salt in the last methylene chloride layer. The white solid was triturated thoroughly with ether, then converted to the free base by treatment with ammonium hydroxide and extraction into ether. The resulting oily base (5 g) was chromatographed on 200 g of neutral activity II–III alumina in cyclohexane. Fractions eluted with cyclohexane crystallized partially on standing and completely on trituration with acetonitrile. Recrystallizations from acetonitrile yielded the analytical sample, mp 93.5–96°. The ultraviolet spectrum showed the expected benzene absorption at 258 mμ (ε 690). In the nmr a three-proton multiplet was observed at 3.25–3.75 ppm. On addition of a drop of hydrochloric acid the C_1H signal shifted to 3.80 ppm. By the position of the signal and the reasoning given above the pyrrolidino group is assigned the axial configuration.

Anal. Calcd for $C_{28}H_{31}N$: C, 88.14; H, 8.19; N, 3.67. Found: C, 88.54; H, 8.24; N, 3.74.

Pyrrolidino Derivatives of 17.—The *cis,trans* ketone (1.60 g) was converted to the enamine by reaction with 0.71 g of pyrrolidine in benzene for 16 hr. The work-up and hydrogenation of the unpurified residue were carried out in the usual fashion; in this case hydrogenation was complete in 2.5 hr. The colorless syrup that resulted was dissolved in methylene chloride and the solution was shaken with 5% hydrochloric acid to convert the product to the salt. Evaporation of the dried methylene chloride yielded 1.88 g of solid, which was triturated thoroughly with ether. After unsuccessful attempts to recrystallize the salt, it was reconverted to the free base, and this was chromatographed on 50 g of activity II–III neutral alumina in hexane solution. After an initial oily fraction, 1.3 g of white crystalline material was eluted with *n*-hexane, mp 146–148.5°. Further elution with benzene afforded 200 mg of the second isomer, mp 124.5–127°. The first product was recrystallized from acetonitrile for analysis, mp 148–151°. In the nmr spectrum a signal assignable to the C_1 equatorial proton was observed at 3.50 ppm; the pyrrolidino group is, accordingly, considered to be in an axial or pseudo-axial arrangement.

Anal. Calcd for $C_{28}H_{31}N$: C, 88.14; H, 8.19; N, 3.67. Found: C, 88.36; H, 8.13; N, 3.70.

The lower melting compound was recrystallized from *n*-hexane for analysis, mp 124–126°. In the nmr spectrum no aliphatic proton signals were observed further downfield than 3.08 ppm. The aromatic regions in the spectra of the two isomers were almost identical. A five-proton singlet was observed at 6.78 in this case and at 6.82 ppm for the previous (axial pyrrolidino) compound. A ten-proton singlet was found at 7.00 ppm for each compound.

Anal. Calcd for $C_{28}H_{31}N$: C, 88.14; H, 8.19; N, 3.67. Found: C, 87.90; H, 8.32; N, 3.51.

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The Stereochemistry and Synthesis of the Lobinaline Ring System

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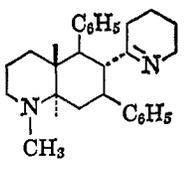
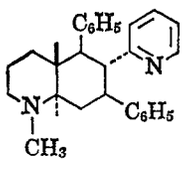
By a combination of spectral and chemical methods it has been established that lobinaline is a *trans*-decahydroquinoline derivative having all-equatorial and hence all-*trans* substituents, as depicted in structure **1** (or its mirror image). "Dehydrolobinaline" (**2**), previously prepared by oxidation of lobinaline with selenium dioxide, has been synthesized in racemic form by cyanoethylation of the pyrrolidine enamine derived from *trans,trans*-3,5-diphenyl-4-(2-pyridyl)cyclohexanone (**3**), hydrolysis of the resulting cyanoethylenamine (**4**) to the cyano ketone (**5**), hydrogenation of **5** with palladium–charcoal in the presence of ammonia, and methylation of the resulting *trans* decahydroquinoline (**6**).

In an earlier study[1] aimed at the elucidation of the skeletal structure of lobinaline the independent, unequivocal synthesis of the dehydrogenated degradation product, 5,7-diphenyl-6-(2-pyridyl)quinoline, was undertaken. This synthesis proceeded by way of a 3-hydroxy-3,5-diphenyl-4-(2-pyridyl)cyclohexanone which, in turn, was obtained by base-catalyzed condensation of 2-phenacylpyridine with benzalactone. An nmr spectral study of the cyclohexanone and of a number of related derivatives[2] led to the conclusion that the condensation product possessed all-*trans* aryl groups. The recognition of striking similarities between the aryl signals in the nmr spectrum of this derivative and the corresponding signals in the lobinaline spectrum, together with spectral and chemical correlations of other related substances,[2] suggested the possibility that lobinaline might possess the most stable all-*trans* configuration and hence that it might be relatively amenable to synthesis. This communication reports the total synthesis of racemic *trans*-1-methyl-5-7-diphenyl-6-(2-pyridyl)decahydroquinoline (**2**) with the relative configurations shown, in which all groups about the cyclohexane ring are equatorial.[3] The identity of this substance with "dehydrolobinaline," a degradation product obtained by treatment of the alkaloid with selenium dioxide,[1,4] made possible the assignment of the complete relative stereochemistry of lobinaline as in **1**.[3]



1



2

The first step in the synthesis of **2** involved cyanoethylation of the pyrrolidine enamine (**3**)[2] of *trans,trans*-3,5-diphenyl-4-(2-pyridyl)cyclohexanone to yield the enamine (**4**). In the initial experiments the rather unstable product was subjected to lithium aluminum hydride reduction followed by hydrolysis to yield the

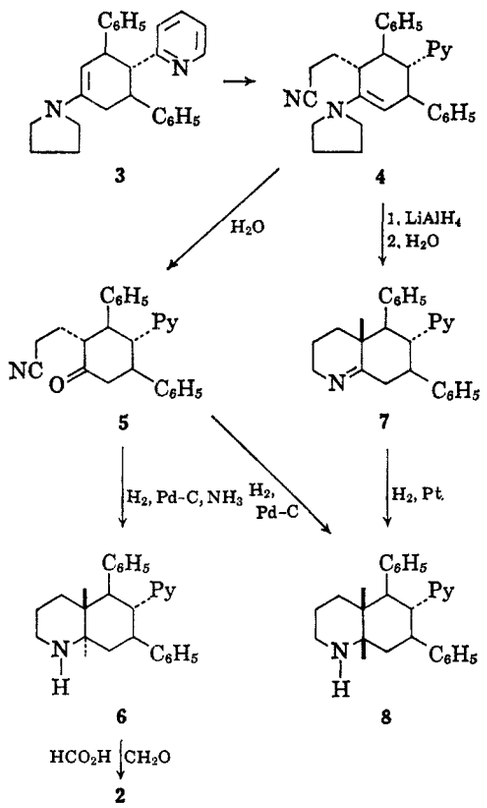
(1) M. M. Robison, W. G. Pierson, L. Dorfman, B. F. Lambert, and R. A. Lucas, *J. Org. Chem.*, **31**, 3206 (1966).

(2) M. M. Robison, W. G. Pierson, L. Dorfman, and B. F. Lambert, *ibid.*, **31**, 3213 (1966).

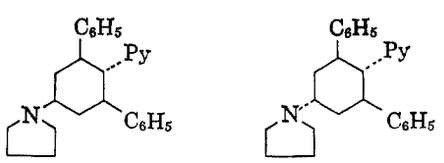
(3) Structural formulas are not intended to indicate absolute configuration.

(4) The synthetic, racemic product was identical with the degradation product of natural origin in all respects except optical rotation and Nujol infrared spectrum.

imine (**7**).[5] Owing to the unstable nature of **3**, **4**, and **7** these intermediates could not be obtained in crystalline, analytically pure form; they were characterized by their infrared spectra. Reduction of the imine (**7**) catalytically or with sodium borohydride yielded a mixture of products from which only one decahydroquinoline derivative (**8**) could be isolated in crystalline form. It was early apparent from the nmr spectrum of this substance that it did not possess the



desired lobinaline configuration at one or both ring-juncture positions, however, and this conclusion was confirmed on methylation of **8** to yield a racemic product which differed from **2** in its nmr spectrum. Since the sequence had involved three noncrystalline and presumably somewhat impure intermediates, it was decided to hydrolyze the cyanoethylenamine (**4**) to the ketonitrile (**5**) in the expectation that the latter substance would be sufficiently stable for characterization. This proved to be the case, and the crystalline, pure **5** was of further utility for the investigation of the configuration of the cyanoethyl group. Treatment of the cyanoethyl ketone with refluxing methanolic sodium methoxide resulted in considerable degradation, but yielded unchanged starting material, with no indication of epimerization. This failure to effect an epimerization of the cyanoethyl group suggested that this moiety possessed the desired equatorial (and hence *trans*) configuration, a suggestion confirmed by a similar experiment with the imine (**7**). Treatment of **7** with sodium hydride in refluxing tetrahydrofuran followed by hydrogenation of the total product yielded the same mixture (predominantly **8**) as in the first experiments. It thus appeared that the configurations of four of the cyclohexane substituents were the desired ones, and that the "wrong" isomer obtained from the imine reduction differed from lobinaline only in the configuration at the carbon–nitrogen ring juncture, if the all-*trans* hypothesis for the structure of lobinaline was correct. Some further support for this idea was obtained by comparison of the nmr spectra of the "wrong" synthetic product and of "dehydrolobinaline"[1] with the spectra of the two epimeric N-pyrrolidino compounds (**9** and **10**) derived from *trans,trans*-3,5-diphenyl-4-(2-pyridyl)cyclohexanone[2]. In the spectrum of the selenium dioxide product[1] no aliphatic signals were found below 3.4 ppm in the nmr. In the supposedly comparable **9**, which had been shown by chemical means to have the equatorial pyrrolidino group (and hence axial proton) at C_1, no aliphatic proton signal appeared below 3.56 ppm. In the "wrong" synthetic decahydroquinoline derivative prepared from **8**, on the other hand, a multiplet (two protons) was observed at 3.4–4.1 ppm; one of these proton signals is assigned to the C_9H. The nmr spectrum of the *trans,trans*-axial pyrrolidino derivative (**10**), with equatorial C_1H exhibited a similar two-proton multiplet at 3.5–3.95 ppm.



With this somewhat more definite indication that a *trans* ring juncture was the proper goal of the sequence, and that this was not readily attainable directly from the imine, attention was turned to alternative methods of synthesis. Hydrogenation of the cyano ketone (**5**) with palladium–charcoal in ethanol in the presence of a small quantity of aqueous ammonia again took the wrong course, presumably through the imine intermediate, to yield **8**. As in the reduction of the imine, other, minor products were detected on thin layer chromatography of the mixture, but these eluded isolation. The synthetic route which was finally successful was suggested by the earlier observation[2] that hydrogenation of *trans,trans*-3,5-diphenyl-4-(2-pyridyl)-cyclohexanone proceeded to yield chiefly the equatorial alcohol. Since certain reductive aminations of the ketone which had been carried out[6] (Pd–C) had been found to proceed very rapidly, as opposed to the relatively slow reduction of the nitrile, it was hoped that the reduction would take a different course in the presence of a large excess of anhydrous ammonia. Specifically it was thought that because of the difference in rates a reductive amination of the carbonyl might first take place to yield, at least partially, the desired equatorial cyclohexylamine, and that this amino group might then add to the nitrile (or its aldimine hydrogenation product) to produce, after a subsequent hydrogenolysis, the desired decahydroquinoline derivative. That the reaction did proceed by this course was indicated by the absorption of the first mole of hydrogen in 1 hr, while the remaining 2 moles were taken up overnight. Thin layer chromatography of the total product indicated a mixture of two major

(5) *Cf.* L. Cohen and B. Witkop [*J. Am. Chem. Soc.*, **77**, 6595 (1955)] for a similar preparation of $\Delta^{1,9}$-octahydroquinoline.

(6) These preparations will be reported at a future date.

components, both of which were present in the more complex mixtures from the earlier reductions. No crystalline material could be separated either by crystallization or chromatography, however; so the mixture was methylated directly, with formaldehyde–formic acid. The methylation product was also found by thin layer chromatographic investigation to consist of two major components, one of which corresponded to dehydrolobinaline. Seeding a concentrated petroleum ether solution of the product with dehydrolobinaline resulted in the crystallization of a 26% yield of optically inactive **2**. The *d* and *dl* compounds form a racemic solid solution, for the melting points were identical and undepressed on admixture. The natural and racemic substances were identical in all respects except rotation and Nujol infrared spectra, as shown by comparison of nmr and infrared solution spectra as well as thin layer chromatography in several systems.

An attempt was also made to combine the last two steps of the synthetic sequence by hydrogenation of the ketonitrile (**5**) in the presence of a large excess of ethanolic methylamine. Interestingly, this reaction took almost exclusively the undesired course to yield mainly the *cis*-N-methyldecahydroquinoline derivative, with only a very small quantity of **2** present.

Experimental Section[7]

Cyanoethylation of the Enamine (3).—Preparation of the enamine (**3**) was carried out as reported in the previous paper[2] from 9.80 g of 3,5-diphenyl-4-(2-pyridyl)cyclohexanone, except that toluene and pyrrolidine were removed as completely as possible from the residual oil by prolonged pumping *in vacuo*. The resulting amorphous froth was dissolved in 75 ml of dry dimethylformamide, 3.18 g of freshly distilled acrylonitrile was added, and the solution was refluxed under nitrogen for 24 hr. The solvent was removed as completely as possible under aspirator vacuum, dry benzene was added, and the evaporation was repeated, after which the residual oil was dried *in vacuo* overnight to yield a gum. The infrared spectrum of the crude **4** showed an enamine absorption at 1635, a weak carbonyl band at 1710 due to traces of unconverted ketone, and the nitrile absorption at 2250 cm^{-1}.

Lithium Aluminum Hydride Reduction of 4.—A solution of the above product in 50 ml of dry ether was added over a 20-min period with stirring to a suspension of 2.4 g of lithium aluminum hydride in 200 ml of the same solvent; the reaction was carried out under nitrogen. After refluxing the mixture for 3 hr, it was chilled and excess hydride was decomposed by addition of wet ether followed by water. The ether layer was decanted, the alumina was washed with two additional portions of ether, and the solvent was evaporated to a yellow froth. This was dissolved in 50 ml of methanol, 25 ml of water and 2 ml of 10% sodium hydroxide were added, and the solution was heated under nitrogen on the steam bath for 1 hr. The methanol was evaporated *in vacuo*, the product was extracted into methylene chloride, and the dried extract was evaporated to yield 11 g of crude imine (**7**). The infrared spectrum showed the imine absorption at 1655, no nitrile band, and only a trace of ketone absorption at 1700 cm^{-1}.

Reductions of the Imine (7).—The imine (2.2 g) was hydrogenated at atmospheric temperature and pressure in 60 ml of glacial acetic acid with the catalyst prepared by prereduction of 0.5 g of platinum oxide. Since hydrogenation was very slow, an additional 0.5 g of catalyst was added during the process. When approximately the theoretical hydrogen had been taken up, the catalyst was separated and the chilled solution was diluted with water and made alkaline with ammonia. Extraction of the product into methylene chloride and evaporation of the dried extracts were followed by trituration of the resulting reddish foam with several portions of hot hexane. The 1.09 g of hexane-soluble product was chromatographed on 30 g of activity II basic alumina. Early fractions eluted by 3:1 benzene–hexane and by benzene crystallized on standing in low-boiling petroleum ether (bp 30–60°) to yield 0.185 g of crude **8**, mp 120–128°. Recrystallizations from hexane yielded the analytical sample, mp 134–136°. In the ultraviolet maxima were observed at 257 mμ (ε 3550), 262 (3870), and 269 (2930), while minima appeared at 233 mμ (ε 890), 259 (3510), and 267 (2650). In the nmr spectrum, which was very similar to that of the axial pyrolidino compound (**10**), a two-proton multiplet which included the C_9H signal appeared at 3.3–3.9 ppm, indicating an equatorial configuration for this proton. The phenyl protons appeared as a single peak at 6.98, the α-pyridyl proton appeared at 8.33, and the C_3' pyridyl hydrogen appeared at 6.25 ppm.

Anal. Calcd for $C_{26}H_{28}N_2$: C, 84.74; H, 7.66; N, 7.60. Found: C, 84.53; H, 7.82; N, 7.79.

The imine (2.0 g) was also reduced by treatment with 2 g of sodium borohydride in 150 ml of methanol at ambient temperature. After stirring the mixture for 3 hr, the solvent was removed and the residue was treated with water and extracted into methylene chloride. Evaporation of the dried extract left 2 g of pink foam which was extracted with hot hexane. The soluble portion (0.78 g) was chromatographed on 25 g of basic alumina as above. The only crystalline material isolated was **8** which, after one recrystallization from hexane, had mp 131–133°, undepressed on admixture with the earlier reduction product.

In another experiment 2.6 g of the imine was dissolved in dry tetrahydrofuran, 0.25 g of sodium hydride was added, and the mixture was refluxed for 2 hr. Ethanol was added to decompose the hydride, the solvent was evaporated, and the residue was extracted into methylene chloride. After filtration and evaporation the residue was hydrogenated as before. The usual work-up yielded 1 g of hexane-soluble material which was compared with the usual hydrogenation product by thin layer chromatography. The major components were the same, though numerous minor decomposition products were formed in the base treatment.

Methylation of 8.—The cyclization product (0.357 g) was treated with 0.2 g of 97–100% formic acid and 0.083 g of 36% aqueous formaldehyde, and the mixture was heated on the steam bath for 4 hr. Water (20 ml) was added, the mixture was made alkaline with ammonium hydroxide, the product was extracted into methylene chloride, and the dried extract was evaporated to yield 0.358 g of amorphous residue. Since this could not be recrystallized, it was purified by chromatography on 20 g of activity II–III neutral alumina. The product (0.31 g) was obtained in the earlier fractions by elution with 1:1 benzene–hexane. Recrystallization from low-boiling petroleum ether yielded 0.22 g of the N-methyl-*cis*-decahydroquinoline derivative, mp 127–130°. The analytical sample, prepared by further recrystallizations from the same solvent, had mp 128–130°. In the ultraviolet, maxima were observed at 258 mμ (ε 3450), 262 (3750), and 269 (2870), while the minima appeared at 233.5 mμ (ε 1220) and 267 (2640). In the nmr the N-methyl signal appeared at 2.28 ppm, and the spectrum was otherwise very similar to that of **8**. The α-pyridyl proton signal appeared at 8.38, the pyridyl $C_3'H$ signal appeared at 6.30, and the benzene protons appeared at 7.03 ppm.

Anal. Calcd for $C_{27}H_{30}N_2$: C, 84.77; H, 7.91; N, 7.32. Found: C, 84.76; H, 8.05; N, 7.15.

Preparation of the Cyano Ketone (5).—The crude nitrile (**4**), obtained *via* **3** from 11.17 g of *trans,trans*-3,5-diphenyl-4-(2-pyridyl)cyclohexanone, was dissolved in 100 ml of ethanol, 100 ml of water was added, and the mixture was refluxed for 1.5 hr under nitrogen. Evaporation of the ethanol followed by extraction into methylene chloride and evaporation of the dried solvent produced a brown residue which yielded 8.9 g of ketone, mp 147–149°, on trituration with ether. The analytical sample was prepared by recrystallizations from benzene–petroleum ether, mp 151–153°. The infrared spectrum exhibited a carbonyl band at 1710 and a weak nitrile absorption at 2245 cm^{-1}. In the nmr spectrum the pyridine α-proton signal appeared at 8.43 and that due to the C_3'-proton at 6.22 ppm. The benzene aromatic protons appeared as a singlet at 7.08 ppm, while the aliphatics were extemely complex.

(7) Melting points and boiling points are uncorrected. The nmr spectra, determined in deuteriochloroform unless otherwise noted, were obtained with the Varian A-60 spectrometer at 60 Mc/sec using tetramethylsilane as internal reference. Chemical shifts are quoted in δ units (ppm) while coupling constants (*J*) are expressed as cps. Ultraviolet spectra (wavelengths expressed in mμ, extinction coefficients as ε) were determined in methanol and infrared spectra as Nujol mulls unless otherwise indicated.

Anal. Calcd for $C_{26}H_{24}N_2O$: C, 82.07; H, 6.36; N, 7.36. Found: C, 82.39; H, 6.52; N, 7.09.

Reduction of the Cyano Ketone to 8.—A solution of 1.52 g of **5** in 80 ml of absolute ethanol and 20 ml of aqueous ammonium hydroxide was stirred with hydrogen at atmospheric pressure in the presence of 0.3 g of 10% Pd–C. Since hydrogen absorption was slow, 0.2 g of fresh catalyst was added during the process. After hydrogenation overnight, approximately the theoretical quantity of hydrogen had been absorbed. The catalyst was separated and the solvent was evaporated to yield 1.43 g of amorphous residue, which consisted of one major and two smaller components by thin layer chromatography. This was dissolved in 3:1 benzene–hexane and chromatographed on 35 g of activity II–III alumina. Combined, early fractions, eluted with benzene–hexane could be crystallized from hexane on seeding with the material from reduction of the imine. After several recrystallizations 0.207 g of **8**, mp 133–136°, was obtained. This was identical with the earlier material as shown by comparison of infrared spectra and thin layer chromatography. No crystalline material could be obtained from later, impure fractions which were mixtures by thin layer analysis.

Attempted Epimerization of 5.—A solution of 381 mg of **5** and 10 mg of sodium in 25 ml of dry methanol was refluxed under nitrogen. Since a sample which was removed for thin layer chromatography after 2 hr showed little change, heating was continued for a total of 19 hr. Chromatographic comparison (chloroform–methanol, 95:5, on alumina GF) showed only starting material plus four small new spots of roughly equal magnitude.

Hydrogenation of 5 in Ethanolic Ammonia.—Approximately 4 g of anhydrous ammonia was dissolved in 125 ml of absolute ethanol, and 1 g of 10% Pd–C was saturated with hydrogen in this mixture. The cyano ketone (1.90 g) was added in 75 ml more of absolute ethanol; the mixture was stirred with hydrogen overnight, during which time exactly the theoretical quantity of hydrogen was absorbed. The usual work-up afforded 1.84 g of white froth, which was seen to consist chiefly of two components by thin-layer investigation. When chromatography on alumina failed to effect a separation of these materials, the combined, recovered product was heated with 1.12 g of 90% formic acid and 0.47 g of 36% aqueous formaldehyde on the steam bath for 4 hr, then allowed to stand overnight. The mixture was diluted with water and made alkaline with ammonia, after which the product was extracted into methylene chloride and the dried extract was evaporated to yield 1.85 g of amorphous product. Thin layer examination disclosed two major components[8] one of which corresponded to dehydrolobinaline.[1] The residue was dissolved in boiling hexane, the solution was filtered through Darco, and the colorless filtrate was evaporated. Dissolution of the residue in a small volume of low-boiling petroleum ether and seeding with a crystal of natural dehydrolobinaline caused crystallization of 496 mg (26%) of shiny plates having mp 135–137°. The analytical sample, prepared by recrystallizations from low-boiling petroleum ether, had mp 141–142° alone and mp 140.5–141.5° on admixture with the lobinaline degradation product. The synthetic substance obtained by seeding was optically inactive (dehydrolobinaline $[\alpha]^{26}D$ +44°). The infrared ($CHCl_3$) and nmr solution spectra of the natural and synthetic substances were superimposable. In the nmr spectrum, which was very similar to that of the equatorial pyrrolidino derivative (**9**), the N-methyl peak appeared at 2.32, the α-pyridyl proton at 8.42, the C_3'-pyridyl hydrogen at 6.15, and the phenyl proton absorptions at 7.03 ppm.

Anal. Calcd for $C_{27}H_{30}N_2$: C, 84.77; H, 7.91; N, 7.32. Found: C, 84.87; H, 8.01; N, 7.21.

Hydrogenation of 5 in Ethanolic Methylamine.—The ketonitrile (380 mg) was hydrogenated in 40 ml of absolute ethanol containing 0.8 g of anhydrous methylamine. The Pd–C catalyst (200 mg, 10%) had been presaturated with hydrogen in this solvent. This hydrogenation, unlike the reaction in ethanolic ammonia, proceeded slowly from the start, and 6 days elapsed before the theoretical hydrogen had been absorbed. The usual work-up afforded 370 mg of froth which, on thin layer chromatography[8] (chloroform–methanol solvent) showed a large, slow spot corresponding to the methylation product derived from **8**, and only a very faint, small spot corresponding to **2**. An infrared spectrum (Nujol) of the froth also corresponded to the spectrum of the *cis* reduction product, and difiered from that of the *trans*.[9] Since the product could not be brought to crystallization, it was chromatographed on activity II–III neutral alumina in 3:1 hexane–benzene. The early hexane–benzene and benzene eluates yielded the *cis*-N-methyldecahydroquinoline derivative which had mp 125–127° after recrystallizations from petroleum ether. The identity with the substance as prepared by methylation of **8** was confirmed by thin layer comparison (hexane–diethylamine, silica gel GF).

Acknowledgment.—The authors wish to express their sincere appreciation to Dr. Emil Schlittler for his interest and encouragement in this study. They are also greatly indebted to Dr. H. B. MacPhillamy for valuable discussions, to Miss Natalie Cahoon and co-workers for spectral results, to Mr. B. Korzun and Mr. S. Brody for thin layer chromatographic analyses, and to Mr. G. Roberston and co-workers for analyses.

(8) Microplates prepared by dipping microscope slides in a chloroform slurry of silica gel G (Merck).

(9) The aromatic absorptions in the 700–800-cm^{-1} region are different and quite characteristic for the isomers.