The Synthesis And Chemistry Of 1,3-disubstituted - Octahydropyrido-(1,2-c)pyrimidines, N,1,2-trisubstituted - Ethylamines And Certain Related Compounds.

THE SYNTHESIS AND CHEMISTRY

OF

1,3-DISUBSTITUTEDOCTAHYDROPYRIDO[1,2-c]PYRIMIDINES,

N,1,2-TRISUBSTITUTEDETHYLAMINES

AND

CERTAIN RELATED COMPOUNDS

by

Richard F. Shuman

A Dissertation

Presented to the Graduate Faculty

of Lehigh University

in Candidacy for the Degree of

Doctor of Philosophy

Lehigh University
1961

Approved and recommended for acceptance as a dissertation in partial fulfillment for the degree of Doctor of Philosophy.

May 13, 1961
(Date)

E D Amstutz
Professor in Charge

Accepted, May 18, 1961
(Date)

Special committee directing the doctoral work of Mr. Richard F. Shuman.

E D Amstutz Chairman

Thomas E Young

Robert S. Rouse

Delmer B. Fish

ACKNOWLEDGEMENTS

The author wishes to extend his sincere thanks to Dr. Edward D. Amstutz for his ideas and constructive criticism during the course of this research and the preparation of this thesis.

To Dr. Charles H. Tilford, Mr. Frank Palopoli, and The William S. Merrell Company the author is indebted for their keen interest in the project during its progress and for the financial assistance rendered.

The author is grateful to his parents whose frequent favors and whose willingness to be inconvenienced made the path an easier one.

To his wife, Judith, the author expresses his heartfelt appreciation for her love, patience, and particularly for her efforts in providing and maintaining a home for her family. The author would like to mention his daughter, Dawn Elizabeth, whose very presence both impeded work and provided impetus.

Miss Roberta Wagner provided her time and talents to the typing of this manuscript and, for this, the author is grateful.

TABLE OF CONTENTS

Page

LIST OF TABLES

PART I

Pyrido [1,2-c] pyrimidines

ABSTRACT

Four 1,3-disubstitutedoctahydropyrido [1,2-c] pyrimidines were synthesized. 2-Phenacylpyridine, prepared from 2-picolyllithium and methyl benzoate, was converted to 2-phenacylpyridine oxime which in turn was reduced to 2-(2-amino-2-phenylethyl)piperidine with platinum dioxide and hydrogen. Condensation of this diamine with diethyl carbonate was effected in a sealed tube at 200° to give 3-phenyloctahydropyrido [1,2-c] -1-pyrimidone. Carbon disulfide also condensed with 2-(2-amino-2-phenylethyl)piperidine to produce hydrogen sulfide and a thiourea, 3-phenyloctahydropyrido [1,2-c] -1-thiopyrimidone. This easily formed an S-methyl homologue, 1-thiomethoxy-3-phenyl- Δ^{1}-hexahydropyrido [1,2-c] pyrimidine, when warmed with methyl iodide. Condensation of benzaldehyde with the diamine was also effected producing 1,3-diphenyloctahydropyrido [1,2-c] pyrimidine.

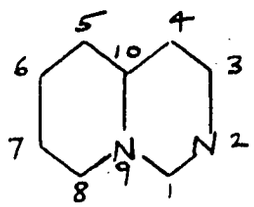
Attempts to prepare 3H-1,3-disubstitutedpyrido [1,2-c] pyrimidines were unsuccessful. 2-Phenacylpyridine oxime was reduced with zinc dust in ethanolic acetic acid to 2-(2-amino-2-phenylethyl)pyridine which was converted both to its acetamide and the corresponding benzamide. Attempted cyclodehydration of the acetamide with $POCl_3$ or P_2O_5 produced 2-stilbazole rather than the expected 3H-1-methyl-3-phenylpyrido [1,2-c] pyrimidine.

Under the same conditions the benzamide was quantitatively recovered. Carbon disulfide and 2-(2-amino-2-phenylethyl)pyridine yielded 1,3-bis-[1-phenyl-2-(2-pyridyl)ethyl]-2-thiourea rather than the hoped for 3H-1-mercapto-3-phenylpyrido[1,2-c]pyrimidine.

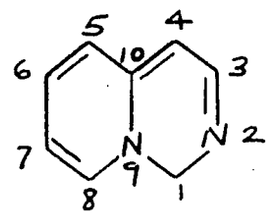
Infrared spectra were run and the band wavelengths tabulated.

INTRODUCTION

The saturated and unsaturated pyrido [1,2-c] pyrimidine nuclei (I and II) have been synthesized and studied only recently. Work in this area has been prompted by the possibility of finding compounds having therapeutic properties.



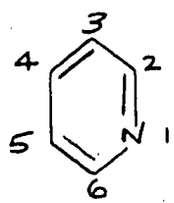
Octahydropyrido [1,2-c] pyrimidine.



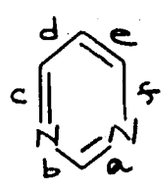
1H-Pyrido [1,2-c] pyrimidine.

It seemed interesting, therefore, to synthesize various saturated and unsaturated representatives of this class of compounds via untried reaction sequences.

The name pyrido [1,2-c] pyrimidine derives from the fact that structure II may be viewed as resulting from the fusion of a pyridine nucleus (III) at the atoms numbered 1 and 2 to the bond lettered c on a pyrimidine nucleus (IV).

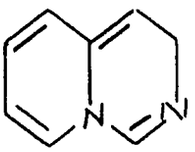


III

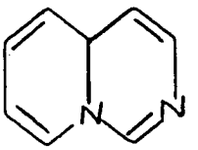


IV

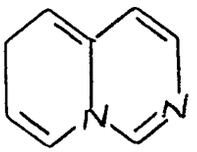
There are five isomeric pyrido [1,2-c] pyrimidines (II,IIa,b,c,d) possible depending upon the positions of the double bonds.



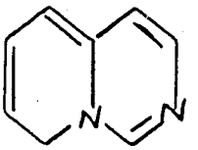
II a
3H-Pyrido [1,2-c] pyrimidine



II b
9H-Pyrido [1,2-c] pyrimidine



II c
7H-Pyrido [1,2-c] pyrimidine

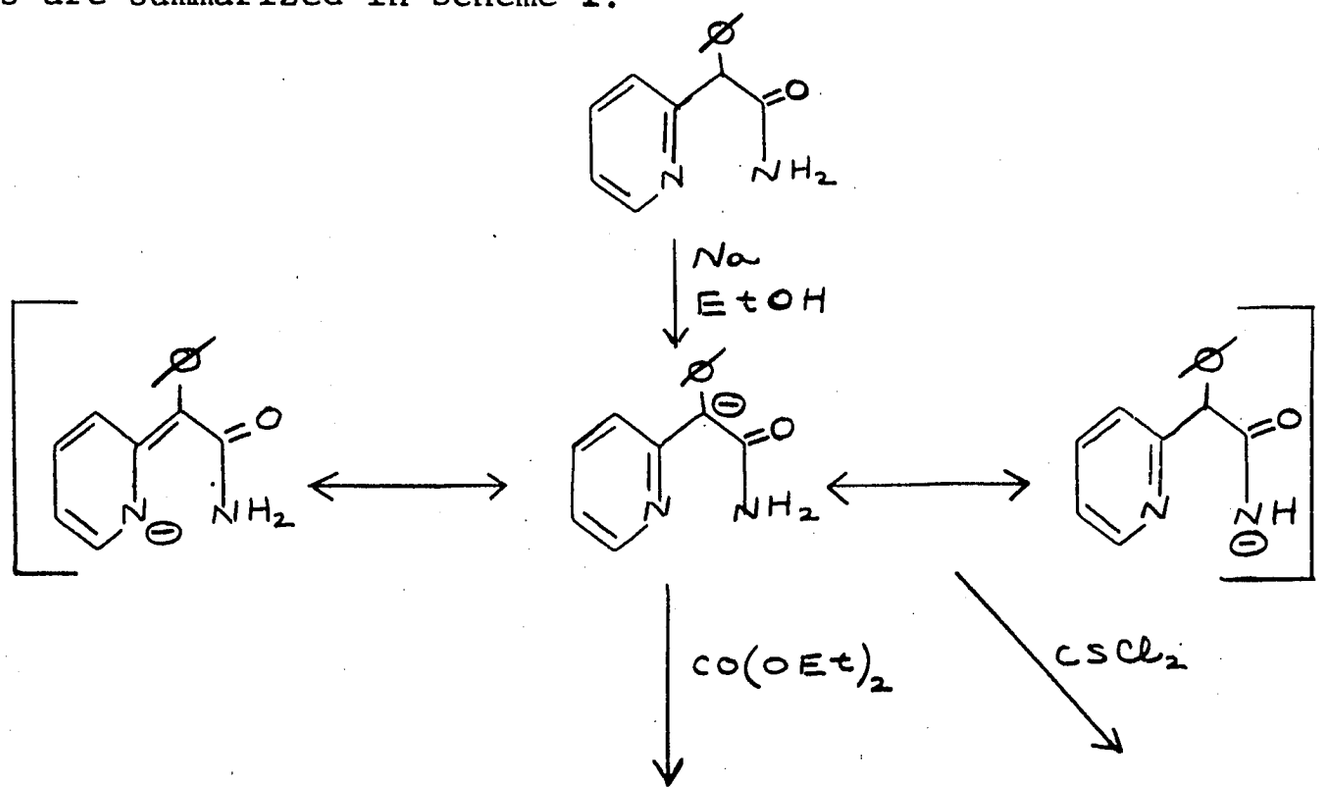


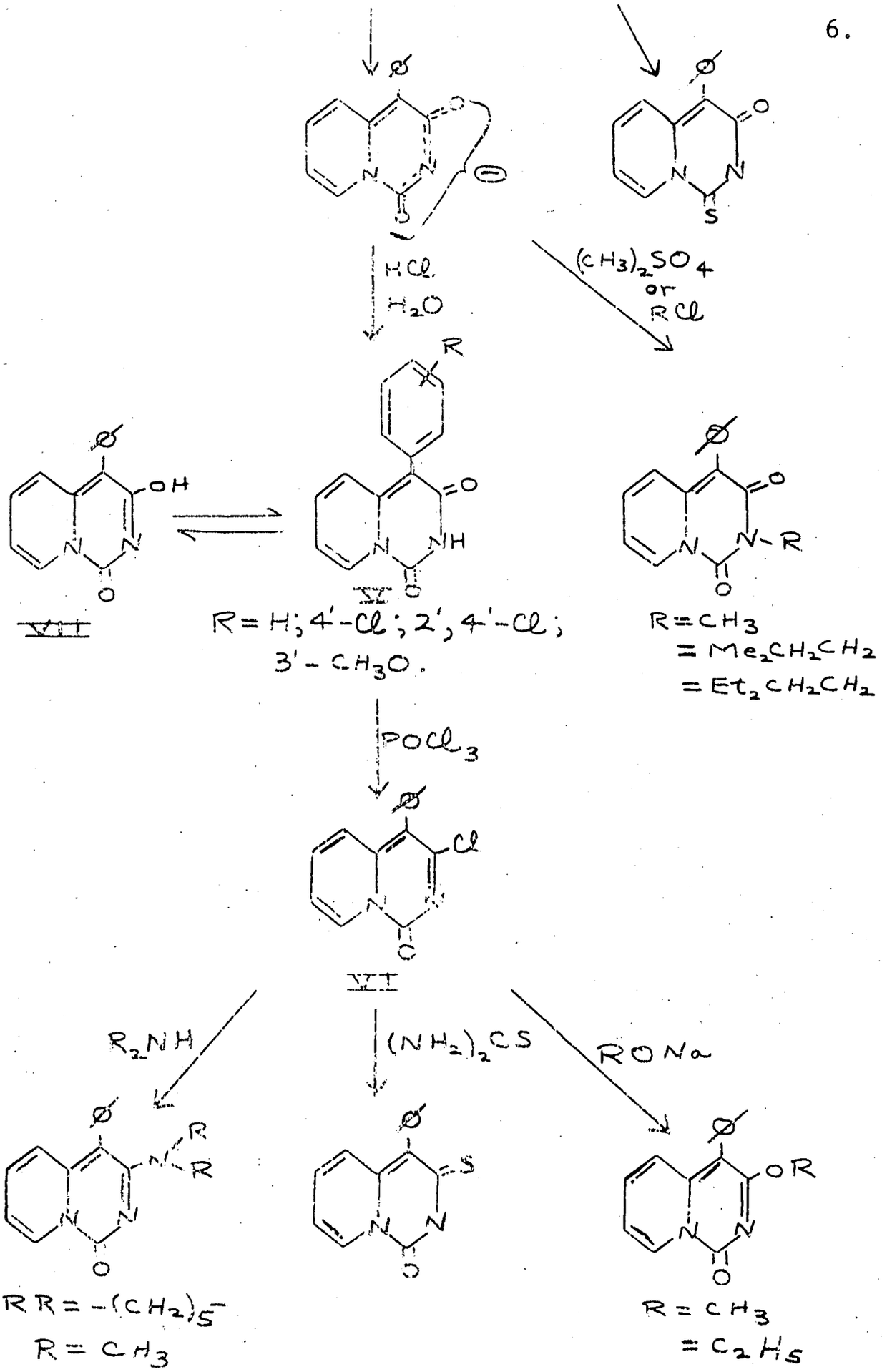
II d
8H-Pyrido [1,2-c] pyrimidine

Although the unsubstituted octahydropyrido [1,2-c] pyrimidine nucleus (I) has been synthesized none of the unsubstituted, unsaturated isomers have been made.

In 1957 Hunger and Hoffman (2) reported the synthesis of 1H-1,3,4-trisubstitutedpyrido [1,2-c] pyrimidines utilizing α-phenyl-2-pyridineacetamide as a starting material. Treatment of α-phenyl-2-pyridineacetamide with sodium in absolute ethanol followed by the addition of diethyl carbonate gave, upon acid hydrolysis, 1H-4- phenyl-pyrido [1,2-c] pyrimidine-1,3(2H)dione (V). Phosphorous oxychloride and V produced the 3-chloro analogue (VI).

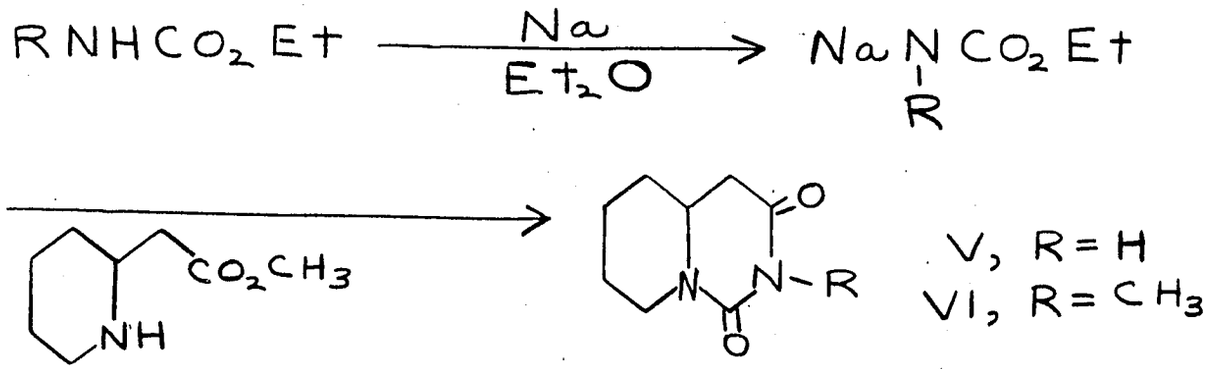
The imino chloride, VI, may be viewed as arising by reaction of the 3-imidol tautomer (VII) of the dione, V. 1H-3-Chloro-4-phenylpyrido-[1,2-c] -1-pyrimidone (VI) was reacted with nucleophiles such as piperidine, dimethylamine, thiourea, sodium methoxide, and sodium ethoxide to give displacement of a chloride ion and introduction of a new group in the 3-position. Treatment of the sodium salt of 1H-4-phenylpyrido-[1,2-c] pyrimidine-1,3(2H)-dione with dimethyl sulfate or N,N-dialkylaminoethylchlorides gives substitution on the nitrogen in the 2-position. In addition, 1H-4-phenylpyrido [1,2-c] pyrimidine-1-thion-3(2H)-one was obtained by treating an ethanolic solution of sodio α-phenyl-2-pyridineacetamide with thiophosgene. These reactions are summarized in Scheme I.





SCHEME I (2)

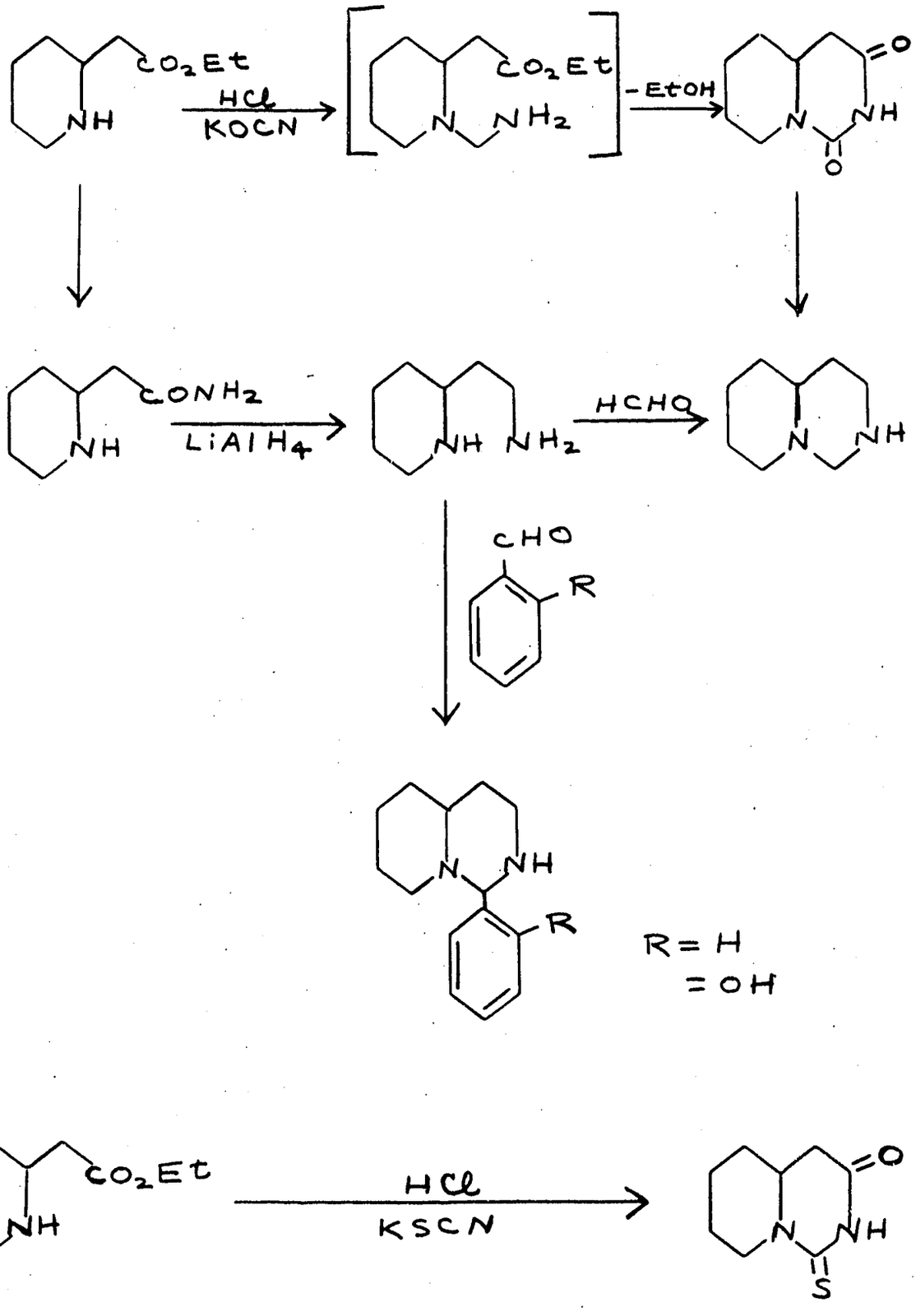
In 1956 Winterfeld and Göbel (3) published a synthesis of octahydropyrido [1,2-c] pyrimidine-1,3-dione (V) and its N-methyl homologue (VI). The addition of methyl 2-piperidyl-acetate to an ether solution of sodio urethane produced the expected product. See Scheme II.



SCHEME II (3)

Three years later Winterfeld and Göbel (1) prepared octahydropyrido [1,2-c] pyrimidine (I) itself as well as various 1- and 3-substituted derivatives. I Was synthesized by treating ethyl 2-piperidylacetate with potassium cyanate in aqueous acid followed by reduction of the resulting octahydropyrido [1,2-c] pyrimidine-1,3-dione with lithium aluminum hydride. An alternate route to I employed reduction of 2-piperidylacetamide with lithium aluminum hydride and condensation of the resulting 2-(β-aminoethyl)piperidine with formaldehyde.

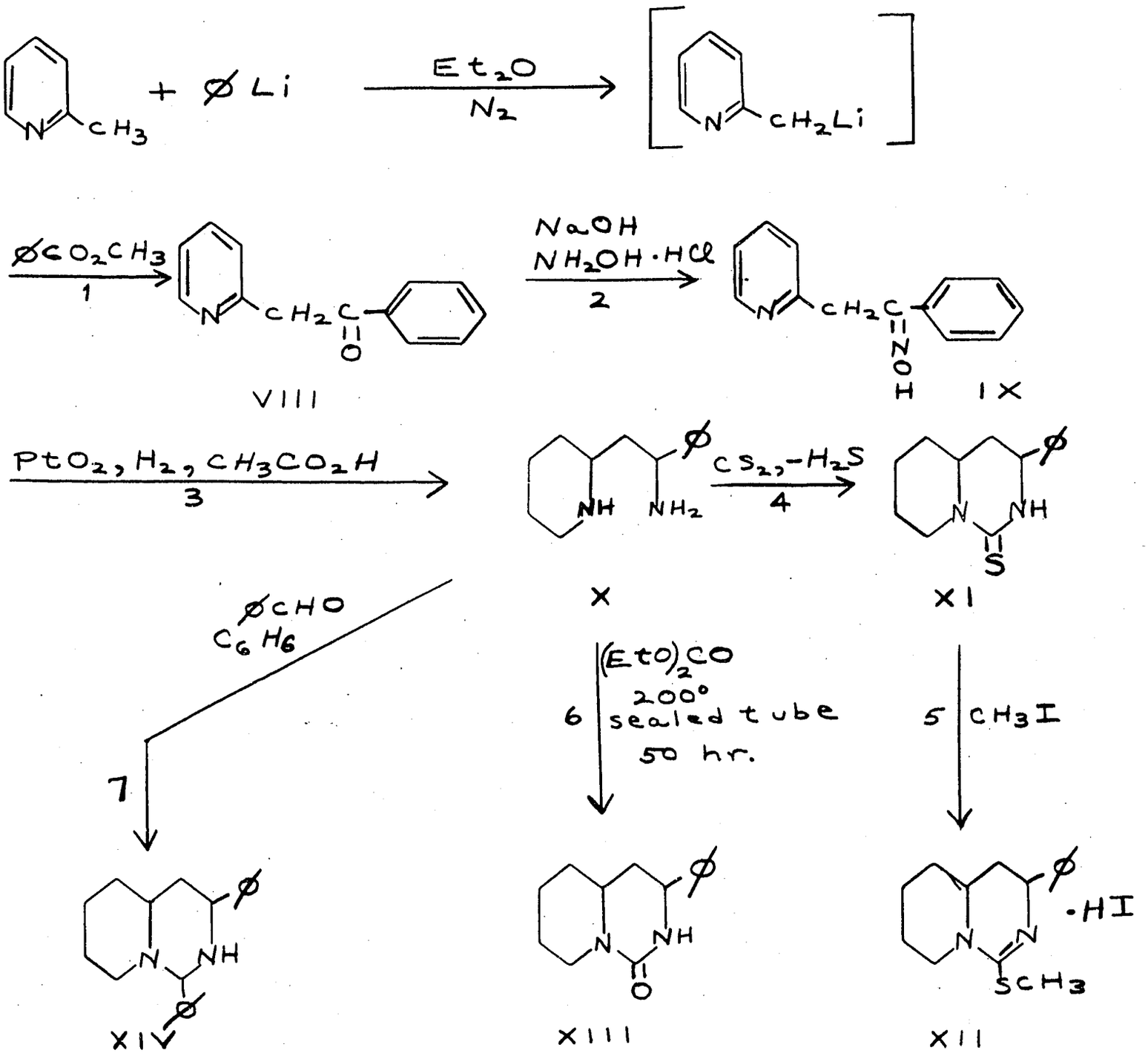
The condensation was also carried out with substituted benzaldehydes to give 1-phenyloctahydropyrido [1,2-c] pyrimidines. Potassium thiocyanate was found to react with ethyl 2-piperidylacetate in acid to produce octahydropyrido [1,2-c] pyrimidine -1-thion-3-one. See Scheme III.



DISCUSSION

Synthesis Of 1,3-Disubstitutedoctahydropyrido [1,2-c] pyrimidines.

The sequence of reactions used in the synthesis of the 1,3-disubstitutedoctahydropyrido [1,2-c] pyrimidines is as follows:

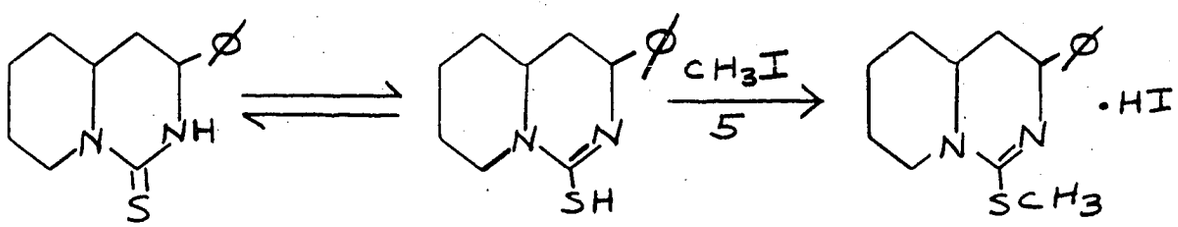


SCHEME IV

Reaction 1 is the same as that used by Goldberg, Barkley and Levine (4,5) for the preparation of 2-phenacylpyridine (VIII). Addition of methyl benzoate to an excess of picolyllithium in ether under dry nitrogen gave a 72% yield of VIII after fractionation. The yields reported by Goldberg, Barkley and Levine range from 81.8% to 85.5%. They were not able to isolate any carbinol in this acylation using methyl benzoate, but using methyl acetate, methyl propioniate, methyl isobutyrate, and methyl isovalerate amounts of carbinol were found in yields of 28.1%, 21.9%, 15.8%, and 8.5% respectively. They concluded that the steric requirements of the ketones are probably such that the extent of carbonyl attack by 2-picolyllithium (to give the carbinol) decreases due to an increase in size of the acyl portion of the ester.

2-Phenacylpyridine oxime (IX) was formed easily (Reaction 2) by heating the ketone (VIII) in refluxing 95% ethanol with hydroxylamine hydrochloride and a slight excess of sodium hydroxide. The oxime (IX) crystallizes from the reaction mixture in a good state of purity. The oximino group and the pyridine ring were reduced simultaneously (Step 3) with platinum dioxide under 3 to 4 atm. of hydrogen using glacial acetic acid as a solvent. The reduction was usually complete in a few hours to give a 75% yield of 2-(2-amino-2-phenylethyl)piperidine (X). Diamine X and an excess of carbon disulfide were then heated in refluxing 95% ethanol accompanied by the evolution of hydrogen sulfide to give, upon cooling, 3-phenyl-

As is the case with most thioureas, compound XI easily underwent S-methylation when stirred with methyl iodide. The resulting 1-thiomethoxy-3-phenyl- Δ^1-hexahydropyrido [1,2-c] pyrimidine hydroiodide (XII) (85%) undoubtedly arises from the reaction of the enethiol form of compound XI with the methyl iodide. This may be shown as follows:



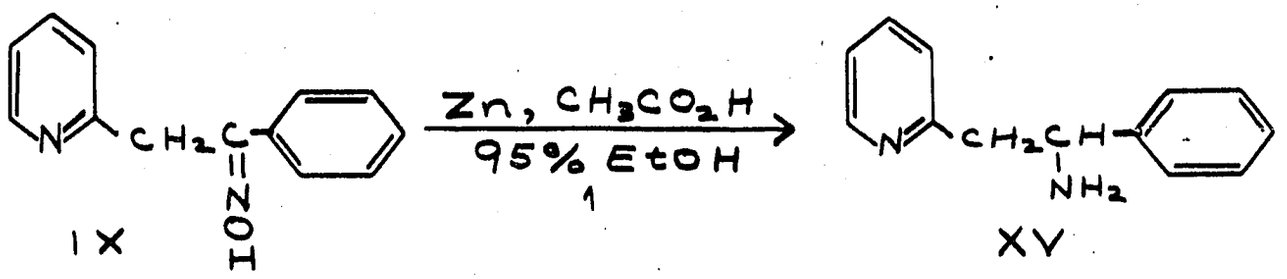
XI XIII

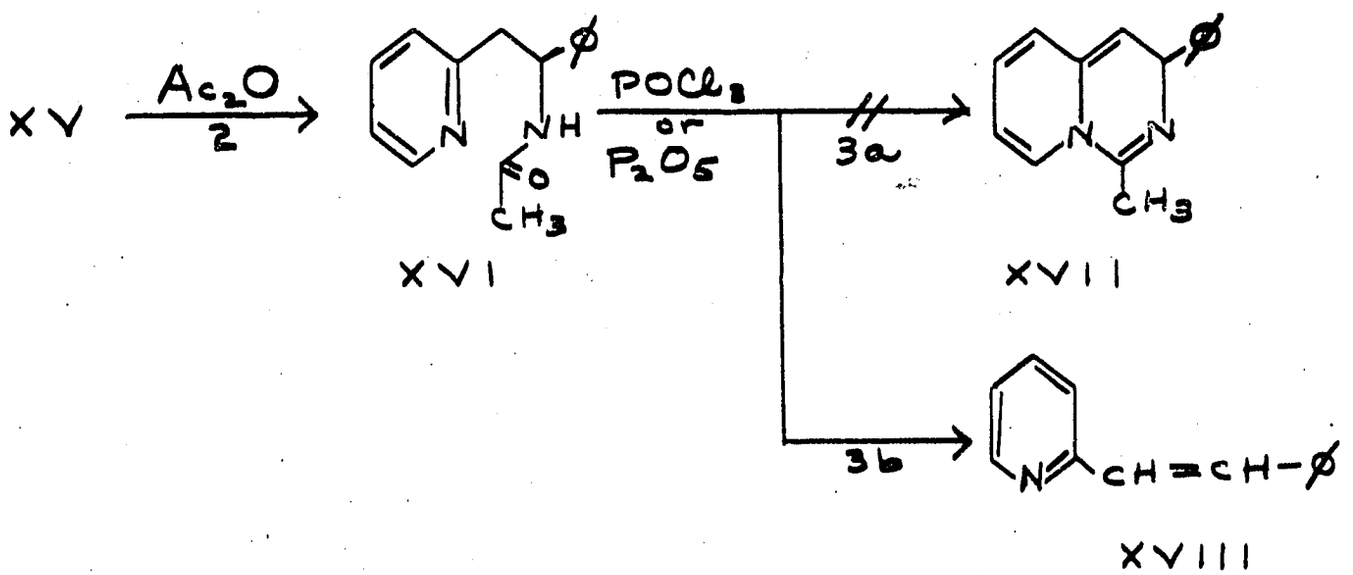
Step 6 took place only under fairly strenuous conditions. Exploratory research in this laboratory by H. V. Hansen revealed that no reaction took place when 2-(2-amino-2-phenylethyl)piperidine (X) and an excess of diethyl carbonate were heated overnight in refluxing 95% ethanol. The conversinn of X to 3-phenyloctahydropyrido-[1,2-c]-1-pyrimidone (XIII) in 39% yield (66% before recrystallization) was effected by heating X with an excess of diethyl carbonate in a sealed tube at 200° for 50 hours. XIII Generally precipitated from the excess diethyl carbonate after cooling the unopened tube in a refigerator overnight.

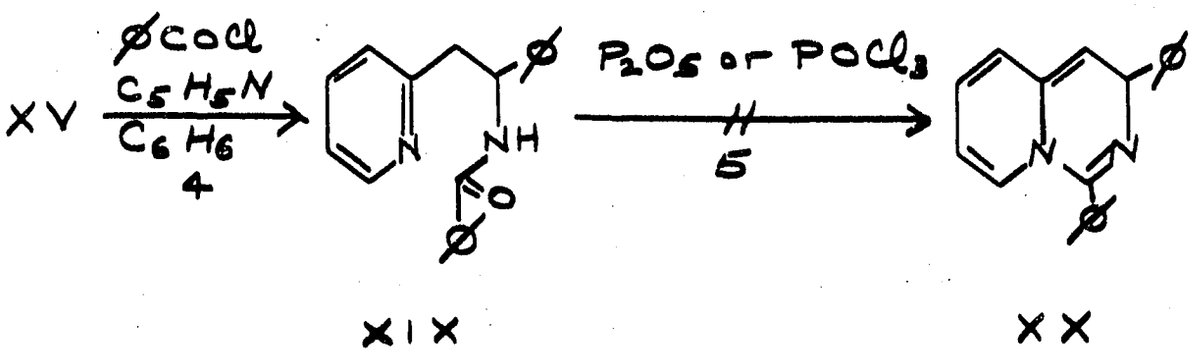
Although it was not attempted, the use of phosgene in an ether-pyridine solution would provide an easier route to 3-phenyloctahydropyrido [1,2-c] -1-pyrimidone (XIII).

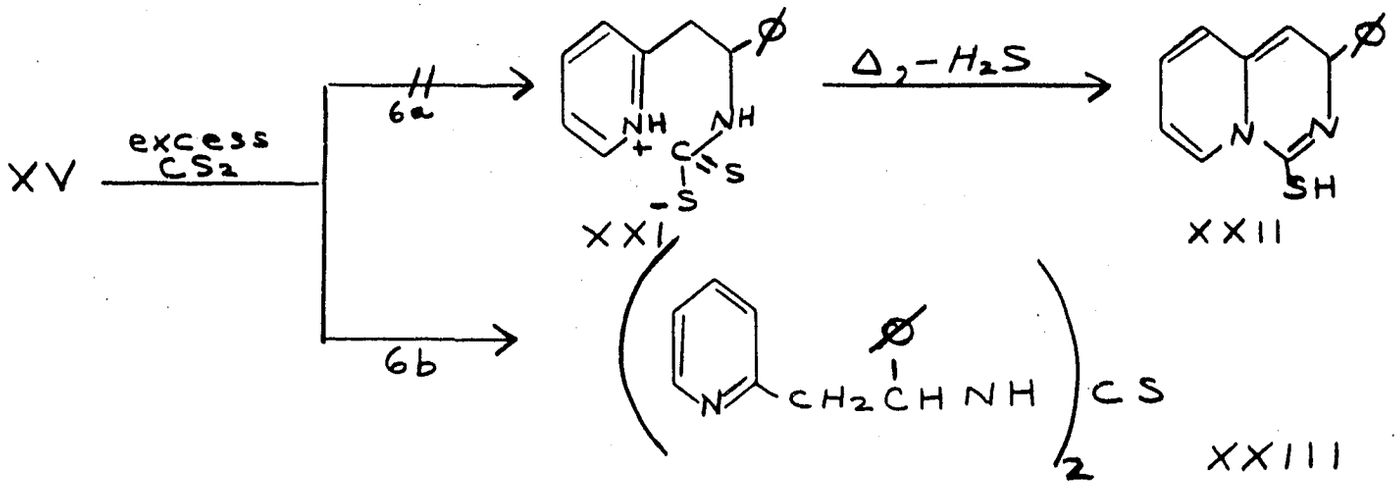
Attempted Synthesis of 3H-1,3-Disubstitutedpyrido [1,2-c] pyrimidines.

The following sequence of reactions was attempted with the hope of obtaining a useful route to 3H-1,3-disubstitutedpyrido-[1,2-c] pyrimidines.









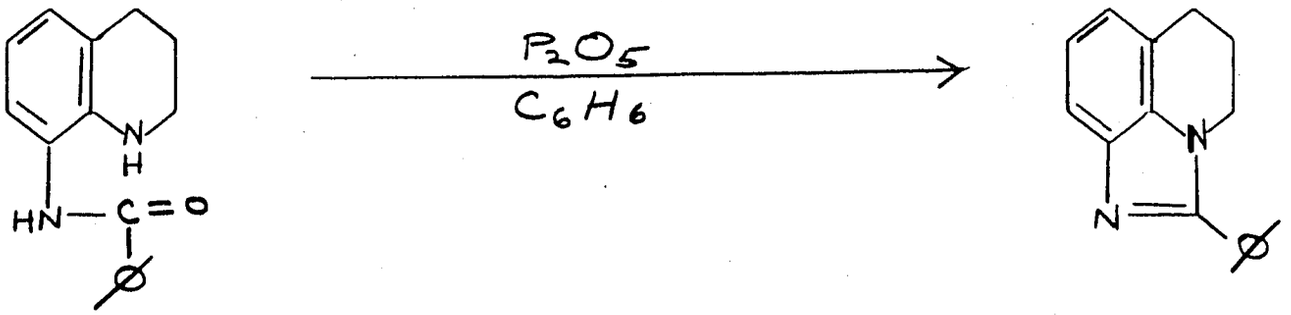
SCHEME V

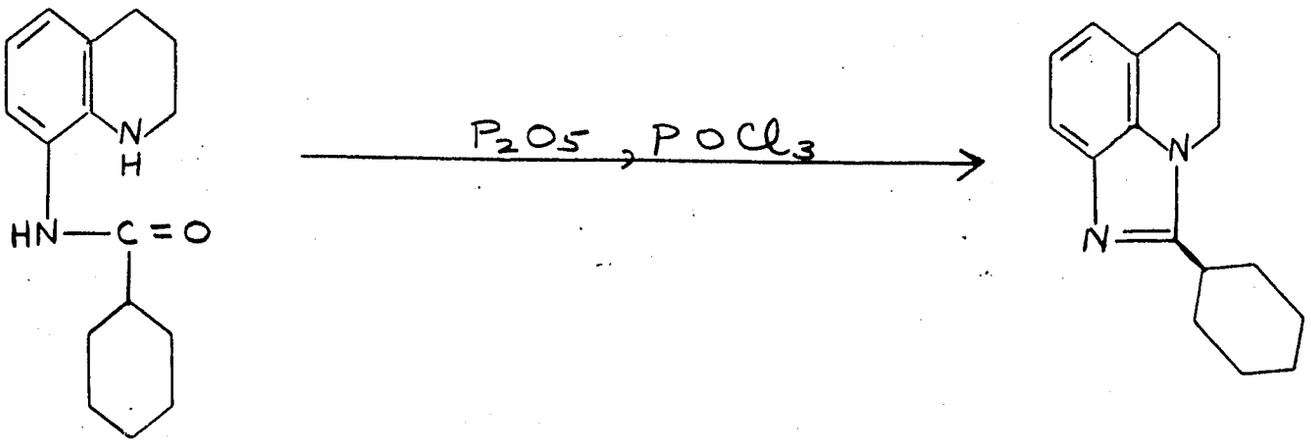
Steps 3a, 5, and 6a proved to be unsuccessful for the preparation of pyrido [1,2-c] pyrimidines.

The conditions for step 1 were identical to those used for the reduction of 2-pyridinecarboxaldehyde oxime to 2-aminomethylpyridine (6). 2-Phenacylpyridine oxime (IX) was treated with zinc dust in a solution of 95% ethanol and glacial acetic acid and a 64% yield of 2-(2-amino-2-phenylethyl)pyridine (XV) was obtained. Acetylation of XV was carried out by heating it with an excess of acetic anhydride (step 2) while benzoylation was effected with benzoyl chloride in a benzene-pyridine solution. The yields of the resulting acetamide (XVI) and benzamide (XIX) were 65% and 67% respectively.

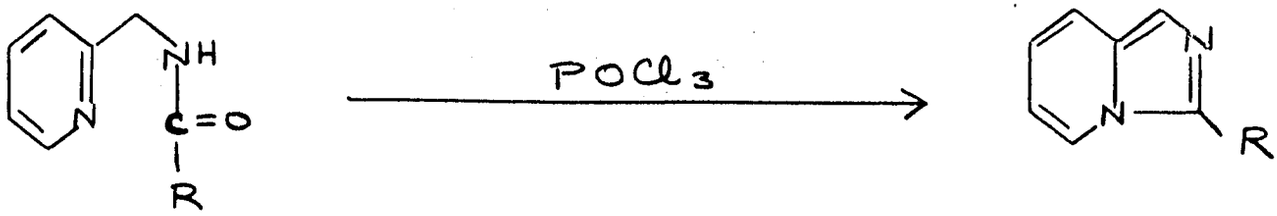
The reaction between amides and amines in the presence of phosphorous pentoxide or phosphorous oxychloride to form amidines is well known (7). Richardson and Amstutz (8) have used these reagents to form 2-substituted-5,6-dihydroimidazo [ij] quinolines from various 8-amido-1,2,3,4-tetrahydroquinolines.

Two examples are as follows:



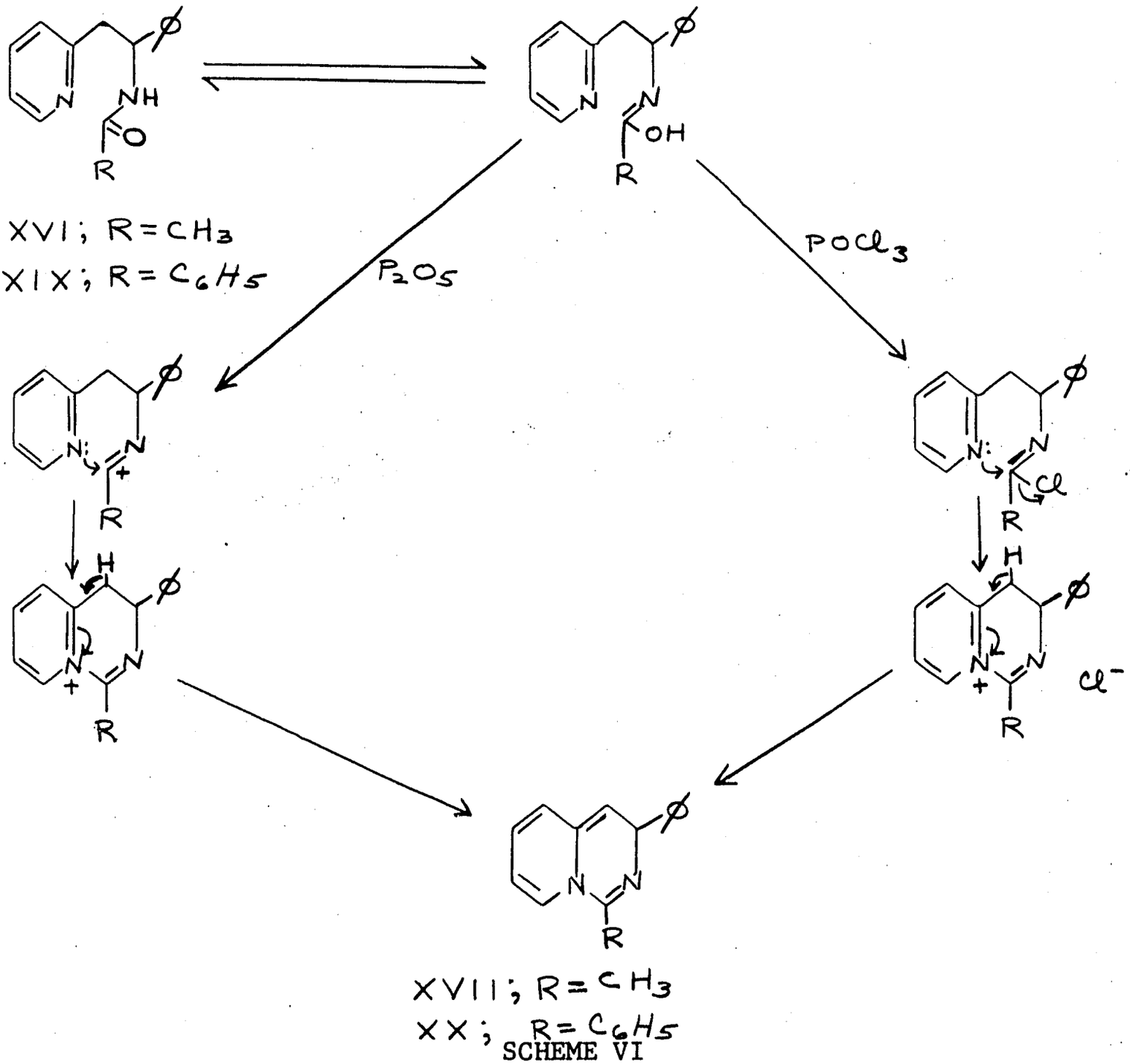


A recently published synthesis of 1-substitutedimidazo [1,5-a] - pyridines (9) involves the cyclodehydration of 2-amidomethylpyridines using $POCl_3$. An example of this reaction is as follows:



R = H, CH_3, C_6H_5

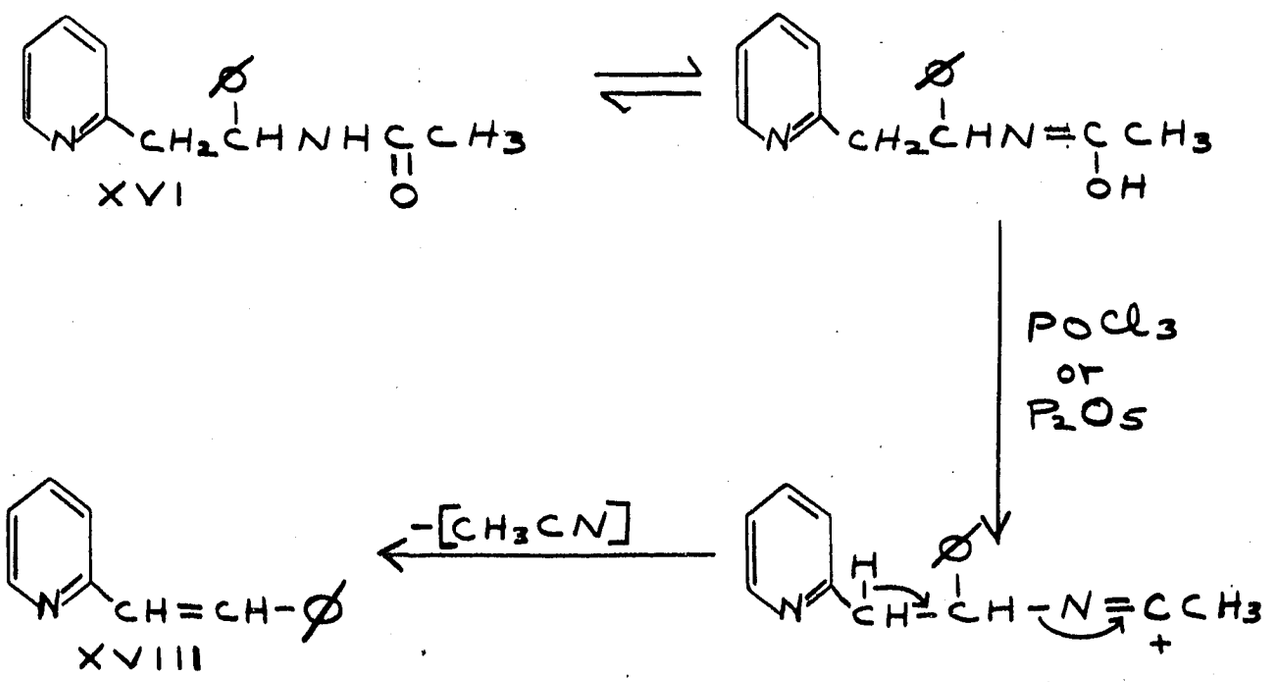
It was hoped that the 2-(2-amido-2-phenylethyl)pyridines (XVI and XIX) would similarly cyclize (steps 3a and 5) in the presence of $POCl_3$ or P_2O_5 to give 3H-1-substituted-3-phenylpyrido [1,2-c] - pyrimidines (XVII and XX). On the basis of previous publications (7,8) the course of the reaction would be expected to proceed as follows:



SCHEME VI

Amides are believed to react with $POCl_3$ via the imidol tautomer to give an imino chloride. Imino chlorides derived from amides XVI and XIX should then form intermediate iminopyridinium chlorides which, with the loss of a proton, would produce the desired pyrido-[1,2-c] pyrimidines (XVII and XX). Using P_2O_5 the imidol tautomer was expected to first lose hydroxide ion followed by neutralization of the resulting iminonium ion by the pyridine's free pair of electrons and then loss of a proton.

The products obtained however were not those predicted. Reaction of the acetamide XVI with $POCl_3$ or P_2O_5 gave 2-stilbazole (XVIII) (73%, 21%) while the benzamide XIX did not react with either reagent in refluxing benzene. The formation of 2-stilbazole is not too surprising when the following mechanistic explanation is considered:



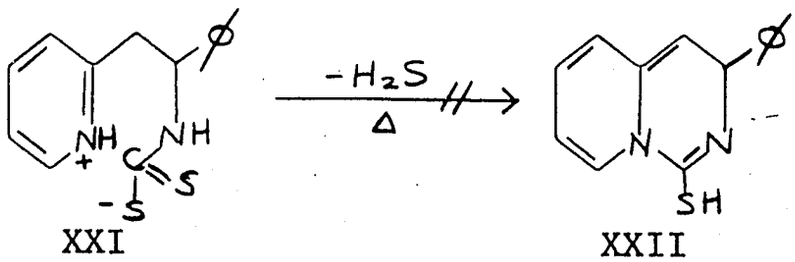
SCHEME VII

The essential difference between Scheme VI and Scheme VII is the fate of the pair of electrons released by the departure of a proton. The deciding factor seems to be the formation of the very stable 2-stilbazole. It has been observed that, unlike 2-vinylpyridine, 2-stilbazole does not undergo a Michael-type addition with aniline and acetic acid; neither does lithium anilide nor sodium anilide add to 2-stilbazole (Part II, this thesis). These and other reactions discussed in Part II of this thesis attest to the ease of formation and stability of 2-stilbazole.

No attempt was made to isolate acetonitrile from the reactions between the acetamide XVI and $POCl_3$ or P_2O_5. The 2-stilbazole was identified by elemental analysis, its mixed melting point, and the melting point of its picrate. An authentic sample of 2-stilbazole (XVIII) was prepared by the method of Shaw and Wagstaff (10).

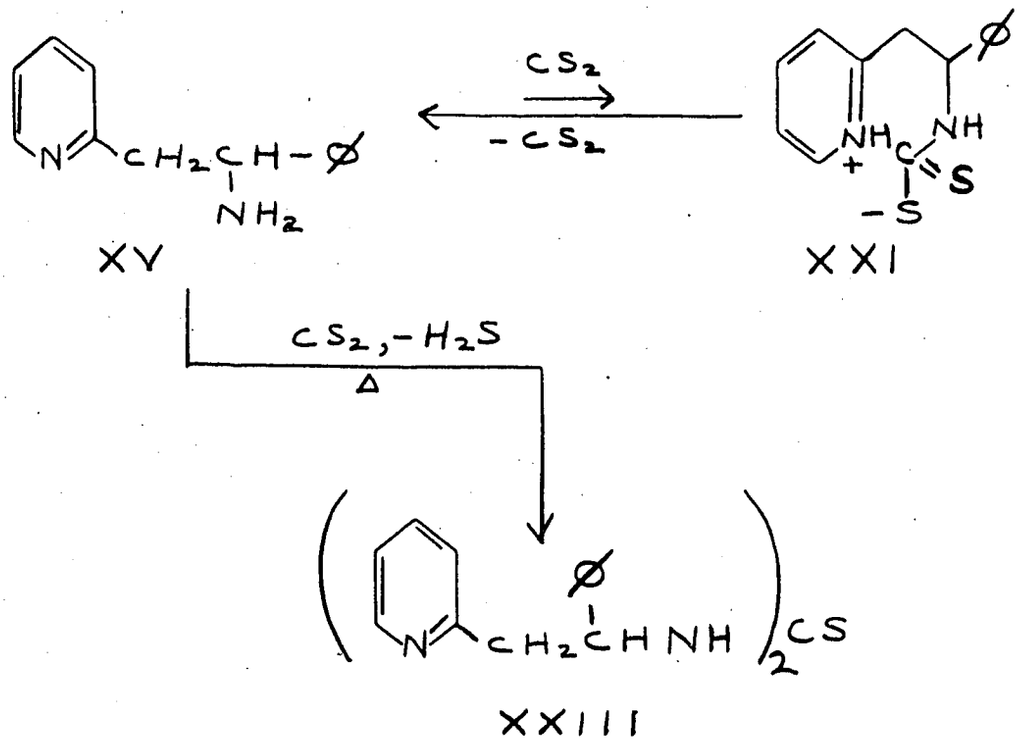
There seems to be no apparent reason for the inertness of 2-(2-benzamido-2-phenylethyl)pyridine (XIX) toward $POCl_3$ or P_2O_5 in refluxing benzene. The benzamide was recovered in yields of 75% and 100% respectively.

2-(2-Amino-2-phenylethyl)pyridine (XV) was heated in a large excess of CS_2 in an attempt to prepare 3H-1-mercapto-3-phenylpyrido-[1,2-c] pyrimidine (Scheme V, compound XXII). It was hoped that an intermediate pyridinium dithiocarbamate (XXI) would form to give, upon heating, compound XXII.



XXI XXII

The product obtained (Scheme V, step 6 b), however, was 1,3-bis-[1-phenyl-2-(2-pyridyl)ethyl] -2-thiourea (XXIII). Apparently the pyridine nitrogen is not basic enough to prevent the internal salt (XXI) from reverting to the parent amine (XV) and CS_2. This may be shown as follows:



XV XXI

XXIII

EXPERIMENTAL DETAILS

All melting points and boiling points are uncorrected. The elemental analyses were performed by Dr. V. B. Fish, Department of Chemistry, Lehigh University and by Schwarzkopf Microanalytical Laboratories unless otherwise stated.

2-Phenacylpyridine (VIII). The method of Goldberg and Levine (4,5) was used to prepare 2-phenacylpyridine. 2-Picolyllithium was prepared from 6.60 g. (0.952 mole) of lithium wire, 75 g. (0.476 mole) of bromobenzene, and 44.4 g. (0.476 mole) of 2-picoline (dried over KOH) in 475 ml. of dry ether. The reaction was carried out in a one liter, three-necked flask equipped with a dropping funnel, nitrogen inlet, stirrer, and condenser. To the picolyllithium was added 32.4 g. (0.238 mole) of methyl benzoate during 20 min. The color of the reaction mixture became a brownish-red. After stirring and refluxing the resulting mixture for 1 hr., it was cooled and poured into 200 ml. of ice water. After separation, the aqueous layer was extracted with three 50 ml. portions of ether. The combined ethereal solutions were dried over Na_2SO_4 and the ether removed in vacuo. The dark red residue was fractionated to give 36.35 g. (72%) of 2-phenacylpyridine contaminated with a small amount of 2-picoline detected by its odor. The boiling point of 2-phenacylpyridine, 148-158°/0.6mm., requires a bath temperature of 210°.

The distillate could be converted directly to the oxime (IX) in good yield. Recrystallization from 30-60° pet. ether furnished pure VIII, m.p. 56-57.5°, in 92-96% recovery. Pure 2-phenacylpyridine can be stored at 5° under nitrogen for periods exceeding one month without noticeable decomposition.

2-Phenacylpyridine oxime (IX). In a 100 ml. flask was placed 5.94 g. (0.03 mole) of crude 2-phenacylpyridine (VIII), b.p. 148-158°/0.6 mm. After dissolving VIII in 30 ml. of warm 95% ethanol a solution of 2.30 g. (0.033 mole) of hydroxylamine hydrochloride in 8 ml. of water was added followed by 1.6 g. (0.04 mole) of NaOH in 10 ml. of water. The resulting solution was refluxed for 1 hr. and then poured into 150 ml. of an ice water mixture containing 0.6 ml. of acetic acid. The resulting crude, oily oxime solidified on scratching to give 6.24 g. (98%) of off-white crystals, m.p. 113-116°. Recrystallization from 95% ethanol furnished 5.75 g. (90%) of slightly pink oxime, m.p. 116.5-118°. It was also possible to precipitate pure oxime directly from the reaction mixture by allowing the flask to stand at room temperature overnight.

2-(2-Amino-2-phenylethyl)piperidine (X). A solution of 8 g. (0.0377 mole) of 2-phenacylpyridine oxime (IX) in 100 ml. of glacial acetic acid and containing 0.50 g. of platinum dioxide was hydrogenated at 23° and an initial pressure of 55.5 p.s.i. A final pressure of 41.7 p.s.i. of hydrogen was calculated as the end point in the 5 liter system.

The hydrogenation was stopped at 41.6 p.s.i. After filtration to remove the catalyst, the acetic acid was evaporated in vacuo and the greenish, very viscous residue treated with 25 ml. of 25% NaOH solution. The alkaline mixture was extracted three times with a total of 75 ml. of ether and the combined extracts dried over Na_2SO_4. The ether was evaporated leaving a pale yellow oil which gave, on distillation, 5.77 g. (75%) of a colorless oil, b.p. 125-135°/0.3 mm. The product forms a monopicrate, m.p. 166-167°, which was used for analysis. A second unidentified, very yellow fraction was obtained at 155-163°/0.3 mm.

Anal. Calcd. for $C_{19}H_{23}N_5O_7$: C, 52.65; H, 5.35; N, 16.16.

Found: C, 52.75; H, 5.48; N, 15.90.

3-Phenyloctahydropyrido [1,2-c] -1-thiopyrimidone (XI).

In a six-inch test tube was placed 0.70 g. (0.0034 mole) of 2-(2-amino-2-phenylethyl)piperidine (X) and 6 ml. of 95% ethanol. Carbon disulfide was added until the solution was no longer basic. A white solid precipitated with the evolution of heat. This precipitate was collected and refluxed overnight in 6 ml. of fresh 95% ethanol with the evolution of H_2S. On cooling the resulting clear solution, white crystals separated. Filtration gave 0.65 g. (77%) of white crystals, m.p. 148.5-149.5°.

Anal. Calcd. for $C_{14}H_{18}N_2S$: C, 68.25; H, 7.36; N, 11.37.

Found: C, 68.15; H, 7.52; N, 11.23.

1-Thiomethoxy-3-phenyl- Δ^1hexahydropyrido [1,2-c] pyrimidine hydroiodide (XII). Eleven hundreths of a gram (0.00044 mole) of 3-phenyloctahydropyrido [1,2-c] -1-thiopyrimidone (IV) was warmed with enough excess methyl iodide to effect solution. The resulting solution was evaporated to dryness by gentle warming giving a yellowish solid which yielded a white powder, 0.15 g. (85%), m.p. 167-168°, upon recrystallization from absolute ethanol.

Anal. Calcd. for $C_{15}H_{22}N_2SI$: I, 32.60.

Found: I, 32.50.

3-Phenyloctahydropyrido [1,2-c] -1-pyrimidone (XIII). One gram (0.005 mole) of 2-(2-amino-2-phenylethyl)piperidine (X) and 0.58 g. (0.010 mole) of diethyl carbonate were sealed in a dry, thick-walled glass tube, volume approx. 13 cc., and the lower half of the tube heated in an oil bath at 200° for 50 hours. On cooling overnight at -20° a light brown solid precipitated. The tube was opened and found to contain some pressure, possibly due to the formation of some CO_2. The solid product was washed with a minimum of ether to give 0.75 g. (66%) of white solid, m.p. 152-155°. Recrystallization from a minimum of benzene gave 0.45 g. (39%) of white powder, m.p. 157-158°.

Anal. Calcd. for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.87; N, 12.17.
Found: C, 73.27; H, 8.00; N, 11.86.

1,3-Diphenyloctahydropyrido [1,2-c] pyrimidine (XIV). One gram (0.0049 mole) of 2-(2-amino-2-phenylethyl)piperidine (X) and 0.55 g. (0.0052 mole) of benzaldehyde in 75 ml. of benzene were placed in a 200 ml. flask fitted with a water trap. The solution was refluxed for 1/2 hr. and then the benzene evaporated in vacuo. Upon vacuum distillation a light yellow, extremely viscous oil, b.p. 186°/1.5 mm., was obtained. The yield was 0.95 g. (65%). This oil was triturated with a small amount of 60-70° pet. ether and the resulting sticky, white solid filtered.

The crude solid was dissolved in hot 60-70° pet. ether, the solution decanted from an insoluble oil, and the solution cooled to yield 0.40 g. (27%) of pure product, m.p. 116-117°.

Anal. Calcd. for $C_{20}H_{24}N_2$: C, 82.14; H, 8.27.

Found: C, 82.14; H, 8.60.

The elemental analysis on this compound was performed by R. Miron and W. E. Tyler.

2-(2-Amino-2-phenylethyl)pyridine (XV). The method of Graig and Hixon (6) for reducing the oxime of pyridine-2-aldehyde to the corresponding amine was used. Three grams (0.014 mole) of phenacylpyridine oxime (IX) were dissolved in 45 ml. of 95% ethanol and treated with small portions of zinc dust and glacial acetic acid over a period of several hours until 24 g. (0.367 mole) of zinc and 24 g. (22.8 ml., 0.40 mole) of acetic acid had been added. The reaction mixture was filtered and the residue of zinc and zinc acetate washed with a small portion of acetic acid. The combined filtrates were evaporated in vacuo on a hot water bath. The greenish residue (the reaction mixture itself exhibited a green fluorescence) was made alkaline with a 20% NaOH solution followed by ether extraction. After drying over Na_2SO_4 the ether was evaporated, and the greenish oil was distilled to give 1.78 g. (64%) of colorless product, b.p. 131-132°/0.4 mm.

The product forms a dipicrate, m.p. 210-211°, which was used for analysis.

Anal. Calcd. for $C_{25}H_{20}N_8O_{14}$: C, 45.74; H, 3.07; N, 17.07.
Found: C, 45.95; H, 3.06; N, 16.42.

2-(2-Acetamido-2-phenylethyl)pyridine (XVI). Three and one-half ml. (0.0374 mole) of acetic anhydride, 7.5 ml. of glacial acetic acid, and 1.78 g. (0.009 mole) of 2-(2-amino-2-phenylethyl)-pyridine (XV) were heated on a steam bath for 30 minutes. The acetic acid and the acetic anhydride were removed by evaporation in vacuo. Upon cooling, a yellow solid formed, m.p. 85-88°. Recrystallization from 1:1 benzene-pet. ether gave 1.41 g. (65%) of a white solid, m.p. 114-117°. Two more recrystallizations raised the m.p. to 123.5-124.5°.

Anal. Calcd. for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66.
Found: C, 75.02; H, 6.77; N, 11.42.

Attempted Syntheses of 1-Methyl-3-phenylpyrido [1,2-c] -pyrimidine (XVII). Method A. One gram (0.004 mole) of 2-(2-acetamido-2-phenylethyl)pyridine (XVI), 2 ml. (3.35 g., 0.02 mole) of $POCl_3$, and 6 ml. of anhydrous benzene were refluxed for 4 hr.

The reaction mixture was extracted with chloroform, the extract dried over Na_2SO_4, and then the chloroform was evaporated on the steam bath to give a sticky, yellow solid. This solid was chromatographed on alumina with benzene to give a white product contaminated with a yellow oil. This oil was removed by filtration at the water pump giving 0.67 gm. (73%) of a white solid, m.p. 74-84°C. Recrystallization of this solid from dioxane gave an amount of white material, m.p. 140-143°, too small for analysis. The dioxane filtrate was evaporated to dryness and the residue (0.63 g.) recrystallized from a minimum of 1:1 benzene-pet. ether to give a good recovery of white solid, m.p. 91-92°, which did not analyze correctly for the desired pyridopyrimidine.

Anal. Calcd. for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.51.
Found: C, 86.29; H, 6.37; N, 7.53.

This material, however, does not show a mixed m.p. depression with an authentic sample of 2-stilbazole (XVIII), m.p. 91-92°C. The elemental analysis is in good agreement with that expected for 2-stilbazole.

Anal. Calcd. for $C_{13}H_{11}N$: C, 86.14; H, 6.12; N, 7.73.
Found: C, 86.29; H, 6.37; N, 7.53.

Method B. One gram (0.004 mole) of 2-(2-acetamido-2-phenylethyl)pyridine (XVI) and 5.7 g. (0.04 mole) of P_2O_5 were heated overnight in 10 ml. of refluxing benzene, the benzene evaporated off at reduced pressure and the residue poured over ice.

The resulting aqueous mixture was basicified with 15% NH_4OH and the light tan product dried in a vacuum desiccator over P_2O_5. The yield was 0.15 g. (21%) of impure 2-stilbazole, m.p.85-90°, determined by its mixed m.p. 89-91°, with an authentic sample, m.p. 91-92°.

2-Stilbazole (XVIII). This compound was prepared by the method of Shaw and Wagstaff (10). In a 500 ml. three-necked flask, equipped with a nitrogen inlet and a reflux condenser were placed 69.8 g. (0.75 mole) of 2-picoline, 91.5 g. (0.863 mole) of benzaldehyde, and 44.0 g. (0.431 mole) of acetic anhydride. The solution was refluxed for 30 hr., steam distilled to remove unreacted benzaldehyde, and then poured over 300 g. of ice. The dark brown solid which separated was treated with 200 ml. of ether and 200 ml. of 2N HCl. The ether layer was extracted twice more with HCl, the combined acidic layers depositing 2-stilbazole hydrochloride on standing. This material was filtered and neutralized with 20% NaOH. Filtration of the basic solution gave 55.0 g. of crude product. An additional 17.2 g. of crude product was obtained by reworking the filtrate from the hydrochloride. Recrystallization of both crops of crude material from 95% ethanol gave 61.8 g. (45.5%) of 2-stilbazole, m.p. 89.5-91°. Recrystallization from a minimum of 1:1 benzene-pet. ether raises the m.p. to 91-92°.

2-(2-Benzamido-2-phenylethyl) pyridine (XIX). Two grams (0.01 mole) of 2-(2-amino-2-phenylethyl)pyridine (XV) were placed in 25 ml. of benzene with 1.41 g. (1.16 ml., 0.01 mole) of benzoyl chloride and 1.5 ml. of pyridine. This solution was refluxed overnight and the precipitate filtered and stirred with an excess of 25% NaOH. The crude, light brown product was filtered and dried to give 2.05 g. (67%), m.p. 147-148°. After one recrystallization from 80% methanol the white product melted at 148-149°.

Anal. Calcd. for $C_{20}H_{18}N_2O$: C, 79.44; H, 6.00; N, 9.27.

Found: C, 79.39; H, 6.01; N, 9.55.

Attempted Syntheses of 1,3-Diphenyl [1,2-c] pyrimidine (XX).

Method A. Eight tenths of a gram (0.00265 mole) of 2-(2-benzamido-2-phenylethyl)pyridine (XIX) and 3.76 g. (0.0265 mole) of P_2O_5 were heated in 7 ml. of refluxing benzene for 2 hr. The benzene was removed and the residue decomposed in ice water. The resulting aqueous mixture was basicified with 20% NaOH and the white precipitate filtered and dried. The m.p. and mixed m.p. were the same as for the starting benzamide. The recovery of starting material was quantitative.

Method B. Eight tenths of a gram (0.00265 mole) of 2-(2-benzamido-2-phenylethyl)pyridine (XIX) was heated in 6 ml. of refluxing benzene with 2 ml. (3.35 g., 0.0219 mole) of $POCl_3$ for 4 hr.

The benzene and $POCl_3$ were removed at reduced pressure and the residue basicified with an excess of 20% NaOH. The reddish-brown precipitate was filtered, washed with water, and dried over P_2O_5 in a vacuum desiccator. The m.p. was 110-112°C. and the yield 0.60 g. After recrystallization from benzene-pet. ether the m.p. rose to 145-149°. One recrystallization from 80% methanol raised the m.p. and mixed m.p. to 148-149°, that of the starting benzamide.

1,3-Bis-[1-phenyl-2-(2-pyridyl)ethyl] -2-thiourea (XXIII).

Ten grams (0.05 mole) of 2-(2-amino-2-phenylethyl)pyridine (XV) and 36.1 g. (30.2 ml.,0.5 mole) of CS_2 was added to 150 ml. of benzene. After refluxing for 5 min. the excess CS_2 and benzene were removed at reduced pressure and 150 ml. of 95% ethanol added to the residue. The ethanolic solution was refluxed until evolution of H_2S had ceased (6-7 hours). Twentyfive ml. of water were very slowly added through the top of the condenser to the refluxing solution. Upon cooling overnight pure product, m.p. 194-195°, crystallized out. After filtering, the filtrate was evaporated to dryness and the residue recrystallized twice from 80% ethanol. The yield of pure product was 55% .

Anal. Calcd. for $C_{27}H_{26}N_4$: C, 73.94; H, 5.98; N, 12.78.

Found: C, 73.90; H, 6.12; N, 12.52.

APPENDIX

Tabulation of Infrared Spectra*

The infrared spectra were run on a Perkin-Elmer Model 21 infrared spectrophotometer at Lehigh University or kindly supplied by the Wm. S. Merrell Company, Cincinnati, Ohio. In each case, the source of the spectrum is noted following the name of the compound.

*Note: vs - very strong; s - strong; m - medium; w - weak.

3-Phenyloctahydropyrido [1,2-c]-1-thiopyrimidone (XI); Merrell (KBr plate).

Wavelength (microns)	Wavelength (microns)	Wavelength (microns)
3.18 (vs)	7.82 (vs)	10.55 (m)
3.46 (s)	8.10 (vs)	10.95 (w)
3.53 (s)	8.40 (vs)	11.27 (w)
6.25 (w)	8.63 (vs)	11.51 (w)
6.31 (w)	9.04 (s)	11.67 (w)
6.71 (vs)	9.19 (s)	11.82 (w)
6.97 (vs)	9.38 (s)	12.08 (m)
7.39 (s)	9.59 (m)	13.25 (s)
7.62 (vs)	9.75 (m)	14.36 (s)
7.72 (vs)	10.10 (m)	

1-Thiomethoxy-3-phenyl- Δ^1-hexahydropyrido [1,2-c] pyrimidine Hydroiodide (XII); Merrell (KBr plate).

Wavelength (microns)	Wavelength (microns)	Wavelength (microns)
3.22 (vs)	7.80 (s)	9.93 (w)
3.45 (vs)	7.92 (m)	10.10 (m)
6.25 (vs)	8.02 (s)	10.48 (m)
6.31 (vs)	8.27 (s)	10.65 (w)
6.62 (vs)	8.60 (s)	11.00 (w)
6.71 (s)	8.75 (m)	11.38 (w)
6.97 (s)	9.02 (m)	11.77 (w)
7.33 (m)	9.38 (w)	12.07 (w)
7.52 (s)	9.55 (m)	13.12 (s)
7.70 (s)	9.73 (m)	14.23 (s)

3-Phenyloctahydropyrido [1,2-c] -1-pyrimidone (XIII); Lehigh (KBr plate).

Wavelength (microns)	Wavelength (microns)	Wavelength (microns)
3.12 (s)	7.36 (vs)	9.73 (m)
3.27 (s)	7.50 (vs)	10.00 (m)
3.43 (s)	7.69 (vs)	10.24 (m)
3.50 (s)	7.78 (vs)	10.42 (m)
5.10 (w)	7.93 (vs)	10.56 (w)
5.28 (w)	8.02 (m)	10.77 (m)
5.48 (w)	8.12 (m)	11.32 (m)
6.01 (vs)	8.22 (s)	11.57 (m)
6.07 (vs)	8.38 (m)	11.92 (m)
6.12 (vs)	8.70 (s)	12.60 (s)
6.28 (s)	8.87 (s)	13.22 (vs)
6.45 (m)	9.07 (s)	13.85 (m)
6.75 (vs)	9.22 (m)	14.27 (vs)
6.93 (vs)	9.32 (m)	
7.25 (s)	9.49 (m)	

1,3-Diphenyloctahydropyrido [1,2-c] pyrimidine (XIV); Merrell (KBr plate).

Wavelength (microns)	Wavelength (microns)	Wavelength (microns)
2.93 (m)	7.50 (m)	10.17 (m)
3.02 (m)	7.59 (m)	10.38 (m)
3.32 (m)	7.65 (m)	10.79 (m)
3.44 (s)	7.77 (m)	11.24 (w)
3.60 (s)	7.87 (m)	11.55 (w)
6.23 (m)	7.94 (m)	11.75 (w)
6.46 (w)	8.16 (s)	12.08 (w)
6.70 (m)	8.36 (w)	12.44 (w)
6.83 (s)	8.52 (w)	12.60 (m)
6.91 (s)	8.91 (vs)	13.00 (s)
6.96 (s)	9.13 (s)	13.47 (vs)
7.24 (m)	9.24 (s)	14.03 (vs)
7.35 (m)	9.34 (s)	14.45 (s)
7.44 (m)	9.78 (s)	14.90 (w)

1,3-Bis-[1-phenyl-2-(2-pyridyl)ethyl]-2-thiourea (XXIII); Merrell (KBr plate).

Wavelength (microns)	Wavelength (microns)	Wavelength (microns)
3.13 (vs)	7.92 (vs)	10.35 (w)
3.34 (s)	8.08 (vs)	10.59 (m)
5.12 (w)	8.25 (s)	11.00 (w)
5.32 (w)	8.39 (s)	11.17 (w)
6.28 (vs)	8.53 (m)	11.30 (w)
6.39 (s)	8.73 (s)	11.70 (m)
6.57 (vs)	8.92 (m)	12.72 (w)
6.81 (vs)	9.23 (m)	12.82 (s)
6.91 (s)	9.38 (m)	13.00 (vs)
7.00 (vs)	9.54 (m)	13.12 (vs)
7.18 (s)	9.76 (m)	13.43 (s)
7.40 (m)	9.98 (m)	14.30 (vs)
7.68 (s)	10.08 (s)	15.20 (m)

BIBLIOGRAPHY

1. K. Winterfeld and W. Göbel, Ber., 92, 637 (1959).

2. A. Hunger and K. Hoffmann, Helv. Chim. Acta, 40, 1319 (1957).

3. K. Winterfeld and W. Göbel, Ber., 89, 1642 (1956).

4. N. Goldberg and R. Levine, J. Am. Chem. Soc., 74, 5217 (1952).

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

6. L. C. Craig and R. M. Hixon, J. Am. Chem. Soc., 53, 4367 (1931).

7. R. L. Shriner and F. W. Neumann, Chem. Revs., 35, 351 (1944).

8. A. Richardson, Jr. and E. D. Amstutz, J. Org. Chem., 25, 1138 (1960).

9. J. Bower and G. Ramage, J. Chem. Soc., 2834-7 (1955).

10. B. D. Shaw and E. A. Wagstaff, J. Chem. Soc., 77 (1933).

PART II

N,1,2-Trisubstitutedethylamines

ABSTRACT

Several N,1,2-trisubstitutedethylamines were synthesized by the addition of picolyllithium or benzylmagnesium chloride to Schiff bases.

Used in preparing the Schiff bases were p-substituted-benzaldehydes, furfural, N-methylpyrrole-2-carboxaldehyde, acetophenone, benzophenone, fluorenone and xanthone. The amines used were p-substitutedanilines, 2-aminopyridine and N,N-diethylethylenediamine. Reaction conditions for the condensations ranged from mixing the reactants at room temperature to heating them in refluxing benzene or xylene to heating them without solvent at 170-180°. p-(2-Diethylaminoethoxy)benzaldehyde was converted to its hydrochloride before condensation. This eliminated tertiary amine-carbonyl interaction and thereby facilitated condensation with the less basic aromatic amines. The inertness of the xanthone carbonyl made it necessary to convert it to 9,9-dichloroxanthene which was then reacted with aniline.

Reaction of the Schiff bases with quinaldyllithium, 2-picolyllithium or benzylmagnesium chloride produced N,1,2-trisubstituted-ethylamines in fair to good yields with a few exceptions.

2-Picolyllithium and N-p-(2-diethylaminoethoxy)benzylidene-p-trifluoromethylaniline gave tars. It seems likely that, after the addition step, the negative charge on the anilino nitrogen effects an internal displacement of fluoride ion to give an intermediate N-substituted α,α -- difluoroquinone imine which is subject to furthur attack and to polymerization. The Schiff bases derived from N-methylpyrrole-2-carboxaldehyde produced, after reaction with 2-picolyllithium, 2-{2-[2-(N-methylpyrryl)] vinyl} pyridine by elimination of the aniline. A similar deamination was observed to produce 2-[p-(2-diethylaminoethoxy) styryl] quinaldine and p-chloroaniline. The driving force for such reactions seems to be the stability of the resulting conjugated systems.

N-p-Anisyl-1,2-diphenylethylamine was prepared by separate methods to ascertain whether benzylmagnesium chloride reacts with Schiff bases as a benzyl anion or as an o-tolyl anion. Thus, deoxybenzoin p-methoxyanil was reduced with lithium aluminum hydride and the product was found to be identical with that from the reaction of benzylmagnesium chloride with N-benzylidene-p-anisidine.

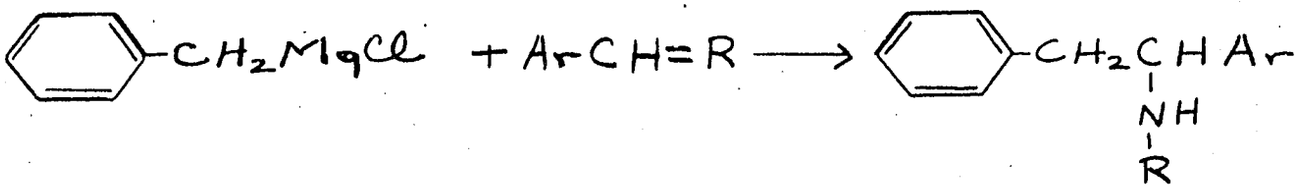
INTRODUCTION

The possibility of synthesizing 1,2,3-triaryloctahydropyrido-[1,2-c] pyrimidines (see part I of this thesis for a discussion of pyrido [1,2-c] pyrimidines) led to consideration of N,1-diaryl-2-(2-pyridyl)ethylamines as possible intermediates. Ethylamines of this type were recognized as an extensive series of compounds of possible therapeutic value. For these reasons their synthesis was undertaken.

The most general and satisfactory method known for the preparation of N,1,2-trisubstitutedethylamines is the addition of Grignard reagents and organolithiums to the imine linkage of Schiff bases. 2-Picolyllithium has not been reported to react with Schiff bases, although there are several examples of this type of addition reaction in the literature.

These examples are:

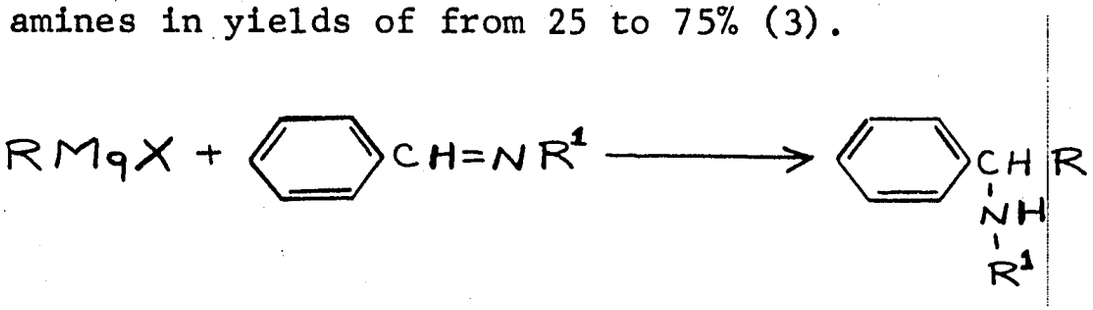
1. Addition of benzylmagnesium chloride to N-benzylidenealkylamines has been effected in yields of from 30 to 95% (1,2).



Ar = phenyl substituted with HO, CH_3O, Me_2N.

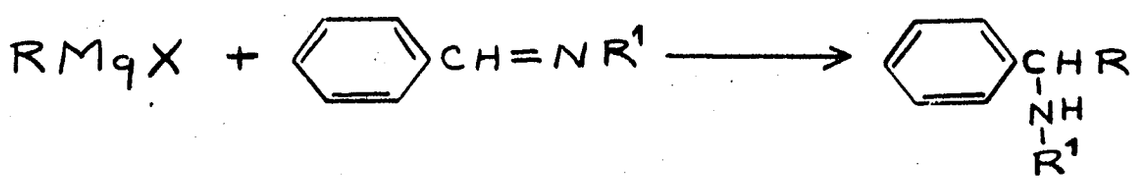
R = CH_3, C_2H_5, $CH_2=CHCH_2$, $HOCH_2CH_2$, ϕCH_2, C_6H_{11}.

2. Alkylmagnesium bromides and phenylmagnesium bromide, as well as benzylmagnesium chloride, have been shown to add to the imine linkage of N-benzylidenealkylamines in yields of from 25 to 75% (3).



R = Et	R^1 = Me
R = n-Pr	R^1 = Et
R = i-Pr	R^1 = n-Pr
R = n-Bu	R^1 = n-Bu
R = Benzyl	R^1 = Benzyl
R = Phenyl	

3. Schiff bases derived from 2-aminopyridine have been utilized in this type of reaction with phenylmagnesium bromide or methylmagnesium iodide in yields of from 70-75% (4).

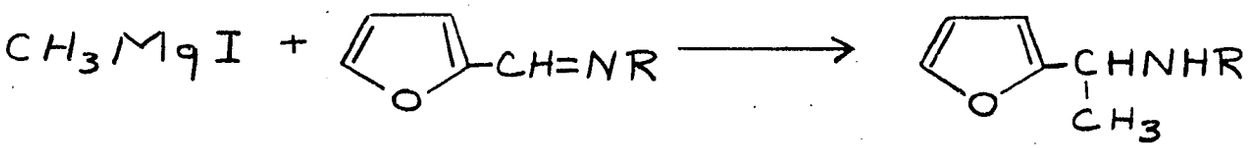


R = Phenyl, methyl.

R^1= 2-Pyridyl, phenyl.

4. N-(2-Pyridyl and 2-Thiazolyl)-1,2-diphenylethylamine have been prepared by reaction of the appropriate N-benzylideneaminoheterocycle with benzylmagnesium chloride (5).

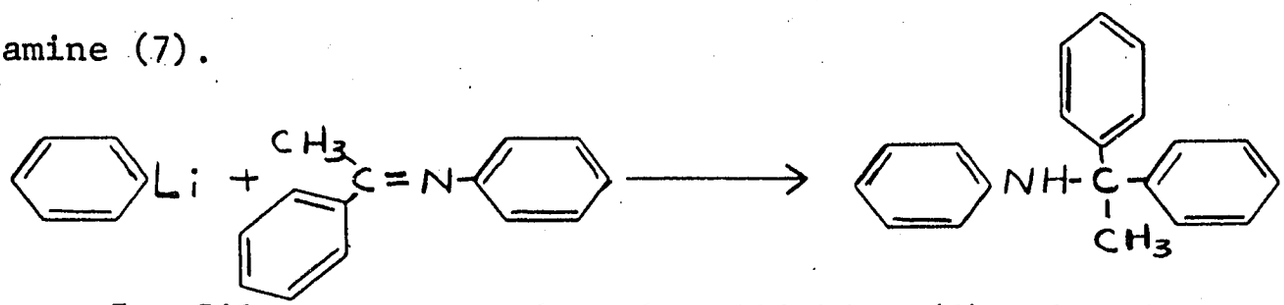
5. N-Furfurylidene-2-aminopyridine and N-Furfurylidene-2-aminothiazole have been prepared and reacted with methylmagnesium iodide (6).



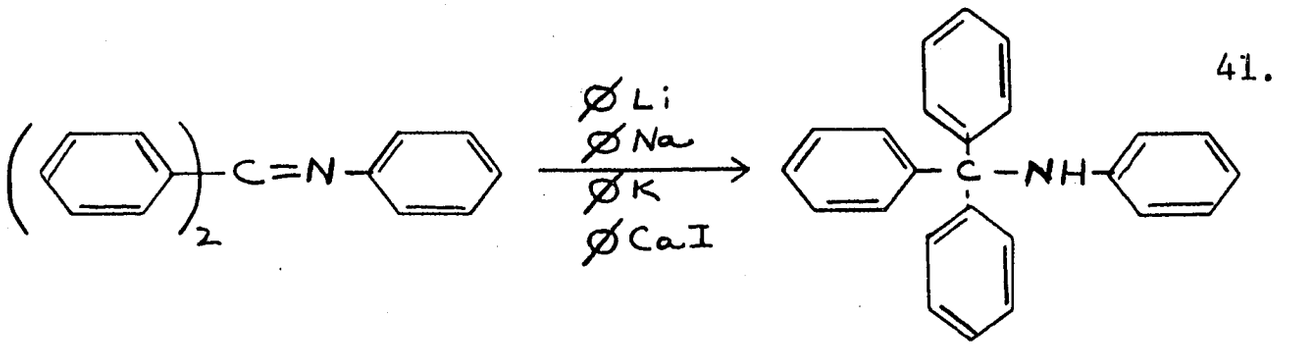
R = 2-Pyridyl

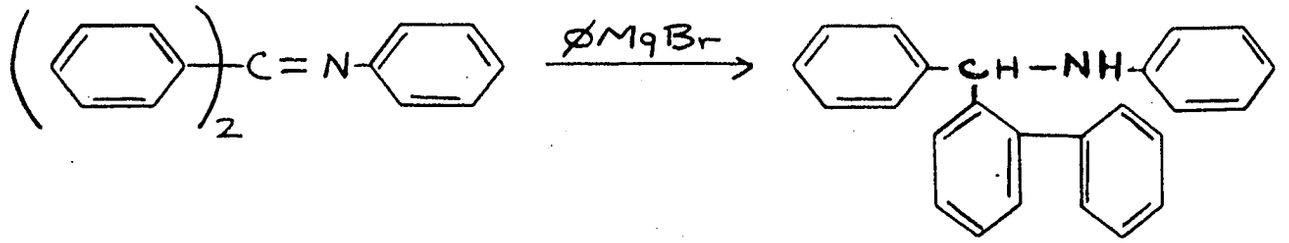
R = 2-Thiazolyl

6. Phenyllithium has been found to react with acetophenone anil to give a 55% yield of N,1,1-triphenylethylamine (7).

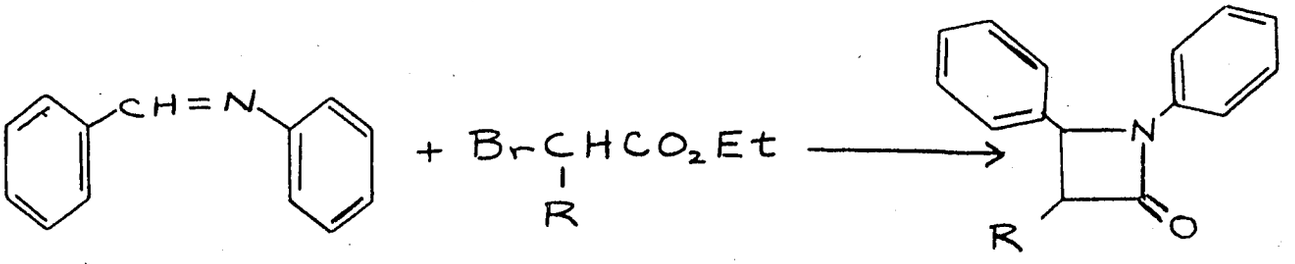


7. Gilman reports that phenyllithium (8), phenylcalcium iodide (9), phenylsodium (10), and phenylpotassium (10) all add to benzophenone anil to give triphenylmethylaniline, whereas the less reactive phenylmagnesium bromide (11) adds 1,4 to give o-phenylbenzohydrylamine.





8. Gilman has also successfully used N-benzylidene-aniline in the Reformatsky reaction with α-bromoesters to provide an interesting method for obtaining β-lactams (12).



R = H, CH_3.

DISCUSSION

Synthesis of Schiff Bases

Several methods were employed to prepare the desired Schiff bases from equimolar amounts of amine and carbonyl compound. These were as follows:

A. The reactants were heated in refluxing 95% ethanol.

B. The same as method A except that methanol was used.

C. The reactants were heated together at 170-180°.

D. The reactants were heated together in refluxing benzene and the water evolved collected in a water trap.

E. The same as method D except that m-xylene was used.

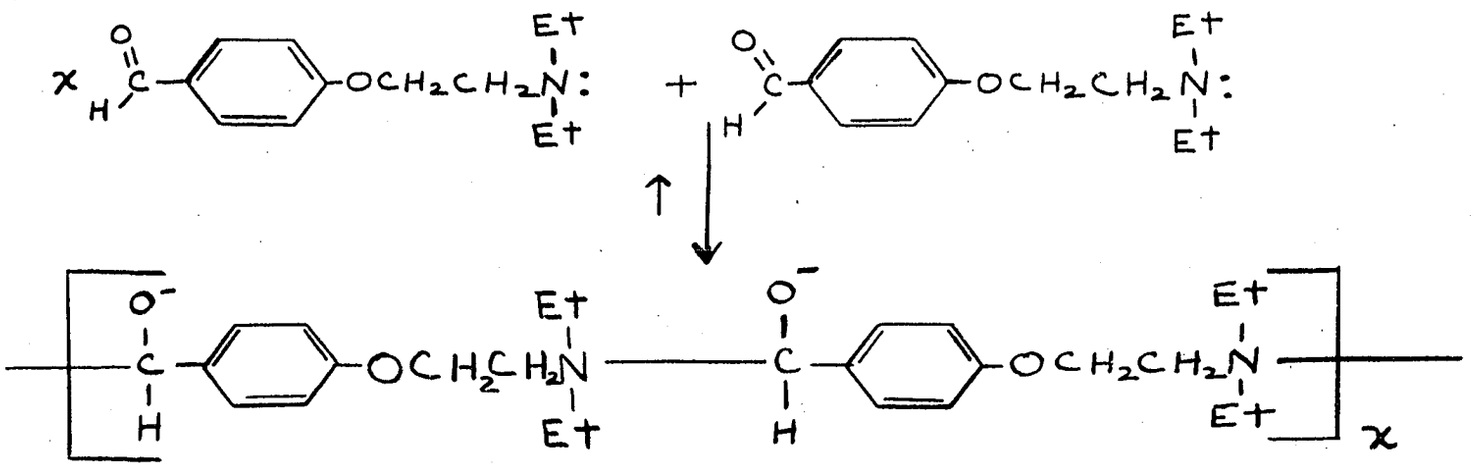
F. p-(2-Diethylaminoethoxy)benzyaldehyde hydrochloride and the appropriate amine were heated in refluxing absolute ethanol. After removal of the ethanol, the hydrochloride was stirred into aqueous base and the free Schiff base collected.

G. The amine and aldehyde were stirred together at room temperature without solvent.

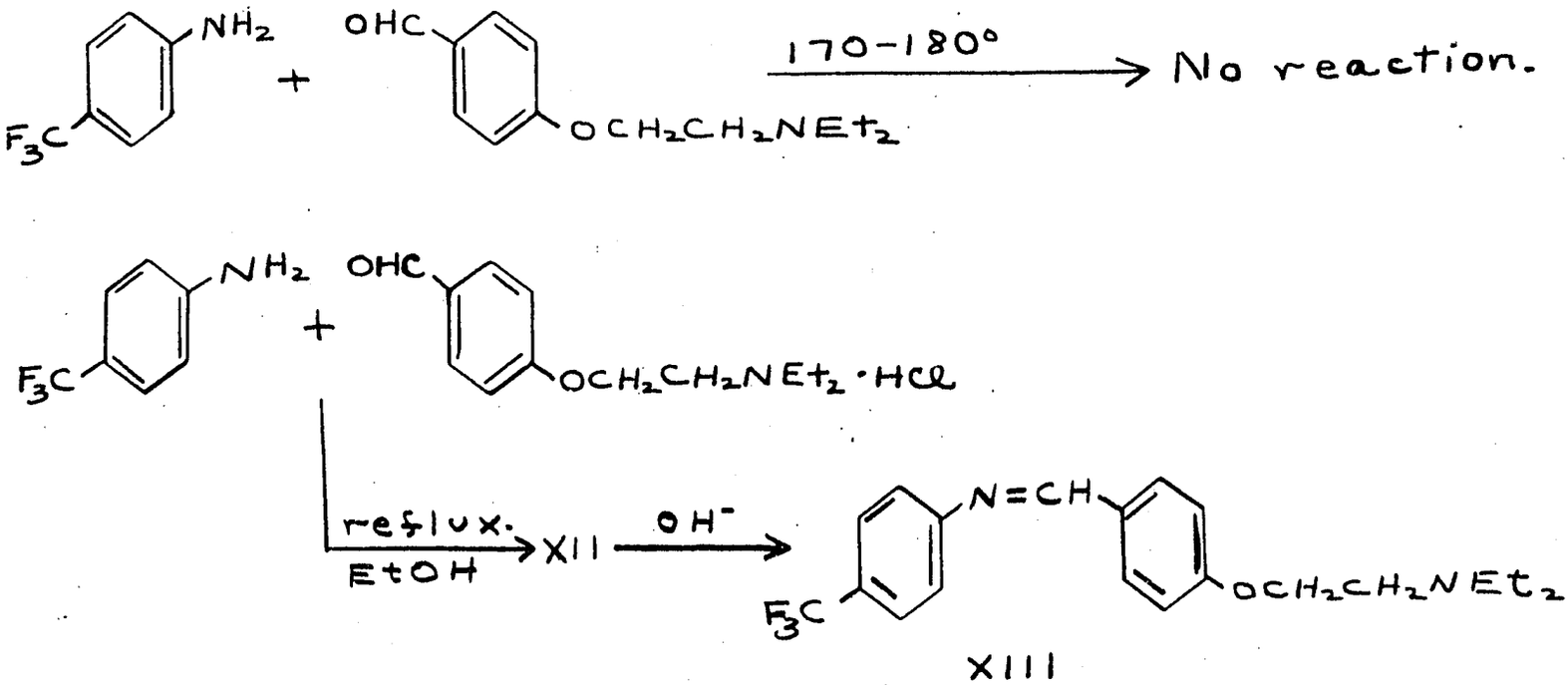
H. A catalytic amount of zinc chloride was heated with the reactants at 170-180° (12,13).

I. Xanthone was converted to 9,9-dichloroxanthene (13) with thionyl chloride and then reacted with aniline in the presence of pyridine.

The N-benzylideneanilines formed very easily in good yields from substituted anilines and benzaldehydes and were usually easily purified by recrystallization from methanol or aqueous ethanol. One exception to the ease of condensation of anilines with benzaldehydes must be noted, however. It was observed that p-trifluoromethyl aniline would not condense with p-(2-diethylaminoethoxy)benzaldehyde at 170-180°. It seems likely that the more basic tertiary nitrogen on the benzaldehyde side chain interacts with the aldehydic carbon of a neighboring molecule to such an extent that attack of p-trifluoromethylaniline is precluded. Such inhibition of condensation may be represented as follows:



It was felt that neutralization of the aliphatic nitrogen as the hydrochloride salt would allow formation of the desired Schiff base to occur. The yield of Schiff base by this method was excellent. After condensation in refluxing absolute ethanol the resulting N-[p-(2-diethylaminoethoxy)benzylidene]-p-trifluoromethylaniline hydrochloride (XII) was stirred into aqueous base to liberate the free Schiff base (XIII) in 96% yield.



Similarly, p-chloroaniline was condensed with the HCl salt of p-(2-diethylaminoethoxy)benzaldehyde (X) in good yield. The N-benzylideneanilines prepared are listed in Table I. Schiff bases IV, X, XI, XII, and XIII are new compounds, hence no references are given.

TABLE I

N-Benzylideneanilines

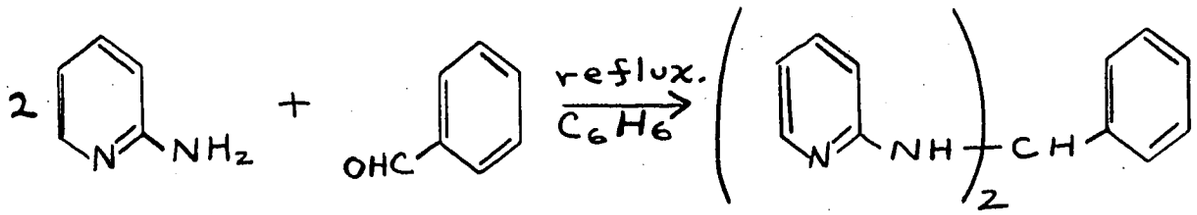
Cmpd.	R^1	R^2	Method	Yield%[a]	M.p.,°C.[b]	B.p. °C/mm.[b]	Ref.
I	H	4-CH_3O	A	63	70		14
II	4-Cl	4-CH_3O	A	88	124-125		15
III	4-Me_2N	4-CH_3O	A	88	138-139		16
IV[g]	4-Cl	4-HO	A	71	183-184		
V	3,4-OCH_2O	4-Me_2N	A	68	113-114		17
VI	4-HO	H	B	74	109-110		14
VII	4-CH_3O	4-CH_3O	C	79	148-149		14
VIII	4-CH_3O	3-CF_3	D	86	42-43	145-147/0.2	18
IX	H	H	G	84	52		19
X[c]	4-$Et_2NCH_2CH_2O$.HCl	4-Cl	F	94	163-164		
XI[d]	4-$Et_2NCH_2CH_2O$	4-Cl	F E	94 69 0	40-41 40-41	 180-185/0.1	
XII[e]	4-$Et_2NCH_2CH_2O$.HCl	4-CF_3	F	96	167-168		

TABLE I
(continued)

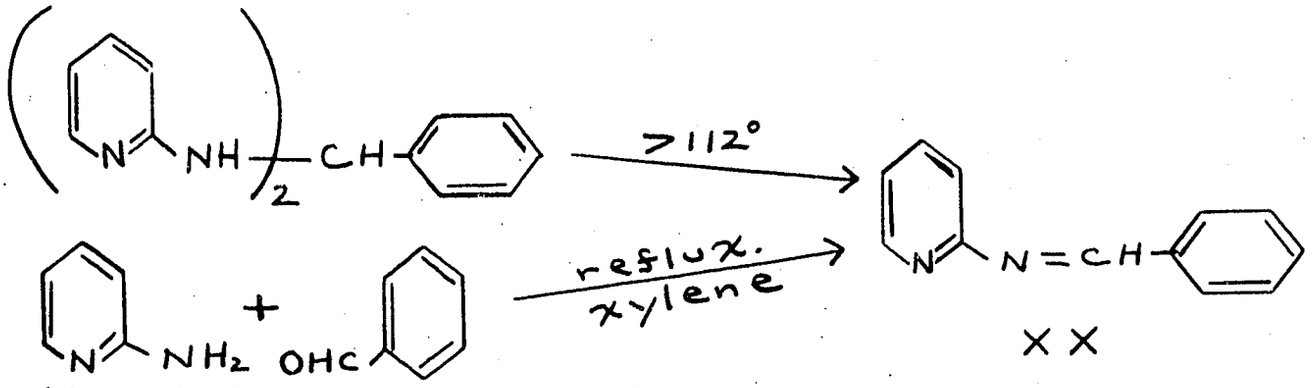
Compd.	R^1	R^2	Method	Yield %[a]	M.p.,°C.[b]	B.p.,°C./mm.[b]	Ref.
XIII[f]	4-$Et_2NCH_2CH_2O$	4-CF_3	F C	96 0	52-53		

[a] The yield after recrystallization or distillation. [b] All melting and boiling points are uncorrected. [c] Calcd. for $C_{19}H_{24}N_2Cl_2O$: C, 62.12; H, 6.59; N, 7.63; Cl, 19.31. Found: C,62.12; H, 6.64; N, 7.60; Cl, 19.40. [d] Calcd. for $C_{19}H_{23}N_2ClO$: C, 68.97; H, 7.01; N, 8.47; Cl,10.72. Found: C, 69.14; H, 6.95; N, 8.54, 8.41; Cl, 10.62. Compound for analysis was prepared by Method E. [e] Calcd. for $C_{20}H_{24}N_2F_3Cl$: N, 7.28; Cl, 9.21. Found: N, 7.23; Cl, 9.12. [f] Calcd. for $C_{20}H_{23}N_2F_3O$: N, 7.69. Found: 7.65. [g] Calcd. for $C_{13}H_{10}N$ ClO: C, 67.39; H, 4.35; N,6.05; Cl, 15.31. Found: C, 67.53; H, 4.62; N, 6.14; Cl, 15.07.

Azomethines were formed from the condensation of furfural (20,21) and N-methylpyrrole-2-carboxaldehyde with various anilines and, in one case, N,N-diethylethylenediamine. 2-Aminopyridine was condensed with benzaldehyde and with p-(2 -diethylaminoethoxy)-benzaldehyde in refluxing m-xylene (method E). Two moles of 2-aminopyridine react with one mole of benzaldehyde in refluxing benzene to form N,N'-benzylidenebis-2-aminopyridine (23).



However, when N,N'-benzylidenebis-2-aminopyridine is heated above its melting point (23) or the starting materials are heated in refluxing m-xylene N-benzylidene-2-aminopyridine is the product.



XX

Also, it has been reported (4,23) that a molar excess of 2-aminopyridine is necessary to attain a yield of Schiff base as high as 81%.

This author has found that by heating equimolar amounts of the reactants in a small volume of refluxing m-xylene it was possible to obtain a comparable yield of the azomethine.

Higher reaction temperatures and, in some cases, zinc chloride catalyst were employed in preparing Schiff bases from aryl ketones. Thus, deoxybenzoin and p-anisidine were condensed in refluxing m-xylene (method E), while acetophenone (24), benzophenone (25), fluorenone (25), and 2-phenacylpyridine were heated to 170-180° with aniline and a catalytic amount of zinc chloride (method H). The reaction of 1-indanone with N,N-diethylethylenediamine produced the calculated amount of water, but 64% of the diamine was recovered and the organic residue was a black tar. One explanation of these results may be that N,N-diethylethylenediamine promotes an aldol condensation of indanone faster than Schiff base formation occurs.

Xanthone, being completely inert toward amines, presents a special case. Only a strong nucleophile such as phenylmagnesium bromide (27) or 2-picolyllithium (28) will react with the carbonyl. The method of Schönberg and Urban (26) was used to prepare xanthone anil by quantitatively converting xanthone to 9,9-dichloroxanthene (29) using thionyl chloride. The dichloride was then treated with 3 moles of aniline to give xanthone anil (XXIV) and aniline hydrochloride. Table II lists Schiff bases, other than N-benzylideneanilines, which were prepared.

The success of the thionyl chloride method of preparing xanthone anil suggests that it might lend itself to the preparation of anils of other unreactive carbonyl compounds such as thioxanthone and 10-methylacridone.

TABLE II

$$R\text{-}C(R^1)=N\text{-}R^2$$

Other Schiff Bases

Compd.	R	R^1	R^2	Method	Yield,%[a]	M.p.,°C.[b]	B.p.,°C./mm[b]	Ref.
XIV	Phenyl	H	Benzyl	D	87.5		120-132/1	20
XV	2-Furyl	H	4-Methoxyphenyl	D	81.5	67-70	150-162/0.5	21
XVI	2-Furyl	H	2-Diethylamino-ethyl	D	77		95-100/1	
XVII	Phenyl	H	2-Diethylamino-ethyl	D	85		90-100/1	22
XVIII[c]	p-(2-Diethylamino-ethoxy)phenyl	H	2-Pyridyl	E	55		160-165/0.1	
XIX[d]	Benzyl	Phenyl	p-Methoxyphenyl	E	41	114-115		
XX[e]	Phenyl	H	2-Pyridyl	E	81		123-125/1	4,5 23
XXI	Phenyl	Methyl	Phenyl	H	55	41	198-200/37	24
XXII	Phenyl	Phenyl	Phenyl	H	80	115-116		25
XXIII	9-Fluorenylidene	-	Phenyl	H	83.7	82-84		25
XXIV	9-Xanthenylidene	_	Phenyl	I	70	106-107[f]		26

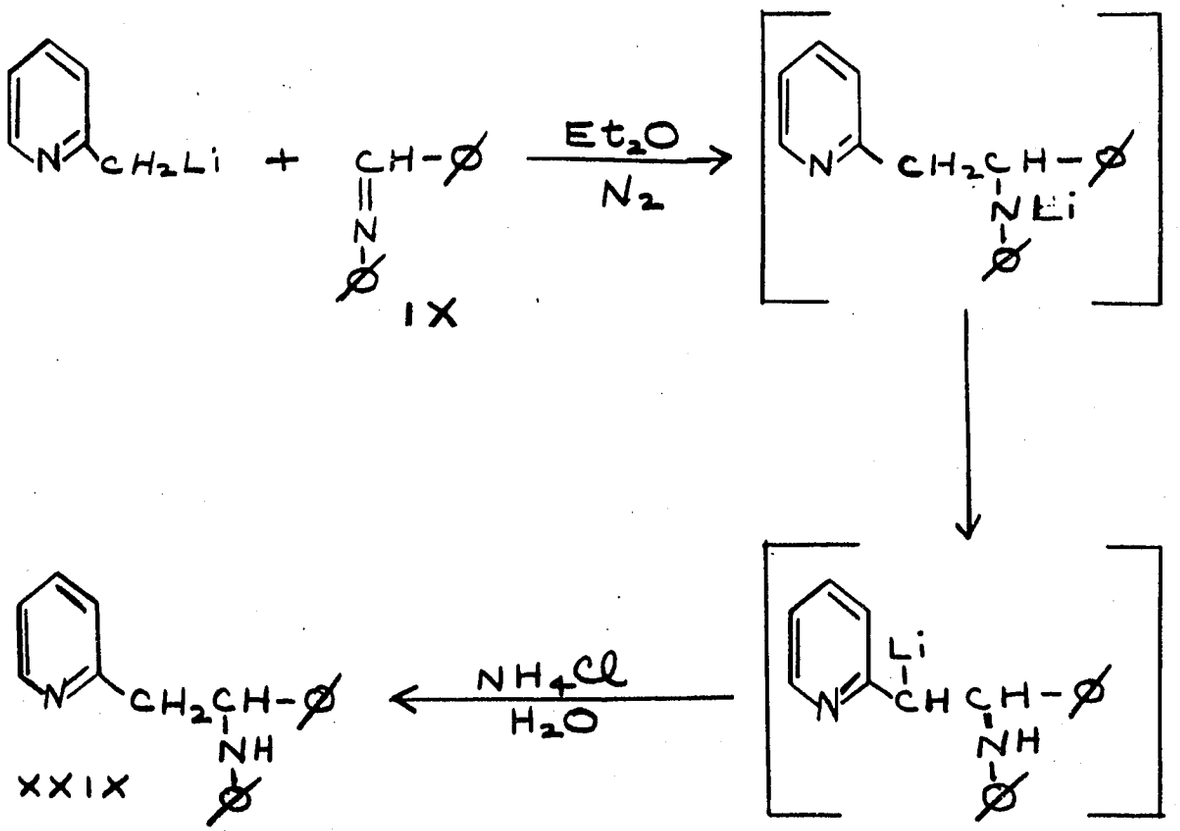
TABLE II
(continued)

Compd.	R	R^1	R^2	Method	Yield,%[a]	M.p., °C[b]	B.p., °C./mm.[b]	Ref
XXV	1-Indanylidene	-	2-Diethylamino-ethyl	D	0			
XXVI	2-(N-Methylpyrryl)	H	p-Chlorophenyl	D	95 (crude)	(not purified)		
XXVII	2-(N-Methylpyrryl)	H	Phenyl	D	63		100-110/0.1	

[a] The yield after recrystallization or distillation. [b] All melting and boiling points are uncorrecte
[c] Calcd. for $C_{18}H_{23}N_3O$: C, 72.69; H, 7.79; N, 14.13. Found: C, 72.75; H, 7.80; N, 14.18.
[d] Recrystallized from 95% ethanol. Calcd. for $C_{21}H_{19}NO$: C, 83.69; H, 6.35; N, 4.65. Found: C, 83.57; H, 6.20; N, 4.53. [e] When distilled, a small forerun of white N,N'-benzylidenebis-2-aminopyridine, m.p. 111-112°, is obtained. See reference 23.
[f] Reference 25 reports m.p. = 134-135°.

Synthesis of N,1-Disubstituted-2-(2-pyridyl)ethylamines and Related Compounds

Although there are no references in the literature to the reaction of 2-picolyllithium with Schiff bases this author has found it to be an excellent method for preparing 2-(2-pyridyl)ethylamines in yields of 30 to 80%. Table III lists several N,1-diphenyl-2-(2-pyridyl)ethylamines that have been prepared. The reaction for their synthesis may be illustrated by the following example using 2-picolyllithium and N-benzylideneaniline (IX):



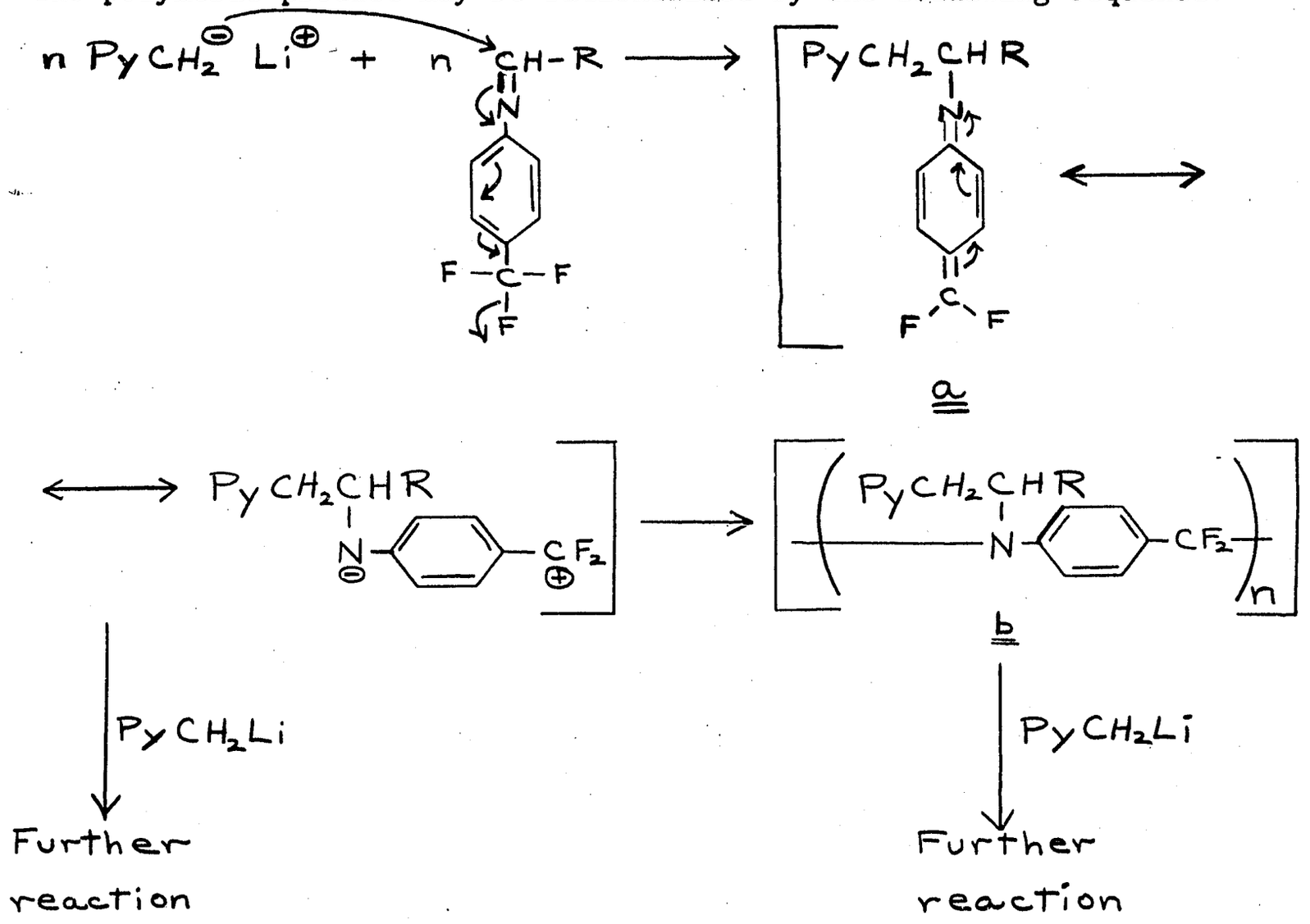
Addition of 2-picolyllithium to the imine linkage is probably followed immediately by an intramolecular proton exchange returning the anionic charge to the carbon adjacent to the pyridine ring. Evidence supporting such an exchange is cited in the next section of this thesis.

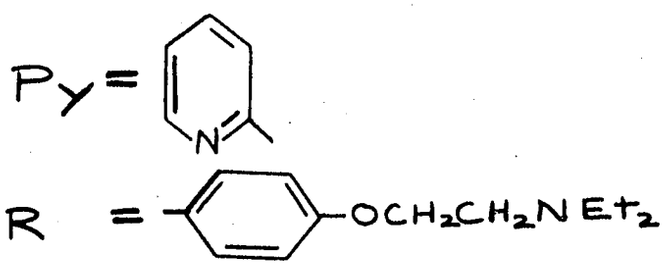
The addition reaction proceeds rapidly as evidenced by vigorous refluxing of the ether, and the yields did not seem to be improved by prolonged stirring or application of heat. The lithium salts were neutralized with aqueous NH_4Cl.

As a rule these diphenyl-2-(2-pyridyl)ethylamines were solids which precipitated from the ether layer and could then be recrystallized from ethanol or 60-70° pet. ether. Similar results were obtained in preparing the 2-(2-pyridyl)ethylamines listed in Table IV. Compounds XXXVII and XLII required special attention, since they were low-melting solids soluble in all organic solvents. Because pyridine compounds generally form hygroscopic acid salts, their picrates were made, recrystallized from ethanol or washed with acetone, and then neutralized in base to obtain a pure product. Compounds XLIV and XLV containing a-diethylaminoethylamino group were the only liquid products.

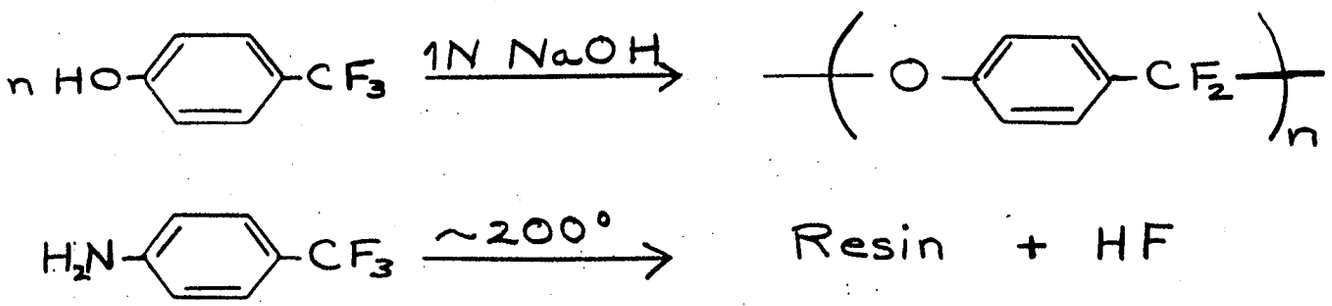
One exception to the utility of this reaction was encountered when N-[p-(2-diethylaminoethoxy)benzylidene]-p-trifluoromethylaniline was used. In this case only a black, brittle, polymeric solid was isolated. Since Schiff base VIII derived from m-trifluoromethylaniline was reacted successfully with 2-picolyllithium the possibility of direct displacement of fluoride ion by 2-picolyl anion is precluded. Also, if such an external nucleophillic attack were to occur defineable products would be expected.

The polymeric product may be rationalized by the following sequence:

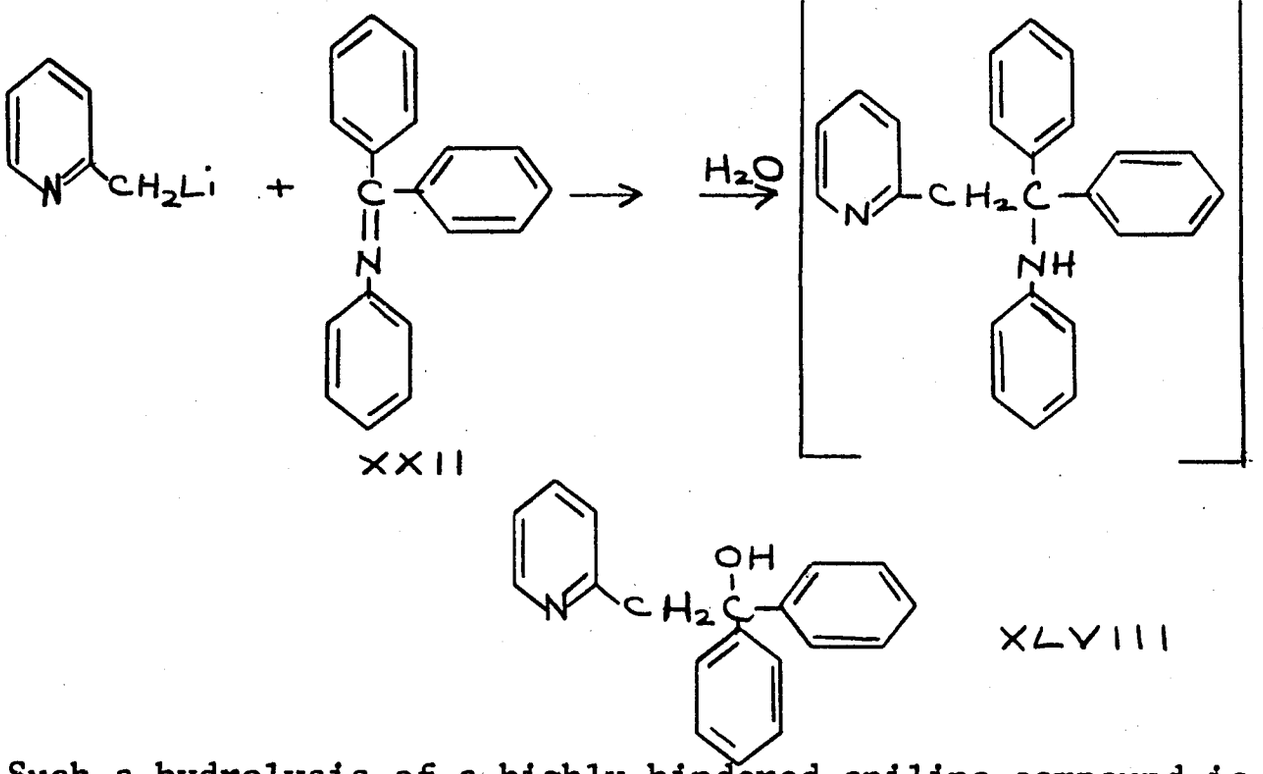




The reaction may be considered a S_{N2}' displacement of fluoride initiated by attack of 2-picolyl anion at the imino carbon. The resulting N-substituted-α,α-difluproquinone imine (intermediate a) would then be capable of giving several product resulting from further attack by 2-picolyl anion or from polymerization of the quinone imine a giving intermediate b. A similar polymerization has been reported to occur when p-trifluoromethylphenol is treated with a cold 1N NaOH solution (29). The same author reports that when p-aminobenzotrifluoride was heated to about 200°, in an attempt to distill it at atmospheric pressure, a vigorous polymerization took place with the evolution of large quantities of HF and formation of a hard glassy resin. Distillation could be accomplished in vacuo only.



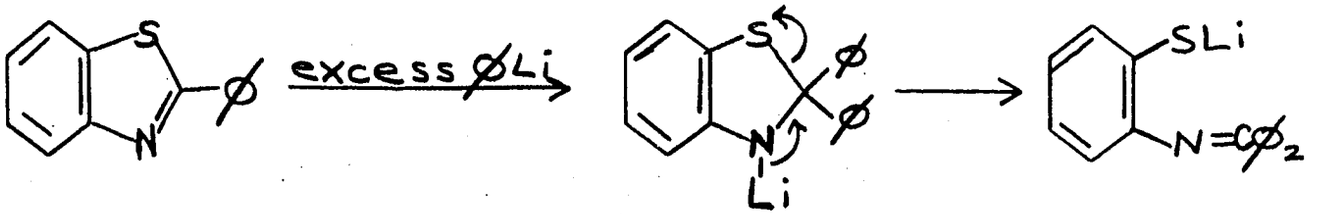
Unexpectedly, 1,1-diphenyl-2-pyridineethanol (XLVIII) resulted from the reaction of benzophenone anil (XXII) and 2-picolyllithium. It appears that, upon hydrolysis of the reaction mixture with aqueous NH_4Cl, the first-formed N,1,1-triphenyl-2-(2-pyridyl)-ethylamine loses aniline through displacement by water or hydroxide ion.



XXII

XLVIII

Such a hydrolysis of a highly hindered anilino compound is not unknown. Gilman and Beel (30) found that triphenylcarbinol was among the products resulting from the reaction of phenyllithium with 2-phenylbenzothiazole. They suggested the following sequence to explain the products.



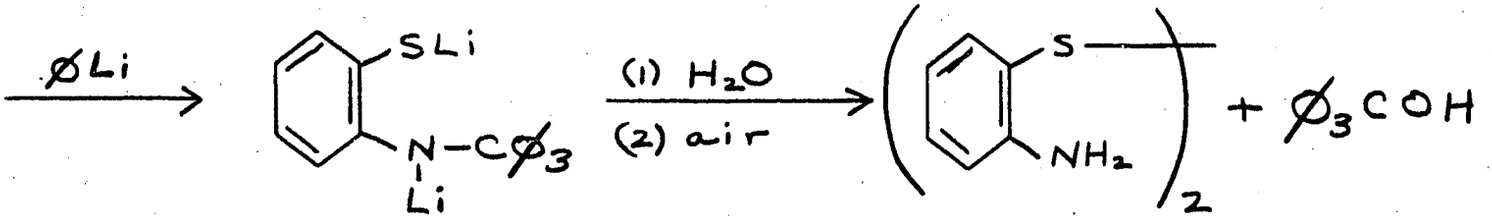
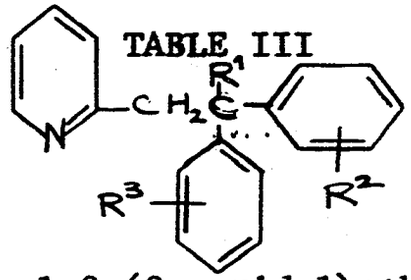


TABLE III



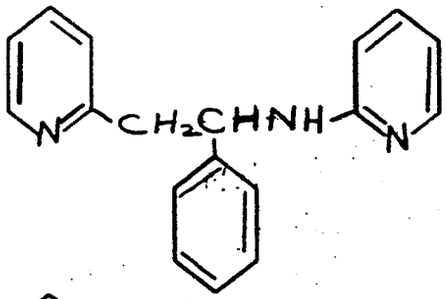
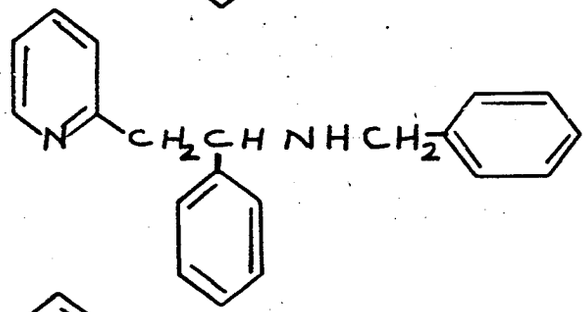
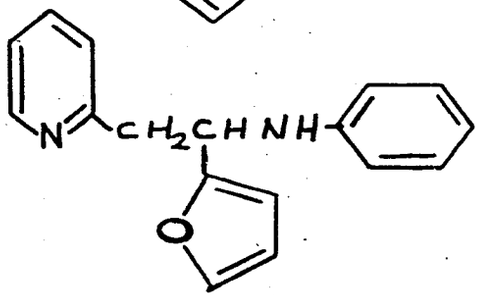
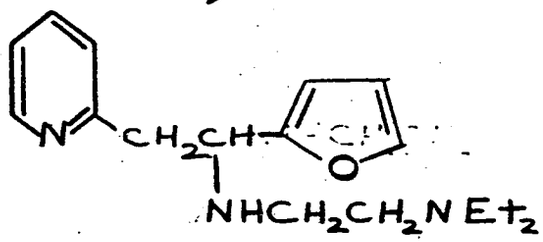
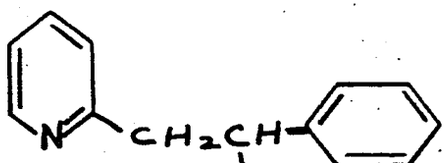
N,1-Diphenyl-2-(2-pyridyl)ethylamines

Cmpd.	R^1 [a]	R^2 [a]	R^3 [a]	Yield,% [d]	M.P.,°C. [b]
XXIX	H	H	H	33	103.5-104.5
XXX	CH_3	H	H	47	96-97
XXXI [c]	CH_3	H	H	25	117-118
XXXII	H	CH_3O	CH_3O	55	103-104
XXXIII	H	Me_2N	CH_3O	82.5	135-136
XXXIV	H	HO	H	42	159-160
XXXV	H	Cl	CH_3O	44	114-115
XXXVI	H	Cl	HO	48	186-187
XXXVII	H	CH_3O	3-CF_3	45	53-54
XXXVIII	H	$Et_2NCH_2CH_2O$	Cl	58.5	76-77
XXXIX	H	3,4-OCH_2O	Me_2N	71	100-101
XL	H	$Et_2NCH_2CH_2O$	CF_3	0	

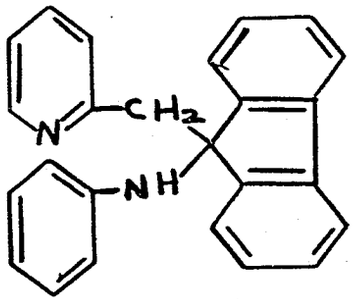
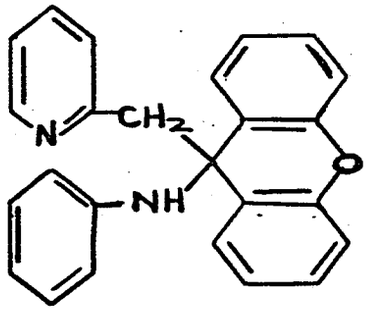
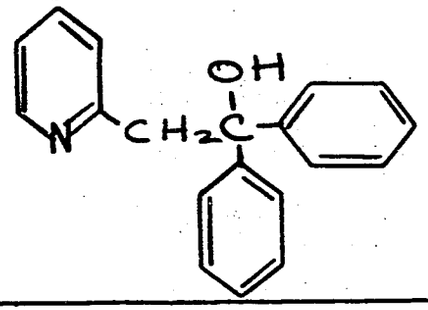
[a] All substituents are in the para position unless otherwise indicated. [b] The melting points are uncorrected. [c] Piperidine analogue of compound XXX. [d] All yields are those after one re-

TABLE IV

Other 2-(2-Pyridyl)ethylamines and Related Compounds

Cmpd.	Structure	Yield,%[e]	M.p.,°C.[a]	B.p.,°C./mm[a]
XL1		77.5	84-85	182-187/0.1
XL11[b]		36	52-53	
XL111		52	132-133	
XLIV		55		140-143/1
XLV[c]		61		150-160/1

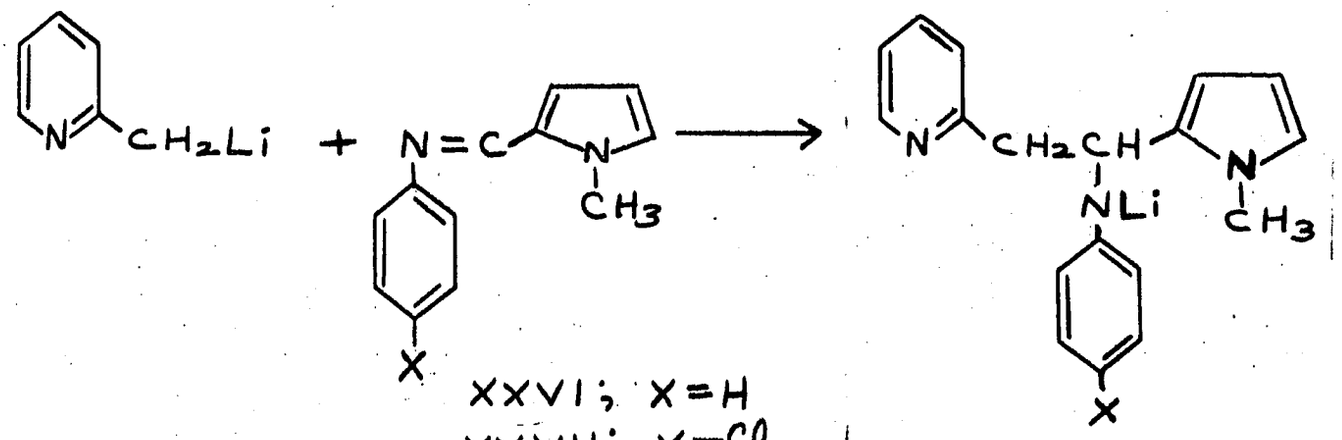
(continued)

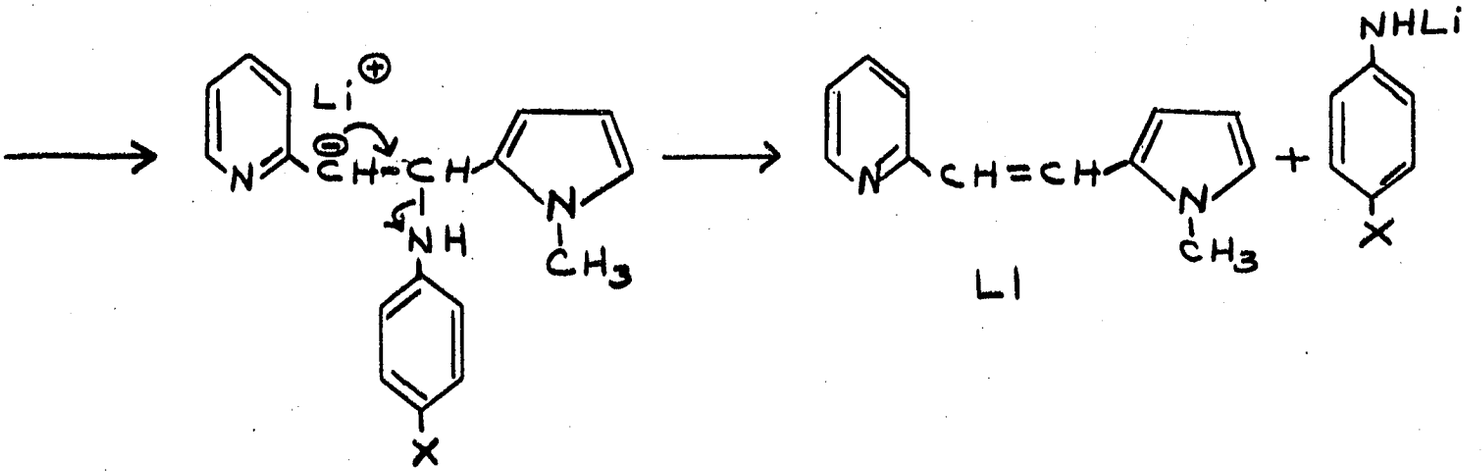
Compd.	Structure	Yield,%[e]	M.p.,°C.[a]	B.p.,°C/mm[a]
XLV1		54.7	170-172	
XLV11		63	194-195	
XLV111[d]		57.6	151-152	

[a] All boiling and melting points are uncorrected. [b] M.p. of dipicrate is 189-190°.
[c] Converted to its citrate monohydrate, m.p.68-80°, for analysis. [d] Known compound. Reference 28. [e] The yields are those after distillation or the first recrystallization.

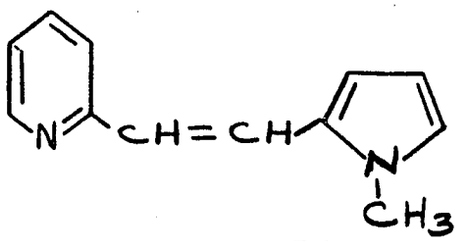
Elimination Products from 2-Picolyllithium, 2-Quinaldyllithium, and Schiff Bases.

The reaction of 2-picolyllithium with 1-methyl-2-(N-phenylformimidoyl)pyrrole (XXVII) or with 1-methyl-2-[N-(p-chlorophenyl)formimidoyl] pyrrole (XXVI) produced 2-{2-[2-(1-methylpyrryl)] vinyl} pyridine (LI) and the appropriate aniline. These unexpected results suggest that after initial addition to the imine linkage proton exchange occurs placing the anionic charge on the carbon adjacent to the pyridine ring. The next step may be considered a base-catalyzed deamination reaction producing compound LI and lithium anilide or lithium p-chloroanilide. The suggested sequence is as follows:

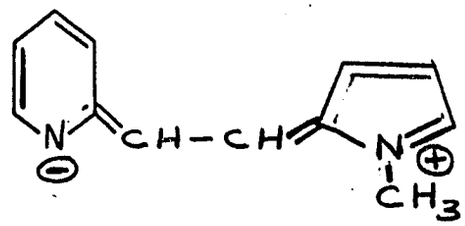




Base-catalyzed eliminations have been studied extensively (31a,32) using quaternary ammonium compounds, but in such cases the deamination is aided by the positive charge on the quaternary nitrogen. In the absence of a strong electron-withdrawing substituent on the anilino group another explanation must be considered for the elimination of aniline observed by this author. Examination of resonance forms L1 and L1a suggest that the driving force for the formation of L1 may be its stability.



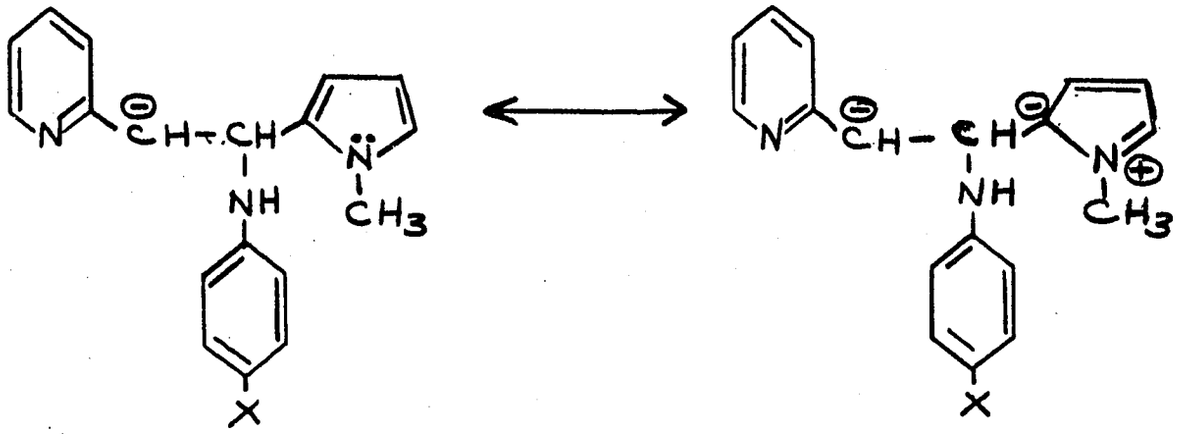
L1



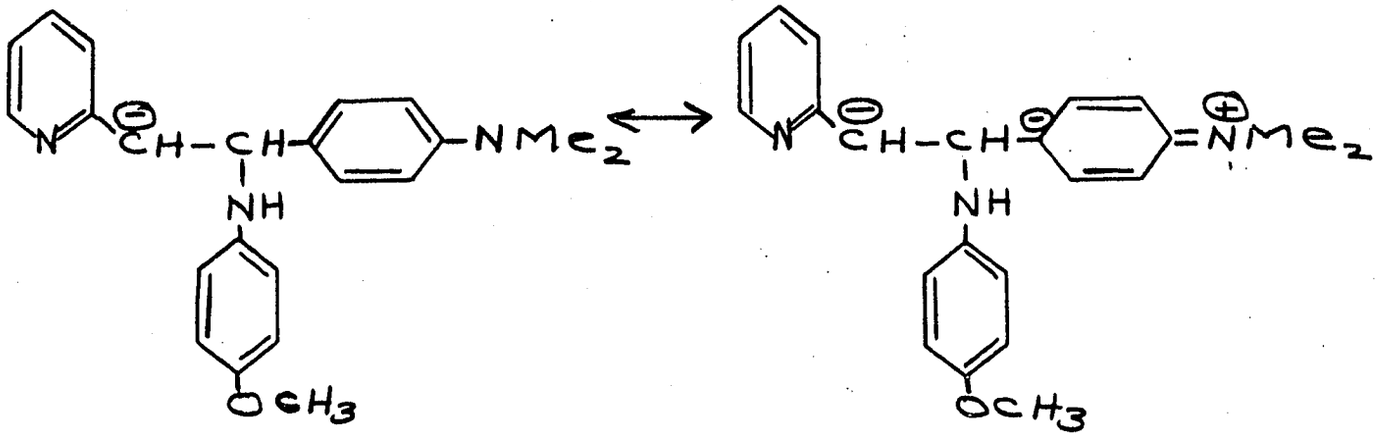
L1a

That the dipolar form L1a is a major contributor is supported by the fact that the ultraviolet spectrum of L1 shows a maximum at 362 mμ as opposed to a maximum of 309 mμ for 2-stilbazole (XL1X).

Why p-dimethylaminobenzylidene-p-anisidine (III) does not react with 2-picolyllithium to give elimination products may be explained by considering the relative contributions of resonance forms b and d to the ground states of anionic intermediates a and c.



a b



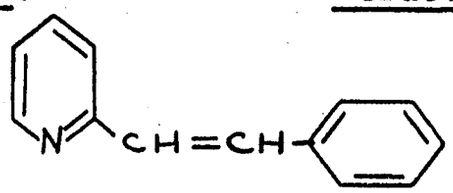
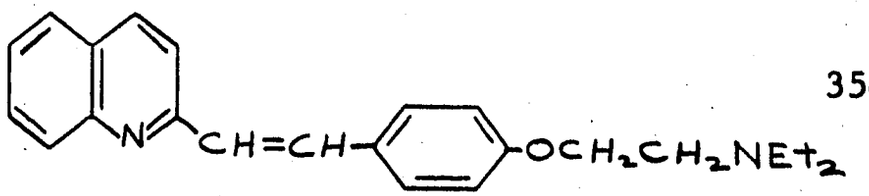
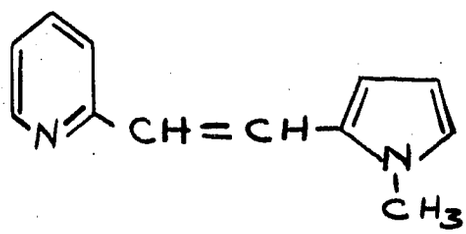
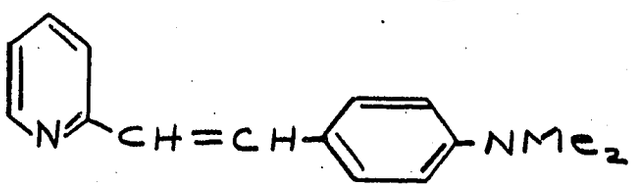
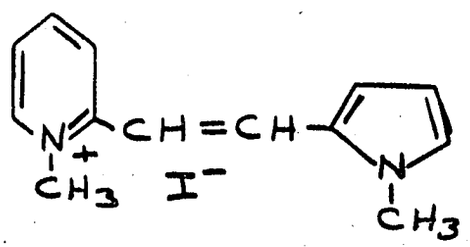
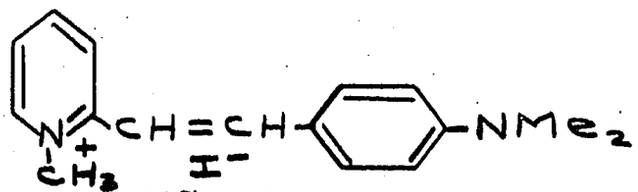
c d

Knowing that the pKb of N,N-dimethylaniline (33a) is 9.62 and that of 1-methylpyrrole is approximately 13.6 (33b) one would expect form d to be relatively more important than form b. In other words, the electron density of the p-dimethylaminophenyl group is higher at its point of attachment to the ethylamine than is the electron density at the 1-methylpyrryl group's point of attachment. This being so, intermediate c should be less likely to undergo deamination than intermediate a. The more basic dimethylaminophenyl group would, to a greater degree, discourage introduction of a double bond adjacent to it.

The methiodide LIII of compound LI was prepared and found to be a purple-red compound. For the purpose of comparing ultraviolet spectra 2-p-dimethylaminostyrylpyridine (L11) and its methiodide (L1V) were also synthesized. Compound L11 has previously been prepared in 18% yield by condensing 2-picoline with p-dimethylaminobenzaldehyde in the presence of piperidine acetate (34). This author has found it more convenient to react 2-picolyllithium with the aldehyde and to dehydrate the resulting 1-(p-dimethylaminophenyl)-2-pyridineëthanol (LV) with warm 4N HC1. The overall yield of L11 by this method is 37.8%. The methiodide LIV (35) was prepared by condensing 2-picoline methoidide with p-dimethylaminobenzaldehyde using a small amount of piperidine. The ultraviolet K-bands of all these compounds are listed in Table V and a reproduction of their complete spectra may be found in the Appendix.

TABLE V

2-β-Substitutedvinylpyridines, Related Compounds and Ultraviolet Spectra

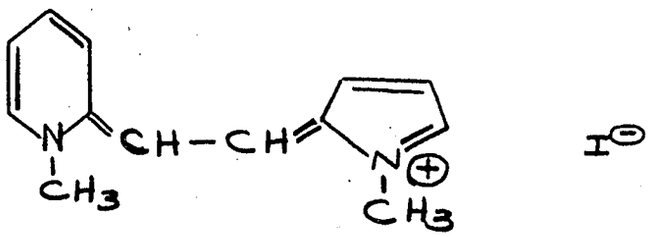
Compd.	Structure	K-bands λ_{max}, mμ	K-bands ε
XL1X		309[a]	5,450
L		354[b]	49,200
L1		362[b]	22,400
L11		370[b]	32,800
L111		414[c]	27,100
LIV		440[c]	30,100

[a] Solvent, aq. 50% ethanol.

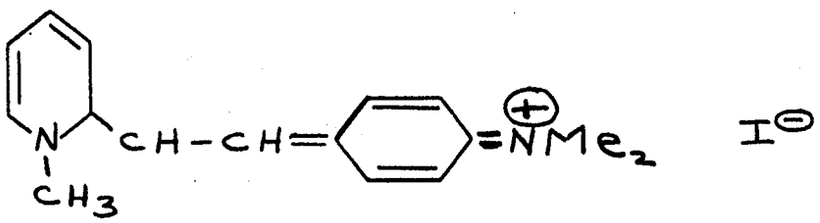
[b] Solvent, 95% ethanol.

[c] Solvent, distilled water.

2-Stilbazole methiodide is reported to be a yellow solid having λmax at 334 mμ (35). The purple-red color and longer wave lengths of absorption of p-dimethylamino-2-stilbazole methiodide (L1V) and of the 1-methylpyrrylvinylpyridine methiodide L111 may be laid to the relatively greater importance of resonance forms L111 a and L1V a.



L111 a



L1V a

The same argument may be used to explain the longer wavelengths of absorption of the free bases L1 and L11 as compared to λmax. of 2-stilbazole (XL1X).

2-Picolyllithium gave the normal addition product when reacted with N-[p-(2-diethylaminoethoxy)benzylidene]-p-chloroaniline (X1), but 2-quinaldyllithium was observed to give elimination products. Thus, 2-[p-(2-diethylaminoethoxy)-styryl] quinoline (L) was produced in 93% yield and some p-chloroaniline recovered.

The appearance of compound L rather than the addition product may be attributed to the greater number of contributing resonance structures possible for the quinoline nucleus as opposed to the pyridine nucleus. Compound L has also been synthesized by condensation of 2-quinaldine with p-(2 -diethylaminoethoxy)benzaldehyde using acetic anhydride.

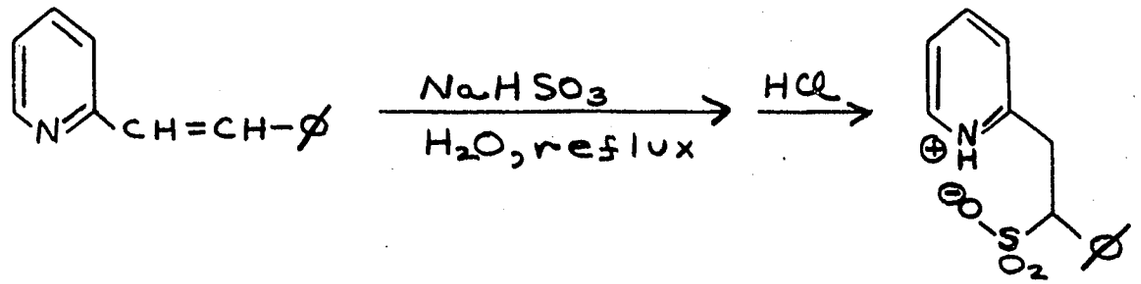
Except for 2-stilbazole (XL1X), the free bases in Table V exhibit a white fluorescence under an ultraviolet lamp. The methiodide L111 gives a bright red fluorescence while methiodide L1V is a very deep, barely visible purple.

Attempted Synthesis of N,1-Diphenyl-2-(2-pyridyl)ethylamine.

Michael-type reactions of 2-vinylpyridine with various nucleophiles have been known for several years. Doering and Weil (36) have successfully added sodio diethyl malonate, hydrogen cyanide, diethylamine, piperidine, sodium ethoxide, and sodium bisulfite to give 2-(2-substitutedethyl)pyridines in fair to excellent yields. More pertinent to this thesis, Reich and Levine have added a wide variety of primary and secondary amines to 2-vinylpyridine using either acetic acid, hydrochloric acid, or sodium as catalysts (37,38).

It was hoped that similar reactions using 2-stilbazole in place of 2-vinylpyridine would provide a useful synthetic route to N,1-diaryl-2-(2-pyridyl)ethylamines.

Sodium bisulfite was successfully reacted with 2-stilbazole in refluxing water to give, after acidification, an 86% yield of 1-phenyl-2-(2-pyridyl)ethanesulfonic acid (LV1).



XLIX LV

Compound LV is interesting in that, unlike many sulfonic acids and pyridinium salts, it is not hygroscopic and may be purified by recrystallization from water.

Four different procedures were used in unsuccessful attempts to add aniline to stilbazole.

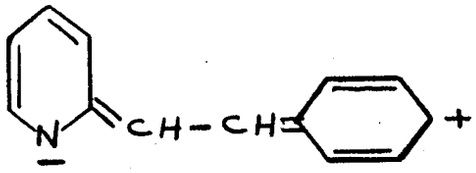
A. The sulfonic acid LV was heated in refluxing aniline.

B. 2-Stilbazole and sodium anilide were heated in refluxing aniline to give unidentified products.

C. 2-Stilbazole was added to lithium anilide in ether.

D. 2-Stilbazole, aniline and a catalytic amount of acetic acid were heated in a sealed tube at 200° for 60 hours.

The Michael reaction apparently fails with 2-stilbazole because the structure has been stabilized by incorporation of the reactive double bond into an extended conjugated system. The existence of resonance forms such as XLIX a discourages reaction with nucleophiles.



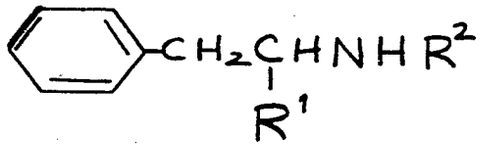
XLIXa

A similar explanation has been offered for the failure of α-phenylcinnamic ester to undergo the Michael reaction (31b).

Synthesis of N,1-Disubstituted-2-phenethylamines.

Benzylmagnesium chloride has been used in exactly the same manner as 2-picolyllithium to synthesize trisubstitutedethylamines. Previous reactions of benzyl Grignard reagents with Schiff bases are discussed in the Introduction. The phenethylamines obtained are listed in Table VI.

TABLE VI



N,1-Disubstituted-2-phenethylamines

Cmpd.	R^1	R^2	Yield,%[a]	M.p.,°C.[b]	B.p.,°C/mm[b]
LVI	Phenyl	p-Anisyl	59 90[c]		177-181/0.1
LVII	p-Anisyl	p-Anisyl	67.5	102-103	
LVIII	p-(2-Diethylamino-ethoxy)phenyl	p-Chlorophenyl	50		195-205/0.1
LIX	p-(2-Diethylamino-ethoxy)phenyl	2-Pyridyl	60	75-76	

[a] The yields are those after one distillation or recrystallization.

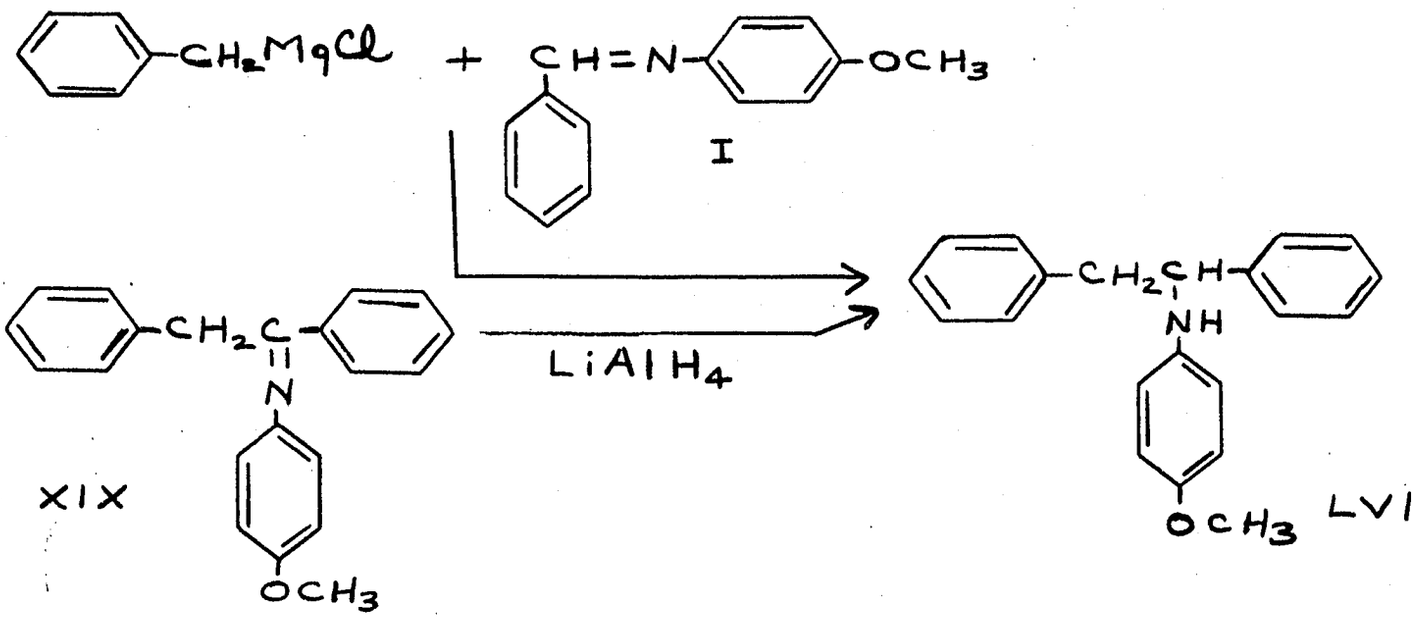
[b] All boiling and melting points are uncorrected.

[c] From the $LiAlH_4$ reduction of deoxybenzoin p-methoxyanil.

Benzyl Anion vs. o-Tolyl Anion Attack on Schiff Bases.

Benzylmagnesium chloride is known to give o-substituted-toluenes when reacted with certain aldehydes and acid chlorides. For instance, benzylmagnesium chloride and formaldehyde are reported to give o-tolylcarbinol (39,40,41). Higher aliphatic aldehydes give mixtures of products resulting from benzyl and o-tolyl anion attack (41). With acetyl chloride and acetic anhydride, o-methyl-acetophenone is obtained (42). These ortho products raise the possibility of o-tolyl anion attack on Schiff bases to give o-tolylmethylamines rather than phenethylamines. This author knows of no previous investigation into this possibility.

To determine the actual product from such reactions, N-(p-methoxyphenyl)-1-phenyl-2-phenethylamine (LVI) was prepared by the $LiAlH_4$ reduction of deoxybenzoin p-methoxyanil (XIX) and found to have an infrared spectrum and a boiling point identical to the product obtained by the reaction of benzylmagnesium chloride with N-benzylidene-p-anisidine (I).



EXPERIMENTAL DETAILS

All melting points and boiling points are uncorrected. The elemental analyses were performed by Dr. V. B. Fish, Department of Chemistry, Lehigh University.

Schiff Bases (I-XXVII). Method A. One-tenth of a mole of aldehyde was dissolved in 50-150 ml. of refluxing 95% ethanol. Through the top of a condenser was added 0.1 mole of amine dissolved in a minimum amount of 95% ethanol. The solution was refluxed for 10 minutes and then cooled to precipitate the Schiff base which was then filtered off and dried.

Method B. The procedure is the same as Method A except that absolute methanol was used as the solvent.

Method C. Equimolar amounts of amine and aldehyde were heated to 170-180° in an open flask for 20 minutes. The hot mixture was poured into an evaporating dish and allowed to crystallize. The crude product was broken up and recrystallized from 95% ethanol.

Method D. One-tenth of a mole of aldehyde or ketone and 0.1 mole of amine were heated in 75 ml. of refluxing benzene until 95-100% of the theoretical amount of water was collected in a water trap. The benzene was removed in vacuo and the residue vacuum distilled.

When 1-indanone and N,N-diethylethylenediamine were reacted the reaction turned black. Approximately 60% of the diamine was recovered during the work-up. The diamine was identified by the m.p. and mix. m.p. of its dipicrate, m.p. 213° (43).

Method E. One-tenth of a mole of amine and 0.1 mole of aldehyde or ketone were heated in 75 ml. of refluxing m-xylene for 4 to 10 hr. until 90-95% of the theoretical amount of water was collected in a Dean-Stark trap. The xylene was distilled off at atmospheric pressure and the residue vacuum distilled.

In the case of N-benzylidene-2-aminopyridine (XX) a small forerun of white, solid N,N'-benzylidenebis-2-aminopyridine (23) m.p. 111-112°, was collected.

Deoxybenzoin p-methoxyanil (XIX) was not distilled but purified by recrystallization from 95% ethanol.

Method F. Three grams (0.0128 mole) of p-(2 -diethylaminoethoxy)benzaldehyde hydrochloride and an equimolar amount of amine were heated in 20 ml. of refluxing absolute ethanol for 24 hr. The yellow solution was evaporated to dryness in vacuo on a hot water bath. The resulting solid was washed with dry ether and the pure hydrochloride dried in a vacuum desiccator over P_2O_5. The dry hydrochloride was slowly stirred into an excess of 5% NaOH to give the free base which was filtered and dried.

Method G. Equimolar amounts of aldehyde and amine were swirled together in a flask with cooling.

The resulting mixture (dark when furfural is the aldehyde) was vacuum distilled to give a light yellow, liquid product.

Method H. This is the method of G. Reddelein (24,25). One-tenth of a mole of ketone, 0.20 mole of aniline and 2 g. of zinc chloride were heated in an open flask to 170-180° for 1/2 hr. with the evolution of steam.

To isolate acetophenone anil (XXI) the cooled reaction mixture was stirred with 100 ml. of hot chloroform. After removal of the insoluble zinc chloride-aniline complex the chloroform and excess aniline were removed at reduced pressure and the product vacuum distilled to give white crystals of pure product.

To isolate benzophenone anil (XXII) the cooled reaction mixture was extracted with three 40 ml. portions of hot benzene. After removal of the benzene and the excess aniline at reduced pressure the product was vacuum distilled to give a yellow oil which solidified to give white crystals.

To isolate fluorenone anil (XXIII) the cooled reaction mixture was dissolved in 75 ml. of hot i-propanol. Insoluble zinc chloride-aniline complex was filtered off upon cooling of the propanolic solution. Fifteen ml. of absolute ethanol were added and the solution cooled in a refrigerator overnight to precipitate yellow product, m.p. 82-84°. Concentration of the filtrate to 1/2 its volume and cooling at -20° for several days precipitated an additional substantial quantity of product.

Recrystallization of the product from 60-70° pet. ether raised the m.p. to 86-87°. The crude material was quite satisfactory for further use.

Method I. 9,9-Dichloroxanthene was prepared according to the method of Schönberg and Asker (13). Thirty grams (0.153 mole) of xanthone were dissolved in 45 ml. (74.5g., 0.625 mole) of $SOCl_2$ and the solution refluxed for 8 hr. The excess, unreacted $SOCl_2$ was distilled in vacuo from the resulting dark reaction mixture to give a quantitative yield of brown crystalline product contaminated with a small amount of $SOCl_2$. 9,9-Dichloroxanthene reacts vigorously with water, so it was stored for short periods of time in a tightly stoppered flask.

Thirty-six grams (0.143 mole) of 9,9-dichloroxanthene were dissolved in 200 ml. of dry ether and 100 ml. of dry benzene. To this solution, with rapid stirring, was added 40 ml. (0.430 mole) of aniline accompanied by a vigorous reaction. The aniline hydrochloride was filtered off and the filtrate washed with water. The organic layer was evaporated in vacuo and the yellow-orange residue recrystallized from 100 ml. of 60-70° pet. ether to give 27.1 g. (70%) of yellow xanthone anil (XXIV), m.p. 106-107°.

General Procedure for Formation of 2-(2-Pyridyl)ethylamines XXIX, XXX, XXXII - XLVII and 1,1-Diphenyl-2-pyridineëthanol(XLVIII).

In a 500 ml. 2-necked flask equipped with a reflux condenser, stirrer, dropping funnel and nitrogen inlet, 0.2 mole of phenyllithium were prepared by slowly adding 0.2 mole of bromobenzene to 0.4 mole of lithium wire in 200 ml. of rapidly stirred anhydrous ether. The rate of addition was such as to insure constant refluxing of the ether. After nearly complete reaction of the lithium wire, 0.2 mole of 2-picoline was added to the dark solution of phenyllithium. The solution of 2-picolyllithium was a characteristic reddish color. One-tenth of a mole of the Schiff base to be reacted was slowly added,with stirring, to the ethereal solution of 2-picolyllithium, the rate of addition being fast enough to insure an even refluxing of the ether. Stirring was continued for 15 to 30 minutes after addition of the Schiff base. Hydrolysis was effected by very cautiously adding 200 ml. of an aq. 20% NH_4Cl solution with rapid stirring. See Isolation and Purification Procedures.

Isolation and Purification of 2-(2-Pyridyl)ethylamines XXIX, XXX, XXXII - XLVII and 1,1-Diphenyl-2-pyridineëthanol (XLVIII). Tables III and IV.

XXIX. After standing for 1/2 to 1 hour a solid precipitated from the ether layer. The tan product was collected, washed with water, and dried.

Recrystallization was effected with a minimum of 95% ethanol.

Analysis: for $C_{19}H_{18}N_2$.

Calcd.: C, 83.17; H, 6.61; N, 10.21.

Found: C, 83.20; H, 6.62; N, 10.28.
N, 10.26.

XXX. The layers were separated and the ether layer evaporated. Excess 2-picoline was distilled off in vacuo and the residue triturated with an equal volume of 60-70° pet. ether to give a tan solid.

Analysis: for $C_{20}H_{20}N_2$. Calcd.: C, 83.29; H, 6.99; N, 9.72.

Found: C, 83.12; H, 7.02; N, 9.95.

XXXII. The layers were separated and the ether layer evaporated. Excess 2-picoline was distilled off in vacuo and the residue dissolved in twice its volume of hot 95% ethanol. Upon cooling the product precipitated and the recrystallization was repeated.

Analysis: for $C_{21}H_{22}N_2O_2$. Calcd.: C, 75.42; H, 6.63; H, 8.38.

Found: C, 75.80; H, 7.01; N, 8.38.
C, 75.70; H, 6.69; N, 8.50.

XXXIII. The product precipitated upon hydrolysis of the reaction mixture. The solid was filtered and recrystallized from methanol.

Analysis: for $C_{22}H_{25}N_3O$. Calcd.: C, 76.05; H, 7.25; N, 12.10.

Found: C, 76.05; H, 7.31; N, 12.03.
C, 76.20; H, 7.31; N, 11.92.

XXXIV. The product precipitated after hydrolysis of the reaction mixture. The solid was filtered, then stirred with and filtered from three 100 ml. portions of hot water. The washed solid was dissolved in a minimum of boiling 95% ethanol, water added until the cloud point was reached, and the resulting solution cooled to give pure product.

Analysis: for $C_{19}H_{18}N_2O$. Calcd.: C, 78.61; H, 6.25; N, 9.65.

Found: C, 78.80; H, 6.41; N, 9.50.
N, 9.54.

XXXV. The layers were separated and half of the ether allowed to evaporate at room temperature. The remaining ether solution was cooled for a few hours and the solid which precipitated was filtered. Two recrystallizations from 95% ethanol gave pure product.

Analysis: for $C_{20}H_{19}ClN_2O$. Calcd.: C, 70.89; H, 5.65; N, 8.27; Cl,10.47

Found: C, 71.10; H, 5.85; N, 7.95; Cl, 9.87

XXXVI. After hydrolysis of the reaction mixture the pH of the aqueous layer was adjusted to neutrality with 4N HCl. The layers were filtered together and the product washed with water and ether. Two recrystallizations from 95% ethanol gave pure, white product.

Analysis: for $C_{19}H_{17}N_2ClO$. Calcd.: C,70.24; H,5.28; N,8.63; Cl,10.92.

Found: C,70.60; H,5.18; N,8.75; Cl,10.60.
N,8.74; Cl,10.58.

XXXVII. The layers were separated and the ether layer evaporated in vacuo. The residue was dissolved in 500 ml. of hot 60-70° pet. ether.

Upon cooling, a dark viscous residue settled out and when the solution became clear it was decanted and evaporated to dryness to give a light orange, viscous oil. This crude oil was dissolved in 300 ml. of 95% ethanol and the resulting solution added, with stirring at room temperature, to 64 g. (0.28 mole) of picric acid dissolved in approx. 1 l. of 95% ethanol. The resulting picrate was recrystallized from 95% ethanol and then stirred with 500 ml. of water and decomposed with NH_4OH. The insoluble ammonium picrate was filtered and washed with ether. The filtrate was extracted with ether, and the extract washed twice with saturated aq. $NaHCO_3$ and twice with water. The ether was removed in vacuo. The residue was heated in 200 ml. of boiling methanol with a small amount of decolorizing carbon. Removal of the carbon and methanol gave a clear, viscous oil which solidified after 2 months, m.p. 53-54°.

Analysis: for $C_{21}H_{19}N_2OF_3$. Calcd.: N, 7.52.
Found: N, 7.51.

The dimethiodide monoethanolate was prepared in and recrystallized from absolute ethanol.

Analysis: for $C_{28}H_{31}N_2O_2F_3I_2$. Calcd.: N, 3.99; I, 36.14.
Found: N, 3.97; I, 36.10.

XXXVIII. The layers were separated and the ether layer evaporated in vacuo. Unreacted 2-picoline was distilled off at reduced pressure.

The residue was stirred vigorously with 250 ml. of refluxing 60-70° pet. ether to give a cloudy solution which was allowed to cool and stand until clear. The clear solution was decanted, allowed to evaporate to two-thirds its original volume and cooled overnight in a refigerator to precipitate pure product.

Analysis: for $C_{25}H_{30}N_3$ ClO. Calcd.: C,70.82; H,7.13; N,9.91; Cl,8.36.

Found: C,70.90; H,7.34; N,9.64; Cl,8.13.
N,9.66

XXXIX. The ethereal layer was evaporated in vacuo to give a brown solid. This solid was washed with ether and recrystallized from a minimum of 95% ethanol.

Analysis: for $C_{22}H_{23}N_3O_2$. Calcd.: C,73.10; H,6.41; N,11.63.

Found: C,73.15; H,6.63; N,11.48.

XL. The ether layer was evaporated in vacuo and unreacted 2-picoline was distilled from the residue at reduced pressure. The remaining organic materials solidified to a black, brittle resin, which was somewhat soluble in most organic solvents but could not be recrystallized. It formed a dirty, gummy picrate which became an insoluble, sticky, brown mass upon attempted recrystallization from 95% ethanol or acetone.

XLI. The ether layer was evaporated in vacuo and unreacted 2-picoline distilled off at reduced pressure. The residue was vacuum distilled, b.p. 182-187°/0.1 mm., to give a yellow, viscous liquid which crystallized over several days.

The liquid product was dissolved in hot 60-70° pet. ether to give, on cooling, a white solid.

Analysis: for $C_{18}H_{17}N_3$. Calcd.: C, 78.51; H, 6.23; N, 15.26.
Found: C, 78.56; H, 6.18; N, 15.14.

XLII. The ether layer was evaporated in vacuo and the unreacted 2-picoline removed by distillation at 1 mm. The dark, viscous residue was swirled with six 60 ml. portions of boiling 60-70° pet. ether. After each such extraction the flask was allowed to stand a few minutes before the pet. ether solution was decanted. The combined extracts were evaporated to give an orange oil.

Sixty grams of picric acid were dissolved in 1 l. of 95% ethanol. The orange oil dissolved in 500 ml. of 95% ethanol was added with rapid stirring at room temperature to the picric acid solution. The resulting picrate was collected and stirred with enought acetone to make a slush, the picrate filtered, and the acetone washing repeated. The picrate, m.p. 189-90°, was stirred with 500 ml. of water and basicified with NH_4OH. One hundred and fifty ml. of ether were added, ammonium picrate filtered off and the ether layer removed from the filtrate. The ethereal solution was washed twice with sat. aq. $NaHCO_3$ and thrice with water. After drying over Na_2SO_4 a small amount of decolorizing carbon was added, the mixture stirred and then filtered through Celite.

Evaporation of the ether gave an orange oil which solidified after two weeks..

Analysis: for $C_{20}H_{20}N_2$. Calcd.: C, 83.29; H, 6.99; N, 9.72.

Found: C, 83.02; H, 7.12; N, 9.86.
N, 9.88.

XLIII. The aqueous and ethereal layers were filtered together to isolate crude product. The ether layer was evaporated and unreacted 2-picoline was evaporated in vacuo. The residue was recrystallized from 95% ethanol to give additional crude material. Recrystallization of the total product from 95% ethanol after treatment with decolorizing carbon gave short, silky, white needles.

Analysis: for $C_{18}H_{18}N_2O_2$. Calcd.: C, 73.45; H, 6.16; N, 9.52.

Found: C, 73.60; H, 6.30; N, 9.58.

XLIV. The ether layer was evaporated and the dark residue vacuum distilled through a Claisen distilling head to give a clear, light orange oil. This product was redistilled discarding the first 3 ml. of distillate.

Analysis: for $C_{17}H_{25}N_3O$. Calcd.: C, 71.04; H, 8.77; N, 14.62.

Found: C, 71.20; H, 8.70; N, 14.60.
N, 14.58.

XLV. The ether layer was evaporated and the dark residue distilled to give a yellow oil.

The oil was converted to its citrate monohydrate by adding it to an equimolar amount of citric acid monohydrate dissolved in a minimum amount of dry acetone. The white salt was washed with acetone and ether and then dried over P_2O_5 at 20 mm. for 2 days before analysis. The citrate is somewhat hygroscopic.

Analysis: for $C_{25}H_{37}N_3O_8$. Calcd.: C, 59.16; H, 7.38; N, 8.28.
Found: C, 59.30; H, 7.25; N, 8.21.

XLVI. The aqueous and ether layers were poured into a beaker and allowed to stand for 2 hours. The white, crystalline solid which slowly precipitated was filtered off and washed with a small amount of ether and dried. This product was heated in 250 ml. of refluxing 95% ethanol for 5 minutes, and then 35 ml. of benzene were added to effect solution. Cooling the solution overnight gave an 81% recovery of colorless crystals.

Analysis: for $C_{25}H_{20}N_2$. Calcd.: C, 86.17; H, 5.79; N, 8.04.
Found: C, 86.10; H, 5.86; N, 8.00.
N, 7.90.

XLVII. The product precipitated from the ether layer and was recrystallized in 79% recovery from 1:1 i-propanol-benzene with no change in m.p. Additional product was obtained by evaporating the ether layer and recrystallizing the residue.

Analysis: for $C_{25}H_{20}N_2O$. Calcd.: C, 82.39; H, 5.53; N, 7.69.
Found: C, 82.30; H, 5.80; N, 7.60.

XLVIII. White product precipitated from the ether layer. It was collected, washed with cold water and cold ether. M.p.150-151°. Recrystallization from methanol raised the m.p. to 151-152°.

The product gave no depression when a mixed m.p. with authentic 1,1-diphenyl-2-pyridineethanol (28) was taken.

N,2-Diphenyl-1-(2-piperidyl)isopropylamine (XXXI). Eight grams (0.028 mole) of N,2-diphenyl-1-(2-pyridyl)isopropylamine (XXX) were dissolved in 80 ml. of glacial acetic acid and hydrogenated in a Parr low-pressure bomb using 0.3 g. (0.0013 mole) of platinum dioxide. The initial pressure was 50 p.s.i. in the 5-liter system. After the calculated decrease in hydrogen pressure the catalyst and acetic acid were removed followed by basicification of the residue with 25% NaOH solution and ether extraction. The ether was dried over sodium sulfate and then evaporated in vacuo. The residue was distilled to give 4.12 g. (50%) of light yellow, extremely viscous, crude product, b.p. 150-162°/0.5 mm. Three recrystallizations from 80% ethanol gave 2g. (25%) of white solid, m.p. 117-118°.

Analysis: for $C_{20}H_{26}N_2$. Calcd.: C, 81.58; H, 8.90; N, 9.52.

Found: C, 81.70; H, 8.85; N, 9.58.
N, 9.48.

2-Stilbazole (XLIX). The method of Shaw and Wagstaff was used. See reference 44 or page 27 in Part I of this thesis.

2-{2-[4-(2-Diethylaminoethoxy)phenyl]vinyl}quinoline (L).

Method A. Twenty grams (0.0605 mole) of N-[4-(2-diethylaminoethoxy)benzylidene]-p-chloroaniline (XI) in 100 ml. of ether were added to 0.121 mole of quinaldyllithium (prepared in the same manner as 2-picolyllithium) in 150 ml. of ether. A mild refluxing of the ether ensued. After the flask had cooled to room temperature the reaction mixture was hydrolyzed with aqueous NH_4Cl and the ether layer separated, dried and evaporated. p-Choroaniline and unreacted quinaldine were distilled off at reduced pressure and the residue recrystallized from 300 ml. of 60-70° pet. ether to give 14.7 g. (70%) of white product, m.p. 52-53°.

Analysis: for $C_{23}H_{26}N_2O$. Calcd.: C, 79.73; H, 7.56; N, 8.09.
Found: C, 80.20; H, 7.76; N, 8.05.

The dipicrate, m.p. 199-200° dec., was formed in and recrystallized from acetone.

Analysis: for $C_{35}H_{32}N_8O_{15}$. Calcd.: C, 52.17; H, 4.13; N, 13.91.
Found: C, 52.36; H, 4.20; N, 14.02.

Method B. Seven and fifteen hundreths grams (6.5 ml., 0.05 mole) of quinaldine, 11.05 g. (0.05 mole) of 4-(2-diethylaminoethoxy)benzaldehyde, and 10.8 g. (10 ml., 0.106 mole) of acetic anhydride were refluxed for 6 hours. Unreacted materials were removed at reduced pressure, the black residue stirred with 50 ml. of aqueous 5% NaOH and the organic layer taken up by ether extraction.

The ether solution was dried over Na_2SO_4, evaporated in vacuo, and the residue dissolved in acetone. The acetone solution was added to 0.15 mole of picric acid dissolved in 200 ml. of acetone. After standing for a few minutes the dipicrate, m.p. 196-199°, precipitated. The dipicrate was filtered and then stirred with 300 ml. of boiling acetone and refiltered to give 24.35 g. (60.5%), m.p. 199-200°, of pure yellow salt. The dipicrate was stirred into 500 ml. of hot water and basicified with NH_4OH. The hot mixture was extracted with 150 ml. of hot benzene. The benzene solution was washed with aqueous 5% NaOH and then with water. The benzene extract was dried over Na_2SO_4 and evaporated. The residue was recrystallized from 40 ml. of 60-70° pet. ether to give 5 g. of pure product. An additional 1.5 g. of product in the form of colorless plates were collected by allowing the filtrate to evaporate at room temperature to 1/2 its volume. The total yield was 6.5 g. (36%), m.p. 52-53°.

Analysis: for $C_{23}H_{26}N_2O$. Calcd.: C, 79.73; H, 7.56; N, 8.09.

Found: C, 79.77; H, 7.08; N, 8.17.
N, 8.19.

This compound gave a white fluorescence under an ultraviolet lamp.

2-{2-[2-(1-Methylpyrryl)]vinyl}pyridine (LI). Ten grams (0.0543 mole) of 1-methyl-2-(N-phenylformimidoyl)pyrrole (XXVII) in 50 ml. of ether were slowly added to approx. 0.109 mole of 2-picolyllithium in 100 ml. of ether.

Addition was accompanied by refluxing of the ether. When the reaction began to cool it was carefully hydrolyzed with an excess of saturated aqueous NH_4Cl. The ether layer was separated and dried over Na_2SO_4 and the ether evaporated in vacuo. After vacuum distillation of aniline and unreacted 2-picoline the residue was distilled to give a light yellow oil, b.p. 130-135°/0.1 mm., which gradually solidified to a yellow solid, m.p. 88-89°. The solid was recrystallized once from a minimum of 60-70° pet. ether to give 4.15 g. (41.5%), m.p. 95-96°, of pale yellowish-tan crystals.

Analysis: for $C_{12}H_{12}N_2$. Calcd.: C, 78.22; H, 6.57; N, 15.21.
Found: C, 78.43; H, 6.68; N, 14.96.

When 1-methyl-2-[N-(p-chlorophenyl)formimidoyl]pyrrole (XXVI) was reacted with 2-picolyllithium similar results were obtained. The ether residue was distilled to give a 47% yield of crude product LI and a 66% recovery of p-chloroaniline.

Compound LI gave a faint blue-white fluorescence under an ultraviolet lamp.

2-{2-[2-(1-Methylpyrryl)] vinyl}pyridine Methiodide (LIII).

Method A. Compound LI was dissolved in an excess of methyl iodide and allowed to stand overnight. After removal of excess methyl iodide the crude purple-red product, m.p. 230-231°, was recrystallized from 95% ethanol to give an 84% yield of pure methiodide LIII, m.p. 245-246°.

Analysis: for $C_{13}H_{15}N_2I$. Calcd.: C, 47.87; H, 4.64; N, 8.59; I,38.91.

Found: C, 47.95; H, 4.81; N, 8.48; I, 38.80.
N, 8.50

Method B. Using the method of Phillips (35) 5 g. (0.0226 mole) of 2-picoline methiodide, 5 g. (0.0458 mole) of 1-methylpyrrole-2-carboxaldehyde and 1 ml. of piperidine were heated in 30 ml. of refluxing absolute methanol. When bumping due to precipitated product LIII made further refluxing impossible the flask was cooled and 6 g. (81.5%) of pure brick-red product was collected, m.p. 245-246°. A mixed m.p. of the products obtained via methods A and B showed no depression. The methiodide exhibited a blood-red fluorescence under an ultraviolet lamp.

2-(4-Dimethylaminostyryl)pyridine (LII). Ten grams (0.067 mole) of p-dimethylaminobenzaldehyde were slowly added with stirring to approx. 0.134 mole of 2-picolyllithium in 150 ml. of ether. Stirring was continued for an additional 30 minutes and the reaction mixture then hydrolyzed with saturated NH_4Cl solution. A solid precipitated from the ether layer to give 9 g. of product, m.p. 114-115°. An additional 1.8 g.,m.p. 122-123°, were collected by evaporating the ether layer to 1/2 its volume. Total yield of crude product was 10.8 g. (66.6%). Recrystallization from a minimum of i-propanol gave 8.25 g. (46.6%), m.p. 121.5-122.5°, of white, pure product.

Analysis: for $C_{15}H_{18}N_2O$. Calcd.: C, 74.35; H, 7.49; N, 11.56.
Found: C, 74.65; H, 7.53; N, 11.78.

One gram (0.00413 mole) of the impure 1-(p-dimethylaminophenyl)-2-pyridineëthanol was dissolved in 10 ml. of 4N HCl and the solution warmed to 60° overnight. The reaction solution was poured into an excess of 10% KOH and the 0.85 g. (91.7%) of yellow-orange compound LII collected m.p. 141-142°. Recrystallization from 75% ethanol gave pale yellow-tan product, m.p. 141-142°, in 94% recovery.

Analysis: for $C_{15}H_{16}N_2$. Calcd.: C, 80.32; H, 7.19; N, 12.49.
Found: C, 81.32; H, 7.23; N, 11.49.

Two recrystallizations from acetone gave yellow crystals, m.p. 141-142°, which gave a slightly better analysis.

Analysis: for $C_{15}H_{16}N_2$. Calcd.: C, 80.32; H, 7.19; N, 12.49.
Found: C, 81.23; H, 7.35; N, 12.12.

Parker and Furst (34) report a melting point of 239.4-240° which, in view of similar ultraviolet maxima, appears to be a typographical error.

2-(4-Dimethylaminostyryl)pyridine Methiodide (LIV). The method of Phillips (35) was used to prepare methiodide LIV. Five g. (0.021 mole) of 2-picoline, 5 g. (0.0336 mole) of 2-(4-dimethylaminostyryl)-pyridine (LII), and 1 ml. of piperidine were heated in 50 ml. of refluxing absolute methanol until bumping caused by the product prevented furthur heating.

Recrystallization of the product from methanol gave 4.28 g. (56%) of purple-red crystals, m.p. 273-274° dec.

1-Phenyl-2-(2-pyridyl)ethanesulfonic acid (LV). One gram (0.0055 mole) of 2-stilbazole was refluxed for 3 hr. with 15 ml. of a saturated aqueous solution of $NaHSO_3$. During the reaction period the liquid layer of melted 2-stilbazole gradually disappeared. At the end of 3 hr. the reaction mixture was clear. The solution was evaporated to dryness in vacuo on a boiling water bath and the white residue treated with an excess of hydrochloric acid with the evolution of sulfur dioxide and precipitation of sodium chloride. The NaCl was filtered off, washed with conc. HCl, and the combined filtrates evaporated to dryness at reduced pressure on a hot water bath. The resulting dark residue was dissolved in 20-25 ml. of hot 70% ethanol, a little decolorizing carbon added to the resulting solution, and the hot mixture filtered. The clear filtrate was evaporated to dryness and the resulting yellowish solid recrystallized from a small amount of water with the pure product very gradually precipitating as off-white, round crystals, m.p. 251-252° dec., upon cooling and standing for 1 to 3 days. The yield was 1.35 g. (86%).

Analysis: for $C_{13}H_{13}NO_3S$. Calcd.: C,59.30; H,4.98; N,5.32; S,12.18.
Found: C,59.20; H,5.19; N,5.19; S,12.07.

The sulfonic acid exhibits none of the hygroscopic tendencies of either pyridinium acid salts or many sulfonic acids.

Attempted Syntheses of N,1-Diphenyl-2-(2-pyridyl)ethylamine (XXIX).

Method A. Two g. of 1-phenyl-2-(2-pyridyl)ethanesulfonic acid (LV) were heated in 10 ml. of refluxing aniline for 3 hr. One hundred ml. of water were added and the aniline steam distilled. Concentration of the aqueous solution to 8-9 ml. followed by cooling overnight gave a 97.5% recovery of sulfonic acid LV.

Method B. Five g. (0.0276 mole) of 2-stilbazole (XLIX), 10 ml. (0.11 mole) of aniline and 0.52 g. (0.014 mole) of sodium were heated slowly. With the first appearance of molten sodium a dark brown color appeared. The reaction mixture was heated at reflux for 4 hr. to give a nearly black solution. Unreacted aniline was removed by steam distillation and the aqueous, alkaline residue extracted with ether. The ethereal extract was dried over Na_2SO_4 and the ether evaporated to give a dark brown, viscous oil. The oil distilled at 130-140°/0.5 mm. to give 2 g. of a light yellow oil which formed a picrate, m.p. 183-190°, whose m.p. did not change upon recrystallization from 95% ethanol. Elemental analysis of the picrate agreed more closly with that expected for 2-stilbazole picrate, m.p. 210-211°, than for the picrate or dipicrate of compound XXIX.

Analysis: for 2-stilbazole picrate, Calcd.: C,55.61; H,3.44; N,13.66.
Found: C,54.16; H,3.87; N,13.24.

A mixed m.p. with authentic 2-stilbazole picrate gave no depression.

Method C. Five g. (0.0276 mole) of 2-stilbazole was dissolved in 15 ml. of ether and added to an equimolar amount of lithium anilide (from adding an equimolar amount of aniline to phenyllithium) in 50 ml. of ether. There was no noticeable evolution of heat. Hydrolysis with ice water followed by ether extraction gave a quantitative recovery of 2-stilbazole.

Method D. Two g. (0.011 mole) of 2-stilbazole, 2g. (0.0225 mole) of aniline, and 0.12 g. (0.002 mole) of glacial acetic acid were heated at 200° for 6 hr. in a sealed tube. Upon cooling 48 hr. at -20° 1.5g. (75%) of 2-stilbazole crystallized from the reaction mixture as a white solid. An additional 0.44 g. (22%) of 2-stilbazole was obtained by basicification of the filtrate with 25% NaOH followed by steam distillation to remove the aniline and finally filtration. The recovery of 2-stilbazole was 97%.

General Procedure for Formation of N,1-Disubstituted-2-phenethylamines LVI-LIX. Benzylmagnesium chloride was prepared from 0.2 mole of magnesium sand and 0.2 mole of benzylchloride in 200 ml. of ether. One-tenth of a mole of the Schiff base to be reacted was slowly added, with stirring, to the ethereal solution of benzylmagnesium chloride and refluxing of the ether usually occurred. Being only slightly soluble in ether p-methoxybenzylidene-p-anisidine (VII) reacted only very slowly over 1/2 hr.

In all cases the reaction mixture was stirred for 1/2 to 1 hr. after addition of the Schiff base. Hydrolysis was effected by very cautiously adding 200 ml. of an aq. 20% NH_4Cl solution with rapid stirring. See Isolation and Purification Procedures.

Isolation and Purification of N,1-Disubstituted-2-phenethylamines LVI - LIX, Table VI.

LVI. The ether layer was dried over Na_2SO_4, the ether removed in vacuo and the residue vacuum distilled to give toluene and a yellow oil (59%), b.p. 177-181°/0.1 mm.

Analysis: for $C_{21}H_{21}NO$. Calcd.: C, 83.13; H, 6.98; N, 4.62.
Found: C, 82.75; H, 7.02; N, 5.07.

LVII. The product slowly precipitated from the ether layer and was collected in 79.5% yield. One recrystallization from i-propanol gave pure white product (67.5%).

Analysis: for $C_{22}H_{23}NO_2$. Calcd.: C, 79.25; H, 6.95; N, 4.20.
Found: C, 79.30; H, 6.97; N, 4.10.
N, 4.12.

LVIII. The ether layer was dried over Na_2SO_4 and the ether evaporated to give a nearly clear, very viscous yellow oil. Distillation on a Wood's metal bath gave a light orange oil, b.p.195-205°/0.1 mm.

Analysis: for $C_{26}H_{31}N_2Cl$ O. Calcd.: C,73.82; H,7.39; N,6.63;Cl,8.38.
Found: C,73.40; H,7.51; N,6.54;Cl,8.48.

LIX. The ether layer was dried over Na_2SO_4 and the ether evaporated in vacuo. The viscous, orange residue solidified to a tan, crystalline solid (94%), m.p. 70-72°. Recrystallization from a minimum of 60-70° pet. ether gave a 63.8% recovery of light tan plates (60%).

Analysis: for $C_{25}H_{31}N_3O$. Calcd.: C, 77.08; H, 8.02; N, 10.79.
Found: C, 77.20; H, 8.04; N, 10.71.

Alternate Synthesis of Compound LVI.

This is the method of Billman and Tai (45). To 2.6 g. (0.0067 mole) of lithium aluminum hydride in 100 ml. of ether was added 4.03 g. (0.0133 mole) of deoxybenzoin-p-methoxyanil (XIX). The reaction mixture was refluxed for 30 minutes and then the lithium salts were cautiously hydrolyzed with ice water. The inorganic salts were filtered off, the ether layer separated and dried over $NaSO_4$ and the ether evaporated in vacuo. The residue was vacuum distilled to give 3.6 g. (90%) of yellow oil, b.p. 177-181°/0.1 mm.

Analysis: for $C_{21}H_{21}NO$. Calcd.: C, 83.13; H, 6.98; N, 4.62.
Found: C, 82.98; H, 6.82; N, 5.08.

APPENDIX

Ultraviolet and Visible Spectra

The absorption spectra which appear on the following pages were obtained using a Bausch and Lomb Spectronic 505 spectrophotometer for both the ultraviolet and visible regions. The original spectra were in terms of absorbance vs. $\lambda(m\mu)$. For purposes of comparison the absorbance values were converted to molar extinction coefficients as follows:

$$\text{Absorbance} = \epsilon\, C\, 1, \text{ where}$$

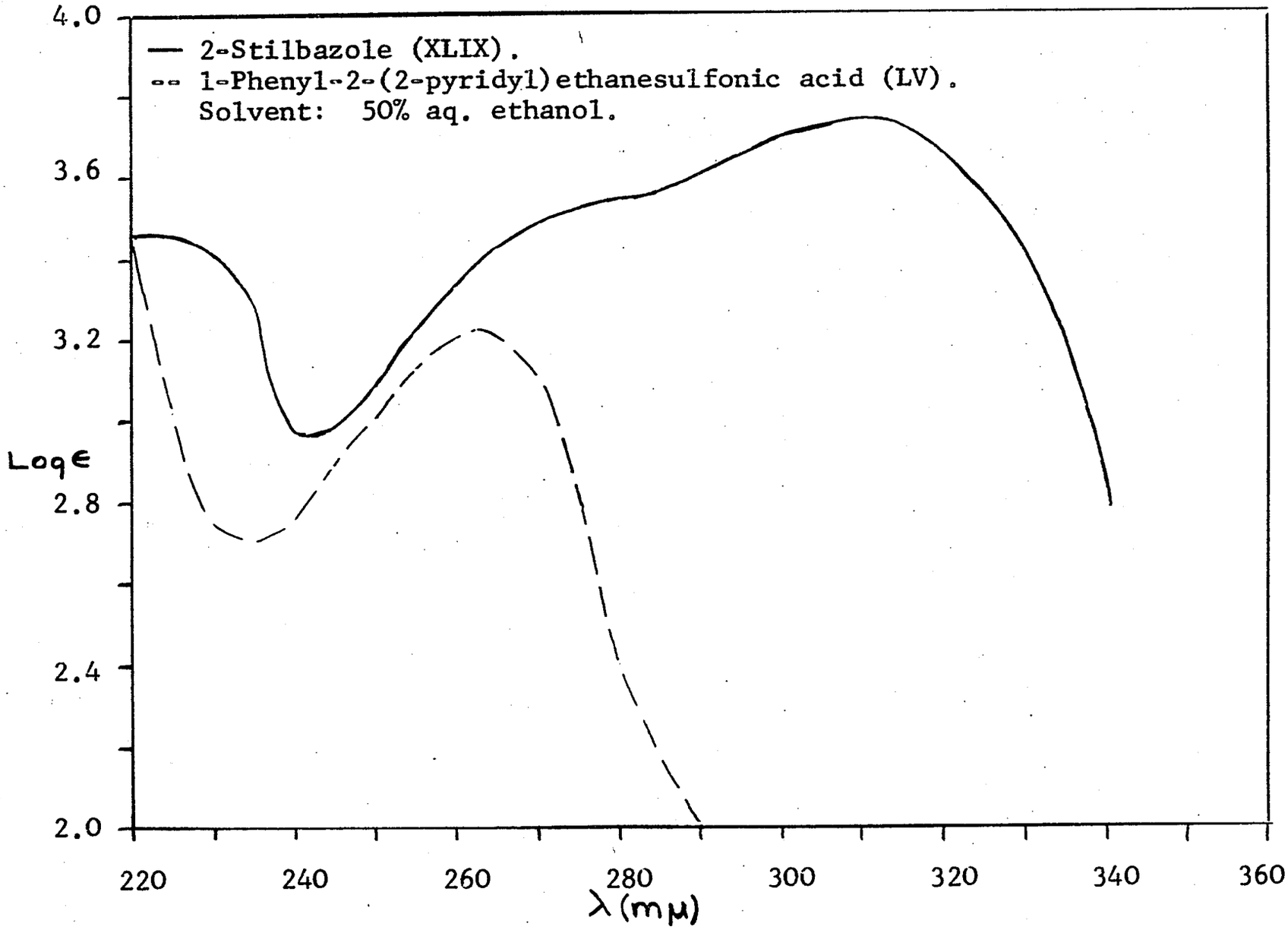
ϵ = molar extinction coefficient

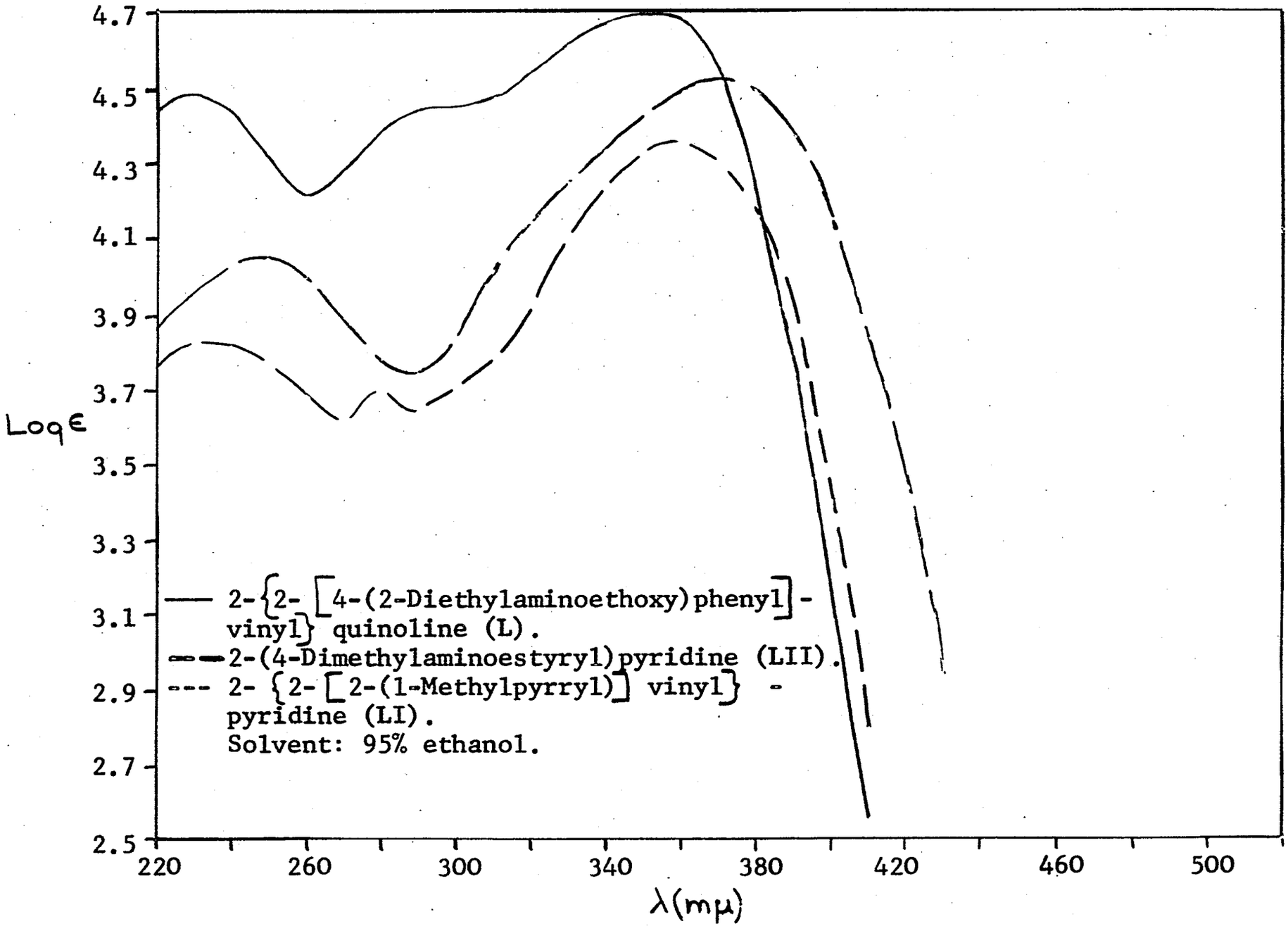
C = molar concentration

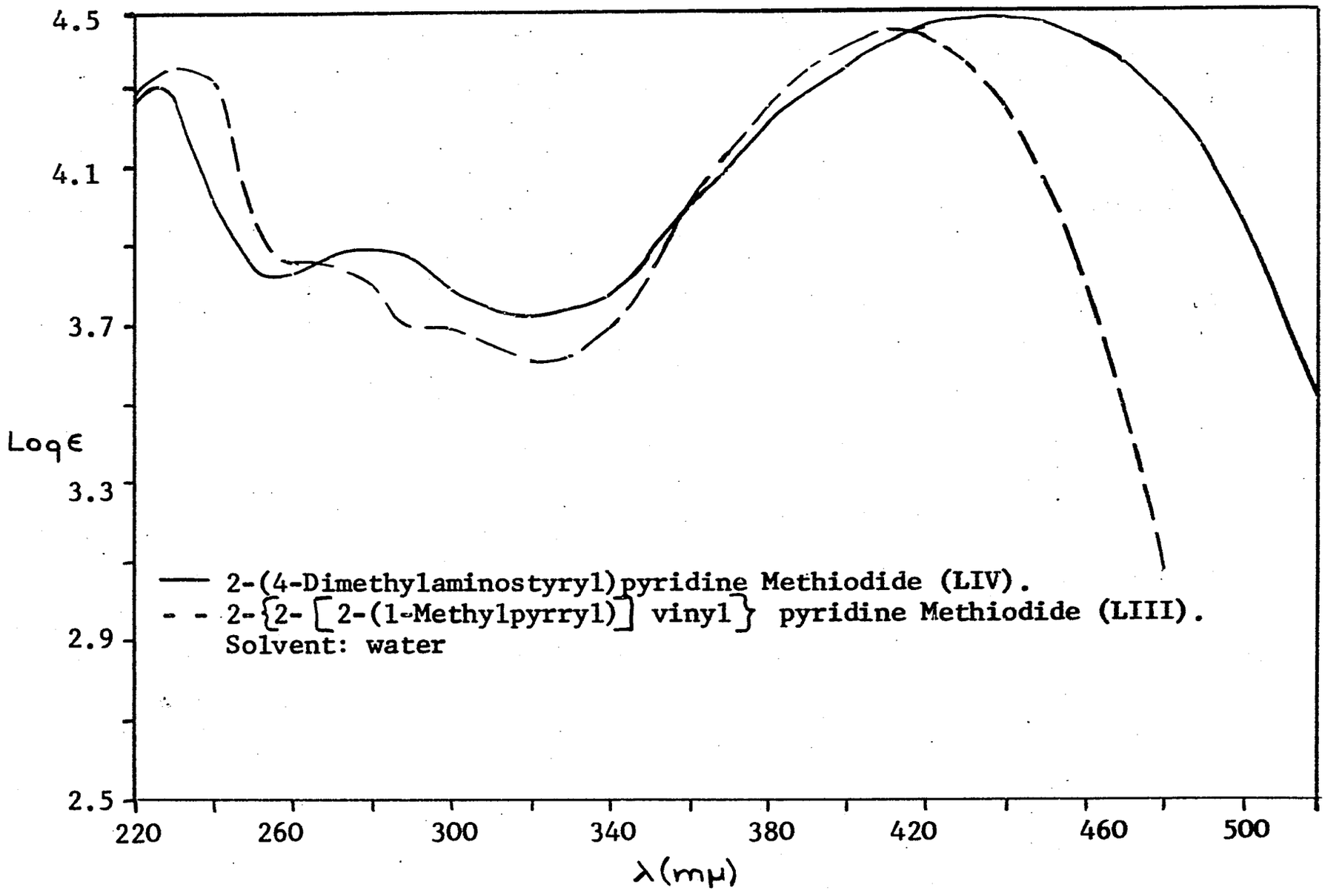
1 = cell length in centimeters

$$\therefore \epsilon = \frac{\text{absorbance}}{C \times 1}$$

The spectra were then plotted in terms of $\log \epsilon$ vs. $\lambda(m\mu)$.







Tabulation of Representative Infrared Spectra*

The infrared spectra were run on a Perkin-Elmer 21 infrared spectrophotometer at Lehigh University or kindly supplied by the Wm. S. Merrell Co., Cincinnati, Ohio. In each case, the source of the spectrum is noted following the name of the compound. The author has arbitarily chosen the spectra of those compounds which he feels are likely to be most important pharmacologically and which are representative of the series.

*Note: vs - very strong; s - strong; m - medium; w - weak.

N,2-Diphenyl-1-(2-piperidyl)isopropylamine (XXX1). Merrell (KBr plate).

Wavelength (microns)	Wavelength (microns)	Wavelength (microns)
2.95 (m)	7.64 (s)	10.08 (w)
3.12 (s)	7.76 (s)	10.35 (m)
3.33 (m)	7.94 (m)	10.58 (w)
3.45 (s)	8.21 (s)	11.05 (s)
6.25 (vs)	8.50 (m)	11.46 (m)
6.53 (s)	8.69 (m)	11.67 (w)
6.68 (vs)	8.87 (m)	11.87 (m)
6.87 (m)	8.98 (m)	12.16 (w)
6.95 (s)	9.16 (m)	12.32 (w)
7.05 (m)	9.27 (w)	12.85 (s)
7.30 (m)	9.38 (m)	13.20 (vs)
7.37 (w)	9.51 (m)	13.67 (w)
7.48 (m)	9.78 (m)	14.35 (vs)

N-(4-Chlorophenyl)-1-[4-(2-diethylaminoethoxy)phenyl]-2-(2-pyridyl)-ethylamine (XXXVIII). Merrell (KBr plate).

Wavelength (microns)	Wavelength (microns)	Wavelength (microns)
3.02 (m)	7.16 (m)	9.04 (m)
3.38 (m)	7.25 (m)	9.22 (m)
3.43 (m)	7.60 (s)	9.41 (m)
3.57 (m)	7.69 (s)	9.78 (s)
6.25 (s)	7.73 (m)	10.05 (m)
6.37 (m)	7.93 (s)	11.47 (w)
6.63 (vs)	8.08 (s)	12.10 (s)
6.79 (s)	8.35 (m)	12.43 (s)
6.97 (m)	8.54 (s)	13.24 (s)
7.02 (m)	8.73 (m)	13.77 (m)
	8.92 (w)	14.27 (w)
		14.86 (m)

9-Anilino-9-(2-pyridylmethyl)fluorene (XLVI). Merrell (KBr plate).

Wavelength (microns)	Wavelength (microns)	Wavelength (microns)
2.97 (s)	8.50 (m)	12.78 (s)
3.35 (s)	8.66 (m)	13.38 (vs)
6.26 (vs)	8.77 (m)	13.65 (vs)
6.38 (m)	8.97 (w)	14.49 (s)
6.63 (vs)	9.10 (w)	15.17 (m)
6.82 (s)	9.33 (m)	
6.93 (s)	9.55 (w)	
6.98 (s)	9.74 (w)	
7.04 (s)	10.09 (m)	
7.48 (m)	10.40 (w)	
7.61 (s)	10.60 (w)	
7.79 (s)	11.05 (w)	
8.12 (w)	11.22 (w)	
8.27 (w)	11.55 (w)	
	12.35 (w)	

9-Anilino-9-(2-pyridylmethyl)xanthene (XLVII). Merrell (KBr plate).

Wavelength (microns)		Wavelength (microns)		Wavelength (microns)	
3.01	(s)	8.10	(s)	11.25	(w)
3.33	(m)	8.35	(m)	11.43	(m)
6.26	(vs)	8.50	(m)	11.66	(w)
6.37	(s)	8.73	(m)	12.16	(w)
6.58	(s)	8.88	(w)	12.90	(m)
6.70	(s)	9.15	(s)	13.21	(vs)
6.80	(vs)	9.23	(m)	14.38	(s)
6.92	(vs)	9.37	(m)	15.05	(m)
7.05	(s)	9.53	(w)		
7.58	(s)	9.65	(m)		
7.63	(s)	10.08	(m)		
7.72	(s)	10.52	(w)		
7.85	(vs)	10.61	(w)		
8.02	(s)	11.02	(w)		

N-(4-Anisyl)-1,2-diphenethylamine (LVI). Lehigh (CCl_4).

Wavelength (microns)		Wavelength (microns)	
2.94	(w)	7.11	(m)
3.31	(m)	7.40	(m)
3.43	(m)	7.73	(s)
3.53	(m)	8.08	(vs)
4.31	(w)	8.48	(s)
5.15	(w)	8.97	(m)
5.35	(w)	9.15	(m)
5.53	(w)	9.23	(m)
6.22	(m)	9.38	(s)
6.62	(vs)	9.60	(vs)
6.83	(s)	9.72	(s)
6.88	(s)	11.00	(w)
6.93	(s)	14.32	(vs)

N-(4-Chlorophenyl)-1-[4-(2-diethylaminoethoxy)phenyl]-2-phenethylamine (LVIII). Merrell (KBr plate).

Wavelength (microns)	Wavelength (microns)	Wavelength (microns)
2.93 (w)	7.17 (m)	9.72 (s)
3.32 (w)	7.25 (m)	9.92 (m)
3.38 (s)	7.31 (m)	10.25 (w)
3.50 (m)	7.43 (m)	11.30 (w)
3.57 (m)	7.65 (s)	12.30 (s)
6.24 (vs)	7.71 (s)	13.25 (m)
6.35 (m)	8.05 (vs)	13.55 (m)
6.63 (vs)	8.33 (m)	14.33 (s)
6.69 (vs)	8.42 (m)	14.75 (m)
6.88 (m)	8.63 (s)	15.03 (m)
7.05 (m)	9.23 (s)	

N-(2-Pyridyl)-1-[4-(2-diethylaminoethoxy)phenyl]-2-phenethylamine (LIX). Merrell (KBr plate).

Wavelength (microns)	Wavelength (microns)	Wavelength (microns)
2.93 (w)	6.98 (vs)	9.51 (m)
3.12 (s)	7.06 (m)	9.73 (s)
3.32 (m)	7.25 (m)	9.91 (m)
3.39 (s)	7.32 (m)	10.15 (m)
3.51 (m)	7.48 (s)	10.56 (w)
3.58 (m)	7.58 (s)	11.07 (w)
5.16 (w)	7.73 (s)	11.48 (w)
5.33 (w)	7.81 (s)	12.12 (s)
5.55 (w)	8.06 (vs)	12.40 (m)
6.25 (vs)	8.31 (m)	12.92 (s)
6.33 (vs)	8.55 (s)	13.18 (s)
6.54 (vs)	8.72 (m)	13.64 (m)
6.63 (vs)	8.90 (m)	13.82 (m)
6.70 (m)	9.06 (m)	14.40 (vs)
6.90 (vs)	9.26 (s)	

BIBLIOGRAPHY

1. R. B. Moffett and W. M. Hoehn, J. Am. Chem. Soc., 69, 1792 (1947).

2. "Organic Synthesis" , Vol. 34, John Wiley and Sons, Inc., New York, 1954, p. 64.

3. K. N. Campbell, C. H. Helbing, M. P. Florkowski and B. K. Campbell, J. Am. Chem. Soc., 70, 3868 (1948).

4. F. J. Villiani, M. S. King and D. Papa, J. Am. Chem. Soc., 73, 5916 (1951).

5. I. A. Kaye and C. L. Parris, J. Am. Chem. Soc., 74, 1566 (1952).

6. K. Hayes, G. Gever and J. Orcutt, J. Am. Chem. Soc., 72, 1205 (1950).

7. B. M. Mikhailov and K. N, Kurdyumova, Zhur. Obshchei Khim., 26, 786 (1956); C. A., 50, 1465i (1956).

8. H. Gilman and R. H. Kirby, J. Am. Chem. Soc., 55, 1265 (1933).

9. H. Gilman, R. H. Kirby, M. Lichtenwalter and R. V. Young, Rec. trav. chim., 55, 79 (1936).

10. H. Gilman and R. H. Kirby, J. Am. Chem. Soc., 63, 2046 (1941).

11. H. Gilman, J. E. Kirby and C. R. Kinney, J. Am. Chem. Soc., 51, 2252 (1929).

12. H. Gilman and M. Speeter, J. Am. Chem. Soc., 65, 2255 (1943).

13. A. Schönberg and W. Asker, J. Chem. Soc., 725 (1942).

14. H. H. Keashing and F. W. Schueler, J. Am. Pharm. Assoc., 39, 87 (1950).

15. J. S. Dave and M. J. S. Dewar, J. Chem. Soc., 4616 (1954).

16. M. Katayanagi, J. Pharm. Soc. Japan, 68, 232, (1948); C. A., 48, 4546a (1954).

17. I. S. Gupta, H. Kaur and Vasudev, J. Indian Chem. Soc., 34, 528 (1957).

18. P. M. Maginnity and J. L. Eisenmann, J. Am. Chem. Soc., 74, 6119 (1955).

19. "Organic Syntheses", Coll. Vol. I, John Wiley and Sons, Inc., New York, 1941, p. 80.

20. R. E. Juday and H. Adkins, J. Am. Chem. Soc., 77, 4559 (1955).

21. J. Rombaut and G. Smets, Bull. soc. chim. Belges, 58, 421 (1949); C. A., 45, 569 d (1951).

22. A. R. Surrey, J. Am. Chem. Soc., 71, 3105 (1949).

23. A. Kirpal and E. Reiter, Chem. Ber., 60, 666 (1927).

24. G. Reddelien, Chem. Ber., 43, 2476 (1910).

25. G. Reddelien, Chem. Ber., 42, 4759 (1909).

26. A. Schönberg and W. Urban, J. Chem. Soc., 530 (1935).

27. A. Schönberg and W. Asker, J. Chem. Soc., 609 (1946).

28. C. H. Tilford and M. G. VanCampen, Jr., J. Am. Chem. Soc., 76, 2431 (1954).

29. R. G. Jones, J. Am. Chem. Soc., 69, 2346 (1947).

30. H. Gilman and J. A. Beel, J. Am. Chem. Soc., 71, 2328 (1949).

31. (a) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Company, New York, New York, 1959, p. 478; (b)p.393.

32. E. R. Alexander, "Ionic Organic Reactions," John Wiley and Sons, Inc., New York, New York, 1950, p. 105.

33. (a) L. F. Fieser and M. Fieser, "Organic Chemistry," Reinhold Publishing Corporation, New York, New York, 1956, p. 597; (b) p. 800.

34. E. D. Parker and A. Furst, J. Org. Chem., 23, 201 (1958).

35. A. P. Phillips, J. Org. Chem.,12, 333 (1947).

36. W. E. Doering and R. A. N. Weil, J. Am. Chem. Soc., 69, 2463 (1947).

37. H.E. Reich and R. Levine, J. Am. Chem. Soc., 77, 4913 (1955).

38. H. E. Reich and R. Levine, J. Am. Chem. Soc., 77,5434 (1955).

39. M. Tiffeneau and Delange, Compt. rend., 137, 573 (1903); J. Chem. Soc., 86, I, 48 (1904).

40. M. S. Newman, J. Am. Chem. Soc., 62, 2295 (1940).

41. S. Siegel, W. M. Moyer and R. R. Jay, J. Am. Chem. Soc., 73, 3237 (1951).

42. P. R. Austin, S. Coburn and D. Levering, J. Am. Chem.Soc., 73, 3163 (1951).

43. I. Heilbron, "Dictionary of Organic Compounds," Oxford University Press, New York, New York, 1953, p. 184.

44. B. D. Shaw and E. A. Wagstaff, J. Chem. Soc., 77 (1933).

45. J. H. Billman and K. M. Tai, J. Org. Chem., 23, 535 (1958).

VITA

The author, son of John and Elsie Shuman, was born in Williamsport, Pennsylvania, on April 28, 1935. In Williamsport he attended Samuel Transeau Elementary School and Thaddeus Stevens Junior High School where he was editor of the school magazine. In September 1950 his family moved to Allentown, Pennsylvania, where he attended Allentown High School. He graduated from Allentown High School in June 1953.

In September 1953 he entered Dickinson College, Carlisle, Pennsylvania as a chemistry major with a minor in biology. While at Dickinson College he participated in the following activities: Alpha Chi Rho Fraternity, Steward, Executive Committee, Song-leader, and Pledge master; Tennis (four letters); D Club (athletic club); Squash; and College Choir. He graduated from Dickinson in June 1957 with the degree of Bachelor of Science in Chemistry.

In September 1957 he entered the graduate school of chemistry at Lehigh University. All his research was done under the supervision of Dr. E. D. Amstutz. In September 1958 the author was appointed to the National Lead Fellowship which expired in January 1959.

In February 1959 the author was appointed to the William S. Merrell Research Assistantship under the supervision of Dr. E. D. Amstutz to begin work for the degree of Doctor of Philosophy.

This thesis is the result of that research.

On June 8, 1957 the author was married to the former Judith Ann Pinkerton of Pottstown, Pennsylvania. She is a 1957 graduate of Dickinson College, Phi Beta Kappa. The author has a daughter, Dawn Elizabeth, born September 2, 1958.