Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.44; H, 9.50. Found: C, 75.22; H, 9.65.

B. Buffered.—The buffered acetolysis solution was prepared by heating a solution prepared from 3.5 g of anhydrous potassium carbonate, 5.0 ml of acetic anhydride, and 250 ml of glacial acetic acid under reflux overnight.

A solution prepared from 2.45 g of the methanesulfonate III and 120 ml of the buffered acetolysis solution was heated at 100° for 16 hr. The product (2.17 g of orange oil) was isolated by ether extraction as described above and then heated under reflux for 1 hr in 80 ml of 5% methanolic potassium hydroxide solution. The product (1.82 g of orange oil) was isolated by ether extraction and chromatographed on 120 g of alumina. Elution with benzene (4 × 100 ml) gave 140 mg (8%) of 3β-methoxy-5β,19-cycloandrost-6-en-17-one (VII), the infrared and nmr spectra of which were identical with those of a previously prepared sample.[2b,c]

Elution with 1:2 ether–benzene solution gave 1.52 g (77%) of 3β-methoxy-7β-hydroxy-B-homoestr-5(10)-en-17-one (Va), mp 105–115°. Two recrystallizations from benzene–petroleum ether yielded 1.11 g, mp 118–120°, undepressed on admixture with previously prepared material.[2] The infrared and nmr spectra of the product were identical with those of previously prepared material.

Rearrangement of 3β-Methoxy-7β-acetoxy-B-homoestr-5(10)-en-17-one (Vb)[2] under Unbuffered Acetolysis Conditions.—A solution prepared from 769 mg of Vb, 0.138 ml of methanesulfonic acid, and 2.1 ml of acetic anhydride was heated at 100° for 3 hr. The product (740 mg of black oil) was isolated by ether extraction in the usual manner and then heated under reflux for 1 hr in 25 ml of 5% methanolic potassium hydroxide solution. The product (581 mg) was chromatographed on 50 g of alumina. Elution with benzene (3 × 100 ml) gave 65 mg of orange oil. This was followed by elution with 1:1 ether–benzene solution which gave 390 mg of product. Three recrystallizations from acetone–petroleum ether solution gave 230 mg (34%) of 3β-methoxy-6β-hydroxymethylestr-5(10)-en-17-one (VIa), mp 126–128°, $[\alpha]^{25}D$ +131°, identical in all respects with the material described above.

Rearrangement of 3β-Methoxy-6β-acetoxy-5β,19-cycloandrostan-17-one (IVb) under Conditions of Buffered Acetolysis.—A solution prepared from 578 mg of IVb, 0.104 ml of methanesulfonic acid, and 31 ml of the buffered acetolysis solution, prepared as described above, was heated at 100° for 5 hr. The product (549 mg of orange oil) was isolated by ether extraction in the usual manner and then heated under reflux for 1 hr in 30 ml of 5% methanolic potassium hydroxide solution. The product (434 mg of orange oil) was chromatographed on 42 g of alumina. Elution with benzene (25 ml) and 1:15 ether–benzene solution (75 ml) gave 69 mg (14%) of 3β-methoxy-5β,19-cycloandrost-6-en-17-one (VII) identified by its infrared and nmr spectra.[2]

Elution with 1:2 ether–benzene solution yielded 323 mg (63%) of 3β-methoxy-7β-hydroxy-B-homoestr-5(10)-en-17-one (Va), mp 108–117°. Recrystallization from benzene–petroleum ether solution gave 248 mg, mp 117–120°, identical in all respects with previously prepared material.[2]

Buffered Acetolysis of 3β-Methoxy-5β,6β-methanoestr-9-en-17-one (X).—A solution prepared from 511 mg of the vinylcyclopropane X, 0.104 ml of methanesulfonic acid, and 31 ml of the buffered acetolysis solution described above was heated at 100° for 5 hr. The product (551 mg) was isolated by ether extraction and heated under reflux for 1 hr in 30 ml. of 5% methanolic potassium hydroxide solution, and the product (451 mg) was chromatographed on 45 g of alumina. Elution with benzene (20 ml) and 1:15 ether–benzene solution (80 ml) gave 53 mg of an oil. Nmr and infrared spectra of this material showed the absence of vinyl protons and thus the absence of 3β-methoxy-5β,-19-cycloandrost-6-en-17-one (VII). The presence in the nmr spectrum of two methoxyl absorptions of approximately equal area at 199 and 201 cps and two angular methyl absorptions at 53.5 and 54.8 cps indicated a mixture which was not characterized further.

Elution of the column with 1:2 ether–benzene solution (3 × 100 ml) yielded 345 mg. (64%) of 3β-methoxy-7β-hydroxy-B-homoestr-5(10)-en-17-one (Va), mp 108–115°. Recrystallization from benzene–petroleum ether solution gave 288 mg, mp 117–121°, identical in all respects with a previously prepared sample.[2]

Preparation of 3β-Methoxy-6β-acetoxymethylestr-5(10)-en-17-one (VIb) and 3β-Methoxy-6β-acetoxy-5β,19-cycloandrostan-17-one (IVb).—The acetates were prepared by treatment of the corresponding alcohols with acetic anhydride in pyridine solution as described previously.[2] Pertinent physical data are listed. 3β-Methoxy-6β-acetoxymethylestr-5(10)-en-17-one (VIb) (an oil) showed $[\alpha]^{25}D$ +124; infrared, ν_{max} 1730 cm^{-1}; nmr, 54.2(s), C_{18}-H; 125(s), $OCOCH_3$; 201(s), OCH_3; 250(s), 245, 242(d), 6β-CH_2.

Anal. Calcd for $C_{22}H_{32}O_4$: C, 73.29; H, 8.95. Found: C, 73.01; H, 8.86.

3β-Methoxy-6β-acetoxy-5β,19-cycloandrostan-17-one (IVb) showed mp 130–133°; $[\alpha]^{25}D$ +115°; infrared, ν_{max} 3064 and 1726 cm^{-1}; nmr, 21.4, 27.0(d), one cyclopropyl proton; 53.4(s), C_{18}-H; 124(s), $OCOCH_3$; 197(s), OCH_3; 310(m), $W_{1/2}$ = 7 cps, $C_{6\alpha}$-H.

Anal. Calcd for $C_{22}H_{32}O_4$: C, 73.29; H, 8.95. Found: C, 73.34; H, 8.99.

Acknowledgment.—The author wishes to thank Mrs. Ruth Stanaszek for the nmr spectra, Mr. W. Washburn for the infrared spectra, and Mr. O. Kolsto for analyses.

The Skeletal Structure of Lobinaline[1]

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Received May 2, 1966

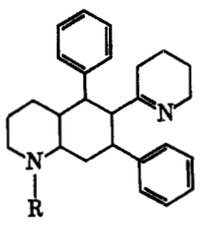
By a combination of degradative, spectral, and synthetic studies, lobinaline, the major alkaloid of *Lobelia cardinalis L.*, has been shown to have the skeletal structure **1a**. The degradative studies on the alkaloid proceeded by way of a Von Braun demethylation followed by dehydogenation to 5,7-diphenyl-6-(2-pyridyl)-quinoline. The latter was synthesized for comparison by a Skraup synthesis with 3,5-diphenyl-4-(2-pyridyl)-aniline which, in turn, was prepared by an unequivocal route. Various other transformations of the alkaloid as well as a synthesis of the isomeric 6,7-diphenyl-5-(2-pyridyl)quinoline are also described.

Lobinaline, the major alkaloid of *Lobelia cardinalis L.*, was first isolated in 1938 by Manske,[2] who carried out some preliminary chemical studies on the constitution of the compound. Since that time little has been published on the subject other than a report[3] on the, paper chromatographic behavior of the alkaloid. In the course of a program of routine plant screening in this laboratory, a crystalline alkaloid was isolated from *L. cardinalis* which appears to be the same as the earlier reported lobinaline. In this paper are reported the results of degradative, spectral, and synthetic studies

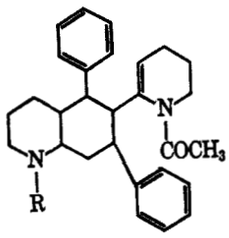
(1) Preliminary communication: M. M. Robison, W. G. Pierson, L. Dorfman, B. F. Lambert, and R. A. Lucas, *Tetrahedron Letters*, 1513 (1964).

(2) R. H. F. Manske, *Can. J. Res.*, **16B**, 445 (1938).

(3) F. Kaczmarek and E. Steinegger, *Pharm. Acta. Helv.*, **33**, 852 (1958).



1a, R = CH_3
b, R = H

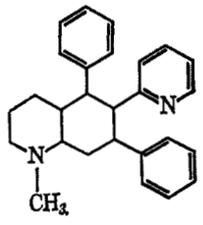


2a, R = CH_3
b, R = CN

which made possible the assignment of skeletal structure **1a** to lobinaline.[4]

Manske reported lobinaline to be a crystalline substance, mp 94–95°, $[\alpha]^{24}D$ +22.3°, with the empirical composition $C_{28}H_{38}N_2O$, though this formula was later recognized as that of a monohydrate and modified to $C_{28}H_{36}N_2$.[5] In this laboratory the alkaloid was isolated by what was essentially Manske's method, except that the crude free base was purified as such by rough chromatography on small alumina columns. In this manner crystalline material was readily obtained. Although the melting points of various batches were somewhat variable, an analytical sample prepared by recrystallizations from hexane and sublimation had mp 108–110°, $[\alpha]^{26}D$ +38°. The analysis, mass spectrum, and nmr spectrum of the alkaloid as well as the structural studies indicated that the correct empirical formula is $C_{27}H_{34}N_2$. The ultraviolet spectrum showed only benzene absorption, while the infrared (Nujol) indicated the absence of NH groups and the presence of a monosubstituted benzene moiety. A strong absorption band was also observed at 1665 cm^{-1}. Potentiometric titration showed the presence of two weakly basic groups with pK_a values of 5.7 and 8.2. The nmr spectrum confirmed the proton count as well as the presence of two monosubstituted benzene rings, and revealed the presence of one N-methyl group but *no* vinyl protons.

The alkaloid proved to be remarkably inert to a wide variety of reagents. Thus, in early experiments, starting material was recovered from attempted reductions with sodium borohydride, from hydrogenations with Pd–C (ethanol), or PtO_2 (acetic acid), from attempted hydrolyses with strong acid or base, and from attempted dehydrogenations with chloranil or with Pd–C (xylene). Although reaction did take place when the substance was treated with Pd–C in refluxing Dowtherm, an intractible mixture was formed and no product could be isolated. One successful transformation carried out at an early stage involved the removal of four hydrogen atoms by treatment of lobinaline with selenium dioxide. The resulting "dehydrolobinaline," which was subsequently recognized as having structure **3**, did not cast appreciable light on the lobinaline structure at the time of its preparation, however, except that the loss of four hydrogen atoms, the disappearance of the 1665-cm^{-1} absorption in the infrared, a total aromatic proton count of 14 protons, and the appearance of a doublet of doublets (α-pyridine H) at 8.42 ppm in the nmr spectrum suggested the presence of a monosubstituted tetrahydropyridine moiety in the alkaloid.



3

The degradation scheme finally employed for structure elucidation followed from the initially somewhat unexpected observation that lobinaline reacted readily with refluxing acetic anhydride to form a monoacetyl derivative, $C_{29}H_{36}N_2O$, having a single pK_a value of 8.2. The appearance of an unresolved, broad (W_H = 12 cps) vinyl proton signal in the nmr spectrum (indicative of a >C=$CHCH_2$ group) and of a split absorption band at 1670 and 1655 cm^{-1} in the infrared, the ready hydrolysis to regenerate lobinaline, and the above-mentioned observations on "dehydrolobinaline" suggested acetylation of a 6-substituted 2,3,4,5-tetrahydropyridine at the nitrogen atom, and eventually allowed formulation of the acetyl derivative as **2a**.

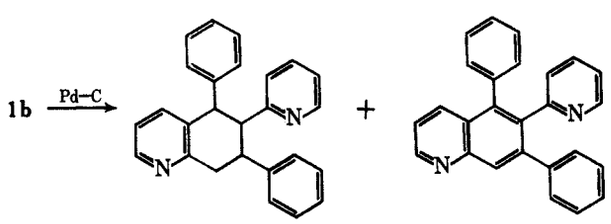
To make possible a more complete and meaningful dehydrogenation of the ring system, attention was next turned to the removal of the methyl group at the remaining basic nitrogen in acetyllobinaline. Treatment of the substance with cyanogen bromide in ether resulted almost exclusively in demethylation without ring opening to form the corresponding desmethyl N-cyano compound (**2b**), $C_{29}H_{33}N_3O$. Although it could not be obtained in crystalline form, the glassy substance was brought to analytical purity by chromatography on alumina and evaporative distillation *in vacuo*. The nitrile amide showed infrared absorptions at 2215, 1670, and 1650 cm^{-1}, and no N-methyl signal in the nmr spectrum.

Hydrolysis and decarboxylation of **2b** in refluxing 6 *N* hydrochloric acid yielded mainly desmethyllobinaline (**1b**), $C_{26}H_{32}N_2$, again obtained only as an uncrystallizable glass and purified as above. The observed optical rotation of this derivative was, coincidentally, 0 ± 2°. The NH proton, which was exchangeable on treatment with deuterium oxide, appeared in the nmr spectrum as a signal at 1.65 ppm. When the hydrolysis was carried out on a large scale, a by-product was isolated which added further information. The new crystalline substance had no C=N absorption band in the infrared, as did desmethyllobinaline, but showed a ketone carbonyl at 1698 cm^{-1}. This absorption, the finding of *three* exchangeable protons in the nmr, and an analysis in agreement with the addition of 1 mole of water to desmethyllobinaline suggested a hydrolysis of the supposed tetrahydropyridine (or its acetyl derivative) to the open-chain δ-amino ketone. Since such substances do not ordinarily exist in the open-chain form, the isolation in this case was taken as evidence for a markedly crowded steric environment about the tetrahydropyridine moiety—a supposition seemingly substantiated by the above-mentioned resistance of the imine to reduction. It was found, further, that the by-product was converted to desmethyllobinaline on heating above its melting point.

(4) See the second accompanying article: M. M. Robison, B. F. Lambert, L. Dorfman, and W. G. Pierson, *J. Org. Chem.*, **31**, 3220 (1966), for the elucidation of the stereochemistry of lobinaline and the synthesis of the ring system.

(5) Reference 3, footnote 2.

Dehydrogenation of desmethyllobinaline was effected by palladium–charcoal in refluxing diphenyl ether. Difficulty was at first encountered in the separation of the reaction products, and repeated chromatography on alumina afforded as the only crystalline material a partially dehydrogenated substance, $C_{26}H_{22}N_2$, later shown to be **4**. It was apparent from the ultraviolet spectra that the compound, $[\alpha]^{27}D$ +161°, contained two isolated alkylpyridine rings. In ethanol solution the values for λ_{max} were 262 mμ (ε 7920), 269 (7830), and 277 (4520) and minima were observed at 235 mμ (ε 1870), 266 (7560), and 275 (4470). In acid solution the maximum was observed at 267 mμ (ε 13,700) and the minimum at 236 mμ (ε 4130). The nmr spectrum revealed the presence of two overlapping α-pyridine protons centered at 8.47 ppm as well as four aliphatic protons at 3.4–3.9 (complex) and one tertiary aliphatic proton centered at 4.88 ppm. The last-named appeared as a doublet (J = 10.4 cps) with indication of additional long-range coupling. Treatment of the compound with sodium methoxide in deuteriomethanol at 100° for 2 weeks resulted in about 40% replacement of the 4.88-ppm proton by deuterium[6] and about 80% replacement of two of the protons in the 3.4–3.9-ppm region. In the latter signal it was now possible to recognize the presence of an AB quartet (J = 11.8 cps) which became still more easily recognizable when the signal at 4.88 ppm was decoupled.[7]



4 **5**

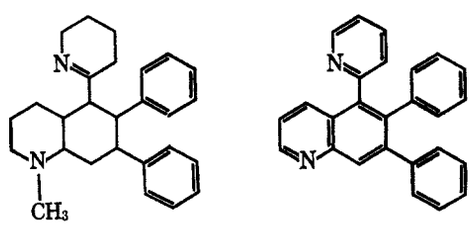
Chemical evidence for the nature of the bonding of the pyridine rings was gained by oxidation of **4** with potassium permanganate. Although extensive degradation was encountered, it was possible to isolate (in addition to benzoic acid) a very small, polar, acidic fraction which had an ultraviolet absorption maximum at 262 mμ. Since the quantity obtained was insufficient for separation, the mixture was methylated directly with diazomethane and compared by paper and thin layer chromatography with known methyl esters of pyridine mono- and dicarboxylic acids. Comparisons in several systems demonstrated that the two oxidation products obtained were dimethyl quinolinate and methyl picolinate. It could thus be concluded at this point that the pyridine ring yielding methyl picolinate represented the original tetrahydropyridine grouping in lobinaline (**6**)

6 **7**

since a vinyl proton had been observed on acetylation; accordingly, the ring yielding dimethyl quinolinate represented an N-methylpiperidine moiety (**7**).

The preceding results became much clearer when an effective method for separating the total desmethyllobinaline dehydrogenation mixture was found. Partitioning the mixture between methylene chloride and 0.1 N hydrochloric acid in seven funnels resulted in an essentially complete separation to yield the previously known **4** as well as the completely dehydrogenated **5**. The weaker base **5** which was optically inactive and which showed only aromatic proton signals in the nmr had the constitution $C_{26}H_{18}N_2$. The isolation of an aromatic product which differed from **4** by the loss of four hydrogen atoms prompted the recognition of a possible quinoline–tetrahydroquinoline relationship, and the ultraviolet spectrum of **5** was consistent with this concept. The spectrum was entirely appropriate for a quinoline bearing three large, planar aromatic rings in adjacent positions, with resulting marked steric inhibition of conjugation.[8] The maximum (methanol) was observed at 242 mμ (ε 41,000) with a shoulder at 320 mμ (ε 4600) while the minimum was found at 226 mμ (ε 32,800). These data, together with consideration of the frequent occurrence of the phenylethylpiperidine moiety in alkaloids of related *Lobelia* species, suggested **5** as the most likely structure for the quinoline and structure **1a** for lobinaline itself. These structures were also compatible with the previously mentioned deuteration studies on **4**, on the basis that the two replaceable protons at 3.4–3.9 ppm would be C_8 hydrogens and the partially replaced 4.88-ppm proton would be in the 5 position. If the α-picolyl proton at C_6 were prevented from exchanging by steric effects, then the two unexchange d3.4–3.9-ppm protons would occupy positions 6 and 7 of the ring and would be expected to appear as doublets, as observed, on blanking out of the C_5 and C_8 hydrogens by deuteration and decoupling.

Although the above data, together with biogenetic considerations, seemed to point most strongly to structure **1a** for lobinaline, they did not preclude the biogenetically less attractive expressions **8** for lobinaline and **9** for the dehydrogenation product. That the first-mentioned formulation was the correct one was shown by independent, unequivocal syntheses of the two isomeric diphenylpyridylquinolines. The properties of 5,7-diphenyl-6-(2-pyridyl)quinoline (**5**) were found to be those of the dehydrogenation product while compound **9** was clearly different.



8 **9**

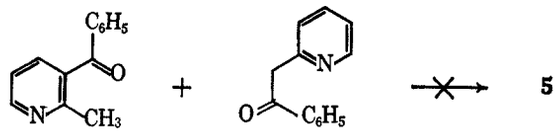
In an initial, unsuccessful attempt at the synthesis of **5**, benzoylacetone was first converted to 3-amino-1-

(6) It is interesting to note that, although the intensity of the 4.88-ppm band was reduced, the general shape was unchanged, indicating that the other protons involved in the long-range coupling were not greatly affected.

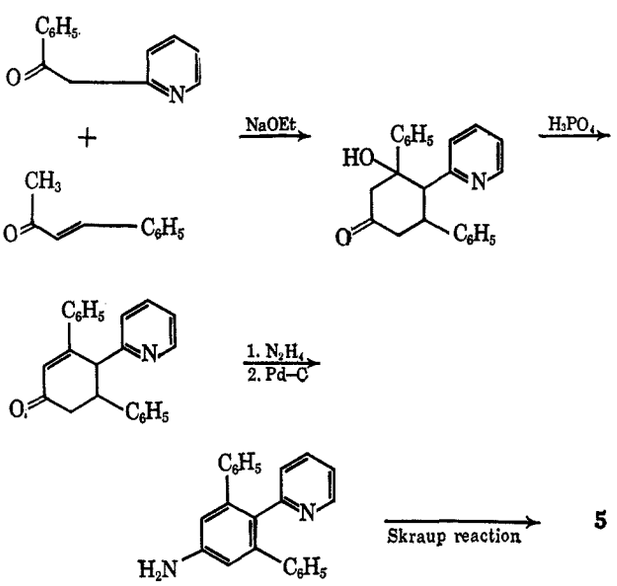
(7) We wish to thank Professor E. Wenkert of the Department of Chemistry, Indiana University, for his kindness in carrying out the spin–spin decoupling experiments on a Varian HR-60 instrument.

(8) *Cf.* D. Buza and W. Polaczkowa [*Bull. Acad. Polon. Sci. Chim.*, **8**, 531 (1960); *Chem. Abstr.*, **58**, 2341h (1963)] for spectra of the isomeric triphenylbenzenes.

phenylbuten-2-one-1 by reaction with ethanolic ammonia. That the enamine is the product of reaction at the acetyl group of the diketone rather than at the benzoyl group was established by Claisen[9] and confirmed by spectral studies in this investigation. Reaction of the enamine with acrolein yielded 3-benzoyl-1,4-dihydro-2-picoline[10] which was oxidized to 3-benzoyl-2-picoline by chromic acid in acetic acid. Numerous attempts to condense 3-benzoyl-2-picoline with 2-phenacylpyridine[11] were, however, unsuccessful. None of the desired product was detected and in most cases starting materials were at least partially recovered under such conditions as polyphosphoric acid or zinc chloride at 240° for 23 hr, sodium methoxide at 350° for 0.5 hr, and similar extreme treatments with sodium hydride, aluminum chloride, and other vigorous acidic and basic catalysts. Accordingly, an alternate approach was investigated.

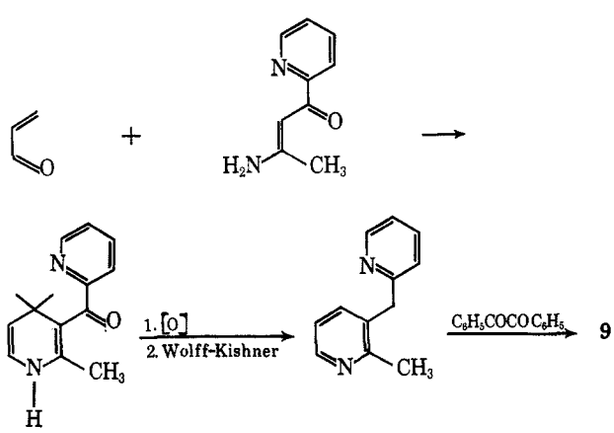


The first step in this sequence was condensation of 2-phenacylpyridine with benzalacetone in ethanolic sodium ethoxide to yield 3-hydroxy-3,5-diphenyl-4-(2-pyridyl)cyclohexanone[12] in high yield. Dehydration



with phosphoric acid to 3,5-diphenyl-4-(2-pyridyl)-cyclohexen-2-one[12] was followed by conversion to the azine, which substance, in turn, was dehydrogenated to 3,5-diphenyl-4-(2-pyridyl)aniline by use of palladium–charcoal.[13] A Skraup quinoline synthesis completed the sequence to 5,7-diphenyl-6-(2-pyridyl)quinoline (**5**), which proved to be identical with the lobinaline degradation product by all the usual criteria.

The synthesis of the isomeric 6,7-diphenyl-5-(2-pyridyl)quinoline (**9**) was effected by a route analogous to that originally planned for **5**. 2-Acetoacetylpyridine[14] was treated with ethanolic ammonia to yield 3-amino-1-(2-pyridyl)buten-2-one-1. This enamine was prepared in 1896,[15] but it had not been established, until this investigation, whether the ammonia reacted at the acetyl or picolinoyl carbonyl. That the substance had the above, desired structure was demonstrated by comparison of ultraviolet, infrared, and nmr spectra of compound pairs from this and the earlier benzoylacetone sequence. An attempt was first made to condense the enamine with propargylaldehyde to prepare 3-(2-picolinoyl)-2-picoline directly,[16] but, since in the single attempt only starting amine and polymerized aldehyde were obtained, the condensation was carried out with acrolein, as in the first reaction series. The resulting 3-(2-picolinoyl)-1,4-dihydro-2-picoline was aromatized most effectively by treatment with chloranil. In view of the discouraging results encountered in the final reaction of the benzoylpicoline series, no attempt was made to condense the product with desoxybenzoin. Rather, the ketone carbonyl was first reduced and the resulting picolylpicoline was condensed with benzil. Reaction took place at 185° without catalysis, in agreement with a report[17] that 2-picoline reacts with benzil and other reactive ketones (but not simple ketones) to yield aldol-type products.



As expected, the ultraviolet spectrum of **9** was very similar to that of the lobinaline degradation product. That the new substance was clearly different, however, was shown by a considerably higher melting point, by marked changes in the fingerprint region of the infrared spectrum, and by the appearance of phenyl proton signals at two positions in the nmr spectrum. The last phenomenon was not observed in the spectrum of **5**.

(9) L. Claisen, *Ber.*, **59**, 147 (1926).

(10) *Cf.* K. Tsuda, Y. Satch, N. Ikekawa, and H. Mishima [*J. Org. Chem.*, **21**, 800 (1956)] for an analogous condensation with ethyl β-aminocrotonate, and P. Baumgarten and A. Dornow [*Ber.*, **72**, 564 (1939)] for a condensation of the above benzoylacetone derivative with β-ethoxyacrolein diethylacetal to yield 3-benzoyl-2-picoline directly.

(11) N. N. Goldberg, L. B. Barkley, and R. Levine, *J. Am. Chem. Soc.*, **73**, 4301 (1951).

(12) The elucidation of the stereochemistry of this substance, which has been correlated with that of the lobinaline ring system,[4] is discussed in the accompanying article, M. M. Robison, W. G. Pierson, L. Dorfman, and B. F. Lambert, *J. Org. Chem.*, **31**, 3213 (1966).

(13) *Cf.* E. C. Horning, M. G. Horning, and E. J. Platt [*J. Am. Chem. Soc.*, **70**, 288 (1948)] for similar reactions.

(14) R. Levine and J. K. Sneed, *ibid.*, **73**, 5614 (1951).

(15) Micko, *Monatsh.*, **17**, 451 (1896).

(16) *Cf.* F. Bohlmann and D. Rahtz [*Chem. Ber.*, **90**, 2265 (1957)] for similar reactions.

(17) S. M. McElvain and H. G. Johnson, *J. Am. Chem. Soc.*, **63**, 2213 (1941).

Experimental Section[18]

Lobinaline.—The dried, whole plant[19] (9.9 kg) was extracted several times with methanol at room temperature and finally with boiling methanol. The combined extracts (approximately 30 l.) were then concentrated *in vacuo* to 3 l. This extract was diluted with 1000 ml of water and 30 ml of 20% hydrochloric acid, evaporated to a lower volume, and again treated with the same volumes of water and dilute hydrochloric acid. The mixture was next filtered to remove the somewhat granular, acid-insoluble solids and concentrated *in vacuo* to about 2 l. The acid solution was next extracted with six 1-l. portions of ether, which were discarded, then made alkaline with aqueous ammonia, and again extracted with ether. Evaporation of the dried extracts yielded 21.6 g of tan, semicrystalline solid.

The crude lobinaline was purified by filtration of a hexane solution through several small alumina columns, using only sufficient adsorbent to remove strongly held impurities. The substance was first dissolved in about 700 ml of warm hexane and filtered through a 15 × 20 mm column of grade II–III neutral (Woelm) alumina. When about half of the solution had been applied to the column the filtrates became turbid and it was apparent that the adsorbent was saturated with impurities. The column was rinsed with *n*-hexane and the unprocessed material was passed through another, larger alumina column. By evaporating filtrates to low volumes and allowing crystallization, then passing mother-liquor materials through a second chromatographic process, a total of about 13 g of alkaloid was obtained. At this stage the combined, oily mother-liquor residue was again dissolved in dilute acid and the solution again was extracted with ether to remove neutral impurities. Basification and extraction followed by further chromatography allowed a recovery of a total of 16.0 g of lobinaline from the process, typical mp 104–110°. The analytical sample, prepared by recrystallizations from *n*-hexane and sublimation at 110–115° (20 μ), had mp 108–110°.

Anal. Calcd for $C_{27}H_{34}N_2$: C, 83.89; H, 8.87; N, 7.25. Found: C, 83.55; H, 8.80; N, 7.30.

The mass spectrum[20] of the substance showed a small parent peak at *m/e* 386, the strongest signal at 186 (100%), and further significant peaks at 200 (90%), 201 (40%), and 187 (20%). In the nmr spectrum the N-methyl signal was observed at 2.30 and the phenyl peak at 7.24 ppm.

Dehydrolobinaline (3).—A solution of 1.93 g of lobinaline and 1.11 g of selenium dioxide in 100 ml of dioxane (purified by passage through a column of Woelm activity I basic alumina) was refluxed for 6 hr, then allowed to stand overnight. Separation of the mixed solids and washing with more solvent was followed by evaporation of the combined, orange filtrate to dryness. Addition of water, basification with ammonia, extraction into methylene chloride, and evaporation of the dried extract yielded 1.81 g of amorphous product, which was chromatographed on 75 g of grade II–III neutral alumina. Early fractions, eluted with benzene and 2% ether in benzene and crystallized from *n*-hexane weighed 0.37 g. Further recrystallizations from the same solvent yielded the analytical sample, mp 142.5–144°, $[\alpha]^{26}D$ +44°. The N-methyl signal in the nmr appeared at 2.32 ppm. The ultraviolet spectrum showed maxima at 258 mμ (ε 4200), 263 (4460), and 269 (3380) and minima at 234 mμ (ε 1860), 259 (4150), and 267 (3210).

Anal. Calcd for $C_{27}H_{30}N_2$: C, 84.77; H, 7.91. Found: C, 84.63; H, 8.03.

Acetyllobinaline (2a).—A solution of 3.86 g of lobinaline in 100 ml of acetic anhydride was refluxed in a nitrogen atmosphere for 20 min, then allowed to stand overnight. After evaporation of the acetic anhydride *in vacuo*, 20 ml of water was added and the turbid solution was basified with ammonia. The precipitate was separated by filtration, washed with water, and dried, then dissolved in ether. The solution was filtered through Darco, after which the ether was gradually replaced with *n*-hexane by addition of the latter while boiling off solvent. Crystallization from 50 ml followed by concentration of the mother liquors yielded a total of 3.8 g (87%) of product, mp 153–157°. The analytical sample, obtained by an evaporative distillation at 170° (0.02 mm) and further recrystallizations, had mp 159–160°, $[\alpha]^{26}D$ +67°. The ultraviolet spectrum consisted of a plateau at 232–243 mμ (ε 6360), while significant nmr signals were observed at 2.19 for the N-methyl group and at 1.63 ppm for the highly shielded acetyl methyl. In addition the vinyl proton appeared at 5.0 ppm as a broad, nondefinable peak, indicative of an adjacent methylene group, with a width at half-band height of 13 cps.

Anal. Calcd for $C_{29}H_{36}N_2O$: C, 81.26; H, 8.47; N, 6.54. Found: C, 81.43; H, 8.48; N, 6.47.

Hydrolysis of Acetyllobinaline.—A solution of 0.1 g of acetyl compound in 15 ml of concentrated hydrochloric acid was refluxed for 3.75 hr, then evaporated to dryness *in vacuo*. Water and potassium carbonate were added, the product was extracted into methylene chloride, and the dried extract was evaporated to a froth. The resulting residue had an infrared spectrum identical with that of amorphous lobinaline and consisted of at least 95% lobinaline as shown by thin layer chromatographic comparison in several systems.

von Braun Reaction with Acetyllobinaline.—A solution of 8.56 g of acetyllobinaline in 400 ml of anhydrous ether was added over a 6-hr period to a solution of 2.96 g of cyanogen bromide in the same volume of ether, while stirring vigorously. Insoluble salts were separated by filtration and the turbid filtrate was extracted twice with 5% aqueous hydrochloric acid which was also used, in turn, to wash the initial partially soluble salts. The aqueous layer was made alkaline with ammonia, the precipitate was extracted into methylene chloride, and the dried extract was evaporated to yield (after crystallization) 1.29 g of unchanged acetyllobinaline. The original ether solution was washed with water, dried, and evaporated to yield 7.66 g of product as a white froth. No means of crystallizing the substance was found. For analysis a 220-mg sample was adsorbed on 11 g of activity I neutral alumina from 1:1 hexane–cyclohexane. Eventual elution of a 135-mg midfraction with 3:1 benzene–ether and evaporative distillation of the colorless glass at 140–170° (0.1 mm) yielded a pure product as indicated by analysis, thin layer chromatography, and nmr investigation. The acetyl nitrile, $[\alpha]^{24}D$ +64°, had an ultraviolet maximum at 244 mμ (ε 6030). In the nmr the vinyl proton signal was observed at 5.0 ppm and the acetyl methyl at 1.82 ppm.

Anal. Calcd for $C_{29}H_{33}N_3O$: C, 79.23; H, 7.57; N, 9.56. Found: C, 79.25; H, 7.78; N, 9.15.

Hydrolysis and Decarboxylation of 2a.—The von Braun product (7.46 g) was added to 57 ml of 6 *N* hydrochloric acid and the solution was refluxed for 6 hr under nitrogen, then allowed to stand overnight. The slightly oily, orange solution was filtered through a pad of Darco, which was washed with an equal volume of 6 *N* acid. The combined filtrates were made weakly alkaline with concentrated ammonium hydroxide, during which process a salt, presumably mainly monohydrochloride of desmethyllobinaline, precipitated. The salt was separated by filtration and washed with cold water. Since no means of purifying the material was found, it was converted to the free base by partial dissolution in warm water followed by the addition of solid potassium carbonate. After extraction into methylene chloride and evaporation of the dried extract the material was dissolved as completely as possible in ether. A small, crystalline fraction (0.39 g) which remained undissolved was separated from the chilled solution and washed with cold ether, mp 197–200°. The filtrate was evaporated to dryness to yield 4.9 g of **desmethyllobinaline** as a white froth. The combined, aqueous filtrates from the precipitation of the salt were next made strongly alkaline with solid potassium carbonate, which resulted in the precipitation of crystalline solid. This was extracted into methylene chloride and the dried extract was evaporated to yield 0.68 g of crude amino ketone, mp 194–196°. This was combined with the above 0.39-g crystalline fraction, also shown to be amino ketone by undepressed mixture melting point.

The desmethyllobinaline, which could not be obtained in crystalline form, was partially purified by an evaporative distillation at 120–140° at approximately 0.1 mm. In the ultraviolet the resulting colorless glass had λ_{max} 251 mμ (ε 610), 257 (620), 264

(18) Melting points and boiling points are uncorrected. Rotations were determined in chloroform and nmr spectra were determined in deuteriochloroform, unless otherwise specified. The nmr spectra were obtained with the Varian A-60 spectrometer 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 in cps. Ultraviolet spectra (wave lengths expressed in mμ, extinction coefficients as ε) were determined in ethanol and infrared spectra were determined as Nujol mulls unless otherwise indicated.

(19) We wish to express our appreciation to Mr. Harry E. Ahles, curator of the Herbarium, Botany Department, University of North Carolina, who identified and collected the specimen of *Lobelia cardinalis L.* in North Carolina.

(20) This spectrum was determined by Dr. R. Ryhage, Karolinska Institute, Stockholm.

(470), and 268 (330) and λ_{min} 232 mμ (ε 370), 255 (540), and 263 (440). The infrared spectrum was very similar to that of lobinaline, except for the appearance of a broad, weak NH absorption at about 3250 cm^{-1}.

Anal. Calcd for $C_{26}H_{32}N_2$: C, 83.82; H, 8.66; N, 7.52. Found: C, 83.25; H, 8.73; N, 7.40.

The amino ketone, although crystalline, was difficult to purify, apparently because of a fairly ready reversion to desmethyllobinaline. When a sample was held above its melting point for 3 min conversion was essentially complete as shown by thin layer chromatographic comparison. The analytical sample, obtained by careful recrystallizations from 1:2 ethanol–water, had mp 206–208°. The NH absorption in the infrared appeared as a broad band at 3250–3300 cm^{-1}.

Anal. Calcd for $C_{26}H_{34}N_2O$: C, 79.95; H, 8.78; N, 7.17. Found: C, 79.45; H, 8.73; N, 7.04.

5,7-Diphenyl-6-(2-pyridyl)-5,6,7,8-tetrahydroquinoline (4).—A mixture of 1.99 g of desmethyllobinaline, 1.0 g of 10% palladium–charcoal, and 45 ml of diphenyl ether was refluxed under nitrogen for 6 hr, then allowed to stand overnight. The catalyst was separated by filtration and washed thoroughly with methylene chloride. The combined filtrate was extracted with 125 ml of 5% hydrochloric acid in four portions and the yellow acid layer was washed thoroughly with ether, then made alkaline with ammonium hydroxide. The resulting oil was extracted into methylene chloride, and the dried extract was evaporated to yield 1.17 g of tan froth, subsequently found to consist chiefly of **4** and **5**, together with minor impurities. In the initial work-up the froth was chromatographed on 120 g of grade II–III neutral alumina in 1:1 benzene–*n*-hexane. After elution of 0.13 g of oily materials with this solvent, compound **4** was eluted in partially purified form with 3:2 benzene–hexane, as shown by the characteristic ultraviolet maxima at 270 and 262 mμ. Later fractions were less pure, as shown by the appearance of increasingly strong absorption in the 240-mμ region. The purest fractions (0.51 g) were subjected to rechromatography on 12.5 g of grade II–III alumina. The combined first fractions (0.35 g) from this process crystallized on warming with pentane. Recrystallizations from hexane produced the analytical sample, mp 121.5–122°.

Anal. Calcd for $C_{26}H_{22}N_2$: C, 86.18; H, 6.12; N, 7.73. Found: C, 86.06; H, 6.29; N, 7.57.

The deuteriomethanol equilibration for nmr studies was initially carried out by dissolving 140 mg of sodium in 5 ml of deuteriomethanol and heating 0.5 ml of this solution with 81 mg of **4** in a sealed tube at 70° for 4.5 days. Evaporation of the solvent, quenching of the residue in aqueous sodium bicarbonate, extraction into methylene chloride, and evaporation of the dried extract yielded, after trituration with pentane, 77 mg of partially deuterated **4**, mp 121–122°, undepressed on admixture with untreated material. The spectrum of this sample indicated replacement of about one proton in the 3.4–3.9-ppm region. Accordingly, the sample was retreated with 2.2 ml of deuteriomethanol containing approximately 0.1 g of dissolved soldium at 100° for 11 days longer. The product from this process had the spectral properties described in the text.

Oxidation of 4.—A mixture of 0.18 g of **4**, 0.5 g of potassium permanganate, and 10 ml of water was refluxed and stirred for 24 hr, during which period more permanganate was added whenever decolorization was observed. A total of 2.0 g of oxidant was used. At the end of the period very little undissolved organic matter was noted. After decolorization of excess reagent by addition of ethanol, the hot solution was filtered through Celite and the MnO_2 was washed thoroughly with water and with hot 5% sodium carbonate solution. The combined water layers were washed with ether, evaporated to about 10 ml *in vacuo*, and acidified to pH 1 with concentrated hydrochloric acid to yield a crystalline precipitate. This was extracted into ether. Evaporation of the dried extract yielded 90 mg of crude benzoic acid, as shown by melting point, mixture melting point, and infrared spectrum. The aqueous layer was next evaporated to dryness *in vacuo* and the residue was extracted in a Soxhlet apparatus with absolute ethanol. The extract, which had λ_{max} 262 mμ, was evaporated to yield 180 mg of a mixture, including inorganic salts. This was next extracted with boiling acetone which on evaporation yielded 92 mg of oily residue. This residue was washed twice with ether to remove soluble impurities and to leave approximately 40 mg of material with the characteristic ultraviolet absorption. This was dissolved in methanol and methylated with ethereal diazomethane solution. Paper chromatographic comparison with methyl picolinate and dimethyl quinolinate indicated that the mixture consisted chiefly of these substances, together with minor impurities. The system employed was 3:1 xylene–methyl ethyl ketone on paper impregnated with formamide (formamide pH adjusted to 5.6). Similar conclusions were drawn from thin layer chromatography on silica gel in 1:1 benzene–ethyl acetate.

5,7-Diphenyl-6-(2-pyridyl)quinoline (5).—Materials eluted in later fractions in several chromatographic purifications of **4** were combined to yield 2.18 g of a mixture which contained **4**, a second major component,[21] and minor impurities. The mixture was subjected to a countercurrent distribution between 420 ml of 0.1 *N* hydrochloric acid and 170 ml of methylene chloride in the first funnel, after which 170-ml lower phases were transferred and partitioned by the usual scheme with six additional 250-ml portions of 0.1 *N* acid. The acid layers were made basic with concentrated ammonia, the products were extracted into methylene chloride, and the extracts were dried and evaporated. Thin layer examination of all residues revealed that the product from the first acid layer was mainly **4**. After three recrystallizations from hexane this had mp 118–120° and weighed 310 mg. The completely dehydrogenated **5** was found in the last four acid layers and in all methylene chloride layers. Recrystallizations from *n*-hexane yielded 390 mg of product, mp 154–156.5°. The analytical sample, prepared by further recrystallizations from the same solvent, had mp 156–157°. In the nmr spectrum the C_2 proton signal appeared at δ 8.97 as a doublet of doublets, the C_6H at 8.30 (dd), the C_4H at 7.98 (broad doublet), and the C_8H at 8.30 (singlet).

Anal. Calcd for $C_{26}H_{18}N_2$: C, 87.12; H, 5.06; N, 7.82. Found: C, 87.22; H, 5.10; N, 7.74.

3-Amino-1-phenyl-buten-2-one-1.—This substance, prepared by the method of Knoevnagel,[22] had mp 141–144° (lit.[22] mp 143°). In the nmr the methyl signal was observed at δ 2.00, the vinyl proton at 6.38, the nonchelated NH at about 5.6, and the chelated NH at 10.2. The ultraviolet spectrum (methanol) showed λ_{max} 240 mμ (ε 8670) and 328 mμ (ε 19,700) and λ_{min} 220 mμ (ε 4940) and 266 mμ (ε 1160). In the infrared NH bands were observed at 3160 and 3310 cm^{-1}, while no absorption was noted in the carbonyl region above 1630 cm^{-1}.

3-Benzoyl-1,4-dihydro-2-picoline.—A solution of 35.2 g of the above amino ketone and 1.32 g of piperidine in 500 ml of absolute ethanol was maintained at 40–50° under nitrogen while a solution of 13.6 g of acrolein in 50 ml of absolute ethanol was added over a period of 2 hr with stirring. The yellow solution was refluxed for 6 hr, during which period it turned brown, then evaporated to dryness *in vacuo*. Addition of ether to the solid residue, filtration, and washing with ether yielded an initial crop of 18 g of yellow product, mp 103–107°. The mother liquor was evaporated to dryness then again treated with a smaller volume of ether to yield an additional 12.3 g of product, mp 102–105°. A sample recrystallized from ethanol for analysis had mp 106–108°. Although the analysis was satisfactory for an ethanol solvate, and the nmr spectrum showed the presence of 1 mole of ethanol, the spectrum also indicated that the substance was impure, possibly containing disproportionation products.[23] Because of the limited stability of the substance, however, it was oxidized as such without further purification. The infrared spectrum showed a strong NH absorption at 3280 cm^{-1} and no absorption in the carbonyl region above 1600 cm^{-1}, while in the ultraviolet (methanol) maxima were observed at 240 mμ (ε 8930) and at 322 mμ (ε 19,040) and minima appeared at 223 mμ (ε 6125) and 268 mμ (ε 1476).

Anal. Calcd for $C_{13}H_{13}NO \cdot C_2H_5OH$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.57; H, 7.81; N, 6.02.

3-Benzoyl-2-picoline.—A solution of 9.0 g of chromic anhydride in 20 ml of water was added over a period of 5 min with stirring to a solution of 24.5 g of the dihydro compound in 80 ml of acetic acid. The solution, which had become hot during the addition, was warmed on the steam bath for 30 min, diluted with 200 ml of water, chilled, and made basic with concentrated ammonium hydroxide. The product was extracted into methyl-

(21) The two substances could be readily distinguished by thin layer chromatography on silica gel G (Merck) in 4:1 ethyl acetate–chloroform. Chromatograms were run on microscope slides prepared by dipping in a chloroform slurry, and spots were detected by ultraviolet light or iodine vapor.

(22) E. Knoevnagel, *Ber.*, **36**, 2187 (1903).

(23) *Cf.* Tsuda[10] for similar findings with other dihydropyridines.

ene chloride, the dried extract was evaporated, and the residue was distilled. Redistillation at 100–102° (0.1 mm) yielded 6.4 g of pale yellow oil. The carbonyl absorption in the infrared (liquid film) appeared at 1650 cm^{-1}, while in the ultraviolet (methanol) maxima were observed at 202 mμ (ε 26,300), 251 (14,700), and 316 (352), and the minimum appeared at 225 mμ (ε 5280). In the nmr the 6-pyridyl proton appeared as a doublet of doublets at 8.66, the C_4H signal was at 7.82, (dd) and the C_5H signal appeared as a quartet at 7.22 ppm.

Anal. Calcd for $C_{13}H_{11}NO$: C, 79.16; H, 5.62. Found: C, 78.65; H, 5.78.

3-Benzoyl-2-picoline Picrate.—A picrate was formed in ethanol and recrystallized from the same solvent, mp 183–185°.

Anal. Calcd for $C_{13}H_{11}NO \cdot C_6H_3N_3O_7$: C, 53.52; H, 3.31; N, 13.14. Found: C, 53.68; H, 3.43; N, 13.08.

3-Hydroxy-3,5-diphenyl-4-(2-pyridyl)cyclohexanone.[12]—Sodium metal (23.5 g) was dissolved in 2200 ml of anhydrous ethanol under an atmosphere of dry nitrogen (maintained during the reaction), and 200 g of 2-phenacylpyridine[11] was dissolved in the solution at room temperature with stirring. Benzalacetone (148.9 g) was next added at room temperature and agitation was continued. Within a few minutes the product started crystallizing from solution. The mildly exothermic reaction was allowed to continue in a bath of room-temperature water for 30 min, after which the product was separated by filtration and washed well with ethanol. The yield of slightly impure material was 323 g, mp 235–237°. After recrystallization by dissolution in boiling methylene chloride and gradual replacement of this solvent by boiling off while adding benzene, the substance had mp 248–250°. The ultraviolet maxima (methanol) were observed at 258 mμ (ε 3520), 263 (3710), and 269 (2780), while minima appeared at 234 mμ (ε 1030), 260 (3440), and 267 (2660). The carbonyl absorption in the infrared appeared at 1715 and the OH band was found at 3210 (s) cm^{-1}.

Anal. Calcd for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16; N, 4.08. Found: C, 80.52; H, 6.20; N, 3.99.

3,5-Diphenyl-4-(2-pyridyl)cyclohexen-2-one.—A mixture of 400 g of the hydroxy ketone and 1080 ml of 85% phosphoric acid was stirred and heated (N_2) on the steam bath for 50 min. The mixture was poured into 2000 ml of water, chilled, and made alkaline with concentrated ammonium hydroxide. The solid product was extracted into methylene chloride and the dried extract was evaporated. Recrystallization by dissolution in boiling methylene chloride and gradual replacement of this solvent while adding cyclohexane yielded 358 g of material, mp 123–126°. The analytical sample, prepared by further recrystallizations from cyclohexane and from methanol–water, had mp 123–127°. This material was subsequently recognized to be a gross mixture of the two stereoisomeric *cis*- and *trans*-enones[12] but was used as such without separation for the azine formation and aromatization steps. In the ultraviolet (methanol) the mixture of isomers showed λ_{max} 205 mμ (ε 26,350), 228 (10,620), 265 (14,890), 270 (15,730), and 282 (14,930), while λ_{min} appeared at 240 mμ (ε 6570) and 278 mμ (ε 14,860). The infrared carbonyl absorption appeared at 1665 cm^{-1}.

Anal. Calcd for $C_{23}H_{19}NO$: C, 84.89; H, 5.89; N, 4.30. Found: C, 84.99; H, 6.17; N, 4.21.

3,5-Diphenyl-4-(2-pyridyl)cyclohexen-2-one Azine.—A mixture of 4.87 g of the ketone, 0.40 g of 99% hydrazine hydrate, 25 ml of 95% ethanol, and 1 drop of concentrated hydrochloric acid was refluxed for approximately 2 hr, during which time the yellow azine precipitated from solution. After cooling the product was separated by filtration and digested with 200 ml of boiling ethanol–methylene chloride. The melting point of the 4.1 g of crude product so obtained was approximately 260–280° with gradual decomposition. Because of the extreme insolubility (and stereochemical nonhomogeneity) of the substance no recrystallization medium could be found and it was not obtained analytically pure. It was used as such in the aromatization. The infrared spectrum showed no absorption in the carbonyl region.

3,5-Diphenyl-4-(2-pyridyl)aniline.—A mixture of 3.23 g of the crude azine, 1.5 g of 5% Pd–C, and 250 ml of *p-t*-butyltoluene was refluxed for 2 hr under a nitrogen atmosphere. The catalyst was separated from the warm solution and washed with methylene chloride, and the combined filtrates were poured into 200 ml of 5% hydrochloric acid with stirring, in which process considerable yellow solid precipitated. The mixture was stirred for 20 min, the acid layer was separated, and the slurry was extracted again with a smaller portion of acid. The combined acid extract was washed with ether, then made alkaline with ammonium hydroxide, and the resulting oil was extracted into methylene chloride. Evaporation of the dried extract and trituration of the residue with ether yielded crude, crystalline product. Two recrystallizations from 2:1 cyclohexane–benzene (Darco) yielded 0.82 g of white filaments, mp 178–180°. The analytical sample, prepared by further recrystallizations from the same solvent pair had the same melting point. The ultraviolet spectrum (methanol) showed λ_{max} 240 mμ (ε 31,820) and 284–292 mμ (ε 7530) while λ_{min} was observed at 222 mμ (ε 27,490). In the infrared the NH absorption appeared at 3425 and 3340 cm^{-1}.

Anal. Calcd for $C_{23}H_{18}N_2$: C, 85.68; H, 5.63; N, 8.69. Found: C, 85.87; H, 5.60; N, 8.52.

5,7-Diphenyl-6-(2-pyridyl)quinoline (5).—A mixture of 0.64 g of the above aniline, 0.35 g of arsenic pentoxide, 0.73 g of glycerol, and 1.0 g of concentrated sulfuric acid was heated gradually to 180°, at which temperature reaction took place as evidenced by bubbling and darkening of the mixture. The reaction was held at 180° for 6 hr, then allowed to stand overnight. Water was added to the black, tarry mass which was extracted by heating on the steam bath. The process was repeated several times, the combined aqueous layers were made alkaline with ammonium hydroxide, the resulting precipitate was extracted into methylene chloride, and the dried extract was evaporated. The residue was extracted several times with boiling *n*-hexane and the combined extracts were filtered through a bed of Darco. On concentration the product did not crystallize well; so the solvent was removed and the residue was dissolved in 5% hydrochloric acid to yield a turbid, orange solution. This was filtered through a pad of Darco and the free base was liberated by addition of ammonia, washed with water, and dried. Recrystallization from *n*-hexane with another Darco treatment allowed a facile crystallization of 90 mg of the known quinoline derivative, mp 154–156°, undepressed on admixture with the lobinaline degradation product. The substance was also shown to be identical with the degradation product by comparison of ultraviolet and infrared spectra and by thin layer chromatography.

3-Amino-1-(2-pyridyl)buten-2-one-1.—Although Micko[15] prepared this substance by reaction of 2-acetoacetylpyridine with ethanolic ammonia at 110°, it was found that the reaction did not require heating. Thus 20.9 g of the diketone was dissolved in 300 ml of absolute ethanol and the solution was saturated with ammonia and allowed to stand overnight. The solvent was evaporated *in vacuo* and the residue was washed well with cold ether and recrystallized from 95% ethanol to yield 14.8 g of slightly yellow product, mp 151–153° (lit.[15] mp 149–150°). The sample prepared for spectral studies by additional recrystallizations was white and had the same melting point. The nmr spectrum revealed signals for a strongly chelated NH at 10.35, the other NH at 6.17, the vinyl proton at 6.47, the methyl group protons at 2.08, and the α-pyridyl proton at 8.67 ppm. In the ultraviolet (methanol) maxima were observed at 242 mμ (ε 7320) and 338 mμ (ε 16,550) and the minima occured at 210 mμ (ε 3970) and 282 mμ (ε 1730). In the infrared a broad NH absorption was found in the 3100–3300-cm^{-1} region, and there was no absorption in the carbonyl region above 1600 other than a shoulder at 1625 cm^{-1}.

3-(2-Picolinoyl)-1,4-dihydro-2-picoline.—A solution of 19.4 g of the enamine, 0.4 g of piperidine, and a few crystals of hydroquinone in 420 ml of absolute ethanol was maintained at 40–50° under nitrogen while a solution of 7.5 g of acrolein in 60 ml of absolute ethanol was added over a period of 1.5 hr with stirring. The solution was next refluxed for 2 hr, then allowed to stand overnight at room temperature. The red liquid was evaporated to about 75 ml and chilled, and the resulting 12.25 g of crude product had mp 132–141°. Recrystallizations from acetonitrile yielded nicely formed, translucent, yellow prisms, which melted sharply at 132–134°. These were again a mixture, however, presumably containing disproportionation products. Although the analysis again fitted for the presence of 1 mole of ethanol, which was also seen in the nmr, the spectrum indicated that the substance was impure. It was oxidized as such without further attempts at purification.

Anal. Calcd for $C_{12}H_{12}N_2O \cdot C_2H_5OH$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.48; H, 7.46; N, 11.03.

3-(2-Picolinoyl)-2-picoline.—A solution of 9.0 g of the dihydro compound and 11.0 g of chloranil in 675 ml of benzene was refluxed for 2.5 hr, then allowed to stand overnight. After filtration through Celite the solution was extracted repeatedly with 10% HCl and the acid layer was washed with ether, then filtered through a pad of Darco. Liberation of the free base

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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Received May 2, 1966

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.

(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.