DIASTEREOISOMERIC 1,2,5-TRIMETHYL-4-m-TOLYLPIPERIDIN-4-OLS AND 2,5-DIMETHYL-4-m-TOLYLPYRIDINE

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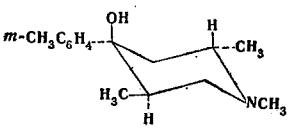
The preparation of 1,2,5-trimethyl-4-m-tolypiperidin-4-ol and the isolation of three of its diastereoisomers are described. The passage from this piperidinol to 2,5-dimethyl-4-m-tolylpyridine has been effected. Some derivatives of the latter compound have been obtained.

Continuing work on the synthesis and the study of the structure of tertiary γ-piperidinols, analogs of 1,2,5-trimethyl-4-phenylpiperidin-4-ol, the propionate of which is an effective anaesthetic ("promedol") [1], we turned to the preparation of the previously undescribed 1,2,5-trimethyl-4-m-tolylpiperidin-4-ol (II). It was obtained by the usual method from 1,2,5-trimethylpiperidin-4-one (I) and m-tolyllithium with a yield of more than 70% in the form of a mixture of diastereoisomers.

By multistage crystallization we isolated three individual diastereoisomers of the piperidinol II, designated as follows: α isomer (mp 106-107°C), β isomer (mp 116-116.5°C), and γ isomer (mp 103-104°C). These symbols are connected with those for the stereoisomeric α-, β-, and γ-1,2,5-trimethyl-4-phenylpiperidin-4-ols, the structure of which has been studied previously [2, 3].

To answer the question of the spatial structure of the isomers II, we used chromatographic analysis and their behavior in acylation reactions. These results were compared with the analogous characteristics for the isomeric 1,2,5-trimethyl-4-phenylpiperidin-4-ols.

In the organolithium synthesis, the γ isomer of the piperidinol II is formed in predominating amount; it has the highest chromatographic mobility (R_f 0.34). The treatment of this isomer of the piperidinol II with propionyl chloride in benzene forms the hydrochloride of its propionate. The γ-isomer of 1,2,5-trimethyl-4-phenylpiperidine-4-ol has the same (comparatively) chromatographic mobility and similar behavior in the acylation reaction. In the latter, the methyl groups at C_2 and C_5 occupy the trans-equatorial position and the hydroxy group at C_4 the axial position. In view of these facts, the γ isomer of the piperidinol II may be ascribed the structure of 1,2e,5e-trimethyl-4e-m-tolylpiperidin-4-ol.



The α isomer of the piperidinol (II) has the lowest chromatographic mobility (R_f 0.18). Its treatment with proionyl chloride in benzene leads to the precipitation of the hydrochloride of this piperidinol, and the hy-

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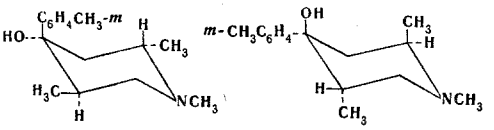
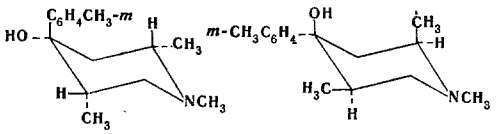
drochloride of propionate can be isolated from the benzene solution. The α isomer of 1,2,5-trimethyl-4-phenylpiperidin-4-ol, which belongs to the same trans-dimethyl (C_2 and C_5) piperidine system with the cis position of the aryl radical at C_4 and the methyl group at C_5, possesses similar properties. Consequently, the α isomer of the piperidinol II may be ascribed the structure of 1,2e-5e-trimethyl-4a-tolylpiperidin-4e-ol or 1,2a,5a-trimethyl-4e-m-tolylpiperidin-4a-ol.



The β isomer of the piperidinol II differs only slightly in its chromatographic mobility (R_f 0.31) from the γ isomer. Acylation forms mainly its ester. This isomer of the piperidinol II probably has the structure of 1,2e,5a-trimethyl-4a-m-tolypiperidin-4e-ol or its conversion form – 1,2a,5e-trimethyl-4e-m-tolypiperidin-4a-ol, like the β isomer of 1,2,5-trimethyl-4-phenylpiperidin-4-ol.



The chromatographic separation of artificially prepared mixtures of the α and γ and the α and β isomers of the piperidinol II takes place clearly. But this is not the case for the γ and β isomers. In this respect, also, the isomeric piperidinols II are analogous to the isomeric 1,2,5-trimethyl-4-phenylpiperidin-4-ols.

Steric factors proved to have a considerable influence on the yield of the α, β, and γ isomers of the piperidinol II in its synthesis from the piperidone I and m-tolyllithium. If it is considered that the initial piperidine I is represented mainly by the configuration with the trans-equatorial position of the methyl groups at C_2 and C_5, the entry of the m-tolyl radical from the spatially less hindered side, i.e., from the peripheral side of the ring, is more probable. The greater yield of the γ isomer of II and of the α and β isomers may also serve as an argument in favour of the structures ascribed to them above.

In view of the structural similarity of the piperidinol II and of 1,2,5-trimethyl-4-phenylpiperidin-4-ol, the following remarks must be made. In a paper by A. F. Casy [4], the configuration and conformation of the hydrochloride of the propionates of the α, β, and γ isomers of 1,2,5-trimethyl-4-phenylpiperidin-4-ol, which we studied previously [2, 3], are considered (provisionally). Conclusions drawn in this paper on the configurations of the esters of all three isomers and on the conformation of the γ isomer are in full harmony with ours. Some apparent contradiction exists concerning the conformation of the α and β isomers. We must first bear in mind the fact that we are speaking of the conformation of piperidinols, and in the paper cited it is the conformation of the hydrochlorides of esters of these piperidinols that is discussed. Furtheremore, in view of the lability of the conformers of compounds of the type under consideration the experimental conditions under which their conformations were studied must be considered.

In Casy's paper [4], a conformation with an equatorial phenyl group at C_4 was proposed for the ester of the β isomer of 1,2,5-trimethyl-4-phenylpiperidin-4-ol. Above, we have put forward two conversion formulas for the β isomers of the piperidinol II (as for its phenyl analog), stating that the conformation with the equatorial aryl radical is, likewise, the more probable. In view of the close values of the chromatographic mobilities of the β and γ isomers, it may be assumed that in these isomers the hydroxy groups occupy analogous positions, i.e., they are axial.

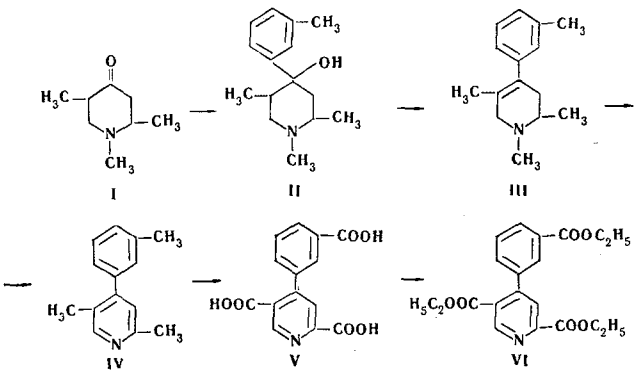
The α isomer of 1,2,5-trimethyl-4-phenylpiperidin-4-yl propionate was ascribed a conformation with an equatorial phenyl group by Casy [4]. For the piperidinol II (as for the phenyl analog), while adopting the same configuration as Casy, we have given two conformational formulas. But it must apparently be considered that under the conditions of chromatography the α isomers of the piperidinols are represented by conformations with axial aryl radicals, and, consequently, an equatorial hydroxy group. This is shown by their considerable lower chromatographic mobility as compared with the β and γ isomers in which the hydroxy groups are axial.

TABLE 1. Assignment of the Bands in the IR Spectra of the Diastereoisomers of 1,2,5-Trimethyl-4-m-tolylpiperidin-4-ol

Nature of the vibrations	ν, cm^{-1}			
	α-	β-	γ-	literature data [5]
Stretching vibrations of an OH group participating in an intermolecular hydrogen bond of the polymer type	3230	3200 (strong broad band)	3200	3400-3200
Stretching vibrations of the benzene ring	1608m	1608m	1607m	1600-1580
	1497m	1500 (shoulder)	1545w 1495w	1500-1450
Nonplanar deformation vibrations of isolated aromatic CH bonds	855w	855w	855w	900-860
Nonplanar deformation vibrations of three adjacent aromatic CH bonds	793s	797s	794s	810-750s
	784s	782s	770m	725-680m
	756s	725m	728s	
	726s			

Table 1 gives features of the IR spectra of the α, β, and γ isomers of the piperidinol II which characterize their structures [5]. A comparison of the IR spectra in the "fingerprint" region of 1300-900 cm^{-1} confirms the chromatographic information on the individuality of these isomers.

Using a method developed in our laboratory [6], 1,2,5-trimethyl-4-m-tolylpiperidin-4-ol (II) was converted into 2,5-dimethyl-4-m-tolylpyridine (IV).



The dehydration of the piperidinol II by means of hydrochloric or sulfuric acid gave a yield of about 90% of 1,2,5-trimethyl-4-m-tolyltetrahydropyridine (III) (the position of the double bond is shown provisionally). By catalytic dehydrogenation and N-demethylation on a type K-16 industrial catalyst, the III was converted into the pyridine base IV.

2,5-Dimethyl-4-m-tolylpyridine was oxidized to the corresponding tribasic acid – 4-m-carboxyphenylpyridine-2,5-dicarboxylic acid (V) – the esterification of which yielded its ethyl ester VI.

EXPERIMENTAL

1,2,5-Trimethyl-4-m-tolylpiperidin-4-ol (II). At 0°C, 77 g (550 mmoles) of 1,2,5-trimethylpiperidin-4-one (I) was added to the m-tolyllithium prepared from 10 g (1.43 g-atom) of lithium and 122 g (715 mmoles) of m-bromotoluene in 300 ml of absolute ether. The mixture was stirred at room temperature for 3 h and at the boiling point of the ether for 1 h. Then, with cooling, 100 ml of water and 100 ml of 18% hydrochloric acid were added, followed by concentrated hydrochloric acid to give an acid reaction to Congo Red. The aqueous layer was made alkaline with caustic potash, and the organic bases were extracted with ether. Dis-

tillation yielded 105.8 g of a mixture of the diastereoisomeric piperidinols II in the form of a very viscous liquid with bp 141-145°C (1 mm), the crystallization of which (from n-heptane) yielded 93.5 g (73.5%) of crystals of II. The stepwise crystallization of these crystals from n-heptane yielded the three individual diastereoisomers of II (described in order of isolation). The chromatographic characteristics were obtained on alumina of activity grade II using ether–hexane (1:1).

The γ Isomer of II. 51.3 g (89.2%), mp 103-104°C, R_f 0.34. Found, %: C 77.03; 76.97; H 9.67; 9.70; N 6.03; 5.69. $C_{15}H_{23}NO$. Calculated, %: C 77.25; H 9.87; N 6.00. Hydrochloride: mp 164-165°C (from methanol–ethyl acetate). Found, %: N 5.25; 5.35; Cl 13.14; 12.97. $C_{15}H_{23}NO \cdot HCl$. Calculated, %: N 5.19; Cl 13.17.

The β Isomer of II. 5 g (8.6%), mp 116-116.5°C, R_f 0.31. Found, %: C 77.23; 77.05; H 9.71; 9.84; N 6.09; 5.82.

The α Isomer of II. 1.5 g (2.2%), mp 106-107°C, R_f 0.18. Found, %: C 77.12; 77.16; H 9.83; 10.04; N 5.89; 6.07. Hydrochloride: mp 182-184°C (from methanol–ethyl acetate). Found, %: N 4.96; 5.00; Cl 13.07; 13.03.

35.75 g (38.2%) of crystals of a mixture of the diastereoisomers of II was left. Mixtures of the isomeric piperidinols had the following mp's: γ and β 80-83°C, γ and α 76-78°C, β and α 89-91°C.

When II was synthesized by the Grignard method using m-tolylmagnesium bromide, a mixture of the same three stereoisomers of II (according to thin-layer chromatography) was obtained with a yield of 79.8% on the I that had reached and 21% on the amount taken initially.

1,2,5-Trimethyl-4-propionyloxy-4-m-tolylpiperidine. a) A mixture of 2 g (8.6 mmoles) of the γ isomer of the piperidinol II and 0.95 g (10 mmoles) of propionylchloride in 20 ml of benzene was heated at a gentle boil for 2 h, and then the benzene was distilled off. After drying and repeated trituration with ether, 2.82 g of solid residue was obtained from which 0.01 g of the hydrochloride of the propionate of the γ isomer of the piperidinol II, bp 188-190°C (from methanol–ethyl acetate) was obtained. Found, %: N 4.19. $C_{18}H_{27}NO_2 \cdot HCl$. Calculated, %: N 4.30. A chromatographic analysis [Al_2O_3 of activity grade II, ether–hexane (1:1)] of the substances isolated from the alkaline solution (free bases) showed that they consist of approximately equal amounts of the initial piperidinol (R_f 0.30) and its propionate (R_f 0.55).

b) The reaction was performed with 1.5 g (6.4 mmoles) of the β isomer of the piperidinol II, 0.72 g (7.8 mmoles) of propionyl chloride, and 15 ml of benzene. The mixture was heated for 2 h, and the precipitate was separated off. This gave 1.3 g (62.2%) of the hydrochloride of the propionate of the β isomer of the piperidinol II with mp 177-178°C (from methanol–ethyl acetate). Found, %: N 4.31; 4.09; Cl 10.49; 10.53. $C_{18}H_{27}NO_2 \cdot HCl$. Calculated, %: N 4.30; Cl 10.90. The free base from the propionate had R_f 0.62 (in the same system). The mother solution remaining after the isolation of the hydrochloride of the propionate contained a small amount of the initial alcohol (according to chromatographic analysis).

c) A mixture of 0.5 g of the α isomer of the piperidinol II and 0.25 g of propionyl chloride in 15 ml of benzene was heated for 2 h. The crystals formed at the beginning of the experiment (0.12 g) consisted of the hydrochloride of the initial piperidinol, mp 185-186°C (no depression of the melting point in a mixture with an authentic sample). The benzene filtrate was evaporated. From the residue (0.44 g), 0.06 g of the hydrochloride of the propionate of the α isomer of the piperidinol II was obtained with mp 193-195°C (from methanol–ethyl acetate); a mixture with the piperidinol hydrochloride melted with considerable depression (106-116°C). The mother solution contained the hydrochloride of the initial piperidinol. The free base from the propionate had R_f 0.72 (same system).

In mixture of the hydrochlorides of the propionates of the various isomers of the piperidinol II, considerable depressions of the melting points were observed (the samples melted in the range from 105 to 120°C).

1,2,5-Trimethyl-4-m-tolyltetrahydropyridine (III). a) A mixture of 97.6 g (419 mmoles) of the piperidinol II (mixture of isomers) and 400 ml of concentrated hydrochloric acid was boiled for 8 h. Then the acid was distilled off, and the residue was diluted with water, saturated with sodium carbonate, and heated for 1 h. The organic bases were extracted with ether and the extract was dried and distilled. This gave 81.5 g (91.5%) of III, bp 131-132°C (3 mm); n_D^{20} 1.5426; d_4^{20} 0.962. Found, %: C 83.59; 83.67; H 9.91; 9.75; N 6.59; 6.29. MR_D 70.41. $C_{15}H_{21}N$. Calculated, %: C 83.72; H 9.77; N 6.51. MR_D 69.55. Methiodide: mp 180-181°C (from a mixture of methanol and ethylacetate). Found, %: N 3.75; 3.67. $C_{16}H_{24}IN$. Calculated, %: N 3.92.

b) A mixture of 73.8 g (321 mmoles) of the piperidinol II (mixture of isomers) and 97.2 g of 80% sulfuric acid was heated at 100°C for 4 h. The reaction mixture was treated with 500 ml of water, saturated with sodium carbonate, and heated at 100°C for an hour. Then the organic bases were isolated in the usual way. This gave 50.8 g (75%) of III, bp 119-121°C (2 mm); n_D^{22} 1.5435.

2,5-Dimethyl-4-m-tolylpyridine (IV). A solution of 37 g (170 mmoles) of III in 100 ml of benzene was passed at a constant rate over type K-16 catalyst for 3 h 30 min. The temperature in the catalyst zone was 380-390°C; 8.8 liters of gas (20°C, 746 mm; C_nH_{2n+2} 43%, H_2 42%) was collected. The condensate was dried with granulated caustic potash. On distillation, 28 g of a fraction with bp 138-146°C (5 mm) was collected, and this was crystallized from petroleum ether (bp 40-60°C). The piperidine IV formed colorless crystals with mp 40-41°C. Found, %: C 85.12; 85.29; H 7.69; 7.83; N 6.84; 6.82. $C_{14}H_{15}N$. Calculated, %: C 85.28; H 7.61; N 7.10. Picrate: mp 167-168°C (from ethanol). Found, %: N 13.09; 13.19. $C_{14}H_{15}N \cdot C_6H_3N_3O_7$. Calculated, %: N 13.14.

4-m-Carboxyphenylpyridine-2,5-dicarboxylic acid (IV). 48.12 g (306 mmoles) of potassium permanganate was added in portions to 10 g (51 mmoles) of IV in 350 ml of water at 100°C. The manganese dioxide was filtered from the hot reaction mixture, and it was then washed repeatedly with hot water and with ether. The aqueous layer was also extracted with ether. The ethereal extract yielded 0.67 g of the initial IV (picrate: mp 164-166°C). The aqueous solution was evaporated to 100 ml and treated with dilute (1:1) sulfuric acid to neutrality. This yielded 9.4 g (64%) of V in the form of colorless crystals with mp 270-271°C (from aqueous ethanol). Found, %: C 58.96; 58.65; H 3.30; 3.53; N 4.90; 4.75. $C_{14}H_9NO_6$. Calculated, %: C 58.53; H 3.14; N 4.87.

A mixture of 6 g (21 mmoles) of V, 54 ml of absolute ethanol, and 48 ml of concentrated sulfuric acid was boiled for 4 h. After the ethanol had been distilled off, the residue was treated with 30 ml of water and 50 ml of ether, and then sodium carbonate was added until the acid had been neutralized. The residue (4.7 g) obtained after the evaporation of the ethereal extract was crystallized from gasoline. This gave 3.45 g (44.5%) of 2,5-diethoxycarbonyl-4-m-ethoxycarbonylphenylpyridine (VI) in the form of colorless crystals with mp 62-63°C. Found, %: C 64.76; 64.93; H 5.31; 5.56; N 3.78; 3.50. $C_{20}H_{21}NO_6$. Calculated, %: C 64.69; H 5.65; N 3.77.

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