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1, 2, 5-TRIMETHYL-4-PHENYLETHYNYLPIPERIDOL-4 AND ITS REACTIONS

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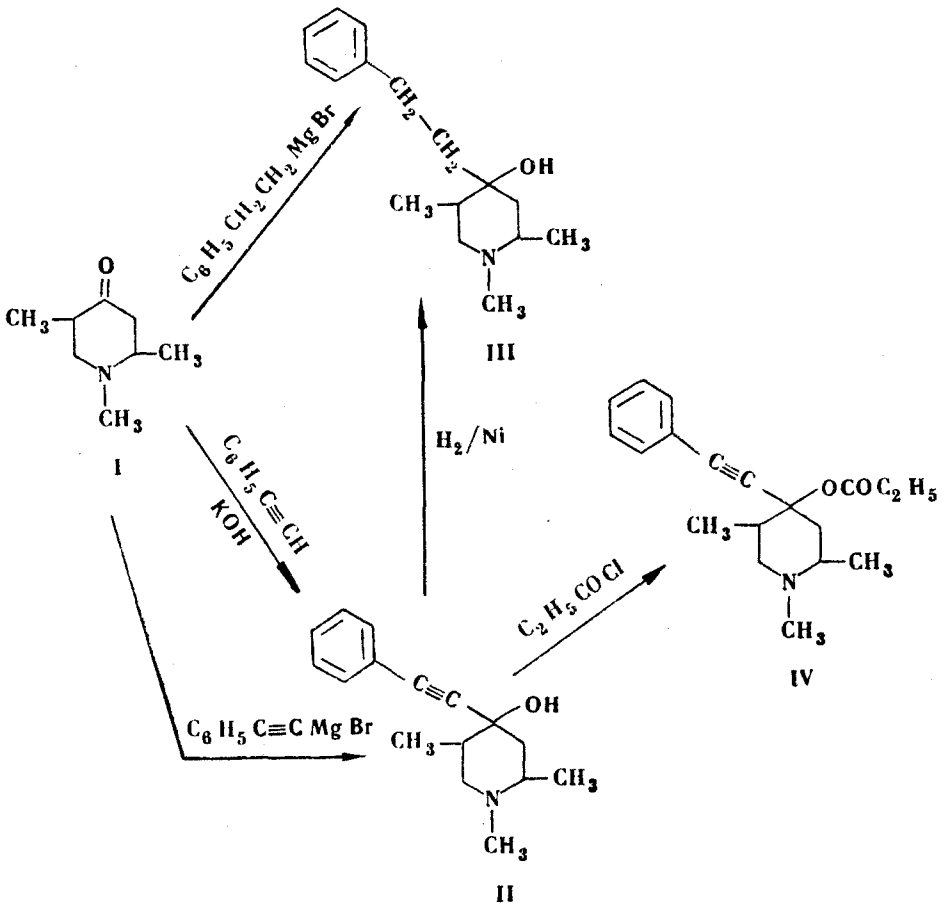
1, 2, 5-Trimethyl-4-phenylethynylpiperidol-4 and 1,2,5-trimethyl-4-β-phenylethynylpiperidol-4 are prepared by various methods. Their interconversion is studied, and individual stereoisomeric forms of these piperidols isolated. 1, 2, 5-Trimethyl-4-phenylethynylpiperidol-4 is hydrated, and the resultant ω-(1,' 2', 5'-trimethyldidehydropiperidyl-4') acetophenone used to effect synthesis of a number of secondary and tertiary carbinols. 2, 5-Dimethyl-4-β-phenylethylpyridine is prepared from 1, 2, 5-trimethyl-4-β-phenylethylpiperidol-4.

Many tertiary amino alcohols containing aromatic and aliphatic groups, are highly active physiologically. In particular, they include effective spasmolytics, and compounds with a tranquilizing action on the central nervous system. Continuing work on preparing various piperidine and pyridine derivatives, the authors turned to synthesizing some tertiary amino alcohols containing these ring systems.

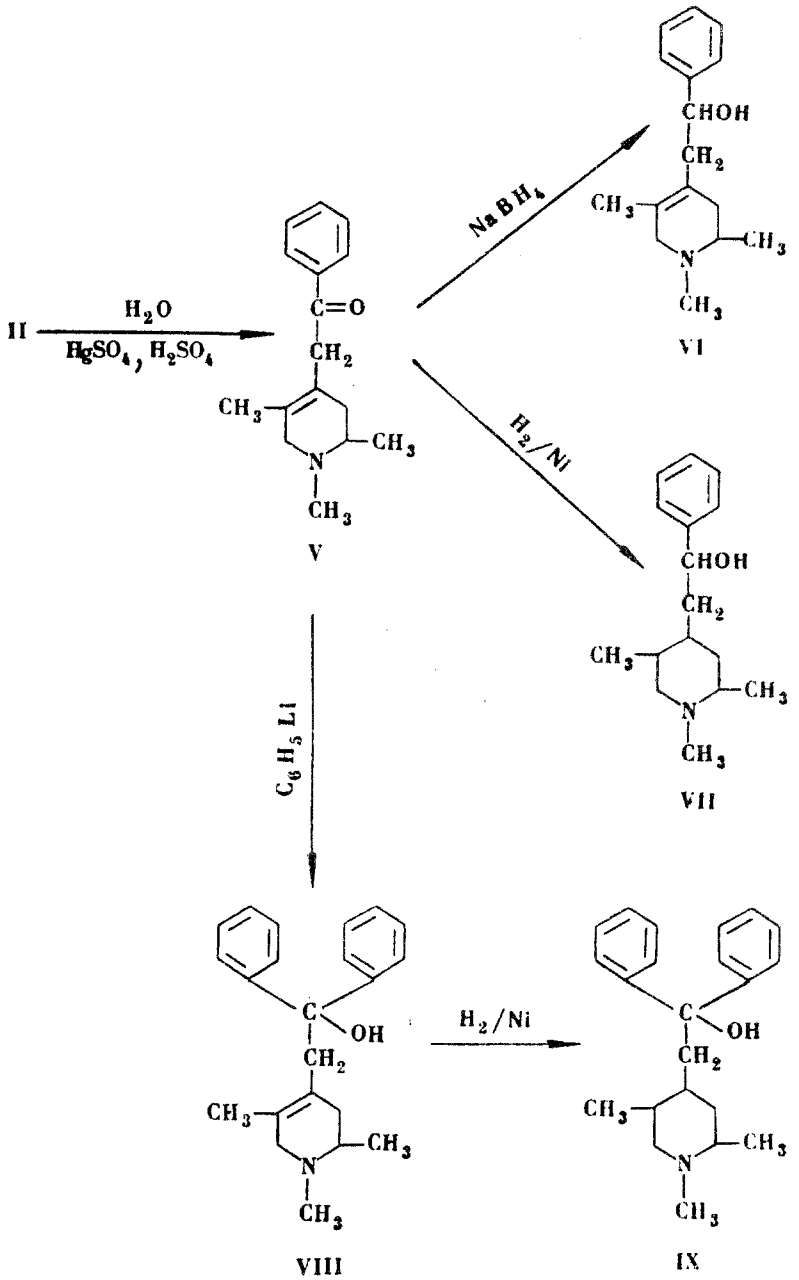
The starting compound used was 1, 2, 5-trimethylpiperidone-4 (I) [1]. Condensation of that ketone with phenylacetylene in the presence of potassium hydroxide gave a mixture of isomeric 1, 2, 5-trimethyl-4-phenylethynylpiperidols-4 (II) [2], from which two isomers of the piperidol II, having melting points 136-139.5° and 101-103°, were isolated by chromatography on alumina. The mixed isomeric piperidols II were also prepared by reacting the piperidone I with phenylacetylene magnesium bromide. Complete hydrogenation of the triple bond of these stereoisomeric piperidols led to the isolation of two isomeric 1, 2, 5-trimethyl-4-β-phenylethylpiperidols-4 (III), melting points 122-123° and 88-91°. The last of these isomeric piperidols III was obtained in low yield (3.5%) by reacting 1, 2, 5-trimethylpiperidone-4 (I) with β-phenylethylmagnesium bromide. The piperidol II and propionyl chloride gave 1, 2, 5-trimethyl-4-phenylethynyl-4-propionoxypiperidine (IV), which is a structural analog of the known analgesic promedol [3]:



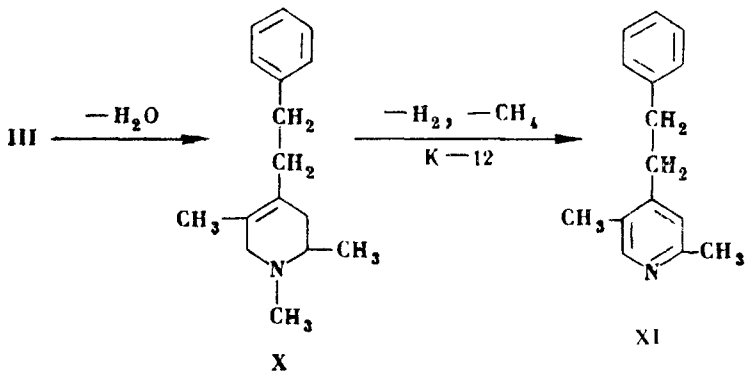
Further 1, 2, 5-trimethyl-4-phenylethynylpiperidol-4 (II) has been hydrated with 47% sulfuric acid and the sulfate of mercuric oxide. Under these conditions triple bond hydration was accompanied by dehydration to give ω-(1', 2', 5'-

trimethyldidehydropiperidyl-4') acetophenone (V). From spectrum characteristics it can be assumed that the carbonyl group in that compound is conjugated with the phenyl group. It would also be expected that under the hydration reaction conditions for compound II, an acetylene-allene rearrangement will occur, leading to formation of ω-(1', 2', 5'-trimethylpiperidylidene-4') acetophenone. To test this hypothesis, on the one hand 1, 2, 5-trimethyl-4-phenylethynylpiperidol-4 was treated with mixed glacial acetic acid – sulfuric acid (50-60°), and on the other with 5% sulfuric acid plus mercuric sulfate (80-85°), i.e., conditions suitable for the acetylene-allene transformation were brought about. However, in both cases the piperidol II was recovered unchanged. Reduction of ketone V with sodium borohydride, i.e., under conditions preserving the double bond, led to isolation of 1-phenyl-2-(1', 2', 5'-trimethyldidehydropiperidyl-4') ethanol-1 (VI), while catalytic hydrogenation gave 1-phenyl-2-(1', 2', 5'-trimethylpiperidyl-4') ethanol-1 (VII).

Treatment of ketone V with phenyllithium led to isolation of 1, 1-diphenyl-2-(1', 2', 5-trimethyldidehydropiperidyl-4') ethanol-1 (VIII), hydrogenation of the double bond of which gave 1, 1-diphenyl-2-(1', 2', 5'-trimethylpiperidyl-4') ethanol-1 (IX).



The piperidol III was used to synthesize 2, 5-dimethyl-4-β-phenylethylpyridine (XI). Dehydration of the piperidol III with hydrochloric acid led to isolation of 1, 2, 5-trimethyl-4-β-phenylethyldidehydropiperidine (X). The latter was converted to the pyridine base XI by catalytic N-demethylation and dehydrogenation over Mark K-12 catalyst.



Experimental

1, 2, 5-Trimethyl-4-phenylethynylpiperidol-4 (II). a) A three-necked flask was fitted with reflux condenser, stirrer, and dropping funnel. In it were placed 54 g powdered potassium hydroxide, 600 ml dry ether, and 100 g (0.71 mole) 1, 2, 5-trimethylpiperidone-4 (I) (n_D^{21} 1.4575). 48 g (0.47 mole) phenylacetylene (n_D^{21} 1.5501) was added to the mixture which was stirred and held at −5°. The products were stirred for 4 hr at room temperature, then made acid to congo red with 18% hydrochloric acid. The aqueous solution of organic bases was treated with sodium hydroxide, the bases extracted with ether, dried over sodium sulfate, and then vacuum-distilled. Fraction I: bp 50-140° (4 mm), 27.5 g, n_D^{22} 1.4581; fraction II: bp 140-165° (4 mm), 1.8 g; fraction III: bp 165-170° (4 mm) 71.0 g. The first fraction was starting piperidone I. The third fraction gave, after recrystallization from petrol ether, 65 g (62%) mixed stereoisomers of II, mp 86-88°. Found: 78.59; H 8.38; N 5.52, 5.58%. Calculated for $C_{16}H_{21}NO$: C 78.97; H 8.70; N 5.76%.

The picrate of one of the isomeric piperidols II had mp 193-194°. Found, N 11.83, 11.97%. Calculated for $C_{16}H_{21}NO \cdot C_6H_3N_3O_7$: N 11.86%.

Thin-layer chromatography showed that II consisted of two stereoisomers. 20 × 10 cm plates were used for chromatographing, with acetone – heptane 1:1, and a 1.5 mm thick layer of activity II unfixed Al_2O_3. Two spots were found: R_f 0.68; R_f 0.35.

Absorption chromatography was used for preparative separation of these isomers. A mixture of stereoisomeric alcohols II (5 g, mp 86-88°) in ethanol was column-chromatographed (H=82 cm, d=1.7 cm, Al_2O_3 200 g activity II), to give: 1.37 g II isomer mp 136-139.5°; 0.98 g intermediate fraction mp 89-95°, and 1.76 g II isomer mp 101-103°. Thin-layer chromatography was used to check on the isomers after separation.

High-melting II isomer. Found: C 78.99, 79.33; H 8.51, 8.74; N 5.83, 6.06%. Calculated for $C_{16}H_{21}NO$: C 78.97; H 8.70; N 5.76%.

Low-melting II isomer. Found: C 78.83, 78.77; H 9.04, 8.73; N 5.59, 5.73%. Calculated for $C_{16}H_{21}NO$: C 78.97; H 8.70; N 5.76%.

b) A three-necked flask was fitted with a reflux condenser, stirrer, and dropping funnel. In it were placed 12.2 g (0.5 g at) magnesium ribbon and 0.5 l dry ether. 55 g (0.5 mole) ethyl bromide was added, with stirring, over an hour. The reaction products were then refluxed for 1 hr 30 min, cooled to 0° and held there, and 51 g (0.5 mole) phenylacetylene dissolved in an equal volume of ether, added, at such a rate that the ether was kept refluxing. Then the reaction mixture was heated under reflux for 5 hr. The ether was distilled off from the phenylacetylene magnesium bromide formed, which precipitated as a heavy dark green oil, insoluble in ether, and 270 ml benzene added. The mixture was then cooled to 0°, and 67.5 g (0.48 mole) I added gradually, the resultant mixture heated for 4 hr at 50-60°, and treated with 200 ml water and 70 ml concentrated hydrochloric acid, to make it acid to congo red. The aqueous solution of organic bases was treated with sodium hydroxide. The base which separated was extracted with ether, dried over sodium sulfate, and then vacuum-distilled: fraction I bp 45-140° (3 mm), 29.8 g, n_D^{21} 1.4624; fraction II bp 140-158° (3 mm), 30.1 g, residue 2.3 g. The first fraction consisted of starting I. Two recrystallizations of the second fraction from petrol ether gave 18 g (12%) mixed II stereoisomers mp 92-116°. Found: N 5.46, 5.27%. Calculated for $C_{16}H_{21}NO$: N 5.76%. Thin-layer chromatography showed the mixture to contain two stereoisomers of piperidols II.

1, 2, 5-Trimethyl-4-phenylethyl-4-propionoxypiperidine (IV). 3 g II (mp 87-89°) and 4.6 g freshly-distilled propionyl chloride in 25 ml benzene was heated for 8 hr at 80-90°. The colorless crystals which separated on cooling were

recrystallized from acetone. There was obtained 2.3 g hydrochloride of IV, mp 170-171°. Found: N 4.25, 4.12%. Calculated for $C_{19}H_{25}NO_2 \cdot HCl$: N 4.17%.

1, 2, 5-Trimethyl-4-β-phenylethylpiperidol-4 (III). a) The Grignard reagent was prepared from 82 g β-phenylethylbromide, 10.6 g magnesium, and 500 ml ether, and 75 g I added with stirring and ice-water cooling. Then the reaction products were treated with 100 ml water, 100 ml 18% hydrochloric acid, then 150 ml concentrated hydrochloric acid. The aqueous solution was treated with sodium hydroxide, and the organic bases extracted with ether. Vacuum-distillation gave: fraction I bp 70-100° (5 mm), 65.7 g, n_D^{21} 1.4596; fraction II bp 100-140° (4 mm), 0.3 g; fraction III bp 140-170° (4 mm), 3.81 g; residue 0.5 g. The first fraction consisted of unchanged piperidone I. The third fraction was recrystallized, and III isolated, mp 89-90.5° (from petrol ether), yield 3.5%. Found: N 5.51, 5.68%. Calculated for $C_{16}H_{25}NO$: N 5.66%.

b) 5 g mixed II stereoisomers (mp 87-89°) was hydrogenated at 20° using Raney nickel in 80 ml ethanol. Over 10 hr, 1.1 *l* of hydrogen was absorbed. Removal of the ethanol, and recrystallization of the residue from petrol ether gave 4 g mixed stereoisomers III mp 75-77°. Found: N 5.93, 5.93%. Calculated for $C_{16}H_{25}NO$: N 5.66%.

c) Pressure hydrogenation was carried out with 20 g mixed II stereoisomers (mp 84-87°), 2 g Raney nickel, and 30 ml ethanol. The hydrogenation was carried out at 80°, initial hydrogen pressure 100 atm. After the theoretical amount of hydrogen had been absorbed, the ethanol was distilled off, and the residue recrystallized from petrol ether. 16 g mixed III stereoisomers were obtained, mp 77-93°. Found: N 5.96, 5.99%. $C_{16}H_{25}NO$: N 5.66%.

Thin-layer chromatography revealed the presence of two stereoisomers of III: R_f 0.5 and R_f 0.2 (Al_2O_3 activity IV, chloroform).

Preparative separation was by absorption chromatography. Chromatography of 1.68 g mixed stereoisomeric piperidols III mp 77-93° on an Al_2O_3 (135 g, activity IV) column (H = 50 cm, d = 1.7 cm) gave 0.14 g piperidol III mp 88-91°; 0.49 g intermediate fraction mp 74-102°, and 0.85 g piperidol III mp 122-123.5°. Separation of the isomers was checked by thin-layer chromatography.

d) The piperidol II stereoisomer (0.2 g) mp 136-139.5° was hydrogenated for 8 hr at 22°, using Raney nickel catalyst. Recrystallization of the product from petrol ether gave one of the III stereoisomeric piperidols mp 90-94°, mixed mp with III isomer (mp 88-91°) undepressed, this latter isomer being isolated by chromatography, and the mixed melting point with the III isomer (mp 89-90.5°) described in (a) above, was also undepressed. Found: C 77.53, 77.89; H 9.74, 10.06; N 6.03, 5.74%. Calculated for $C_{16}H_{25}NO$: C 77.68, H 10.19; N 5.66%.

e) The piperidol II stereoisomer mp 101-103° (0.15 g) was hydrogenated under similar conditions. Two recrystallizations of the product from petrol ether gave the second of the stereoisomers of the piperidol III, mp 121-123°. Mixed mp of this piperidol III isomer with the isomer (mp 122-123.5°) isolated by chromatographic separation of mixed stereoisomeric piperidols, was undepressed. Found: C 77.77, 78.06; H 9.82, 9.80; N 5.42, 5.31%. Calculated for $C_{16}H_{25}NO$: C 77.68; H 10.19; N 5.66%.

So complete hydrogenation of the triple bond of II isomer mp 136-139.5° gives a III isomer mp 88-91°, also formed by reacting I with β-phenylethyl magnesium bromide. Complete hydrogenation of the acetylenic bond of the piperidol II second isomer mp 101-103° gives the piperidol III isomer mp 121-123°.

ω-(1', 2', 5'-Trimethyldidehydropiperidyl-4') acetophenone (V). 145 ml 47% sulfuric acid, 2.4 g mercuric sulfate, and 35 g II (mp 87-91°) were stirred and heated on a water bath for 5 hr. The reaction products were first treated with 60 ml 10% soda solution, with cooling, and then crystalline sodium carbonate added until the solution was saturated. The organic bases were extracted with ether, and then vacuum-distilled, to give: fraction I bp 45-155° (3 mm), 0.76 g, n_D^{21} 1.4914; fraction II bp 155-166° (3 mm), 18.32 g, n_D^{21} 1.5478; fraction III bp 166-168° (3 mm), 7.58 g, n_D^{21} 1.5510. The second and third fractions consisted of V, which distilled over colorless, but darkened on standing in air. Found: N 5.76, 6.00%. Calculated for $C_{16}H_{21}NO$: N 5.76%.

The IR spectrum of ketone V had a band at 1689 cm^{-1}, evidently related to vibrations of a carbonyl group conjugated with an aromatic ring. Hydrogenation of 47 g V at 22° (180 ml ethanol, 5 g Raney nickel, initial pressure 120 atm) till the theoretical quantity of hydrogen was absorbed, gave 30.34 g ω-(1', 2', 5'-trimethylpiperidyl-4') acetophenone (bp 155-160° (1 mm), n_D^{19} 1.5458), whose IR spectrum showed a band at 1688 cm^{-1}, characteristic of a carbonyl group conjugated with an aromatic ring. The IR spectrum of ketone V did not show any vibrations corresponding to a hydroxyl group.

Picrate of base V mp 150-153° (ex ethanol). Found: N 11.75, 11.70. Calculated for $C_{16}H_{21}NO \cdot C_6H_3N_3O_7$: N 11.86%.

On standing, colorless crystals mp 47-51° separated from an ether solution of V; they rapidly darkened in air.

The following experiments were run to check that hydration of piperidol II did not involve an acetylene-allene

rearrangement.

a) A mixture of 15 g II (mp 83-100°), 70 ml glacial acetic and 3 ml sulfuric acid were held at 50-60° for 2 hr, after which the acetic acid was distilled off under reduced pressure. The residue was treated first with 10% aqueous sodium carbonate (50 ml) and then saturated with sodium carbonate. Then organic bases were extracted with ether, and 8 g starting piperidol II mp 87-96° (from petrol ether) recovered, mixed mp with the starting piperidol undepressed.

b) 10 g II (mp 83-100°), 50 ml 5% sulfuric acid, and 0.3 g mercuric sulfate were heated and stirred for 3 hr at 80-85°. The products were worked up in the way described above to give 6.8 g starting piperidol (mp 81-83°), mixed mp with authentic compound undepressed.

1-Phenyl-2-(1', 2', 5'-trimethylpiperidyl-4') ethanol-1 (VII). For pressure hydrogenation 30 g V (n_D^{22} 1.5500), 0.25 g Raney nickel, and 30 ml ethanol were charged to an autoclave. Hydrogenation was run at 100°, and the initial pressure was 80 atm. In 2 hr 30 min 5 *l* hydrogen (90% theory) was absorbed. The catalyst was filtered off, the ethanol distilled off, and the residue vacuum-distilled, to give: fraction I bp 86-153° (4 mm), 1.76 g; fraction II bp 153-162° (4 mm), 1.37 g; fraction III bp 162-175° (4 mm), 21.66 g. After adding petrol ether to fraction III there was isolated 9.8 g VII mp 107-112°. Found: N 5.57, 5.89%. Calculated for $C_{15}H_{25}NO$: N 5.66%.

1-Phenyl-2-(1', 2', 5'-trimethyldidehydropiperidyl-4') ethanol-1 (VI). A solution of 3 g sodium borohydride in 10 ml 86% isopropanol was gradually added to a solution of 9 g V (n_D^{20} 1.5500) in 40 ml 86% isopropanol held at 10°. The reaction mixture was then heated for 1 hr at 90-95°, and made acid to congo red with 18% hydrochloric acid, after which it was saturated with sodium carbonate. Organic bases and isopropanol were extracted with ether. The ether was distilled off and the alcohol in the residue vacuum-distilled: fraction I bp 100-150° (2 mm), 0.5 g; fraction II bp 150-180° (2 mm), 6.1 g. On standing for a long time a petrol ether solution of fraction II deposited 1.0 g crystals of VI mp 98-101°. Mixed mp of carbinol VI with its analog VII (mp 107-112°), 75-82°. Found: N 5.62, 5.66%.. Calculated for $C_{16}H_{23}NO$: N 5.71%.

Base VI picrate mp 132-134°. Found: N 11.76, 11.96%. Calculated for $C_{16}H_{23}NO \cdot C_6H_3N_3O_7$: N 11.81%.

1, 1-Diphenyl-2-(1', 2', 5'-trimethyldidehydropiperidyl-4') ethanol-1 (VIII). 10 g V was added slowly, and with cooling, to the phenyllithium prepared from 0.75 g lithium and 8.4 g bromobenzene in 100 ml dry ether. The reaction mixture was refluxed for 3 hr, and then decomposed with water and hydrochloric acid (successively 20 ml water and 20 ml 18% hydrochloric acid, then 25 ml concentrated hydrochloric acid). Excess sodium hydroxide was added to the water layer. The organic bases which separated were extracted with ether, dried over sodium sulfate, and then vacuum-distilled to give: fraction I, bp 160-190° (2 mm), 3.8 g; fraction II bp 190-220° (2 mm), 5.6 g; residue 2 g. Fraction II gave base VIII hydrochloride mp 214-215° (from ethyl acetate – methanol mixture). Found: N 3.91, 3.97%. Calculated for $C_{22}H_{27}NO \cdot HCl$: N 3.91%.

Base VIII methiodide mp 192-203° (from ethanol).

1, 1-Diphenyl-2-(1', 2', 5'-trimethylpiperidyl-4') ethanol-1 (IX). 9 g VIII, 1 g Raney nickel, and 40 ml ethanol were taken for pressure hydrogenation, the initial pressure being 100 atm, and the temperature throughout 50-60°. When the theoretical amount of hydrogen had been taken up, the solvent was distilled off. The residue gave base IX hydrochloride mp 216-217.5° (ex ethyl acetate-methanol mixture). Found: N 3.91, 3.97%. Calculated for $C_{22}H_{29}NO \cdot HCl$: N 3.89%.

Base IX methiodide mp 205-211° (ex ethanol).

1, 2, 5-Trimethyl-4-β-phenylethyldidehydropiperidine (X). A mixture of 14 g III (mp 77-93°) and 50 ml concentrated hydrochloric acid was refluxed for 8 hr, and the hydrochloric acid then distilled over under slightly reduced pressure. 50 ml water, 30 ml 10% sodium carbonate solution was added to the residue, and the solution then saturated with sodium carbonate. The organic bases were extracted with ether, dried over magnesium sulfate, and vacuum-distilled, to give 6.14 g X, bp 140-150° (3 mm), n_D^{20} 1.5283, d_4^{20} 0.9559. Found: N 6.49, 6.03% MR_D 73.8. Calculated for $C_{16}H_{23}N$: N 6.11%; MR_D 74.3.

Base X picrate mp 202-205° (ex ethanol). Found: N 12.26, 12.35%. Calculated for $C_{16}H_{23}N \cdot C_6H_3N_3O_7$: N 12.22%.

2, 5-Dimethyl-4-β-phenylethylpyridine (XI). A reactor tube was packed with Mark K-12 catalyst, catalyst volume 16 ml, tube diameter 1 cm, reaction zone temperature 415-430°. A solution of 8 g X in 35 ml benzene was put through the reactor over a period of 1 hr 30 min. 2040 ml gas was evolved (740 mm, 25°). Vacuum-distillation of the reaction products gave 7.6 g XI, a mobile, transparent liquid, bp 144-155° (4 mm), n_D^{20} 1.5585; d_4^{20} 1.0091.

Purified via the hydrochloride, base XI formed colorless crystals mp 32-35°. Found: N 6.80, 6.66%. MR_D 67.46. Calculated for $C_{15}H_{17}N$: N 6.63%. MR_D 67.36.

Base XI picrate mp 169-171°. Found: N 12.63, 12.63%. Calculated for $C_{15}H_{17}N \cdot C_6H_3N_3O_7$: N 12.72%.

Base XI hydrochloride mp 171-175°. Found: N 5.32, 5.37%. Calculated for $C_{15}H_{17}N \cdot HCl$: N 5.66%.

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