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Sodium-catalyzed Side Chain Alkylation of Alkylpyridines. Synthesis of Alkylpyridines^{1a,1b}

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The side chain alkylation of 2- and 4-alkylpyridines has been accomplished using sodium as a catalyst; 2- and 4-ethyl-, *n*-propyl-, isopropyl-, *sec*-butyl-, isobutyl-, (ethylpropyl)- and (methylisobutyl)-pyridine reacted with ethylene under pressure at 130–160° to produce the corresponding *sec*-butyl-, (ethylpropyl)-, *t*-amyl-, (methyllethylpropyl)-, (ethylisobutyl)- (diethylpropyl)- and (methyllethylisobutyl)-pyridines. The 2- and 4-ethylpyridines and 2- and 4-*n*-propylpyridines react with propylene under pressure at 160° to produce the corresponding (*i*-C₃H₇)(CH₃)CH- and (*i*-C₃H₇)(C₂H₅)CH-pyridines. It has been observed that 4-substituted pyridines undergo alkylation more easily than the 2-isomers. The mechanism of the side chain alkylation is substantiated by kinetic results. The alkylated alkylpyridines were analyzed by means of infrared spectroscopy and gas chromatography. For that reason alkylpyridines having the following alkyl groups were synthesized: 2-(*i*-C₃H₇)(CH₃)(CH), 2-(*i*-C₃H₇)(C₂H₅)CH, 2-*t*-C₄H₉, 2-(C₂H₅)₂(CH₃)C, 2-(*i*-C₃H₇)(C₂H₅)(CH₃)C, 4-*i*-C₄H₉, 4-(*i*-C₃H₇)(CH₃)CH, 4-(C₂H₅)₂CH, 4-(*i*-C₃H₇)(C₂H₅)CH, 4-*t*-C₄H₉, 4-(C₂H₅)₂(CH₃)C, 4-(C₂H₅)₂C, 4-(*i*-C₃H₇)(C₂H₅)(CH₃)C. The procedure used consisted in contacting equimolar amounts of alkylpyridines, alkyl halides and potassium amide in liquid ammonia.

I. Alkylation of Alkylpyridines

The side chain ethylation^{3,4} and propylation⁴ of picolines in the presence of sodium as catalyst was described previously. This study has been extended to include higher monoalkylpyridines. The main object of this study was to determine the influence of substitution at the reactive center on the ease and selectivity of alkylation and also to gain additional information as to the mechanism of side chain alkylation.

The side chain ethylation and propylation reactions were carried out in apparatus and under conditions similar to those described previously.⁴ The results obtained are presented in Tables I and II, respectively.

The side chain alkylation of alkylpyridines follows the general mechanism proposed for alkylaromatics⁵ and for picolines.⁴

Ethylation.—It is seen from Table I that large variations in reaction rates occurred according to the nature of the starting alkylpyridines. When 4-substituted pyridines were used the reaction proceeded satisfactorily at about 140–155° and in the absence of a promoter, at least in the case of the lower homologs of alkylpyridines. However, when 2-substituted pyridines were used the reaction required higher temperatures (expt. 1 *vs.* 2) or the use of a promoter, as in the case of propylpyridines (expt. 3 *vs.* 4, 5 *vs.* 6).

When the alkyl group in the alkylpyridines was more highly branched as in 2-(methylisobutyl)-pyridine the ethylation reaction was greatly hindered. In the case of the 2-isomer at 180° and in the presence of a promoter, only 4% of the alkylpyridine underwent ethylation, while with the 4-isomer the extent of ethylation was 32% (expts. 12 and 20).

(1) (a) Paper XVIII of the series Base-Catalyzed Reactions. For paper XVII see W. O. Haag and H. Pines, *THIS JOURNAL*, **82**, 387 (1960). (b) This research was supported by a grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is hereby made to the donors of this Fund.

(2) Petroleum Research Fund Postdoctoral Fellow, 1958–1959. On leave of absence from Ente Nazionale Idrocarburi, San Donato Milanese, Milano, Italy.

(3) E. Proffitt and F. Schneider, *Arch. Pharm.*, **289**, 99 (1956).

(4) H. Pines and D. Wunderlich, *THIS JOURNAL*, **81**, 2568 (1959).

(5) H. Pines and V. Mark, *ibid.*, **78**, 4316 (1958).

These facts together with the observed greater acidity of 4-alkylpyridine as compared with the 2-isomers⁶ indicate that the initiation step in these reactions was the attack of sodium on the acidic α -hydrogen of the alkyl substituent. The acidity of the α -hydrogen in alkylpyridine most probably decreases, as in the case of alkylbenzene,⁷ with the number of substituents on the carbon atom which is attached to the pyridine ring and also with the extent of branching of the substituents. With increasing substitution only the more acidic 4-alkylpyridines will undergo an ethylation reaction. The less acidic 2-isomers will require, as in the case of alkylaromatics, the presence of a promoter.⁵

The yield of ethylated alkylpyridines, especially in the case of the less branched alkylpyridines, was relatively high. There was a considerable decrease in the amount of high boiling product inasmuch as the ethylation was made at lower temperatures than reported previously.⁴ The rate of ethylation varied considerably and depended on the structure of the alkylpyridines used. A relative rate study of the ethylation reaction was made and will be reported in the subsequent paper of this series. It may be stated at present that the presence of a β -methyl group in the alkyl side chain hinders the ethylation reaction.

Propylation.—2- and 4-ethyl- and *n*-propylpyridine reacted with propylene in the presence of sodium and anthracene to form the corresponding 2- and 4-methylisobutyl- and ethylisobutylpyridine. The infrared spectra of the monoprolylated product were identical (superimposable) with the spectra of the synthetic alkylpyridines.^{1a} This demonstrates that the addition of the pyridylethyl and -propyl carbanions to the double bond of propylene occurred in a selective way, adding further evidence to the ionic nature of the reaction and to the importance of a polar rather than steric effect.³

Discussion and Mechanism

The alkylation of alkylpyridines requires lower temperatures than the alkylation of alkylbenzenes.

(6) The relative acidities of 2- and 4-picoline were determined by a competitive metalation using sodium amide in liquid ammonia (unpublished work by these authors).

(7) H. Hart and R. E. Crocker, *THIS JOURNAL*, **82**, 418 (1960).

TABLE I
 SODIUM-CATALYZED ETHYLATION OF ALKYLPIRIDINES

Experimental conditions											Ethylated products		
Reagents					Starting pyridines						Yield		
Expt.	Starting material C_5H_4NR , R =	Mole	Na, g.	Anthra- cene, g.	Temp., °C.	Dura- tion, hr.	Max. press., atm. ^a	Min. press., atm. ^a	Starting pyri- dines re- covered, moles, %	Residue, wt. % ^b	Compound ^c	moles % based on charged ma- terial	moles % based on reacted ma- terial
1	2-C ₂ H ₅	0.2	0.2		150	5	46	46	100		No reactn.		
2	2-C ₂ H ₅	.26	.44		175	2.75	28.5	15	46	5	II	51	88 ^e
3	2- <i>n</i> -C ₃ H ₇	.23	.35		150	4	74	71	86	5	IV	7	86
4	2- <i>n</i> -C ₃ H ₇	.23	.33	0.1	150	3	49.5	23	0	8	IV	86	86 ^d
5	2- <i>i</i> -C ₃ H ₇	.2	.48		150	10	33	33	100		No reactn.	0	
6	2- <i>i</i> -C ₃ H ₇	.28	.35	.1	150	4.25	20.5	11	6	5.7	VI	88	93
7	2- <i>sec</i> -C ₄ H ₉	.17	.35	.05	150	7	28.5	14	22	4	VII	73	94
8	2- <i>i</i> -C ₄ H ₉	.1	.3		150	7	63	50	85	6	V	6	90
9	2- <i>i</i> -C ₄ H ₉	.2	.30		180	6	44	36	90	6	V	3	90
10	2- <i>i</i> -C ₄ H ₉	.27	.40	.1	155	6	105	84	13	7	V	77	90
11	2-(C ₂ H ₅)CH	.10	.15	.05	165	10	45	40	67	8	<div style="display: inline-block; vertical-align: middle; text-align: center;">CC 2-C—CC CC</div>	25	87
12	2-(<i>i</i> -C ₃ H ₇)(CH ₃)CH	.23	.4	.1	180	5	104	100	75	15	VIII	4	80
13	4-C ₂ H ₅	.9	.65		150	5	28	10	30	11	XI	58	88
14	4- <i>n</i> -C ₃ H ₇	.15	.3		150	3	32	19.5	23	11	XIII	65	87
15	4- <i>i</i> -C ₃ H ₇	1.0	1.4		150	1.5	30	10	31	7	XV	61	92
16	4- <i>sec</i> -C ₄ H ₉	0.27	0.85		140	8	34	15	32	5	XVI	62	93
17	4- <i>i</i> -C ₄ H ₉	.13	.25		155	6	59	53		9	XIV	40	88
18	4- <i>i</i> -C ₄ H ₉	.13	.25	.05	165	8	62	58.8	35	10	XIV	54	90
19	4-(C ₂ H ₅) ₂ CH	.09	.15	.05	160	4	70	67	25	10	XVII	65	88
20	4-(<i>i</i> -C ₃ H ₇)(CH ₃)CH	.14	.25	.05	180	20	55	45	57	11	XVIII	32	88

^a Maximum and minimum pressures at the reaction temperature. ^b Based on alkylpyridines charged. ^c Plus a 3% yield of C₅H₄NC(C₂H₅)₂(CH₃), dialkylated product. ^d Plus a 6% yield of C₅H₄NC(C₂H₅)₃, dialkylated product. ^e For structure see Table V.

 TABLE II
 SODIUM-CATALYZED PROPYLATION OF ALKYLPIRIDINES

Experimental conditions										Propylated product			
Reagents										Yield			
Expt.	Starting material C_6H_4NR , R =	Mole	Sodium, g.	Anthra- cene, g.	Temp., °C.	Dura- tion, hr.	Max. press., atm. ^a	Min. press., atm. ^a	Starting pyridines recovered, moles %	Residue, wt. % ^b	Compound ^c	moles % based on charged material	moles % based on reacted materials
21	2-C ₂ H ₅	0.44	1	0.1	150	5.5	50	50	61	14	III	24	83
22	2- <i>n</i> -C ₃ H ₇	.15	0.8	.1	160	8	59	59	40	10	V	49	80
23	4-C ₂ H ₅	.44	1	.1	160	6	57	57	51	12	XII	36	74
24	4- <i>n</i> -C ₃ H ₇	.15	0.8	.1	160	5	66	65	60	15	XIV	25	80

^a Maximum and minimum pressures at the reaction temperature. ^b Based on alkylpyridine charged. ^c For structure see Table V.

This probably is due to a greater stabilization of the pyridyl carbanions



It was observed previously that the ethylation of 3-picoline proceeded less satisfactorily than that of 2- or 4-picoline and was accompanied by the formation of large amounts of higher boiling products. The reluctance of 3-picoline to undergo alkylation was not due to the difficulty of formation of 3-picolyl carbanion since the latter was found when 3-picoline was treated with sodium in liquid ammonia.⁸

The formation of 3-picolyl carbanion was not the limiting step in the ethylation reaction and the occurrence of a competing reaction was responsible for the low yields of ethylated product. This was

demonstrated by two experiments in which the respective 2- and 3-picolylsodium were prepared by treating an excess of 2- and of 3-picoline with sodium amide in liquid ammonia. After the elimination of the ammonia the respective picolyl sodiums were heated with ethylene. The results obtained (Table III) show that with preformed picolylsodium, under similar experimental conditions, 2-picoline was extensively ethylated whereas 3-picoline gave poor yields of ethylated material together with a large amount of residue consisting of compounds containing more than one pyridyl ring per molecule.

These and other observations lead us to believe that the addition of sodium to an azomethine linked reported in the literature^{9,10} may occur to a considerable extent only with the more reactive

(9) F. B. Ahrens, *Ber.*, **38**, 155 (1905).

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

(10) A. Heuser and C. Stoeck, *J. prakt. Chem.*, [2] **42**, 430 (1890); **44**, 404 (1891).

carbanions or at higher temperatures. The 3-picolyl carbanion, due to its lack of an ionic stabilization involving the nitrogen, is more reactive than the 2- or 4-picolyl carbanions. A more detailed study of the side-chain alkylation of 3-alkylpyridines is necessary in order to obtain a better understanding of its behavior.

Sodium amide and sodium methoxide were tested as catalysts for the ethylation of 4-picoline. The former acted as a catalyst and the product formed consisted of 4-*n*-propylpyridine, 4-(ethylpropyl)-pyridine and of a higher boiling material. Sodium methoxide did not catalyze the ethylation of picoline.

The reaction mechanism previously proposed^{4,5} was given further support by a kinetic investigation. This was made possible by the fact that during the ethylation of alkylpyridines *all* of the sodium used as a catalyst entered into reaction in contrast to the observation in the study of alkylbenzenes where a large amount of the sodium was found unreacted. This observation made it possible to obtain more precise information about the kinetics of the ethylation of alkylpyridines.

TABLE III

ETHYLATION OF PICOLINES IN THE PRESENCE OF SODIUM AMIDE

The experiments were made in a 250-ml. capacity autoclave in the presence of 1.5 g. of sodium amide and 70 atm. of ethylene pressure; 0.5 mole of picoline was used.

-Picoline	Conditions		Residue, g.	Product obtained Propylpyridine yield, % ^a
	Temp., °C.	Duration, hr.		
2-	150	5	8	60 ^b
3-	150-170	7	14	3

^a Yields were based on picolines charged. ^b This includes 10% of 2-(ethylpropyl)-pyridine.

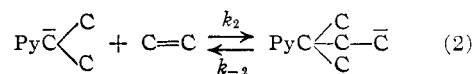
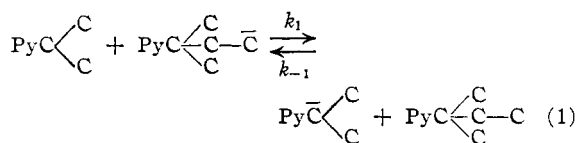
TABLE IV

RATES OF ETHYLATION OF 4-ISOPROPYLPYRIDINE AT 125°

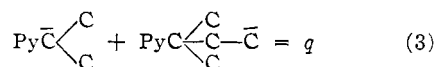
Ethylene pressure, atm.	Reagents		Initial rate of ethylene absorption, liters/hour
	Sodium, g.	4-Isopropylpyridine, moles	
5	0.5	0.5	0.58
10	0.5	.5	1.10
5	1.0	.5	1.18
10	1.0	.5	2.32
20	1.0	1.0	2.74
40	1.0	1.0	3.35

4-Isopropylpyridine was used for the kinetic study of ethylation as it did not require the use of a promoter to initiate the reaction and because it yielded only one ethylated product. The experiments were made at 125° where the rate of ethylation is not too excessive (Table IV). Using sodium as a catalyst it was found that the rate of ethylation was: (1) proportional to the amount of sodium in the range investigated, namely, 0.8-1.6% based on 4-isopropylpyridine charged; (2) independent of the amount of isopropylpyridine used; (3) first order in respect to ethylene pressure, in the range of 1-15 atmospheres. At higher ethylene pressures the dependency of the rate of alkylation upon the ethylene pressure gradually decreases until it becomes practically independent at pressures of 30-40 atmospheres.

Kinetic expressions (1) and (2) can be written based on the mechanism of alkylation.⁵



Expression (3) can be written assuming that no substantial deterioration of the catalyst occurs



where q is the amount of catalyst.

With the steady state treatment relation (4) is obtained

$$\frac{d \left[\text{PyC} \begin{array}{c} \text{C} \\ \diagup \quad \diagdown \\ \text{C} \end{array} \right]}{dt} = \frac{-d \left[\text{PyC} \begin{array}{c} \text{C} \\ \diagup \quad \diagdown \\ \text{C}-\bar{\text{C}} \end{array} \right]}{dt} =$$

$$-k_2[\text{C}=\text{C}] \left[\text{PyC} \begin{array}{c} \text{C} \\ \diagup \quad \diagdown \\ \text{C} \end{array} \right] + k_1 \left[\text{PyC} \begin{array}{c} \text{C} \\ \diagup \quad \diagdown \\ \text{C}-\bar{\text{C}} \end{array} \right]$$

$$\left[\text{PyC} \begin{array}{c} \text{C} \\ \diagup \quad \diagdown \\ \text{C} \end{array} \right] = 0 \quad (4)$$

By appropriate substitutions an expression can be derived for the accumulation of ethylated material or disappearance of ethylene

$$\frac{d \left[\text{PyC} \begin{array}{c} \text{C} \\ \diagup \quad \diagdown \\ \text{C}-\text{C} \end{array} \right]}{dt} = - \frac{d[\text{C}=\text{C}]}{dt} =$$

$$q \frac{k_1 \left[\text{PyC} \begin{array}{c} \text{C} \\ \diagup \quad \diagdown \\ \text{C} \end{array} \right] k_2[\text{C}=\text{C}]}{k_1 \left[\text{PyC} \begin{array}{c} \text{C} \\ \diagup \quad \diagdown \\ \text{C} \end{array} \right] + k_2[\text{C}=\text{C}]} \quad (5)$$

The above equation leads to more simplified expressions in two extreme cases. In the ethylation reaction at a very low pressure of ethylene

$$-d[\text{C}=\text{C}]/dt = pk_2[\text{C}=\text{C}] \quad (6)$$

since

$$k_1 \left[\text{PyC} \begin{array}{c} \text{C} \\ \diagup \quad \diagdown \\ \text{C} \end{array} \right] \gg k_2[\text{C}=\text{C}] \quad (7)$$

A first-order reaction in respect to ethylene and direct proportionality to the amount of catalyst is expected under these conditions. It was indeed found that the rate doubled when the ethylene pressure was increased from 5 to 10 atm., and also that the rate doubled when the amount of catalyst is increased from 0.5 to 1.0 g.

Another relation is obtained by assuming

$$k_2[\text{C}=\text{C}] \gg k_1 \left[\text{PyC} \begin{array}{c} \text{C} \\ \diagup \quad \diagdown \\ \text{C} \end{array} \right] \quad (8)$$

This condition is expected to be satisfied at high pressures of ethylene. From equation 5 equation (9) may thus be derived

$$-d[\text{C}=\text{C}]/dt = qk_1 \left[\text{PyC} \begin{array}{c} \text{C} \\ \diagup \quad \diagdown \\ \text{C} \end{array} \right] \quad (9)$$

TABLE V
SYNTHESIS OF 2-ALKYLPYRIDINES

Expt.	Starting materials C_5H_4NR R =	Alkylating agent	Product $C_5H_4NR_1$ R_1 =	Alkyl- pyri- dines reacted, %	Yield, mole % ^a	B.p., °C.	mm.	n_D^{20}	d_4^{20}	Picrate m.p., °C.
1	2-CH ₃	<i>i</i> -C ₃ H ₇ Br	2- <i>i</i> -C ₄ H ₉ ^b (I)	85	97	181	760	1.4831	0.8973	97
2	2-C ₂ H ₅	C ₂ H ₅ Br	2- <i>sec</i> -C ₄ H ₉ ^c (II)	81	84	177	748			
3	2-C ₂ H ₅	<i>i</i> -C ₃ H ₇ Br	2-(<i>i</i> -C ₃ H ₇)(CH ₃)CH (III)	91	95	193	740	1.4875	.9028	121.5
4	2- <i>n</i> -C ₃ H ₇	C ₂ H ₅ Br	2-(C ₂ H ₅) ₂ CH ^d (IV)	86	98	196	755	1.4860	.8988	72-73
5	2- <i>n</i> -C ₃ H ₇	<i>i</i> -C ₃ H ₇ Br	2-(<i>i</i> -C ₃ H ₇)(C ₂ H ₅)CH (V)	83	54	204	750	1.4859	.8976	92
6	2- <i>i</i> -C ₃ H ₇	C ₂ H ₅ Br	2- <i>t</i> -C ₃ H ₁₁ (VI)	77	90	188	750	1.4924	.9132	118
7	2- <i>sec</i> -C ₄ H ₉	C ₂ H ₅ Br	2-(C ₂ H ₅) ₂ (CH ₃)C ^e (VII)	5	90	110	107			114
8	2- <i>sec</i> -C ₄ H ₉	C ₂ H ₅ Br	2-(C ₂ H ₅) ₂ (CH ₃)C (VII)	100	39	110	107			
9	2-(<i>i</i> -C ₃ H ₇)(CH ₃)CH	C ₂ H ₅ Br	2-(<i>i</i> -C ₃ H ₇)(C ₂ H ₅)(CH ₃)C (VIII)	0
10	2- <i>sec</i> -C ₄ H ₉	<i>i</i> -C ₃ H ₇ Br	2-(<i>i</i> -C ₃ H ₇)(C ₂ H ₅)(CH ₃)C (VIII)	30	80	225.5	755	1.4985	0.9197	
11	4-CH ₃	C ₂ H ₅ Br	4- <i>n</i> -C ₃ H ₇ ^f (IX)	74	80	186	748	1.4961		
12	4-CH ₃	<i>i</i> -C ₃ H ₇ Br	4- <i>i</i> -C ₄ H ₉	61	79	199.6	750	1.4896	0.9109	122
13	4-C ₂ H ₅	C ₂ H ₅ Br	4- <i>sec</i> -C ₄ H ₉ (XI)	94	85	199	747			
14	4-C ₂ H ₅	<i>i</i> -C ₃ H ₇ Br	4-(<i>i</i> -C ₃ H ₇)(CH ₃)CH (XII)	99	98	159	173	1.4930	0.9185	153
15	4- <i>n</i> -C ₃ H ₇	C ₂ H ₅ Br	4-(C ₂ H ₅) ₂ CH (XIII)	93	87	150	134	1.4912	.9113	125.5
16	4- <i>n</i> -C ₃ H ₇	<i>i</i> -C ₃ H ₇ Br	4-(<i>i</i> -C ₃ H ₇)(C ₂ H ₅)CH (XIV)	90	76	166	155	1.4921	.9096	115
17	4- <i>i</i> -C ₃ H ₇	C ₂ H ₅ Br	4- <i>t</i> -C ₃ H ₁₁ (XV)	94	95	159	176	1.4975	.9251	113.5
18	4- <i>sec</i> -C ₄ H ₉	C ₂ H ₅ Br	4-(C ₂ H ₅) ₂ (CH ₃)C (XVI)	80	70	130	110	88
19	4-(C ₂ H ₅) ₂ CH	C ₂ H ₅ Br	4-(C ₂ H ₅) ₃ C (XVII)	50	50	150	110	101
20	4-(<i>i</i> -C ₃ H ₇)(CH ₃)CH	C ₂ H ₅ Br	4-(<i>i</i> -C ₃ H ₇)(C ₂ H ₅)(CH ₃)C (XVIII)	0
21	4- <i>sec</i> -C ₄ H ₉	<i>i</i> -C ₃ H ₇ Br	4-(<i>i</i> -C ₃ H ₇)(C ₂ H ₅)(CH ₃)C (XVIII)	100	50	245	760	1.4924	0.9138	

^a Based on reacted alkylpyridines. ^b Reported: b.p. 110–111° (55 mm.), n_D^{20} 1.4831, d_4^{20} 0.8973, picrate m.p. 97° [H. Pines and D. Wunderlich, *THIS JOURNAL*, **81**, 2568 (1959)]. ^c Reported: b.p. 63–68° at 12 mm. [C. Osuch and R. Levine, *ibid.*, **78**, 1723 (1956)]. ^d Reported: b.p. 191–193° (747 mm.), picrate m.p. 72–73° [Ref. footnote b]. ^e Sodium amide instead of potassium amide was used. ^f Reported: b.p. 79–84° at 22 mm. [Ref. footnote c].

TABLE VI
ANALYSIS OF ALKYLPYRIDINES

Expt.	Compound	Formula	Analyses, %						Picrates		
			Calcd.			Found			Formula	Nitrogen, %	
			C	H	N	C	H	N		Calcd.	Found
3	III	C ₁₀ H ₁₅ N	80.48	10.13	9.39	80.10	10.11	9.57	C ₁₆ H ₁₈ O ₇ N ₄	14.81	15.03
5	V	C ₁₁ H ₁₇ N			8.58			8.76	C ₁₇ H ₂₀ O ₇ N ₄	14.30	14.11
	2- <i>t</i> -C ₃ H ₁₁ VI	C ₁₀ H ₁₅ N	80.48	10.13	9.39	80.49	10.37	9.51	C ₁₆ H ₁₈ O ₇ N ₄	14.81	14.93
7	VII	C ₁₁ H ₁₇ N	80.93	10.47	8.58	80.78	10.67	8.79	C ₁₇ H ₂₀ O ₇ N ₄	14.30	14.06
11	2-(<i>i</i> -C ₃ H ₇)(C ₂ H ₅)(CH ₃)C	C ₁₂ H ₁₉ N	81.29	10.80	7.90	81.62	10.72	8.09			
13	IX	C ₉ H ₁₃ N	79.95	9.69	10.36	79.66	9.53	10.17	C ₁₅ H ₁₆ O ₇ N ₄	15.4	15.18
14	XII	C ₁₀ H ₁₅ N	80.48	10.13	9.39	80.05	10.28	9.78	C ₁₆ H ₁₈ O ₇ N ₄	14.81	14.96
15	XIII	C ₁₀ H ₁₅ N	80.48	10.13	9.39	79.87	10.10	9.28	C ₁₆ H ₁₈ O ₇ N ₄	14.81	15.12
16	XIV	C ₁₁ H ₁₇ N	80.93	10.47	8.58	81.11	10.61	8.74	C ₁₇ H ₂₀ O ₇ N ₄	14.30	14.39
17	XV	C ₁₀ H ₁₅ N	80.48	10.13	9.39	80.17	10.27	9.39	C ₁₆ H ₁₈ O ₇ N ₄	14.81	15.07
18	XVI	C ₁₁ H ₁₇ N	80.93	10.47	8.58	81.11	10.61	8.74	C ₁₇ H ₂₀ O ₇ N ₄	14.30	14.65
19	XVII	C ₁₂ H ₁₉ N	81.29	10.80	7.90	81.67	10.88	7.97	C ₁₈ H ₂₂ O ₇ N ₄	13.79	13.97
21	XVIII	C ₁₂ H ₁₉ N	81.29	10.80	7.90	81.22	10.48	8.19			

In equation 9 the rate is independent of the ethylene pressure and directly proportional to the amount of catalyst and to the concentration of starting material.

Between these two extremes, the dependency of the rate with respect to the ethylene pressure will gradually decrease with increasing ethylene pressure. It was found that the change in rate is only 50% when the pressure was increased from 10 to 20 atm. By doubling the ethylene pressure to 40 atm., the rate changed only 20%.

It would be expected from the aforesaid that the greater the acidity of the starting alkylpyridine, the larger will be the pressure range in which a first-order reaction in ethylene would be maintained; conversely, this range will become smaller

when alkylpyridines of lower acidity are used. In other words at higher ethylene pressures metalation becomes the rate-determining step.

II. Synthesis of Alkylpyridines

During the course of the study of the side chain alkylation of alkylpyridines it was necessary to prepare several compounds of this series. Since most of these compounds were prepared for the first time, it seemed worthwhile to report briefly on the method of their preparation, yields and physical properties.

The procedure described by Brown and Murphey⁸ was used and in most of the cases satisfactory yields were obtained. Experimental results and some of the physical constants are summarized

in Table V; analyses of new compounds and their picrates are reported in Table VI.

In preliminary experiments sodium and potassium were used interchangeably; however, it soon became evident that the use of potassium gave generally better yields. Comparison of experiments 7 and 8 shows that starting from 2-*sec*-butylpyridine and ethyl bromide, a 5% yield of 2-(methylethylpropyl)-pyridine was obtained when sodium amide was used; however, when potassium amide was employed, a 39% yield was obtained. The absence of recovered starting material shows that the more active potassium compound is subject to a competitive reaction, most probably condensation of the carbanion at the azomethine position of another molecule of alkylpyridine.

Unsuccessful attempts were made to synthesize 2- or 4-(methylethylisobutyl)-pyridine starting with 2- or 4-(methylisobutyl)-pyridine (expts. 9 and 20, Table V). The desired alkylpyridines were however, obtained when the reactants were 2- and 4-*sec*-butylpyridine and isopropyl bromide (expts. 10 and 21, Table V). The condensation reaction could be explained as taking place through an intermediate formation of a carbanion with subsequent condensation with an alkyl halide.

The yields of 4-alkylpyridines usually were higher than those of the corresponding 2-alkylpyridines. This also probably is related to the greater stability in liquid ammonia medium of 4-picolyl carbanion as compared with the 2-picolyl carbanion.⁶

Experimental Part

I. Alkylation of Alkylpyridines.—The alkylation reactions were carried out in either a 100- or 250-ml. capacity Magne-Dash autoclave¹¹ according to the procedure described previously.

The product was analyzed by means of infrared spectroscopy, comparing the alkylated product with the syntheti-

(11) Autoclave Engineers, Inc., Erie, Pa.

cally prepared alkylpyridines and by gas chromatography using as a stationary phase ethyltrihydroxypropylethylenediamine on Chromosorb.¹²

The kinetic experiments were carried out in a 100-ml. Magne-Dash autoclave. The 4-isopropylpyridine and sodium were placed in the autoclave which then was flushed with nitrogen. The autoclave was attached to an ethylene storage tank of about 125-ml. capacity which was kept in a constant temperature bath. The tank was equipped with a precision pressure gauge. The autoclave was heated to 125°. At this point the ethylene was introduced to the desired pressure and the agitating device on the Magne-Dash was started. The pressure in the Magne-Dash was kept constant and the drop in the pressure in the ethylene tank was recorded at frequent intervals. From the rate of pressure drop it was possible to determine the rate of reaction. The rate of ethylene consumption remained constant over the length of the experiment which usually lasted from 0.75 to 1.0 hour.

II. Synthesis of Alkylpyridines.—The alkylpyridines were prepared according to the general procedure described by Brown and Murphey.⁸ The following describes a typical synthesis: to a solution of 0.2 g. of ferric nitrate in 200–300 ml. of liquid ammonia was added 0.5 g. atom of clean potassium metal. The solution turned dark blue. After all the potassium had dissolved (10–15 minutes) 0.5 mole of alkylpyridine was added and the solution was allowed to stir for about 15 minutes. To this was added over a period of 1–1.5 hours 0.5 mole of alkyl halide. The reaction was maintained at the boiling temperature of liquid ammonia.

The solution was allowed to warm up slowly to room temperature and the contents of the flask was added slowly into water. The pyridine layer was decanted and the water layer was extracted thrice each time with 20 ml. of ether. The ether and pyridine layers were combined and the ether was removed by distillation. Benzene was added to the alkylpyridines and distilled to remove the dissolved water as an azeotrope. The dry alkylpyridines then were distilled on a Podbielniak Hypercal or on a Whirling Band column.¹³

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(12) A. W. Decora and G. V. Dinnen, paper presented before the Analytical Division, American Chemical Society Meeting, September, 1958, Chicago, Ill.

(13) Podbielniak, Inc., Chicago, Ill.

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, TULANE UNIVERSITY]

The Preparation of 6,7-Disubstituted Quinoxalines¹

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Reduction of 1,2-dinitroso-4-nitroso-5-azidobenzene (III) with an insufficient amount of hydrogen iodide produces 1,2-diamino-4-nitro-5-azidobenzene (IV), whereas an excess of hydrogen iodide produces 2,4,5-triaminonitrobenzene (I). Condensation with 1,2-dicarbonyl derivatives gives 6-azido-7-nitroquinoxalines (VIII) from IV and 6-amino-7-nitroquinoxalines (VII) from I. The azides VIII also are obtained from corresponding diazotized amines VII and sodium azide. Certain 6-chloro-7-nitroquinoxalines are unreactive toward nucleophilic displacement of chlorine.

Condensation of an aromatic *o*-diamine with a 1,2-dicarbonyl compound, a preparative method for quinoxalines bearing carbocyclic substituents, has provided certain 6,7-disubstituted quinoxalines required for other purposes. The synthesis of 6-amino-7-nitroquinoxaline, an attractive goal since

amino and nitro groups are easily transformed into other functional groups, requires initial preparation of 2,4,5-triaminonitrobenzene (I).

Each of two different methods for the preparation of I starts with 1,5-dichloro-2,4-dinitrobenzene obtained by nitrating *m*-dichlorobenzene. Transformation into 1,5-diazido-2,4-dinitrobenzene (II) and then, by pyrolysis, into 1,2-dinitroso-4-nitro-5-azidobenzene (III) has been reported previously.³ In a one-step operation, an excess of hydrogen

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(3) R. J. Gaughran, J. P. Picard and J. V. R. Kaufman, *THIS JOURNAL*, **76**, 2233 (1954).