CONDENSATION OF 1,2,5-TRIMETHYL-4-PIPERIDONE WITH ETHYL- AND NAPHTHYLACETYLENES AND SYNTHESIS OF SUBSTITUTED PYRIDINES

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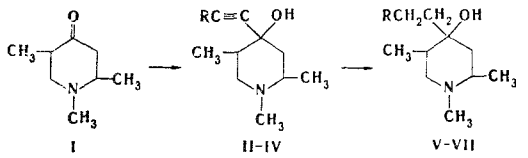
The Favorskii reaction with 1,2,5-trimethyl-4-piperidone and ethyl- and naphthylacetylenes gave the corresponding piperidols, the hydrogenation of which gave 1,2,5-trimethyl-4-n-butyl(or 2-naphthylethyl)-4-piperidols. 4-Phenyl- and 4-butyl-2,5-dimethylpyridine were condensed with formaldehyde, and some of the transformations of the resulting β-hydroxyethyl derivatives were studied.

Several ethynyl alcohols of the aliphatic series have an efficient soporific effect. The search for medicinal preparations of this sort seems necessary, since the barbiturates that are usually employed as somnifacients often have a negative side effect. In this connection, we turned to the synthesis of some ethynyl-substituted γ-piperidols obtained from 1,2,5-trimethyl-4-piperidone (I). These ethynyl amino alcohols can be subsequently used for the synthesis of hard-to-obtain substituted pyridine bases.

4-(1-Butynyl)- (II) and 4-naphthylethynyl-1,2,5-trimethyl-4-piperidols (III, IV) were obtained by condensation of I under the conditions of the Favorskii reaction with, respectively, 1-butyne and α- and β-naphthylacetylenes. The hydrogenation of II-IV was accomplished on Raney nickel to give 4-n-butyl- (V), 4-(2-α-naphthylethyl)-, and 4-(2-β-naphthylethyl)-4-piperidols (VI, VII). The synthesis of V via this route gave its diastereoisomer with mp 97.5-99°C, which was previously isolated in the hydrogenation of a mixture of diastereoisomers of 1,2,5-trimethyl-4-(3-butynyl)-4-piperidol (obtained by condensation of I with vinylacetylene) [1]. Reaction of n-butyllithium with I gives a diastereoisomer of V with mp 70-71°, which we obtained from I and butylmagnesium bromide [2, 3].



II, V R = C_2H_5; III, VI R = α-$C_{10}H_7$; IV, VII R = β-$C_{10}H_7$

According to the method that we developed, the γ-piperidols are converted to substituted pyridine bases by dehydration, catalytic dehydrogenation, and N-demethylation. We have previously used this method to obtain 2,5-dimethyl-4-phenylpyridine (VIII) from 1,2,5-trimethyl-4-phenylpiperideine [4]. Compound VIII was isolated as a mobile liquid after several distillations of the reaction products. We were unable to isolate VIII in the crystalline state via this route. It was chromatographically established that the VIII obtained contains small amounts of three other substances, which correspond (with respect to the R_f values) to the starting piperideine. The latter is apparently represented by three isomers that differ from one another with respect to the position of the ring double bond. More thorough purification – distillation

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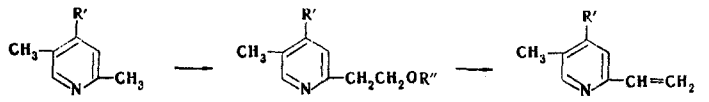
of the reaction products with an efficient column (35 theoretical plates) – gave colorless crystals of VIII with mp 29°.



VIII, IX X, XI, XIII–XV XVI, XVII

VIII, X, XI, XVI R′ = C_6H_5; IX, XIII–XV, XVII R′ = C_4H_9; X, XIII R″ = H; XI, XIV R″ = $CONHC_6H_5$; XV R″ = COC_6H_5

Condensation of VIII with formaldehyde gave a mixture of 5-methyl-2-(β-hydroxyethyl)-4-phenylpyridine (X) and 2-(5-methyl-4-phenyl-2-pyridyl)-1,3-propanediol (XII), which was separated chromatographically on aluminum oxide (94% X and 6% XII). A urethane – N-phenyl-β-(5-methyl-4-phenyl-2-pyridyl)ethyl carbamate (XI) – was formed in quantitative yield from X. Dehydration of X (by heating with potassium hydroxide) gave 5-methyl-2-vinyl-4-phenylpyridine (XVI) in 70% yield as a colorless vacuum-distillable liquid that did not undergo practically any change on storage.

The conversion of piperidol V to 2,5-dimethyl-4-n-butylpyridine (IX) was previously described in [3]. 5-Methyl-2-(β-hydroxyethyl)-4-n-butylpyridine (XIII) was obtained in 45% yield by condensation of IX with formaldehyde. Derivatives of XIII – N-phenyl-β-(5-methyl-4-n-butyl-2-pyridyl)ethyl carbamate (XIV) and 5-methyl-2-(β-benzoxyethyl)-4-n-butylpyridine (XV) – were obtained. Alcohol XIII was dehydrated (by heating with potassium hydroxide) to 5-methyl-2-vinyl-4-n-butylpyridine (XVII). Compound XVII (a mobile colorless liquid) was distilled in vacuo and did not change on storage.

EXPERIMENTAL

1,2,5-Trimethyl-4-(1-butynyl)-4-piperidol (II). A mixture of 39 g (0.28 mole) of I, 15 g (0.27 mole) of potassium hydroxide, and 10 g (0.85 mole) of 1-butyne was heated in an autoclave at 95° for 4 h. Water (20 ml) and 18% hydrochloric acid (until the mixture was acid to Congo Red) were then added to the mixture, and the neutral substances were extracted with ether. The organic bases were isolated from the aqueous solution after treatment with potassium hydroxide and extraction with ether to give 19 g (0.13 mole) of I with bp 63° (4 mm) and 29 g (100%, based on the converted I) of II with bp 105–110° (3 mm) and R_f 0.29, 0.58 [ethyl acetate–heptane (3 : 1)].* Found: N 6.9%. $C_{12}H_{21}NO$. Calculated: N 7.2%. Crystallization from ligroin gave 2.3 g of one of the diastereoisomers of II with mp 88–89.5° and R_f 0.29 (in the same system). Found: C 73.5; H 10.7; N 7.1%. $C_{12}H_{21}NO$. Calculated: C 73.8; H 10.8; N 7.2%.

1,2,5-Trimethyl-4-(α-naphthylethynyl)-4-piperidol (III). A mixture of 36 g (0.23 mole) of α-naphthylacetylene, 36 g (0.25 mole) of I, and 30 g (0.54 mole) of powdered potassium hydroxide in 140 ml of dry ether was heated in an autoclave at 100° for 2.5 h. The mixture was then cooled, and 200 ml of water was added. The ether layer was separated, and the aqueous layer was washed with three 200-ml portions of ether. The extract was dried with magnesium sulfate, and the ether was partially removed to give 13 g (17%) of III with mp 162–163° (from alcohol) and R_f 0.16 (ether). IR spectrum: 3100 (OH), 2810 (NCH_3), 2227 cm^{-1} (C≡C). Found: C 81.9; H 8.0; N 4.5%. $C_{20}H_{23}NO$. Calculated: C 81.9; H 7.9; N 4.8%. The picrate of III had mp 231° (from alcohol). Found: N 10.6%. $C_{20}H_{23}NO \cdot C_6H_3N_3O_7$. Calculated: N 10.7%.

1,2,5-Trimethyl-4-(β-naphthylethynyl)-4-piperidol (IV). A mixture of 6 g (0.04 mole) of β-naphthylacetylene, 9 g (0.06 mole) of I, and 5.6 g (0.1 mole) of powdered potassium hydroxide in 30 ml of dry ether was heated at 100° in an autoclave for 3 h, after which 50 ml of water was added, and the reaction products were extracted with ether. The ether extract was dried, the starting I was removed by distillation, and the residue (9 g) was crystallized from ether–benzene (1 : 1) to give 6 g (52%) of IV with mp 133–134° and R_f 0.06 (ether). IR spectrum: 3534 and 3300 (OH), 2805 (NCH_3), 2225 cm^{-1} (C≡C). Found: C 81.7; H 8.0; N 4.4%. $C_{20}H_{23}NO$. Calculated: C 81.9; H 7.9; N 4.8%. The picrate of IV had mp 227° (from alcohol). Found: N 10.5%. $C_{20}H_{23}NO \cdot C_6H_3N_3O_7$. Calculated: N 10.7%.

1,2,5-Trimethyl-4-n-butyl-4-piperidol (V). A. A 100-g (0.71 mole) sample of I was added at 0° to butylmagnesium bromide, prepared from 73 g (0.53 mole) of butyl bromide and 13 g (0.53 g-atom) of magnesium in 300 ml of ether. The mixture was then treated successively with 150 ml of water and 100 ml of 18% and 36% hydrochloric acid until it was acid to Congo Red. The organic bases were extracted from the aqueous solution with ether after treatment with potassium hydroxide. Distillation gave 78.5 g (0.56 mole)

*When the sorbent is not indicated, the chromatography was carried out on a thin layer of activity-II aluminum oxide.

of I and 12.56 g (42%) of V with bp 110-120° (3 mm) and R_f 0.47 and 0.33 [ethyl acetate–heptane (3 : 1)]. Crystallization from ligroin gave 3.8 g of one of the diastereoisomers of V with mp 70-71° and R_f 0.47.

B. A 1-g (5 mmole) sample of II (mp 88-89.5°) in 10 ml of alcohol was hydrogenated over Raney nickel at 20°. A total of 230 ml of hydrogen was absorbed after 10 h, and 0.93 g (94%) of V with mp 97.5-99° (from ligroin) and R_f 0.33 (same system) was isolated. Found: C 72.4; H 12.2; N 7.0%. $C_{12}H_{25}NO$. Calculated: C 72.4; H 12.5; N 7.0%.

1,2,5-Trimethyl-4-(2-α-naphthylethyl)-4-piperidol (VI). A 1.5-g (5 mmole) sample of III in 15 ml of alcohol was hydrogenated over Raney nickel at 20°. The theoretical amount of hydrogen (190 ml) was absorbed after 96 h. Crystallization of the hydrogenation products from hexane gave 1.3 g (85.5%) of VI with mp 156-158° and R_f 0.06 (ether). IR spectrum: 3320 (OH) and 2812 cm^{-1} (NCH_3). Found: C 80.8; H 9.2; N 4.8%. $C_{20}H_{27}NO$. Calculated: C 80.9; H 9.2; N 4.7%.

1,2,5-Trimethyl-4-(2-β-naphthylethyl)piperidol (VII). A 1.3-g (4 mmole) sample of IV in 13 ml of alcohol was hydrogenated under the same conditions for 80 h. A total of 166 ml of hydrogen was absorbed, and 1.1 g (88.7%) of VII with mp 122-123.5° (from ligroin) and R_f 0.08 (ether) was isolated. IR spectrum: 3200 (OH), 2795 cm^{-1} (NCH_3). Found: C 80.9; H 9.0; N 4.7%. $C_{20}H_{27}NO$. Calculated: C 80.9; H 9.0; N 4.7%. The picrate of VII had mp 210.5-211.5° (from alcohol). Found: N 10.6%. $C_{20}H_{27}NO \cdot C_6H_3N_3O_7$. Calculated: N 10.7%.

Isolation of 2,5-Dimethyl-4-phenylpyridine (VIII). A 100-g sample of freshly distilled 1,2,5-trimethyl-4-phenylpiperideine with bp 100.5-101.5° (1 mm), n_D^{20} 1.5446, and R_f 0.20, 0.31, and 0.41 [on a thin layer of KSK silica gel in ether–methanol (10 : 1)] was used in the dehydrogenation and N-demethylation. The reaction was carried out as described in [4]. Distillation of the reaction products gave 46 g of a first fraction with bp 118-119° (2 mm), n_D^{20} 1.5826, and R_f 0.20, 0.31, and 0.61, and 27 g of a second fraction with bp 119-121° (2 mm), and n_D^{20} 1.5859. The first fraction was distilled with a column with 35 theoretical plates to give three fractions (6 ml) boiling at 50-81° (1 mm) with n_D^{20} from 1.5618 to 1.5735, four fractions (11 ml) boiling at 81-104° (1 mm) with n_D^{20} from 1.5760 to 1.5822, and 21 ml of a fraction with bp 104 (1 mm) and n_D^{20} 1.5841 and R_f 0.61. The last fraction crystallized completely, and needles of VIII with mp 29° (from ligroin) were isolated. The perchlorate of VIII had mp 185.7-186° (from alcohol). Found: C 55.0; H 4.9; Cl 12.2; N 4.7%. $C_{13}H_{13}N \cdot HClO_4$. Calculated: C 55.0; H 4.9; Cl 12.5; N 4.9%.

5-Methyl-2-(β-hydroxyethyl)-4-phenylpyridine (X) and 2-(5-Methyl-4-phenyl-2-pyridyl-1,3-propanediol (XII). A mixture of 19.5 g (0.11 mole) of VIII and 12 ml of 27% formalin was heated at 220-230° for 3 h. The reaction products were extracted with ether, and the ether extract was dried with sodium sulfate and distilled to give 9.9 g of VIII with bp 110-125° (1 mm) and 6.5 g of a second fraction with bp 173-178° (1 mm) as a viscous mass that crystallized in ligroin. Two crystallizations gave 3.5 g of crystals with mp 84-96°. Chromatographic purification of these crystals with a column (H 60 cm, d 2.5 cm, activity-II Al_2O_3, chloroform) initially gave 3 g (27%, based on the converted VIII) of X with mp 101-102° (from ligroin). ν_{OH} 3170 cm^{-1} (intense broad band). Found: C 79.1; H 6.9; N 6.2%. $C_{14}H_{15}NO$. Calculated: C 79.0; H 7.0; N 6.6%.

N-Phenyl-β-(5-methyl-4-phenyl-2-pyridyl)ethyl carbamate (XI). This compound had mp 148-149° (from carbon tetrachloride). Found: N 8.1%. $C_{21}H_{20}N_2O_2$. Calculated: N 5.8%. At the end of the chromatography, 0.2 g (0.08 mole) of XII with mp 136.5-138° (from ligroin) was isolated. Found: N 5.6%. $C_{15}H_{17}NO_2$. Calculated: N 5.8%.

5-Methyl-2-(β-hydroxyethyl)-4-butylpyridine (XIII). A mixture of 4.8 g (0.03 mole) of 2,5-dimethyl-4-butylpyridine (IX) and 3 ml of 27% formalin was heated in an autoclave at 160-170° for 4 h, after which 10 ml of water was added to the mixture. The reaction products were extracted with ether, and the extract was dried and distilled to give 1.23 g of IX with bp 78-110° (3 mm) and 2.1 g (45%) of XIII with bp 150-160° (3 mm) and mp 73-74.5° (from ligroin). Found: C 74.6; H 9.7; N 7.2%. $C_{12}H_{19}NO$. Calculated: C 74.6; H 9.8; N 7.2%.

N-Phenyl-β-(5-methyl-4-butyl-2-pyridyl)ethyl carbamate (XIV). This compound had mp 119.5-121° (from carbon tetrachloride). Found: N 8.7%. $C_{19}H_{24}N_2O_2$. Calculated: N 8.9%. A 0.6-g (3 mmole) sample of XIII and 0.6 g (4 mmole) of benzoyl chloride in 7 ml of benzene (heating for 2 h) gave 0.3 g (30%) of 5-methyl-2-(β-benzoxyethyl)-4-butylpyridine hydrochloride (XV) with mp 103-104° (from benzene). Found: N 3.9%. $C_{19}H_{23}NO_2 \cdot HCl$. Calculated: N 4.2%. Base XV had mp 80.5-82° (from ligroin). Found: C 76.8; H 7.5; N 4.7%. $C_{19}H_{23}NO_2$. Calculated: C 76.8; H 7.7; N 4.7%.

5-Methyl-2-vinyl-4-phenylpyridine (XVI). A 3.6-g (0.017 mole) sample of X was heated in a Claisen flask with 1 g of ground potassium hydroxide at 180° and 5 mm, and the resulting XVI was removed by distillation. It was dried and distilled to give 2.3 g (70%) of XVI with bp 146-147° (4 mm) n_D^{20} 1.6111 and d_4^{20} 1.0540. Found: C 86.3; H 6.7; N 7.0%; MR_D 64.22. $C_{14}H_{13}N$. Calculated: C 86.2; H 6.7; N 7.2%. MR_D 64.12.

5-Methyl-2-vinyl-4-butylpyridine (XVII). A 2.5-g (0.013 mole) sample of XIII was heated with 0.5 g of ground potassium hydroxide at 150° and 75 mm in a Claisen flask. The distilled substances were dried and distilled to give 1.6 g (70%) of XVII with bp 120-123° (14 mm), n_D^{20} 1.6509, and d_4^{20} 0.9270. UV spectrum (in ethanol), λ_{max}, nm (ε): 250 (2800), 265 (2910). Found: C 82.3; H 9.7; N 8.0%; MR_D 56.33. $C_{12}H_{17}N$. Calculated: C 82.3; H 9.7; N 8.0%; MR_D 56.70.

The IR spectra of KBr pellets of the compounds were measured with a UR-20 spectrophotometer.

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