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REDUCTIVE ALKYLATION OF PYRIDINE BASES

E.A.Mistryukov, E.L.Ilkova and M.A.Ryashentseva

N.D.Zelinsky Institute of Organic Chemistry, USSR Academy of Sciences, Moscow

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N-Alkylation as a side reaction of Raney nickel reduction of pyridine bases in alcoholic solvents has been reported [1-4]. In the present communication it is shown that this N-alkylation may be made the main reaction pathway if the hydrogenation of pyridine bases is carried out over rhenium sulphide*/. In most studied cases the yields of corresponding N-alkylpiperidines were close to quantitative provided no excessive steric hindrance to such reductive alkylation exists in either alkyl or nitrogen component.

Rhenium sulphide was prepared as described [5]. Hydrogenation was carried out in a glass tube inserted in a 70 ml rotating stainless steel autoclave under a hydrogen pressure of 110-130 kg/cm^2 at 230±10°C for 5-6 hours. Pyridine bases and alcohols were of commercial grade. The reaction products were analyzed by GLC on glass capillary columns with β-cyanoethyl- or phenylsilicon oils as the stationary phases and nitrogen or ammonia as the carrier gas [6,7].

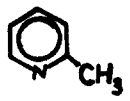
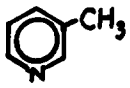
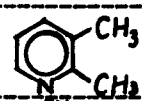
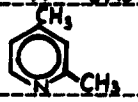
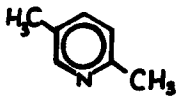
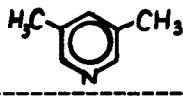
The results are summarized in Table I. Yields of hydrogenation products were in the range ac 80-95% (after distillation). In cases where just one isomer is formed, acidification with HCl and subsequent crystallization from CH_3OH - EtOAc gave pure hydrochlorides of the N-alkylpiperidines in 70-85% yield. To demonstrate the redox nature of $Re_2S_7/AlkOH/H_2$ — alkylation

$$>CH-OH \xrightleftharpoons{Re_2S_7} >C=O \xrightleftharpoons{HN<} >C\begin{matrix}-OH\\ \diagdown N<\end{matrix} \longrightarrow >C\begin{matrix}-H\\ \diagdown N<\end{matrix}$$

*/ Platinum and palladium sulphides do not catalyse hydrogenation of pyridine bases.

Table I

Reductive Alkylation of Pyridine Bases over Rhenium Sulphide

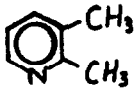
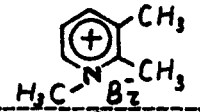
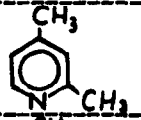
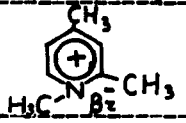
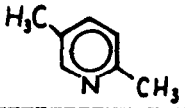
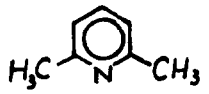
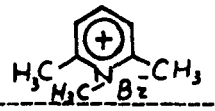
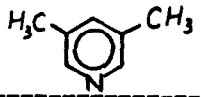
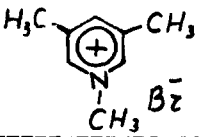
No.	Pyridine base		Solvent	Resulting Piperidine	Product composition, %*
1		a	CH_3OH	1,2-dimethyl- (I)	98 of I
		b	C_2H_5OH	1-ethyl-2-methyl- (II)	97 of II
		c	$i\text{-}C_3H_7OH$	1-isopropyl-2-methyl- (III) and 2-methyl- (IV)	52 of III 48 of IV
		d	$t\text{-}C_4H_9OH$	2-methyl- (IV)	100 of IV
2		a	CH_3OH	1,3-dimethyl- (V)	99 of V
		b	$i\text{-}C_3H_7OH$	1-isopropyl-3-methyl- (VI)	95 of VI
		c	$t\text{-}C_4H_9OH$	3-methyl- (VII)	98 of VII
3		a	CH_3OH	1,4-dimethyl- (VIII)	100 of VIII
		b	C_2H_5OH	1-ethyl-4-methyl (IX)	100 of IX
		c	$i\text{-}C_3H_7OH$	1-isopropyl-4-methyl- (X)	95 of X
		d	$t\text{-}C_4H_9OH$	4-methyl- (XI)	98 of XI
4		a	CH_3OH	1,2,3-trimethyl-	trans 67, cis 33
		b	C_2H_5OH	1-ethyl-2,3-dimethyl-	trans 62, cis 38
5		a	CH_3OH	1,2,4-trimethyl-	cis 92, trans 8
		b	C_2H_5OH	1-ethyl-2,4-dimethyl-	cis 96, trans 4
6		a	CH_3OH	1,2,5-trimethyl- (XII) and 2,5-dimethyl- (XIII)	72 of XII /cis 17, trans 83/ 28 of XIII /cis 12, trans 88/
		b	C_6H_6	XIII	trans 74, cis 26
		c	dioxane	XIII	trans 80, cis 20
7		a	CH_3OH	1,2,6-trimethyl-	cis 95
		b	C_2H_5OH	1-ethyl-2,6-dimethyl-	cis 95
8		a	CH_3OH	1,3,5-trimethyl-	cis 73, trans 27

*/ Composition of the distillated reaction mixture.

Table II.

Stereochemistry of Reduction of Lutidines over Adams Catalyst

(room temperature, atmospheric pressure)

No.	Starting compound	Solvent	Resulting piperidine	Product composition, %
1		CH_3COOH	2,3-dimethyl	trans - 83 cis - 17
2		H_2O	1,2,3-trimethyl	trans - 95
3		CH_3COOH	2,4-dimethyl	cis - 95
4		H_2O	1,2,4-trimethyl	cis - 98
5		H_2O	1,2,5-trimethyl	trans - 65 cis - 35
6		CH_3COOH	2,6-dimethyl	cis - 98
7		H_2O	1,2,6-trimethyl	cis - 100
8		CH_3COOH	3,5-dimethyl	cis - 98
9		H_2O	1,3,5-trimethyl	cis - 88 trans - 12

runs in non-alkylating alcohol (t-BuOH) and other solvents are also included in Table I.

For comparison of Re_2S_7-catalyst stereoselectivity some pyridine bases were hydrogenated over Adams catalyst (Table II).

From Table I it is seen that one or two methyls adjacent to nitrogen present no appreciable hindrance to alkylation with methyl or ethyl alcohols to N-methyl or N-ethyl piperidines, respectively. The same is true for other positions of methyl-substitution (or two methyls) with the possible exception of 2,5-lutidine where the proportion of a non-alkylated product (2,5-dimethylpiperidine) was greatest (6a, Table I). Reductive alkylation with i-PrOH is more sensitive to steric factors than methylation or ethylation. Thus, whereas one methyl at $C_{(2)}$ of pyridine ring (Ic, Table I) makes the method impracticable for isopropylation, isopropylation of bases such as β- and γ-picolines proceeds smoothly (2b and 3c, Table I).

As to the stereochemistry of hydrogenation over rhenium sulphide, the ratio of (e)(e)- and (e)(a) isomers is similar to that of with Adams catalyst (Table II).

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