The second route employed for preparing 3,4-diethylpyridine consisted of direct methylation of 3-ethyl-4-methylpyridine (β-collidine) according to the method of Chichibabin[7] ($NaNH_2$–CH_3I) as developed by Brown and Murphey.[8] By this route a yield greater than 80% of 3,4-diethylpyridine, as measured by vapor phase chromatography, could be realized. Separation of the product from β-collidine is difficult by distillation; however, isolation through its picrate derivative permitted 3,4-diethylpyridine to be obtained in 50–60% yield by this route.



Experimental

Ethylation of 3-Ethylpyridine.[5]—In a three-necked flask equipped with reflux condenser, stirrer, and thermometer was placed a solution of 13 g. (0.121 mole) of 3-ethylpyridine[9] in 30 ml. of acetic anhydride. To the stirred mixture maintained at 80° was added 9.0 g. of iron powder (Merck reagent, iron by hydrogen) portionwise over a period of 20 min. and the mixture was kept at 80° for 1 hr. At the end of this period 3 ml. of glacial acetic acid was added followed by 4.0 g. of iron powder over a period of 20 min. At this point 15 ml. of acetic anhydride was added and the temperature was raised to 135°. After 1 hr. an additional 10 ml. of acetic anhydride was added and the temperature was lowered to 125° with addition of 5 g. of iron powder over a 20-min. period. The temperature was subsequently raised to 135° again and at the conclusion of 25 min. an additional 6-ml. portion of acetic acid was added followed again by 2.5 g. of iron powder over a 15-min. period and the reaction mixture was held for 30 min. at 135°.

At this juncture the reaction mixture was cooled to 110° and treated cautiously with 50 ml. of water, while maintaining the temperature at 110° by external cooling. The reaction mixture was subsequently maintained at 75° during the careful addition of 50 ml. of 50% aqueous potassium hydroxide. At the conclusion of this operation the reaction mixture was transferred to a 1-l. three-necked flask with 200 ml. of water and 100 ml. of benzene and steam distilled. The aqueous layer from the distillate was extracted with benzene. The benzene extract was washed with saturated sodium chloride solution and dried over potassium carbonate. Removal of the benzene and fractionation of the residue through a Vigreux column packed with protruded metal packing gave a small forerun of unreacted 3-ethylpyridine (5%) followed by 9.05 g. (55%) of 3,4-diethylpyridine, b.p. 208–209°.

Anal. Calcd. for $C_9H_{13}N$: C, 79.95; H, 9.69; N, 10.36. Found: C, 79.91; H, 9.20; N, 10.62.

The spectral characteristics of this material were identical with those of an authentic sample of 3,4-diethylpyridine as was the melting point and mixture melting point of its crystalline picrate salt, 136–138°.

Methylation of 3-Ethyl-4-methylpyridine.—To a mechanically stirred mixture of 70 mg. of finely powdered ferric nitrate in 200 ml. of liquid ammonia contained in a 500-ml. round-bottomed flask fitted with a Dry Ice reflux condenser (protected by a soda lime tube) was added 0.5 g. of sodium. The blue color was discharged within 5 min. to a gray slurry. An additional 3.18 g. of sodium (3.68 g. in total, 0.16 g.-atom) was added at intervals in small pieces. After stirring for 0.5 hr., 3-ethyl-4-methylpyridine (19.39 g., 0.16 mole) was added at a fast dropping rate to the suspension of sodamide in liquid ammonia. The reaction mixture changed color from dark gray to deep purple. Stirring was continued for 30 min. and methyl iodide (22.71 g., 0.16 mole) was then added dropwise at such a rate that a gentle reflux was secured. As soon as the equivalent quantity was introduced, the reaction mixture lost its intense color. The final

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(9) 3-Ethylpyridine is available in high yield from 3-acetylpyridine by Wolff–Kishner reduction [T. I. Fand and C. F. Lutomski, *J. Am. Chem. Soc.*, **71**, 2931 (1949)] or from 2-methyl-5-ethylpyridine by oxidative decarboxylation [D. Jerchel, E. Bauer, and H. Hippchen, *Chem. Ber.*, **88**, 156 (1955)].

grayish slurry was stirred for 1 additional hr. After the ammonia had evaporated, 50 ml. of water was added dropwise. The resulting solution was extracted with ether, and the organic extract was washed with saturated salt solution and dried over sodium sulfate. The ether was removed *in vacuo* to provide 21.2 g. of oil, which vapor phase chromatography indicated to contain 80% of the desired 3,4-diethylpyridine and 13% of 3-ethyl-4-methylpyridine. This product could be purified by fractional distillation (preferably with a 70-plate column) to afford pure 3,4-diethylpyridine, b.p. 208–209°, $n^{29.5}$D 1.5025.

Anal. Calcd. for $C_9H_{13}N$: C, 79.95; H, 9.69; N, 10.36. Found: C, 79.64; H, 9.68; N, 10.08.

More simply, the total product was treated with picric acid, and the crystalline picrate of 3,4-diethylpyridine, m.p. 136–138°, was separated by crystallization from methanol in 50–60% yield. The picrate, on treatment with ammonia, released pure 3,4-diethylpyridine essentially quantitatively.

Isomerization in Residual Alkyls from Pyrolytic and Ester Interchange Reactions of Tributyl Phosphate[1]

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In previous work[2] considerable isomerization of butenes was observed during the pyrolysis of tri-*n*-butyl phosphate (TBP). The amount of isomerization increased as the acid concentration in the reaction mixture increased. Whether concurrent alkyl group rearrangement took place in the phosphate ester products during pyrolysis was not known.

After finding some rearrangement in the residual alkyl groups from TBP pyrolysis, we wanted to know if rearrangement occurred during ester interchange between TBP and its acid degradation products [dibutyl phosphate (HDBP), monobutyl phosphate (H_2MBP), and H_3PO_4]. The ester interchange reaction occurs at temperatures lower than those necessary for the pyrolytic production of butene.[2a,3] We also needed to know if ester interchange between TBP and phosphoric acid caused any rearrangement since the method had been used for the preparation of labeled TBP.[3] Therefore, TBP to H_3PO_4 ratios and reaction temperatures were chosen at the extremes and intermediate of conditions used in the ester interchange investigation.

The analytical method for determining the alkyl composition in the residues was based on the dealkylation of TBP with other acids.[4,5] Virtually pure (99.7%) *n*-butyl bromide was isolated by distillation when TBP was heated with constant-boiling HBr. The composition of the mixture of butyl bromide isomers recovered from the residue samples was determined by gas chromatography.

Results from the ester interchange between TBP and phosphoric acid are listed in Table I. Very little rearrangement occurred within the alkyl groups; the most that was found resulted from the most acid mixture. Only 0.8% of all butyl groups in the reaction products were *sec*-butyl after TBP·H_3PO_4 was heated for 3 hr. at 176°. Under the latter conditions about one-fifth of the butyl groups decomposed into a butene mixture comprised mainly (62%) of *cis*- and *trans*-butene-2. Thus, most isomerization was evident in the gas phase with relatively little observed in the liquid phase.

TABLE I

ISOMERIZATION IN ALKYL GROUPS FROM TBP–H_3PO_4 ESTER INTERCHANGE

Mole ratio of TBP to H_3PO_4	Bath temp. ±1°	Time, hr.	Substance dealkylated	Alkyl composition, % *n*-Butyl	Alkyl composition, % *sec*-Butyl
1[a]	176	3	Pot residue	99.2	0.8
4	177	5	HDBP–H_2MBP	99.8	0.2
			TBP	100	...
100	206	1	TBP–P^{32}	100	...

[a] TBP decomposition = 23%.

Labeled TBP is best prepared at TBP to anhydrous, radioactive H_3PO_4 mole ratios of between 40 and 100 to 1 by heating the solution for 1 hr. in a boiling tetralin (206°) bath. Under these conditions, as shown in Table I, no rearrangement occurs. However, when decomposition takes place during the exchange, rearrangement in the esters does occur.

When TBP was pyrolyzed to almost three-fourths completion some isomerization in the ester residue was observed. The results are shown in Table II. Conversion of *n*-butyl groups to *sec*-butyl increased slightly throughout the reaction; about 3% *sec*-butyl was found in the residue from the reaction at 72% decomposition (Table II, column 6). This was about 0.8% yield of *sec*-butyl groups based on the total butyl groups at the start (column 7). Extrapolation of the values in column 7 to 100% reaction indicates that the total *sec*-butyl yield would probably not exceed 1.5%.

The distribution of *sec*-butyl groups in the residue compounds was uniform. TBP, HDBP, and H_2MBP, isolated from the residue, had the same percentage rearrangement, within experimental error, as the residue itself.

The ratios of butene-2 (*cis* + *trans*) and *sec*-butyl yields are shown in column 9, Table II. The ratio doubled over the range 30–72% decomposition; at 72% reaction 23 butene-2 molecules had formed for every *sec*-butyl group left in the residue products. Over this same range the frequency of *sec*-butyl formation increased from one in every 150 C–O scissions to one in every 80–90 (column 10 = per cent TBP decomposed/per cent *sec*-butyl yield). Thus the yield of *sec*-butyl groups increased, but the frequency of formation with respect to butene-2 decreased.

The presence of *sec*-butyl groups in the ester residue products may be due in part to reaction of the acids with dissolved butene product. The electrophilic addition of halogen acids and sulfuric acid to olefins is well known.[6] Phosphoric acid has been shown by

(1) Research sponsored by the U. S. Atomic Energy Commission under contract with the Union Carbide Corp.

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