

## SYNTHESIS OF 1,2,5-TRIMETHYL-4-ETHOXYCARBONYLMETHYL-4-HYDROXYPIPERIDINE AND ITS HOMOLOGS

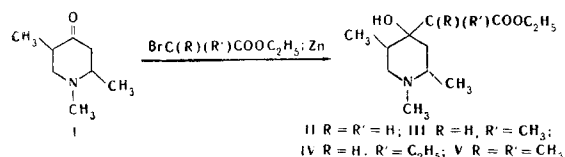
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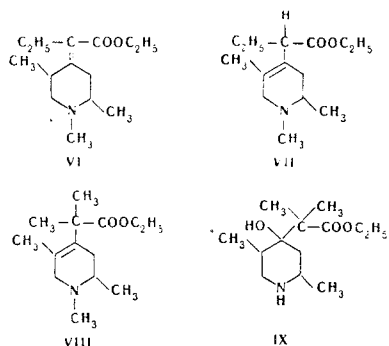
1,2,5-Trimethyl-4-ethoxycarbonylmethyl-4-hydroxypiperidine was obtained by the Reformatsky reaction between 1,2,5-trimethyl-4-piperidone and ethyl bromoacetate. Homologs were obtained from the same piperidone and ethyl  $\alpha$ -bromo- $\alpha$ -alkylacetates. Some further reactions of these hydroxypiperidines were studied.

Derivatives of tertiary  $\gamma$ -hydroxypiperidines are, as a rule, physiologically active. In particular, some of them show powerful analgesic and local anesthetic properties. In a continuation of work on the synthesis of  $\gamma$ -hydroxypiperidines and their derivatives, we turned to the Reformatsky reaction of the readily accessible 1,2,5-trimethyl-4-piperidone (I) [1] as a means of obtaining new tertiary  $\gamma$ -hydroxypiperidines having in the  $\gamma$ -position either substituted or unsubstituted ethoxycarbonylmethyl groups.



Condensation of piperidone I with ethyl bromoacetate in the presence of zinc dust in anhydrous benzene gave a yield of about 39% of 1,2,5-trimethyl-4-ethoxycarbonylmethyl-4-hydroxypiperidine—ethyl (1,2,5-trimethyl-4-hydroxy-4-piperidyl)acetate (II).

Similarly, ethyl esters of  $\alpha$ -(1,2,5-trimethyl-4-hydroxy-4-piperidyl)propionic (III),  $\alpha$ -(1,2,5-trimethyl-4-hydroxy-4-piperidyl)butyric (IV), and  $\alpha$ -(1,2,5-trimethyl-4-hydroxy-4-piperidyl)isobutyric (V) acids were obtained from the same piperidone and the esters of the corresponding  $\alpha$ -bromo-substituted carboxylic acids in from 20 to 40% yields. The hydroxypiperidine IV was a crystalline material melting at 102–104° C, while the other hydroxypiperidines, II, III, and V were liquids which were vacuum-distilled.



In the synthesis of the hydroxypiperidine IV, a significant amount of a comparatively low-boiling fraction (116–118° C at 1.5 mm) was obtained, which,

by the use of thin-layer chromatography, was shown to contain the hydroxypiperidine IV together with its dehydration products to which the structures ethyl  $\alpha$ -(1,2,5-trimethyl-4-piperidylidene)butyrate (VI) and  $\alpha$ -(1,2,5-trimethyl- $\Delta^4$ -dehydro-4-piperidyl)butyrate (VII) were assigned.

The dehydration of the hydroxypiperidine V was achieved using phosphorus oxychloride. Naturally, in this case, the formation of an unsaturated compound with the double bond in the ring—ethyl  $\alpha$ -(1,2,5-trimethyl- $\Delta^4$ -dehydro-4-piperidyl)isobutyrate (VIII)—was to be expected.

2,5-Dimethyl-4-piperidone was used as another heterocyclic carbonyl compound in the Reformatsky reaction. From this piperidone and ethyl  $\alpha$ -bromo-isobutyrate, a 10% yield of ethyl  $\alpha$ -(2,5-dimethyl-4-hydroxy-4-piperidyl)isobutyrate was obtained (IX).

The stereochemistry of our compounds will be discussed separately.

## EXPERIMENTAL

1,2,5-Trimethyl-4-piperidone (I) (bp 83° C at 12 mm,  $n_D^{20}$  1.4632) and 2,5-dimethyl-4-piperidone (bp 87–90° C, at 12 mm,  $n_D^{20}$  1.4670) were used in the syntheses. Thin-layer chromatography was carried out on alumina, second degree of activity, in ethyl acetate.

1,2,5-Trimethyl-4-ethoxycarbonylmethyl-4-hydroxypiperidine (Ethyl [1,2,5-trimethyl-4-hydroxy-4-piperidyl]acetate) (II). The reaction was performed with 75 g (0.53 mole) of the freshly distilled piperidone I, 66 g (0.4 mole) of ethyl bromoacetate (bp 158–160° C) and 34 g (0.52 g-at) of zinc dust. The zinc dust and 100 ml of anhydrous benzene were put into a four-necked flask equipped with a reflux condenser, stirrer, and two dropping funnels. The mixture was heated to 70° C, and ethyl bromoacetate and the piperidone I were added in 5 g portions with stirring. When a vigorous reaction started, the heating of the flask and the speed of addition of the remaining reagents were regulated so that the mixture boiled steadily. After the reagents had been added, the stirring and boiling of the solution were continued for 45 min. The reaction mixture was cooled to room temperature and poured onto 200 g of ice. The mixture was treated with dilute HCl (1:1) to a weakly acid reaction. The benzene layer was separated off, and the aqueous layer was saturated with sodium carbonate, and was then, in the presence of ether and with ice cooling, carefully saturated with KOH. The sodium-sulfate-dried ether extracts were vacuum-distilled. The fractions were: 1 (initial piperidone), bp 62° C (2 mm), 30 g,  $n_D^{20}$  1.4614; 2, bp 62–120° C (2 mm), 10 g,  $n_D^{20}$  1.4692; 3, bp 121–126° C (3 mm), 45 g,  $n_D^{20}$  1.4726; residue, 10 g. In a second distillation, the third fraction gave 35 g (38.7%) of 1,2,5-trimethyl-4-ethoxycarbonylmethyl-4-hydroxypiperidine (II) as a light green liquid, bp 131–132° C (4 mm).

The hydrochloride was hygroscopic, turning to a liquid in air; the picrate was an oily substance.

By similar methods 1,2,5-trimethyl-4-piperidone (I) was subjected to Reformatsky reaction conditions with the ethyl esters of other  $\alpha$ -bromocarboxylic acids (propionic, butyric and isobutyric), and 2,5-dimethyl-4-piperidone—with ethyl  $\alpha$ -bromobutyrate. Data on the

## Characteristics of the Hydroxypiperidines Synthesized

Com- pound	Yield %	$R_f$	Bp °C (mm)	$\nu^*$ , $\text{cm}^{-1}$		$n_D^{20}$	Found, %***			$MR_D$	
				OH	$\begin{array}{c} \text{O} \\    \\ -\text{C}- \end{array}$		C	H	N	Found	Calc.
II	40	0.42	131—132 (4)	3530, 3200	1734	1.4738	62.53, 62.64	9.78, 9.69	5.97, 6.17	62.21	62.58
III	30	0.60	105—107 (0.5)	3530	1735	1.4710	63.87, 63.90	10.52, 10.66	5.53, 5.73	67.26	67.23
IV**	23	0.57	134—140 (3)	3250	1728		65.46, 65.38	10.88, 10.73	5.25, 5.23		
V	43		123—125 (2)			1.4796	65.46, 65.01	10.67, 10.11	5.69, 5.72	71.68	71.83
IX	10		111—112 (0.5)	3570, 3300	1700	1.4862	64.51, 64.31	10.20, 10.51	6.15, 6.20	67.25	67.04

\*IR spectra run on a UR-10 spectrophotometer in mineral oil.

\*\*Mp, 102–104° C (from benzene).

\*\*\*For compound II, calculated for  $\text{C}_{12}\text{H}_{23}\text{NO}_3$ , %: C 62.84; H 10.04; N 6.11; for III, calculated for  $\text{C}_{13}\text{H}_{25}\text{NO}_3$ , %: C 64.14; H 10.36; N 10.36; for IV and V, calculated for  $\text{C}_{14}\text{H}_{27}\text{NO}_3$ , %: C 65.31; H 10.58; N 5.45.

properties and yields in obtaining these compounds are given in the table.

Products of the dehydration of the hydroxypiperidine (IV). For the synthesis of ethyl  $\alpha$ -(1, 2, 5-trimethyl-4-hydroxy-4-piperidyl)butyrate, 113.4 g (0.8 mole) of the piperidone I, 113.4 g (0.58 mole) of ethyl  $\alpha$ -bromobutyrate, 51 g (0.78 g-at) of zinc dust and 200 ml of anhydrous benzene were used. 32 g (21.5%) of the hydroxypiperidine IV was obtained together with a liquid fraction of 44 g boiling at 116–118° C (1.5 mm),  $n_D^{20}$  1.4730, which was a mixture of the hydroxypiperidine IV and its dehydration products VI and VII. Found, %: C 67.12; H 11.20; N 5.48, 5.89;  $MR_D$  68.87. Calculated for  $\text{C}_{14}\text{H}_{25}\text{NO}_2$ , %: C 70.24; H 10.54; N 5.86;  $MR_D$  69.78;  $R_f$  0.57, 0.75, and 0.83.

Crystalline derivatives could not be obtained from this mixture: the hydrochloride deliquesced in air and the picrate was an oil. The fraction was dissolved in 150 ml of anhydrous benzene. To the solution at 4–0° C was carefully added a solution of 31.4 g of thionyl chloride in 15 ml of anhydrous benzene over a period of 30 min. The mixture was then stirred for 1 hr at room temperature, then for 1.5 hr under reflux. The benzene and excess of thionyl chloride were distilled off under vacuum; the residue was dissolved in 70 ml water and with cooling in the presence of ether it was saturated with sodium carbonate and then with potassium hydroxide. After drying the ether extract over sodium sulfate and distilling twice, 24 g of a green mobile liquid was obtained, bp 91–92° C (0.5 mm),  $n_D^{20}$  1.4688, which consisted of the dehydration products VI and VII. Found, %: N 5.98, 5.89. Calculated for  $\text{C}_{14}\text{H}_{25}\text{NO}_2$ , %: N 5.86;  $R_f$  0.75 and 0.86.

Ethyl  $\alpha$ -(1, 2, 5-trimethyl  $\Delta^4$ -dehydro-4-piperidyl)isobutyrate (VIII). To a solution of 66 g (0.26 mole) of the hydroxypiperidine V in 250 ml of anhydrous benzene was added 16 ml of phosphorous oxychloride at room temperature over a period of 15 min. The mixture was stirred 1 hr at room temperature then 30 min at the boiling point. The solvent and excess of phosphorous oxychloride were removed under vacuum. The residual oil was dissolved in 200 ml water and with cooling in the presence of ether it was saturated with sodium carbonate and then with potassium hydroxide. After drying the ether extract over sodium sulfate and distilling twice, 30 g (49.3%) of VIII was obtained; bp 120–122° C (3 mm),  $n_D^{20}$  1.5016. Found, %: N 5.77, 5.88;  $MR_D$  70.50. Calculated for  $\text{C}_{14}\text{H}_{25}\text{NO}_2$ , %: N 5.86%;  $MR_D$  69.78. Attempts to prepare a crystalline hydrochloride, methiodide, and picrate were not successful.

## REFERENCE

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