ESTERS OF (1, 2, 5-TRIMETHYL-4-HYDROXY-4-PIPERIDYL)- AND PHENYL-(1, 2, 5-TRIMETHYL-4-HYDROXY-4-PIPERIDYL)ACETIC ACIDS

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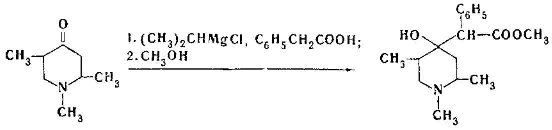
The methyl ester of a new hydroxy acid of the piperidine series (α-phenyl-α-(1, 2, 5-trimethyl-4-hydroxy-4-piperidyl)acetic acid) has been prepared. Ethyl α-(1, 2, 5-trimethyl-4-hydroxy-4-piperidyl)acetate has been converted into the substituted pyridine, 1, 1-diphenyl-2-(2'-5'-dimethyl-4-pyridyl)ethylene.

In continuation of investigations into the synthesis of piperidines, both in search of new physiologically active compounds, and also in order to study the structure of polyfunctionally-substituted piperidines, we have returned to the examination of the reaction of substituted chloromagnesiumphenyl acetate with 1, 2, 5-trimethyl-4-piperidone (I). It is known that α-aryl-substituted-β-hydroxy acids are accessible by this route [1–4].

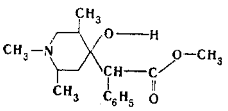
In carrying out this synthesis, the hydroxy acid itself was not isolated on account of the difficulty in separating the mixture of the hydrochlorides of the hydroxy acids and the starting piperidone I. Subsequent esterification gave methyl α-phenyl-α-(1, 2, 5-trimethyl-4-hydroxy-4-piperidyl)acetate (II) in 40% yield.

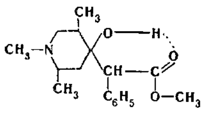


I

II

The IR spectra (Fig. 1) indicate that the hydroxyl group is associated in the crystalline state (vaseline oil) in the β-hydroxyester II. On dissolving the hydroxy ester II in carbon tetrachloride (concentration 0.01 molar), the intermolecular hydrogen bonds (3250 cm^{-1}) disappear almost completely, and very strong bands appear with maxima at 3590 and 3515 cm^{-1}. These are apparently due to the hydroxyl group which is intramolecularly hydrogen bonded to the oxygen of the carbonyl group (1st band), and to the oxygen of the methoxyl of the ester group (2nd band). In the IR spectrum of the methiodide of the piperidine hydroxyester II (Fig. 1), two bands are also seen (3515 and 3380 cm^{-1}) in the region of valency stretching of the hydroxy group. The bands at 1740 and 1719 cm^{-1} are characteristic of valency stretching of, respectively, the free and the bound carbonyls of the ester group. Comparison of these spectral characteristics with those published for similar compounds [5–8] suggests that two types of six-membered chelate rings are present in II, formed from the hydroxyl and ester groups.





Similar to the hydroxy-ester II is ethyl α-(1, 2, 5-trimethyl-4-hydroxy-4-piperidyl)acetate (III), which we have described previously [9]. Benzoylation of this hydroxy-ester is difficult. Its O-benzoyl derivative, ethyl α-(1, 2, 5-trimethyl-4-benzoyloxy-4-piperidyl)acetate (IV), was obtained as the hydrochloride in 13.5% yield.

Reaction of the hydroxy ester III with an excess of phenylmagnesium bromide gives the ditertiary diol 1, 1-diphenyl-2-(1', 2', 5'-trimethyl-4'-hydroxy-4'-piperidyl)ethanol (V, 10% yield), and the product of the complete dehydration of this diol, 1, 1-diphenyl-2-(1', 2', 5'-trimethyl-4'-ene-4'-piperidyl)ethylene (VI). The latter is also obtained directly by dehydration of the diol V.

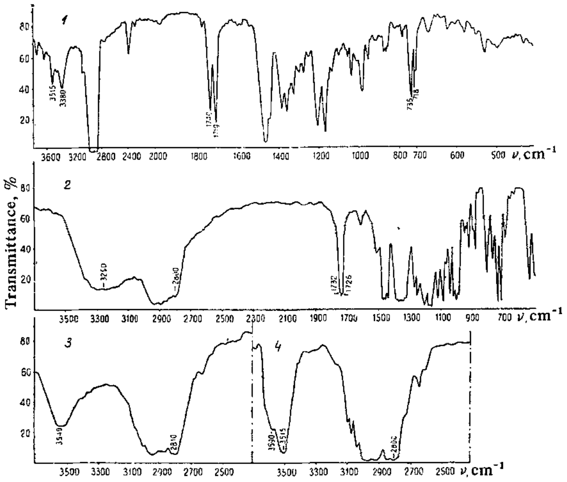


Fig. 1. IR Spectra: 1) methiodide of hydroxy ester II in vaseline oil; 2) hydroxy ester II in vaseline oil; 3) saturated solution of hydroxy ester II in CCl_4; 4) 0.01 M solution of hydroxy ester II in CCl_4.

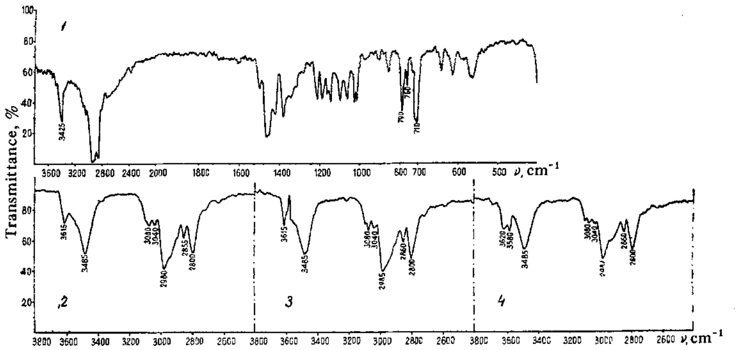
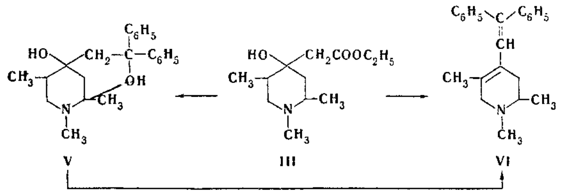
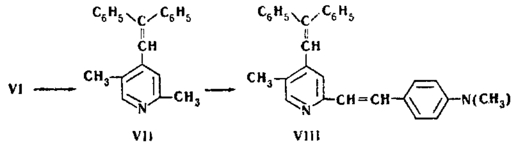


Fig. 2. IR spectra of 1, 1-diphenyl-2-(1', 2', 5'-trimethyl-4'-hydroxy-4'-piperidyl)ethanol (V): 1) in vaseline oil; 2) 0.005 M solution in CCl_4; 3) 0.0025 M solution in CCl_4; 4) 0.001 M solution in CCl_4.



The diol V shows fairly high chromatographic mobility (R_f 0.69, alumina, ethyl acetate). The IR spectrum of the crystalline diol V has a maximum ν_{OH} at 3425 cm^{-1}, indicating the associated nature of the hydroxyl group. On passing from the crystalline state to solution in CCl_4 (Fig. 2), the valency stretching bands of the hydroxyl groups with a maximum at 3425 cm^{-1} shift to 3485 cm^{-1}. When the concentration is reduced to 0.001 M, at which concentration intermolecular association cannot occur, the position of the band with a maximum at 3495 cm^{-1} did not change, showing the intramolecular character of the hydrogen bond. In addition to this band, in carbon tetrachloride solution, other bands appear at 3620–3615 cm^{-1} which are characteristic of the valency stretching of the free hydroxyl group. The intensity of these bands is, however, only about half that of the band at 3485 cm^{-1}. It is possible that, as in the case of the hydroxy ester II described above, in the diol V the hydrogen bonds may be involved in the formation of six-membered chelate structures involving the two hydroxyl groups. Finally, the possibility of the formation of intramolecular hydrogen bonds between the C-4 hydroxyl group and the nitrogen of the piperidine ring must not be excluded. The question of the exact spatial structure of the diol V, of course, requires special investigation.

The product of the complete dehydration of the β-glycol (VI; the position of the double bond is shown provisionally in the structural formula) undergoes further catalytic dehydrogenation and demethylation to give 1, 1-diphenyl-2-(2', 5'-dimethyl-4'-pyridyl)-ethylene (VII) in 35% yield, as a light rose-pink crystalline solid, mp 97–100° C.



Condensation of the methiodide of this compound with p-dimethylaminobenzaldehyde afforded bright red crystals of 1-(4'-dimethylaminophenyl)-2-[5''-methyl-4''-(β, β-diphenylvinyl)-2''-pyridyl]ethylene (VIII).

EXPERIMENTAL

Methyl α-phenyl-α-(1, 2, 5-trimethyl-4-hydroxy-4-piperidyl)acetate (II). To isopropylmagnesium chloride, obtained from 33 g (1.38 g-at) of magnesium and 146 ml (1.6 mole) of isopropyl chloride in 550 ml of ether, was added, during 3 hr at 5° C, a solution of 91.2 g (0.67 mole) of phenylacetic acid in 300 ml of benzene. The reaction mixture was stirred for 1 hr at 0° C, 12 hr at 20° C, and 7 hr at 40° C. Then, during 3 hr, a solution of 63 g (0.477 mole) of I in 200 ml of benzene was added dropwise with cooling at 5° C. The mixture was stirred for 2 hr at 20° C and 7 hr at 40° C, then 700 ml of 7% HCl was added with cooling. The benzene-ether layer was separated (it contained 25 g of phenylacetic acid), and washed with 10% HCl (2 × 150 ml). The solution of base hydrochlorides was washed with ether and evaporated to dryness in vacuo. The residue was treated with boiling nitromethane (5 × 100 ml). Removal of the nitromethane left 145.9 g of a hygroscopic material.

The latter was mixed with 500 ml of absolute methanol and 45 ml of conc H_2SO_4, and heated for 20 hr at 40° C and 6 hr at 60° C. The methanol was distilled off, the residue dissolved in 400 ml of water, and the solution treated with sodium carbonate in the presence of ether, followed by potassium hydroxide (with cooling). The ether extract afforded 61 g of oily residue. Chromatography (grade II alumina, ether) showed it to contain starting material I (R_f 0.7), and the hydroxy ester II (R_f 0.5). Crystallization afforded 52 g of II, needles, mp 117–117.5° C (from light petroleum). Yield 40%, calculated on I. Found, %: C 69.85; H 8.31; N 4.70. Calculated for $C_{17}H_{25}NO_3$, %: C 70.07; H 8.65; N 4.81.

Methiodide of hydroxy ester II, mp 194° C (from alcohol). Found, %: N 3.07. Calculated for $C_{17}H_{25}NO_3 \cdot CH_3I$, %: N 3.23.

Ethyl-(1, 2, 5-trimethyl-4-benzoyloxy-4-piperidyl)acetate hydrochloride (IV). To 6.87 g (0.03 mole) of the ester III, 15 ml of dry benzene and 5 ml of pyridine was added at 0° C during 15 min 8.5 g (0.06 mole) of benzoyl chloride. The mixture was stirred for 1 hr with cooling, 12 hr at 20° C, and 1 hr at 80° C. The benzene and pyridine were distilled off in vacuo, and the residue washed with ether and dissolved in 60 ml of water. The solution was treated with sodium carbonate with cooling, in the presence of ether, then with potassium hydroxide. The ether extract was washed with water, dried over magnesium sulfate, and a stream of dry hydrogen chloride passed through the solution. From the precipitate which separated there was obtained 1.5 g (4.06 mm) of IV, mp 195–197° C (from 2 : 1 methanol–ether). Found, %: C 61.57; H 7.35; N 3.84; Cl 9.91. Calculated for $C_{19}H_{27}NO_4 \cdot HCl$, %: C 61.69; H 7.63; N 3.78; Cl 9.59.

1, 1-Diphenyl-2-(1', 2', 5'-trimethyl-4'-hydroxy-4'-piperidyl)ethanol (V). The preparation was carried out in a stream of nitrogen. To phenylmagnesium bromide, obtained from 53.56 g (0.34 mole) of bromobenzene and 7.28 g (0.3 g-at) of magnesium in 300 ml of ether, was added with stirring at 0° C a solution of 22.9 g (0.1 mole) of III in 20 ml of ether. The mixture was stirred for 1 hr with cooling, 32 hr at 20° C and 7 hr at the boil. The mixture was treated, with cooling, with 50 ml of water, followed by 100 ml of HCl (1 : 1). The ether layer was separated, and the aqueous layer, together with water-insoluble hydrochlorides, was treated with sodium carbonate in the presence of ether, followed by potassium hydroxide. The residue after removal of the ether was distilled; fraction 1, bp 70–154° C (2 mm), 5 g; fraction 2, bp 154–222° C (1.5 mm), 10.5 g; fraction 3, bp 222–225° C (1.5 mm), 5 g; residue, 3.5 g. Fractions 2 and 3 afforded 6 g of the diol V as colorless needles, mp 148–149.5° C (from light petroleum). Yield 10%, R_f 0.69 (alumina, grade II, ethyl acetate). Found, %: C 77.58; H 8.80; N 4.10. Calculated for $C_{22}H_{29}NO_2$, %: C 77.84; H 8.61; N 4.13.

Methiodide of the diol V, mp 188–191° C (from alcohol). Found, %: C 57.09; H 6.99; N 2.65. Calculated for $C_{22}H_{29}NO_2 \cdot CH_3I$, %: C 57.38; H 6.70; N 2.91.

Picrate of diol V, mp 165–168° C (from alcohol). Found, %: N 9.66. Calculated for $C_{22}H_{29}NO_2 \cdot C_6H_3N_3O_7$, %: N 9.86. The mother liquors from the isolation of V afforded 8 g of the complete dehydration product (VI) as a viscous liquid, bp 169–187° C (1 mm); R_f 0.88 (grade II alumina, ethyl acetate). Found, %: C 86.70; H 8.00; N 4.39. Calculated for $C_{22}H_{25}$, %: C 87.07; H 8.31; N 4.62. The diene V was unstable in air, turning red. Its IR spectrum showed no valency stretching band due to the hydroxyl group. UV spectrum of the free base VI: λ_{max} 289 nm, ε 6440. The diol V (17 g, 0.05 mole) was heated to boiling in 100 ml of conc HCl for 2 hr. The cooled reaction mixture was treated with an excess of potassium hydroxide, and the mixture heated at 100° C for 30 min. The free base was extracted with ether and distilled in vacuo to afford 10.5 g (70%) of the diene VI, bp 165–180° C (0.5 mm) with the same R_f value and position of the absorption maximum in the UV spectrum as the material described above. Found, %: C 86.91; H 8.12; N 4.45.

1, 1-Diphenyl-2-(2', 5'-dimethyl-4'-pyridyl)ethylene (VI). A solution of 30.3 g (0.1 mole) of diene VI in 200 ml of benzene was passed at a constant rate over 8 hr through a contact tube filled with type K-16 catalyst (100 ml). The temperature in the catalyst zone was 420–430° C. The volume of gas collected was 4200 ml (23° C, 754 mm). Vacuum distillation of the reaction products gave a fraction (16.3 g) with bp 160–191° C (0.5 mm), from which was isolated 10 g of VII as a light rose-pink crystalline solid, mp 97–100° C (from light petroleum). Yield 35%. Found, %: C 88.68; H 6.44; N 4.67. Calculated for $C_{21}H_{19}N$, %: C 88.38; H 6.71; N 4.91.

Methiodide of VII, elongated bright green needles, mp 198–200.5° C (from alcohol). Found, %: C 62.32; H 5.63; N 2.96. Calculated for $C_{21}H_{19}N \cdot CH_3I$, %: C 61.84; H 5.19; N 3.28.

Picrate of VII, mp 164–166° C (from alcohol). Found, %: N 10.86. Calculated for $C_{21}H_{19}N \cdot C_6H_3N_3O_7$, %: N 10.89.

Perchlorate of VII, mp 161° C (from alcohol). Found, %: Cl 9.42; N 3.96. Calculated for $C_{21}H_{19}N \cdot HClO_4$, %: Cl 9.19; N 3.63. UV spectrum of the free base VII: λ_{max} 300 nm, ε 7120.

1-(4'-Dimethylaminophenyl)-2-[5"-methyl-4"-(β, β-diphenylvinyl)-2"-pyridyl]ethylene methiodide (VIII). One gram (2.34 mM) of VII methiodide, 0.4 g (2.68 mM) of p-dimethylaminobenzaldehyde, 0.3 ml of piperidine and 25 ml of absolute ethanol were heated for 10 hr at the bp of the solvent. Three recrystallizations from alcohol gave 0.4 g (30.6%) of VIII as fine, bright red crystals with mp 255–258° C. Found, %: N 4.89. Calculated for $C_{30}H_{28}N_2 \cdot CH_3I$, %: N 5.11.

The IR spectra of the solutions in carbon tetrachloride were recorded on a UR-20 spectrophotometer with LiF prisms, and those in vaseline oil were recorded on a UR-10 spectrophotometer in the 3800–4000 cm^{-1} region with

LiF, NaCl, and KBr prisms. The UV spectra were taken on an SF-4 spectrometer in the 220–400 nm region, in solution in ethanol at concentrations from 10^{-3} to 10^{-4} M.

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