

## REARRANGEMENT OF FIVE-MEMBERED HETEROCYCLIC ENAMINES\*

Otakar ČERVINKA, Anna FÁBRYOVÁ and Tomáš JURŠÍK

*Department of Organic Chemistry**Prague Institute of Chemical Technology, 166 28 Prague 6*

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Addition of bromine to 1-methyl-2-benzylidenepyrrolidine (*Ia*) and subsequent treatment with sodium hydroxide afforded unstable 1-methyl-2-phenyl-3-piperidone (*IVa*) which was reduced with lithium aluminium hydride to an isolable mixture of diastereoisomeric 1-methyl-2-phenyl-3-piperidinols (*Va*). Analogous reaction with 1-methyl-2-ethylidenepyrrolidine (*Ib*) led to mixture of products containing, in addition to diastereoisomeric 1,2-dimethyl-3-piperidinols (*Vb*), also the substitution products 1-methyl-2-(1-hydroxyethyl)pyrrolidines *VI* and 1-methyl-2-ethyl-3-pyrrolidinols *VII* (as detected by mass spectrometry).

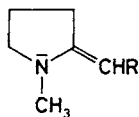
As reported in the literature<sup>1</sup>, enamines react with bromine to give unstable  $\beta$ -bromoimmonium salts that are hydrolyzed to  $\alpha$ -halogeno aldehydes or ketones. The formation of  $\alpha$ -amino acetals in reaction with alkoxides, observed in several cases<sup>2</sup>, can be explained by reaction via an aziridine intermediate. Also the isomerization of 1-methyl-2-phenyl-2-piperidine to 1-methyl-2-benzoylpyrrolidine and a similar reaction of a benzomorphine derivative, described by Japanese authors<sup>3</sup>, proceed in this way.

Within the framework of investigations of heterocyclic enamines<sup>4,5</sup> we studied the alkaline isomerization of bromoimmonium salts arising by addition of bromine to 1-methyl-2-benzylidenepyrrolidine (*Ia*) and 1-methyl-2-ethylidenepyrrolidine (*Ib*). Both the compounds are easily accessible by the Lukeš reaction<sup>6</sup> of alkylmagnesium halides with 1-methyl-2-pyrrolidone. The position of the double bond has been determined already earlier<sup>7</sup> by analysis of their IR spectra.

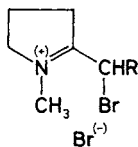
The rearrangement of compound *IIa* proceeds uniformly and affords compound *IV* with the enlarged ring. It starts apparently by nucleophilic attack of the bromoimmonium salt *IIa* by the hydroxyl ion under simultaneous bond shift (see formula *III*). Since the arising  $\alpha$ -aminoketone *IVa* was unstable, we proved its existence in the reaction mixture only by the IR spectra ( $\nu(\text{CO}) 1724 \text{ cm}^{-1}$ ) and reduced the product immediately to the stable diastereoisomeric amino alcohols *Va*. Their structure was consistent with elemental analysis and IR spectra and was confirmed by <sup>1</sup>H NMR spectra, exhibiting two signals of methyl groups bonded to a nitrogen atom ( $\delta 1.97 \text{ ppm}$

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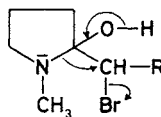
and  $\delta$  2.05 ppm) whose ratio indicated that both diastereoisomers are present as a 1 : 1 mixture, doublet of doublets of doublets of C(1)—H at  $\delta$  3.62 ppm ( $J = 4.5, 8.8, 11.0$  Hz), a doublet of C(2)—H proton at  $\delta$  2.61 ppm ( $J = 8.8$  Hz), a singlet of hydroxyl proton at  $\delta$  4.68 ppm, and signals of aromatic protons at  $\delta$  7.26 ppm.



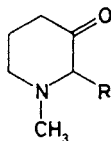
I



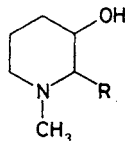
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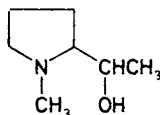
III



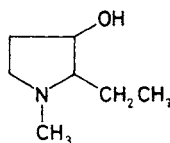
IV



V



VI



VII

In formulae I—V  $a R = C_6H_5$ ,  $b R = CH_3$

The rearrangement of compound *Ib* was more complex. In the obtained mixture of six products we detected by mass spectrometry 1-methyl-2-(1-hydroxyethyl)-pyrrolidine (*VI*) and 1-methyl-2-ethyl-3-pyrrolidinol (*VII*), in addition to the expected 1,2-dimethyl-3-piperidinol (*Vb*). Both the former compounds obviously arise by replacement of the bromine atom in the bromoimonium salt by hydroxyl ion.

## EXPERIMENTAL

The boiling and melting points are uncorrected.  $^1H$  NMR spectra were measured on a Varian 200 MHz instrument, mass spectra on a JEOL DX 303 spectrometer.

1-Methyl-2-phenyl-3-piperidinol (*Va*)

Bromine (4.8 g; 30 mmol) was added dropwise at  $-60^{\circ}\text{C}$  during 30 min to a stirred ethereal solution (10 ml) of *Ia*, liberated from 7.7 g (28 mmol) of perchlorate, m.p.  $105-107^{\circ}\text{C}$  (ethanol). After addition of the bromine, the mixture was warmed to  $-20^{\circ}\text{C}$ , mixed portionwise with 10% aqueous sodium hydroxide (28 ml) and stirred for 2 h at room temperature. The product was taken up in ether, dried over magnesium sulfate and its IR spectra were measured. This ethereal solution (100 ml) was added dropwise to lithium aluminium hydride (1 g; 26 mmol) in ether (100 ml). The mixture was refluxed for 3 h, cooled, treated successively with water (5.6 ml), 15% aqueous sodium hydroxide (5.6 ml) and water (17 ml), and filtered. The filtrate was dried over potassium carbonate and taken down affording 3.1 g (58%) of the product, b.p.  $97-100^{\circ}\text{C}/0.05\text{ kPa}$ . For  $\text{C}_{12}\text{H}_{17}\text{NO}$  (191.3) calculated: 75.35% C, 8.96% H, 7.32% N; found: 75.2% C, 8.61% H, 7.52% N.

Rearrangement of Compound *Ib*

Bromine (7.7 g; 48 mmol) was gradually added at  $-60^{\circ}\text{C}$  to a stirred ethereal solution (10 ml) of *Ib* (liberated from the perchlorate, m.p.  $202-212^{\circ}\text{C}$ ; 10.7 g; 51 mmol). After warming to  $-20^{\circ}\text{C}$ , 10% aqueous sodium hydroxide (45 ml) was added and the mixture was stirred at room temperature for 3 h. The product was taken up in ether, dried over magnesium sulfate and its IR spectrum was measured, showing a  $\nu(\text{C}=\text{O})$  band at  $1724\text{ cm}^{-1}$ . The ethereal solution (50 ml) was added dropwise to lithium aluminium hydride (1.8 g; 47 mmol) in ether (110 ml). The mixture was refluxed for 2 h, cooled and worked up as in the preceding experiment, affording 2.6 g of a mixture, boiling at  $36-40^{\circ}\text{C}/0.027\text{ kPa}$ . Gas-liquid chromatography on weakly polar OV 17 (polymethylphenylsiloxane) stationary phase (expected to separate compounds according to their boiling point) combined with mass spectrometry, revealed the presence of six products: Product 1 (mol. wt. 129; 8.4% in the mixture) afforded fragments 114, **84**, 70, 57, **42**, corresponding to structure *VI*. Product 2 (mol. wt. 129; 10.8%) afforded the same fragments as product 1 but of different intensity; it is probably a diastereoisomer of *VI*. Product 3 (mol. wt. 129, 35.5%) gave fragments **114**, 100, 85, 72, **57**, 42, corresponding to structure *VII*. Product 4 (mol. wt. 129, 37.8%) afforded fragments **114**, 85, 72, **57**, 42, corresponding to the rearrangement product *Vb*. Products 5 and 6 (mol. wt. 155, 5.0% and 2.5%, respectively) yielded fragments **140**, 122, 111, 97, **84**, **70**, 58, 42 of identical intensities and were not studied further.

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7. Ref.<sup>1</sup>, p. 253.

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