

STUDIES IN THE PYRIDINE SERIES. XLV.*

ELECTROLYTIC REDUCTION OF METHOMETHYL SULFATES OF SOME ACYLPYRIDINES

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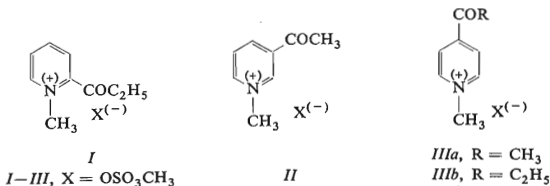
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Electrolytic reduction of methomethyl sulfate of 2-propionylpyridine gives 1-methyl-2-propylpiperidine, 1-methyl-2-propyl-3-piperidine and 1-methyl-6-propyl-3-piperidine. In a similar manner methomethyl sulfate of 3-acetylpyridine gave a mixture of 1-methyl-3-ethylpiperidine, 1-methyl-3-ethyl-3-piperidine and 1-methyl-5-ethyl-3-piperidine. Reduction of methomethyl sulfate of 4-acetylpyridine and 4-propionylpyridine gave a mixture of 1-methyl-4-ethylpiperidine or 1-methyl-4-propylpiperidine, and 1-methyl-4-ethyl-3-piperidine or 1-methyl-4-propyl-3-piperidine, respectively.

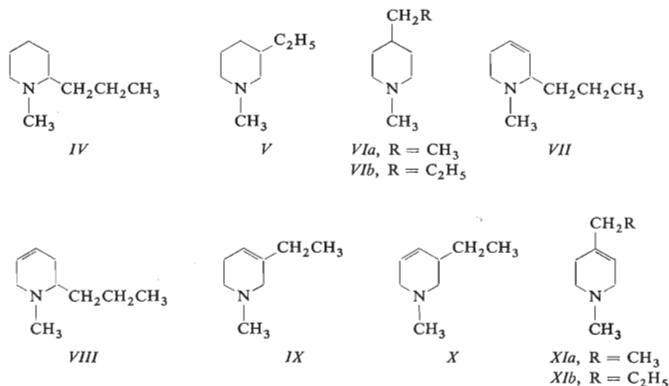
Recently we have shown that electrolytic reduction of ketones of the pyridine series gives rise to mixtures of piperidine and 3-piperidine derivatives¹. Similarly, quaternary salts of some alkyipyridines² also can be reduced electrolytically. In the present investigation electrolytic reduction of methomethyl sulfates of some acetylpyridines and propionylpyridines on lead electrodes in dilute sulfuric acid was followed.

Electrolytic reduction of 2-propionylpyridine methomethyl sulfate (*I*) gave a mixture of 1-methyl-2-propylpiperidine (*IV*), 1-methyl-2-propyl-3-piperidine (*VII*) and 1-methyl-6-propyl-3-piperidine (*VIII*). The structure of these unsaturated bases which were also obtained on reduction of the methiodide of 2-propylpyridine with sodium borohydride was determined on the basis of the PMR spectra. Electrolytic



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reduction of methomethyl sulfate of 3-acetylpyridine (*II*) again gave a mixture of three products: 1-methyl-3-ethylpiperidine (*V*), 1-methyl-3-ethyl-3-piperideine (*IX*), and 1-methyl-5-ethyl-3-piperideine (*X*). The base *IX* is known from our earlier paper³, and the structure of the base *X* was determined by PMR spectroscopy.



Both bases, *IX* and *X*, were also obtained by reduction of 3-ethylpyridine methiodide with lithium tetrahydridoaluminate. Electrolytic reductions of methomethyl sulfates of 4-acetylpyridine (*IIIa*) and 4-propionylpyridine (*IIIb*) afforded two bases each: 1-methyl-4-ethylpiperidine (*VIa*) and 1-methyl-4-ethyl-3-piperideine (*XIa*) or 1-methyl-4-propylpiperidine (*VIb*) and 1-methyl-4-propyl-3-piperideine (*XIb*), respectively. Both bases, *XIa* and *XIb*, were prepared earlier^{3,4} by sodium boro-hydride reduction of the corresponding 4-alkylpyridine methiodide.

EXPERIMENTAL

The melting points and the boiling points are uncorrected. For analysis crystalline products were dried at 0.5 Torr for 6 h. The PMR spectra were measured on a Varian (100 Mc/s) apparatus in deuteriochloroform using tetramethylsilane as internal standard. Gas chromatography was carried out on a Chrom II apparatus (column length 2.5 m, diameter 0.6 cm, stationary phase 15% Tridox on Celite of 20% Carbowax M on Chromosorb W, carrier gas nitrogen, ionisation detection). Preparative gas chromatography was carried out on an apparatus of non-commercial origin⁵.

Methomethyl Sulfates of Acylpyridines

These quaternary salts were prepared from the corresponding acylpyridines on refluxing with an equimolar amount of dimethyl sulfate in methanolic solution for 9 hours. With the exception of methomethyl sulfate of 4-acetylpyridine (m.p. 65°C) all quaternary salts prepared were syrupy.

Electrolytic Reduction of 2-Propionylpyridine Methomethyl Sulfate

A solution of 12.3 g of the quaternary salt in 130 ml of 20% sulfuric acid was reduced on lead electrodes with a current of 56 A (7A/hour). The catholyte was alkalisied and steam distilled. The bases were neutralised (7.5 ml of 4.90M-HCl) and the hydrochlorides transformed to bases by alkalisation, b. p. 174–176°C/752 Torr, yield 3.1 g (47%). For the analysis of the reaction mixture see Table I. The reaction mixture was hydrogenated (PtO₂) to 1-methyl-2-propylpiperidine, b.p. 174–176°C/752 Torr (literature⁶ gives b.p. 175.5°C). Electrolytic reduction of methomethyl sulfates of other acylpyridines was carried out in a similar manner. For the results see Table I.

Reduction of 2-Propylpyridine Methiodide with Sodium Borohydride

To an aqueous solution of the quaternary salt (25 g, m.p. 71–72°C) mixed with a solution of 4 g of sodium hydroxide in 20 ml of water 4 g of sodium boro-hydride were added and the reaction mixture steam distilled. After the conventional working up 11 g (90%) of product of b.p. 174 to 179°C/741 Torr were obtained. Preparative gas chromatography gave the following fractions: *a*) b.p. 138–140°C/744 Torr, corresponding to 1-methyl-2-propyl-3-piperidine. For C₉H₁₇N (139.2) calculated: 77.63% C, 12.31% H, 10.06% N; found: 77.71% C, 12.46% H, 10.25% N. PMR spectrum (δ): CH₂CH₃ 0.91–0.96 (m), CH₂CH₃ 1.32–1.60 (m), N—CH₃ 2.37 (s), CH 5.6–5.68 (m); *b*) b.p. 150–151°C/745 Torr, corresponding to 1-methyl-6-propyl-3-piperidine. For C₉H₁₇N (139.2) calculated: 77.63% C, 12.31% H, 10.06% N; found: 77.76% C, 12.44% H, 10.15% N. PMR spectrum (δ): CH₃—N, 2.32 (s), CH₂—N 2.76–3.34 (m), =CH 5.64 (m), 5-CH 1.90–2.16 (m), 6-CH 2.20–2.58 (m).

TABLE I
Electrolytic Reduction of Acylpyridine Methomethyl Sulfates

Salt	Product		Composition of the reaction mixture
	b.p., °C/Torr	%	
<i>I</i>	174–176/752	47	35% <i>IV</i> ^a , 24% <i>VII</i> ^b , 23% <i>VIII</i> ^{b,i}
<i>II</i>	161–163/758	62	34% <i>V</i> ^c , 40% <i>IX</i> ^d , 26% <i>X</i> ^e
<i>IIIa</i>	166/758	39	38% <i>VIa</i> ^f , 62% <i>XIa</i> ^g
<i>IIIb</i>	181–182/755	63	32% <i>VIIb</i> ^h , 68% <i>XIb</i> ^g

^a Identical with the hydrogenation product of the mixture of *IV*, *VII*, *VIII*. ^b Identical with the reduction product of 2-propylpyridine methiodide with NaBH₄. ^c Identical with the hydrogenation product of the mixture of *V*, *IX*, *X*. ^d Identical with the reduction product of 3-ethylpyridine methiodide with LiAlH₄. ^e For C₈H₁₅N (125.2) calculated: 76.74% C, 12.08% H, 11.18% N; found: 76.41% C, 12.26% H, 11.19% N. ^f Identical with the hydrogenation product of the mixture of *VIa* and *XIa*. ^g Identical with an authentic sample⁴. ^h Identical with the hydrogenation product of the mixture of *VIIb* and *XIb*. ⁱ The residue was not identified.

3-Ethylpyridine Methiodide

This was prepared by boiling 3-ethylpyridine⁷ with methyl iodide in methanol; m.p. 90–91°C (methanol). For C₈H₁₂IN (249.1) calculated: 38.57% C, 4.86% H, 50.95% I, 5.62% N; found: 38.78% C, 4.92% H, 50.82% I, 5.50% N.

Reduction of 3-Ethylpyridine Methiodide with Lithium Tetrahydridoaluminate

To a suspension of 3.8 g of lithium tetrahydridoaluminate in 300 ml of diethyl ether 24.9 g of the quaternary salt were added and the mixture refluxed under stirring for 7 hours. After decomposition with 20% hydrochloric acid (74 ml) ether was separated and the aqueous layer alkalinised and steam-distilled. After the usual isolation procedure 7.3 g (73%) of product of b.p. 155–159°C/746 Torr were obtained. Analysis by gas chromatography indicated that it was mixture of 0.5% of 1-methyl-3-ethylpiperidine, 27.5% of 1-methyl-5-ethyl-3-piperidine, and 62% of 1-methyl-3-ethyl-3-piperidine (both isolated from electrolytic reduction of 3-acetylpyridine methomethyl sulfate, see below).

Electrolytic Reduction of 3-Acetylpyridine Methomethyl Sulfate

A solution of 20.7 g of the quaternary salt in 150 ml of 20% sulfuric acid was reduced on lead electrodes with a 54 A current (8A/hour). The catholyte was alkalinised and steam-distilled. After the conventional work-up 7.2 g (62%) of product were obtained. b.p. 161–163°C/758 Torr. According to gas chromatography it was a three-component mixture in which the percentage of 1-methyl-3-ethylpiperidine was 34%. By preparative gas-liquid chromatography, the following fractions were obtained: a) b.p. 158–159°C/744 Torr, 1-methyl-3-ethyl-3-piperidine, b) b.p. 150–151°C/745 Torr, 1-methyl-5-ethyl-3-piperidine. For C₈H₁₅N (125.2) calculated: 76.74% C, 12.08% H, 11.18% N; found: 76.41% C, 12.26% H, 11.19% N. PMR spectrum (δ): CH₂CH₃ 0.88 (t), N—CH₃ 2.28 (s), N—CH₂ 5.62 (m), CH₂—CH₃ 1.14–1.32 (m), other protons 1.80–2.20 (m). Other electrolytic reductions were carried out in a similar manner (see Table I).

Elemental analyses were carried out in the analytical laboratory of our Department, the PMR spectra were measured by Dr P. Trška.

REFERENCES

1. Ferles M., Tesařová A.: *This Journal* 32, 1631 (1967).
2. Ferles M.: *This Journal* 24, 2221 (1959).
3. Ferles M., Kovařík M., Vondráčková Z.: *This Journal* 31, 1348 (1966).
4. Ferles M., Štern P., Trška P., Vyšata F.: *This Journal* 38, 1206 (1973).
5. Lukeš V., Herout V.: *This Journal* 25, 2770 (1960).
6. Lukeš R., Smetáčková M.: *This Journal* 6, 231 (1934).
7. Fand T. I., Lutomski C. J.: *J. Am. Chem. Soc.* 71, 2931 (1949).

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