with ammonia, extraction into methylene chloride, and evaporation of the dried extract produced 7.3 g of an amber oil which was subjected to a prolonged evaporative distillation up to 85° (~0.1 mm). The distillate, which was transformed to a crystalline solid on trituration with petroleum ether (bp 30–60°) was dissolved as completely as possible in boiling *n*-hexane. Evaporation to a low volume and crystallization followed by work-up of mother liquors yielded a total of 3.7 g of product, mp 83–85.5°. In the initial small-scale preparation a similar processing yielded crystals, mp 59–60°, which were used for the analytical sample. On storage the crystal form changed to yield the higher melting modification. The carbonyl absorption in the infrared appeared at 1667 cm^{-1}, while in the nmr spectrum the N-methyl signal appeared at 2.58 and the α-pyridyl protons at 8.70 ppm. The ultraviolet (methanol) λ_{max} appeared at 201 mμ (ε 18,480), 238 (9240), 272 (8880), and 340 (570), and λ_{min} appeared at 222 mμ (ε 7000), 254 (6580), and 314 (410).

Anal. Calcd for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.09; N, 14.13. Found: C, 72.50; H, 4.93; N, 14.17.

2-Pyridyl-3-(2-methyl)pyridylmethane.—A mixture of 8.72 g of ketone, 5.0 ml of 99% hydrazine hydrate, 0.9 ml of water, 4.95 g of potassium hydroxide, and 40 ml of triethylene glycol was stirred at room temperature for 2 hr, then warmed to 110–125°. The red solution, from which gas was evolved, was held at this temperature for 1 hr, then warmed to about 170° and maintained at this temperature for 45 min. It was then cooled and poured into 300 ml of cold water, and the product was extracted into methylene chloride. Evaporation of the dried extracts and distillation produced 6.95 g of colorless liquid, bp 116–120° (0.5 mm). For analysis a small sample was redistilled in a bulb apparatus at 0.05 mm using a bath temperature of approximately 100°. In the ultraviolet (methanol) the substance showed a maximum at 263 mμ (ε 8000) and a minimum at 229 mμ (ε 1540) thus indicating the presence of isolated pyridine rings.

Anal. Calcd for $C_{12}H_{12}N_2$: C, 78.23; H, 6.57; N, 15.21. Found: C, 78.46; H, 6.62; N, 15.40.

A dipicrate was prepared from a sample of the substance in ethanol and recrystallized from 4:1 ethanol-water, mp 202–203°.

Anal. Calcd for $C_{12}H_{12}N_2 \cdot 2C_6H_3N_3O_7$: C, 44.90; H, 2.81; N, 17.45. Found: C, 45.00; H, 3.04; N, 17.54.

5-(2-Pyridyl)-6,7-diphenylquinoline (9).—Benzil (210 mg) and the picolylpicoline (185 mg) were sealed in a Carius tube and heated at 185° for 18 hr. The product was dissolved as completely as possible in 35 ml of ether and the solution filtered through Darco several times to remove the red color. The light yellow solution was extracted thoroughly with 10% hydrochloric acid, the extracts were washed with ether and filtered through Darco, and the free base was liberated by addition of ammonium hydroxide. Extraction into methylene chloride and evaporation of the dried extracts yielded a gum which crystallized on trituration with petroleum ether to yield 140 mg of crude product, mp 185–190°. Recrystallizations from acetonitrile produced the analytical sample, mp 193–194°. In the nmr the C_6' pyridyl proton signal appeared at 8.68, the C_2H at 8.96 (dd), the C_8H at 7.30 (s), the C_4H at 7.89 (dd), the $C_4'H$ at about 6.4, and the 5′, 3′, and 3 proton signals at 6–6.3 ppm. The two phenyl signals appeared as narrow bands at 6.93 and 7.17 ppm. The ultraviolet maxima (methanol) were found at 207 mμ (ε 46,070), 238 (47,960), and 321 (5040) while minima were observed at 223 mμ (ε 33,360) and 317 mμ (ε 5010).

Anal. Calcd for $C_{26}H_{18}N_2$: C, 87.12; H, 5.06; N, 7.82. Found: C, 87.10; H, 5.27; N, 7.79.

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 coworkers for spectral results, to Mr. B. Korzun and coworkers for thin layer chromatographic analyses, and to Mr. G. Robertson and staff for analytical results.

The Preparation and Characterization of Some Triarylcyclohexanes Related to Lobinaline

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3-Hydroxy-3,5-diphenyl-4-(2-pyridyl)cyclohexanone (1), which is prepared by base-catalyzed condensation of 2-phenacylpyridine with benzalacetone, has been shown by nmr spectral investigations to have all *trans*-aryl groups. Dehydration of 1 with phosphoric acid at room temperature proceeds to yield *trans*-3,5-diphenyl-4-(2-pyridyl)cyclohexen-2-one (3), while at 100° epimerization at the 4 position results in the production of a mixture of *cis*- and *trans*-enones. Hydrogenations of the cyclohexenones to the corresponding saturated ketones are described, as well as conversion of the latter through their pyrrolidine enamines to 1-N-pyrrolidinocyclohexanes. The configurations of the various derivatives were correlated by chemical as well as spectral methods. Preparation and characterization of some compounds in the closely related triphenylcyclohexane series are also described.

In the course of an investigation of the structure of the alkaloid lobinaline,[1] certain aromatized degradation products of the alkaloid were synthesized *via* 3-hydroxy-3,5-diphenyl-4-(2-pyridyl)cyclohexanone (1). The initial studies involved dehydration of the hydroxy ketone to what was subsequently recognized as being a mixture of epimeric diphenylpyridylcyclohexenones, and aromatization of the azine derivative of the latter to 3,5-diphenyl-4-(2-pyridyl)aniline. In subsequent studies we became interested in the stereochemistry of the cyclohexane derivatives, because of certain early recognized similarities between these and lobinaline. It was felt that a study of the stereochemistry of the simpler cyclohexane derivatives might provide a possible basis for the subsequent elucidation of the relative configurations of the five asymmetric centers of lobinaline, and perhaps for a rational approach to the synthesis of the alkaloid.[2] This paper describes the clarification of the stereochemistry of the cyclohexane derivatives by a combination of spectral and chemical methods.

Reaction of benzalacetone and 2-phenacylpyridine to produce the hydroxy ketone (1) also yielded the uncyclized 1,3-diphenyl-2-(2-pyridyl)-1,3-hexanedione (2) as a minor by-product. The structure of the latter followed from the analysis and the presence of two carbonyl absorptions at 1685 and 1700 cm^{-1} in the infrared.

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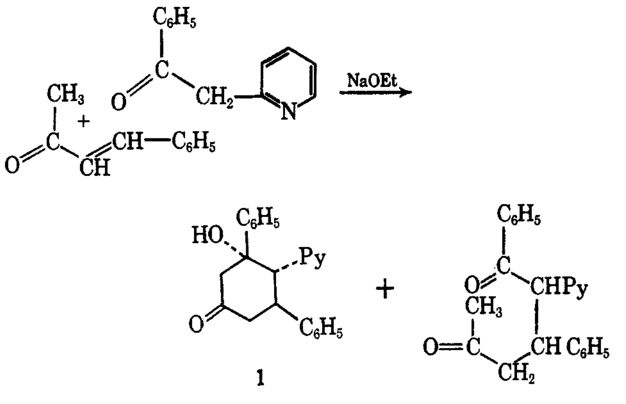
(1) *Cf.* preceding communication: M. M. Robison, W. G. Pierson, L. Dorfman, B. F. Lambert, and R. A. Lucas, *J. Org. Chem.*, **31**, 3206 (1966).

(2) *Cf.* the accompanying paper [M. M. Robison, B. F. Lambert, L. Dorfman, and W. G. Pierson, *ibid.*, **31**, 3220 (1966)] for the total synthesis of the lobinaline ring system.

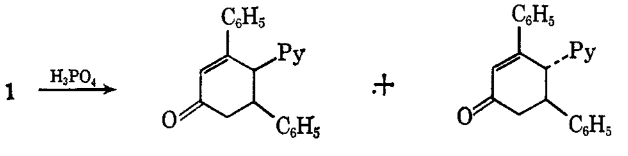


1

2

The *trans,trans* configuration of the aryl groups in **1** was based on the nmr spectra of this and related compounds in the series. The hydroxyl proton (replaceable by D_2O) was found in the aromatic region at about 7.0 ppm. The two methylene groups appeared as a pair of overlapping AB quartets, in which the C_6 protons have added complexity due to the adjacent tertiary hydrogen. The C_4H appeared as a doublet at 3.76 ppm ($J = 11.4$ cps), while the C_5H appeared as a very broad multiplet in the 3.5–4.1-ppm region. The breadth of the latter was such as to indicate two diaxial interactions, and thus diequatorial conformations for the C_4 and C_5 aryl groups. It could also be concluded that the C_3 phenyl is equatorial because of the similarity of the aromatic and aliphatic regions of the spectrum to those of another compound in the series (**5**, *vide infra*). The two phenyl groups appeared at 7.12 ppm as a single, strong signal. The narrowness of the band is indicative of relatively free rotation of the groups resulting in magnetic equivalence of the protons involved, a situation only possible with equatorial aryl substituents.

The hydroxy ketone was originally dehydrated in phosphoric acid at 100°, under which conditions epimerization took place at C_4 to produce a mixture of *cis*- (**3**) and *trans*-cyclohexenones (**4**). Such an epimerization can be easily rationalized when it is realized that the C_4 hydrogen is activated not only by the conjugated carbonyl, but also by the adjacent protonated pyridine ring. The structures of the two substances, which were separated by preparative thin layer chromatography, were demonstrated by the nmr spectra.

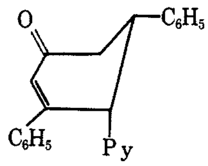


3

4

In the case of **3**, the signals of the four alicyclic protons give the appearance of a first-order ABXY spectrum in which little if any coupling is seen between A, B, and Y, and the couplings are recorded accordingly. The protons of the methylene group are widely separated and the pseudo-equatorial hydrogen appears as a doublet of a doublet centered at 2.51 ppm ($J_{AB} =$ 16 cps, $J_{A_{eq}}J_{5_{ax}} = 3.8$ cps). The deshielded C_6 pseudo-axial proton signal is at 3.32 ppm ($J_{B_{ax}}J_{5_{ax}} = 14.3$ cps); the unusually large diaxial coupling must be due to the aromatic substitution. The axial hydrogen at C_5 is centered at 4.03 ppm and has the appearance of a triplet of a doublet (center band is composed of two bands), while the pseudo-equatorial hydrogen at C_4 is a doublet centered at 4.48 ppm ($J_{4,5} = 4.5$ cps). It is interesting to note that the protons of the two phenyl rings produce a complex pattern. The vinyl proton is at 6.77 ppm and is undoubtedly split by the C_4 hydrogen ($W_H = 2$ cps).

The spectrum of **4** is deceptively simple owing to the near magnetic and chemical equivalence of the methylene protons, which are symmetrically disposed with respect to the pseudo-axial C_4 and C_5 aromatic systems. The methylene protons appear as a doublet centered at 2.84 ppm. The equatorial proton at C_5 is a quartet at 3.84, while the C_4 equatorial hydrogen is a slightly broadened doublet at 4.70 ppm ($J =$ approximately 5 cps). The small coupling constant substantiates the conformational relationship of C_4H and C_5H. The phenyl proton signals appear as a singlet at 7.20, as would be expected if the two groups are diaxial with minimum interactions. The vinyl proton at 6.67 ppm is slightly split by the C_4H ($J = 1$ cps).



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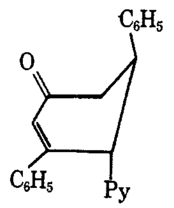
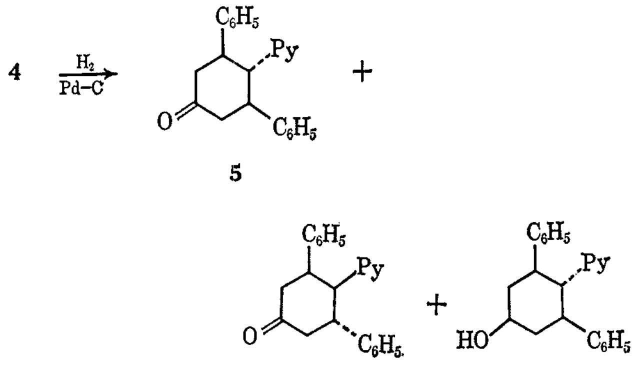


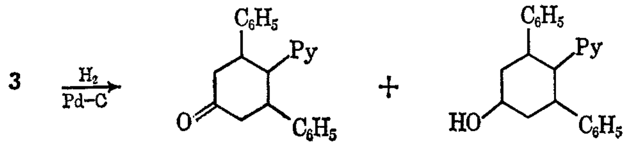
4

Hydrogenation (Pd–C) of the carbon–carbon double bond to afford an entry into the saturated ring system was originally carried out on the mixture of **3** and **4** obtained from the high-temperature dehydration. From the mixture of products a 40% yield of the relatively insoluble, highly crystalline *trans,trans*-3,5-diphenyl-4-(2-pyridyl)cyclohexanone (**5**) was isolated. Subsequent hydrogenations of the pure enones as well as careful large-scale chromatography of the mother liquor residue from hydrogenation of the mixture revealed that the hydrogenations are complex. Reduction of **4** (Pd–C) yields, in addition to **5**, an appreciable fraction of *cis,trans*-3,5-diphenyl-4-(2-pyridyl)cyclohexanone (**6**), a smaller amount of *trans,trans*-equatorial alcohol (**7**), and unidentified trace impurities. Use of Raney nickel, on the other hand, yields mainly **6** and **7**. It may be noted that the concomitant formation of the *cis,trans* and *trans,trans* reduction products is in accord with expectations, since neither side of **4** (in the "flip form" with equatorial aryl groups) should be appreciably more readily accessible to the catalyst surface. Hydrogenation of **3** was also unexceptional. Whether the molecule be viewed as having the above structure as indicated by the nmr analysis or as existing to an appreciable extent in the other "flip form," it would be expected to approach the catalyst on the side without the axial aryl group. Hydrogenation in either form would yield *cis,cis*-3,5-diphenyl-4-(2-pyridyl)cyclohexanone (**8**), which was the major product. In addition, a smaller quantity of the *cis,cis*-equatorial alcohol (**9**) was detected. This could be reoxidized to the parent ketone by CrO_3.



5

6 7



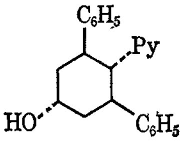
8 9

The four methylene-group protons of **5** appear in the nmr as a broad multiplet centered at 2.81, while the C_4H signal appears as a multiplet centered at 3.31 ppm. The C_3 and C_5 protons appear as a broad multiplet (width at least 25 cps) at about 3.5–4.0 ppm. It may be assumed that the C_4H signal appears farther upfield owing to increased shielding by the two phenyl groups. It may further be noted that the C_3 and C_5 protons can only appear at the same location in a symmetrical, *i.e.*, all-*trans* situation. The phenyl group proton signals appear as a narrow band at 7.08 ppm as in the spectrum of **1**, and the pyridyl proton signals are similar in complexity and position to those in the spectrum of **1** as well.

The nmr spectrum of **8** also lent itself to ready interpretation. As was also observed in the case of the enone, a characteristic, almost first-order pattern can be observed for the methylene protons when the C_4 substituent is axial, owing to deshielding of the $C_{2,6}$ axial protons by the C_4 group. The two equatorial methylene protons appear as a broad doublet at 2.58 ppm ($W_{H,6e5a/2e3a}$ = 4.6 cps, $J_{6,6/2,2}$ = 13 cps), while the two axial methylene protons appear as a doublet of a doublet at 4.17 ($J_{6a5a/2a3a}$ = 12.3 cps, $J_{6,6/2,2}$ = 13 cps). The $C_3'H$ pyridyl proton signal was observed at 6.07 and $C_6'H$ at 8.60 ppm.

The structure of **6** follows mainly from its mode of preparation and from a process of elimination after the above assignments, since the spectrum was considerably more complex. The fact that the methylene protons did not resolve into a clear-cut AB pattern would indicate that the pyridine ring is equatorial, in agreement with expectation if the ring is in a pure chair form. It seems probable, however, that the ring is distorted considerably in this, as in other *cis,trans* compounds (*vide infra*).

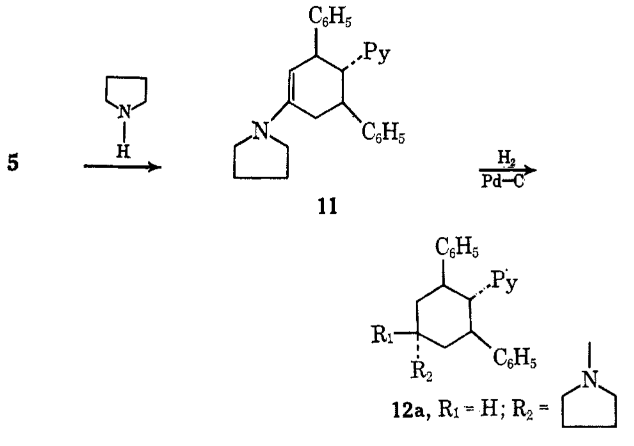
The determination of the hydroxyl group configurations in **7** and **9**, which was based on the positions of the C_1 proton signals in the nmr, was made possible by the preparation of the *trans,trans*-axial epimer of **7**. The third alcohol (**10**) was obtained as the minor product (7% yield) from hydrogenation of the ketone (**5**) with Adams catalyst. It was separated from the equatorial alcohol by preparative thin layer chromatography. The *p*-bromobenzenesulfonate esters of the alcohols were also prepared to ensure, by the shifts of the C_1 proton signals, that the proper assignments had been made for these protons.



10

It is well established that an equatorial proton signal is farther downfield than an axial proton signal, and this was observed in these series. Further proof was given by the width at half-height of the signals. In the case of the equatorial protons, W_H was observed to be about 9.5 cps indicating only axial–equatorial and equatorial–equatorial interactions, while the axial proton signals showed a W_H of about 20–23 cps reflecting the large axial–axial interaction together with the smaller axial–equatorial coupling. In the spectrum of compound **7**, the C_1H signal was observed at 4.17 ppm as a broad band, W_H = approximately 23 cps. The signal was shifted in the corresponding brosylate to 4.90 ppm with a similar width. Compound **10**, on the other hand, showed a C_1H signal downfield at 4.44 ppm (W_H = 9.5 cps), while in the brosylate spectrum the signal appeared at 5.13 ppm (W_H = 7.0 cps). That the hydroxyl in **9** was equatorial was shown by the C_1H signal at 4.13 (W_H = 20 cps) and the equally broad, shifted signal in the brosylate spectrum at 4.88 ppm.

For the purpose of attaching a side chain at position 2 of the ring to effect a synthesis of the lobinaline ring system,[2] compound **5** was converted to its pyrrolidine enamine derivative (**11**). The enamine was also hydrogenated to what was subsequently recognized to be the axial pyrrolidinocyclohexane (**12a**). The *trans,trans*-equatorial pyrrolidino epimer (**12b**, R_1 = pyrrolidino, R_2 = H) was obtained as a minor byproduct (7% isolated) from a one-step reductive amination of **5** and separated by fractional crystallization. The configurational assignments for the two epimers were originally made on the basis of the nmr spectra, using the same reasoning applied to the alcohols. In the case of **12a** (equatorial C_1H) a two-proton multiplet was observed at 3.5–3.95 ppm; one of the protons is considered to be that at C_1. The spectrum of **12b**, on the other hand, showed no aliphatic proton signals



11

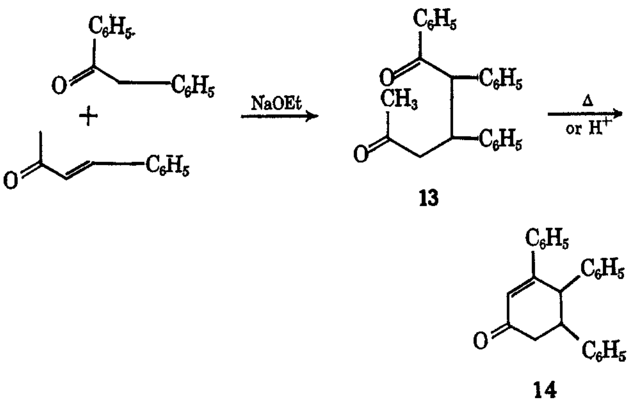
12a, R_1 = H; R_2 =

downfield of 3.56 ppm. These nmr conclusions were subsequently confirmed in two ways. First, it was found that the equatorial pyrrolidino compound (**12b**) on treatment with methyl iodide in acetonitrile undergoes methylation 700 times faster than does the axial pyrrolidino compound.[3] Such a result is to be expected on the basis of the greatly increased steric hindrance in the axial epimer which is evident on examination of models. Second, the axial epimer was prepared by reaction of pyrrolidine with the equatorial brosylate referred to above.

Hydrogenation of the pyrrolidine enamine derived from the *cis,cis* ketone (**8**) took a different course, in that roughly equal amounts of the axial and equatorial N-pyrrolidinocyclohexanes were formed. These were also separated by fractional crystallization, and configurations were again assigned on the basis of the nmr spectra. In the case of the axial pyrrolidino compound, the C_1 equatorial proton signal was observed in a broad band (two protons) centered at about 3.87 ppm, while the axial proton in the epimer could not be placed with certainty; no aliphatic proton signal was found below 3.31 ppm, however. Treatment of the equatorial brosylate with pyrrolidine again resulted in a displacement reaction which served to confirm the structure assigned to the axial pyrrolidino epimer. It may be noted that the aromatic proton patterns in the nmr spectra of the two epimers are almost identical, unlike the situation for the *trans* pair. Such an insensitivity to the pyrrolidino group configuration may indicate a considerable distortion of the cyclohexane ring.

Reduction of the enamine from the *cis,trans* ketone yielded only one isomer, the structure of which could not be determined with certainty. The position of a band (two protons) at about 3.58 ppm would imply an equatorial hydrogen and hence an axial pyrrolidino group—a result not to be expected on the basis of either possible structure if these are considered to exist in the chair form, since this would necessitate a 1,3-diaxial interaction with a phenyl group. The general similarity of the spectrum to that of the all-*trans* system, however, would imply a fair degree of freedom of rotation of the aromatic rings and hence probable great distortion of the cyclohexane moiety. The same product was also formed in a one-step reductive amination of the *cis,trans* ketone. Interestingly, this hydrogenation proceeded rapidly, while the reduction of the enamine was unusually slow.

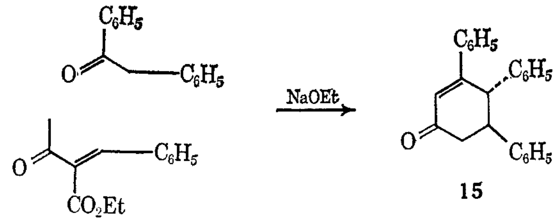
A series of triphenylcyclohexane derivatives was also prepared, and, although the results generally correlated well with the diphenylpyridyl series, some significant differences were observed, which are noted here. Treatment of benzalacetone with desoxybenzoin in the presence of sodium ethoxide at room temperature resulted almost exclusively in the formation of the open-chain dione (**13**), the properties of which were in accord with those reported by Chapurlat and Dreux.[4] It was found that **13** could be transformed directly into the enone (**14**) by heating with ethanolic HCl as reported[4] or that the same product was formed on heating the original reaction mixture.



13

14

That the enone possesses the *cis* configuration (and that **13** is thus *erythro*) was demonstrated by the nmr spectra. Hydrogenation, in this case, did not proceed to yield *cis,cis* saturated ketone; overreduction to the corresponding equatorial alcohol could not be avoided and the saturated ketone was only obtained by reoxidation with chromic acid. What was in this study shown to be the *trans*-enone (**15**) was prepared by condensation of desoxybenzoin with benzalacetoacetic ester according to the method of Cornubert.[5] Hydrogenation again yielded a mixture of *trans,trans*- (**16**) and *cis,trans*-cyclohexanones (**17**) which were separated by fractional crystallization. Treatment of **16** with pyrrolidine and hydrogenation of the enamine proceeded as in the pyridine series to yield solely the axial pyrrolidino compound. Reduction of the enamine derived from the *cis,trans* ketone, however, yielded two products. The major compound, by nmr, appeared to have an axial pyrrolidine group, while that formed in lower yield seemed to have this group equatorial. The spectra gave very similar aromatic patterns, however, and these were also much like the pattern in the spectrum of the all-*trans* derivative. It seems certain that the presence of the four bulky groups in this system necessitates that the ring exist in a distorted, flexible form.



15

Experimental Section[6]

1,3-Diphenyl-2-(2-pyridyl)-1,3-hexanedione (2).—This substance was obtained from the ethanol mother liquor after repeated concentration to collect several batches of the less soluble hydroxycyclohexanone (1).[1] Compound 1 could be separated essentially completely by crystallization from this solvent. The

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[3] We wish to express our appreciation to Dr. Carl Rehm of these laboratories who carried out the conductometric rate studies and who will report the results in detail elsewhere. *Cf.* also M. Shamma and J. B. Moss, *J. Am. Chem. Soc.*, **83**, 5038 (1961).

[4] R. Chapurlat and J. Dreux, *Compt. Rend.*, **251**, 1529 (1960).

[5] R. Cornubert, C. Borrel, M. de Demo, J. Garnier, R. Huneau, H. le Bihan, and G. Sarkis, *Bull. Soc. Chim. France*, [5] **2**, 195 (1935).

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

diketone **2** was recrystallized from benzene for analysis, mp 168–170°. The ultraviolet spectrum showed maxima at 249 mμ (ε 14,780), 265 (9260), 270 (6370), and 318 (330), and minima appeared at 228 mμ (ε 7130) and 308 mμ (ε 300).

Anal. Calcd for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16; N, 4.08. Found: C, 80.62; H, 6.26; N, 3.91.

***cis-* and *trans*-3,5-Diphenyl-4-(2-pyridyl)cyclohexen-2-one (3 and 4).**—Preparative thin layer chromatography of 1 g of the mixture of enones obtained from the high-temperatue dehydration[1] of the hydroxyketone yielded **3** and **4**. The separation, carried out on alumina "GF" in 1:1 benzene–chloroform yielded 0.19 g of the crude, faster moving **3**, and 0.54 g of **4**. The *cis* compound was recrystallized from cyclohexane by addition of methylene chloride to effect dissolution, then evaporation of the lower boiling solvent. The stout needles had mp 170.5–171.5° with slight decomposition. In the ultraviolet the maxima were observed at 228 mμ (ε 10,270), 265 (15,270), 271 (16,620), and 282 (16,870) while the minima appeared at 237 mμ (ε 6040) and 274 mμ (ε 16,340), The carbonyl band in the infrared appeared at 1660 cm^{-1}.

Anal. Calcd for $C_{23}H_{19}NO$: C, 84.89; H, 5.89; N, 4.30. Found: C, 85.42, 85.25; H, 5.97, 6.07; N, 4.18.

The *trans*-enone (**4**), recrystallized in the same manner, showed infrared carbonyl absorption at 1660 cm^{-1} and had mp 140–141°. In the ultraviolet the maxima were at 228 mμ (ε 10,490), 263 (14,880), 270 (16,130), and 282 (14,740) while the minimum appeared at 240 mμ (ε 6660).

Anal. Calcd for $C_{23}H_{19}NO$: C, 84.89; H, 5.89; N, 4.30. Found: C, 84.62; H, 5.98; N, 4.32.

Compound **4** was obtained directly from a room-temperature dehydration in pure form. Five grams of the hydroxy ketone was added to 15 ml of 85% phosphoric acid and the resulting thick, white paste was stirred in a cool-water bath overnight, during which time the starting material gradually reacted and dissolved. After about 20 hr the yellow solution was poured into ice–water, the solution was made alkaline with ammonium hydroxide, and the precipitate was extracted into methylene chloride. The dried extract was evaporated to a low volume, cyclohexane was added, and boiling was continued to expel the first solvent. Essentially pure **4**, mp 136–138°, crystallized on cooling, yield 4.40 g.

When a sample of **4** was heated in phosphoric acid for 1 hr at steam-bath temperature, then worked up as above, a quantitative yield of mixed isomers was obtained, mp 121–127°. Thin layer chromatography indicated the presence of *approximately* equal amounts of the two isomers.

Hydrogenation of the *cis–trans*-Enone Mixture.—The enone mixture obtained from a high-temperature dehydration (358 g) was hydrogenated in 10,800 ml of ethyl acetate at room temperature and 100 psig pressure, using 50 g of 10% Pd–C. After about 30 hr of stirring, the ultraviolet spectrum of a sample was determined. The appearance of a maximum at 282 mμ indicated incomplete hydrogenation, and an additional 25 g of catalyst was added; stirring was continued 24 hr longer to bring the process to completion. After separation of the catalyst the solvent was evaporated, first *in vacuo*, then at atmospheric pressure to the point of incipient crystallization. The resulting ***trans,trans* ketone** (**5**) was recrystallized twice from methylene chloride–ethyl acetate to yield 140 g of product, mp 240–242°. The substance showed ultraviolet maxima at 258 mμ (ε 3370), 262 (3590), and 269 (2700) and minima at 234 mμ (ε 940) and 267 mμ (ε 2530). In the infrared the carbonyl absorption appeared at 1710 cm^{-1}.

Anal. Calcd for $C_{23}H_{21}NO$: C, 84.37; H, 6.47; N, 4.28. Found: C, 84.06; H, 6.65; N, 4.15.

Part of the residue from the crystallization (35 g) was dissolved in 500 ml of benzene and chromatographed on 500 g of activity II–III neutral alumina. The first benzene eluate yielded relatively pure *cis,cis* ketone (**8**) followed by a large fraction which was a mixture of **8**, **5**, and **6**. Further elution with benzene yielded the *cis,cis* alcohol **9** in relatively pure form, and the last substance, which was eluted by 3:1 benzene–ether, was the *trans,trans* alcohol (**7**).

The ***cis,cis* ketone** (**8**) was purified for analysis by recrystallizations from cyclohexane, mp 157–158°. In the ultraviolet, maxima were observed at 258 mμ (ε 3200), 262 (3100), and 271 (2300) and the minimum appeared at 235 mμ (ε 1020). The carbonyl absorption in the infrared appeared at 1700 cm^{-1}.

Anal. Calcd for $C_{23}H_{21}NO$: C, 84.37; H, 6.47; N, 4.28. Found: C, 84.82; H, 6.46; N, 4.27.

The large (20 g) mixed fraction consisting of **8**, **5**, and **6** was separated by fractional crystallizations. It was first dissolved in a mixture of 5:1 cyclohexane–benzene and two successive crops of crystals were taken; these consisted mainly of crude *trans,trans* ketone (**5**) together with some of the *cis,cis* isomer (**8**).[7] The residual oil obtained on evaporating the solvent mixture was next dissolved in 10 ml of ether, from which crude *cis,trans* ketone (**6**), mp 113–133°, crystallized. Successive recrystallizations from methanol and from cyclohexane yielded pure ***cis,trans*-3,5-diphenyl-4-(2-pyridyl)cyclohexanone** (**6**), as first obtained in this investigation. The substance, mp 139.5–140.5°, showed ultraviolet maxima at 259 mμ (ε 3920), 263 (4260), and 270 (3340) and minima at 236 mμ (ε 1170) and 268 mμ (ε 3150). The ketone carbonyl absorption appeared at 1705 cm^{-1}.

Anal. Calcd for $C_{23}H_{21}NO$: C, 84.37; H, 6.47; N, 4.28. Found: C, 84.52; H, 6.45; N, 4.19.

The *cis,cis*-equatorial alcohol (**9**) was purified by recrystallizations from 1:3 benzene–cyclohexane and from cyclohexane–methylene chloride, mp 162.5–163.5°. In the ultraviolet maxima were observed at 208 mμ (ε 22,640), 258 (3240), 261 (3190), and 268 (2390) and minima were found at 232 mμ (ε 830), 260 (3170), and 267 (2380). In the infrared hydroxyl absorptions were noted at 3470 and 3570 cm^{-1}.

Anal. Calcd for $C_{23}H_{23}NO$: C, 83.85; H, 7.04; N, 4.25. Found: C, 83.78; H, 7.00; N, 4.35.

The *trans,trans*-equatorial alcohol (**7**) was recrystallized once from benzene to yield long filaments, mp 213–217°. It was identified by thin layer chromatographic comparison with the analytical sample obtained from PtO_2 reduction of **5** (*vide infra*).

Hydrogenation of *trans*-3,5-Diphenyl-4-(2-pyridyl)cyclohexen-2-one.—A mixture of 5.52 g of the *trans*-enone, 250 ml of ethyl acetate, and approximately 10 g of Raney nickel was shaken at 50 psig for 13 hr at room temperature and then for 28 hr at 50°. After separation of the catalyst and evaporation of the solvent the residue was dissolved in 25 ml of ether, from which 1.62 g of crude *trans,trans*-equatorial alcohol crystallized. The impure material, mp approximately 190–200°, was identified by thin layer chromatographic comparison with authentic **7**. The ether was evaporated; the residual syrup was dissolved in 100 ml of boiling *n*-hexane, filtered through Darco, evaporated to 50 ml, and seeded with *cis,trans* ketone (**6**). The crude **6** which formed was recrystallized from cyclohexane to yield 1.5 g of product, mp 135–137°, undepressed on admixture with authentic material.

The hydrogenation was also carried out at atmospheric pressure using 1.5 g of 10% Pd–C and 4.37 g of enone in 250 ml of ethyl acetate. When the theoretical hydrogen was absorbed the catalyst was separated and the solution was concentrated to 35 ml. The resulting crystals were separated and the solution was concentrated further for a second batch of crude *trans,trans* ketone (**5**). Recrystallization of the combined batches from ethyl acetate yielded 1.90 g of **5**, mp 237–240°. The mother-liquor residue from the initial crystallizations consisted chiefly of *cis,trans* ketone (**6**) as well as smaller amounts of *trans,trans* alcohol (**7**), *trans,trans* ketone (**5**), and unreacted enone (**4**) as shown by thin layer chromatographic comparisons. The *cis,trans* ketone could not be induced to crystallize from the mixture.

Hydrogenation of *cis*-3,5-Diphenyl-4-(2-pyridyl)cyclohexen-2-one.—The *cis* enone (**3**, 162 mg) was hydrogenated at atmospheric pressure in 20 ml of ethyl acetate using 50 mg of 10% Pd–C. The product obtained from the usual work-up consisted mainly of *cis,cis* ketone (**8**) and *cis,cis*-equatorial alcohol (**9**), as shown by thin layer chromatographic comparison with the known substances. No more than a trace of *cis,trans* ketone (**6**) was present in the 161 mg of product.

Hydrogenation of 3,5-Diphenyl-4-(2-pyridyl)cyclohexanone (5).—The ketone (6.54 g) was hydrogenated at atmospheric pressure in 250 ml of absolute ethanol, using the catalyst from prereduction of 0.5 g of platinum oxide. The theoretical quantity of hydrogen was taken up in about 7 hr. After separation of the catalyst and evaporation of the solvent the residue was stirred for 1 hr with 100 ml of ether, after which 5.47 g of the *trans,trans*-equatorial alcohol (**7**), mp 225–227°, was separated by filtration. The sample for analysis after recrystallizations from benzene had mp 227–229°. In the ultraviolet the maxima were observed

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(7) The courses of this and other separations were routinely followed by thin layer chromatographic comparisons on microscope slides. The plates were prepared by dipping in a chloroform slurry of silica gel G (Merck) and developed with chloroform–ethyl acetate mixtures. Spots were detected in an iodine chamber.

at 257 mμ (ε 3540), 263 (3780), and 270 (2780) and the minima at 232 mμ (ε 965) and 267 mμ (ε 2650).

Anal. Calcd for $C_{23}H_{23}NO$: C, 83.85; H, 7.04; N, 4.25. Found: C, 83.70; H, 7.09; N, 4.24.

The ether mother liquor from **7** was evaporated to a gum which was subjected to preparative thin layer chromatography. The more strongly adsorbed ***trans,trans*-axial alcohol (10)** was readily separated on silica gel GF in 1:1 ethyl acetate–hexane. After recrystallizations from cyclohexane the substance had mp 163–165°. In the ultraviolet the maxima were at 209 mμ (ε 21,170), 258 (3540), 262 (3770), and 269 (2840), and the minima appeared at 232 mμ (ε 870), 259 (3500), and 267 (2670).

Anal. Calcd for $C_{23}H_{23}NO$: C, 83.85; H, 7.04; N, 4.25. Found: C, 83.76; H, 7.27; N, 4.31.

Oxidation of the *cis,cis* Alcohol (9).—A solution of 500 mg of the alcohol in 25 ml of acetone was treated at ice-bath temperature with 1.17 ml of a chromic anhydride solution (prepared from 8.4 g of CrO_3, 45 ml of H_2O, and 7.2 ml of concentrated H_2SO_4) with stirring. The mixture was maintained at 0° for 20 min, then at room temperature for 75 min. It was poured into a solution of 1 g of sodium bicarbonate in 25 ml of water, the acetone was evaporated *in vacuo*, and the product was extracted into methylene chloride, which was dried and evaporated. The residue, after recrystallization from cyclohexane, weighed 426 mg and had mp 152–153.5°, undepressed on admixture with authentic **8**. The identity of the product was also demonstrated by thin-layer comparison[7] in ethyl acetate.

***p*-Bromobenzenesulfonate of the *trans,trans*-Equatorial Alcohol.**—Two grams of the alcohol (**7**) was dissolved in 30 ml of anhydrous pyridine, 1.65 g of *p*-bromobenzenesulfonyl chloride was added, and the mixture was allowed to stand in the dark under nitrogen for 3 days. The amber solution was poured slowly into 150 ml of ice–water with stirring. The supernatant liquid was decanted from the resulting pink gum. Repeated washings with fresh portions of water yielded a solid, which was dried and then dissolved in ether. The solution was filtered through Darco and concentrated to a low volume at which point crystals formed. The mixture was diluted with a large excess of low-boiling petroleum ether (bp 30–60°). The resulting crystals had mp 164–164.5°.

Anal. Calcd for $C_{29}H_{26}BrNO_3S$: C, 63.50; H, 4.78; N, 2.56. Found: C, 63.44; H, 4.79; N, 2.47.

***p*-Bromobenzenesulfonate of the *trans,trans*-Axial Alcohol.**—This derivative was prepared by reaction of 300 mg of **10**, 5 ml of pyridine, and 240 mg of *p*-bromobenzenesulfonyl chloride for 26 hr. The solution was poured into ice–water and the resulting gum was washed with fresh water, then extracted into methylene chloride, and the dried extract was evaporated. The residual oil solidified on trituration with petroleum ether. The solvent was decanted, the residue was dissolved as completely as possible in ether, and the solution was filtered and concentrated to yield the crystalline derivative, mp 164–164.5°. On admixture with the derivative obtained from the equatorial alcohol this substance melted at 153–156°. The lack of identity of the two materials was further demonstrated by significant differences in the fingerprint region of the infrared spectra as well as the above-mentioned differences in the nmr spectra.

Anal. Calcd for $C_{29}H_{26}BrNO_3S$: C, 63.50; H, 4.78; N, 2.56. Found: C, 63.55; H, 4.82; N, 2.47.

***p*-Bromobenzenesulfonate of the *cis,cis*-Equatorial Alcohol.**—This derivative was prepared from **9** by the above method; the reaction period was 5 days. The product was recrystallized from acetone for analysis, mp 166.5–167°.

Anal. Calcd for $C_{29}H_{26}BrNO_3S$: C, 63.50; H, 4.78; N, 2.56. Found: C, 63.57; H, 4.95; N, 2.27.

The *trans,trans*-Axial Pyrrolidino Derivative (12a).—A mixture of 25.8 g of **5**, 16.8 g of pyrrolidine, and 250 ml of toluene was refluxed for 3 hr in a nitrogen atmosphere under a Dean–Stark water separator, after which the solvent was evaporated under aspirator vacuum. The orange, residual syrup, which still contained toluene and pyrrolidine, was hydrogenated in 400 ml of absolute ethanol using 1.5 g of 10% Pd–C at atmospheric pressure; the theoretical hydrogen was absorbed in about 3 hr. After separation of the catalyst and evaporation of the solvent the residual oil was caused to crystallize by trituration with ether. The product was recrystallized from *n*-hexane for analysis; the melting range was frequently rather broad in different samples, but typically about 106–111°. It was not recognized until later that the compound retains solvents, including hexane, exceedingly tenaciously; a solvent-free sample, mp 120–121°, was obtained by drying at 100° for 12 hr *in vacuo*. The ultraviolet spectrum showed maxima at 256 mμ (ε 3710), 262 (3990), and 269 (2920), while minima occurred at 236 mμ (ε 1450) and 267 (2860).

Anal. Calcd for $C_{27}H_{30}N_2$: C, 84.77; H, 7.91; N, 7.32. Found: C, 84.69; H, 8.33; N, 7.14.

The substance was also prepared by reaction of 0.44 g of the equatorial brosylate and 0.71 g of pyrrolidine in 10 ml of purified dioxane. The mixture was heated on the steam bath under nitrogen for 24 hr, the solvent was evaporated, and the residue was partitioned between 25 ml of ether and 25 ml of water. The ether layer was washed with 5% sodium bicarbonate solution, dried, and evaporated and the residue was dissolved in boiling *n*-hexane (Darco) and evaporated to a low volume. On standing the solution deposited 100 mg of unchanged brosylate. The solvent was evaporated, the residue was dissolved in ether, and the product was extracted into 5% hydrochloric acid. Liberation of the free base, extraction into methylene chloride, evaporation of the dried solvent, and crystallization of the residue from *n*-hexane yielded 150 mg of slightly impure axial pyrrolidino compound (**12a**), mp 93–104°, alone, and 101–107° on admixture with **12a**. The melting point was depressed on admixture with **12b** (*vide infra*). Further proof of identity was obtained by thin layer comparisons in several systems.

The *trans,trans*-Equatorial Pyrrolidino Derivative (12b).—A mixture of 6.54 g of *trans,trans* ketone (**5**), 28.8 g of pyrrolidine, 0.5 g of 10% Pd–C, and 200 ml of absolute ethanol was stirred with hydrogen at atmospheric pressure for 2 hr, during which time the theoretical hydrogen was absorbed. After separation of the catalyst and evaporation of the solvent the residue was dissolved in 125 ml of *n*-hexane and allowed to stand. The axial pyrrolidino derivative (**12a**, 3.8 g) crystallized, mp 107–110°, undepressed on admixture with authentic material. Several subsequent concentrations of the mother liquors produced crops of the mixed epimers (**12a** and **12b**) which were set aside. After most of the axial epimer had been removed in this fashion the desired **12b** crystallized (0.77 g) in relatively pure form, mp 129–132°. Recrystallization from *n*-hexane produced the analytical sample with the same melting point.

Anal. Calcd for $C_{27}H_{30}N_2$: C, 84.77; H, 7.91; N, 7.32. Found: C, 84.23; H, 8.01; N, 7.55.

Pyrrolidino Derivatives from the *cis,cis* Ketone.—A solution of 2.70 g of the *cis,cis* ketone (**8**), 1.78 g of pyrrolidine, and a trace of *p*-toluenesulfonic acid in 75 ml of benzene was refluxed in a nitrogen atmosphere for 2 hr under a Dean–Stark trap, then for an additional hour under a Soxhlet apparatus containing KOH pellets. After evaporation of the solvent the residue was dissolved in 75 ml of anhydrous ethanol, 0.25 g of 10% Pd–C was added, and hydrogenation was carried out at atmospheric pressure. After separation of the catalyst and evaporation of the solvent the residual 3.14 g of syrup was taken up in 15 ml of low-boiling petroleum ether. On standing, after a small quantity of amorphous solid had been separated, the yellow solution deposited 0.82 g of crude **equatorial pyrrolidino compound**, mp 136–145°. Recrystallizations from *n*-hexane yielded the analytical sample, mp 145.5–146.5°.

Anal. Calcd for $C_{27}H_{30}N_2$: C, 84.77; H, 7.91; N, 7.32. Found: C, 84.52; H, 8.08; N, 7.30.

The petroleum ether mother liquors from the crystallization of the equatorial isomer were evaporated to dryness, the residue was dissolved in a small volume of methanol, and the solution was filtered through Darco and chilled. The resulting **axial isomer** was recrystallized several times from methanol for analysis, mp 133.5–134.5°.

Anal. Calcd for $C_{27}H_{30}N_2$: C, 84.77; H, 7.91; N, 7.32. Found: C, 84.90; H, 8.00; N, 7.35.

The axial isomer was also prepared by reaction of the brosylate derivative of the *cis,cis*-equatorial alcohol (**9**) with pyrrolidine. Thus 3.46 g of the brosylate, 4.5 g of pyrrolidine, and 75 ml of purified dioxane were heated in a sealed vessel on the steam bath for 7 days, the solvent was evaporated, and the residue was partitioned between methylene chloride and 5% aqueous sodium bicarbonate. The dried methylene chloride layer was filtered through Darco and evaporated. The residue was extracted repeatedly with boiling *n*-hexane and the hexane solution was filtered through Darco and evaporated. Dissolution of the residue in a small volume of methanol and chilling yielded, eventually, the axial isomer, mp 132–134°, undepressed on admixture with the material from the above preparation. The identity of the two materials was also checked by thin layer chromatography.

The Pyrrolidino Derivative from the *cis,trans* Ketone.—Reaction of 1.96 g of **6** with 1.28 g of pyrrolidine was carried out in benzene solution as in the *cis,cis* case. The unpurified enamine was also hydrogenated as usual except that this hydrogenation was unique in requiring 18 hr for completion; all of the others were complete in 2–3 hr. After separation of the catalyst and removal of the solvent the residue was taken up as completely as possible in hot cyclohexane and the solution was filtered through Darco and evaporated. The residual gum, which appeared to be homogeneous by thin layer chromatography, was finally brought to crystallization by dissolution in a few milliliters of acetone and chilling and scratching. The resulting product could then be recrystallized from *n*-hexane to yield 1.59 g of pure amine, mp 123.5–124.5°.

Anal. Calcd for $C_{27}H_{30}N_2$: C, 84.77; H, 7.91; N, 7.32. Found: C, 84.94; H, 8.08; N, 7.22.

The same product was also obtained from a direct reductive amination in which 327 mg of the *cis,trans* ketone was hydrogenated in the presence of 1.44 g of pyrrolidine and 0.1 g of 10% Pd–C in 25 ml of absolute ethanol. In this case the theoretical hydrogen was absorbed in 25 min. After the usual work-up the residual oil was dissolved in *n*-hexane, a small quantity of amorphous solid was separated, and the solution was concentrated to 3 ml and seeded with the above product. There was thus obtained 290 mg of pyrrolidino derivative, mp 122–123°, undepressed on admixture with the material from the previous reduction. Evaporation of the mother liquors yielded 90 mg of amorphous material which consisted mainly of the same isomer by thin layer chromatographic indications.

***erythro*-1,2,3-Triphenylhexane-1,5-dione (13).**—To a solution prepared from 7.68 g of sodium in 600 ml of absolute ethanol, 65.5 g of desoxybenzoin was added with stirring, followed by 48.8 g of benzalacetone. The reaction was carried out at room temperature under nitrogen. The product began to precipitate at once. The mixture was stirred vigorously at room temperature for 30 min, then in an ice bath for a similar period. The product was separated by filtration, washed with ethanol and with water, and dried. After recrystallization from 95% ethanol it had mp 180–183° (lit.[4] mp 177°). In the infrared the carbonyl absorptions were observed at 1700 and 1680 cm^{-1}.

Anal. Calcd for $C_{24}H_{22}O_2$: C, 84.17; H, 6.47. Found: C, 84.30; H, 6.49.

***cis*-3,4,5-Triphenylcyclohexene-2-one (14).**—Hydrogen chloride was bubbled through a stirred suspension of **13** (15.0 g) in 600 ml of methanol for 3 hr, during which period the dione dissolved. The red solution was allowed to stand at room temperature overnight and was then chilled to deposit 10.6 g of enone, mp 189–191°. The product was separated and recrystallized from benzene and from acetonitrile, mp 190–192.5° (lit.[4] mp 188°). The ultraviolet maximum appeared at 284–288 mμ (ϵ 17,380) and the minimum was found at 242 mμ (ϵ 7080). The carbonyl absorption band appeared at 1660 cm^{-1}. The nmr spectrum was similar to that of **3**. It was observed in the previous cases that when the C_4 substituent is pseudo-axial the C_6 protons are dissimilar and a complex AB system results. In this case, however, an overlapping AB system resulted and the chemical shift between the methylene protons was not sufficiently large to permit a first-order interpretation of the coupling constants. The proton *cis* (pseudo-axial) to the C_4 phenyl group is centered at δ 2.79, while the other C_6H signal is at 2.48 ppm (J_{AB} = 18.5 cps). The C_5 proton is a triplet of a doublet at δ 3.92, indicating that the coupling constants with two vicinal protons are almost equal. The C_4H signal is a relatively sharp doublet at 4.36 ppm ($J_{4,5}$ = 4.5 cps) indicating little if any coupling with the C_6 protons. The vinyl proton is a sharp singlet at 6.82 ppm, while the aromatic region consists of a complex multiplet in which four protons are centered at 6.81 and 11 are centered at 7.28 ppm.

Anal. Calcd for $C_{24}H_{20}O$: C, 88.85; H, 6.21. Found: C, 88.63; H, 6.21.

The above enone was also obtained directly in 51% yield from reaction of 1.96 g of desoxybenzoin, 1.46 g of benzalacetone, and 0.25 g of sodium in 50 ml of anhydrous ethanol by refluxing for 1 hr. Evaporation of the solvent to half-volume and chilling yielded the slightly crude product, mp 181–195°, λ_{max} 280 mμ.

Hydrogenation of the *cis*-Enone.—Two grams of the enone was hydrogenated in 200 ml of ethyl acetate in the presence of 0.65 g of 10% Pd–C for 3 hr at 40 psig. Separation of the catalyst, evaporation of the solvent, and recrystallizations of the residue from cyclohexane yielded 1.14 g of the *cis,cis*-equatorial alcohol, mp 156–159°. The ultraviolet maximum appeared at 258 mμ (ϵ 580). The axial C_1H signal appeared at 4.22 ppm (W_H = approximately 32 cps) as a complex multiplet. The three benzylic hydrogens appeared as a multiplet centered at about 3.38, and a multiplet at about 2.28 ppm contained the methylene protons and the OH signal. Although it was possible to recognize an AB system in this area, because of the multiplicity of the system it was not possible to extract the coupling constants by simple observation, as could be done with the *cis,cis* ketone (*vide infra*).

Anal. Calcd for $C_{24}H_{24}O$: C, 87.76; H, 7.36. Found: C, 87.87; H, 7.37.

Oxidation of the Alcohol to *cis,cis*-Cyclohexanone.—To a cold solution of 200 mg of the alcohol in 10 ml of acetone was added 0.5 ml of 1.3 *M* Jones reagent (prepared as above) and the mixture was stirred for 10 min at ice-bath temperature and for 45 min at room temperature. It was then worked up as in the oxidation of **9** and recrystallized from *n*-hexane to give an 86% yield of *cis,cis* ketone, mp 143–144°. The carbonyl band appeared at 1700 cm^{-1}. The nmr spectrum was of a type reminiscent of the spectrum of **8**. The two equatorial protons of the α-methylene groups appeared as a doublet of a doublet centered at 2.70 ppm ($J_{6e,5a/2e,3a}$ = 4.1 cps, $J_{6,6/2,2}$ = 14.5 cps). The corresponding axial protons appeared as a doublet of a doublet centered at 3.33 ppm ($J_{6a,5a/2a,3a}$ = 14.2 cps, $J_{6,6/2,2}$ = 14.5 cps). The three tertiary protons appeared as a multiplet at 3.4–4.0 and the aromatic multiplet was observed at 6.8–7.2 ppm.

Anal. Calcd for $C_{24}H_{22}O$: C, 88.31; H, 6.79. Found: C, 88.30; H, 7.03.

***trans*-3,4,5-Triphenylcyclohexen-2-one (15).**—This substance, which was prepared by the method of Cornubert[5] had mp 138.5–140° (lit.[5] mp 139°). The ultraviolet maximum appeared at 280–284 mμ (ϵ16,280) and the carbonyl absorption was at 1665 cm^{-1}. The nmr spectrum had the appearance of a relatively simplified system in which all coupling constants appear to be similar. The C_6 methylene proton signals appear as a doublet at 2.81, the C_5 proton is a broad quartet at 3.63, and the C_4H is a doublet at 4.53 ppm (J = 3.8 cps). The vinyl proton signal is a sharp singlet at 6.75 and the aromatic protons produce a single sharp peak at 7.25 ppm, indicating almost complete freedom of rotation of the rings.

Anal. Calcd for $C_{24}H_{20}O$: C, 88.85; H, 6.21. Found: C, 88.90; H, 6.25.

Hydrogenation of the *trans*-Enone.—Compound **15** (5.72 g) was hydrogenated in 150 ml of ethyl acetate with 1.5 g of 10% Pd–C at atmospheric pressure for 7 hr, during which period about 150% of the theoretical hydrogen appeared to be absorbed. The usual work-up afforded a residue which on treatment with ethanol deposited crystals of what was subsequently recognized to be crude *trans,trans* ketone. After taking several crops by concentration of the solutions, the combined materials were recrystallized several times from isopropyl alcohol and from methanol to yield 0.83 g of **16**, mp 174–176.5°. The carbonyl absorption appeared at 1700 cm^{-1} and the ultraviolet maximum appeared at 259 mμ (ϵ 670). The aliphatic signals in the nmr spectrum showed two areas of multiplicity, one being at 2.67–3.08 ppm. This four-proton signal is undoubtedly due to the α-methylene protons, while the other area, 3.33–3.83 ppm, is composed of the signals from the three tertiary protons. The aromatic region was also composed of two complex areas in which four protons appeared at 6.50–6.75 and 11 at 6.83–7.25 ppm.

Anal. Calcd for $C_{24}H_{22}O$: C, 88.31; H, 6.79. Found: C, 88.47; H, 6.82.

The methanol filtrate from **16** was concentrated and cooled to yield a fraction of mixed isomers, mp 158–188°. Separation and concentration of the filtrate a second time yielded 0.34 g of ***cis,trans*-3,4,5-triphenylcyclohexanone (17)**, mp 204–206°. This substance had the ultraviolet absorption maximum at 258 mμ (ϵ 530) and the carbonyl band at 1705 cm^{-1}. In the nmr a multiplet of four protons appeared at 2.83 and three additional protons were centered at about 3.33 ppm.

Anal. Calcd for $C_{24}H_{22}O$: C, 88.31; H, 6.79. Found: C, 88.26; H, 6.74.

Pyrrolidino Derivative of 16.—The *trans,trans* ketone (6.52 g) was converted to the enamine in the usual fashion by reaction with 1.75 g of pyrrolidine in benzene for 12 hr. Hydrogenation of the crude residue proceeded normally to yield an oil which resisted crystallization. Purification was first attempted by partitioning between 0.1 *N* HCl and methylene chloride, in five funnels. Most of the product was obtained as the hydrochloride 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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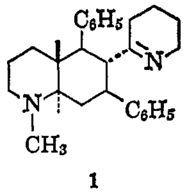
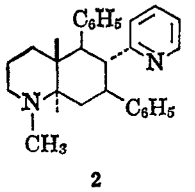
By a combination of spectral and chemical methods it has been established that lobinaline is a *trans*-decahydroquinoline derivative having all-equatorial and hence all-*trans* substituents, as depicted in structure **1** (or its mirror image). "Dehydrolobinaline" (**2**), previously prepared by oxidation 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

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[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.