CYANOETHYLATION OF 2,5-DIMETHYLTETRAHYDRO-4-THIOPYRANONE ISOMERS AND SELECTIVE REDUCTION OF 2,5-DIMETHYL-5-(β-CYANOETHYL)TETRAHYDRO-4-THIOPYRANONE AND -4-PIPERIDONE

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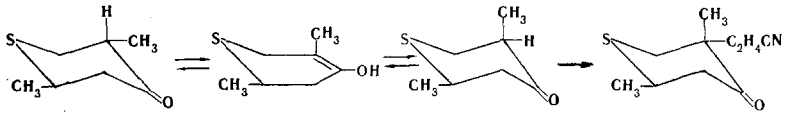
It has been found that only the cis isomer (liquid) of 2,5-dimethyltetrahydro-4-thiopyranone is cyanoethylated under the usual conditions. 2,5-Dimethyl-5-(β-carboxyethyl)tetrahydro-4-thiopyranone was synthesized by the acid hydrolysis of 2,5-dimethyl-5-(β-cyanoethyl)-tetrahydro-4-thiopyranone. The selective reduction with aluminum isopropoxide of 2,5-dimethyl-5-(β-cyanoethyl)tetrahydro-4-thiopyranone and of the individual isomers of 2,5-dimethyl-5-(β-cyanoethyl)-4-piperidone gave the isomeric 2,5-dimethyl-5-(β-cyanoethyl)-tetrahydro-4-thiopyranols and -4-piperidols. The reaction of the isomeric 5-cyanoethyl-4-piperidols with allyl bromide gave the corresponding 1-allyl-2,5-dimethyl-5(β-cyanoethyl)-4-piperidols.

The cyanoethylation of diverse aliphatic and cyclic ketones has been studied quite thoroughly [1]. However, there are no papers in the literature devoted to the study of the cyanoethylation of the stereoisomers of cyclic ketones.

We have carried out the cyanoethylation of the pure cis and trans isomers (liquid and crystalline) of 2,5-dimethyltetrahydro-4-thiopyranone (I) [2] by the reaction of I and acrylonitrile in equimolecular ratios in the presence of potassium hydroxide. At 20°C, the cis isomer (cis-I) gave 2e,5a-dimethyl-5e-(β-cyanoethyl)tetrahydro-4-thiopyranone (II) in 30% yield, while the trans isomer (trans-I) gave the same compound (II) in very low yield (4%). The yield of II increases to 43% when the temperature of the cyanoethylation reaction of trans-I is raised to 35-40°. This fact attests to the difficulty involved in the cyanoethylation of trans-I and its prior isomerization to cis-I, which is confirmed by the results of the isomerization of trans-I at 35-40° in the presence of potassium hydroxide. Acid hydrolysis of 5-cyanoethyltetrahydro-4-thiopyranone (II) converts it to 2,5-dimethyl-5-(β-carboxyethyl)tetrahydro-4-thiopyranone.



trans-I cis-I II

The reduction of the cis isomer of 2,5-dimethyl-5-(β-cyanoethyl)tetrahydro-4-thiopyranone (II) and the previously obtained crystalline and liquid isomers of 2,5-dimethyl-5-(β-cyanoethyl)-4-piperidone (III) [3] with aluminum isopropoxide, which is a specific reducing agent for the ketone group [4], gave two individual 2,5-dimethyl-5-(β-cyanoethyl)tetrahydro-4-thiopyranols (IVα,β) from the cis isomer of II, two individual crystalline 2,5-dimethyl-5-(β-cyanoethyl)-4-piperidols (Vα,β) from the crystalline isomer of III, and a liquid piperidol (Vγ) from the liquid isomer of III. The corresponding 1-allyl-2,5-dimethyl-5-(β-cyanoethyl)-4-piperidols (VIα-γ) were synthesized by the action of allyl bromide on the isomeric 5-cyanoethyl-4-piperidols (Vα-γ).

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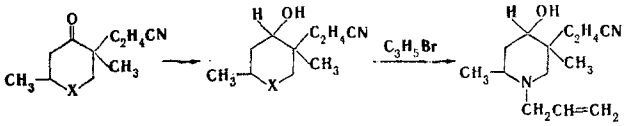

II, III IV α, β; V α-γ VI α-γ

II, IV X=S; III, V X=NH

The composition and structures of the tetrahydrothiopyranols and piperidols obtained (IV-VI) were confirmed by elementary analysis, determination of the molecular refractions (for the liquids), and the IR spectra, in which there are absorption bands in the region of the stretching vibrations of the nitrile (2240-2248 cm^{-1}) and hydroxyl (3627-3640 cm^{-1}) groups, and none in the region of the stretching vibrations of the ketone group [5, 6].

EXPERIMENTAL

2,5-Dimethyl-5-(β-cyanoethyl)tetrahydro-4-thiopyranone (II). A solution of 2.65 g (0.05 mole) of acrylonitrile in 10 ml of ether was slowly added dropwise with stirring at 20° to a mixture of 7.2 g (0.05 mole) of the liquid isomer of 2,5-dimethyltetrahydro-4-thiopyranone (cis-I) (n_D^{20} 1.5040) and 0.14 g of powdered potassium hydroxide in 20 ml of absolute ether, and the mixture was stirred at 20° for 5 h. The following day, the ether was removed by distillation, and the residue was distilled to give 4.3 g of I and 3 g (30%) of II with bp 165-170° (2 mm), n_D^{20} 1.5150, and d_4^{20} 1.095. Found: C 61.1; H 7.8, S 16.0%; MR_D 54.25. $C_{10}H_{15}NOS$. Calculated: C 60.9; H 7.7; S 16.3%; MR_D 54.01.

Under the same conditions, only 4.3% of II was obtained from the crystalline isomer of 2,5-dimethyltetrahydro-4-thiopyranone (trans-I), and 90% of unchanged trans-I was isolated. After 5 h at 35-40°, 43% of II was obtained, and 39% of the starting trans-I was isolated.

Isomerization of the trans Isomer of 2,5-Dimethyltetrahydro-4-thiopyranone (trans-I). A mixture of 2.7 g of trans-I and 0.05 g of powdered potassium hydroxide in 20 ml of absolute ether was heated with stirring at 35-40° for 6 h. The next day, the ether solution was evaporated, and the residue partially crystallized. Recrystallization from petroleum ether gave 1.9 g (70%) of trans-I with mp 70-71°. The mother liquor yielded 0.6 g (22%) of cis-I with n_D^{20} 1.5050.

2,5-Dimethyl-5-(β-carboxyethyl)tetrahydro-4-thiopyranone. A 1 g sample of II in 4 ml of concentrated HCl was heated at 95° for 15 h. The precipitated oily product was separated from the ammonium chloride and water and recrystallized from ligroin (80-100°) to give 0.85 g (78%) of 2,5-dimethyl-5-(β-carboxyethyl)tetrahydro-4-thiopyranone with mp 96-97°. Found: C 55.6; H 7.2; S 14.6%. $C_{10}H_{16}O_3S$. Calculated: C 55.5; H 7.5; S 14.8%.

2,5-Dimethyl-5-(β-cyanoethyl)tetrahydro-4-thiopyranols (IVα,β). A mixture of 6 g (0.03 mole) of II and 6.1 g (0.03 mole) of aluminum isopropoxide in 50 ml of isopropyl alcohol was heated at 60-70° with simultaneous slow distillation of the acetone that formed. The isopropyl alcohol was then removed by distillation, and the residue was cooled and hydrolyzed with dilute hydrochloric acid (1:5) until the mixture was acid to Congo. The aqueous solution was evaporated, and the residue was extracted with ether. The ether extracts were dried and distilled to give two fractions. The first fraction [1 g (16%)] was the α-isomer of 2,5-dimethyl-5-(β-cyanoethyl)tetrahydro-4-thiopyranol (IVα) with bp 184° (1 mm), n_D^{20} 1.5210, and d_4^{20} 1.103. Found: C 60.1; H 9.1; S 15.7%. MR_D 55.03. $C_{10}H_{17}NOS$. Calculated: C 60.3; H 8.6; S 16.1%; MR_D 55.52. The second fraction [4.3 g (72%)] was the β-isomer (IVβ) with bp 188° (1 mm), n_D^{20} 1.5250, and d_4^{20} 1.107. Found: C 60.1; H 9.1; S 15.7%; MR_D 55.17. $C_{10}H_{17}NOS$. Calculated: C 60.3; H 8.6; S 16.1%; MR_D 55.52.

2,5-Dimethyl-5-(β-cyanoethyl)-4-piperidols (Vα-γ). Under the conditions described above, 11 g (85%) of a mixture of isomers of V with bp 165-170° (1 mm) and n_D^{20} 1.5030 was obtained from 12.8 g (0.07 mole) of the crystalline isomer of 2,5-dimethyl-5-(β-cyanoethyl)-4-piperidone (III) and 14.2 g (0.07 mole) of aluminum isopropoxide in 100 ml of isopropyl alcohol. The mixture of isomers of V crystallized when it was triturated in ether. The isomers were separated by treatment of the mixture with hot benzene, and the insoluble portion was crystallized from acetone to give 2.2 g (20% of the total amount of isomer mixture) of Vα with mp 137-138° (from acetone). Found: N 14.8%. $C_{10}H_{18}N_2O$. Calculated: N 15.4%. The hydrochloride of V had mp 212-213° (from alcohol). Found: C 53.3; H 8.2; Cl 15.7%. $C_{10}H_{18}N_2O \cdot HCl$. Cal-

culated: C 53.6; H 8.1; Cl 15.9%. Compound Vβ [4.7 g (43% of the total amount of the isomer mixture)] had mp 108-109° (from benzene–acetone). Found: C 65.8; H 10.4; N 14.9%. $C_{10}H_{18}N_2O$. Calculated: C 65.9; H 10.0; N 15.4%. The hydrochloride of Vβ had mp 201-202° (from alcohol). Found: C 53.9; H 8.6; Cl 16.1%. $C_{10}H_{18}N_2O \cdot HCl$. Calculated: C 53.6; H 8.1; Cl 15.9%.

A total of 2.5 g (66%) of Vγ was similarly obtained as a very viscous, uncrystallizable oil with bp 155-156° (1 mm) and n_D^{20} 1.5050 from 3.7 g (0.02 mole) of the liquid isomer of III by reduction with 6.1 g (0.03 mole) of aluminum isopropoxide. Found: N 15.6%. $C_{10}H_{18}N_2O$. Calculated: N 15.4%. The hydrochloride of VIIIγ did not crystallize.

1-Allyl-2,5-dimethyl-5-(β-cyanoethyl)-4-piperidols (VIα-γ). A mixture of 1.8 g (0.01 mole) of any isomer of V, 3.5 g of anhydrous potassium carbonate, and 1.2 g (0.01 mole) of allyl bromide in 50 ml of dry acetone was heated with stirring at 60° for 7 h. The acetone was removed by distillation, and the residue was distilled to isolate the corresponding isomer of VI. Isomer VIα [1.7 g (77%)] had bp 160° (2 mm), n_D^{20} 1.4910, and d_4^{20} 0.9986. Found: N 12.9%; MR_D 64.48. $C_{13}H_{22}N_2O$. Calculated: N 12.6%; MR_D 64.85. The hydrochloride of VIα had mp 182-183° (from alcohol). Found: C 60.7; H 9.0; Cl 14.0%. $C_{13}H_{22}N_2O \cdot HCl$. Calculated: C 60.3; H 9.0; Cl 13.7%. Isomer VIβ [1.9 g (86%)] had bp 165° (2 mm), n_D^{20} 1.4990, and d_4^{20} 1.009. Found: N 12.6%; MR_D 64.71. $C_{13}H_{22}N_2O$. Calculated: N 12.6%; MR_D 64.85. The hydrochloride of VIβ had mp 195-196° (from alcohol). Found: C 60.6; H 8.8; Cl 14.0%. $C_{13}N_{22}N_2O \cdot HCl$. Calculated: C 60.3; H 9.0; Cl 13.7%. Isomer VIγ [1.5 g (70%)] had bp 146° (1 mm), n_D^{20} 1.4980, and d_4^{20} 1.010. Found: N 12.1%; MR_D 64.52. $C_{13}H_{22}N_2O$. Calculated: N 12.6%; MR_D 64.85. The hydrochloride of VIγ was an uncrystallizable liquid.

The IR spectra of CCl_4 solutions (10^{-4} M, d 0.5 cm) were recorded with a UR-20 spectrometer.

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