CYANOETHYLATION OF SOME N-SUBSTITUTED 2,5-DIMETHYL-4-PIPERIDONES

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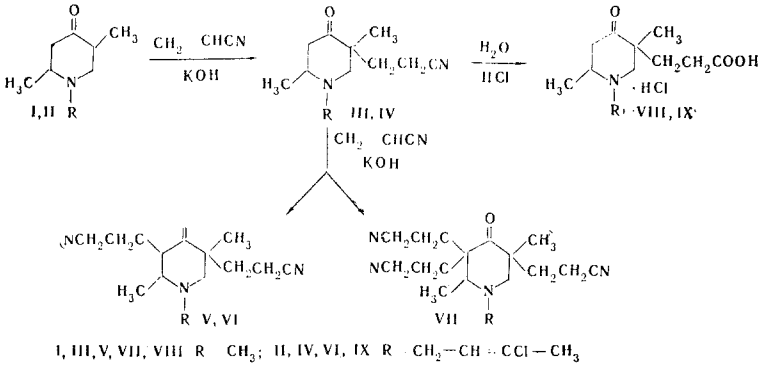
1,2,5-Trimetnyl- and 1-(γ-chlorocrotyl)-2,5-dimethyl-5-(β-cyanoethyl)-4-piperidones were synthesized and separated into individual isomers. The corresponding isomeric 5-(β-carboxyethyl)-4-piperidones were obtained by hydrolysis. The isomeric 1,2,5-trimethyl-3,5-bis(β-cyanoethyl)- and 1,2,5-trimethyl-3,3,5-tris(β-cyanoethyl)-4-piperidones were synthesized by subsequent cyanoethylation of the individual 1,2,5-trimethyl-5-(β-cyanoethyl)-4-piperidone isomers.

We previously [1] studied the cyanoethylation of some N-substituted 2,5-dimethyl-4-piperidones. Continuing these investigations, we have cyanoethylated 1,2,5-trimethyl- and 1-(γ-chlorocrotyl)-2,5-dimethyl-4-piperidones (I and II).



Nazarov and co-workers [2] obtained only one crystalline 1,2,5-trimethyl-5-(β-cyanoethyl)-4-piperidone isomer (III) by the reaction of 1,2,5-trimethyl-4-piperidone (I) with acrylonitrile in a ratio of about 3:1. Under similar conditions, in addition to the crystalline isomer (74%), we also isolated a second liquid isomer in 6% yield (based on the total amount of the isomer mixture). The relative amounts of the isolated isomers depend on the ratio of acrylonitrile to piperidone taken in the reaction. The crystalline isomer of piperidone III is chiefly formed when a threefold excess of piperidone I is used, while 58% of the crystalline isomer and 30% of the liquid isomer are formed in the reaction of equimolecular amounts of piperidone and acrylonitrile under the same temperature conditions using solid potassium hydroxide as the catalyst. In the latter case, in addition to monocyanoethylpiperidone III, bis(cyanoethyl)piperidone V was isolated. Since piperidone I was used as an unseparated mixture of stereo isomers (1,2e,5e-trimethyl- and 1,2e-5a-trimethyl-4-piperidones) [3], this sort of dependence of the yield of isomers on the ratio of reagents taken in the reaction can be explained by the different reactivities of the stereo isomers of piperidone I. The cyanoethylation of 1-(γ-chlorocrotyl)-2,5-dimethyl-4-piperidone proceeds similarly to form two isomers (liquid and crystalline) of monocyanoethylpiperidone IV and bis(cyanoethyl)piperidone VI.

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It is known [2, 4, 5] that the cyanoethylation of ketones proceeds most readily at a methine group, with greater difficulty at a methylene group, and with greatest difficulty at a methyl group. Consequently, the cyanoethyl groups in the isomers of monocyanoethylpiperidone III and IV should be situated at C_5 and have a different three-dimensional orientation. The purity of the isomers was established by thin-layer chromatography on aluminum oxide and also by the subsequent transformations to the corresponding isomeric bis(cyanoethyl)piperidones (V), tris(cyanoethyl)piperidones (VII), and carboxyethylpiperidones (VIII and IX).

EXPERIMENTAL

Cyanoethylation of 1,2,5-Trimethyl-4-piperidone. A. A solution of 15.9 g (0.3 mole) of acrylonitrile and 50 ml of ether was slowly added dropwise with stirring at 20° to a mixture of 42.3 g (0.3 mole) of 1,2,5-trimethyl-4-piperidone (I) (n_D^{20} 1.4600 [6]) and 0.8 g of powdered potassium hydroxide in 200 ml of absolute ether. The stirring was continued at 20° for 6 h. The next day, the ether solution was separated from the alkali, the ether was removed by distillation, and the residue was distilled to give 13 g of starting piperidone I with bp 53-55° (2 mm) and n_D^{20} 1.4600, 26.9 g (46%) of 1,2,5-trimethyl-5-(β-cyanoethyl)-4-piperidone (III) with bp 135° (2 mm) and 10.1 g (27%) of 1,2,5-trimethyl-3,5-bis(β-cyanoethyl)-4-piperidone (V) with bp 210° (2 mm), n_D^{20} 1.4910, and d_4^{20} 1.059. Found %: N 17.3, 17.4; MR_D 67.63. $C_{14}H_{21}N_3O$. Calculated %: N 17.0; MR_D 68.24. Piperidone III began to crystallize. The crystals were filtered and recrystallized from petroleum ether (bp 35-60°) to give 15.6 g (58% of the total amount of the isomer mixture) of the crystalline isomer of piperidone III with mp 68-69° and R_f 0.70 [acetone–n-hexane–benzene (1:3:3)]. Found %: N 14.7, 14.4. $C_{11}H_{18}N_2O$. Calculated %: N 14.5. The hydrochloride had mp 184-186° (from alcohol). Found %: N 12.4, 12.3; Cl 15.2, 15.3. $C_{11}H_{18}N_2O \cdot HCl$. Calculated %: N 12.1; Cl 15.4. The methiodide had mp 145-146° (from alcohol). Found %: C 43.0, 43.4; H 6.6, 6.2; I 37.4, 37.6; N 8.1, 8.2. $C_{12}H_{21}IN_2O$. Calculated %: C 42.9; H 6.3; I 37.7; N 8.3.

The filtrate and mother liquors from the crystalline isomer were distilled to give 8 g (30% of the total amount of the isomer mixture) of liquid isomer of piperidone III with bp 135° (2 mm), n_D^{20} 1.4790, d_4^{20} 1.010, and R_f 0.65 [acetone–n-hexane–benzene (1:3:3)]. Found %: N 14.8, 14.6; MR_D 54.54. $C_{11}H_{18}N_2O$. Calculated %: N 14.5; MR_D 54.56. The hydrochloride was an uncrystallizable oil. Found %: N 12.1, 12.1; Cl 15.7, 15.6. $C_{11}H_{18}N_2O \cdot HCl$. Calculated %: N 12.1; Cl 15.4. The methiodide had mp 165-166° (from alcohol). Found %: I 38.0, 37.6; N 8.6, 8.5. $C_{12}H_{21}IN_2O$. Calculated %: I 37.7; N 8.3.

B. A total of 7 g (0.13 mole) of acrylonitrile was slowly added dropwise with stirring at 20° to a mixture of 50 g (0.35 mole) of 1,2,5-trimethyl-4-piperidone (I) and 3 g of 40% aqueous potassium hydroxide. The stirring was continued at 20° for 6 h. The next day, the alkali was neutralized with an equivalent amount of concentrated hydrochloric acid. The precipitated potassium chloride was filtered, and the filtrate was distilled to give 28.3 g of starting piperidone I and 23 g (90%) of 1,2,5-trimethyl-5-(β-cyanoethyl)-4-piperidone (III) with bp 128-130° (1.5 mm). The crystallized piperidone III was converted to the hydrochloride and treated with refluxing dry acetone. A sodium carbonate solution was used to isolate 17 g (74% of the total amount of the isomer mixture) of the crystalline isomer of piperidone III with mp 68-69° (from petroleum ether) from the acetone-insoluble hydrochloride. The acetone was removed from the filtrate from the crystalline hydrochloride, and the base was isolated to give 1.4 g (6% of the total amount of the isomer mixture) of the liquid isomer of piperidone III with bp 117-120° (1 mm) and n_D^{20} 1.4790.

Cyanoethylation of 1-(γ-Chlorocrotyl)-2,5-dimethyl-4-piperidone (II). A total of 5.8 g of starting piperidone II with bp 105-110° (2 mm) and n_D^{20} 1.4950, 13.4 g (50%) of 1-(γ-chlorocrotyl)-2,5-dimethyl-5-(β-cyanoethyl)-4-piperidone (IV) with bp 167° (2 mm) and n_D^{20} 1.5030, and 4 g (25%) of 1-(γ-chlorocrotyl)-2,5-dimethyl-3,5-bis(β-cyanoethyl)-4-piperidone (VI) with bp 215° (2 mm), n_D^{20} 1.5090, and d_4^{20} 1.118 were obtained under the conditions described above from 21.6 g (0.1 mole) of piperidone II (n_D^{20} 1.4950 [7]) in 100 ml of absolute ether and 5.3 g (0.1 mole) of acrylonitrile in the presence of 0.3 g of powdered potassium hydroxide. Found %: N 13.5, 13.4; MR_D 85.96. $C_{17}H_{24}ClN_3O$. Calculated %: N 13.0; MR_D 86.49. The precipitated crystals were separated from piperidone IV and recrystallized from petroleum ether to give 0.9 g of the crystalline isomer of piperidone IV with mp 52-53° and R_f 0.74 [acetone–n-hexane–benzene (1:3:3)]. Found %: C 62.9, 63.0; H 7.9, 7.9; N 10.6, 10.6; Cl 13.0, 13.4. $C_{14}H_{21}ClN_2O$. Calculated %: C 62.5; H 7.9; N 10.4; Cl 13.2. The hydrochloride had mp 168-169° (from alcohol–ether). Found %: N 9.2, 9.1; Cl 22.9, 22.9. $C_{14}H_{21}ClN_2O \cdot HCl$. Calculated %: N 9.2; Cl 23.2. The oily base which remained in the filtrate was converted to 6.4 g of the hydrochloride of the crystalline isomer with mp 168-169° (alcohol–ether). A total

of 6.5 g (49%) of the total amount of the isomer mixture) of the crystalline isomer of piperidone IV was isolated. The base [5.1 g (38% of the total amount of the isomer mixture)] of the liquid isomer of piperidone IV with bp 168° (2 mm), n_D^{20} 1.5000, d_4^{20} 1.090, and R_f 0.69 [acetone–n-hexane–benzene (1:3:3)] was isolated from the filtrate and mother liquor from the crystalline hydrochloride. Found %: N 10.3, 10.3; MR_D 72.54. $C_{14}H_{21}ClN_2O$. Calculated %: N 10.4; MR_D 72.82. The hydrochloride was an uncrystallizable oil. Found %: C 55.3, 55.4; H 8.0, 7.9; Cl 23.6, 23.2. $C_{14}H_{21}ClN_2O \cdot HCl$. Calculated %: C 55.1; H 7.9; Cl 23.2.

Cyanoethylation of the Crystalline Isomer of 1,2,5-Trimethyl-5-(β-cyanoethyl)-4-piperidone (III). A solution of 2.65 g (0.05 mole) of acrylonitrile in 10 ml of ether was slowly added dropwise with stirring at 30° to a mixture of 11.3 g (0.058 mole) of the crystalline isomer of piperidone III and 0.1 g of powdered potassium hydroxide in 60 ml of absolute ether. Stirring was continued at 30° for 6 h. The next day, the precipitate was recrystallized from benzene to give 2.5 g (34%) of 1,2,5-trimethyl-3,3,5-tris(β-cyanoethyl)-4-piperidone (VII) with mp 97-98°. Found %: N 18.9, 18.5. $C_{17}H_{24}N_4O$. Calculated %: N 18.6. The hydrochloride had mp 202-203° (from alcohol). Found %: N 17.0, 17.1; Cl 10.3, 10.2. $C_{17}H_{24}N_4O \cdot HCl$. Calculated %: N 16.6; Cl 10.5. The filtrate and mother liquors from piperidone VII were distilled to give 5.8 g of the starting crystalline piperidone III with bp 125° (1.5 mm) and 3.2 g (26%) of 1,2,5-trimethyl-3,5-bis-(β-cyanoethyl)-4-piperidone (V) with bp 209° (2 mm), n_D^{20} 1.4930, and d_4^{20} 1.058. Found %: C 67.8, 67.7; H 8.3, 8.5; N 17.2, 17.2; MR_D 67.92. $C_{14}H_{21}N_3O$. Calculated %: C 68.0; H 8.6; N 17.0; MR_D 68.24. The hydrochloride was an uncrystallizable oil. Found %: N 14.7, 14.3. $C_{14}H_{21}N_3O \cdot HCl$. Calculated %: N 14.8.

Cyanoethylation of the Liquid Isomer of 1,2,5-Trimethyl-5-(β-cyanoethyl)-4-piperidone (III). A total of 2.8 g (23%) of 1,2,5-trimethyl-3,3,5-tris(β-cyanoethyl)-4-piperidone (VII) with mp 145-146° was obtained under the conditions described above from 15.5 g (0.08 mole) of the liquid isomer of piperidone III in 50 ml of absolute ether and 4.2 g (0.08 mole) of acrylonitrile in the presence of 0.2 g of powdered potassium hydroxide. Found %: N 18.6, 18.4. $C_{17}H_{24}N_4O$. Calculated %: N 18.6. The hydrochloride had mp 177-179° (from alcohol). Found %: C 60.9, 61.1; H 7.4, 7.5; N 16.4, 16.8; Cl 10.3, 10.7. $C_{17}H_{24}N_4O \cdot HCl$. Calculated %: C 60.6; H 7.5; N 16.7; Cl 10.5. The filtrate and mother liquors from piperidone VII were distilled to obtain 5.6 g of the starting liquid piperidone III with bp 127° (1 mm) and n_D^{20} 1.4790 and 6.3 g (32%) of 1,2,5-trimethyl-3,5-bis(β-cyanoethyl)-4-piperidone (V) with bp 195° (2 mm), n_D^{20} 1.4900, and d_4^{20} 1.057. Found %: C 67.5, 67.8; H 8.3, 8.7; N 17.5, 17.2; MR_D 67.64. $C_{14}H_{21}N_3O$. Calculated %: C 68.0; H 8.6; N 17.0; MR_D 68.24. The hydrochloride was an uncrystallizable oil. Found %: N 14.6, 14.3. $C_{14}H_{21}N_3O \cdot HCl$. Calculated %: N 14.8.

Isomeric 1,2,5-Trimethyl-5-(β-carboxyethyl)-4-piperidones (VIII). A. A mixture of 7.7 g of the crystalline isomer of 1,2,5-trimethyl-5-(β-cyanoethyl)-4-piperidone (III) and 32 ml of concentrated hydrochloric acid was heated at 95° for 20 h. The resulting precipitate of ammonium chloride was filtered, the aqueous solution was evaporated, and the residue was recrystallized from alcohol to give 8.5 g (85%) of the hydrochloride of piperidone VIII with mp 159-160°. Found %: N 5.7, 5.7. $C_{11}H_{19}NO_3 \cdot HCl$. Calculated %: N 5.6.

B. Under similar conditions, 6.1 g (61%) of the hydrochloride of piperidone VIII with mp 188-190° (from alcohol) was obtained from 7.7 g of the liquid isomer. Found %: N 5.6, 5.5; Cl 14.2, 14.4. $C_{11}H_{19}NO_3 \cdot HCl$. Calculated %: N 5.6; Cl 14.2.

Isomeric 1-(γ-Chlorocrotyl)-2,5-dimethyl-5-(β-carboxyethyl)-4-piperidones (IX). A. A mixture of 2.7 g of the crystalline isomer of 1-(γ-chlorocrotyl)-2,5-dimethyl-5-(β-cyanoethyl)-4-piperidone (IV) and 3 ml of concentrated hydrochloric acid was heated at 95° for 15 h. The precipitated ammonium chloride was filtered, the aqueous solution was evaporated, and the residue was dissolved in dry acetone and precipitated with absolute ether to obtain 2.8 g (87%) of the hydrochloride of piperidone IX as a hygroscopic powder. Found %: N 4.2, 4.0; Cl 11.1, 11.0. $C_{14}H_{22}NO_3Cl$. Calculated %: N 4.3; Cl 10.9.

B. Under similar conditions, 2.9 g (90%) of the hydrochloride of piperidone IX was obtained as a hygroscopic powder from 2.7 g of the liquid isomer. Found %: N 4.0, 4.1; Cl 10.6, 10.9. $C_{14}H_{22}NO_3Cl \cdot HCl$. Calculated %: N 4.3; Cl 10.9.

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