NONCONDENSED POLYPIPERIDINE SYSTEMS

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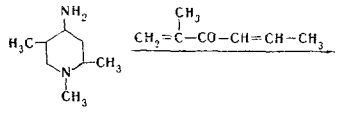
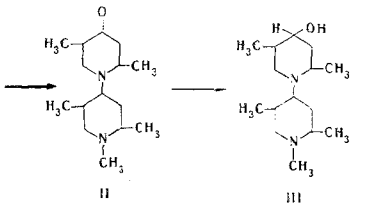
The synthesis of noncondensed dipiperidylbenzene and tripiperidyl systems has been effected. Some derivatives of compounds of this series have been obtained.

The preparation of γ-piperidones by the condensation of divinyl ketones with ammonia or primary amines has been long known [1]. This method was used with particular success by I. N. Nazarov for obtaining piperidones substituted in the ring, and here he was assisted by his work on the synthesis of the initial divinyl ketones of various structures. We decided to use this method for building up noncondensed polypiperidine systems by converting the γ-piperidones into γ-aminopiperidines with their subsequent condensation with divinyl ketones.

As the initial aminopiperidine we used 4-amino-1,2,5-trimethylpiperidine (I) [3], which was synthesized from 1,2,5-trimethylpiperid-4-one [2]. The aminopiperidine I was condensed with isopropenyl propenyl ketone. A ketone of the bipiperidyl series—2,5-dimethyl-1-(1',2',5'-trimethylpiperid-4'-yl)piperid-4-one (II)—was obtained with a yield of more than 50%. Its reduction with sodium in ethanol led to a secondary alcohol—2,5-dimethyl-1-(1',2',5'-trimethylpiperid-4'-yl)piperid-4-ol (III), from which the benzoate (IV), isolated in the form of the hydrochloride, was obtained.



I



II III

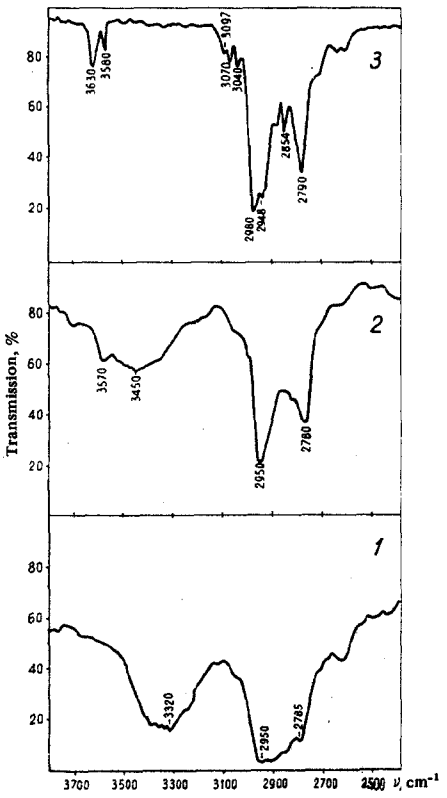
By the usual method (reaction with phenyllithium), a phenyl radical was introduced into the γ-position of compound II, giving a noncondensed dipiperidylbenzene system. To some extent, 2,5-dimethyl-4-phenyl-1-(1',2',5'-trimethylpiperid-4'-yl)piperid-4-ol (V) is an analog of 4-phenyl-1,2,5-trimethylpiperid-4-ol, an alcohol the propionate of which is the effective analgesic "promedol" [4].

Attempts to convert the tertiary piperidol V into its propionate were unsuccessful. Under the propionylation conditions that we have described, it did not undergo esterification. A similar difficulty in esterification has been reported previously for sterically hindered tertiary piperidols [5]. Questions of the stereochemistry of the piperidol V are of particular interest. In order to elucidate the type of hydrogen bond in this alcohol, we examined its IR spectrum in the crystalline state (paraffin oil) and in carbon tetrachloride solution. In the region of the stretching vibrations of the hydroxyl group in the crystalline state (figure, curve 1) there is a strong broad band of an intermolecularly bound hydroxyl with a maximum at 3320 cm^{-1}, and also a strong broad band in the 2785-2950 cm^{-1} region. On passing from the crystalline state to a saturated solution of the piperidol V in carbon tetrachloride (figure, curve 2), the intensity of the 3320 cm^{-1} band decreases markedly and at a concentration of 0.0012 M (figure, curve 3) it disappears completely, and a band appears in the region of the stretching vibration of a free hydroxyl group at 3630 cm^{-1}. A very narrow low-intensity band at 3580 cm^{-1} apparently relates to an OH group bound by an intramolecular hydrogen bond. An intense band at 2790 cm^{-1} is characteristic of a $>N-CH_3$ bond. A number of bands in the 2854–3097 cm^{-1} region (curve 3), is due, as has been established for the promedol alcohols [6], to the stretching vibrations of C—H bonds and a hydroxyl group bound by a kind of intramolecular hydrogen bond to the tertiary nitrogen atom.

The results of thin-layer chromatography show that the piperidol V is produced in the form of an individual diastereoisomer (R_f 0.263). The formation of a single isomer under the conditions of the phenyllithium synthesis can be explained by the influence of steric factors determining the approach of the organometallic compound mainly from the least screened side of the keto group [7, 8]. On the basis of what has been said above, it may be assumed that the piperidol V has the axial configuration of the hydroxyl and, consequently, the equatorial position of the phenyl radical at C-4, which links it to the γ-isomer of promedol alcohol.

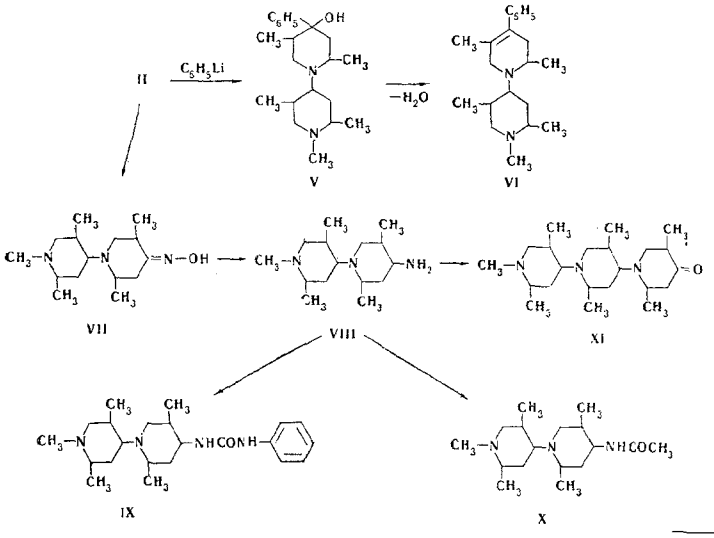
The dehydration of the alcohol V with hydrochloric acid took place with a yield of 70%, leading to 2,5-dimethyl-4-phenyl-1-(1',2',5'-trimethylpiperid-4-yl)-didehydropiperidine (VI). In the scheme, the position of the double bond in VI is shown tentatively.

The addition to the bipiperidyl system II of yet another piperidine ring was carried out by the same cycle of conversions. The piperidone II was converted into the oxime VII. The reduction of the latter with sodium in isopentanol led to 4-amino-2,5-dimethyl-1-(1',2'-5'-trimethylpiperid-4'-yl)piperidine (VIII). This amine was characterized by its derivatives—N-[2,5-dimethyl-1-(1',2',5'-trimethylpiperid-4'-yl)piperid-4-yl]-N'-phenylurea (IX) and 4-acetylamino-2,5-dimethyl-1-(1',2',5'-trimethylpiperid-4'-yl)piperidine



IR spectrum of 2,5-dimethyl-4-phenyl-1-(1',2',5'-trimethylpiperid-4'yl)-piperid-4-ol (V): 1) in paraffin oil; 2) saturated solution in CCl_4; 3) 0.0012 M solution in CCl_4.

(X). Finally, the aminodipiperidine VIII was condensed with isopropenyl propenyl ketone. This gave a 15% yield of the tripiperidyl ketone 2,5-dimethyl-4-(2",5"-dimethyl-4"-oxopiperid-1"-yl)-1-(1',2',5'-trimethylpiperid-4'-yl)piperidine XI.



The tricyclic piperidone XI was characterized in the form of its oxime. This oxime could presumably be used for the construction of a noncondensed tetracyclic piperidine system by the same cycle of transformations.

EXPERIMENTAL

2,5-Dimethyl-1-(1',2',5'-trimethylpiperid-4'-yl)piperid-4-one (II). A mixture of 24 g (0.17 mole) of I, 60 ml (~0.4 mole) of a mixture of isopropenyl propenyl ketone and the products of the addition to it of one or two molecules of methanol (technically known as "methoxyketones"), 35 ml of water, and 35 ml of methanol was heated with stirring at the boil for 6 hr. The mixture was acidified to Congo Red with 18% HCl. The methanol was distilled off in a slight vacuum. The neutral substances were extracted with ether. The aqueous solution was saturated with caustic potash and the organic bases were extracted with ether and, after drying with sodium sulfate, distilled. This gave 20.5 g (53%) of II, bp 142° C (1 mm); d_4^{20} 0.9752; n_D^{20} 1.4892; MR_D, found: 74.63; calculated: 74.96; R_f 0.742 (Al_2O_3, activity grade II, ethyl acetate). Monopicrate of II—small prisms, mp 143-144° C (from ethanol). Found, %: N 14.52, 14.49. Calculated for $C_{15}H_{28}N_2O \cdot C_6H_3(NO_2)_3OH$, %: N 14.55. Monomethiodide of II—mp 179-181° C (from acetone). Found, %: N 6.63, 6.75. Calculated for $C_{15}H_{28}N_2O \cdot CH_3I$, %: N 7.11. IR spectrum: 1718 cm^{-1} (>CO).

2,5-Dimethyl-1-(1',2',5'-trimethylpiperid-4'-yl)piperid-4-ol (III). To a solution of 12 g (0.05 mole) of II in 50 ml of absolute ethanol at the boil was gradually added 4.4 g (0.2 g-at) of sodium. The mixture was heated until the sodium had dissolved completely and it was then treated with water (100 ml) and dil (1:1) HCl until it had an acid reaction to Congo Red. The ethanol was distilled off and the residue was saturated with alkali and extracted with ether. Distillation yielded 5.25 g (40%) of III, bp 155-160° C (1.5 mm). Monopicrate of III—mp 133-134° C (from ethanol). Found, %: N 14.50, 14.50. Calculated for $C_{15}H_{30}N_2O \cdot C_6H_3(NO_2)_3OH$, %: N 14.50.

With cooling and stirring, a solution of 4.2 g (0.03 mole) of benzoyl chloride in 5 ml of benzene was gradually added to a solution of 3 g (0.01 mole) of II in 5 ml of benzene. The mixture was heated to the boil for 3 hr. The crystals that had formed were separated off, washed with ether, and recrystallized from acetone. This gave 0.45 g of the dihydrochloride of the benzoate (IV) of the piperidol III, mp 264-265° C. Found, %: Cl 16.26, 16.38; N 6.33, 6.28. Calculated for $C_{22}H_{34}N_2O_2 \cdot 2HCl$, %: Cl 16.93; N 6.47.

2,5-Dimethyl-4-phenyl-1-(1',2',5'-trimethylpiperid-4'-yl)piperid-4-ol (V). At −5 to 0° C, a solution of 20 g (0.083 mole) of II in 30 ml of ether was added over 2 hr to the phenyllithium obtained from 1.44 g (0.2 g-at) of lithium and 16.2 g (0.1 mole) of bromobenzene in 200 ml of ether. Then the reaction mixture was stirred at 20° C for 1 hr and at the boiling point of the ether for 2 hr, after which it was treated with water and was acidified to Congo Red with 18% HCl. The aqueous layer was saturated with caustic potash. The organic bases were extracted with ether, and after drying and the distillation of the ether, a crystalline residue was obtained. It was recrystallized from gasoline to give 3.56 g (12%) of V, mp 164-166° C, R_f 0.263 [Al_2O_3 of activity grade II, ethyl acetate—heptane (1:1)]. Found, %: C 76.18, 75.88; H 10.22, 10.11; N 8.36, 8.27. Calculated for $C_{21}H_{34}N_2O$, %: C 76.36; H 10.31; N 8.48.

When 0.5 g (1.5 mM) of V, 0.45 g (5 mM) of propionyl chloride, and 10 ml of benzene was heated for 3 hr, 0.6 g (1.4 mM) of the hydrochloride of V with mp 268-269° C was obtained. The free base V with mp 164-166° C was isolated from it. Thus, no esterification of the piperidol V took place. The propionic ester of the piperidol V could not be obtained by the use of propionic anhydride, either. In this case, likewise, the initial V was recovered quantitatively.

The dehydration of V was effected by means of concentrated HCl. A mixture of 0.65 g (0.2 mM) of V and 10 ml of acid was heated to the boil for 5 hr. The HCl was distilled off in vacuum. The residue was treated with sodium carbonate and extracted with ether. This gave 0.43 g (70%) of VI, mp 76-79° C. Dipicrate of VI—mp 203-204° C (from ethanol). Found, %: N 14.79, 14.98. Calculated for $C_{21}H_{32}N_2 \cdot 2C_6H_3(NO_2)_3OH$, %: N 14.55.

2,5-Dimethyl-1-(1',2',5'-trimethylpiperid-4'-yl)piperid-4-one oxime (VII). A mixture of 6.1 g (0.025 mole) of II, 15 g (0.14 mole) of sodium carbonate, 9.1 g (0.13 mole) of hydroxylamine hydrochloride, 30 ml of water, and 20 ml of ethanol was heated at the boil for 1 hr. After 12 hr, the crystals that had deposited were separated off and recrystallized from acetone. This gave 5.8 g (92%) of the oxime VII, mp 176-178° C. Found, %: C 67.46, 67.59; H 10.63, 11.01; N 15.88, 15.88. Calculated for $C_{15}H_{29}N_3O$, %: C 67.45; H 10.86; N 15.73. IR spectrum, cm^{-1}: 3180 and 3080 (−OH); 2800 cm^{-1}(>N−CH_3) 1660 (=C=N−). The spectrum contains no stretching vibrations of a >CO−group, which shows the complete conversion of the ketone II into the oxime.

4-Amino-2,5-dimethyl-1-(1',2',5'-trimethylpiperid-4'-yl)piperidine (VIII). In portions over 15 min, 2.3 g (0.1 g-at) of sodium was added to a boiling solution of 6.6 g (0.025 mole) of the oxime VII in 70 ml of absolute isopentanol. The mixture was heated until the sodium had dissolved completely. The reaction products were treated with 30 ml of water and were acidified to Congo Red with 18% hydrochloric acid. The isopentanol was distilled off in a slight vacuum. The residue was treated with alkali and extracted with ether, and the extract was dried with caustic potash. Distillation of the ether yielded

5.7 g of the unpurified dipiperidylamine VIII in the form of a viscous light yellow oil.

The reaction of the amine VIII with phenyl isocyanate (in benzene) gave N-[2,5-dimethyl-1-(1',2',5'-trimethylpiperid-4'-yl)piperid-4-yl]-N'-phenylurea (IX), mp 226-228° C (from ethanol). Found, %: C 71.06, 71.32; H 10.13, 9.86; N 14.54, 14.32. Calculated for $C_{21}H_{36}N_4O \cdot C_{22}H_{36}N_4O$, %: C 70.96; H 9.68; N 15.05.

With cooling, 7 ml (0.07 mole) of acetic anhydride was added to 1.2 g (5 mM) of VIII in 20 ml of 5% caustic soda solution. The mixture was stirred at room temperature for 3 hr and was then treated with caustic potash and extracted with ether, giving 0.8 g (2.7 mM) of X, mp 168-169° C (from gasoline). Found, %: C 69.08, 68.90; H 11.19, 11.11; N 14.11, 14.28. Calculated for $C_{17}H_{33}N_3O$, %: C 69.15; H 11.18; N 14.24. IR spectrum, cm^{-1}: 3300-3100 cm^{-1} (>N-H); 2790 cm^{-1} (>N-CH_3); 1640 cm^{-1} (>C=O); 1570 cm^{-1} ().

2,5-Dimethyl-4-(2",5"-dimethyl-4"-oxopiperid-1"-yl)-1-(1',2',5'-trimethylpiperid-4'-yl)piperidine (XI). A mixture of 5.5 g (0.022 mole) of the amine VIII, 20 ml of 50% aqueous methanol, and 20 ml (~0.12 mole) of freshly-distilled "methoxyketones" (see first experiment) was heated at the boil with stirring for 4 hr. The reaction mixture was acidified to Congo Red with 18% HCl. The methanol was distilled off and the neutral reaction products were eliminated with ether. The aqueous solution was saturated with caustic potash and the organic bases were extracted with ether. Distillation of the ether yielded a crystalline residue from which 1.15 g (15%) of XI was isolated; mp 172-173° C (from gasoline). Found, %: C 72.51, 72.77; H 11.46, 11.60; N 10.94, 11.15. Calculated for $C_{22}H_{41}N_3O$, %: C 72.72; H 11.28; N 11.57. IR spectrum, cm^{-1}: 2800 (CH_3-N <); 1723 cm^{-1} (>C=O). Oxime of the piperidone XI-mp 197-200° C (from ethanol). Found, %: N 14.27, 14.10. Calculated for $C_{22}H_{42}N_4O$, %: N 14.82.

The IR spectra of the piperidol V were recorded on a UR-20 spectrophotometer in the region of a LiF prism from 3800 to 2400 cm^{-1}. The IR spectra of the other compounds in paraffin oil were recorded on a UR-10 spectrophotometer in the regions of LiF, NaCl, and KBr prisms from 3800 to 400 cm^{-1}.

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