SYNTHESIS OF BENZOATES OF 1,4-BIS(2,5-DIMETHYL-4-HYDROXYPIPERIDINO)-2-BUTENE AND 1,4-BIS-(2,5-DIMETHYL-4-HYDROXYPIPERIDINO)-2-BUTYNE

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1,4-Bis(2,5-dimethyl-4-hydroxypiperidino)-2-butene and 1,4-bis(2,5-dimethyl-4-hydroxypiperidino)-2-butyne (II and III) were obtained by the action of 1,4-dibromo-2-butene and 1,4-dibromo-2-butyne on the α form of 2,5-dimethyl-4-piperidol (I). The benzoates (IV and V) were obtained by acylation of II and III with benzoyl chloride.

Continuing our investigations of the synthesis of new physiologically active compounds and our study of the dependence between their physiological properties and chemical structures [1-3], we have synthesized 1,4-bis(2,5-dimethyl-4-hydroxypiperidino)-2-butene and 1,4-bis(2,5-dimethyl-4-hydroxypiperidino)-2-butyne (II and III) and their benzoates (IV and V).

The bispiperidols (II and III) were obtained by the reaction of the α form of 2,5-dimethyl-4-piperidol (I) with an unseparated mixture of stereoisomeric 1,4-dibromo-2-butenes and, respectively, 1,4-dibromo-2-butyne [4]. The hydrogen bromide formed during the reaction of 1,4-dibromo-2-butyne with piperidol I gives predominantly the dihydrobromide of the reaction product and a considerably smaller amount of the hydrobromide of the starting compound.

1,4-Bis(2,5-dimethyl-4-hydroxypiperidino)-2-butene (II) was obtained in the form of two geometrical isomers (the first with mp 153-154°, the second with mp 170-171°). On the basis of the high intensity of the absorption bands in the UV spectra of the high-melting isomer and its benzoate, the trans configuration was assigned to it [5-7]. The symmetrically substituted double bond does not appear in the IR spectrum [8].

Benzoates IV and V were obtained by acylation of bispiperidols II and III with benzoyl chloride.

EXPERIMENTAL

1,4-Bis(2,5-dimethyl-4-hydroxypiperidino)-2-butene (II). A total of 8.4 g (0.03 mole) of an unseparated mixture of isomers of 1,4-dibromo-2-butene in 20 ml of butanol was added dropwise with stirring to a mixture of 8 g (0.06 mole) of the α form of 2,5-dimethyl-4-piperidol (I) and 25 g of potassium carbonate in 50 ml of anhydrous butanol. The reaction mixture was heated for 6 h at 80-85°. At the end of the reaction the precipitate was filtered, washed with butanol, and the butanol was removed by distillation. The residue was extracted with hot ligroin (80-100° fraction). Removal of the ligroin by distillation yielded 2 g of isomer II with mp 153-154°. Found %: C 69.2, 69.5; H 11.3, 11.4; N 9.5, 9.3. $C_{18}H_{34}N_2O_2$. Calculated %: C 69.7; H 11.0; N 9.0. UV spectrum (in ethanol, c $1.5 \cdot 10^{-3}$ M): λ_{max} 222 nm, log ε 1.63. IR spectrum: 1080 and 3170 cm^{-1} (OH). The dihydrochloride had mp 248° (decomp., from alcohol). The ligroin-insoluble portion of the reaction product was recrystallized from benzene to give 1.2 g of a second isomer of II with mp 170-171°. Found %: C 70.4, 70.2; H 11.3, 11.3; N 8.8, 8.9. $C_{18}H_{34}N_2O_2$. Calculated %: C 69.7; H 11.0; N 9.0. UV spectrum: λ_{max} 223 nm, log ε 1.81 (same conditions). IR spectrum: 1080 and 3150 cm^{-1} (OH). The dihydrochloride had mp 273-274° (decomp.).

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1,4-Bis(2,5-dimethyl-4-hydroxypiperidino)-2-butyne (III). A total of 3.4 g (0.015 mole) of 1,4-dibromo-2-butyne (n_D^{20} 1.5952 [4]) was added dropwise to 8.27 g (0.06 mole) of the α form of piperidol I in 80 ml of anhydrous benzene in the course of 40 min, and the mixture was heated with vigorous stirring for 6 h at 75-80°. The resulting precipitate was filtered and washed with benzene to give 9.8 g of precipitate. This was treated with a saturated solution of sodium hydroxide, and the liberated base was extracted with ether. The ether solution was dried with calcined potassium carbonate, the ether was removed by distillation, and the residue was treated with hot ligroin and recrystallized from benzene to give 2.5 g of III with mp 186-187°. Found %: C 70.1, 70.0; H 10.7, 10.7; N 8.8, 8.8. $C_{18}H_{32}N_2O_2$. Calculated %: C 70.1; H 10.4; N 9.1. The dihydrochloride had mp 215-216°. Found %: N 7.2, 7.2; Cl 18.5, 18.3. $C_{18}H_{32}N_2O_2 \cdot 2HCl$. Calculated %: N 7.3; Cl 18.4. Distillation of the benzene from the benzene mother liquor yielded 0.1 g of I, and the wash ligroin yielded 0.8 g of I.

Benzoate of 1,4-Bis(2,5-dimethyl-4-hydroxypiperidino)-2-butene (IV). A. Benzoyl chloride [5.4 g, (0.03 mole)] was added in two portions to a solution of 2 g (0.006 mole) of isomer II (mp 153-154°) in 10 ml of dry pyridine, and the mixture was heated for 8 h at 90-95°. At the end of the reaction the congealed mass was filtered, washed with pyridine, and the precipitate was refluxed in benzene. The precipitate that formed from the benzene extract was recrystallized from benzene–acetone (1 : 1) to give 0.7 g of the dihydrochloride of dibenzoate IV with mp 279° (decomp.). IR spectrum: 1220, 1280, 1286, 1720 cm^{-1} (COOR); 2380, 2670 cm^{-1} ($\overset{+}{N}$H). Found %: C 65.4, 65.6; H 7.0, 7.3; N 4.4, 4.7; Cl 11.8, 12.0. $C_{32}H_{42}N_2O_4 \cdot 2HCl$. Calculated %: C 65.2; H 7.1; N 4.8; Cl 12.0.

B. A total of 0.4 g of the dihydrochloride of dibenzoate IV [mp 297° (decomp.)] was obtained under the conditions described above from 1.5 g (0.005 mole) of isomer II (mp 170-171°) and 4.2 g (0.03 mole) of benzoyl chloride in 10 ml of dry pyridine. IR spectrum: 1220, 1280, 1718 cm^{-1} (COOR), 2360, 2680 cm^{-1} ($\overset{+}{N}$H). Found %: C 65.4, 65.4; H 7.2, 7.0; N 4.4, 4.6; Cl 11.4, 11.4. $C_{32}H_{42}N_2O_4 \cdot 2HCl$. Calculated %: C 65.2; H 7.1; N 4.8; Cl 12.0.

Benzoate of 1,4-Bis(2,5-dimethyl-4-hydroxypiperidino)-2-butyne (V). A total of 2.9 g of the dihydrochloride of dibenzoate V (mp 204-205°) was obtained under the conditions described above from 2.5 g (0.008 mole) of III, 6.7 g (0.05 mole) of benzoyl chloride, and 10 ml of dry pyridine. Found %: C 64.9, 64.6; H 7.1, 7.1; N 4.6, 4.8; Cl 12.0, 11.8. $C_{32}H_{40}N_2O_4 \cdot 2HCl$. Calculated %: C 65.2; H 7.1; N 4.8; Cl 12.0.

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