1,4-BIS(4'-HYDROXY-1',2',5'-TRIMETHYL-4-PIPERIDYL)-1,3-BUTADIYNE AND ITS DERIVATIVES

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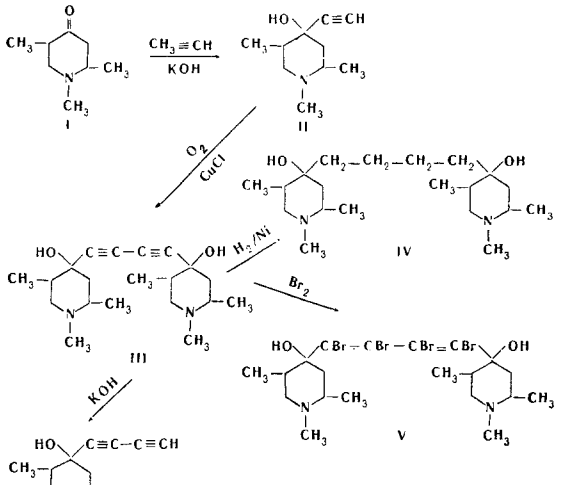
1,4-Bis(4'-hydroxy-1',2',5'-trimethyl-4'-piperidyl)-1,3-butadiyne has been synthesized from the individual isomers of 4-ethynyl-1,2,5-trimethyl-4-piperidol. Hydrogenation, bromination, and cleavage have given, respectively, 1,4-bis(4'-hydroxy-1',2',5'-trimethyl-4'-piperidyl)butane, 1,4-bis(4'-hydroxy-1',2',5'-trimethyl-4'-piperidyl)-1,2,3,4-tetrabromo-1,3-butadiene, and 4-(1,3-butadiynyl)-1,2,5-trimethyl-4-piperidol.

Acetylenic amino alcohols are an extremely interesting class of compounds from the point of view of their chemical and physiological properties. Effective anaesthetic substances [1,2] and bactericides and fungicides [3] are found among such amino alcohols and their derivatives. Continuing our work on the preparation of various piperidine derivatives, we turned to the synthesis of a tertiary diacetylenic amino alcohol containing this cyclic system as a promising physiologically active compound.

As the starting material we used 1,2,5-trimethyl-4-piperidone (I) [4]. When this ketone was condensed with acetylene in the presence of potassium hydroxide, we obtained a mixture of isomeric 4-ethynyl-1,2,5-trimethyl-4-piperidols (II), from which the γ- and β-isomers were isolated [5]. The oxidative dimerization [6] of the isomers of II obtained in the presence



of copper salts yielded the γ- and β-isomers of 1,4-bis(4'-hydroxy-1',2',5'-trimethyl-4'-piperidyl)-1,3-butadine (III). Analysis by thin-layer chromatography showed the individuality of these isomers.

The exhaustive hydrogenation of the isomers of III gave the corresponding isomers of 1,4-bis(4'-hydroxy-1',2',5'-trimethyl-4'-piperidyl)butane (IV). Incomplete bromination of the isomers of III gave the corresponding 1,4-bis-(4'-hydroxy-1', 2', 5'-trimethyl-4'-piperidyl)-1,2,3,4-tetrabromo-1,3-butadienes (V).

Then the possibility of the cleavage of the diacetylenic glycol III under various conditions [7,8] was studied in order to obtain VI. It was found that the cleavage was accompanied by the vigorous decomposition of the diacetylenic alcohol VI formed, in the same way as took place previously on the preparation of analogous cyclic diacetylene derivatives [9], and the main product was the initial 1,2,5-trimethyl-4-piperidone (I). However, when the experiment was carefully repeated, we succeeded in obtaining a small yield of 4-(1,3-butadiynyl)-1,2, 5-trimethyl-4-piperidol (VI).

EXPERIMENTAL

1,4-Bis(4'-hydroxy-1',2',5'-trimethyl-4'-piperidyl)-1,3-butadiyne (III). a) A mixture of 16.7 g (0.1 mole) of the γ-isomer of 4-ethynyl-1,2,5-trimethyl: 4-piperidol (II) and 0.4 g of CuCl in 300 ml of dry piperidine was shaken in an atmosphere of oxygen at an initial temperature of 20° C. The reaction took place with a rise in the temperature. After 30 min, the theoretical amount of oxygen had been absorbed. The reaction mixture was left overnight. The precipitate was separated off and washed with water until copper ions were absent from the wash waters. After recrystallization from pyridine, 15.5 g (92%) of the γ-isomer of III was obtained with mp 231–232° C. Found, %: N 8.36. Calculated for $C_{20}H_{32}N_2O_2$, %: N 8.43. On thin-layer chromatography, one spot was formed with R_f 0.92 (Al_2O_3, activity II, acetone–methanol, 1:1). IR spectrum: 2160 and 2170 cm^{-1} (—C≡C—). The dihydrochloride of the γ-isomer of the base III was obtained by adding a dry ethereal solution of hydrogen chloride to an alcoholic solution of 1.66 g (0.005 mole) of the base and recrystallizing from methanol the dihydrochloride that precipitated. Yield, 1.8 g (91%), mp 251–252$_1$ C. Found, %: N 7.24. Calculated for $C_{20}H_{32}N_2O_2 \cdot 2HCl$, %: N 6.91. The dimethiodide of the γ-isomer was obtained by heating 1.66 g (0.005 mole) of the base with 2.85 g (0.02 mole) of methyl iodide in methanolic solution. Yield 2.8 g (92%), mp 267–268° C (from methanol). Found, %: N 4.38. Calculated for $C_{20}H_{32}N_2O_2 \cdot 2CH_3I$, %: N 4.54.

b) Under the conditions described above, 16.7 g (0.1 mole) of the β-isomer of II and 0.4 g of CuCl in pyridine solution gave 14.9 g (89%) of the β-isomer of III with mp 207–208° C (from acetone). Found, %: N 8.38. Calculated for $C_{20}H_{32}N_2O_2$, %: N 8.43. On thin-layer chromatography, one spot was found with R_f 0.94 (Al_2O_3, activity II, acetone–methanol, 1:1). IR spectrum: 2160 cm⁻ (—C≡C—). A mixture of the γ- and β-isomers melted at 185–192° C. The dihydrochloride of the β-isomer of the base III had mp 245–246° C (from ethanol). 1.66 g of the base yielded 1.78 g (89%) of the dihydrochloride. Found, %: N 6.88. Calculated for $C_{20}H_{32}N_2O_2 \cdot 2HCl$, %: N 6.91. The dimethiodide of the β-isomer of the base III had mp 249–250° C (from ethanol). 1.66 g of the base yielded 2.5 g (90%) of the dimethiodide. Found, %: N 4.25. Calculated for $C_{20}H_{32}N_2O_2 \cdot 2CH_3I$, %: N 4.45.

1,4-Bis(4'-hydroxy-1',2',5'-trimethyl-4'-piperidyl)butane (IV). a) 1.66 g (0.005 mole) of the γ-isomer of III was hydrogenated at 30° C in the presence of Raney nickel (0.3 g) in 100 ml of methanol. After the absorption of the calculated amount of hydrogen, the methanol was distilled off, and the residue was recrystallized from ethanol.

This yielded 1.45 g (85%) of the γ-isomer of IV, mp 204°-205° C. Found, %: N 8.27. Calculated for $C_{20}H_{40}N_2O_2$, %: N 8.23.

b) Under similar conditions, 1.66 g of the β-isomer of III was hydrogenated. This yielded 1.5 g (90%) of the β-isomer of IV with mp 184–185° C (from acetone). Found, %: N 8.20. Calculated for $C_{20}H_{40}N_2O_2$, %: N 8.23.

1,4-Bis(4'-hydroxy-1',2',5'-trimethyl-4'-piperidyl)-1,2,3,4-tetrabromo-1, 3-butadiene (V). a) With stirring and cooling to –20° C, 1.6g (0.01 mole) of bromine in 50 ml of chloroform was added slowly to a solution of 1.66 g (0.005 mole) of the γ-isomer of III in 100 ml of chloroform. An hour after the addition of the bromine, the chloroform was distilled off and the residue was recrystallized from ethanol. This gave 2.8 g (87%) of V, mp 196–197° C. Found, %: N 3.99. Calculated for $C_{20}H_{32}N_2O_2$, %: N 4.29.

b) Under similar conditions, 1.66 g of the β-isomer of III and 1.6 g of bromine yielded 2.6 g (80%) of V, mp 234–235° C (from ethanol). Found, %: N 4.24. Calculated for $C_{20}H_{32}Br_4N_2O_2$, %: N 4.29. The IR spectrum of compound V obtained by methods (a) and (b) exhibited the characteristic bands of conjugated double bonds.

4-(1,3-Butadiynyl)-1,2,5-trimethyl-4-piperidol (VI). A carefully ground mixture of 13.28 g (0.04 mole) of the β-isomer of III and 60 mg of KOH was charged into a Claisen flask and melted, and vacuum was applied. Redistillation of the decomposition product yielded 5.5 g of 1,2,5-tetramethyl-4-piperidone (I) and 0.4 g of 4-(1,3-butadiynyl)-1,2,5-trimethyl-4-piperidol (VI), bp 179–176° C (1 mm), n_D^{20} 1.4957. Found, %: N 7.61. Calculated for $C_{12}H_{17}NO$, %: N 7.35. The IR spectrum had bands of the –C≡C bond (2240 cm^{-1}) and the C–H of an ethynyl group (3320 cm^{-1}).

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