reaction with 1 ml. of glacial acetic acid, and the process was repeated at one-hour intervals an additional two times. The heating was continued for a total of six hours. On cooling, 0.64 g. of white needles were collected, m.p. 99.5–100.5°. Addition of water to the filtrate yielded 0.39 g. of white powder, m.p. 98.5–100.5°, total yield 88%. Two recrystallizations from ethanol gave an analytical sample, m.p. 100.1–101.4°.

Anal. Calcd. for $C_{15}H_{16}O_2S$: C, 69.20; H, 6.20. Found: C, 69.33; H, 6.14.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF PURDUE UNIVERSITY]

A Convenient Synthesis of the Monoalkylpyridines; a New Prototropic Reaction of 3-Picoline[1,2]

BY HERBERT C. BROWN AND WILBUR A. MURPHEY[3]

The monoalkylpyridines, 2-, 3- and 4- ethyl-, isopropyl and *t*-butylpyridines, have been synthesized and isolated in a state of high purity, as established by freezing point determinations. The reaction of methyl chloride with 2-, 3- and 4-picoline in the presence of sodium amide has been developed into a convenient synthesis for these monoalkylpyridines. The reaction presumably involves a prototropic reaction of the picoline, followed by an attack of the carbanion on the alkyl halide. Contrary to published reports, methyl chloride, methyl iodide and ethyl bromide can all be used successfully to alkylate 2-picoline, although it had been previously considered that only the higher alkyl chlorides were satisfactory. Quite surprisingly, 3-picoline reacts smoothly, although prototropic reactions of this isomer have not been previously reported.

Introduction

In order to estimate quantitatively the effect of steric strain on displacement reactions of monoalkylpyridines,[4] we required 2-, 3- and 4-methyl-, ethyl-, isopropyl- and *t*-butylpyridines. The picolines are commercially available. Unfortunately, the remaining nine compounds are not available and a search of the literature revealed that two (2- and 3-*t*-butylpyridine) had not been previously prepared, while several others had been obtained only by relatively unsatisfactory procedures and had been poorly characterized. It was therefore considered essential to undertake the development of convenient procedures for the synthesis of these compounds to permit their ready preparation in quantity, their rigorous purification, and careful characterization.

It appeared that the alkylation of 2- and 4-picoline by methyl halides in the presence of sodium amide might be developed into a satisfactory procedure. Unfortunately, published information on the applicability of this reaction did not appear promising for the synthesis of all the derivatives needed in our studies.

In 1914 Chichibabin and Seide[5] reported that their attempts to alkylate 2-picoline by treating it with sodium amide and methyl iodide were unsuccessful. In 1931 Bergstrom[6] attempted to prepare homologs of pyridine derivatives (2-methyl-, 2,6-dimethyl- and 2,4,6-trimethylpyridine) by the action of ethyl bromide and potassium amide on the bases, but failed. However, he was successful in alkylating 2- and 4-methylquinoline in this way. Later Chichibabin[7] was successful in alkylating 2- and 4-picoline, utilizing predominantly the higher primary alkyl chlorides. Either one or two groups, such as *n*-butyl, could be introduced. Recently, Bergstrom, Norton and Seibert[8] reported the arylalkylation of 2- and 4-picoline with potassium amide in liquid ammonia.

2- and 4-picoline have also been condensed with esters,[9,10] aldehydes[9] and α,β-unsaturated ketones or esters.[11]

Fortunately, a detailed study of the alkylation of 2- and 4 picoline with methyl chloride and sodium amide led to the discovery of conditions suitable for the introduction of one, two or three methyl groups into the side-chain. In this way 2- and 4- ethyl-, isopropyl- and *t*-butylpyridines were prepared, purified, and characterized.

The synthesis of the 3-alkylpyridines at first offered greater difficulties. Both 3-ethylpyridine[12,13,14] and 3-isopropylpyridine[15,16] were synthesized in several steps from nicotinic acid. (Conditions were established for the successful hydrogenation of 3-isopropenyl- to 3-isopropylpyridine.) However, a number of attempts to prepare 3-*t*-butylpyridine by similar common reactions failed.

There seemed little reason to doubt that 3-picoline would be inert to methyl chloride and sodium amide. The literature abounds with evidence that 2- and 4-picoline undergo prototropic reactions with ease,[10,11] but no prototropic reactions of the 3-isomer could be located. However, an experiment confirming this conclusion appeared desirable. Accordingly, 3-picoline in liquid ammonia was treated with sodium amide and methyl chloride in the usual manner. Surprisingly, the reaction proceeded smoothly to form 3-ethylpyridine. 3-Isopropyl- and 3-*t*-butylpyridine could be prepared by the same reaction (the latter in relatively low conversion).

(1) Steric Effects in Displacement Reactions. I.

(2) This paper is taken from a thesis submitted by Wilbur A. Murphey in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(3) E. I. du Pont de Nemours and Company Fellow, 1948–1949.

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TABLE I

PHYSICAL PROPERTIES AND PICRATES OF MONOALKYLPYRIDINES, RC_5H_4N

Alkyl pyridine R	B.p. °C.	Mm.	$n^{20}D$	F.p. range, °C.	Estimated m.p., °C.	Picrate M.p., °C. Obsd.	Picrate M.p., °C. Lit.	Picrate N, % Calcd.[a]	Picrate N, % Found[b]
2-Et	148.7	746	1.4979	−63.2 to −63.6	−63.1	107.8–108.3	107–107.5[c] 108.5–110[d]	16.67	16.58
2-*n*-Pr	164–167.5	750	1.4930	.....	....	74.6–75.1	76[e]	16.00	16.09
2-*i*-Pr	159.8	753	1.4915	Glass at −141	....	118.1–118.7	116–117[f]	16.00	15.92
2-*t*-Bu[n,o]	169.0	743	1.4891	−33.0 to −33.5	−32.8	104.6–105.2	.....	15.38	15.38
3-Et	165.0	740	1.5021	−77.1 to −77.9	−76.9	128.1–128.5	129–130[g] 128–130[h] 128.5–130.0[i]	16.67	16.69
3-*i*-Pr	179.3	744	1.4965	−45.8 to −46.7	−45.7	138.1–138.6	136[j]	16.00	16.09
3-*t*-Bu[n,p]	194.3	742	1.4965	−43.3 to −44.4	−42.9	153.9–154.4	.....	15.38	15.34
4-Et	167.7	751	1.5020	−90.7 to −91.5	−90.5	169.4–169.8	169–170[k] 168–169[l]	16.67	16.68
4-*i*-Pr	181.5	743	1.4962	−55.1 to −56.3	−54.9	138.4–139.6	135[m]	16.00	16.10
4-*t*-Bu[n,q]	196.3	749	1.4958	−40.1 to −41.0	−39.7	130.9–131.4	.....	15.38	15.35

[a] Calcd. for 1:1 compound. [b] Analyses by Dr. Harry Galbraith. [c] A. Furst, THIS JOURNAL, **71**, 3550 (1949). [d] E. C. Gregg, Jr., and D. Craig, *ibid.*, **70**, 3138 (1948). [e] A. E. Chichibabin, *Bull. soc. chim.*, [5] **3**, 1607 (1936). [f] W. Koenigs and G. Happe, *Ber.*, **35**, 1343 (1902). [g] T. E. Fand and C. F. Lutomski, THIS JOURNAL, **71**, 2931 (1949). [h] C. Stoehr, *J. prakt. Chem.*, [2] **45**, 41 (1892). [i] C. F. Woodward, A. Eisner and P. G. Haines, THIS JOURNAL, **66**, 911 (1944). [j] M. P. Oparina, *J. Russ. Phys.-Chem. Soc.*, **57**, 319 (1925); *C. A.*, **20**, 2499 (1926); *Brit. Chem. Abstracts*, A, 844 (1926); *Chem. Zentr.*, **97**, I, 3337 (1926). [k] J. P. Wibaut and J. F. Arens, *Rec. trav. chim.*, **60**, 119 (1941). [l] J. T. Hackmann, J. P. Wibaut and H. P. L. Gitsels, *ibid.*, **62**, 229 (1943). [m] G. R. Clemo and E. Hoggarth, *J. Chem. Soc.*, 41 (1941). [n] *Anal.* Calcd. for $C_9H_{13}N$: C, 79.95; H, 9.69; N, 10.36. [o] Found: C, 79.9; H, 9.49; N, 10.40. [p] Found: C, 79.8; H, 9.75; N, 10.41. [q] Found: C, 80.0; H, 9.60; N, 10.58.

This discovery furnishes a highly convenient route to the 3-alkylpyridines. It appears that 3-picoline possesses an unexpected capacity for prototropic reactions which should prove very useful for the synthesis of other 3-substituted pyridines.

Results

Properties.—The monoalkylpyridines were purified by rectification in a 48-in. column with a 12 mm. i.d. tube packed with 1/16 in. stainless steel helices and rated at 70 theoretical plates. The temperature measurements were made with a set of short precision thermometers (12″), graduated to 1/10° and calibrated by the National Bureau of Standards. Refractive indices were measured with a Bausch and Lomb Abbe refractometer calibrated with purified benzene.

Freezing points were taken using apparatus similar to that developed at the National Bureau of Standards.[17] A calibrated 10-junction copper–constantan thermocouple, in conjunction with a Rubicon Portable Precision potentiometer, was used for the temperature measurements in the freezing tube. The freezing points of the pure compounds were estimated by addition of the difference of the initial freezing temperature and midpoint freezing temperature to the initial freezing temperature.

The freezing ranges were all quite sharp, indicating purities of better than 99 mole per cent., with the exception of 3-*t*-butylpyridine where a purity of 97–98 mole per cent. was indicated. Unfortunately, at this stage of the investigation, time did not permit further purification of this substance.

Picrates[18] were prepared of all the bases, recrystallized twice to constant melting point, and the melting points determined with the precision thermometers mentioned above. All temperatures are corrected for exposed stem.

The data on the properties of the pyridine bases prepared in the present investigation are summarized in Table I.

Preparation.—Two procedures were developed for the synthesis of the monoalkylpyridines by the alkylation of their lower homologs. For convenience these procedures will be referred to as Method A and Method B.

In Method A a suspension of sodium amide in the alkylpyridine was treated with methyl chloride. An inert diluent, such as ether or benzene was sometimes used to facilitate contact. A secondary reaction of methyl chloride and sodium to form methylamine made it desirable to use an excess of these reagents for optimum conversion of the alkylpyridine.

In Method B the alkylpyridine was added to the calculated quantity of sodium amide suspended in liquid ammonia and the alkyl halide was rapidly added to the reaction mixture.

Method A proved satisfactory for the synthesis of the 2-alkyl derivatives. A detailed study was therefore made of the effect of reaction conditions on the yield.

At low temperatures (15–20°), using one mole of sodium amide to one mole of 2-picoline, the conversion to 2-ethylpyridine was 51–66% in several experiments. At 45–50° the conversion was 42% and at 80° it dropped to 31%. A low temperature evidently favors the desired reaction.

With a molar ratio of sodium amide to 2-picoline of 2:1, the 2-picoline was quantitatively converted to products. At 15–20° the product was substantially 2-ethylpyridine (81%) with a relative small quantity (10%) of the dialkylated product, 2-isopropylpyridine. Little alkylation of 2-ethylpyridine occurs at these low temperatures. Treatment of 2-ethylpyridine with methyl chloride and sodium amide at 15–20° resulted in less than 10% conversion. However, at 75–80° the 2-ethylpyridine is alkylated to give a 36% conversion to 2-isopropylpyridine. The use of two moles of sodium amide to one of 2-picoline, with an excess of methyl chloride, at 75–80° brought about complete conversion of the 2-picoline to products. The conversion to 2-ethylpyridine was 41% and that to 2-isopropylpyridine was 45%.

These conditions proved to be less satisfactory for the synthesis of the 4-derivatives. Thus, attempts to prepare 4-ethylpyridine from 4-picoline yielded a product which contained approximately equal quantities of 4-picoline, 4-ethylpyridine and 4-isopropylpyridine.

The results obtained with Method A are summarized in Table II.

Method B proved far superior to A for the synthesis of the 4-alkylpyridines. Treatment of the 4-picoline with an equimolar amount of sodium amide and methyl chloride gave a 72% conversion to 4-ethylpyridine. In the same way 4-ethyl- could be transformed into 4-isopropyl- and the latter into 4-*t*-butylpyridine in conversions of 68 and 70%. The procedure was also satisfactory for the synthesis of the 2- derivatives and was later found applicable to the synthesis of the 3-alkylpyridines. Method B therefore constitutes a single simple procedure for the synthesis of any of the monoalkylpyridines.

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(18) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 180.

TABLE II

SUMMARY OF ALKYLATION OF ALKYLPYRIDINES, RC_5H_4N, BY METHOD A

Alkyl pyridine R	Reactants, moles RC_5H_4N	$NaNH_2$	CH_3Cl	Temp., °C.	Time,[a] hr.	Product RC_5H_4N R	Conversion[b] to product, %
2-Me	1.0[c]	1.0	2.0	15–20	3[d]	2-Et	56
2-Me	0.5[c]	1.0	2.6	75–80	6	2-Et	41
						2-*i*-Pr	45
2-Me	1.5	1.9	2.0	15–20	5.5[e,h]		
		1.9	2.0	125–130	8.5	2-*i*-Pr	58
2-Et	1.0[c]	1.0	2.0	75–80	3.5	2-*i*-Pr	36
2-Et	1.5	1.9	2.6	115–120	5.7	2-*i*-Pr	66
2-*i*-Pr	1.0	1.9	3.0	125–130	8.0	2-*t*-Bu	49
4-Me	1.5	1.9	2.2	15–20	6.0[g]	4-Et	25
						4-*i*-Pr	23
4-Me	1.5[g]	1.5	2.1	15–20	4.5[f]	4-Et	29
						4-*i*-Pr	22
4-Me	1.5[g]	1.5	2.1	0–5	9.8[e]	4-Et	28
						4-*i*-Pr	21
4-Me	3.0[g]	1.5	2.2	15–20	3.5	4-Et	43
						4-*i*-Pr	16
4-Me	1.0[g]	2.0	3.0	15–20	5.0	4-Et	22
						4-*i*-Pr	39
						4-*t*-Bu	21
4-Me	0.5	1.5	3.5	15–20	8.0	4-Et	22
						4-*i*-Pr	56
						4-*t*-Bu	8

[a] The time required for the addition of methyl chloride. [b] Conversion is yield based on starting material. [c] Solvent was benzene. [d] Stirred 3.5 hr. before hydrolysis. [e] Left overnight before hydrolysis. [f] Stirred 7 hr. before hydrolysis. [g] Solvent was ether. [h] The product from the first stage (largely 2-ethylpyridine) was heated to 125–130° and retreated with methyl chloride and sodium amide. The 58% conversion is the over-all conversion for both stages.

The speed of the reaction in most instances is noteworthy. In the cases mentioned above, the synthesis of the 4-ethyl-, isopropyl- and *t*-butylpyridines, the methyl chloride was passed into the reaction mixture in a matter of 10–15 min. The halide appears to react almost instantaneously. As a matter of fact, the reaction mixtures are deeply colored, presumably due to the presence of salts of the type, $Na^{+-}CH_2C_5H_4N$. These colored solutions may, in effect, be titrated to a sharp end-point with the methyl chloride. As soon as the equivalent quantity has been introduced, the reaction mixture loses its intense color.

In the conversion of the 2-isopropylpyridine to 2-*t*-butylpyridine a poor conversion was obtained with the usual short reaction time. By increasing the reaction time from 35 min. to 8 hr., the conversion was increased from 7 to 60%.

The 3-derivatives exhibited the opposite effect. In the case of these compounds a short reaction time leads to an improved conversion to the desired product. For example, treatment of 1 mole of 3-picoline and 1 mole of sodium amide in 700 ml. of liquid ammonia with 1 mole of methyl chloride produced 0.54 mole of 3-ethylpyridine when the alkyl chloride was added over a period of 16 min.; however, the conversion dropped to 0.39 mole of 3-ethylpyridine (in addition to 0.12 mole of 3-isopropylpyridine) when the reaction time was increased to 95 min.

These peculiarities are understandable in terms of the proposed reaction scheme outlined in the following section.

The results obtained with Method B are summarized in Table III.

TABLE III

SUMMARY OF ALKYLATION OF ALKYLPYRIDINES, RC_5H_4N, BY METHOD B

Alkyl pyridine R	Reactants, moles RC_5H_4N	$NaNH_2$	CH_3Cl	Reaction time, min.	Product RC_5H_4N R	Conversion to product, %
2-Me	1.0	1.0	1.1	10	2-Et	50
2-Me	1.0	1.0	1.4	17	2-Et	45
2-Me	1.0	2.0	2.2	60	2-*i*-Pr	54
2-Et	1.0	1.0	1.0	19	2-*i*-Pr	73
2-*i*-Pr	1.0	1.5	1.2	35	2-*t*-Bu	7
2-*i*-Pr	1.0	1.0	1.2	50	2-*t*-Bu	9
2-*i*-Pr	1.0	1.5	1.0	8 hr.	2-*t*-Bu	60
3-Me	1.0	1.0	1.0	16	3-Et	54
3-Me	1.0	1.0	1.0	95	3-Et	39
					3-*i*-Pr	12
3-Me	0.67	2.0	2.0	85	3-Et	39
					3-*i*-Pr	51
3-Me	1.0	2.0	2.0	55	3-Et	52
					3-*i*-Pr	31
3-Me[a]	2.0	2.2	2.2	110		
		2.2	2.2	150		
		2.4	2.4	215	3-*i*-Pr	74
					3-*t*-Bu	13
3-Et	1.0	1.0	1.0	75	3-*i*-Pr	47
3-*i*-Pr	1.0	2.0	2.0	8 hr.	3-*t*-Bu	23
3-*i*-Pr	1.0	2.0 (KNH_2)	2.0	130	3-*t*-Bu	16
4-Me	1.0	1.0	1.0	10	4-Et	72
4-Me	1.0	1.0	1.0	17	4-Et	72
4-Me	1.0	2.0	2.2	55	4-Et	23
					4-*i*-Pr	29
					4-*t*-Bu	25
4-Me	0.67	2.0	2.0	3 hr.	4-*t*-Bu	50
4-Et	1.0	1.0	1.0	12	4-*i*-Pr	68
4-Et	1.0	1.0	1.0	6	4-*i*-Pr	55
4-*i*-Pr	1.0	1.0	1.2	15	4-*t*-Bu	70
2-Me	1.0	1.0	1.0 (CH_3I)	2.5 hr.	2-Et	59
					2-*i*-Pr	12
2-Me	0.75	0.75 (KNH_2)	0.75 (C_2H_5Br)	50	2-*n*-Pr	55

[a] Reaction carried out in three stages as indicated.

Discussion

All of our observations are consistent with the generally accepted reaction scheme for base-catalyzed condensations of α- and γ-alkylpyridines. This scheme must now be extended to the β-substituted isomers.

Addition of any of the picolines to a solution of sodium amide in liquid ammonia leads instantly to the development of an intense color. Therefore, conversion of the picoline to the carbanion must be relatively rapid. Moreover, the observation that in a number of cases the colored solutions may in effect be titrated with methyl chloride to a sharp end-point in a matter of minutes suggests that the reaction of the carbanion with the alkyl halide must be exceedingly rapid. In these cases the ionization of the alkylpyridine must either be essentially complete or the ionization must proceed at a very rapid rate as the carbanion is removed by reaction with methyl chloride.

In the conversion of 2-isopropyl- to 2-*t*-butylpyridine the evidence is that only a few per cent. of the 2-isopropylpyridine is converted to the carbanion at equilibrium and the rate of conversion is relatively slow. Thus, when methyl chloride was passed into the reaction mixture rapidly (35 min.), the color was soon discharged and a low conversion, 7%, was obtained. When the methyl chloride was passed into the liquid ammonia solution at a rate sufficiently

slow to maintain the color in the solution (8 hr.), the conversion rose to 60%. Similar results were obtained in the synthesis of 3-*t*-butylpyridine.

In this reaction there are two obvious paths whereby alkyl halide can be consumed, other than in the desired reaction: reaction with the free pyridine base to form a quaternary salt, and reaction with the amide base to form either an amine or an olefin (the elimination reaction would of course be possible only in the case of the higher alkyl halides).

Bergstrom[6] reported failure in his attempt to alkylate pyridine derivatives in liquid ammonia with potassium amide and ethyl bromide. Chichibabin[7] attributed this failure to loss of ethyl bromide resulting from quaternary salt formation. He therefore assigned great importance to the use of alkyl chlorides instead of bromides and iodides to minimize quaternary salt formation and to obtain satisfactory yields of side-chain alkylation.

This interpretation offers difficulties. Pyridine bases are weak and react relatively slowly with alkyl halides. It does not appear reasonable, therefore, that a relatively dilute solution of a pyridine base should be able to compete successfully for the alkyl halide against equal concentrations of amide ion and far larger concentrations of ammonia. Moreover, in the present experiments the recovery of 92–97% of the theoretical quantity of pyridine bases from the reaction mixture demonstrates that quaternary salt formation cannot be important.

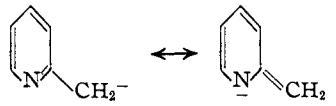
If the proposed reaction scheme is correct, alkyl bromides and iodides should react as successfully as alkyl chlorides. An experiment utilizing methyl iodide for the alkylation of 2-picoline by Method B gave a conversion of 59% to 2-ethyl-, and 12% to 2-isopropylpyridine. These yields are, if anything, somewhat better than those obtained with methyl chloride under similar conditions.

It was therefore puzzling why Bergstrom[6] reported failure to alkylate pyridine bases with ethyl bromide and potassium amide. Repetition of this experiment gave a 55% conversion to 2-*n*-propylpyridine. Bergstrom[6] described his reaction products as "clear colorless liquids of rather sharp odor, whose picrates were precipitated as uncrystallizable yellow tars." The difficulty probably stemmed from his failure to purify the reaction products before forming the picrates.

The exchange reaction, $NC_5H_4CH_2^- + NC_5H_4CH_2R \rightleftarrows NC_5H_4CH_3 + NC_5H_4CRH^-$, readily accounts for the mixture of products obtained when Method A was applied to the synthesis of the 4-derivatives. In Method A the reaction time is necessarily longer and hence there is more opportunity for the exchange reaction to occur. It is probable that mixtures would have resulted in Method B had the methyl chloride been added to the 4-picoline and sodium amide in liquid ammonia over a long period of time. Unfortunately, a test of this deduction was not made.

The decrease in yield of 3-ethylpyridine with increasing reaction time is also readily accounted for in terms of this exchange reaction. The low conversion of 3-isopropylpyridine to 3-*t*-butylpyridine appears to be due to the presence of only low concentrations of the carbanion at equilibrium. Methyl chloride then reacts preferentially with sodium amide rather than with the small concentrations of 3-isopropylpyridine carbanion present in the reaction mixture.

The participation of 3-alkylpyridines in this reaction is unexpected. The easy prototropic reactions of 2- and 4-picoline are usually attributed to resonance structures which stabilize the carbanions.



Since similar structures which place a negative charge on the electronegative nitrogen atom cannot be written for 3-picoline, an alternative explanation must be sought. It is suggested that the inductive effect of the ring nitrogen atom must be quite important. By reducing the electron density within the ring, the hydrogen atoms on the 3-alkyl group become sufficiently active to be removed by the strongly basic amide ion. The effect must also operate in 2- and 4-alkylpyridines where, in conjunction with the resonance effect, the ionization of hydrogen from alkyl groups in these positions must thereby be rendered particularly easy.

This reaction would appear quite promising for the synthesis of many 3-pyridyl compounds and related derivatives of quinoline, isoquinoline, as well as other heterocyclic compounds. Since our present research activities lie in other directions, we are not planning further work on this reaction.

Experimental Part

Materials.—The picolines were redistilled Reilly Tar and Chemical Corp. products specified to be 98% pure. Methyl chloride was obtained in cylinders from the Matheson Company and used directly. Sodium amide was synthesized by the procedure of Vaughn, Vogt and Nieuwland.[19] All other chemicals were standard laboratory reagents.

Method A.—A 1-liter 3-necked flask was equipped with a sealed Hershberg stirrer, a Dry Ice condenser (soda-lime drying tube) and a stopper. Sodium amide (1.25 moles, from 29 g. of sodium) was prepared in about 500 ml. of liquid ammonia.[19] As the ammonia evaporated, ether or benzene (80 to 100 ml.) was added. If no solvent was used, the pyridine base was introduced here. By introducing the solvent at this point, "caking" of the sodium amide was minimized. The Dry Ice condenser was replaced by a 60-cm. Allihn watercooled condenser (protected by a soda-lime tube). One mole of the pyridine base to be alkylated was added to the mixture and the temperature was adjusted to 15–20° (for preparation of 2-ethylpyridine) or 115–130° (for preparation of 2-isopropylpyridine or 2-*t*-butylpyridine). A glass tube extending below the level of the liquid in the flask was placed in the third neck of the flask. This tube contained a thermometer and a side-arm for the introduction of methyl chloride. A total of 2 moles (101 g.) of methyl chloride was introduced into the mixture over a period of 3 to 5 hours. After the addition of the methyl chloride, the mixture was stirred several hours at 0–5°. It was then treated with 100 ml. of water with cooling and stirring. The layers were separated. The aqueous layer was extracted with ether or benzene and the extract combined with the non-aqueous layer. This was dried over potassium hydroxide or barium oxide and rectified in a 14-inch column, 12 mm. i.d., packed with $^1/_{16}$ in. stainless steel helices. The conversion was obtained from the rectification curve.

Method B.—A 1-liter 3-necked flask was fitted with a Dry Ice reflux condenser (protected by a soda-lime tube)

(19) T. H. Vaughn, R. R. Vogt and J. B. Nieuwland, THIS JOURNAL, **56**, 2120 (1934).

and a sealed Hershberg stirrer. A metal pail with mica insulation was placed around the flask. Liquid ammonia (700–750 ml.) was collected in a clear quart dewar and transferred to the flask. Sodium amide (1.0 mole, from 23 g. of sodium) was prepared in the liquid ammonia according to the procedure of Vaughn, Vogt and Nieuwland.[19] To the suspension of sodium amide in liquid ammonia was added the pyridine base to be alkylated. After this was added, a second Dry Ice condenser was fitted to the third neck of the flask. Through this condenser methyl chloride (51 g., 1.0 mole) was introduced into the reaction mixture from a small weighed cylinder. The rate of addition was usually rapid but slow enough to prevent boiling up into the condensers. The color usually changed to dark gray within 5–10 minutes after the addition. After the ammonia had evaporated (overnight), the mixture was treated dropwise with 50 ml. of water. The liquid was separated from the solid and the solid was dissolved in 150–200 ml. of water. The resulting solution or suspension was extracted twice with 50-ml. portions of ether. The ether was removed and the residue was combined with the liquid reaction product and dried over potassium hydroxide pellets. The product was rectified at atmospheric pressure in the column described in Method A.

Ethyl Nicotinate.—The procedure of Burrus and Powell[12] was used. The average yield of ethyl nicotinate, b.p. 92–93° at 7 mm., $n^{20}D$ 1.5034, for 16 runs was 73.6%. Burrus and Powell reported 61% ethyl nicotinate, b.p. 84° at 5 mm.

3-Acetylpyridine.—The procedure of Kolloff and Hunter[13] was used except for minor modifications. The yield of product, b.p. 65–66° (1 mm.), $n^{20}D$ 1.5341, was 72–73%.

Reduction of 3-Acetylpyridine to 3-Ethylpyridine.—The procedure of Fand and Lutomski[14] was used. The yield of product, b.p. 164.5–166°, uncor., $n^{20}D$ 1.5020, was 82.4%.

α,α-Dimethyl-3-pyridinemethanol.—A solution of 151 g. (1.0 mole) of ethyl nicotinate in 350 ml. of anhydrous ether was added with stirring during 2 hours to a solution of 3.25 moles of methylmagnesium iodide in 600 ml. of anhydrous ether. After refluxing for 3 hours the addition complex was decomposed by cautiously pouring the ethereal suspension into a mixture of 200 ml. (3.3 moles) of glacial acetic acid in 1 l. of cracked ice. The ether was evaporated by the heat of reaction. To the viscous mixture 600 ml. of water was added and the solution was thoroughly extracted with chloroform. The chloroform was removed and the product was distilled in a Vigreux column, b.p. 126° (8 mm.), $n^{20}D$ 1.5256 (supercooled); yield 62–78%; m.p. 53.5–55°; picrate, m.p. 149–150°. The following values are reported: m.p. 58°,[15] 53°[16]; b.p. 130° (11 mm.)[16]; picrate, m.p. 150°.[15]

3-Isopropenylpyridine.—3-Isopropylpyridine was prepared by the dehydration of α,α-dimethyl-3-pyridinemethanol by boiling for 0.5 hour with 27% sulfuric acid in glacial acetic acid.[15] The material was vacuum rectified in a 36-in. column, 12-mm. i.d., packed with $^3/_{16}$-in. glass helices. The average yield of product was 72%. The following constants were observed: b.p. 89° (25 mm.); $n^{20}D$ 1.5431, picrate, m.p. 155.5–156°, uncor. The following values are reported: b.p. 75° (10 mm.),[20] 187–188°[15]; $n^{25}D$ 1.5381[20]; picrate, m.p. 156°.[15]

Hydrogenation of 3-Isopropenylpyridine.—3-Isopropenylpyridine (83.6 g., 0.70 mole) was hydrogenated in the presence of 0.33 g. of platinum oxide catalyst during 25 hours at an initial pressure of 51 lb. A total of 57.8 lb. of hydrogen was taken up while the theoretical amount was 58.1 lb. The catalyst was filtered out and the product distilled: 65 g. boiled at 178–182°, uncor. Because of the wide boiling range this material was thought to contain some of the piperidine derivative. It was treated with a small amount of dilute hydrochloric acid (0.03 mole), dried over potassium hydroxide and calcium hydride, and distilled over phosphorus pentoxide, b.p. 179°.

Preparation and Properties of Monoalkylpyridines.—The results on the preparation and physical properties of the monoalkylpyridines are summarized in Tables I–III.

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(20) G. B. Bachman and D. D. Micucci, THIS JOURNAL, **70**, 2381 (1948).

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[CONTRIBUTION FROM THE NORTHERN REGIONAL RESEARCH LABORATORY[1]]

Methylation and Ethylation of Corn Starch, Amylose and Amylopectin in Liquid Ammonia

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To obtain completely methylated corn starch fractions without severe degradation of the polyglucose chains, the authors adapted Freudenberg's liquid ammonia procedure. The cause of the degradation produced by Freudenberg's method was established and a way of avoiding it was found. Trimethyl ethers of corn starch, amylose and amylopectin of high intrinsic viscosity were prepared. Contrary to the findings of Freudenberg and Boppel, trimethyl amylose is distinctly different from trimethyl amylopectin in appearance, melting range, iodine sorption, viscosity characteristics, solubility, X-ray diffraction pattern, resistance to grinding and film-strength. Trimethyl corn starch was fractionated into trimethyl amylose (25%) and trimethyl amylopectin (75%) by means of their different solubilities in Diethyl Cellosolve. Triethyl ethers of corn starch, amylose and amylopectin were prepared for the first time. The disorganizing effect of liquid ammonia on starch granules was used to prepare dry granular starches dispersible in water. Use of this ammonia-treated starch allowed the omission of autoclaving in the starch fractionation procedure of Schoch.

Significant contributions to our knowledge of the structure of starch and other polysaccharides have been made by methylating the polysaccharide, hydrolyzing or methanolyzing the product, and determining the methylated sugars obtained. The importance of preparing a completely methylated polysaccharide without alteration of its structure is evident, but this goal has not been satisfactorily achieved. We have directed our experiments toward attaining this goal for starch and starch fractions.

The procedure of K. Freudenberg and co-workers[2a] for methylating starch in liquid ammonia is the most efficient.[3] However, this method has been avoided in favor of the laborious dimethyl sulfate–alkali procedures, because solutions of the ethers produced showed very low viscosities indicating

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

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(2a) K. Freudenberg, H. Boppel and M. Meyer-Delius, *Naturwissenschaften*, **26**, 123 (1938); K. Freudenberg and H. Boppel, *Ber.*, **71**, 2505 (1938).

(3) Recently E. J. Bourne, K. H. Fantes and S. Peat, *J. Chem. Soc.*, 1109 (1949), have acknowledged the superiority of the Freudenberg procedure of methylation.