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The Reduction Products of 2-Phenyl-1,3-di(4-pyridyl)-2-propanol

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A number of chemical modifications of 2-phenyl-1,3-di(4-pyridyl)-2-propanol are described. Dehydration, alkylation and hydrogenation, concomitant and independent, gave a variety of novel compounds. Independent syntheses produced the related compounds X and XVI which were subjected to some of the same reactions. Structural assignments (spectral) were corroborated by the synthesis of common reaction products.

The ready availability of 2-phenyl-1,3-di(4-pyridyl)-2-propanol (1) (I) prompted a study of its chemistry, and a number of syntheses and interconversions were effected (Schemes I, II and III).

When dehydrated in sulfuric acid at 75°, I gave a high yield of a 1:1 mixture (2) of the *cis* and *trans* isomers of 1,3-di(4-pyridyl)-2-phenyl-1-propene, IIa and IIb respectively. The isomeric olefins were separated by fractional crystallization and characterized by spectral measurements. It was found that each of the pure isomers IIa and IIb, when treated in a solution of concentrated hydrochloric acid at 100°, equilibrated to give approximately a 1:1 mixture (2) of the two isomers.

As with the isomeric α-methylstilbenes (3), the *cis* olefin IIa would be expected to absorb ultraviolet light at a shorter wave length and to a lesser degree than IIb. Accordingly, the isomer having λ max at 258 mμ (log ϵ 4.16) was assigned structure IIa and that having λ max at 282 mμ (log ϵ 4.24) was assigned structure IIb. As such, the structure-spectra relationships are in accord with the argument presented by Cram (4) for the relationship of coplanarity to ultraviolet spectra in stilbenes.

These structural assignments were corroborated by nmr measurements. Both isomers exhibited signals in the aromatic region for the appropriate number of protons and demonstrated the classical pattern for the 4-pyridyl moiety (5). Isomer IIa exhibited a two proton singlet at 3.82 ppm (the methylene protons) and a one proton singlet (the vinyl proton) at 6.42 ppm; the *trans* isomer, IIb, had a two proton singlet at 4.10 ppm and the vinyl proton signal was shifted toward the aromatic region.

The signal for the vinyl protons of the *cis* isomer of stilbene is at 6.55 ppm and for the *trans* isomer, at 7.10 ppm (6). Thus, in the nmr, the relative locations of the vinyl protons in IIa and IIb are consistent with the structural assignments and are comparable to the vinyl protons in *cis* and *trans* stilbene. Furthermore, the relative locations of the signals obtained for the methylene protons for IIa and IIb are consistent with the theoretical arguments presented for the positions of the methyl groups in *cis* and *trans* α-methylstilbenes (7).

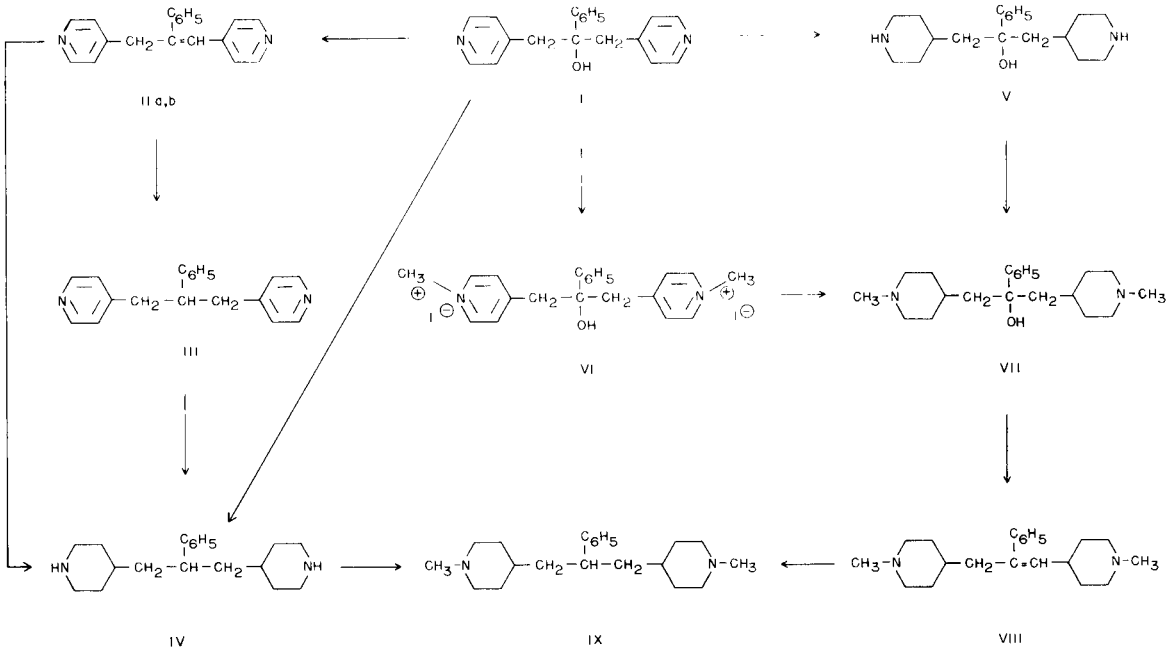
The hydrogenation of a mixture of IIa and IIb with a palladium catalyst at room temperature and at atmospheric pressure gave a high yield of 2-phenyl-1,3-di(4-pyridyl)propane (III). Under mild conditions then, the olefin was selectively hydrogenated and neither the phenyl nor the pyridyl rings were attacked. At an elevated temperature and increased pressure with rhodium as the catalyst, the pyridyl rings of III were hydrogenated. This resulted in the formation of 2-phenyl-1,3-di(4-piperidyl)propane (IV), the phenyl ring remaining unchanged. The course of the reaction was clearly defined by the nmr spectrum. Five aromatic protons were retained; the signals for the protons of the 4-pyridyl rings disappeared while twenty additional protons (two exchangeable) were observed in the aliphatic region (1.08-3.17 ppm).

Hydrogenation of a mixture of IIa and IIb at elevated temperature and pressure with a platinum catalyst also gave IV as the major product, the reduction probably proceeding through III. The totally reduced compound, 2-cyclohexyl-1,3-di(4-piperidyl)propane (XIII), was also isolated. The structure of XIII, indicated by spectral data, was confirmed by an independent synthesis (Scheme II).

The synthesis of 2-cyclohexyl-1,3-di(4-pyridyl)-2-propanol (X), was effected from hexahydrobenzoyl chloride and 4-picolyl lithium as described for I (1). The acid catalyzed dehydration of X gave a mixture of the olefins XII, which was hydrogenated over rhodium at elevated temperature and pressure to give XIII, identical in all respects with that obtained as above.

A reference compound, 2-cyclohexyl-1,3-di(4-piperidyl)-2-propanol (XIV) was then prepared by the hydrogenation of X over rhodium at elevated temperature and pressure. When I was hydrogenated under these conditions, the pyridyl rings were reduced and 2-phenyl-1,3-di(4-piperidyl)-2-propanol (V) was obtained in a 98% yield. Here again, the phenyl ring showed remarkable resistance to hydrogenation in the presence of a catalyst, which under such conditions, frequently causes the reduction of the phenyl moiety (8).

SCHEME I



It was found that IV could also be synthesized directly from I by hydrogenation over a platinum catalyst in hydrochloric acid solution. The course of the reaction is probably best defined as an initial dehydration of I to IIa, b, and subsequent hydrogenation of the olefinic linkage and the pyridyl rings. Although none of the other possible hydrogenation products were isolated, their presence was not definitely excluded. (It would be reasonable to expect that the totally hydrogenated product XIII, isolated from the hydrogenation of IIa, b under identical conditions should also be present.) An indication that the reduction of I to IV proceeded via the olefins was given by the hydrogenation of I under neutral conditions which negated dehydration. This reduction gave an excellent yield of the di-piperidylpropanol (V). As with other compounds in this series, hydrogenation over rhodium cleanly reduced the pyridyl rings and left the phenyl ring intact (shown by the presence of five aromatic protons in the nmr spectrum). The hydroxyl absorption (3610 cm^{-1}, sharp) in the infrared spectrum was clearly distinguishable from the NH absorption of the piperidyl rings (broad band at 3250 cm^{-1}). Methylation of V with methyl iodide in the presence of base gave a compound which exhibited no NH absorption in the infrared and showed two unsplit methyl groups (six protons, 2.15 ppm) in the nmr spectrum. The structure was therefore assigned as 1,3-bis(1-methyl-4-piperidyl)-2-phenyl-2-propanol (VII). This structure was confirmed by a comparison with an authentic sample prepared by hydrogenation of the dimethiodide salt of I, compound VI.

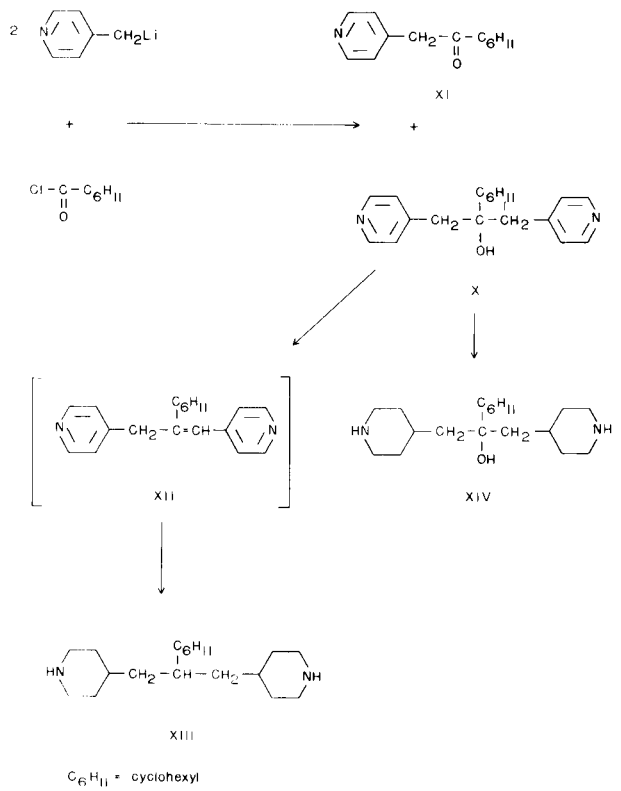
The existence of the OH function in VII as indicated in the infrared spectrum (3620 cm^{-1}) was corroborated by dehydration to the corresponding olefin VIII.

The dihydrochloride salt of VIII incorporated one mole of water of crystallization and was analyzed as such. Distinction was readily made between the dihydrochloride hydrate and the alcohol VII by both physical and spectral comparisons of the free bases. The hydrogenation of VIII, at room temperature and atmospheric pressure gave the bis-methylpiperidyl compound IX, which proved to be identical to the product obtained by the Eschweiler-Clarke methylation of IV.

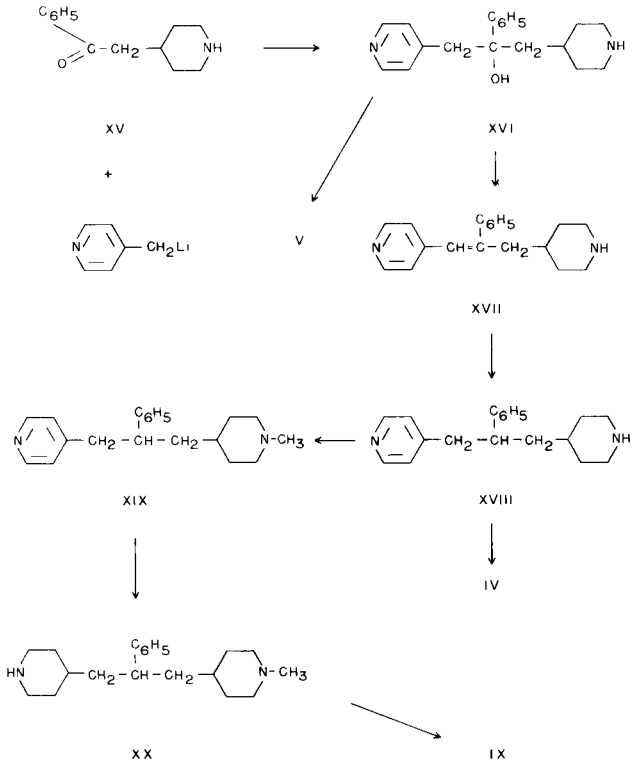
In order to prepare the piperidylpyridyl-2-propanol (XVI) an alternate approach was necessary (Scheme III). Accordingly, 4-phenacylpiperidine (XV) was synthesized (9) and was allowed to react with 4-picolyl lithium. Unlike the reaction of picolyl lithium with 4-phenacylpyridine (1), addition occurred rapidly and XVI was isolated in excellent yield. Hydrogenation of XVI with three equivalents of hydrogen again gave the dipiperidyl compound (V).

By treating the carbinol (XVI) with strong acid at elevated temperature, dehydration was effected and a mixture of the *cis* and *trans* olefins (XVII) was isolated. It was of interest to note that in the

SCHEME II



SCHEME III



preparation of the maleate from the mixture we could isolate only the *cis* salt. The *cis* conformation was assigned by a comparison of the ultraviolet spectrum of the free base (λ max at 263 mμ, log ε 4.04) with the spectra of the previously assigned *cis* and *trans* isomers IIa and IIb.

Treatment of XVII with hydrogen at room temperature and atmospheric pressure over a palladium catalyst gave the propane (XVIII). When XVIII was then subjected to hydrogenation under more rigorous conditions, the 4-pyridyl group was reduced and the product was identical in all respects with compound IV. Methylation of XVIII with formaldehyde and formic acid gave the expected 1-(1-methyl-4-piperidyl)-2-phenyl-3-(4-pyridyl)propane (XIX). When XIX was hydrogenated in acid over platinum, three moles of hydrogen were absorbed, and the product (XX) was isolated as the *p*-toluenesulfonate. Methylation of XX gave compound IX of established structure.

EXPERIMENTAL (10)

Cis and *trans* 1,3-di(4-pyridyl)-2-phenyl-1-propene (IIa and IIb).

A solution of 25 g. (86 mmoles) of I (1) in 150 ml. of 60% by volume sulfuric acid was allowed to stand 16 hours at 75°. The reaction mixture was cooled to room temperature and was stirred into an excess of ice cold ammonium hydroxide, the resultant mixture was extracted with methylene chloride. Unreacted I, insoluble in the aqueous organic system, was removed by filtration. The organic liquid phase was separated, dried and concentrated to give 21.2 g. (90%) of a colorless crystalline mixture of IIa and IIb. Three recrystallizations from hexane gave colorless needles of the pure *trans* olefin, IIb, m.p. 126-128°.

Anal. Calcd. for $C_{19}H_{16}N_2$: C, 83.79; H, 5.92. Found: C, 84.08; H, 6.00.

The hexane mother liquor from the first recrystallization was concentrated *in vacuo* by about 50%, the remaining IIb crystallized and was removed by filtration. The filtrate was reduced *in vacuo* to an oil which was crystallized from hexane to give colorless needles of IIa, m.p. 71-73°.

Anal. Calcd. for $C_{19}H_{16}N_2$: C, 83.79; H, 5.92. Found: C, 84.15; H, 6.16.

2-Phenyl-1,3-di(4-pyridyl)propane (III).

A mixture of 10.0 g. (37 mmoles) of a 1:1 mixture of IIa and IIb, 1 g. of 10% palladium on carbon (prereduced) and 250 ml. of ethyl acetate was hydrogenated at 25° and atmospheric pressure. Over a period of 72 hours, 38 mmoles of hydrogen was absorbed. The catalyst was removed by filtration through celite and the filtrate was concentrated to 9.1 g. (90%) of a colorless oil which crystallized slowly, m.p. 45-60°. Recrystallization from ether-hexane gave colorless prisms, m.p. 53-60°.

Anal. Calcd. for $C_{19}H_{18}N_2$: C, 83.17; H, 6.61. Found: C, 82.99; H, 6.45.

2-Phenyl-1,3-di(4-piperidyl)propane (IV). A. From III.

A solution of 5.3 g. (19.3 mmoles) of III in 200 ml. of ethanol in the presence of 1 g. of rhodium was hydrogenated at 90-96° for 1 hour under an initial hydrogen pressure of 1500 psi. The catalyst and the solvent were removed to give the theoretical amount of a solid, m.p. 60-70°, which was recrystallized to give 5.0 g. (91%) of colorless needles, m.p. 70-72°.

Anal. Calcd. for $C_{19}H_{30}N_2$: C, 79.66; H, 10.56; N, 9.78. Found: C, 79.89; H, 10.74; N, 9.60.

The dihydrochloride monohydrate, as colorless needles, m.p. 170-175° was prepared in 2-propanol, and recrystallized from methanol-ether.

Anal. Calcd. for $C_{19}H_{30}N_2 \cdot 2HCl \cdot H_2O$: C, 60.47; H, 9.08. Found: C, 60.48; H, 9.29.

B. From IIa, b.

A mixture of IIa and IIb synthesized as above from 100 g. (0.344 mole) of I was hydrogenated in 1 l. of 3 *N* hydrochloric acid over 5 g. of platinum at 50-55° and under 900 psi of hydrogen. The catalyst was removed by filtration and the filtrate was stirred into an excess of ice cold sodium hydroxide. The mixture was extracted with ether which was dried and concentrated to an oil which crystallized on standing. The crystalline base (IV) was dissolved in 2-propanol and treated with a solution of hydrogen chloride in 2-propanol. The resulting dihydrochloride monohydrate was removed by filtration after the addition of ether and cooling to 0°. Recrystallization from methanol-ether gave 128 g. (79%) of colorless needles, m.p. 170-175°.

Concentration of the mother liquors and crystallization from methanol-ether gave XIII as the dihydrochloride, m.p. 240-250°, dec. Neutralization gave the base which was crystallized from hexane as colorless prisms, m.p. 78-80°, identical in all respects to that synthesized independently.

C. From I.

A solution of 50 g. (0.17 mole) of I in 600 ml. of 3 *N* hydrochloric acid was hydrogenated and worked up as described in B to give 33.2 g. (51%) of the dihydrochloride monohydrate as colorless needles, m.p. 170-175°. A portion of the neutralized material was distilled at 176°/0.5 mm. Upon cooling, the distillate crystallized and upon recrystallization from hexane gave IV as colorless prisms, m.p. 69-72°.

2-Phenyl-1,3-di(4-piperidyl)-2-propanol (V). A. From I.

A solution of 25 g. (86 mmoles) of I in 200 ml. of ethanol was hydrogenated at 105 ± 5° for 3.5 hours over 0.5 g. of rhodium catalyst under an initial hydrogen pressure of 1475 psi. The catalyst was removed by filtration and the solvent was removed *in vacuo* to give a solid, m.p. 64-72°. The product was washed with boiling hexane and 26.0 g. (98%) of colorless solid, m.p. 123-126° was removed by filtration. Recrystallization from methylene chloride-hexane gave colorless needles, m.p. 125-126°.

Anal. Calcd. for $C_{19}H_{30}N_2O$: C, 75.45; H, 10.00; N, 9.26. Found: C, 75.45; H, 9.95; N, 9.03.

Dimethylation to VII was effected in a yield of 50.7% with methyl iodide in ethanolic potassium hydroxide. The product was identical to that synthesized from VI as described below.

B. From XVI.

A solution of 8.0 g. (21.7 mmoles) of XVI (as the dihydrochloride monohydrate) in 150 ml. of water was hydrogenated over a platinum catalyst at atmospheric pressure and room temperature. After reaction of the required amount of hydrogen, the catalyst was removed by filtration and the filtrate was basified and chilled. The resulting oil crystallized on standing. It was recrystallized from hexane to give 3.45 g. (53%) of V as colorless needles, m.p. 120-124°.

2-Phenyl-1,3-di(4-pyridyl)-2-propanol Dimethiodide (VI).

A solution of 20 g. (68 mmoles) of I in 400 ml. of 2-propanol and an excess of methyl iodide was allowed to stand 18 hours at room temperature. Filtration and recrystallization from 2-propanol gave 39.3 g. (99%) of the quaternary salt as colorless prisms, m.p. 189-191°.

Anal. Calcd. for $C_{21}H_{24}I_2N_2O$: C, 43.92; H, 4.21. Found: C, 43.63; H, 4.34.

1,3-Bis(1-methyl-4-piperidyl)-2-phenyl-2-propanol (VII).

A solution of 30 g. (52 mmoles) of VI in 200 ml. of ethanol was hydrogenated for 8 hours at 510 psi. and at room temperature in the presence of 1 g. of platinum oxide and 10 g. of potassium acetate. The catalyst was removed by filtration, the solvent was evaporated *in vacuo* and the residue was partitioned between ether and water. The aqueous layer was made basic and extracted with ether. The combined ether layers were dried, and concentrated to a residue which was crystallized and recrystallized from cyclohexane giving 12.3 g. (73%) of colorless prisms, m.p. 119-121°.

Anal. Calcd. for $C_{21}H_{34}N_2O$: C, 76.31; H, 10.37. Found: C, 75.98; H, 10.29.

1,3-Bis(1-methyl-4-piperidyl)-2-phenylpropene Dihydrochloride Monohydrate (VIII).

A solution of 8.1 g. (24.7 mmoles) of VII in 100 ml. of concentrated hydrochloric acid was refluxed for 15 hours. The reaction mixture was chilled, basified with 10 *N* sodium hydroxide and extracted with ether. The extract was dried and concentrated to an oil which was dissolved in 40 ml. of petroleum ether (b.p. 30-60°) and chromatographed on 100 g. of basic alumina. The column was eluted with 100 ml. of benzene and 250 ml. of ether, the two fractions were combined and the solvent was removed. The residual colorless oil was dissolved in ethanol, and treated with hydrogen chloride. Addition of ether caused the precipitation of 6.5 g. (65%) of the dihydrochloride monohydrate of VIII as colorless needles, m.p. 185-195° which resolidified and remelted at 270-275°.

Anal. Calcd. for $C_{21}H_{32}N_2 \cdot 2HCl \cdot H_2O$: C, 62.52; H, 8.99. Found: C, 62.42; H, 9.24.

1,3-Bis(1-methyl-4-piperidyl)-2-phenylpropane (IX). A. From IV.

A solution of 5.0 g. (17.6 mmoles) of IV in 4.5 g. of 90% formic acid and 1.1 g. of 37.5% formaldehyde was refluxed for 15 hours. A 5 ml. portion of concentrated hydrochloric acid was added, the solution was reduced to near dryness *in vacuo*, basified with 10 *N* sodium hydroxide and extracted with ether. Evaporation of the dried ether extract left a colorless oil which was crystallized from ether to give 3.3 g. (60%) of IX as colorless rods, m.p. 96-97°.

Anal. Calcd. for $C_{21}H_{34}N_2$: C, 80.19; H, 10.90. Found: C, 80.22; H, 11.04.

B. From VIII.

A solution of 100 mg. (3.23 mmoles) of VIII in 20 ml. of glacial acetic acid and 20 ml. of water was hydrogenated at atmospheric pressure and room temperature over a platinum catalyst. The catalyst was removed by filtration, the reaction mixture was basified with 10 *N* sodium hydroxide and extracted with ether. The extract was dried and the solvent was removed. Crystallization from ether gave 40 mg. (40%) of IX as colorless rods, m.p. 96-97°.

C. From XX.

A solution of 2.7 g. (9.0 mmoles) of XX in 25 ml. of 90% formic acid and 10 ml. of 37.5% formaldehyde was refluxed for 21 hours. Concentrated hydrochloric acid (2 ml.) was added and the reaction mixture was concentrated to an oil. The residue was dissolved in water, basified with 10 *N* sodium hydroxide and extracted with ether. The ethereal solution was washed with water, dried and evaporated to give 2.1 g. (74%) of oil which crystallized to colorless prisms of IX, m.p. 96-97°.

4-Phenacylpiperidine Hydrochloride (XV).

A solution of 19.7 g. (0.10 mole) of 4-phenacylpyridine (1) in 200 ml. of ethanol and 9 ml. of concentrated hydrochloric acid was hydrogenated over 1 g. of platinum at 30°, under 500 psi. of hydrogen. Removal of the catalyst and the solvent gave 22.9 g. (95%) of XV as the hydrochloride which was crystallized from methanol as colorless prisms, m.p. 245-249°.

Anal. Calcd. for $C_{13}H_{17}NO \cdot HCl$: C, 65.13; H, 7.57. Found: C, 64.94; H, 7.74.

2-Phenyl-1-(4-piperidyl)-3-(4-pyridyl)-2-propanol (XVI).

To a cold solution (-25 ± 5°) containing 0.88 mole of γ-picolyl lithium (1), 71.5 g. (0.35 mole) of XV in tetrahydrofuran was added dropwise over a period of 25 minutes. Stirring was continued at -25° for 1 hour and the reaction mixture was hydrolyzed with 50 ml. of water and poured into an excess of ice cold hydrochloric acid. The acid solution was washed several times with ether and basified with sodium hydroxide. The resulting precipitate was removed by filtration, washed with copious quantities of water and recrystallized from acetone-ether to give 90 g. (86%) of XVI as colorless rods, m.p. 125-128°.

Anal. Calcd. for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16. Found: C, 77.01; H, 8.31.

Treatment of a 2-propanol solution of the base with hydrogen chloride gave, upon the addition of ether, a residue which was crystallized from methanol-ether to give the dihydrochloride monohydrate of XVI as colorless prisms, m.p. 168-178° dec.

Anal. Calcd. for $C_{19}H_{24}N_2O \cdot 2HCl \cdot H_2O$: C, 59.26; H, 7.55. Found: C, 59.10; H, 7.27.

Cis-2-Phenyl-3-(4-piperidyl)-1-(4-pyridyl)-1-propene Maleate (XVII).

A solution of 90 g. (0.303 mole) of XVI in 1 l. of 9 *N* hydrochloric acid was refluxed for 17 hours and poured into an excess of ice cold sodium hydroxide. The oily mixture was extracted with a 1:1 mixture of ether-benzene which was washed with water, dried and evaporated. The residue was dissolved in ethanol containing an equivalent of maleic acid. Removal of the salt by filtration and recrystallization from ethanol gave 7 g. (5.6%) of the monomaleate as colorless prisms, m.p. 172-178°, dec.

Anal. Calcd. for $C_{19}H_{22}N_2 \cdot C_4H_4O_4$: C, 70.03; H, 6.44. Found: C, 69.82; H, 6.73.

The mother liquors gave 70 g. (82.8%) of the free base (mixture of *cis* and *trans*) as a colorless oil which was used in further transformations.

2-Phenyl-1-(4-piperidyl)-3-(4-pyridyl)propane Hydrochloride (XVIII).

A solution of 15.45 g. (55.5 mmoles) of XVII in 200 ml. of ethanol was hydrogenated at 45-50° under 1000 psi. pressure in the presence of a 10% palladium on carbon catalyst. When the required amount of hydrogen had been absorbed, the catalyst was removed by filtration and the solvent was removed *in vacuo*. The residue was treated with one equivalent of hydrogen chloride in 2-propanol. The chilled solution was diluted with ether and the resulting salt was removed by filtration and recrystallized from 2-propanol-ether to give 11.1 g. (63%) of the monohydrochloride salt as colorless prisms, m.p. 196-207°, dec.

Anal. Calcd. for $C_{19}H_{24}N_2 \cdot HCl$: C, 72.02; H, 7.95. Found: C, 71.69; H, 8.30.

1-(1-Methyl-4-piperidyl)-2-phenyl-3-(4-pyridyl)propane Disulfate (XIX).

To a solution of 9.3 g. (33.2 mmoles) of XVIII in 25 ml. of 90% formic acid chilled in an ice bath, 10 ml. of a 37.5% solution of formaldehyde was added. The reaction mixture was heated under reflux for 17 hours, 6 ml. of concentrated hydrochloric acid was added and the reaction mixture was concentrated *in vacuo*. The residue was dissolved in water and basified with sodium hydroxide, the aqueous solution was extracted with ether and the ether extract was washed with water, dried and evaporated to give 9.45 g. (96%) of the base as an oil. Treatment of a methanolic solution of the base with an excess of sulfuric acid and the addition of ether gave, on chilling, 85% of the disulfate as colorless prisms, m.p. 210-222°.

Anal. Calcd. for $C_{20}H_{26}N_2 \cdot 2H_2SO_4$: C, 48.96; H, 6.16. Found: C, 49.09; H, 6.38.

1-(1-Methyl-4-piperidyl)-2-phenyl-3-(4-piperidyl)propane *p*-Toluenesulfonate (XX).

A solution of 4.9 g. (16.7 mmoles) of XIX in 200 ml. of 1 *N* hydrochloric acid was hydrogenated at atmospheric pressure and 25° in the presence of platinum. The reaction was halted after absorption of the required amount of hydrogen and the catalyst was removed. The filtrate was made strongly basic and extracted with a 1:1 ether-benzene mixture. The extract was washed with water, dried and the solvent was removed *in vacuo*. The residual oil was dissolved in ethanol, chilled and one equivalent of *p*-toluenesulfonic acid was added. The mono *p*-toluenesulfonate, 2.35 g. (30%), was crystallized as colorless prisms, m.p. 153-156°, upon the slow addition of ether.

Anal. Calcd. for $C_{20}H_{32}N_2 \cdot C_7H_8O_3S$: C, 68.61; H, 8.53. Found: C, 68.86; H, 8.71.

2-Cyclohexyl-1,3-di(4-pyridyl)-2-propanol (X) and Cyclohexyl-4-pyridylmethylketone Hydrochloride (XI).

A solution of 23.9 g. (0.2 mole) of hexahydrobenzoyl chloride in 75 ml. of THF was added slowly to a 0.5 *M* solution of picolyl lithium maintained at -20 ± 3°. The mixture was stirred and allowed to warm to room temperature. Addition of 1 l. of water and acidification with 3 *N* hydrochloric acid resulted in the formation of an organic layer which was separated and extracted with 3 *N* hydrochloric acid. The acid layers were combined and washed with ether before basification with 10 *N* sodium hydroxide. The resulting precipitate was removed by filtration and washed with water and with ether. Recrystallization from acetone-hexane gave 9.4 g. (15.2%) of X as colorless prisms, m.p. 176-178°.

Anal. Calcd. for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16. Found: C, 77.25; H, 8.01.

The basic filtrate above was extracted with methylene chloride and combined with the ether washes to give a solution which was dried and evaporated. The residual oil was extracted with several portions of boiling hexane which were cooled and saturated with hydrogen chloride to give 12.1 g. (25.2%) of XI. Recrystallizations from methanol-ether gave pale yellow plates, m.p. 161-167°.

Anal. Calcd. for $C_{13}H_{17}NO \cdot HCl$: C, 65.13; H, 7.57. Found: C, 65.21; H, 7.83.

2-Cyclohexyl-1,3-di(4-piperidyl)propane (XIII).

A solution of 5.0 g. (17 mmoles) of X in 70 ml. of 75% by volume sulfuric acid was stirred at 100° for 45 minutes. The reaction mixture was cooled and stirred into an excess of ice cold ammonium hydroxide. Ether extraction gave, after drying and removal of the solvent, 3.45 g. of residue which was dissolved in 200 ml. of ethanol and hydrogenated at 92° over rhodium under 1500 psi. of hydrogen. Removal of the catalyst by filtration and the solvent by evaporation gave 3.3 g. of a pale yellow oil which was crystallized from hexane to give 2.5 g. (50.3%) of colorless prisms, m.p. 74-80°. Recrystallization from hexane gave prisms, m.p. 78-80°, identical in all respects to those obtained above as a by-product from IIa and IIb.

Anal. Calcd. for $C_{19}H_{36}NO_2$: C, 78.02; H, 12.41; N, 9.58. Found: C, 78.38; H, 12.10; N, 9.39.

2-Cyclohexyl-1,3-di(4-piperidyl)-2-propanol (XIV).

A solution of 11.5 g. (38.8 mmoles) of X in 300 ml. of ethanol was hydrogenated at 100° ± 2° in the presence of 1 g. of rhodium at a pressure of 1515 psi. Removal of the catalyst and the solvent left 13.7 g. of an oil which was crystallized from hexane to give 8.9 g. (74.4%) of XIV, m.p. 110-113°. Recrystallization from hexane gave colorless plates, m.p. 113-115°.

Anal. Calcd. for $C_{19}H_{36}N_2O$: C, 73.97; H, 11.76; N, 9.08. Found: C, 74.25; H, 11.72; N, 9.18.

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(2) The isomer ratios were determined visually on thin layer chromatographic plates of fluorescent silica using the pure isomers as reference. The chromatograms were developed in a bath of 60% ethyl acetate, 20% hexane, 19% ethanol and 1% concentrated ammonium hydroxide by volume.

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