STUDIES IN THE PYRIDINE SERIES. XXXVIII.* ELECTROLYTIC REDUCTION OF 3-HYDROXYPYRIDINE QUATERNARY SALTS

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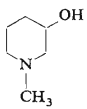
Very little has been known on reductions of quaternary salts of hydroxy pyridines. Thus, hydrogenation of the most accessible compound of this type, namely, 1-phenyl-3-hydroxypyridinium chloride on platinum catalyst affords a mixture of 1-phenyl-3-piperidinol and 1-phenylpiperidine[1] while 1-phenyl-3-piperidinol is obtained as the exclusive product in the formic acid reduction[2]. In the present paper, we wish to report the electrolytic reduction of 1-methyl-3-hydroxypyridinium methosulfate, 1-ethyl-3-hydroxypyridinium ethosulfate, and 1-phenyl-3-hydroxypyridinium chloride in aqueous sulfuric acid on lead electrodes.

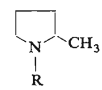
Electrolytic reduction of 1-methyl-3-hydroxypyridinium methosulfate afforded a mixture of substances identified as 1-methyl-3-piperidinol (*I*), methylpentylamine (*IIa*), and 1,2-dimethylpyrrolidine (*IIIa*). A mixture of 1-ethylpiperidine (*IV*), ethylpentylamine (*IIb*), and 1-ethyl-2-methylpyrrolidine (*IIIb*) was obtained on reduction of 1-ethyl-3-hydroxypyridinium ethosulfate. On the other hand, no piperidine derivative was isolated in the electrolytic reduction of 1-phenyl-3-hydroxypyridinium chloride, only products of pyridine ring fission being formed, namely, pentylaniline (*IIc*) and 1-phenyl-2-methylpyrrolidine (*IIIc*).

It may be seen that pyridine ring fission occurs in all cases examined. The course of electrolytic reductions is being explained as follows. Addition of hydrogen to positions 1 and 4 of the quater-

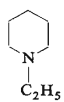


I

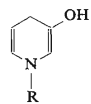
IIa, R = CH_3
IIb, R = C_2H_5
IIc, R = C_6H_5



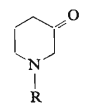
IIIa, R = CH_3
IIIb, R = C_2H_5
IIIc, R = C_6H_5



IV



V



VIa, R = CH_3
VIb, R = C_2H_5
VIc, R = C_6H_5

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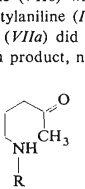
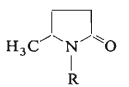
nary salt affords the dihydropyridine derivative *V* which undergoes a further reduction to the corresponding 1-alkyl-3-piperidones *VIa,b* or 1-phenyl-3-piperidone (*VIc*). The latter compounds are hydrogenolytically cleaved to the corresponding alkylpentylamines *IIa* and *IIb* or the pentylaniline (*IIc*). The other reduction products of aminoketones *VI* are represented by the corresponding 1-alkyl-2-methylpyrrolidines *IIIa* and *IIIb*, and 1-phenyl-2-methylpyrrolidine (*IIIc*). The attempted isolation of aminoketones *VI* from the reaction mixture failed, but the separately performed electrolytic reduction of 1-methyl-3-piperidone afforded a mixture of 1,2-dimethylpyrrolidine (*IIIa*) and methylpentylamine (*IIa*). Formation of these derivatives is analogous to the Clemmensen reduction of variously substituted 3-piperidones. Thus, 1-methyl-3-piperidone (*VIa*) afforded[3] 1,2-dimethylpyrrolidine (*IIIa*) and 1-phenyl-3-piperidone (*VIc*) gave[4] 1-phenyl-2-methylpyrrolidine (*IIIc*). Concerning the formation of alkylpentylamines *IIa* and *IIb* or the pentylaniline *IIc*, the hydrogenolysis of 1-alkyl-3-piperidones *VIa* and *VIb* or of 1-phenyl-3-piperidone (*VIc*) to the corresponding 5-alkylamino-2-pentanone *VIIa* and *VIIb* or 5-anilino-2-pentanone (*VIIc*) was considered, followed by reduction to alkylpentylamines *IIa* and *IIb* or the pentylaniline (*IIc*). Contrary to expectations, the actual reduction of 5-methylamino-2-pentanone (*VIIa*) did not afford any compound *IIa*, but the exclusive formation of the ring contraction product, namely, 1,2-dimethylpyrrolidine (*IIIa*), was observed.



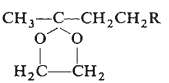
VIIa, R = CH_3
VIIb, R = C_2H_5
VIIc, R = C_6H_5

$CH_3(CH_2)_3CONHR$

VIIIa, R = CH_3
VIIIb, R = C_2H_5
VIIIc, R = C_6H_5



IXa, R = CH_3
IXb, R = C_2H_5
IXc, R = C_6H_5



Xa, R = $CONHCH_3$
Xb, R = CH_2NHCH_3

The formation of 1-methyl-3-piperidinol might be explained also on the basis of the 1,4-dihydro adduct *V*, namely, by a further reduction of both en-amine systems. In contrast to 1-methyl-3-hydroxypyridinium methosulfate, the electrolytic reduction of 1-ethyl-3-hydroxypyridinium ethosulfate afforded as the final product 1-ethylpiperidine. Its formation, however, cannot be satisfactorily explained. We assume that 1-ethylpiperidine is formed neither by reduction of 1-ethyl 3-piperidone (thus, *e.g.*, the analogous reduction of compound *VIa* does not lead to 1-methylpiperidine), nor by reduction of the intermediary 1-ethylpyridinium ethosulfate. The latter reduction is known to afford a mixture of 1-ethylpiperidine and 1-ethyl-3-piperideine[5]; no 1-ethyl-3-piperideine could be however found in the reaction mixture resulting after the electrolytical reduction of 1-ethyl-3-hydroxypyridinium ethosulfate.

The required authentic specimens were prepared as follows. Methylpentylamine (*IIa*), ethylpentylamine (*IIb*), and pentylaniline (*IIc*) were obtained by the lithium aluminium hydride reduction of substituted valeramides *VIIIa*, *VIIIb*, and *VIIIc*. An analogous reduction of 1-alkyl-5-methyl-2-pyrrolidinones *IXa* and *IXb* or 1-phenyl-5-methyl-2-pyrrolidone (*IXc*) afforded the

corresponding pyrrolidine derivatives *IIIa*, *IIIb*, and *IIIc*. The pyrrolidinones *IXa—c* were obtained by the Wallach-Leuckart reduction from levulinic acid[6]. 5-Methylamino-2-pentanone (*VIIa*) was obtained in the form of the ethyleneacetal from ethyl levulinate ethyleneacetal which was converted to levulinic methylamide ethyleneacetal (*Xa*) and this reduced with lithium aluminum hydride.

EXPERIMENTAL

Methods

Gas chromatography was performed on the Chrom 2 apparatus (Laboratorní přístroje, Prague) on Tridox. For the preparation of amides *VIII*, lactams *IX*, and amines *II* or *III* see Table I and II.

TABLE I
Survey of Amides *VIII* and Lactams *IX*

Compound	Method[a]	B.p., °C/Torr (lit.)	Compound	Method[a]	B.p., °C/Torr (lit.)
VIIIa	*A*	116—118/8 (169/90)[7]	*IXb*	*C*	89/91/9[b] —
VIIIb	*B*	120/8 (113—115/7)[9]	*IXc*	*C*	164/9[c] —

[a] A, from valeric acid and methylamine; B, from an acyl chloride and an alkylamine; C, by the Wallach-Leuckart reaction of levulinic acid and an alkylamine[8]; [b] for $C_7H_{13}NO$ (127·2) calculated: 66·10% C, 10·30% H, 11·01% N; found: 66·48% C, 10·40% H, 11·13% N; [c] for $C_{11}H_{13}NO$ (175·2) calculated: 75·40% C, 7·48% H, 7·99% N; found: 75·74% C, 7·54% H, 8·31% N.

Electrolytic Reduction of 1-Methyl-3-hydroxypyridinium Methosulfate

A mixture of 3-hydroxypyridine, dimethyl sulfate, and methanol was refluxed to afford the corresponding quaternary salt (11·3 g) which was electrolytically reduced on lead electrodes in 150 ml of 20% aqueous sulfuric acid (20 ampere hours). The catholyte was made alkaline, steam-distilled, and the distillate processed as usual to afford fraction boiling at 96—100°C (1·3 g) and fraction, b.p. 115—128°C (0·3 g). Both fractions were gas-chromatographed. 1,2-Dimethylpyrrolidine, methylpentylamine, and 1-methyl-3-piperidinol[16] were identified as the main components.

An analogous electrolytic reduction of 1-ethyl-3-hydroxypyridinium ethosulfate afforded a mixture of 1-ethylpiperidine, 1-ethyl-2-methylpyrrolidine, and ethylpentylamine. A mixture of pentylaniline and 1-phenyl-2-methylpyrrolidine was obtained by reduction of 1-phenyl-3-hydroxypyridinium chloride[17].

1-Phenyl-2-methylpyrrolidine picrate. M.p. 108·5—109°C, in accordance with literature[4]. For $C_{17}H_{18}N_4O_7$ (390·4) calculated: 52·26% C, 4·65% H, 14·36% N; found: 52·56% C, 4·85% H, 14·41% N.

TABLE II
Survey of Amines *II* and *III*

Compound	Starting material	B.p., °C/Torr (lit.)	Compound	Starting material	B.p., °C/Torr (lit.)
IIa	*VIIIa*	118–119/754 (114/745)[10]	*IIIa*	*IXa*[6]	87 (93–96)[3]
IIb	*VIIIb*	125 (134–136/745)[11]	*IIIb*	*IXb*	118 (119–120)[14]
IIc	*VIIIc*[12]	125–126/9 (130/11)[13]	*IIIc*	*IXc*	120/8 (136–138/16)[15]

Electrolytic Reduction of 1-Methyl-3-piperidone (*VIa*)

A solution of 1-methyl-3-piperidone[18] (2·1 g) in 20% aqueous sulfuric acid (100 ml) was electrolytically reduced on lead electrodes (7 ampere hours). The catholyte was processed as above to afford 1 g of a liquid, b.p. 20–24°C/8 Torr, which represents a mixture of 1,2-dimethylpyrrolidine and methylpentylamine as shown by gas chromatography.

Levulinic Methylamide Ethyleneacetal (*Xa*)

A mixture of ethyl levulinate ethyleneacetal[19] (84 g) and 14·4% aqueous methylamine (150 ml) was vigorously shaken for 9 hours. Excess aqueous methylamine and the unreacted ester were evaporated under diminished pressure and the residue was distilled to afford 57·5 g (74%) of compound *Xa*, b.p. 125·5°C/1 Torr. For $C_8H_{15}NO_3$ (173·2) calculated: 55·45% C, 8·73% H, 8·09% N; found: 55·20% C, 8·77% H, 7·94% N.

5-Methylamino-2-pentanone Ethyleneacetal (*Xb*)

A solution of compound *Xa* (48 g) in ether (50 ml) was added dropwise to a suspension of lithium aluminum hydride (10·54 g) in ether (400 ml). The reaction mixture was refluxed under stirring for 15 hours and then decomposed according to the Yugoslav authors[20]. Work-up of the ethereal solution afforded 16 g of compound *Xb* (36%), b.p. 103–105°C/9 Torr. For $C_8H_{17}NO_2$ (159·2) calculated: 60·35% C, 10·76% H, 8·80% N; found: 60·73% C, 10·74% H, 8·84% N.

Electrolytic Reduction of Compound *Xb*

A solution of compound *Xb* (13 g) in 20% aqueous sulfuric acid (200 ml) was refluxed for one hour to effect the hydrolysis of the acetal. The resulting reaction mixture was then electrolytically reduced on lead electrodes (24 ampere hours). Usual work-up afforded 5·3 g (65%) of a liquid, b.p. 95–96°C, which was identified by gas chromatography as 1,2-dimethylpyrrolidine. For $C_6H_{13}N$ (99·2) calculated: 72·66% C, 13·21% H, 14·12% N; found: 72·34% C, 13·22% H, 14·16% N.

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