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Sodium-catalyzed Side Chain Alkylation of Picolines[1]

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The side chain alkylation of picolines in the presence of ethylene and propylene was accomplished using sodium as a catalyst. Unlike the side chain alkylation of alkylbenzenes the reaction does not require the addition of promoters which could initiate the alkylation by forming organosodium compounds. 2- and 4-Picoline react with ethylene under pressure at 150° to produce the corresponding *n*-propyl- and 1-ethylpropylpyridines. 3-Picoline reacts with difficulty with ethylene. Propylene reacts with 2- and 4-picoline to form 2- and 4-isobutylpyridine. The mechanism of the side chain alkylation of picolines is discussed.

As a continuation of the study of side-chain alkylation of alkylbenzenes[1,3-6] the reaction of picolines with olefins in the presence of sodium was investigated.

It was reported that picolines react with sodium at room temperature and that the products of decomposition with water yield dimethylbipyridyls.[7,8] Similarily, 3-picoline was reported to form 3,3′-dimethyl-x,x′-dipyridyl.[8]

Wegler and Pieper[9] found that 2-picoline reacts with either 1,3-butadiene or with styrene at 100–120° in the presence of catalytic amounts of sodium to form 2-(3-pentenyl)-pyridine and 2-(3-phenylpropyl)-pyridine, respectively.

It was presently found that 2- and 4-picoline reacts with ethylene to form the corresponding *n*-propyl- and 3-pentylpyridine. The reaction takes place at 135–150° under pressure. Unlike the side-chain alkylation of alkylbenzenes[3-6] the reaction does not require the addition of promoters, which could initiate the alkylation by forming organosodium compounds. It seems that the interaction of picoline with sodium forms the necessary chain initiator for the side chain alkylation of picolines.

The condensation of 2- and 4-picoline with ethylene proceeds at 150°, which is a somewhat lower temperature than that required for the ethylation of toluene. The monoethylation of picolines is accompanied by a diethylation reaction, which indicates that the ethylation of the monoethylated picolines, namely of 2- or 4-*n*-propylpyridine, occurs with greater ease than that of picoline. This is in line with the observation made during the study of the relative rate of ethylation of toluene and *n*-propyltoluene.[6]

When a molar excess of ethylene was used over that of 2-picoline, a product was obtained corresponding to triethylated picoline, 2-(triethylmethyl)-pyridine. Attempts failed to synthesize this compound by the usual methods.

The ethylation of 2- and 4-picoline was accompanied by the formation of higher boiling compounds, which are presumably products of condensation of two or more molecules of picoline.

3-Picoline reacts with difficulty with ethylene. The temperature required to accomplish this reaction was of the order of 200°; under these conditions a great part of the 3-picoline underwent a self-condensation.

Propylene reacts with 2- and 4-picoline to form the 2- and 4-isobutylpyridine, respectively. The alkylation with propylene requires higher temperatures than that with ethylene, and therefore it is not surprising that the propylation reaction is accompanied by the formation of higher boiling compounds resulting from the self-condensation of picolines.

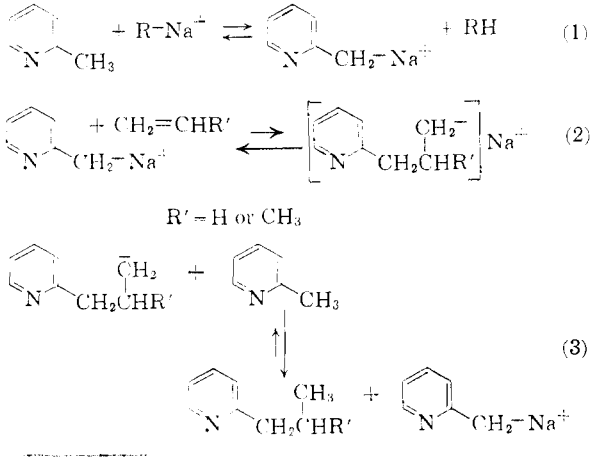
Isobutylene reacts with 2-picoline with difficulty; only a small yield of an alkylate corresponding to neopentylpyridine was obtained.

An attempt was made to ethylate pyridine in the presence and absence of anthracene as promoter[3-6] and sodium as catalyst. Ethylation did not occur even at 300°, although at this temperature a considerable part of the pyridine underwent self-condensation.

The alkylation of picolines is summarized in Table I.

The yields of alkylpyridines obtained from the side-chain alkylation reactions were based on recovered picolines; mechanical losses were not taken into consideration. The yields could be greatly increased by modifying experimental conditions.[10]

The alkylation of picolines proceeds most likely by a mechanism similar to the one proposed for the



(1) Paper XVI of the series Base-catalyzed Reactions. For paper XV see H. Pines and D. Wunderlich, THIS JOURNAL, **80**, 6001 (1958).

(2) Vladimir N. Ipatieff Postdoctoral Fellow, 1957–1958.

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TABLE I

SODIUM-CATALYZED ALKYLATION OF PICOLINES

Reagents				Experimental conditions						Picoline recovd., %	Residue		Alkylated picolines	
	Olefins													
-Picoline[a]	Kind	Moles	Sodium, g.	Temp., °C.	Duration, hr.	Max. press., atm.	Temp., °C.	Min. press, atm.	Temp., °C.		g.	wt. %[b]	Mono- yield, %[c]	Di- yield, %[c]
2	C_2H_4	0.37	1.0	155–160	4	29	146	5	153	60	16.7	17.8	37[d]	11[e]
2	C_2H_4	1.41[n]	1.0	157	1					5	14.5	15.5	2[d]	64[e,f]
2	C_3H_6	0.5	1.5	220–245	19	21	227	6	225	56	27.1	28.8	5[g]	
2	C_3H_6	1.5	1.5	213	2.5	100	193	91	213	76	9.5	10.1	13[g]	
2	i-C_4H_8	1.5	1.5	200–215	2	75	194	48	202	80	12.5	13.2	1[h]	
3	C_2H_4	0.5	1.0[i]	200	7	42	166	39	200	74	14.1	15.0	4[j]	
4	C_2H_4	0.5	1.0	155	4	29	154	2	154	51	13.9	14.8	19[k]	18[l]
4	C_3H_6	0.5	1.0	190–216	5	27	182	27	216	60	29.4	31.4	4[m]	

[a] One mole of picoline was used. [b] Based on the weight of picoline and sodium used in the reaction. [c] Yield based on picoline reacted. [d] 2-n-Propylpyridine. [e] 2-(Diethylmethyl)-pyridine. [f] In addition 4.6 g. or 2.6 mole % of triethylated picoline was obtained, presumably 2-(triethylmethyl)-pyridine. [g] 2-Isobutylpyridine. [h] The product was not investigated. [i] Anthracene, 1.0 g., was added. [j] 3-n-Propylpyridine; the higher boiling compounds were not investigated. [k] 4-n-Propylpyridine. [l] 4-(Diethylmethyl)-pyridine. [m] 4-Isobutylpyridine. [n] The autoclave was charged initially with 50 atm. of ethylene at 25°. When the temp. reached 150° the maximum pressure was 120 atm., and after 1.5 hr. of heating it dropped to 27 atm. It was recharged to 50 atm. at 150° and when the pressure dropped again to 27 atm. it was recharged. This was repeated four times until a total of 1.4 moles of ethylene was absorbed.

TABLE II

CHARACTERIZATION OF ALKYLPYRIDINES OBTAINED FROM THE ALKYLATION OF PICOLINES

$-C_5H_4NR$, R =	B.p. °C.	Mm.	$n^{20}D$	Formula	Analyses,[a] % Calcd.	Found	Picrates M.p., °C.	Formula	Nitrogen, % Calcd.	Found
2-n-C_3H_7	169–171	759	1.4914	$C_8H_{11}N$	C, 79.29	79.47	75	$C_{14}H_{14}O_7N_4$	16.00	16.09
					H, 9.15	9.08				
					N, 11.56	11.79				
3-n-C_3H_7	65–67	25.5	1.4950	$C_8H_{11}N$	C, 79.29	78.91	100.5	$C_{14}H_{14}O_7N_4$	16.00	15.73
					H, 9.15	9.17				
					N, 11.56	11.67				
4-n-C_3H_7	188	756	1.4961	$C_8H_{11}N$	C, 79.29	79.02	130[b]	$C_{14}H_{14}O_7N_4$	16.00	15.76
					H, 9.15	8.96				
					N, 11.56	11.77				
2-i-C_4H_4	74	23	1.4862	$C_9H_{13}N$	C, 79.95	80.54	97	$C_{15}H_{16}O_7N_4$	15.37	15.70
					H, 9.69	9.36				
					N, 10.36	10.41				
4-i-C_4H_9	63–66	8.5	1.4902	$C_9H_{13}N$	C, 79.95	79.75	120[c]	$C_{15}H_{16}O_7N_4$	15.37	15.44
					H, 9.69	9.72				
					N, 10.36	10.66				
2-$(C_2H_5)_2CH$	197	759	1.4866	$C_{10}H_{15}N$	C, 80.48	80.53	72	$C_{16}H_{18}O_7N_4$	14.81	14.92
					H, 10.13	9.98				
					N, 9.39	9.84				
4-$(C_2H_5)_2CH$	80–82	12	1.4918	$C_{10}H_{15}N$	C, 80.48	80.43	125	$C_{16}H_{18}O_7N_4$	14.81	14.76
					H, 10.13	9.73				
					N, 9.39	9.56				
2-$(C_2H_5)_3C$	88–91	16	1.4970	$C_{12}H_{19}N$	C, 81.29	81.39	101–102	$C_{18}H_{22}O_7N_4$	13.79	13.98
	70	2			H, 10.80	10.64				
					N, 7.90	8.12				

[a] The elementary analyses were made by Miss Hilda Beck. [b] Reported 134° [A. E. Chichibabin, *Bull. soc. chim.*, [5] **3**, 1607 (1936)]. [c] Reported 120–120.4° [C. Osuch and R. Levine, THIS JOURNAL, **78**, 1723 (1956)].

TABLE III

SYNTHESIS OF ALKYLPYRIDINES

Starting material[a] $-C_5H_4NR$, R =	Alkylating agent	Product $-C_5H_4NR$, R =	Yield, mole %	B.p. °C.	Mm.	$n^{20}D$	d^{20}_4	Picrate m.p., °C.
2-CH_3	C_2H_5Br	2-n-C_3H_7	65	170–177	740	1.4915	0.9191	71–72[b]
3-CH_3	C_2H_5Br	3-n-C_3H_7	62	186	746	1.4960	.9264	101–102[c]
2-CH_3	i-C_3H_7Br	2-i-C_4H_9	68	110–111	55	1.4831	.8973	97[d]
2-n-C_3H_7	C_2H_5Br	2-$(C_2H_5)_2CH$[e]	21	191–193	747	1.4841	.9017	72–73
2-i-C_4H_9	i-C_3H_7Br	2-$(i$-$C_3H_7)_2CH$[f]	14	211–217	745	1.4870	.8998	108[g]

[a] 1 M each of alkylpyridine, alkyl halide and sodium amide was used. [b] Reported: 65–66.2°; Table II, ref. c; 64° [R. P. Mariella, L. F. A. Peterson and R. C. Ferris, THIS JOURNAL, **70**, 1494 (1948)]; 74.6–75.1°, ref. 11. [c] Reported 99–100° [E. Hardegger and E. Nikks, *Helv. Chim. Acta*, **39**, 505 (1956)]. [d] Reported 97–97.6°, Table II, ref. b. [e] New compound. *Anal.* Calcd. for $C_{10}H_{15}N$: C, 80.48; H, 10.13; N, 9.39. Found: C, 80.12; H, 10.15; N, 9.62. [f] New compound. *Anal.* Calcd. for $C_{12}H_{19}N$: C, 81.29; H, 10.80; N, 8.15. Found: C, 81.36; H, 10.76; N, 8.15. [g] *Anal.* Calcd. for $C_{18}H_{22}O_7N_4$: N, 13.79. Found: N, 13.73.

TABLE IV

INFRARED SPECTRA OF ALKYLPYRIDINES

2-C_5H_4NR, R =					3-C_5H_4NR, R =		4-C_5H_4NR, R =		
I n-C_3H_7	II $(C_2H_5)_2CH$	III $(C_2H_5)_3C$	IV i-C_4H_9	V $(i$-$C_4H_9)_2CH$	VI n-C_3H_7	VII $(C_2H_5)_2CH$	VIII n-C_3H_7	IX $(C_2H_5)CH$	X i-C_4H_9
3.32m	3.26m	3.32m	3.30m	3.30m	3.34w	3.37w	3.30w	3.32w	3.32w
3.38m	3.38m		3.36m		3.44s	3.5s	3.40s	3.4s	3.4s
3.41s	3.41s	3.45s	3.40–3.50s	3.40–3.50s	3.53s		3.50s	3.5s	3.5s
3.52s	3.50s								
4.35w	4.35w	4.35w	4.35w	4.35w					
5.10w	5.09w	5.10w	5.10w	5.10w	5.10w	5.10w	5.15m	5.17m	5.17m
5.19w	5.15w	5.19w	5.18w	5.18w	5.20w	5.20w	5.40w	5.42w	5.41w
5.24w	5.22w	5.26w	5.22w	5.22w	5.40w	5.40w	5.82w	5.65w	5.58w
5.42w	5.42w	5.40w	5.40w	5.35w				5.94w	5.94w
5.66w	5.66w	5.46w	5.64w	5.42w					
5.83w		5.68w	5.83w	5.63w					
				5.90w			6.00w		
6.32s	6.28s	6.30s	6.30s	6.30s	6.30s	6.30s	6.22s	6.22s	6.22s
6.40s	6.39s	6.39s	6.39s	6.39s	6.38s	6.38s	6.40s	6.40s	6.40s
6.8s	6.8s	6.82s	6.80s	6.80s	6.80s	6.78s	6.68ms	6.70ms	6.70ms
6.98s	6.98s	7.00s	6.98s	6.98s	6.85–6.90s	6.84s	6.82s	6.84s	6.82s
7.28ms	7.24ms	7.29s	7.21s	7.21s	7.03s	7.02s	7.08s	7.10s	7.08s
			7.33s	7.31s	7.29s	7.26s	7.23s	7.23s	7.23s
7.49m	7.50m	7.50m	7.49m		7.46m	7.46m	7.42m	7.44m	7.30s
	7.60w								7.40w
7.72m	7.72ms	7.70ms	7.70ms	7.61s	7.80w	7.60w	7.78mw	7.58m	7.52mw
7.80w	7.80w	7.79m	7.80w	7.90m	7.96mw	7.92w	7.93w	7.70w	7.78m
7.96w	7.96w	8.01wm	8.02w	8.02w				7.93w	8.00w
8.18m	8.08w	8.20w	8.23ms	8.22m	8.20mw	8.20w	8.19s	8.20s	8.20s
8.30m	8.25ms	8.39mw	8.55s	8.57ms	8.43ms	8.41ms			8.55s
8.70s	8.70s	8.68s	8.70s	8.68s	8.65m	8.74ms		8.76ms	8.90w
9.01m	9.01m	8.88s	8.95w	8.90w	8.86m	9.02m	9.12m	9.12m	9.00w
9.14m	9.35m	9.12m	9.00ms	9.09m	9.02m	9.28w	9.32m	9.34ms	9.32ms
9.50s	9.50s	9.34m	9.39m	9.21m	9.76s	9.57w	9.60w	9.60m	
9.61w	9.58w	9.46ms	9.50s	9.48ms		9.78s			
	9.88w	9.61m							
		9.86m							
10.06s	10.06s	10.06s	10.03s	10.03s	10.12m	10.14mw	10.04s	10.06s	10.06s
10.45w	10.46w	10.46w	10.43w	10.44mw	10.59w	10.58w	10.42w		10.42w
	10.81m	10.82s	10.81m	10.77m	10.83w	10.95m		10.83w	10.83w
11.22m	11.22ms	11.30ms	11.20m	11.23mw	11.20mw	11.24m	11.48m	11.30m	11.32m
11.53w	11.82ms		12.02ms	11.7m	11.60mw	11.97m	11.92s	11.96m	11.82s
12.00m	12.54s	12.40s	12.42w	12.42s	12.10m	12.4s	12.5s	12.2s	12.02m
13.1–13.4s	12.7s	12.74s	13.1–13.4s	12.98s	12.7s	12.92m		12.85m	12.85s
	13.0s	13–13.4s		13.3s	13.28m	13.38m	13.30s	13.26m	
	13.2s				14.0s	13.95s		13.60s	13.55m

[a] The peaks are referred to as: s, strong; ms, medium strong; m, medium; mw, medium weak; w, weak; sodium chloride, 0.04-mm. cell was used. Compounds I, II, IV, V, VI, were prepared synthetically; the remaining compounds were obtained by the side chain alkylation reaction.

side-chain alkylation of alkylbenzenes. The organosodium compound necessary to initiate the side-chain alkylation is most probably produced by the interaction of sodium with picoline. The organosodium compound thus formed metalates the methyl group in picoline, which subsequently adds to the ethylene.

In equation 1 the carbanion chain initiator abstracts a proton from 2- or 4-picoline to form a resonance stabilized picolyl carbanion. The equilibrium is shifted to the right the larger the difference between the pK_a of the conjugate acid of R^- and the picoline.

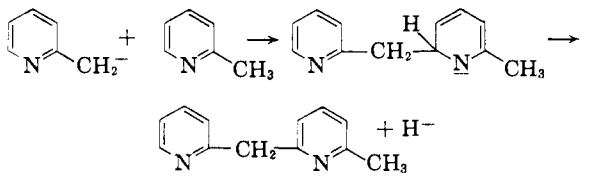
In equation 2 through the addition of picolyl carbanion to the olefin a resonance non-stabilized carbanion is produced. It is therefore assumed that the addition is energetically unfavorable, as indicated by the short arrow. The carbanion thus formed can react, however, with the more acidic picoline, as indicated in equation 3.

The formation of isobutylpyridine in the reaction of picoline with propylene is not surprising and it is in agreement with the carbanion chain mechanism.[4] It was shown previously that the mode of addition of a carbanion to an olefin is determined by polar factors and for that reason in step 2 the more stable primary pyridylisobutyl carbanion was produced as the intermediate in the formation of isobutylpyridine. Both steric and inductive factors may account for the reluctance of

picoline to react with propylene as compared with ethylene.

The greater ease of ethylation of 2- and 4-picoline relative to 3-picoline is not unexpected.[11]

The higher boiling compounds, residue, found in the reaction product were probably formed through a competing reaction which involves the addition of a picolyl carbanion to a picoline molecule



Although the structures of these higher boiling compounds were not investigated, the addition of alkyl-, phenyl- and pyridyl- alkali metals to a pyridine nucleus was reported in the literature.[7,8,12-14]

Experimental Part

General Procedure.—The alkylation reactions were carried out in a 250-ml. capacity Magne-Dash[15] autoclave which was charged with one mole, 93 g., of dry picoline and 1 to 2 g. (0.042–0.083 g. at.), of sodium. The autoclave was sealed and after flushing with nitrogen was charged with 0.5 to 1.5 moles of ethylene, propylene or isobutylene. The agitated mixture was heated at 150 to 200° for one to 19 hours (Table I).

The autoclave was then allowed to cool to about 80° and the gases collected. They consisted, according to gas chromatographic analysis, of the corresponding starting olefins contaminated with small amounts of nitrogen.

The dark brown reaction mixture was flash distilled on a one-foot Vigreux column under 20 mm. of pressure. The picolines and the mono- and dialkylated picolines were thus separated from the residue. The alkylated picolines were redistilled on a Podbielniak Whirling Band column.[16]

The alkylpyridines produced (Table II) were identified by comparing their infrared spectra with those of synthetically prepared compounds and/or by the melting and mixed melting point of the respective picrates (Table III).

Attempted Ethylation of Pyridine.—One mole of pyridine 1.0 g. of sodium and ethylene, 50 atm., were heated in a Magne-Dash up to 382° for 8 hours. No pressure drop was observed during the reaction. About 64% of the pyridine charged was recovered. The remaining product consisted of tarry material, probably bi- and polypyridyl. Similar results were obtained when 0.7 g. of *o*-chlorotoluene was added as promoter to the reaction mixture. Ethylation of pyridine was not observed.

Synthesis of Alkylpyridines.—These compounds were prepared according to procedure B described by Brown and Murphey.[11] The starting alkylpyridines were treated with a molar amount of freshly prepared sodium amide[17] and the alkylpyridylsodium compounds thus produced were treated with a molar equivalent of alkyl halides in liquid ammonia under vigorous stirring. The residues, obtained from the evaporation of ammonia, were treated with ice and the aqueous mixtures extracted with ether and distilled (Table III).

Attempts to Synthesize 2-(Triethylmethyl)-pyridine.—An unsuccessful attempt was made to synthesize the *t*-heptylpyridine from 2-(diethylmethyl)-pyridine by the procedure B.[11] Similar failures were encountered when the experiment was made in tetrahydrofuran or in toluene at their respective reflux temperatures.

Infrared spectra were taken on a double beam recording spectrophotometer, equipped with rock salt optics[18] (Table IV).

It was observed that for the 2-alkylpyridines the characteristic absorptions are in the region of 5.10 and 5.70 μ (weak absorptions), 9.50 μ (medium) and 10.0–10.06 μ (strong). For 3-alkylpyridines the characteristic absorption wave is at 9.7 μ (strong); there is no absorption at 10.0 μ as in the case of 2- and 4-monoalkylpyridines. 4-Alkylpyridine has an absorption at 5.15 μ (medium) and at 10.06 μ (strong).

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(11) H. C. Brown and W. A. Murphey, THIS JOURNAL, **73**, 3308 (1951), found that in the non-catalytic methylation of alkylpyridine by means of methyl chloride, using sodamide as a metalating medium, the relative yields of isopropylpyridines produced from the corresponding ethylpyridines are for 2- 73%, 3- 47% and for 4- 68%. For *t*-butylpyridines produced from the corresponding isopropylpyridines the yields are for 2- 60%, for 3- 23% and for 4- 70%; this indicates that only a small amount of *t*-butylpyridine could be produced from ethylpyridine. Since the reaction of the carbanions with methyl chloride is exceedingly rapid, it could be concluded that the rate of formation of the pyridylalkyl carbanions is smaller for the 3-isomer than that for 2- and 4-isomers. No definite conclusion can be derived as to the metalation of picolines since the authors did not report the amount of picolines recovered and the yield of isopropylpyridine obtained when picolines were metalated with methyl chloride.

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