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A NEW PROTOTROPIC REACTION OF 3-METHYLPYRIDINE

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Abstract—It was found that 3-methylpyridine in the presence of catalytic alkaline metals enters into a prototropic reaction with styrene or butadiene, forming 3-(3′-phenylpropyl)-pyridine and a mixture of 3-(3′-pentenyl)- and 3-(4′-pentenyl)-pyridines respectively. The structure of 3-(3′-phenylpropyl)-pyridine was proved by independent synthesis from nicotinic nitrile, and that of 3-pentenylpyridines by hydrogenation into 3-n-amylpyridine, ozonization and IR spectra. The results show a fairly high mobility of the methyl hydrogens in 3-methylpyridine, comparable with the mobility of the hydrogens in the 2- and 4-isomers.

IT IS generally accepted that only in 2- and 4-methylpyridine, and not in the 3-isomer, can the hydrogen atoms of the methyl groups be replaced by a metal.[1,2] These views were advanced by Chichibabin,[3,4] who was the first to investigate the exchange reaction of 2- and 4-picolylsodium with alkyl halides and considered that this reaction was based on the tautomerism of 2- and 4-methylpyridines, which is not possible for the 3-isomer. Later this reaction, frequently used for the synthesis of higher 2- and 4-substituted alkyl- or aralkylpyridines (but not the 3-isomers), was explained on the basis of resonance structures which stabilized the carbanion of picolylsodium derivatives, the latter also being possible only for 2- and 4-alkylpyridines, and not for the 3-isomers.

The considerable induction effect of the nitrogen heteroatom in the pyridine nucleus may induce the hydrogen atoms of the methyl group in the third position to participate in prototropic reactions. Indeed, 3-methylpyridine[5] exchanges a hydrogen atom for metal, with practically the same ease as the 2- or 4-isomers, on reaction with sodium amine in liquid ammonia, while the 3-pycolylsodium formed is a convenient intermediate in the synthesis of various higher 3-alkylpyridines.

These results cannot, however, serve as confirmation of the reactivity of the α-hydrogens of the alkyl group in the third position of the pyridine nucleus as it is known that amides of alkali metals in solvents like liquid ammonia are very strong catalysts of prototropic exchange reactions.[6]

Recently, it was found[7,8] that 2-methylpyridine in the presence of metallic sodium adds to styrene or butadiene forming 2-phenylpropylpyridine and 2-pentenylpyridine respectively.

It was assumed that 3-methylpyridine, under these mild conditions would also enter into prototropic reaction with styrene and butadiene in the presence of sodium.

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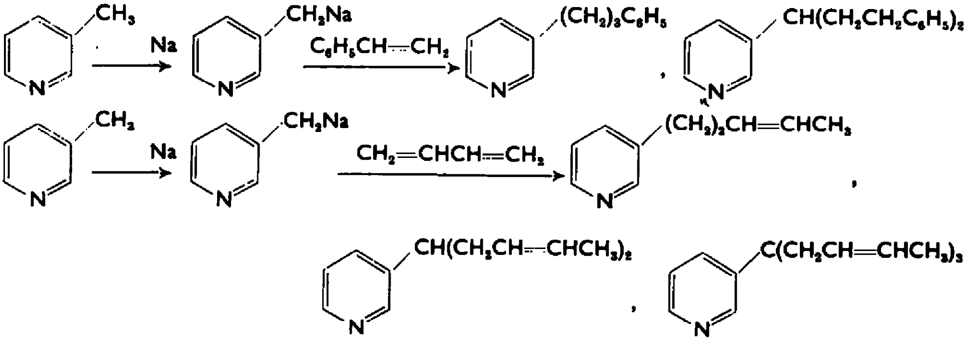
[1] F. Bergstrom, T. Norton and R. Seibert, *J. Org. Chem.* **10**, 452 (1945).
[2] F. Bergstrom and W. Fernelius, *Chem. Rev.* **20**, 413 (1937).
[3] A. E. Chichibabin, *Bull. Soc. Chim. Fr.* (5), **3**, 1607 (1936).
[4] A. E. Chichibabin, *Bull. Soc. Chim. Fr.* (5), **5**, 429 (1938).
[5] H. Brown and W. Murphey, *J. Amer. Chem. Soc.* **73**, 3308 (1951).
[6] A. I. Shatenshtein, *Isotopny obmen i zameshchenie vodoroda v organicheskich soyedineniakh* p. 133, I.A.N. USSR, Moskva (1960).
[7] R. Wegler and G. Pieper, *Chem. Ber.* **83**, 6 (1950).
[8] R. Wegler and G. Pieper, FRG Pat. 831099, 11 February (1952); *Chem. Zentr.* 4815 (1952).

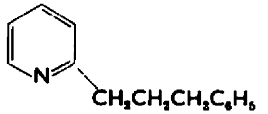
The reaction readily yields the corresponding 3-substituted derivatives of the pyridine series in accordance with the equations:[9,10]



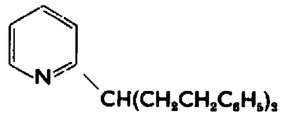
A characteristic feature of this reaction is that, as in the case of 2-methylpyridine,[7,8] metallic sodium is required in amounts far greater than the stoichiometric quantities (0·05–0·1 g-atom per mole of pyridine base). The yields are as high as 40–45% of the theoretical. The synthesis proceeds equally well using metallic lithium or potassium or sodium amide instead of sodium. α-Methylstyrene or isoprene may also be introduced into the reaction.

In addition to monosubstituted products, alkylated compounds are formed as a result of secondary interaction between 3-phenylpropylpyridine (or 3-pentenylpyridine) with the second and third molecule of styrene (or butadiene).

The yield of the di- and trialkylated products is perceptibly lower but may be increased by introducing 3-phenylpropylpyridine or 3-pentenylpyridine instead of 3-methylpyridine (Tables 1 and 2) into the reaction. Wegler and Pieper[1] assigned structures 2-(3′-phenylpropyl)-pyridine (I) and 2-pyridyl-di-(2′-phenylethyl)-methane (II) to the products of the reaction between 2-methylpyridine and styrene and 2-(3′-pentenyl)-pyridine (IV) and 2-(5′-nonadiene-2′,7′-yl)-pyridine (V) to the products of the reaction with butadiene. No proof for these structures was presented, although other possible products such as methyl-substituted 2-(2′-methyl-2′-phenylethyl)-pyridine (III) or 2-(4′-pentenyl)-pyridine (VI) are possible. Hence, an independent synthesis of 3-(3′-phenylpropyl)-pyridine was undertaken from nicotinic nitrile by the



I



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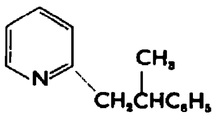

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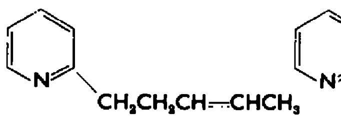

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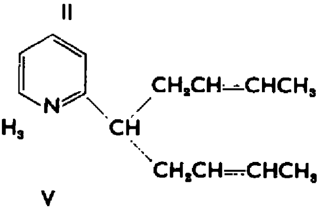

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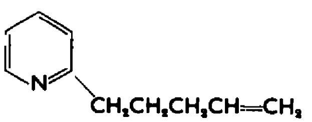

VI

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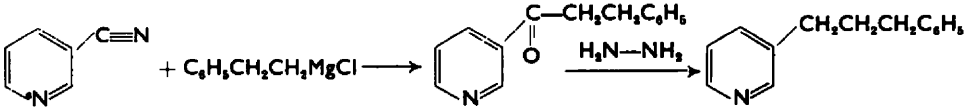
[9] Yu. I. Chumakov and V. M. Ledovskikh, USSR Patent 158574, 17 July (1962); *Bull. izobr. i tovarnykh znakov* p. 12, No. 22 (1963).

[10] Yu. I. Chumakov and V. M. Ledovskikh, USSR Patent 158575, 17 July (1962); *Bull. izobr. i tovarnykh znakov* p. 12, No. 22 (1963).

action of β-phenylethylmagnesium chloride with subsequent reduction of 3-pyridyl-2-phenylethylketone by the method of Kishner–Huang–Minlon:



The 3-(3′-phenylpropyl)-pyridine obtained proved identical with the product of the reaction of 3-methylpyridine with styrene (by the IR spectra and the m.p. of a mixed sample of picrates).

The structure of the product of the reaction of 3-methylpyridine with butadiene was proved by its hydrogenation to 3-n-amylpyridine, identical with a specimen synthesized[11] and confirmed by means of IR spectra and by the m.p. of a mixed sample of picrates. Thus, the normal structure of the lateral chain of the substituent in the third position was established. Ozonization of the 3-pentenylpyridine yielded 70% of acetaldehyde, identified as its 2,4-dinitrophenylphydrazone, which, therefore, proved the formation of 3-(3′-pentenyl)-pyridine.

However, in the IR spectrum of 3-pentenylpyridine, in addition to the intense frequency at 966 cm^{-1} typical of the double bond of olefines of general formula R—CH=CH—R′ (*trans*),[12] a considerably less intense frequency at 909·8 cm^{-1} was discovered typical of the double bond at the end of an aliphatic chain $—(CH_2)n-CH=CH_2$.[13] Thus the reaction between butadiene and 3-methylpyridine, contrary to the data obtained by Wegler and Pieper[7,8] in the reaction of 2-methylpyridine with butadiene, yields a mixture of 3-(3′-pentenyl)-pyridine (IV) with small quantities of 3-(4′-pentenyl)-pyridine (VI). The relegation of frequencies 966 cm^{-1} and 909·8 cm^{-1} to out-of-plane C—H deformations was confirmed by the IR spectrum of 3-n-amylpyridine, in which these frequencies are lacking (Fig. 1).

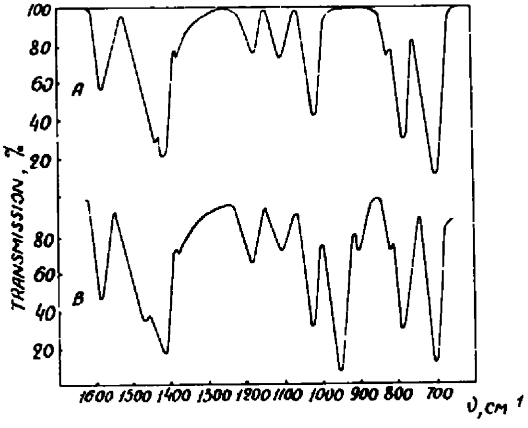


Fig. 1. Infrared absorption spectra:
A, 3-n-amylpyridine;
B, 3-(3′-pentenyl)-pyridine

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[11] E. Hardegger and E. Nikles, *Helv. Chim. Acta* **39**, 505 (1956).
[12] J. Anderson, Jr. and W. Seyfried, *Analyt. Chem.* **20**, 998 (1948).
[13] H. McMurry and V. Thornton, *Analyt. Chem.* **24**, 318 (1952).

TABLE 1. PROTOTROPIC ALKYLATION OF 3-METHYLPYRIDINE WITH STYRENE AND BUTADIENE

No.	3-Methylpyridine		Conjugated diene compound			Sodium, g	Temp of reaction, °C	Time of adding diene, min	Reaction time, hr	Reaction products		Yields[a] %	Total %
	g	moles		g	moles						g		
1.	9·3	0·1	Styrene	10·4	0·1	0·3	145	15–30	2	3-(3′-phenylpropyl)-pyridine	3·3	23·24	40·6
										1·5-diphenyl-3-(3′-pyridyl)-pentane	3·75	17·36	
2.	46·5	0·5	1,3-Butadiene	27	0·5	0·7	180	—[b]	1	3-(3′-pentenyl)-pyridine	13·2	35·4	54·2
										3-(5′-nonadiene-2′, 7′-yl)-pyridine	8·2	16·4	
										3-tri-(2′-n-butenyl)-methylpyridine	1·5	2·4	

[a] Yields are given with the regeneration of the 3-methylpyridine that has not entered into reaction taken into account.

[b] The entire quantity of lowered butadiene was introduced into the reaction after cooling the metalloorganic compound of 3-methylpyridine.

Table 2. Properties and analysis of products of prototropic alkylation of 3-methylpyridine

No.	3-Alkylpyridine	B.p. °C (mm)	n_D^{20}	d_4^{20}	MR_D found	Calc	Analyses Calc %	Analyses Found %	M.p. °C (corr.)	Picrates Analyses, N % Calc	Picrates Analyses, N % Found
1.	3-(3′-phenylpropyl)-pyridine	123·7–127·0 (2 mm)	1·5634	1·0302	62·35	62·03	85·23 7·66 7·11	84·98, 85·10 7·65 7·75 7·35, 7·25	107·5–108	13·08	13·00, 13·15
2.	1,5-Diphenyl-3-(3′-pyridyl)-pentane	209·0–219·0 (2 mm)	1·5778	1·0500	95·01	95·36	87·66 7·69 4·65	87·68, 87·78 7·85, 7·75 4·85, 5·05	—[a]	—	—
3.	3-(3′-Pentenyl)-pyridine	74·2–75·2 (3 mm)	1·5080	0·9286	47·23	46·69	81·58 8·90 9·52	81·70, 81·94 81·93, 9·12 9·42, 9·37	66·3–66·6	14·89	14·86, 14·96
4.	3-(5′-Nonadiene-2′,7′-yl)-pyridine	89·0–92·0 (1 mm)	1·5206	0·9340	65·59	64·69	83·53 9·51 6·96	83·68, 83·36 9·58, 9·41 7·20, 7·15	64·5–65·5	13·02	12·94, 13·10
5.	3-Tri-(2′-n-butenyl)-methylpyridine	138·0–145·0 (1 mm)	1·5290	0·96097	82·16	82·69	84·65 9·86 5·49	85·04, 85·15 9·90, 9·80 5·60, 5·70	—	—	—

[a] The picrate precipitated out in the form of oil.

TABLE 3. INFRARED SPECTRA OF 3-ALKYLPYRIDINES (cm^{-1})

3-(3′-Pentenyl)-pyridine	3-(5′-Nonadiene-2,′7′-yl)-pyridine	3-tri-(2′-n-butenyl)-methylpyridine	3-n-Amyl-pyridine	3-(3′-Phenylpropyl)-pyridine
1583	1583	1583	1583	1583
1471				1471
	1441		1441	1441
1418		1418	1418	1418
1374	1374	1374	1374	
	1320			
	1296			
	1217			1217
1186			1186	1186
	1178	1179		
1107	1107	1107	1107	1107
				1076
1030	1030	1030	1030	1030
		991		
966	966	966		
909·8	909·8	909·8		909·8
			823	
	804			
790		790	790	790
	756			
		749		749
	716			
		713		
703			703	703

[a] The spectra were taken on an NKC-14 spectrophotometer (prism made of sodium chloride, thickness of layer 0·04 mm).

These results confirm the high mobility of the methyl hydrogens in 3-methylpyridine, due to the induction effect of the pyridine heteroatom, which decreases the electron density in the ring, leading to activation of the hydrogens attached to the methyl groups in all three positions of the pyridine nucleus, including the third position. Thus, all three isomeric methylpyridines behave similarly in prototropic reactions including the intermediate formation of metalloorganic derivatives.

EXPERIMENTAL

(1) *Reaction of* 3-*methylpyridine with styrenes*

To a 3-necked flask equipped with a stirrer, reflux condenser, dropping funnel, thermometer and tube for introducing N_2, 3-methylpyridine and a catalytic amount of metallic Na (0·1 g-atom per mole 3-methylpyridine) was added. The mixture was heated with stirring in a stream of N_2 to 145°, after which an equimolecular quantity of freshly distilled styrene or its alkyl-substituted derivative was added during 10–30 min. The mixture was heated an additional 2 hr at the b.p. of 3-methylpyridine. The contents of the flask were cooled and, while stirring, sufficient water for the decomposition of the metalloorganic compound, was carefully added. The upper layer was separated and the lower, aqueous layer extracted with benzene. The extract was added to the main reaction products and dried by boiling with fused KOH for 2 hr. The residue was fractionated *in vacuo* after distilling off the benzene. The results are presented in Tables 1 and 2.

(2) *Interaction of* 3-*methylpyridine with* 1,3-*butadienes*

3-Methylpyridine and metallic Na (0·05–0·1 g-atom per mole of 3-methylpyridine) were placed in a rotating stainless steel autoclave, hermetically sealed, washed with N_2 and heated with stirring to 150° for 20–30 min. The autoclave was cooled successively with water, ice and a mixture of solid CO_2 and acetone. An equimolecular quantity of 1,3-butadiene or its derivatiye, liquefied in the cooling mixture was added in one portion. The autoclave was quickly hermetically sealed and heated during 20–30 min to 150–200°. The autoclave was then allowed to cool slowly in the course of 1 hr to about 100°. Subsequent treatment was carried out in accordance with the description given above. For the results, see Tables 1 and 2.

(3) *3-(3′-Phenylpropyl)-pyridine from nicotinic nitrile*

(a) A solution of 10·0 g (0·2 mole) nicotonic nitrile in 150 ml dry ether was added dropwise during 30 min to a Grignard reagent obtained from 28·1 g (0·2 mole) freshly distilled β-phenylethyl chloride and 5·8 g (0·24 mole) Mg chips in 300 ml dry ether. After the addition, the reaction mixture was heated for another 2 hr, cooled and treated with 200 ml water and 90 ml sat. NH_4Claq. The ether extract was evaporated after drying and the residue distilled *in vacuo*. Besides the fraction with a b.p. 44–60° at 24 mm (3·7 g), consisting of ethylbenzene, a fraction, 154–163° at 2·5–3·5 mm, consisting of 3-pyridyl 2-phenylethyl ketone was obtained. The yield was 5·8 g or 13·8% of the theoretical; picrate, m.p. 142·2–143·2° (corr.). (Found: N, 12·41, 12·50. Calc. for $C_{14}H_{13}NO$: N, 12·72%).

(b) 3-Pyridyl 2-phenylethyl ketone (4·5 g; 0·022 mole), 25 ml triethylene glycol, 3 g (0·07 mole) freshly distilled 80% hydrazine hydrate and 3 g finely ground NaOH were placed in a 100 ml 2-necked flask equipped with a reflux condenser and a thermometer. The mixture was slowly heated to 100–120°. In 0·5 hr after slowing down the N_2 generation, the temp of the bath was raised to 130° and the reaction mixture kept at this temp for 1·5 hr. After cooling, the condenser was replaced by a descending one, and the temp gradually raised to 210–220°. The excess hydrazine hydrate was gradually distilled off in the course of 4 hr and the reaction mixture distilled with superheated steam to a volume of 0·5 l. and extracted with ether. The ether extracts were dried (Na_2SO_4) and the solvent was distilled off. The residue on distillation gave 2·0 g 3-(3′-phenylpropyl)-pyridine, b.p. 133·5–140° at 3 mm; picrate, m.p. 106·7–107° (corr.), yield, 47·1% of the theoretical.

The m.p. of 3-(3′-phenylpropyl)-pyridine picrate, obtained from 3-methylpyridine and styrene was 107·5–108° (corr). The m.p. of a mixed sample of the two picrates was 106·8–107·8° (corr.). The IR spectra of both samples of 3-(3′-phenylpropyl)-pyridines were also identical (Table 3).

(4) *Hydrogenation of a mixture of 3-pentenylpyridines*

An alcoholic solution of a mixture of 3-pentenylpyridines was hydrogenated with Raney Ni and a press. of 30–40 atm. at a temp of 80–90°. An almost quantitative yield of 3-n-amylpyridine was obtained, b.p. 54·5–55° at 1 mm; picrate, m.p. 77·5–77·8°. The m.p. of 3-n-amylpyridine picrate, prepared independently,[11] was 77·3–77·5°. A mixed sample of both picrates had a m.p. of 77·3–77·6°. The IR spectra of both 3-n-amylpyridines were identical (Table 3).

(5) *Ozonization of a mixture of 3-pentenylpyridines*

Ozonization of a mixture of 3-pentenylpyridines (5·3 g) was carried out in glacial acetic acid (150 ml). The reduction decomposition of the ozonide was effected by boiling for 1 hr with water in the presence of 2 g of Zn dust and subsequent distillation with steam to a volume of 50–70 ml. From the distillate treated with 8 g of 2,4-dinitrophenylhydrazine solution in 100 ml of conc. H_2SO_4, acetaldehyde 2,4-dinitrophenylhydrazone was obtained and recrystallized from MeoH aq, wt. 5·67 g, m.p. 146·5–147·5° (corr.), yield 70·0%. A mixed m.p. with 2,4-dinitrophenylhydrazone, obtained under similar conditions from a specimen of acetaldehyde (m.p. 146–147·5° (corr.)) was not depressed (m.p. 146·4–147·5° (corr.)).

The residue after distillation of the acetaldehyde was saturated with KOH and repeatedly extracted with ether. From the ether extract after drying and distillation of the ether; 0·9 g (18·5%) β-(3-pyridyl)-propionaldehyde, b.p. 81–91° at 2 mm was obtained; thiosemicarbazone, m.p. 164–165° (corr.). (Found: C, 52·16, 52·08; H, 6·04, 6·12; N, 26·50, 26·40; S, 15·30, 15·40. Calc. for $C_9H_{12}NS$: C, 51·89; H, 5·81; N, 26·90; S, 15·4%).