

ABSOLUTE CONFIGURATION OF (*R*)-(+)-1-METHYL-2-PHENYLPYRROLIDINE*

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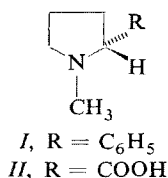
The absolute configuration of (*R*)-(+)-1-methyl-2-phenylpyrrolidine was established by the chemical correlation with (*R*)-(+)-hygric acid.

Several years ago we have obtained partially optically active dextrorotatory 1-methyl-2-alkylpyrrolidines and 1-methyl-2-alkylpiperidines on asymmetric reduction of 1-methyl-2-alkyl-1-pyrrolinium¹ and 1-methyl-2-alkyl-1-piperideinium² perchlorates with lithium aluminium hydride in the presence of (–)-menthole in ether. On the contrary, the reduction of 1-methyl-2-phenyl-1-piperideinium perchlorate and, as we have found now, also of 1-methyl-2-phenyl-1-pyrrolinium perchlorate gives laevorotatory amines. Because of the formation of dextrorotatory alcohols of (*S*) configuration in the asymmetric reduction of methyl alkyl ketones with the agent obtained on partial decomposition of the ethereal solution of lithium aluminium hydride by (–)-quinine³, it was important to determine, whether the similar course is also taking place in the reduction of the enamine salts in which alkyl was replaced by phenyl.

On the asymmetric reduction of 1-methyl-2-phenyl-1-pyrrolinium perchlorate with the agent obtained from the partial decomposition of the ethereal solution of lithium aluminium hydride by (–)-menthole we have obtained (*S*)-(–)-1-methyl-2-phenylpyrrolidine, $[\alpha]_D^{20} -2.13^\circ$ (neat). With respect to the low optical yield of the asymmetric reduction we resolved into optical antipodes the racemic amine obtained by the reduction of the corresponding enamine with formic acid. We have correlated (*R*)-(+)-antipode *I* to (*R*)-(+)-hygric acid *II* in such a way, that the aromatic ring of the base was first nitrated, then reduced to amine and the latter was converted to the hydroxy derivative on diazotisation followed by hydrolysis. The oxidation of the phenyl derivative thus substituted with chromium trioxide in sulphuric acid gave the acid without difficulties⁴. The oxidation trials with the use of ozone were unsuccessful.

* Part I in the series Asymmetric reactions; Part II: This Journal 39; 1869 (1974).

The CD curves of (*S*)-(-)-1-methyl-2-phenylpyrrolidine and (*R*)-(+)-1-phenylethylamine exhibit enantiomeric shape.



The inverse course of the asymmetric reduction of the enamine salts with phenyl replacing the alkyl has shown the phenyl group attached to the arising centre of chirality influencing the course of the reduction also in another than steric way.

EXPERIMENTAL

The melting points and the boiling points are uncorrected. The optical rotations were measured with the aid of Zeiss Opton polarimeter, while Roussell Jouan Dichrographe II was applied to the measurements of CD curves.

1-Methyl-2-phenylpyrrolidine

a) *Reduction with formic acid*⁵: 1-Methyl-2-phenyl-1-pyrrolinium chloride (250 g) was heated together with 750 g of concentrated formic acid and 750 g of remelted potassium formiate at 160°C for 5 hours. After alkalization with the solution of sodium hydroxide the base formed was distilled with water vapour and the distillation product titrated with 3*M*-HCl. The solution was concentrated to a small volume, the base afterwards recovered with sodium hydroxide, extracted with ether and dried over solid potassium hydroxide. The following distillation gave 143 g (70%) of the base, b.p. 92°C/16 Torr.

b) *Reduction with LiAlH₄ in the presence of (-)-menthol*: To the agent obtained upon adding 5.19 g (33.2 mmol) of (-)-menthol, $[\alpha]_D^{20} - 50.3^\circ$ (*c* 2, ethanol), to 1.31 g (33.2 mmol) of lithium aluminium hydride in 100 ml of ether 7.14 g (30 mmol) of 1-methyl-2-phenyl-1-pyrrolinium perchlorate suspended in 30 ml of ether was added. The mixture was heated 4 hours on a water bath and its usual treatment gave 3.9 g (80%) of the base, b.p. 82–84°C/12 Torr, $[\alpha]_D^{20} - 2.13^\circ$ (neat). The reduction was repeated three times with the same results.

c) *Resolution of the racemate into optical antipodes*: The resolution of the racemic base with (+)-camphorsulphonic acid (20 g of (+)-camphorsulphonic acid, 16.1 g of the base in 30 ml of ethyl acetate) gave a salt, m.p. 123°C, $[\alpha]_D^{20} + 27.35^\circ$ (*c* 2.4, ethanol) after four recrystallizations from ethyl acetate. The b.p. of the base recovered in this way was at 83–85°C/12 Torr, $[\alpha]_D^{20} + 8.73$ (neat). The dibenzoyltartrate obtained from 35.3 g of (+)-dibenzoyltartaric acid and 16.1 g of the racemic base in 130 ml of ethanol melted at 136°C, $[\alpha]_D^{20} - 62.3^\circ$ (*c* 2, ethanol) after six recrystallizations from ethanol. The corresponding base exhibited b.p. 83–86°C/13 Torr, $[\alpha]_D^{20} - 53.65^\circ$ (neat).

(R)-(+)-Hygric Acid (*II*)

(R)-(+)-1-Methyl-2-phenylpyrrolidine, $[\alpha]_{\text{D}}^{20} + 13.65^{\circ}$ (neat), (6.4 g, 40 mmol) dissolved in 5 ml of chloroform was nitrated at 10°C with a mixture of 5.8 ml of nitric acid ($d = 1.4$) and 8 ml of concentrated sulphuric acid. The reaction mixture was boiled under reflux, then made alkaline with a solution of sodium hydroxide, extracted with chloroform and dried over anhydrous magnesium sulphate. After chloroform having been distilled off the residue was dissolved in 60 ml of 25 per cent hydrochloric acid. To the solution 20 g of granulated tin was added and the mixture was refluxed 4 hours. After the alkalization with sodium hydroxide the base (5.27 g, b.p. 110 to 113°C/0.3 Torr) was distilled off with water vapour. To the isolated amine dissolved in 100 ml of 1M sulphuric acid the aqueous solution of 2.07 g of sodium nitrite was added at 0°C. The mixture was boiled under reflux for 1 hour, then 26.5 g of chromium trioxide and 100 ml of concentrated sulphuric acid were added, the mixture was refluxed 4 hours and after cooling the SO_4^{2-} ions were removed upon adding a solution of barium hydroxide. The filtrate was concentrated to a small volume and boiled under reflux with freshly prepared cupric hydroxide. The filtrate was then evaporated, the residue extracted with chloroform and the cupric salt, m.p. approx. 209°C, was precipitated with ether. The salt thus obtained was dissolved in 100 ml of ethanol and decomposed with hydrogen sulphide. After cupric sulphide had been removed the filtrate was evaporated and the remaining material recrystallized from the mixture ethanol ether. The hydrate of *(R)*-(+)-hygric acid melted at 116°C, while the anhydrous acid exhibited m.p. 170°, $[\alpha]_{\text{D}}^{20} + 6.3^{\circ}$ (c 2, water). For $\text{C}_6\text{H}_{13}\text{NO}_3$ (147.2) calculated: 48.96% C, 8.94% H, 9.17% N; found: 49.31% C, 9.05% H, 10.03% N. Literature⁶ gives for the hydrate m.p. 116°C, $[\alpha]_{\text{D}}^{20} - 80.1^{\circ}$ (c 2, water).

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