Base-Catalyzed Reactions. XL.[1] Sodium- and Potassium-Catalyzed Reactions of 3-Methyl- and 3-Ethylpyridine with Olefinic Hydrocarbons. Cyclialkylation of 3-Alkylpyridines

S. V. KANNAN AND HERMAN PINES*

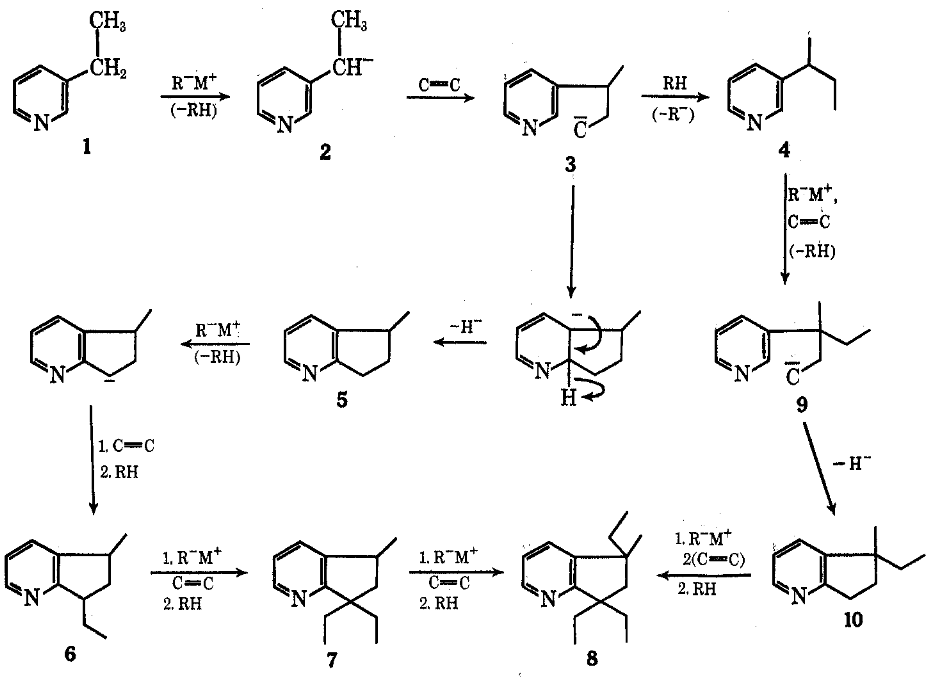
Ipatieff High Pressure and Catalytic Laboratory, Department of Chemistry,
Northwestern University, Evanston, Illinois 60201

Received November 10, 1970

The lower acidity of 3-alkylpyridines compared to the 2 and 4 isomers is manifested in their reactivities, especially in base-catalyzed reactions. They require more vigorous conditions for reactions to occur. A novel cyclialkylation occurs when 3-ethylpyridine or 3-*sec*-butylpyridine reacts with ethylene in the presence of sodium or potassium. Under the same conditions, 3-methylpyridine fails to react. The cyclialkylation is confined to ethylene among the olefins studied. With conjugated olefins such as butadiene, isoprene, and styrene, the norml addition products are formed. A mechanism consistent with the results is proposed.

Base-catalyzed reactions of alkylbenzenes,[2] alkylnaphthalenes,[3] and alkylpyridines[2,4] have been the subjects of extensive investigations in this laboratory. In the presence of sodium, toluene has been shown to form normal addition products with olefins but cyclic products accompany the normal products in the presence of potassium,[2,3] while the more acidic 2- and 4-alkylpyridines gave rise to only normal addition products.[2,4] With their acidities comparable to that of toluene and with the 2 positions of their rings highly susceptible to nucleophilic attack, 3-alkylpyridines were found to behave differently from their 2 and 4 isomers.[5] The present investigation was undertaken to extend the scope of the reaction.

SCHEME I



Results and Discussion

A. Ethylene.—When 2- or 4-alkylpyridines react with ethylene in the presence of sodium or potassium, the benzylic hydrogens are successively displaced to give normal addition products. In addition to requiring longer reactions times and higher temperatures, 3-ethylpyridine (**1**) reacts differently with ethylene as can be seen from Table I. The two primary products from the reaction in the presence of sodium are 3-*sec*-butylpyridine (**4**) and 6,7-dihydro-7,7-diethyl-5-methyl-5*H*-1-pyridine (**7**). Further ethylation occurs with a longer reaction time to yield 6,7-dihydro-5,7,7-triethyl-5-methyl-5*H*-1-pyridine (**8**). The reaction sequence is summarized in Scheme I.

A carbanion mechanism has been proposed for the reactions catalyzed by alkali metals.[2,6] Extending this mechanism to the present reaction, the carbanion formed from **1**, through a mechanism similar to the one described previously,[7] can add to ethylene to form carbanion **3**, which has two courses open for reaction: it can transmetalate to give **4** or attack the 2 position of the ring in the same molecule to give a cyclic product **5**. This new type of cyclization is consistent with our knowledge of the high electrophilicity of the 2 position

---

(1) (a) For paper XXXIX, see H. Pines, W. M. Stalick, T. G. Holford, J. Golab, H. Lazar, and J. Simonik, *J. Org. Chem.*, **36**, 2299 (1971). (b) Paper XI of the series, Alkylation of Heteroaromatics; for paper X, see ref 1a.

(2) H. Pines and L. A. Schapp, *Advan. Catal.*, **12**, 116 (1960).

(3) B. Stipanović and H. Pines, *J. Org. Chem.*, **34**, 2106 (1969).

(4) H. Pines and B. Notari, *J. Amer. Chem. Soc.*, **82**, 2209 (1960).

(5) S. V. Kannan and H. Pines, *Chem. Commun.*, 1360 (1969).

(6) H. Pines and N. C. Sih, *J. Org. Chem.*, **30**, 280 (1965).

(7) Reference 3; see Discussion.

TABLE I

REACTIONS OF 3-ETHYLPYRIDINE WITH ETHYLENE[a] IN THE PRESENCE OF ALKALI METALS

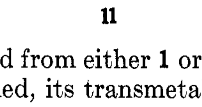
Expt no.	Temp, °C	Duration of reaction, hr	Conversion, %[b]	Composition of product,[c] wt %			
				4	**7**	**8**	Others
			Sodium				
1	160	2.5	17	42	58	0	
2	160	7.0	41	42	47	11	
3	160	15.0	64	34	49	18	
4	160	26.0	82	25	33	35	
			Postassium				
5	120	4.5	12	25	26	20	29
6	120	11.5	44	27	26	17	30
7	120	24.0	64	25	24	21	30
8	160	3.0	26	29	24	15	32
9	160	12.0	60	32	28	19	21
10	160	18.0	78	35	24	22	17

[a] Initial pressure of ethylene at room temperature was 40 atm. [b] Based on 3-ethylpyridine. [c] From vpc peak areas uncorrected for thermal conductivity.

in the pyridine ring.[5] The proportions of the normal and cyclic products in the reaction will depend on the relative rates of transmetalation and cyclization. A consequence of cyclization is the liberation of hydride anion which adds to ethylene, the ultimate product being ethane which was found to be present in the product.

Obviously because of its high reactivity compared with **1** and **4**, the cyclic product **5** could not be detected in the products. Hence, it is presumed that **5** is converted to its carbanion and then to **6** as shown in Scheme I as soon as it is formed. Although the carbanion derived from **6** is tertiary, it appears to be more readily formed than those from **1** or **4**; it reacts with ethylene to form **7**. The relative proportions of **4** and **7** should be a measure of the relative rates of transmetalation and cyclization of the carbanion **3**.

As the reaction progresses, the concentration of **1** decreases and that of **4** and **7** increases. The latter two start competing for ethylene through their anions, which are both tertiary. By starting with pure **4** and allowing it to react with ethylene in the presence of sodium, it was found that it gave rise to only one product in 39% yield, *viz.*, **8**. The reaction took a long time (14 hr), which is to be anticipated for a *sec*-butyl group.[2] As can be seen from Scheme I, **8** can arise both from **4** and **7**. Whereas it is a one-step process for **7**, it is a multistep process for **4**. Of these many steps, only the cyclization is expected to be slow, the displacement of benzylic hydrogens in the 2 position being necessarily faster. The absence of **11** in the reaction products, which can be formed from either **1** or **4**, shows that, once the anion **9** is formed, its transmetalation to give **11** is slower compared to its cyclization to **10**.



11

Potassium has previously been found to bring about such alkylation reactions at lower temperatures, about 120° compared to about 160° for sodium.[3] From Table I it can be seen that side reactions are promoted by potassium accounting for a considerable percentage of other products which were not identified. There were at least eight products at lower conversions which could not be separated by gas chromatography. At higher conversions, the products **4**, **7**, and **8** predominated over others. In all likelihood, potassium is catalyzing nuclear alkylation in addition to cyclization reactions. Potassium-catalyzed nuclear alkylation has already been reported in the case of alkylnaphthalenes.[3]

Lithium failed to bring about the same reaction even at 200°. The black material obtained after decomposition of the product with methanol probably indicates that dimerization and polymerization of 3-ethylpyridine occurred in preference to reaction with ethylene.

Cyclization does not occur in the cases of 2- and 4-ethylpyridine under he influence of the same catalysts, because such a reaction would necessarily involve nucleophilic attack on the 3 position of the ring and that position is resistant to such reactions.

It was found that 3-methylpyridine fails to react with ethylene in the presence of sodium, potassium, and lithium under the same conditions. Varying the temperature and the amount of the catalyst had no effect. It is presumed that the black residue invariably obtained after decomposition of the reaction product at the end of each experiment is an indication that the catalyst is being consumed for dimerization and polymerization reactions of the starting material. Alkali metals are known to catalyze such reactions.[8] It appears that, in the case of 3-methylpyridine, these side reactions are faster than addition to ethylene.

Attempts were made to react propylene with 3-methyl- and 3-ethylpyridine in the presence of sodium and potassium. Propylene being less reactive than ethylene would require high temperatures for the reaction to occur.[2] At temperatures of 200° and higher, however, a self-condensation of alkylpyridines occur,[8] accompanied by the destruction of the catalyst. The product from these reactions consisted of a black residue.

B. Styrene and α-Methylstyrene.—With a more reactive olefin like styrene or α-methylstyrene, both 3-methyl- and 3-ethylpyridine react. Cyclization products were not formed in the reactions. Styrene reacts with 3-ethylpyridine to form only the monoadduct **12**, whereas 3-methylpyridine has been reported to form both mono- and diadducts.[9] A 3% yield of ethylbenzene was also obtained in the former reaction. The re-

---

[8] R. M. Acheson, "The Chemistry of Heterocyclic Compounds," Wiley, New York, N. Y., 1967, p 198.

[9] Y. I. Chumakov and V. M. Ledovskikh, *Tetrahedron*, **21**, 937 (1965).

actions of 3-methylpyridine and 3-ethylpyridine with α-methylstyrene are complex, giving at least five products, respectively, at low conversions which could not be separated by gas chromatography. Obviously, side reactions are competing with the normal addition reactions.

C. Butadiene and Isoprene.—The reaction of 3-methylpyridine with butadiene has been reported to tive 3-(*trans*-3-pentenyl)pyridine with traces of 1 olefin.[9] Under the vigorous conditions used for the reaction, it is probable that the authors had obtained the thermodynamically more stable trans adduct due to equilibration. Reinvestigation of this reaction under milder conditions (60° *vs.* 150°) yielded the cis adduct **13** in predominance over the trans adduct **14** (Table II). The cis/trans ratio, however, decreases with increasing conversion indicating that either the cis adduct reacts faster than the trans adduct with butadiene to form the diadduct or that the former isomerizes to the thermodynamically more stable trans adduct. The same trend is observed in the reaction of 3-ethylpyridine with butadiene when *cis*-**15**, *trans*-**16**, and diadducts are formed. A total gas chromatographic separation of the diadducts to determine their geometry around the double bond could not be accomplished. In the present reactions also, the presence of the terminal olefin was detected by infrared spectroscopy in both mono- and diaddition products. Under comparable conversions, 3-ethylpyridine formed more diadduct than 3-methylpyridine. This probably indicates the greater reactivity of the tertiary anion from the former compared to the secondary anion from the monoadduct of the latter. The formation of diadducts from dienes even at low conversions has also been observed in earlier studies and was interpreted as being due to the intramolecular proton transfer reaction to form a new picolyl anion.[10,11]

TABLE II

REACTION OF 3-ALKYLPYRIDINES WITH BUTADIENE[a] IN THE PRESENCE OF SODIUM AT 60°

3-Methylpyridine

Reaction time, hr	Conversion, %[b]	Wt % of total adducts[c] Mono- *cis*-**13**	*trans*-**14**	Di-	Tri-	Cis/trans
0.5	39	55	33	12		1.67
1.7	70	50	31	19		1.61
2.0	100	32	23	45	Trace	1.39
8.0	100	18	14	63	5	1.29

3-Ethylpyridine

Reaction time, hr	Conversion, %	Wt % of total adducts **15**	**16**	Di-	Tri-	Cis/trans
1.0	15	49	34	17		1.44
3.0	44	45	33	22		1.33
6.0	77	39	34	27		1.15
2.0[d]	100	29	29	42		1.00

[a] 0.05 mol of 3-alkylpyridine and 0.15 mol of butadiene used. [b] Based on alkylpyridine charged. [c] From vpc peak areas, uncorrected for thermal conductivity. [d] Reaction conducted at 90°.

The reaction of isoprene with 3-ethylpyridine was carried out to determine the head/tail addition ratio in the formation of the monoadducts **17** and **18** (Table III). The ratio was 1 to 3 indicating that tail addition is preferred.

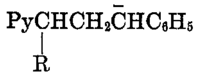
TABLE III

REACTION OF 3-ETHYLPYRIDINE WITH STYRENE AND ISOPRENE[a]

Reactant	Temp, °C	Conversion, %[b]	Wt % of monoadduct[c]
Styrene	135	100	97[d] (**12**)
Isoprene	80	100	100[e] (**17, 18**)

[a] 0.03 mol of 3-ethylpyridine and 0.015 mol of olefinic hydrocarbon were used. [b] Based on olefins used. [c] From vpc peak areas uncorrected for thermal conductivity. [d] The other 3% was identified as ethylbenzene. [e] Nmr showed 25% **17** and 75% **18**.

The absence of cyclialkylation in the reactions of styrene, butadiene, and isoprene has to be accounted for. From previous studies,[12] it is known that only anion **19** is generated by the addition of styrene to an alkylpyridine. Being a secondary anion and being

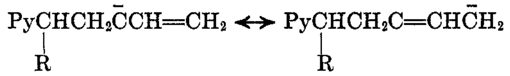


$$\mathrm{Py\underset{\displaystyle R}{C}HCH_2\bar{C}HC_6H_5}$$

19, R = H, CH_3, etc.

stabilized by resonance with the phenyl ring, it is not expected to be as nucleophilic as the primary anion **3**, which has all the negative charge localized on one carbon atom. Hence, it is not able to attack the 2 position of the ring as effectively as the latter. Also, the transmetalation step may be expected to be faster with a secondary anion than a primary one.

In the addition of 3-alkylpyridines to butadiene, allylic anion is generated. This delocalized anion **20** is



$$\mathrm{Py\underset{\displaystyle R}{C}HCH_2\bar{C}CH{=}CH_2 \longleftrightarrow Py\underset{\displaystyle R}{C}HCH_2C{=}CH\bar{C}H_2}$$

20

sufficiently stable that transmetalation is energetically preferred over cyclialkylation. For the same reason isoprene is also reluctant to form cyclic products.

Summary

3-Alkylpyridines form cyclialkylated products on reaction with ethylene; this is in contrast to their 2 and 4 isomers. The cyclialkylation is a consequence of the high electrophilicity of the 2 position of the ring. With vinyl- or aryl-substituted ethylenes, the "normal" mono- and diadditions take place.

Experimental Section

Reagents.—3-Methyl- and 3-ethylpyridine were purchased from Reilly Tar and Chemical Co. The material was dried over barium oxide and distilled in a nitrogen atmosphere. *sec*-Butylpyridine was obtained by reacting 3-ethylpyridine with ethyl-bromide, according to the procedure described in the literature.[13] All the alkylpyridines used in the reaction were over 99.5% pure as adjudged by gas chromatography.

Butadiene was obtained from Matheson Co. Isoprene (Aldrich Co.) was dried over Linde 3A molecular sieves and distilled just before use. Isopropylcyclohexane (internal standard) was obtained by catalytic hydrogenation of isopropylbenzene under 100 atm of hydrogen pressure at 150°, using nickel kieselguhr (Harshaw Chemical Co.) catalyst. Styrene and α-methylstyrene were purchased from Matheson Co.

Alkylation Procedure.—The following general procedure was used for alkylations with ethylene, butadiene, and isoprene. The alkylpyridine, about 1% by weight of the alkali metal, and an internal standard (usually isopropylcyclohexane) were stirred in a flask equipped with a high-speed stirrer[6] under an atmosphere

---

(10) H. Pines and J. Oszczapowicz, *J. Org. Chem.*, **32**, 3183 (1967).

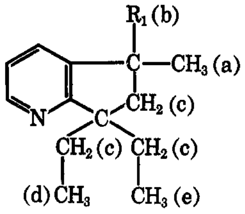
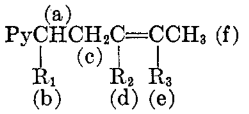
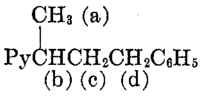
(11) W. M. Stalick and H. Pines, *ibid.*, **35**, 422 (1970).

(12) H. Pines and N. E. Sartoris, *ibid.*, **34**, 2113 (1969).

(13) H. C. Brown and W. A. Murphey, *J. Amer. Chem. Soc.*, **73**, 3308 (1951).

TABLE IV

CHEMICAL SHIFTS IN NMR SPECTRA

Compd	Group	Multiplicity (no. of protons)	δ, ppm
			
7, R_1 = H	a	Doublet (3)	1.23
(b)	b	Multiplet (1)	3.10
	c	Multiplet (6)	2.06
	d	Triplet (3)	0.70
	e	Triplet (3)	0.72
8, R_1 = CH_2CH_3	a	Singlet (3)	1.23
(c) (d)	b		
	c	Multiplet (8)	1.67
	d, e	Multiplet (9)	0.8
 $\mathrm{Py}\overset{(a)}{\underset{\underset{(b)}{R_1}}{C}}H\underset{(c)}{CH_2}\underset{\underset{(d)}{R_2}}{C}{=}\underset{\underset{(e)}{R_3}}{C}CH_3\ (f)$			
13, 14, $R_1 = R_2 = R_3$ = H	a, b, c	Multiplet (4)	2.50
	d, e	Multiplet (2)	5.41
	f, *cis*-13	Doublet (3)	1.51
	f, *trans*-14	Doublet (3)	1.61
15, 16, $R_1 = CH_3$; $R_2 = R_3$ = H	a	Multiplet	2.70
	b	Doublet	1.24
	c	Multiplet	2.29
	d, e	Multiplet	5.30
	f, *cis*-15	Doublet	1.53
	f, *trans*-16	Doublet	1.60
17, $R_1 = R_2 = CH_3$; R_3 = H	a	Multiplet (1)	2.83
	b	Doublet (3)	1.38
	c	Doublet (2)	2.31
	d, f	Doublet (6)	1.62
	e	Quartet (1)	5.14
18, $R_1 = R_3 = CH_3$; R_2 = H	a	Multiplet (1)	2.83
	b	Doublet (3)	1.27
	c	Multiplet (2)	2.31
	d	Triplet (1)	5.14
	e, f	Singlet (6)	1.75
 $\mathrm{Py}\overset{CH_3\,(a)}{\underset{(b)}{C}}H\underset{(c)}{CH_2}\underset{(d)}{CH_2}C_6H_5$ 12			
12	a	Doublet (3)	1.23
	b	Multiplet (1)	2.46
	c	Multiplet (2)	1.85
	d	Triplet (2)	2.46

of nitrogen. After 2.5 hr the black solution was transferred to a Magne-Dash autoclave,[14] olefin was added, and the reaction was conducted for a prescribed length of time at the desired temperature. At the end of the reaction, the contents were cooled, decomposed with methanol, and analyzed directly by gas chromatography. Samples for nmr and ir were obtained by washing the solution with water, distilling, and separating by preparative gas chromatography.

In the case of styrene and α-methylstyrene, these were added to the heated catalyst solution at 135° dropwise and the reaction was quenched 15 min after the addition was finished.

Analytical Procedure.—Analysis of the products formed was conducted on either a 10% Versamide 900 (6 ft) on 60–80 mesh Gas-Pack WAB or on a 20% silicone DC 550 (6 ft) on 60–80 mesh Gas-Pack W column with the temperature programmed between 100 and 250°. Preparative gas chromatography was performed on 10 ft × $^3/_8$ in. 20% silicone DC 550 on 60–80 mesh Gas-Pack W and on 8 ft × $^3/_8$ in. 10% Versamid 900 on 60–80 mesh Gas-Pack WAB columns. The compounds were identified by a combination of ir, nmr, and microanalysis where needed.

Identification of the Products.—The products were identified by a combination of nmr, ir, and vpc (Table IV). In the nmr spectrum of compounds **7** and **8**, one of the α protons was found to be absent but the γ proton was intact showing that the addition had occurred in the α position. The retention times by gas chromatography indicate that **7** is a triadduct and **8** is a tetraadduct. Infrared spectra showed the absence of unsaturation and only the proposed structure fits the facts.

MICROANALYSES[a]

Compd	Calcd, % C	Calcd, % H	Calcd, % N	Found % C	Found % H	Found % N
7	82.48	10.12	7.40	82.41	10.10	7.40
8	82.87	10.67	6.46	82.45	10.97	6.72

[a] W. H. W. Laboratories, Garden City, Mich.

The cis and trans compounds obtained from the reaction of 3-methyl- and 3-ethylpyridine with butadiene were separated by preparative vpc. The ir of the cis adducts had a characteristic peak at 675 cm^{-1}, the trans adducts at 966 cm^{-1}, and the terminal olefin at 909 cm^{-1}. From the extinction coefficients, the terminal olefin was calculated to be present in quantities of <5%. The protons in the vinylic methyl in cis adducts appear at a higher field compared to trans adducts probably due to shielding afforded by the π-electron cloud of the pyridine ring. Also, the J_{cis} for **13** and **15** were 4.4 and 7 cps, respectively, and J_{trans} for **14** and **16** were 2.2 and 3.3 cps, respectively. The hydrogens in the methyl group in the benzylic positions of compounds **17** and **18** have different chemical shifts in nmr (see Table IV). Also, the hydrogens in the allylic methyl groups in **17** appear as a doublet at δ 1.62 and those of **18** appear as a singlet at δ 1.75. Both the peaks were used to compute the relative ratios of the two formed in the reaction of 3-ethylpyridine with isoprene. Compounds **11** and **4** were identified by their relatively simple nmr spectrum.

Registry No.—**1**, 536-78-7; **4**, 25224-14-0; **7**, 25224-15-1; **8**, 25224-16-2; **12**, 29851-07-8; **13**, 29851-08-9; **14**, 29851-09-0; **15**, 29851-10-3; **16**, 29851-11-4; **17**, 29851-12-5; **18**, 29851-13-6; 3-methylpyridine, 108-99-6.

---

[14] Autoclave Engineers Inc., Erie, Pa.