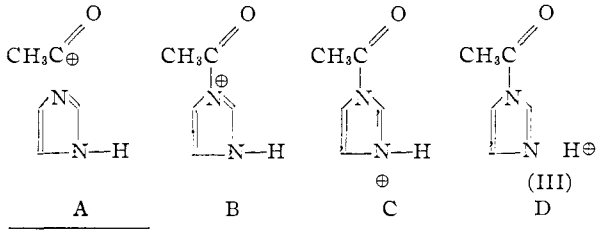
more nearly consistent with those of hydroxide ion and "aqueous" hydrolysis.

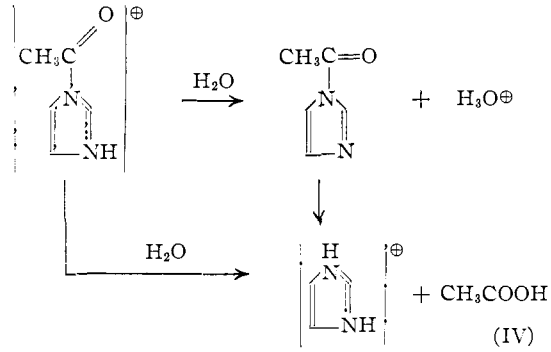
The nature of the proposed intermediate X in mechanism I is at present unclear. It has been suggested[2,35] that an imidazolyl group becomes acylated in the course of the reaction of esterases with substrate to produce an N-acylimidazolyl grouping. It is known[36-39] that the hydrolysis of acyl imidazoles is characterized by very low heats of activation. The identity of acetylimidazole as X is thus consistent with equation I. On this basis it would be expected that N-methylimidazole (pK_a' 7.2),[29] as in the case of the pyridines, would not exhibit catalysis at the low concentrations employed herein for other imidazoles. Actually this is not the case, since when N-methylimidazole was employed as catalyst the value of k_2' was found to approximate 7.6 l. mole^{-1} min.$^{-1}$, and this value compares favorably to that of 12.7 l. mole^{-1} min.$^{-1}$ obtained for imidazole under identical experimental conditions. It is therefore evident that the formation of an N-acetylimidazole intermediate is not a necessary prerequisite for catalysis. The catalyst may act by the formation of an acylium ion–imidazole complex (III) in which



A B C D (III)

the acylium ion is stabilized by an additional ionic resonance effect through the participation of forms A, B, C and D.

With N-methylimidazole, form D would be very improbable, whereas in the case of imidazole, D could be of major importance and the resultant resonance hybrid might be expected to yield either its proton or acylium ion readily to water with the formation of N-acetylimidazole or imidazole and acetate[40] (IV).



(IV)

Addenda: During the preparation of this manuscript, we learned from Dr. M. L. Bender of his studies on the imidazole catalysis of ester hydrolysis (THIS JOURNAL, **79**, 1656 (1957)). The general concordance of the results obtained in these two independent studies is most gratifying.

Acknowledgments.—This work was supported by grants from the Rockefeller Foundation and from the Institute of Arthritis and Metabolic Diseases, National Institutes of Health.

(35) F. Bergmann, *Disc. Faraday Soc.*, **20**, 133 (1955).

(36) E. R. Stadtman, "The Mechanism of Enzyme Action," W. D. McElroy and B. Glass, eds., Johns Hopkins Press, Baltimore, Md., 1954, p. 596.

(37) E. R. Stadtman and F. H. White, THIS JOURNAL, **75**, 2022 (1953).

(38) M. Bergmann and L. Zervas, *Z. physiol. Chem.*, **175**, 145 (1928).

(39) T. Wieland and G. Schneider, *Ann.*, **580**, 159 (1953).

(40) The mechanism proposed herein is analogous to that of Gold and co-workers (*J. Chem. Soc.*, 1406, 1409, 1416 (1953)) for the catalysis of hydrolysis of acetic anhydrides by pyridines. The more profitable association of the acylium ion with imidazole, as compared to pyridine, could well rest on the greater orbital overlap and subsequent delocalization of the formal positive charge of the acylium ion with the former base.

NEW HAVEN, CONNECTICUT

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF TEXAS]

Alkylpyridines. Extension of the Sodamide–Liquid Ammonia Alkylation Method

BY H. L. LOCHTE AND TOM H. CHEAVENS[1]

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Methyl iodide alkylation using the sodamide–liquid ammonia method has been applied to 2,3-, 2,4-, 2,5- and 2,6-lutidines to effect the synthesis of 2-ethyl-3-methyl-, 4-ethyl-2-methyl-, 2-methyl-4(2-propyl)-, 2-ethyl-5-methyl-, 2-ethyl-6-methyl- and 2,6-diethylpyridines. A marked preferential reactivity of the 4-alkyl group in 2,4-lutidine is exhibited. The previously reported activity of alkyl groups in the 3-position on the pyridine ring has been further confirmed by the synthesis of 3-propyl- and 3-(3-pentyl)-pyridines from 3-picoline and ethyl bromide.

In an attempt to identify a base isolated from Colorado shale-oil, a survey of the isomeric $C_8H_{11}N$ pyridines was made. Of the 22 possible isomers in this series, only 2-ethyl-3-methylpyridine and 3,4,-5-trimethyl-pyridine were unreported. However 3-propylpyridine was characterized only by means of its boiling point[2] which seemed too low for a substance of this constitution. In addition, some confusion existed as to the melting point of the picrate of 2-ethyl-5-methylpyridine.[3]

The first synthetic route leading to compounds of this type investigated by the authors was that developed by Brown and Murphy,[4] the side-chain

(1) From the Ph.D. Dissertation of Tom H. Cheavens, University of Texas, 1955; Union Carbide and Carbon Fellow, 1953–1954.

(2) A. Cahours and A. Etard, *Compt. rend.*, **92**, 1082 (1881).

(3) (a) W. A. Jacobs and L. C. Craig, *J. Biol. Chem.*, **129**, 79 (1939); **143**, 427 (1942); (b) W. A. Jacobs, L. C. Craig and G. J. Lavin, *ibid.*, **141**, 51 (1941); (c) V. Prelog and S. Szpilfogel, *Helv. Chim. Acta*, **25**, 1306 (1942).

(4) H. C. Brown and W. A. Murphy, THIS JOURNAL, **73**, 3308 (1951).

alkylation of alkylpyridines with sodamide in liquid ammonia as the condensing agent. Except for the work of Bergstrom,[5] who attempted the ethylation of 2,4-lutidine and 2,4,6-trimethylpyridine, no reports have appeared concerning the side-chain alkylation of pyridine bases other than picolines. With the latter compounds the careful study by Brown and Murphy[4] emphasized the need for careful fractionation of the products and demonstrated the reactivity of the methyl group of 3-picoline for the first time. Lochte and Wheeler[6] employed this method to effect the synthesis of a series of cycloalkylpyridines.

In addition to affording a convenient route to the 3-propyl-, 2-ethyl-3-methyl- and 2-ethyl-5-methylpyridine isomers, the application of this synthesis to the available lutidines afforded an interesting indication of the relative competitive reactivity of the 2-, 3- and 4-methyl groups on the pyridine nucleus. As was expected, 2,3-lutidine yielded 2-ethyl-3-methylpyridine, while 2-ethyl-5-methylpyridine, identical with that previously synthesized,[3c] was obtained from 2,5-lutidine; thus the 3-methyl group is less reactive than that in the 2-position.

When 2,4-lutidine was treated with 2 molar equivalents of methyl iodide, a complex mixture was obtained which could not be separated by fractional distillation. Non-aqueous titration of several of the fractions indicated that reaction had proceeded to the di- and trialkylated stages. A pure picrate believed to be that of the previously unreported 2-methyl-4-(2-propyl)-pyridine was isolated from one of the fractions. When this preparation was repeated on a larger scale with one molar equivalent of methyl iodide, a shorter halide addition time and using refractionated 2,4-lutidine of a better grade, 4-ethyl-2-methylpyridine was formed in high yield. These results indicated that a preferential reactivity of the 4-alkyl group is exhibited, a result which may be explained as due to the enhanced ability of a 4-methyl group to participate in hyperconjugation through *p*-quinoid structures.[7]

In the methyl iodide alkylation of 2,6-lutidine, 2-ethyl-6-methylpyridine was obtained in addition to higher boiling products from which 2,6-diethylpyridine was identified as the picrate.

By alkylation of 3-picoline with ethyl bromide, 3-propylpyridine was formed in high yield and proved to have a higher boiling point than that reported in the literature.[2,8] A small amount of still higher boiling material which was separated was probably 3-(3-pentyl)-pyridine.

Experimental[9]

2-Ethyl-3-methylpyridine.—Following the procedure of Brown and Murphy,[4] sodamide in liquid ammonia was prepared from 8 g. of sodium by the method of Vaughn, Vogt and Nieuwland[10] and 36 g. of 2,3-lutidine was added rapidly, then stirred for 30 min. Methyl iodide (47.5 g.) was added over a 30-min. period, the reaction mixture was stirred for 1 hr. and the ammonia allowed to evaporate. The residue was treated with 100 ml. of water, filtered and extracted 4 times with ether. The combined ether extracts were dried over anhydrous sodium sulfate and concentrated. The residue was fractionated in vacuum using an efficient Todd column at a reflux ratio of 50/1. The total yield of basic material and the conversion to the desired product was estimated graphically from the fractionation curve in this and in subsequent experiments (see Table I). (See Tables II and III for properties and analyses.) The picrate melted at 138–40°, that of 3-ethyl-2-methylpyridine melts at 140°.[11] A sample of this picrate obtained through the courtesy of Professor Wibaut showed a large depression in a mixed melting point with our picrate, thus excluding the possibility that the 3-ethyl isomer had been obtained.

2-Methyl-4-(2-propyl)-pyridine.—Sodamide in liquid ammonia was prepared as before, using 16 g. of sodium. The mixture was stirred for 45 min., 40 g. of 2,4-lutidine (Eastman Practical, 95%) was added rapidly, and stirring was continued for 30 min. The methyl iodide was added in two portions. The first (47.5 g.) in 25 min. and, after stirring for 30 min., the second (47.5 g.) in 20 min. The reaction mixture was stirred for 30 min. longer before allowing the ammonia to evaporate. The product was recovered and fractionated as before. The material boiled over a wide range and no definite plateaus were present in the fractionation curve. Non-aqueous titration of some of the 18 cuts showed that reaction had largely proceeded to the di- and trialkylated stages. The picrate of cut 4, neut. equiv. 118, $n^{25}D$ 1.4962, was prepared and after several recrystallizations from ethanol melted at 165–167°. A mixed melting point with an authentic sample of the picrate of 2,5-lutidine showed no depression. This base must have been present as an impurity in the starting material.

Cut 10, b.p. 98–99° (40 mm.), mol. wt. 137, $n^{25}D$ 1.4939, yielded a pure picrate, m.p. 119–121°. Depression was exhibited in the m.p. on mixing with either the picrate of 2-ethyl-4-methylpyridine, m.p. 122–123°,[12] or that of 4-methyl-2-(2-propyl)-pyridine, m.p. 118–120°.[13] Since the picrate of the only other 2,4-substituted pyridine of the formula $C_9H_{13}N$, 2,4-diethylpyridine, melts at 98–100°[14] and both 3-methyl-2-(2-propyl)-pyridine, picrate m.p. 149–151°,[13] and 5-methyl-2-(2-propyl)-pyridine, picrate m.p. 111–112°,[13] conceivably arising from impurities in the starting material can be eliminated on the basis of difference in melting point, this substance must almost certainly be the previously unreported 2-methyl-4-(2-propyl)-pyridine.

4-Ethyl-2-methylpyridine.—Sodamide in liquid ammonia was prepared as before using 23 g. of sodium, and 107 g. of 2,4-lutidine (Eastman White Label, refractionated) was run in rapidly. The mixture was stirred for 30 min. and 142 g. of methyl iodide added in 20 min. Stirring was continued for 30 min. before the ammonia was allowed to evaporate and the product recovered as usual. The concentrated basic material was fractionated at atmospheric pressure using the Todd column. The main fraction boiling constantly at 178° was collected and converted to the picrate. After one recrystallization this melted at 140–142°, mixed m.p. with an authentic sample[12] undepressed. Infrared spectra of the two picrates (KBr pellets) were identical. The reported melting point of the isomeric 2-ethyl-4-methylpyridine picrate is 120–121°.[15]

2-Ethyl-5-methylpyridine.—Thirty-six grams of 2,5-lutidine (Reilly Tar and Chemical Corp.) was added rapidly to sodamide in liquid ammonia using 16 g. of sodium. After stirring for 30 min., 49 g. of methyl iodide was added in 15 min., and after 30 min. another 49-g. batch of methyl iodide was added as before. The product was isolated as before

(5) F. W. Bergstrom, THIS JOURNAL, **53**, 4065 (1931).

(6) H. L. Lochte and E. N. Wheeler, *ibid.*, **76**, 5548 (1954).

(7) H. C. Brown and X. R. Mihm, *ibid.*, **77**, 1723 (1955).

(8) After the completion of this work the synthesis of 3-propylpyridine by a similar route was reported by W. W. Leake, A. D. Miller and R. Levine at the 129th Meeting of the American Chemical Society, Abstracts p. 25-N.

(9) Melting points are corrected; boiling points uncorrected. Yields are summarized in Table I, most physical constants are found in Table II and analyses in Table III.

(10) T. H. Vaughn, R. R. Vogt and J. A. Nieuwland, THIS JOURNAL, **66**, 2120 (1944).

(11) J. P. Wibaut and E. C. Kooyman, *Rec. trav. chim.*, **63**, 231 (1944).

(12) Obtained through the courtesy of Mr. J. S. Ball of the U. S. Bureau of Mines.

(13) H. L. Lochte, P. F. Kruse, Jr., and E. N. Wheeler, THIS JOURNAL, **75**, 4477 (1953).

(14) A. Ladenburg, *Ann.*, **247**, 1 (1888).

(15) A. Eckert and S. Loria, *Monatsh.*, **38**, 225 (1917).

TABLE I

ALKYLATION PRODUCTS FROM ALKYL HALIDES AND ALKYL PYRIDINES

Pyridine[a]	Mole	Alkyl halide	Mole	$NaNH_2$, mole	Addn. time, min.	Products[a]	Conversion,[b] %	Recovery,[c] %
2,3-diMe	0.34	CH_3I	0.33	0.35	30	2-Et-3-Me	60	47
2,4-diMe	0.37	CH_3I	0.66	0.70	75	2-Me-4-(2-Pr)	..	..
2,4-diMe	1.00	CH_3I	1.00	1.00	20	4-Et-2-Me	87	97
2,5-diMe	0.34	CH_3I	0.69	0.70	60	2-Et-5-Me	53	76
2,6-diMe	0.37	CH_3I	0.66	0.70	130	2-Et-6-Me	56	80
						2,6-diMe	26	..
3-Me	0.69	C_2H_5Br	0.70	0.70	45	3-Pr	63	75
						3-(3-Pen)	..	..

[a] Me, methyl; Et, ethyl, Pr, propyl; Pen, pentyl. [b] Based on total basic material recovered. [c] Total basic material recovered.

TABLE II

PROPERTIES OF ALKYLPYRIDINES

Pyridine[a]	B.p., °C.	Mm.	Lit. b.p. value °C.	Mm.	$n^{25}D$	Picrate, m.p., °C.	Lit. value, m.p., °C.
2-Et-3-Me	89.5–90.0	74	.....		1.5012	138–140	.....
	172–173	Atm.					
4-Et-2-Me	178	Atm.	177–179	Atm.[b]	.....	140–142	141–142[b]
2-Me-4-(2-Pr)	98–99[c]	40	.....		1.4939[c]	119–121	.....
2-Et-5-Me	86	40	73–76	12[d]	.....	142.5–144.0	144–145[d]
						149.5–150.5	150–151
2-Et-6-Me	77[c]	40	160–161.5	Atm.	1.4920[c]	127–130	130
2,6-diEt	91[c]	40	71–73	17[e]	1.4890[c]	115–117	115[e]
3-Pr	94	40	170	Atm.[f]	1.4931	100.5–101.5	.....
	184	751					

[a] Me, methyl; Et, ethyl; Pr, propyl; Pen, pentyl. [b] A. Eckert and S. Loria, *Monatsh.*, **38**, 225 (1917). [c] Physical constants for fractionation cut. [d] V. Prelog and S. Szpilfogel, *Helv. Chim. Acta*, **25**, 1306 (1942). [e] E. E. Blaise and M. Montague, *Compt. rend.*, **180**, 1760 (1925). [f] A. Cahours and A. Etard, *ibid.*, **92**, 1082 (1881).

TABLE III

ANALYSIS OF ALKYLPYRIDINES AND THEIR PICRATES

Pyridine	Formula	Nitrogen, % Calcd.	Found[a]	Picrate formula	Nitrogen, % Calcd.	Found[b]
2-Et-3-Me	$C_8H_{11}N$	11.56	11.38	$C_8H_{11}N\cdot C_6H_3N_3O_7$	16.00	15.90
2-Me-4-(2-Pr)	.....	...	...	$C_9H_{13}N\cdot C_6H_3N_3O_7$	15.38	15.53
3-Pr	$C_8H_{11}N$	11.56	11.52	$C_8H_{11}N\cdot C_6H_3N_3O_7$	16.00	15.82[c]

[a] By the non-aqueous titration method of J. S. Fritz, *Anal. Chem.*, **22**, 1028 (1950). [b] By the Biochemical Institute, Univ. of Texas, and Clark Microanalytical Laboratories, Urbana, Ill. [c] *Anal.* Calcd.: C, 48.00; H, 4.03. Found: C, 47.81; H, 4.29.

and fractionated through the Todd column. The fractionation curve exhibited two well-defined plateaus. The first, due to unreacted 2,5-lutidine, was followed by another, b.p. 86° (40 mm.), due to 2-ethyl-5-methylpyridine.

The picrate of the higher boiling material, after recrystallization from ethanol, melted at 142.5–144.0°, resolidified, then remelted at 149.5–150.5°. Prelog and Szpilfogel[3c] reported a similar dual melting point. A sample of the picrate of 2-ethyl-5-methylpyridine, m.p. 141–143°, was obtained through the courtesy of Professor Prelog; mixed m.p. with our picrate 141–143°.

2-Ethyl-6-methylpyridine and 2,6-Diethylpyridine.—Sixteen grams of sodium was used to prepare sodamide in liquid ammonia as in previous experiments, 40 g. of 2,6-lutidine (Eastman Practical, 95%) was added rapidly, and the reaction mixture was stirred for 30 min. The first portion of methyl iodide (47.5 g.) was added over a 40-min. period, the mixture stirred for 1 hr. and the second 47.5-g. portion added as above. The product was recovered and fractionated. Eighteen 1.5 to 2.0 ml. fractions were collected from 62–96° (40 mm.). No well-defined plateaus were found, but the picrate of cut 8, mol. wt. 123, b.p. 77° (40 mm.), was prepared and after one recrystallization from ethanol melted at 127–130°. The reported melting point of the picrate of 2-ethyl-6-methylpyridine is 130°.[14] The picrate of cut 18, b.p. 91° (40 mm.), mol. wt. 136, melted at 115–117°; literature value for 2,6-diethylpyridine picrate 115°.[15] The only other probable product of this reaction, 2-methyl-6-(2-propyl)-pyridine, has not been reported in the literature.

3-Propylpyridine.—Sodamide in liquid ammonia was prepared using 16 g. of sodium; 65 g. of refractionated 3-picoline was added rapidly, then 77 g. of redistilled ethyl bromide was introduced in 45 min. The product was isolated and fractionated through the Todd column. The fractionation curve exhibited three well-defined plateaus. The first, b.p. 61° (40 mm.), was due to unreacted 3-picoline, while the second, b.p. 94° (40 mm.), represented the desired 3-propylpyridine. The third plateau was probably due to 3-(3-pentyl)-pyridine.

Cahours and Etard,[2] who prepared their product by the rather equivocal process of pyrolyzing nicotine, reported b.p. 170°, which in view of the fact that 4-propylpyridine boils at 186°,[14] is far too low. The b.p. 184° (751 mm.) found in the present work agrees well with the generalization that the boiling points of 3- and 4-substituted pyridines are usually similar.

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(16) E. E. Blaise and M. Montagne, *Compt. rend.*, **180**, 1760 (1925).