THE SYNTHESIS AND REACTIONS OF 2, 6-DIPHENYL-4-ETHYNYL-4-PIPERIDINOL

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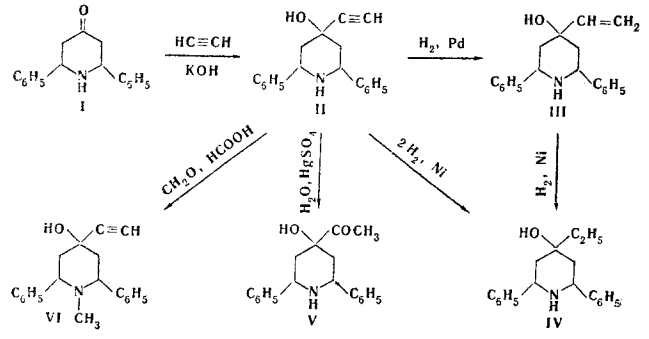
The condensation of 2, 6-diphenyl-4-piperidinol with acetylene under Favorskii reaction conditions has been examined. It is shown that the condensation results in the formation of a single isomer. Selective and exhaustive hydrogenation, hydration, and methylation give the corresponding derivatives.

2, 5-Dimethyl-4-ethynyl(vinyl and ethyl)-4-piperidinol have been synthesized previously [1], and the configuration of the stereoisomers investigated [2, 3]. Several derivatives have been prepared, among which are some showing high biological activity [4–7].

It was considered of interest to investigate further the relation between the structure of the piperidinols and their physiological activity, by synthesizing and studying tertiary acetylenic γ-piperidinols containing phenyl substituents in the ring, which have not previously been described.

We used as starting material 2, 6-diphenyl-4-piperidone [8, 9] (I). Condensation of this ketone with acetylene in presence of powdered potassium hydroxide afforded 60% of 2, 6-diphenyl-4-ethynyl-4-piperidinol (II). Resinification of the starting ketone under the alkaline reaction conditions made it impossible for us to improve the yield. The homogeneity of the piperidinol was shown by thin-layer chromatography on alumina. The combination of acetylene with the carbonyl group in I apparently proceeds with spatial orientation leading to the single, thermodynamically most stable stereoisomer II. It is known [9] that reduction of the ketone I and its N-substituted analogs leads to the formation of the secondary piperidinol, also in only one of the stereoisomeric forms.

In order to prepare various tertiary γ-piperidinols, we have examined various reactions of the acetylenic alcohol thus prepared.



Selective hydrogenation on a palladium catalyst yielded 2, 6-diphenyl-4-vinyl-4-piperidinol (III). Exhaustive hydrogenation of II and III on a skeletal nickel catalyst afforded 2, 6-diphenyl-4-ethyl-4-piperidinol (IV). By hydration of II there was obtained 2, 6-diphenyl-4-acetyl-4-piperidinol (V), and methylation with formaldehyde and formic acid gave 1-methyl-2, 6-diphenyl-4-ethynyl-4-piperidinol (VI) in good yield. The tertiary alcohols III–VI, like the acetylenic piperidinol I, were obtained in one of the isomeric forms. The structures of the compounds synthesized were confirmed by their IR spectra.

EXPERIMENTAL

2, 6-Diphenyl-4-ethynyl-4-piperidinol (II). A suspension of 50 g of powdered potassium hydroxide in 1 *l* of dry ether was saturated with purified acetylene, with vigorous stirring and cooling at −10°, for 2 hr. Then, with continued stirring and passage of a rapid stream of acetylene, there was added dropwise during 2.5 hr a solution of 86.7 g (0.35 mole) of the piperidinol I in 500 ml of ether. After completion of the addition, the passage of acetylene was continued for a further 4 hr. The reaction product was hydrolyzed with cooling with 200 ml of water. The ether layer was separated, and the aqueous layer extracted repeatedly with ether. The ethereal extract was treated with 20 ml of water and dried over potassium carbonate. The residue after removal of the ether (59.8 g) was recrystallized twice from anhydrous ethanol to give 60% of product, mp 111–112° C, R_f 0.44 (Grade 2 alumina, dioxane–benzene 1 : 6). IR spectrum, ν, cm^{-1}: 3280 (HC≡), 740, 3061 (C_6H_5), 3293 (NH). Found, %: C 82.24; H 7.04; N 4.85. Calculated for $C_{19}H_{19}NO$, %: C 82.30; H 6.86; N 5.05.

Thin-layer chromatography on the 1.5 g of unseparated material remaining after the recrystallization showed the presence of a spot with R_f 0.52 (in addition to the starting ketone I), attributed apparently to the second isomer of the acetylenic alcohol II, the isolation of which would appear to be difficult.

The hydrochloride of II was obtained by adding an ethereal solution of dry hydrogen chloride to an ethereal solution of the piperidinol. Mp 279–280° C (from ethanol). Found, %: N 4.39. Calculated for $C_{19}H_{19}NO \cdot HCl$, %: N 4.45.

2, 6-Diphenyl-4-vinyl-4-piperidinol (III). 2.77 g (0.01 mole) of II was hydrogenated in 50 ml of absolute ethanol in presence of 0.1 g of $Pd/CaCO_3$. After absorption of the theoretical amount of hydrogen, the alcohol was removed and the residue recrystallized from light petroleum, giving 2.56 g (92%), mp 76–77° C. IR spectrum ν, cm^{-1}: 1610 (C=C), 3340 (OH), 748, 3060 (C_6H_5). Found, %: 5.25. Calculated for $C_{19}H_{21}NO$, %: N 5.02.

Hydrochloride of III. Mp 240–241° C (from ethanol). Found, %: N 4.34. Calculated for $C_{19}H_{21}NO \cdot HCl$, %: N 4.45.

2, 6-Diphenyl-4-ethyl-4-piperidinol (IV). a) 8.3 g (0.03 mole) of the piperidinol II in 120 ml of ethanol was hydrogenated in the presence of skeletal nickel (0.6 g). Yield 7.6 g (90%), mp 67–68° C (from light petroleum). R_f 0.36 (Grade 2 alumina, dioxane–benzene 1 : 6). Found, %: C 80.91; H 8.73; N 4.98. Calculated for $C_{19}H_{23}NO$, %: C 81.15; H 8.11; N 4.98.

b) 2.79 g (0.01 mole) of III in 50 ml of ethanol was hydrogenated in the presence of skeletal nickel (0.3 g). Yield 2.29 g (83%), mp 67–68° C.

Hydrochloride of IV. Mp 252–253° C (from ethanol). Found, %: N 4.43. Calculated for $C_{19}H_{23}NO \cdot HCl$, %: N 4.42.

2, 6-Diphenyl-4-acetyl-4-piperidinol (V). To a solution of 3 g of mercuric sulfate and 6 ml of sulfuric acid (d 1.84) in 60 ml of water was added with stirring 2.7 g (0.01 mole) of the piperidinol II, and the mixture heated for 6 hr at 90–95° C, after which the solution was

treated with sodium carbonate and carefully extracted with ether. The extract was dried over potassium carbonate, the ether removed and the residue recrystallized from acetone to yield 1.9 g (65%) of **V**, mp 151–152° C. IR spectrum, ν, cm^{-1}: 1717 (C=O), 762, 3064 (C_6H_5), 3304 (NH). Found, %: N 4.75. Calculated for $C_{19}H_{21}NO_2$, %: N 4.76.

Hydrochloride of V. Mp 294–295° C. Found, %: N 4.36. Calculated for $C_{19}H_{21}NO_2 \cdot HCl$, %: N 4.23.

1-Methyl-2,6-diphenyl-4-ethyl-4-piperidinol (VI). A mixture of 27.7 g of the piperidinol **II** (0.1 mole), 16.6 g (0.3 mole) of 85% formic acid and 9 g (0.1 mole) of a 35% solution of formaldehyde was heated for 4 hr (until evolution of carbon dioxide ceased). The solution was neutralized with potassium carbonate and extracted with ether, the extract dried over magnesium sulfate, the ether removed and the residue recrystallized from light petroleum (bp 80–100° C). Yield 25.3 g (87%), mp 120–121° C. R_f 0.8 (Grade 2 alumina, dioxane–benzene 1:6). Found, %: C 81.67; H 7.39; N 4.73. Calculated for $C_{20}H_{21}NO$, %: C 82.44; H 7.21; N 4.81.

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