

AN ABSTRACT OF THE THESIS OF

KALMAN ROBERT KALLAY for the MASTER OF SCIENCE  
(Name of student) (Degree)

in Pharmaceutical Chemistry presented on May 28, 1971  
(Major) (Date)

Title: A MEDICINAL CHEMICAL INVESTIGATION OF SOME  
p-SUBSTITUTED-1, 2-DIPHENYLINDOLIZINES FOR  
POSSIBLE ANTI-INFLAMMATORY ACTIVITY

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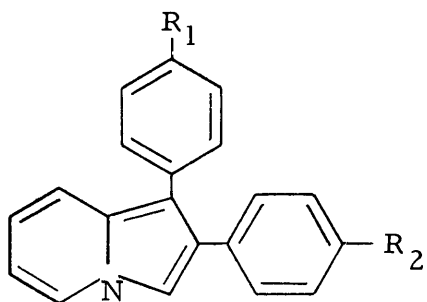
Abstract approved: \_\_\_\_\_  
Robert F. Doerge ✓

The literature contains only a few isolated reports concerning the investigation of indolizines for potential medicinal activity. In an effort to add to knowledge in this field, a series of new p-substituted-1, 2-diphenylindolizines was prepared. They were specifically designed to be investigated as potential anti-inflammatory agents for several reasons. 1, 2-Bis(p-methoxyphenyl)indole and N-(p-chlorobenzoyl)-2, 3-bis(p-methoxyphenyl)-5-methoxyindole have anti-inflammatory activity and are structurally related to the indolizines prepared. Also, 3-benzoyl-2-methoxyindolizine-1-acetic acid and other indolizine-1-acetic acids have anti-inflammatory activity and are structurally related to the potent anti-inflammatory drug indomethacin, 1-(p-chlorobenzoyl)-2-methyl-3-acetyl-5-methoxyindole. In addition, compounds of diverse structure have shown

anti-inflammatory activity. The approach to the design of these agents was necessarily empirical, due to the limited study of the pharmacological properties of indolizines and due to the limited knowledge about the cause and biochemical nature of inflammatory processes.

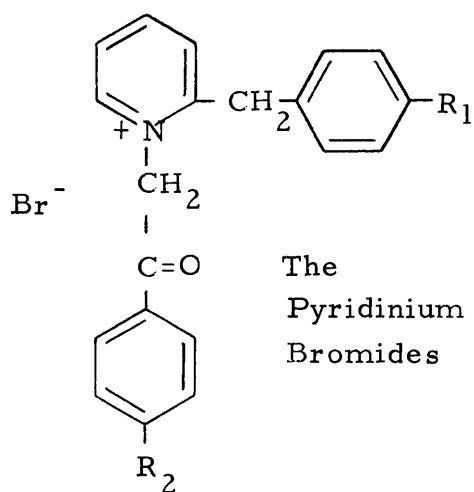
The indolizines were prepared by means of the Chichibabin synthesis. The pyridinium bromides were prepared from properly substituted 2-benzylpyridines and properly substituted phenacyl bromides. Pyridine was used to cyclize the pyridinium salt in most cases. It was necessary to prepare the p-substituted-2-benzylpyridines from 2-bromopyridine and p-substituted benzaldehydes. This was accomplished by first forming the reactive 2-pyridyllithium (via halogen-metal interconversion between n-butyllithium and 2-bromopyridine), which then was reacted with the aldehydes, yielding phenyl-2-pyridylcarbinols. These were then converted to phenyl-2-pyridylchloromethanes using thionyl chloride in benzene. This was followed by reductive dechlorination with zinc and acetic acid to give the corresponding 2-benzylpyridines. 2-(p-Methoxybenzyl)pyridine, 2-(p-chlorobenzyl)pyridine, and 2-(p-isopropylbenzyl)pyridine were prepared.

The new compounds synthesized in this investigation are illustrated on the following page.



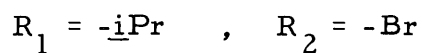
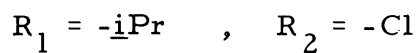
The Indolizines

$R_1$	$R_2$
$-\text{OCH}_3$	$-\text{H}$
$-\text{OCH}_3$	$-\text{CH}_3$
$-\text{OCH}_3$	$-\text{Br}$
$-\text{OCH}_3$	$-\text{Cl}$
$-\text{Cl}$	$-\text{CH}_3$
$-\text{Cl}$	$-\text{Cl}$
$-\text{iPr}$	$-\text{OCH}_3$
$-\text{H}$	$-\text{CH}_3$



The  
Pyridinium  
Bromides

In addition to these compounds, three additional pyridinium bromides were prepared:



A Medicinal Chemical Investigation of Some  
p-Substituted-1, 2-Diphenylindolizines for  
Possible Anti-inflammatory Activity

by

Kalman Robert Kallay

A THESIS

submitted to

Oregon State University

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the requirements for the  
degree of

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June 1972

APPROVED:

*Redacted for Privacy*

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Professor of Pharmaceutical Chemistry  
in charge of major

*Redacted for Privacy*

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Head of Department of Pharmaceutical Chemistry

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Dean of Graduate School

Date thesis is presented May 28, 1971

Typed by Opal Grossnicklaus for Kalman Robert Kallay

## PREFACE

Any venture that a man pursues of his own accord, knowing full-well that it will cost him time, money, and perhaps his sense of humor, must certainly have some strange philosophical basis. Burger (21, p. 1) has explained this phenomenon very aptly in regard to the medicinal chemist:

Investigations in medicinal chemistry, as in all science, are undertaken as an adventure of the human spirit, essentially an artistic enterprise, stimulated largely by curiosity and served by disciplined imagination. Moreover, most medicinal scientists do their work for the fun of it, in spite of the uncertainty of the outcome of their experiments.

This thesis, as any other, must strongly exemplify such motivations.

## ACKNOWLEDGMENTS

I wish to thank Dr. Robert F. Doerge for suggesting this study and for his guidance in my research and the preparation of this thesis.

Also, I wish to express my appreciation to Dr. John Block for his help in securing and interpreting n.m.r. spectra. I further wish to thank Dr. James W. Wilson, Assistant Director of Chemistry, Smith, Kline, and French Laboratories, for providing the anti-arthritic test results presented in this thesis.

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A. MEDICINAL CHEMICAL INVESTIGATION OF SOME  
p-SUBSTITUTED-1, 2-DIPHENYLINDOLIZINES FOR  
POSSIBLE ANTI-INFLAMMATORY ACTIVITY

INTRODUCTION

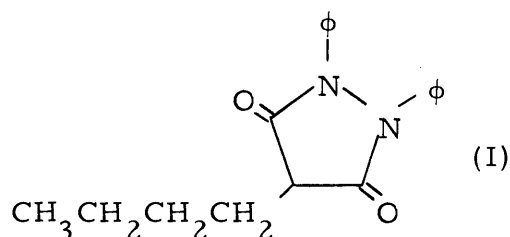
Purpose of the Investigation

As with any study in medicinal chemistry, the main goal of this investigation was to prepare potentially useful new drugs. The indolizine nucleus was considered for possible medicinal activity, and several p-substituted-1, 2-diphenylindolizines were synthesized as potential anti-inflammatory agents.

Anti-inflammatory drugs are very useful medicinal agents and are widely used in conditions as diverse as heart transplants and hayfever. Some of the most effective anti-inflammatory agents available today are steroids (13, p. 140 and 478; 50, p. 1355 and 1453). Unfortunately, steroids may cause a wide variety of undesirable side effects, such as adrenal atrophy, hypokalemic alkalosis, glycosuria, increased susceptibility to infection, peptic ulceration, myopathy, psychoses, seizures, osteoporosis, and hypercoagulability of the blood (47, p. 1642-1643). Also, salt retention, lipid mobilization, and sexual changes may result. These adverse reactions can severely restrict the usefulness of corticosteroids, especially in long-term therapy. Some chemical modifications of active steroids have

decreased or eliminated some of the serious side effects (e.g. mineralocorticoid activity).

In an attempt to find highly active anti-inflammatory agents with fewer adverse effects, major attention has been focused on non-steroid compounds. Some of the "non-steroid anti-inflammatory agents" currently available are phenylbutazone<sup>1</sup> (I), 4-butyl-1, 2-diphenyl-3, 5-pyrazolidinedione, and indomethacin<sup>2</sup> (II), 1-(p-chloro-benzoyl)-2-methyl-3-acetyl-5-methoxyindole. However, these drugs are far from perfect, since they also have rather severe potential side effects.



It has been noted that several indoles and some related indolizines have anti-inflammatory activity. Indoxol (44, 95, 117), 2, 3-bis(p-methoxyphenyl)indole (III), is 18 times as effective as phenylbutazone in the carrageenin edema test in the hind leg of rats (98). A derivative of Indoxol related to indomethacin is N-(p-chloro-benzoyl)-2, 3-bis(p-methoxyphenyl)-5-methoxyindole (IV). This compound has recently been shown to have anti-inflammatory, anti-pyretic, and analgesic activity (116). Analgesic and

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<sup>1</sup>Butazolidin<sup>R</sup> (Geigy Pharmaceuticals)

<sup>2</sup>Indocin<sup>R</sup> (Merck, Sharp and Dohme)

anti-inflammatory properties have been claimed for several indolizine-1-acetic acids related to indomethacin. Among these was 3-benzoyl-2-methylindolizine-1-acetic acid (V) (79). A related compound, 1-indolizinealanine, has been considered a possible tryptophan antimetabolite (25, 69). Since abnormal tryptophan metabolites have been implicated in arthritis (78), indolizine-1-acetic acids may exert their activity by interfering with the formation of such metabolites.

On examining the arrangement of the structures of the above mentioned compounds, as shown in Figure 1, one may note some rather striking similarities between the active<sup>3</sup> compounds shown. The center compound (IV) is an active indole and has functional groups present in both indomethacin (II) and Indoxol (III). The indolizine (V), which possesses functional groups only similar to indomethacin, is also active. This suggests that the change to a bridgehead nitrogen here (i. e. indole to indolizine) may not have destroyed the spacial constitution of the molecule which is needed for anti-inflammatory action. It is therefore also possible that this change in the position of the ring nitrogen in the Indoxol molecule will not destroy its anti-inflammatory activity either. The p-substituted-1, 2-diphenyl-indolizines (VI) were prepared in the hope the analogy would hold.

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<sup>3</sup>The word "active" in this context refers to anti-inflammatory usefulness.

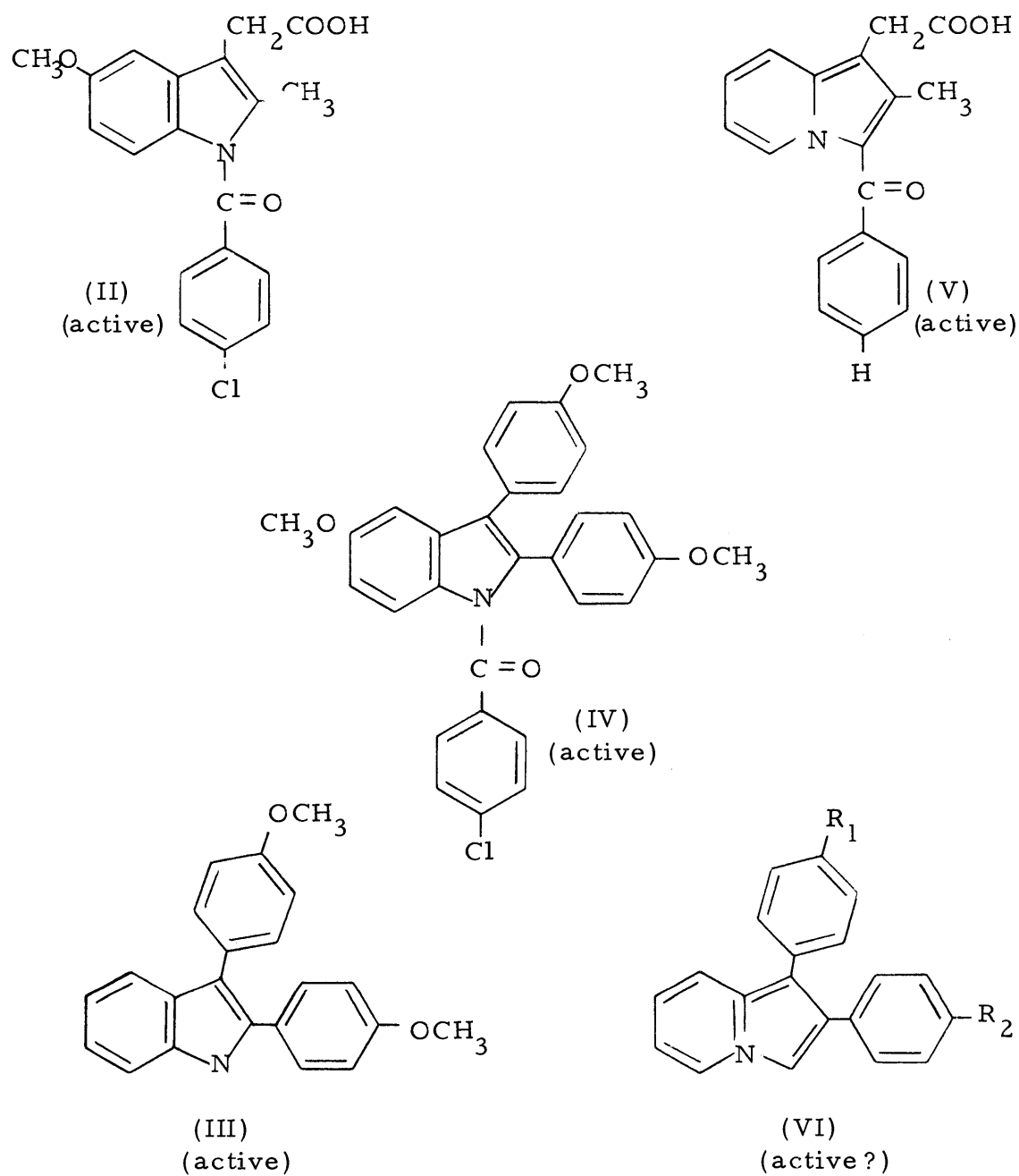


Figure 1. Structural Comparison Among Anti-inflammatory Indoles and Indolizines



One must also be aware of the diversity of chemical structures encompassed by the anti-inflammatory drugs (17). Therefore, any new, even vaguely related chemical entity may be potentially useful.

### A Discussion of Inflammation

#### The Nature of the Local Inflammatory Process

Even though little is known about the etiology of inflammatory diseases, the general nature of the local inflammatory process has been determined. Whitehouse (107), in his extremely broad review of anti-inflammatory drugs, has considered inflammation in three phases. These are increased vascular permeability, leucocyte infiltration, and tissue repair.

Increased vascular permeability allows plasma proteins to "leak out" of capillaries into the tissues, decreasing the osmotic pressure of the blood. This results in tissue edema. Initiation of permeability changes is via factors released as a result of local tissue injury. These include histamine, serotonin (enteramine), leucotaxin, bradykinin, and an "uncharacterized globulin factor." The release of kinins is probably largely mediated by proteolytic enzymes from ruptured lysosomes and perhaps by epinephrine (114, p. 144). After injury occurs, fibrin is deposited on vascular walls. This is probably a result of exogenous thromboplastic factors in the

injured area. Leucocytes adhere to the fibrinated vascular walls, increasing their concentration in the surrounding tissue by migrating through the capillary walls. Fibrinogen, which has likewise passed through the vascular wall, is converted to fibrin via clotting factors in the tissue. This sequence of events seals off the inflamed area and sets the stage for phase two.

Phagocytosis of bacteria and/or particulate matter by leucocytes occurs next. Granulocytes are active initially, followed by monocytes. Macrophages, normally present in connective tissue, are also present. The function of leucocytes is dependent on the calcium ion concentration, and some poorly defined substances called chemotaxins, opsonins, and leucocyte-promoting factors.

The third phase of inflammation is important, for it is here that many of the pathologic changes in the inflammatory disease states occur, e.g. formation of granulation tissue. Tissue repair is dependent on many factors. The fibroblast is active in the synthesis of new tissue matrix, e.g. collagen fibers and acidic mucopolysaccharides. The destroyed vasculature is repaired. This tissue regeneration is stimulated by "local hormones" such as epinephrine and the mast cell components, histamine, heparin, and serotonin. Prostaglandins may be important in the release of bioactive compounds from mast cells (37, p. 139-140). Exogenous endocrine factors, precursors, and nutrients are obviously important for tissue

repair, especially glutamine for the biosynthesis of aminopolysaccharides. The energy for repair comes largely from fibroblast metabolism.

It must be emphasized that inflammation is an extremely complex process. The exact functions and mechanisms of the factors involved are not completely understood.

### Diseases Requiring Anti-inflammatory Therapy

There is a large number of diseases that require therapy to reduce inflammation. These may be simple, acute conditions such as mononucleosis, contact dermatitis, and herpes zoster; or they may be relatively complicated diseases. This latter category encompasses a wide range of disorders and is most important in regard to long-term therapy with anti-inflammatory drugs. Examples of such diseases are systemic lupus erythematosus, severe or chronic bronchial asthma, and, most important, rheumatoid arthritis.

Systemic lupus erythematosus (50, p. 1369-1374; 71, p. 1436-1438) is an autoimmune disease of unknown etiology. Any part of the body may be affected. The pathology involves the presence of abnormal antibodies which immunologically react with the various organs, blood elements, and nucleic acids and their conjugates. Symptomology may vary greatly. Occasionally the disease is terminal within a few weeks. Drug treatment generally includes

salicylates, adrenocortical steroids, and antibiotics when needed.

Bronchial asthma (50, p. 1451-1453; 71, p. 10-18) is an allergic disorder due to any of many possible allergens. Many forms of the disease are seasonal and mild; however, severe paroxysmal attacks occur chronically in some sufferers. The main symptom of bronchial asthma is difficulty in breathing. The symptoms may be mediated by histamine, acetylcholine, serotonin, bradykinin, and/or slow-reacting-substance. Treatment includes maintenance therapy with adrenocortical steroids. Acute attacks may be treated with epinephrine, theophylline, and/or ephedrine.

Rheumatoid arthritis (50, p. 1352-1357; 71, p. 948-958) is a systemic disease affecting the musculoskeletal system. The etiology is obscure even to the point where it is not truly known whether the inflammatory manifestations are the result or the cause of the disorder. Drug treatment includes the use of salicylates, soluble gold compounds, phenylbutazone, chloroquin, indomethacin, and adrenocortical steroids. There are certain biochemical differences between normal and rheumatic persons (107, p. 399-412). Aminoacids, dietary factors, mucoproteins, mucopolysaccharides, hydrolytic enzymes, inorganic sulfate, and rheumatoid factor are involved.

Tyrosine and tryptophan metabolites are found in higher concentrations in the urine of rheumatic patients. It is interesting to note that some highly lipophilic compounds, indole included (78),

have arthritogenic properties (87). Whether the unspecified indoles produced in tryptophan metabolism are present in high enough concentrations in arthritis to cause symptoms is open to conjecture. Arthritic patients generally have low blood pantothenic acid levels and develop megaloblastic anemia more easily than normal subjects. However, these problems can be solved with extra pantothenic acid and vitamin B<sub>12</sub> administration. As might be expected, the blood levels of mucoproteins, e.g. fibrinogen, and hydrolytic enzymes, e.g. proteases, and acid phosphatase (92), are increased in rheumatoid arthritis. Corticometric steroids may prevent the release of proteases and other hydrolytic enzymes by stabilization of lysosomal membranes. Hyaluronidase-like enzymes are also present in elevated amounts, thus causing increased mucopolysaccharide destruction leading to joint damage and less viscid synovial fluid. The rheumatoid factor (R.F.; Rose-Waaler Factor) is an abnormal 19S globulin which is found in the serum of most arthritic patients and some normal individuals. It unites with a normal human 7S gamma-globulin in plasma cells. Rheumatoid factor is not a pathological agent, and its significance is unknown.

## THE ANTI-INFLAMMATORY SUBSTANCES

### Chemical Classification

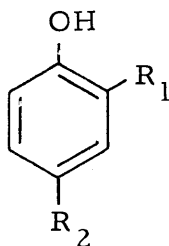
#### Steroids

This class of anti-inflammatory drugs includes the natural corticometric steroids, e. g. hydrocortisone, and a group of modified steroids with enhanced activity and/or less adverse reactions. Table 1 lists some anti-inflammatory steroids commonly used in medical practice.

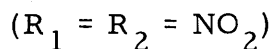
#### Non-steroids

The non-steroid anti-inflammatory agents are made up of extremely diverse chemical types. Some of these are outlined below.<sup>4</sup>

##### I. Phenols



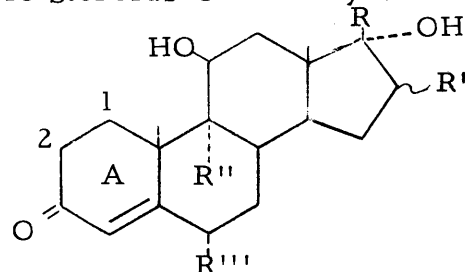
##### A. 2, 4-Dinitrophenol




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<sup>4</sup>The format of this outline, from part I through part VI, was adapted from Whitehouse (107). Winter (114, p. 180) has also presented a chemical classification of anti-inflammatory substances.

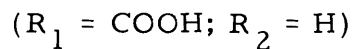
Table 1. Corticometric Steroids Commonly Used in Medical Practice



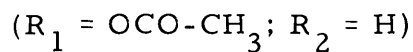
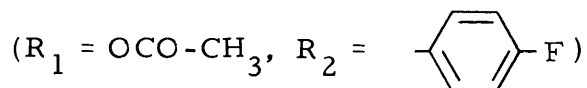
Compound	R	R'	R''	R'''	Ring A unsaturation
Hydrocortisone	C(O)-CH <sub>2</sub> -OH	H	H	H	none
Prednisolone	C(O)-CH <sub>2</sub> -OH	H	H	H	1-2
Methylprednisolone	C(O)-CH <sub>2</sub> -OH	H	H	CH <sub>3</sub>	1-2
Fluprednisolone	C(O)-CH <sub>2</sub> -OH	H	H	F	1-2
Fluorometholone	C(O)-CH <sub>3</sub>	H	F	CH <sub>3</sub>	1-2
Dexamethazone	C(O)-CH <sub>2</sub> -OH	CH <sub>3</sub> (α)	F	H	1-2
Paramethazone Acetate	C(O)-CH <sub>2</sub> -OC(O)CH <sub>3</sub>	CH <sub>3</sub> (α)	H	F	1-2
Betamethazone	C(O)-CH <sub>2</sub> -OH	CH <sub>3</sub> (β)	F	H	1-2
Triamcinolone	C(O)-CH <sub>2</sub> -OH	OH(α)	F	H	1-2
Fluocinolone	C(O)-CH <sub>2</sub> -OH	OH(α)	F	F	1-2

Products from this table were selected from Wilson et al. (109, p. 743-750).

## B. Salicylic acid

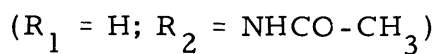


## 1. Acetylsalicylic acid

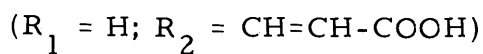
2. o-Acetyl-5-(p-fluorophenyl)salicylic acid (5, p. 52)

## C. Hydroxyanilines

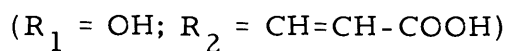
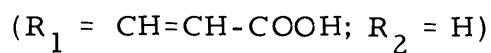
## 1. 4-Acetamidophenol Acetaminophen N. F. )



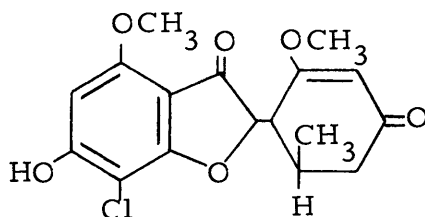
## D. Hydroxycinnamates

1. p-Coumaric acid

## 2. Caffeic acid

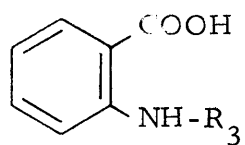
3. o-Hydroxycinnamic acid

## E. 6-Desmethylgriseofulvin

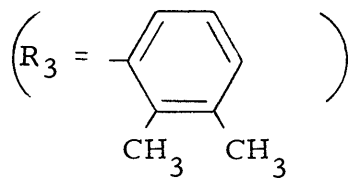




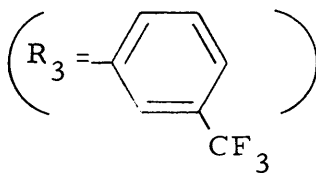
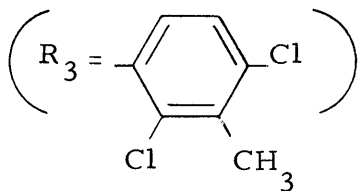
## II. Anthranilates



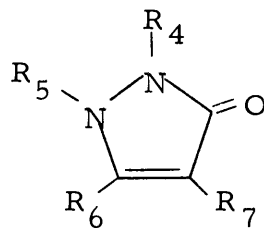
## A. Mefenamic acid



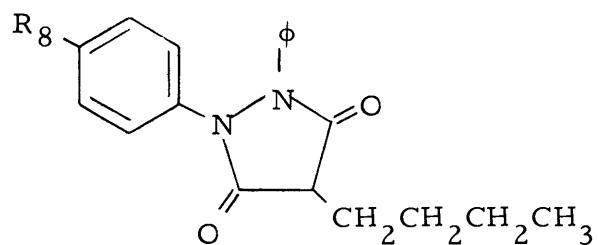
## B. Flufenamic acid

C. N-(2,6-Dichloro-m-tolyl)anthranilic acid (111)

## III. Pyrazolones



## A. Phenylbutazone

(R<sub>8</sub> = H)

## B. Oxyphenbutazone

(R<sub>8</sub> = OH)

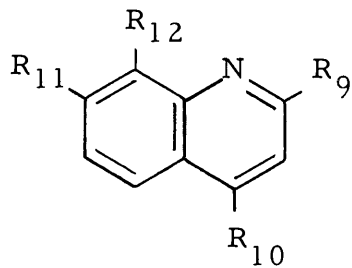
## C. Amidopyrine

(R<sub>4</sub> =  $\phi$ ; R<sub>5</sub> = CH<sub>3</sub>; R<sub>6</sub> = CH<sub>3</sub>; R<sub>7</sub> = N(CH<sub>3</sub>)<sub>2</sub>)

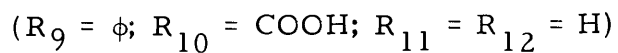
## D. Antipyrine

(R<sub>4</sub> =  $\phi$ ; R<sub>5</sub> = CH<sub>3</sub>; R<sub>6</sub> = CH<sub>3</sub>; R<sub>7</sub> = H)

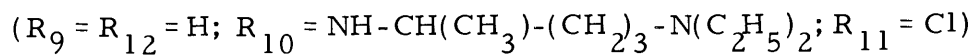
## IV. Quinolines and Acridines



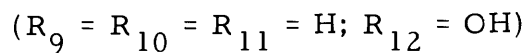
## A. Cinchophen



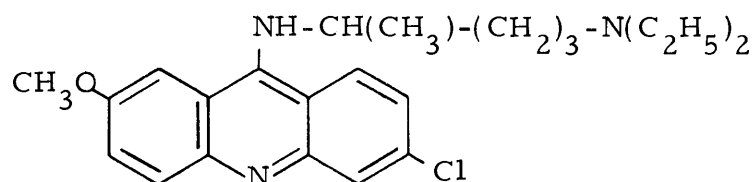
## B. Chloroquin; and similar compounds (2)



## C. Oxine



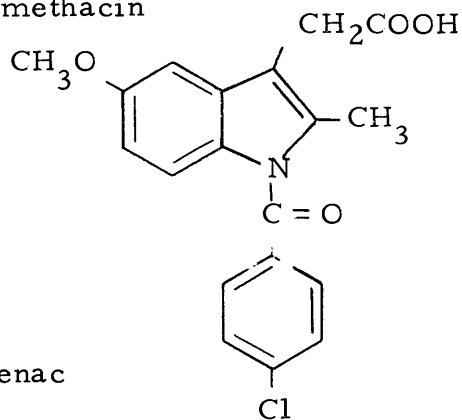
## D. Quinacrin



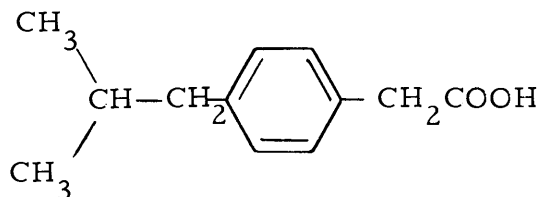
## V. Aliphatic and Alicyclic Acids

## A. Arylacetic acids

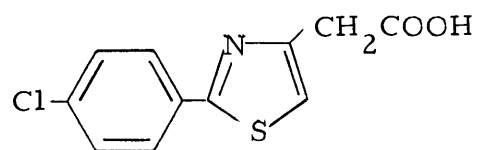
## 1. Indomethacin



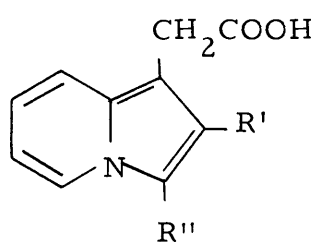
## 2. Ibuprofen



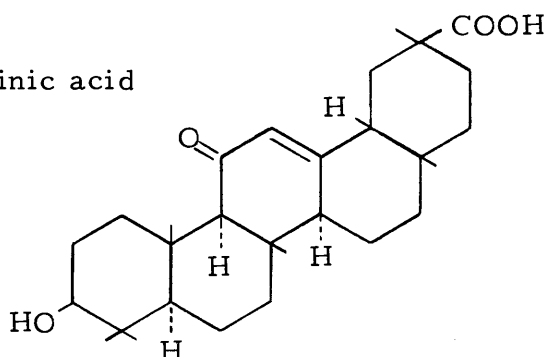
## 3. Fenclozoic acid



## 4. Indolizine-1-acetic acids (79)



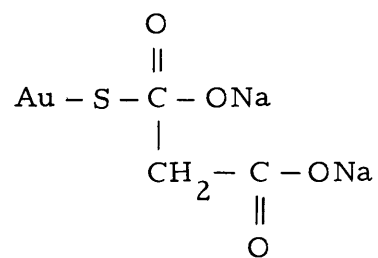
## B. 18β-Glycyrrhetic acid



## VI. Inorganic Based Compounds

## A. Gold

## 1. Sodium aurothiomalate



## 2. Aurothioglucose

3. Sodium aurothiopropionolsulfonate

4. Sodium aurothiosulfate

B. Bismuth and antimony

1. Bismuth tartrate

2. Potassium antimony tartrate

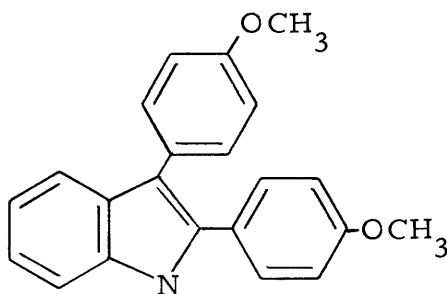
C. Selenium

1. Sodium selenite

## VII. Indoles

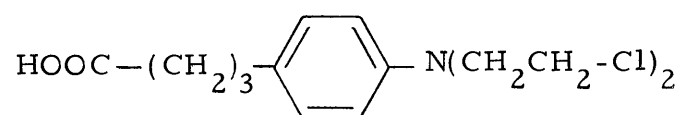
A. Some 3-(3-substituted propyl)dimethylindoles (77)

B. Indoxol

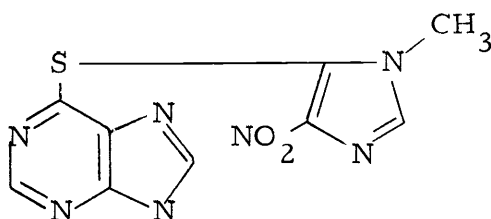


## VIII. Immunosuppressive Agents

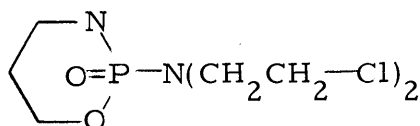
A. Chlorambucil (65)



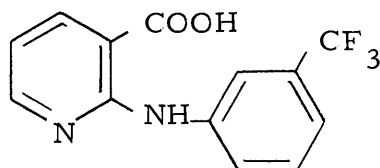
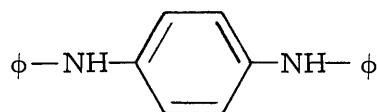
## B. Azathioprine (106)

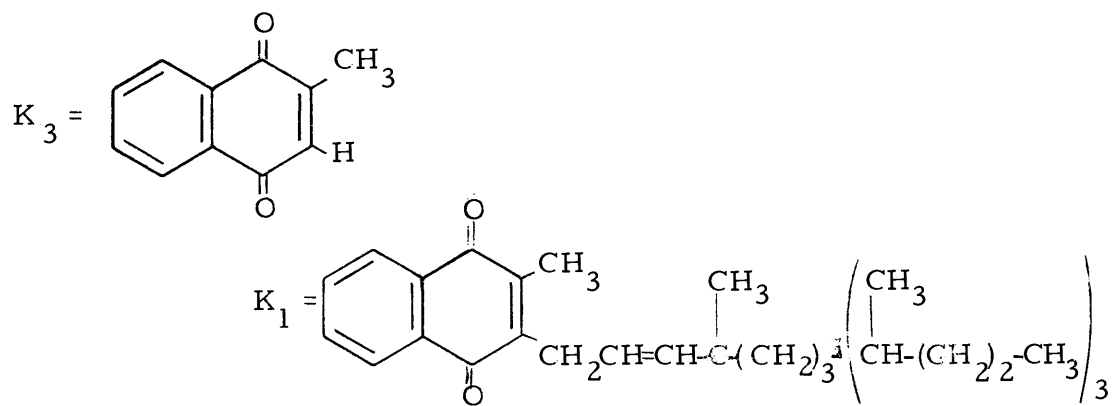


## C. Cyclophosphamide (106)

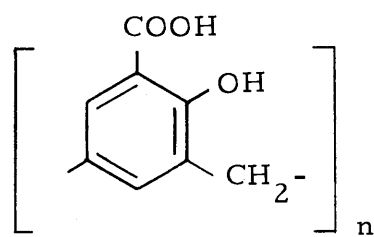


## IX. Miscellaneous

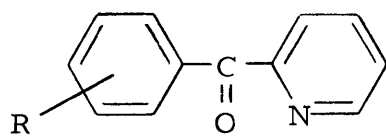
A. 2-(m-Trifluoromethylanilino)nicotinic acid (55)B. N, N' -Diphenyl-p-phenylenediamine (62)

C. Vitamins  $K_1$  and  $K_3$  (35, 106)

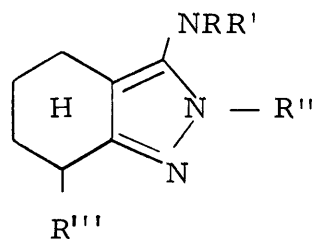
## D. Poly-(4-hydroxy-5-carboxy-1,3-phenylenemethylene) (29)



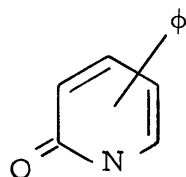
## E. Some arylpyridyl ketones (49)



## F. 3-Aminotetrahydroindazoles (84)



## G. Phenylpyradones (115)



## H. Some substituted hydroquinones (58)

## I. Benzydamine (20)

## J. Non-steroid anti-inflammatory factor(s) in inflammatory exudates (8)

K. L-Asparaginase (53)

Many other substances have been tested for anti-inflammatory activity (34, 70, 94).

### The Functional Nature of Anti-inflammatory Agents

The ideal anti-inflammatory agent would affect the factor(s) directly responsible for the inflammatory disease being considered. Unfortunately, the specific etiologies of the serious inflammatory diseases are unknown. Therefore, attention must be focused on interrupting the inflammatory process, directly or indirectly, and/or to treat the symptoms of the disease. The latter course is concerned mainly with analgesia and is insufficient, since the inflammatory process and its results continue unchecked. Fortunately, many common analgesics possess anti-inflammatory activity as well.



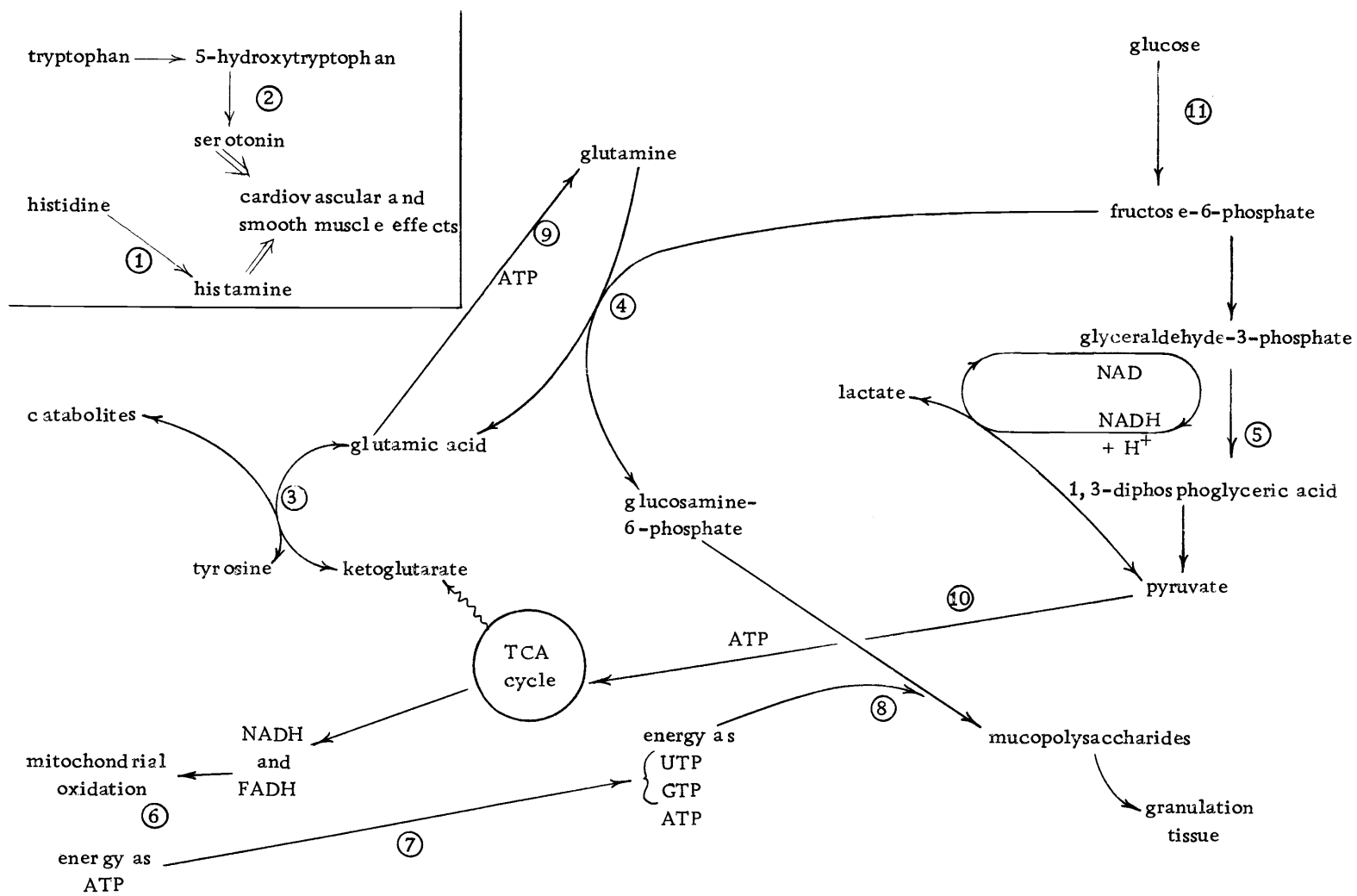
Anti-inflammatory drugs may affect several aspects of inflammation, perhaps simultaneously. Some important actions are effects on amino acid metabolism and mucopolysaccharide biosynthesis. The extent and importance of these actions in various inflammatory disorders is uncertain. Theoretically, however, both the early stages (edema, erythema) and late stages (tissue proliferation) of inflammation could be repressed.

Inhibition of enzymes, notably transaminases, decarboxylases, and dehydrogenases, is a common action of some anti-inflammatory agents. This is achieved by competing with pyridoxal phosphate and pyridine nucleotide coenzymes for their apoenzymes (Figure 2). Chelation of metallic cofactors also seems to be important (Figure 3). Inhibition of inorganic sulfate utilization and of DNA synthesis have been noted as well.

The effects of anti-inflammatory agents on the energy-yielding reactions of the cell are probably quite important. Activation of ATPases, inactivation of dehydrogenases, and, especially, uncoupling of oxidative phosphorylation are primary considerations here. It has been postulated that interaction of the anti-inflammatory agent with some unique, adjacent thiol groups<sup>5</sup> (Figure 3) and/or chelation of metal ions involved with these thiol groups are mechanisms of uncoupling oxidative phosphorylation.

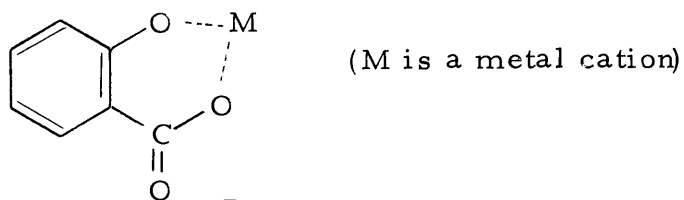
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<sup>5</sup> It is postulated that there may be two or more thiol groups involved and that they are found somewhere in the energy harnessing mechanism of the mitochondrion not involved with electron transport.

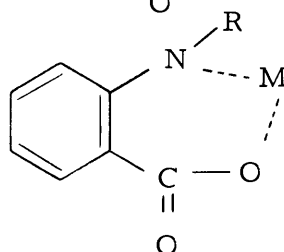


Information for this figure was taken, in part, from Whitehouse (107).

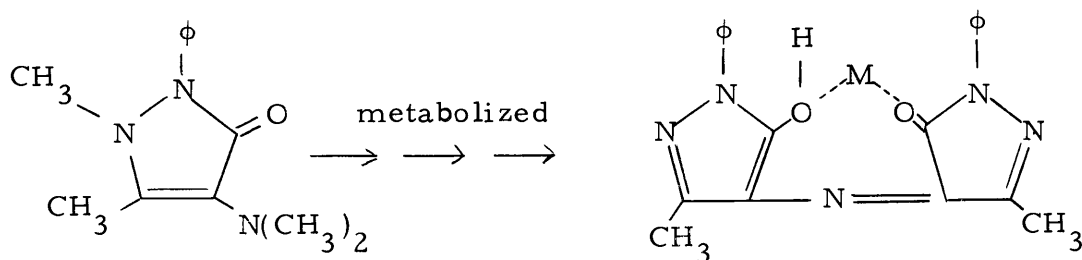
Salicylic Acid:



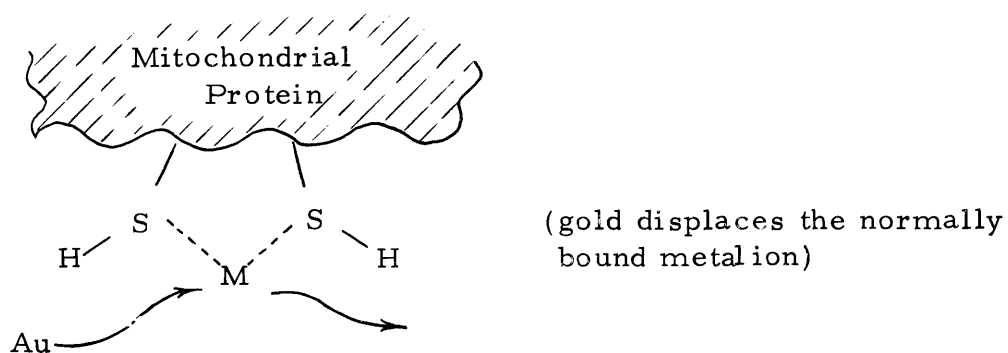
Anthranilic Acids:



Amidopyrine:



Gold Compounds:



Information for this figure was taken from Whitehouse (107)

Figure 3. Postulated Chelation and Complexation Mechanisms of Several Anti-inflammatory Agents

Methods for Testing Anti-inflammatory Agents (114)

The testing methods presently used for screening potential anti-inflammatory drugs leave much to be desired. As in all initial pharmacological screening, potential anti-inflammatory agents are tested in vitro and/or in laboratory animals, where the response to the drug is frequently different (at least with respect to dose) from that observed in man. Also, most anti-inflammatory tests do not deal directly with the pathological condition (most often rheumatoid arthritis) for which the drug may be destined. The tests that do make use of artificially induced arthritis are necessarily insufficient, since the biochemical nature of both the human disorder and the animal induced condition is not fully understood. Also, rheumatoid arthritis as found in man is restricted to primates. Therefore, it is impossible to make consistently accurate predictions about drug efficacy in human arthritis based on experiments conducted in non-primates.

Other inflammatory conditions that are induced for screening purposes (e.g. edema, erythema, and granuloma formation) also cannot be considered good representations of similar, naturally occurring conditions. The manner in which seemingly identical inflammatory responses are induced may make a great difference in the effectiveness of an anti-inflammatory agent. Similarly, an agent

may show varying results when different forms of inflammation are produced (99; 107, p. 336).

It is extremely difficult to design a good experimental model on which to test potential anti-inflammatory agents, without first knowing much more about the origin and biochemistry of the various inflammatory processes. Present testing methods can give only limited indications of possible drug activity.

The experimental approaches to the study of inflammation have been reviewed by Weiner and Piliero (106). An outline of their discussion is presented below. A drug's ability to affect the systems in this outline is considered a measure of its anti-inflammatory potential.

## I. In Vitro Systems

### A. Physical-chemical measurements

1. Uncoupling oxidative phosphorylation
2. Chelation
3. Protein binding

### B. Enzyme inhibition of proteolytic enzymes

### C. Cellular and sub-cellular systems

1. Stabilization of lysosomes
2. Influence on metabolism of cells

## II. In Vivo Systems

- A. Inflammation due to simple, non-specific irritants
  - 1. Physical injury
  - 2. Chemical injury
- B. Specific mediator induced inflammation
  - 1. Histamine
  - 2. Serotonin
  - 3. Kinins
- C. Immunologically induced inflammation
- D. Autoimmune models
  - 1. Adjuvant arthritis
  - 2. "S.I. arthritis" (6-sulfanilamidoindazole induced)
  - 3. N.Z.B. lupus mice (comparable to systemic lupus erythematosus in man)
  - 4. Pig arthritis
  - 5. Rat encephalomyelitis
- E. Toxic arthritis induced by some synthetic aminonitriles
- F. Nutritional models leading to inflammatory states
  - 1. Zinc deficiency
  - 2. Hypo- and hyper-vitaminoses
  - 3. Obesity in rats.

Some specific techniques used in anti-inflammatory screening involve foot edema in rats, erythema in guinea pigs and man, and granuloma

formation (usually in rats). Other tests involve experimental arthritis, liver glycogen-depositing activity in rats and mice, regeneration of cartilage in rabbit ears, thymus involution in immature rats, and bradykinin induced bronchoconstriction in guinea pig lungs. A recent review by Kuzell (65) also covers various experimental techniques.

Foot edema in the rat is usually accomplished by injecting irritants into the hindpaw. Dextran, formalin, yeast, mustard, kaolin, aerosil, and carrageenin have been used. The amount of edema is determined after a predetermined time by either measuring the diameter of the limb directly or via a shadow of the swollen area, weighing after amputation, or using a plethysmometer.<sup>6</sup>

Erythema is induced in guinea pigs by ultraviolet irradiation. In man, a cream of 5% tetrahydrofurfuryl nicotinate is applied to the skin. The amount of reddening is measured subjectively after an arbitrary time.

Granuloma growth is initiated in various ways. A cotton pellet soaked in turpentine, dilute formalin, or carrageenin solution may be implanted subcutaneously. Air may be injected subcutaneously,

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<sup>6</sup>The plethysmometer is an instrument which allows measurement of foot volume by submerging the limb in a cup of mercury. Pressure change due to the rise of the column of mercury is the basis of the determination.

followed by an irritant such as dilute croton oil to form a "granuloma pouch." Also, a portion of skin may be removed from the back of a rat and the exposed area covered with a plastic ring. The size of granulomas are determined by weighing after excision.

Polyarthritis (an experimental animal arthritis) can be induced in male rats by injecting various proteins. The arthritis is long-lasting and similar to human arthritis in some respects. Nonetheless, it must be emphasized again that arthritis as found in man, is a disease developed by primates only.

The "flop-eared" rabbit assay is performed by injecting rabbits with papain which breaks down cartilage in the upper ear. Anti-inflammatory drugs may delay the normal regeneration of the cartilage.



## DISCUSSION OF CHEMISTRY

n-Butyllithium and General Organolithium Chemistryn-Butyllithium (BuLi)

A large number of organolithium compounds have been prepared and studied, e. g. methyllithium (16), ethyllithium (15), phenyllithium, t-butyllithium (105), and n-butyllithium. n-Butyllithium is a commonly used metalating agent and was used in the present research. Some physical properties of n-butyllithium are shown in Table 2. n-Butyllithium is a liquid at room temperature (16); and it is soluble in ether, benzene, and paraffin oils (31), among other organic solvents. As is the case with other alkylolithium compounds, n-butyllithium forms aggregates when in solution. Waack and West (103) and Lewis and Brown (67) have reported that n-butyllithium is predominantly a hexamer in hydrocarbon solvents and a tetramer in diethylether, tetrahydrofuran, and triethylamine. These results are in contrast to earlier work, which indicated that a dimer existed in diethylether and a tetramer in hydrocarbon solvents (26).

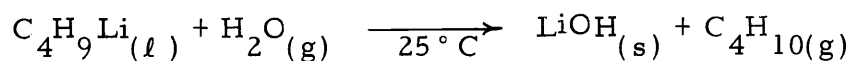
n-Butyllithium may be purchased commercially<sup>7</sup> in solutions of 15% w/v in hexane under an inert atmosphere. It may be prepared

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<sup>7</sup> Available from Foote Mineral Company and Matheson, Coleman, and Bell Company.

Table 2. Some Physical Properties of n-Butyllithium<sup>a</sup>

1. Heat of Reaction with Water:



-57.4±0.7 Kcal. /mole

2. Heat of Combustion:

11,273 cal. /g.

3. Heat of Formation (for  $\text{BuLi}_\ell$ ):

-31.4±0.7 Kcal. /mole

4. Heat of Evaporation (for monomeric butyllithium gas):

33±5 Kcal. /mole

5. Heat of Sublimation:

25.6 Kcal. /mole

6. Vapor Pressures:

$4.38 \times 10^{-4}$  mm at  $60^\circ\text{C}$

$73.8 \times 10^{-4}$  mm at  $80^\circ\text{C}$

$194. \times 10^{-4}$  mm at  $95^\circ\text{C}$

7. Bond Dissociation Energy:

$\text{D}(\text{C}-\text{Li}) = 55.5$  Kcal. /mole

8. Dipole Moment:

0.97 Debye

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<sup>a</sup>Obtained from publication TD-103, May, 1968, Foote Mineral Company.



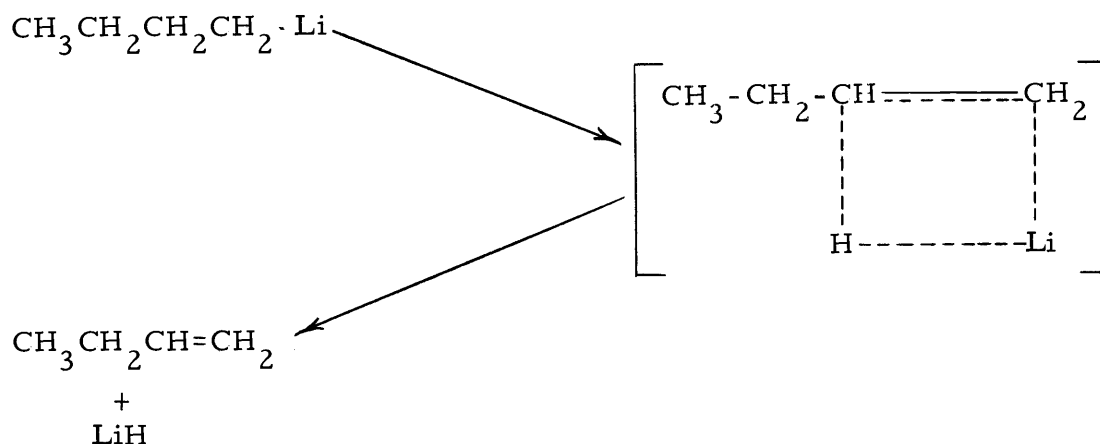
of n-butyllithium may take place also. Decane solutions of n-butyllithium have been found to decompose slowly at 100° and rapidly at 150° (Scheme 3)(39). The overall decomposition approximates first

Scheme 3

1.  $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2 - \text{Li} \longrightarrow \text{CH}_3\text{CH}_2\text{CH}=\text{CH}_2 + \text{LiH}$
2.  $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2 - \text{Li} + \text{CH}_3\text{CH}_2\text{CH}=\text{CH}_2 \longrightarrow$   

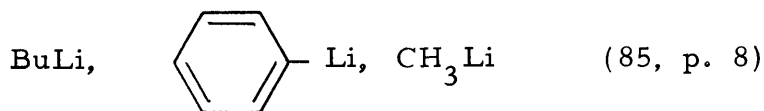
$$\begin{array}{c} \text{CH}_3 - \text{CH} - \text{CH} = \text{CH}_2 + \text{C}_4\text{H}_{10} \\ | \\ \text{Li} \end{array}$$
3.  $\begin{array}{c} \text{CH}_3 - \text{CH} - \text{CH} = \text{CH}_2 \\ | \\ \text{Li} \end{array} \longrightarrow \text{CH}_2 = \text{CH} - \text{CH} = \text{CH}_2 + \text{LiH}$
4.  $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2 - \text{Li} + \text{CH}_2 = \text{CH} - \text{CH} = \text{CH}_2 \longrightarrow \text{polymeric material}$

order kinetics (39). Several mechanisms for the initial hydride elimination have been discussed (19, 76). Finnegan and Kutta (39) have postulated an attractive concerted mechanism:



### Chemical Properties and Reactions of Organolithium Compounds

Alkyl lithium compounds have both ionic<sup>9</sup> (46) and covalent character, the latter predominating (73, p. 148). Their general structure may be expressed as:  $\overset{\delta^-}{R}-\overset{\delta^+}{Li}$ . Lithium alkyls are best described as carbanions and, accordingly, they are bases. The degree of basicity is influenced largely by the relative stability of the carbanion, the more stable carbanion being a weaker base. The relatively unstable carbanion has a greater proton affinity; and, generally, (excluding steric effects) the corresponding lithium compound has greater metalating ability. To illustrate, in the series shown below, metalation capacity decreases and carbanion stability increases from left to right for a reaction of the type:  $R-Li + R'H \rightleftharpoons RH + R'-Li$



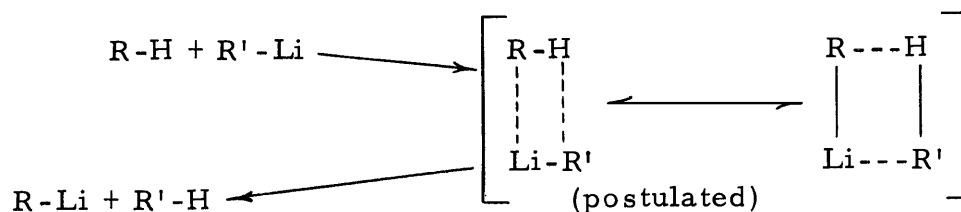
The specific mechanistic pathways used by organolithium reagents are not exactly known, and several theories have been set forth for metalations involving lithium-hydrogen interchange. The possibility of electron-transfer reactions (88) or carbene

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<sup>9</sup>Interestingly, the amount of ionic character has been found to decrease greatly when aggregation of the organolithium compound occurs (43).

intermediates (45) have been discussed in the literature. A free radical mechanism does not seem to be involved (51). The most accepted theory involves nucleophilic attack of  $R^{\delta-}$  (73, p. 469) (of  $R-Li$ ) on the most acidic hydrogen of the substrate. Also, [perhaps simultaneously] the lithium coordinates with the carbon atom bearing this hydrogen (75, 86) to form an intermediate whose nature is not exactly known (Scheme 4) (57). Mallan and Bebb (72) warn

Scheme 4



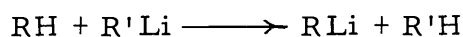
that any mechanism one considers for organolithium reactions must take several things into account, namely solvent, concentration, and temperature. Also, the degree of polymerization of the alkyllithium as well as its degree of contamination with undetected impurities and lithium hydride (96) are important.

The rates of organolithium reactions depend on the solvent system. The solvent will determine the degree of polymerization of the organolithium compound. For example, Lewis and Brown (67) have presented colligative property and n.m.r. evidence to suggest an equilibrium between only tetramers and hexamers of an

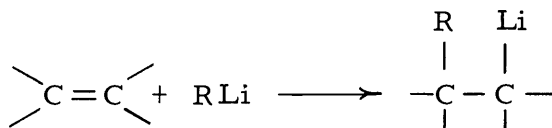
organolithium compound in pure hydrocarbon solvents. Within limits, addition of basic solvents such as tetrahydrofuran or ether produces solvated tetramers, where the number of solvating bases per tetramer is related to the structure of the base. In contrast, it has been suggested that the rate of metalations in hydrocarbon solvents is dependent on the dissociation to the monomer (38). This latter possibility, however, does not seem likely. None-the-less, it is important to note that, in metalation reactions, another organolithium compound (other than the polymer present in solution) is produced; and this can have profound effects on the reaction kinetics (14).

Organolithium compounds undergo a variety of reactions. Several of the more common reactions are listed below. Reactions with halides will be discussed later.

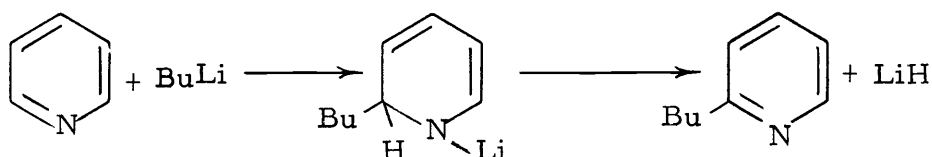
1. Metalation Reactions (73, P. 468-469)



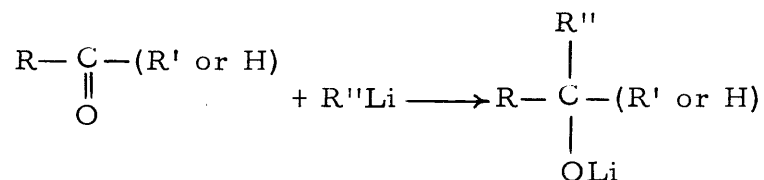
2. Addition to Alkenes (73, p. 650)



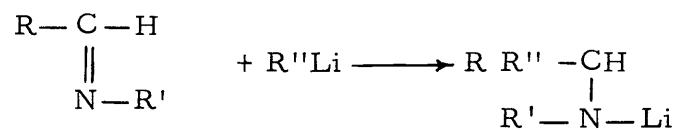
3. Reaction with Arenes (73, p. 509)



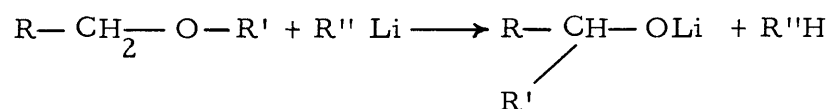
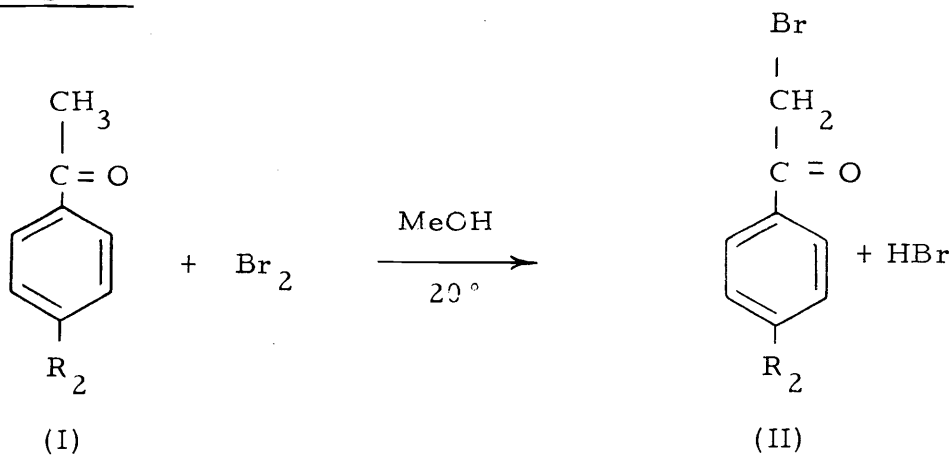
## 4. Reactions with Ketones and Aldehydes (73, p. 684)



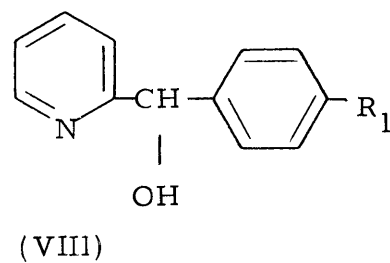
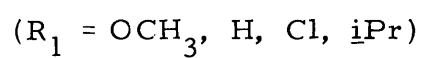
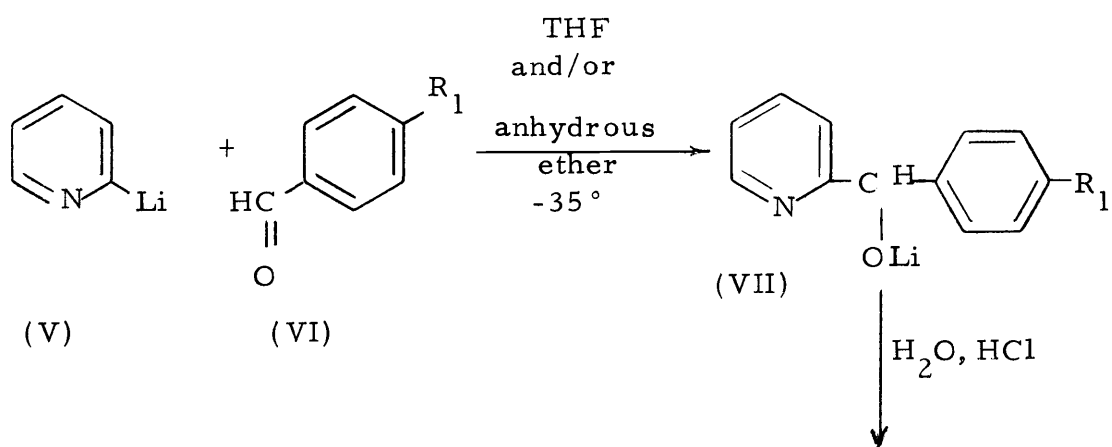
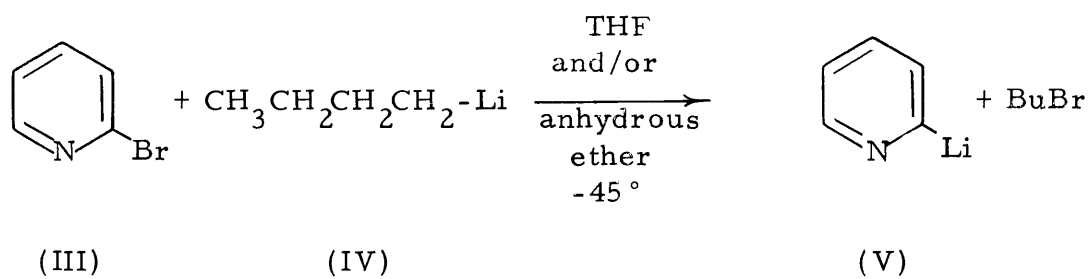
## 5. Reactions with Imines (73, p. 689)

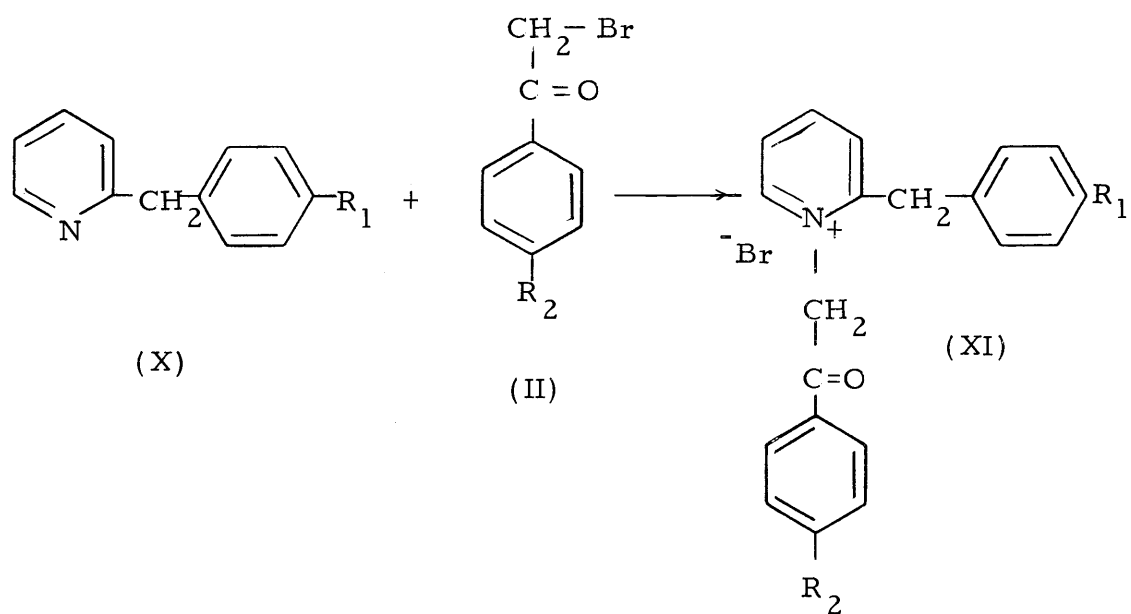
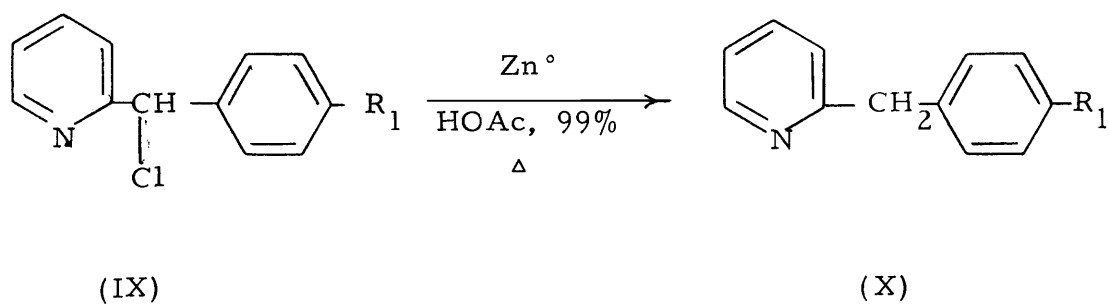
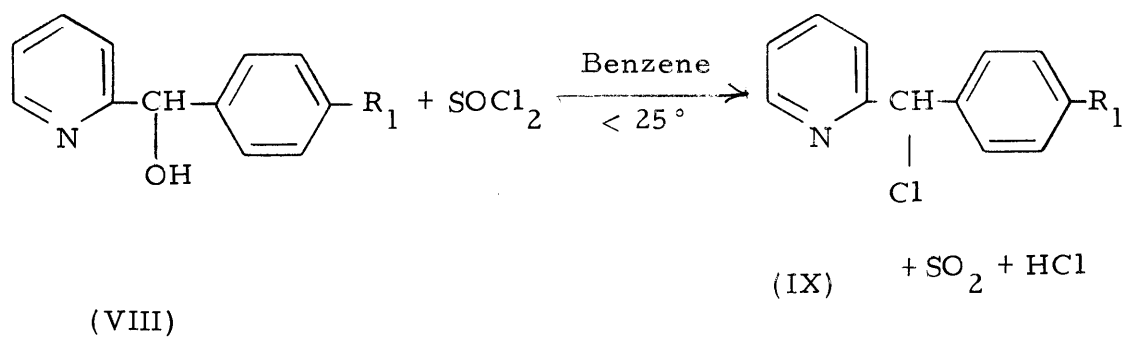


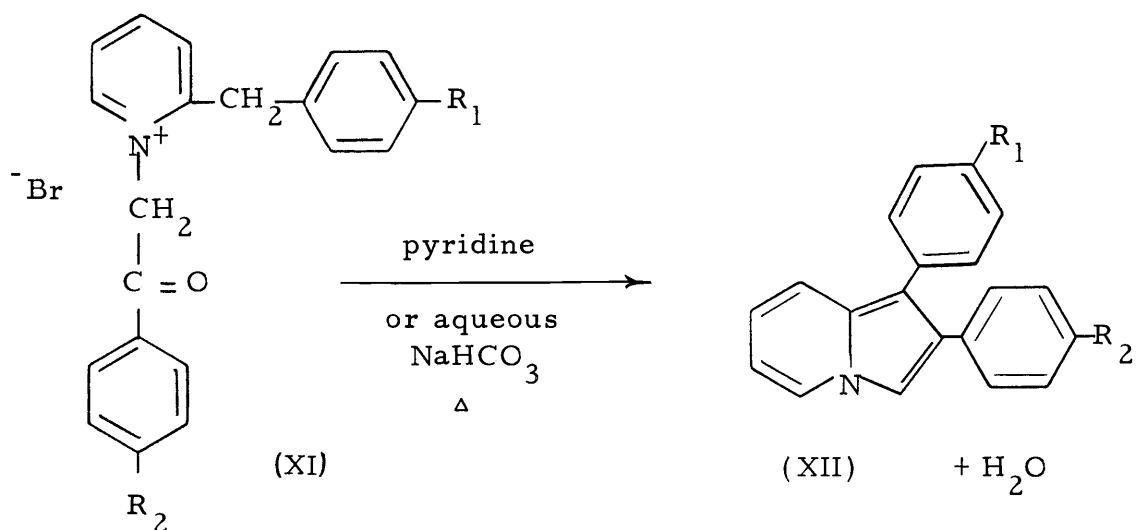
## 6. Reaction with Ethers (Wittig Rearrangement) (73, p. 827)

Flow Sheet and Discussion of the Reactions EmployedFlow Sheet







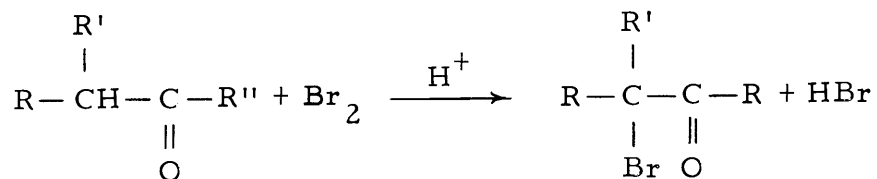


NOTE: Roman numerals (I through XII) appearing in the text below, refer to this flow sheet.

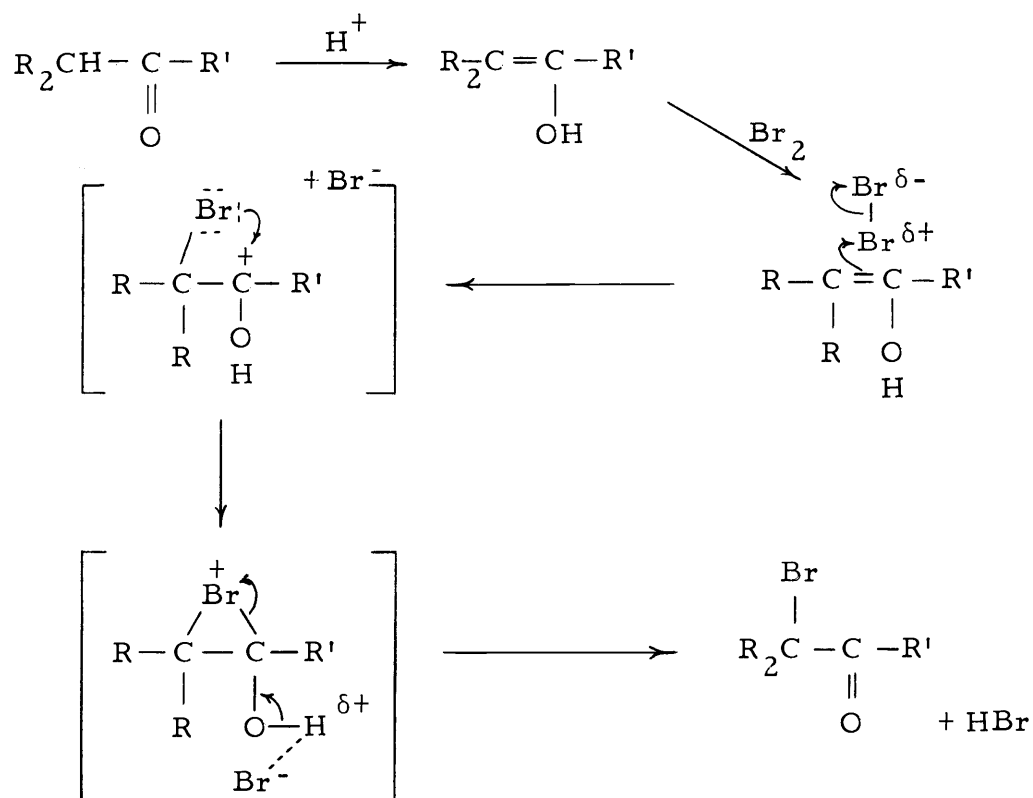
### The Preparation of Phenacyl Bromides

The phenacyl bromides (II) prepared for use in this investigation were p-methoxyphenacyl bromide, p-chlorophenacyl bromide, p-bromophenacyl bromide, and unsubstituted phenacyl bromide. All were prepared in a similar manner (see experimental section); and, except for slight differences in the rate of onset of the reaction, the observations for each reaction were much the same. The procedure used in these preparations was similar to that described in Organic Syntheses (9, p. 480). In general, the yields were similar to those reported in the literature.

The bromination can be represented by the general reaction:



Only minute traces of acid or base are needed to carry out the reaction and usually the environment provides enough impurities or contaminants. The function of the acid or base is to provide a small amount of the enol form of the ketone. The mechanism of halogenation, then, is via electrophilic-like addition of bromine to the double bond of the enol form of the ketone, i.e. the acetophenone (I). The major steps in the overall reaction are illustrated below ( 73, p. 458-459 and p. 562-563):

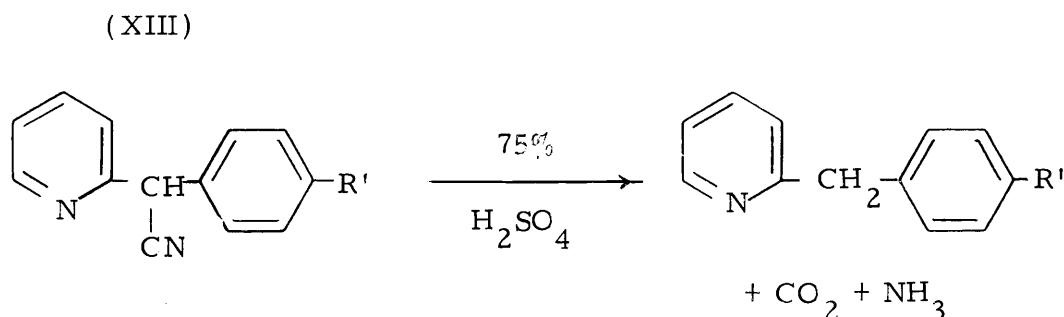


### The Preparation of the 2-Benzylpyridines

The preparation of 1-(p-substituted phenyl)indolizines by means of the Chichibabin synthesis (27) requires 2-(p-substituted benzyl)pyridines (X). Only benzylpyridine, itself, is available commercially. Therefore, it became necessary to select a method of synthesis for these benzylpyridines that gave reasonable yields and employed readily available and relatively inexpensive starting materials. Many methods for the preparation of substituted pyridines have appeared in the literature. Some of these are presented below.

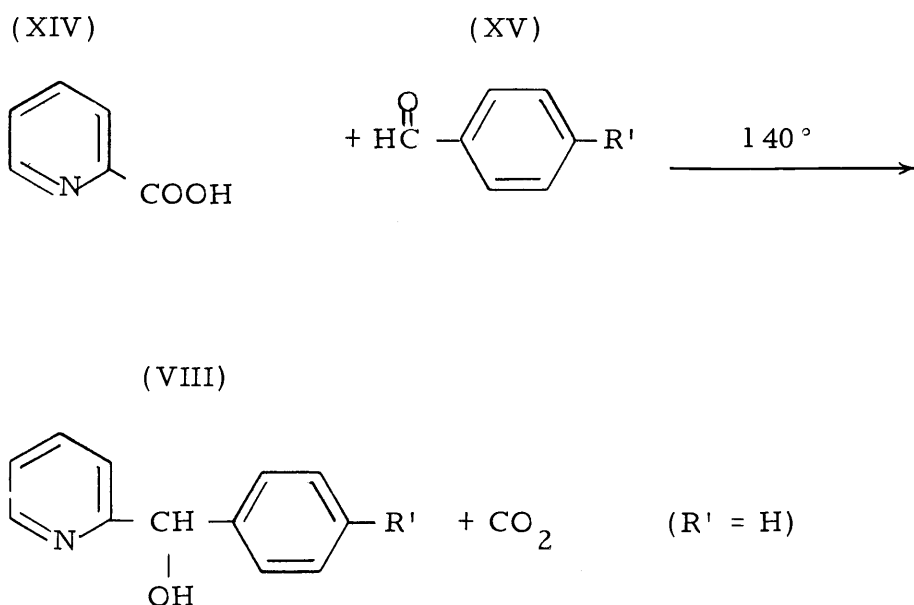
Heating the proper pyridyl-phenyl acetonitrile (XIII) with 75%  $\text{H}_2\text{SO}_4$  will yield the corresponding benzylpyridine (Scheme 5). The yields were reported to be 67% for benzyipyridine (82). This method is obviously limited by the availability of the needed acetonitriles ( $\text{R}' = \text{CH}_3\text{O}-, (\text{CH}_3)_2\text{CH}-, \text{Cl}-$ ).

#### Scheme 5



Decarboxylation of picolinic acid (XIV) in the presence of excess benzaldehyde (XV) at about  $140^{\circ}$  has been used to prepare phenyl-2-pyridylcarbinol (VIII) (Scheme 6) (3, 91). This is known as the Hammick reaction. It is convenient to perform and the product is easy to isolate; however, the yields have been reported to be only on the order of 30-40% (9). More recently, Cantwell (24) has reported yields of 50-60% using p-cymene as the solvent. As will be seen later, the phenyl-2-pyridylcarbinol may be reduced to form the desired 2-benzylpyridine.

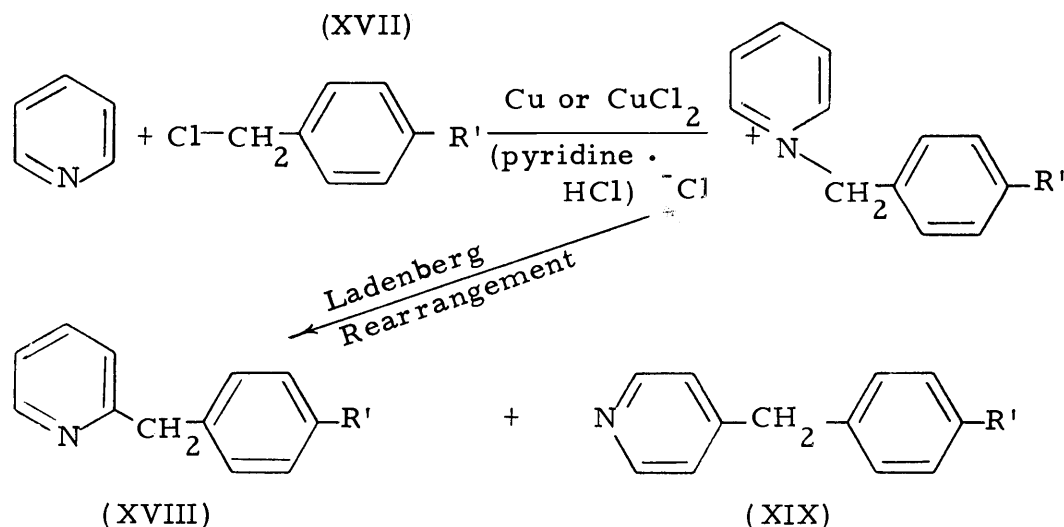
Scheme 6



The Ladenberg rearrangement has been used for the preparation of benzylpyridines (18, 63, p. 163-4). The reaction (Scheme 7)

involves heating a benzyl chloride (XVII) with pyridine at 200-350 °. A powdered copper or copper-bronze catalyst has been used (33, 83) to increase the rate of this reaction. A further modification, found to increase yields, employed the use of a  $\text{CuCl}_2$  catalyst in anhydrous pyridine hydrochloride solvent (30, 32, 93). The major drawbacks in the use of the Ladenberg rearrangement are the separation of the 2- and 4-benzylpyridine isomers<sup>10</sup> (XVIII and XIX) and limited availability of the needed p-substituted benzyl chlorides (XVII). Also, the yields in these reactions were usually only about 40-50% (32). However, Sunagawa *et al.* (93) have reported yields of 70% in their preparation of 2-(p-chlorobenzyl)pyridine.

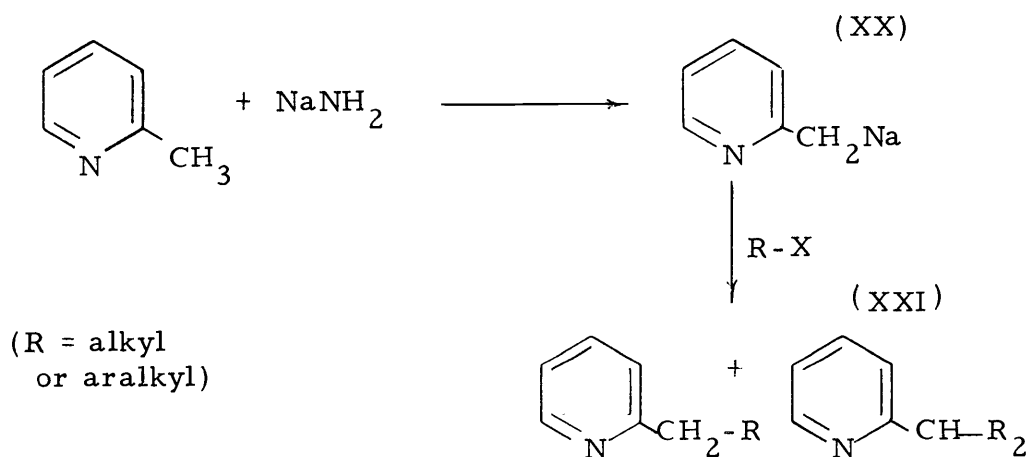
Scheme 7



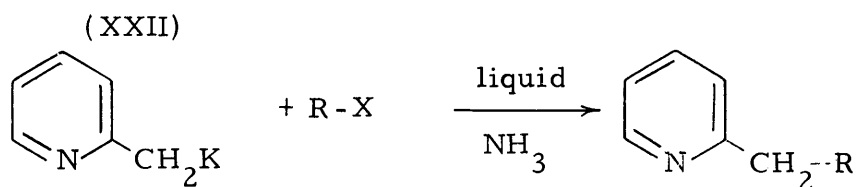
<sup>10</sup> Separation is accomplished either by fractional crystallization of picrates or by fractional distillation.

Other routes to benzylpyridines are via organometallic compounds to directly produce either the desired product or the phenyl-2-pyridylcarbinol (VIII), which, in turn, may be reduced to give the desired product. Picolyl-sodium (XX) has been used to prepare 2-substituted picolines (XXI) also formed (Scheme 8). Bergstrom, Norton, and Seibert (7) were able to eliminate disubstitution by using picolylpotassium (XXII) in liquid ammonia solution (Scheme 9). Their yields were 56-99%. Benzylpyridines were not prepared by this method, however.

Scheme 8



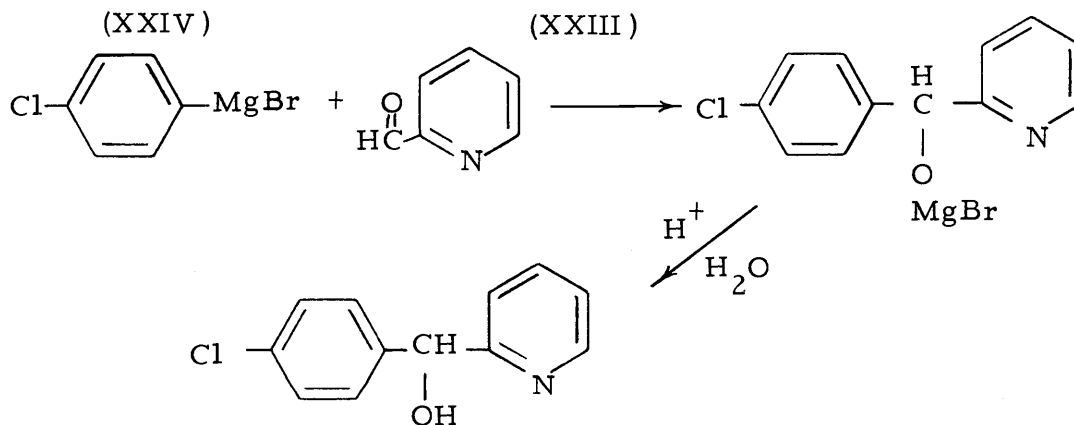
Scheme 9



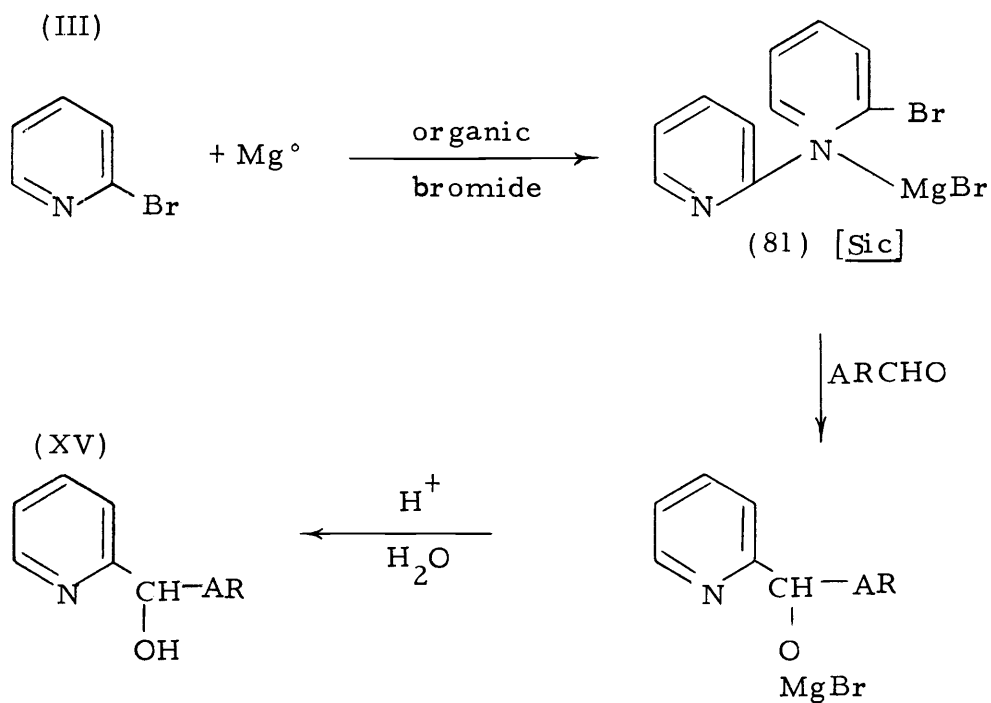


Grignard reagents have also been used to produce benzylpyridines or their carbinol precursors (VIII).  $\alpha$ -(p-Chlorophenyl)-2-pyridinemethanol (VIII,  $R_1=Cl$ ) has been prepared by reaction of p-chlorophenylmagnesium bromide (XXIV) with 2-pyridinecarboxaldehyde (XXIII) (Scheme 10) (74). The yield was 95%. The major drawback to this method is the limited availability of the proper p-substituted bromobenzenes with which to form the Grignard reagent starting material.

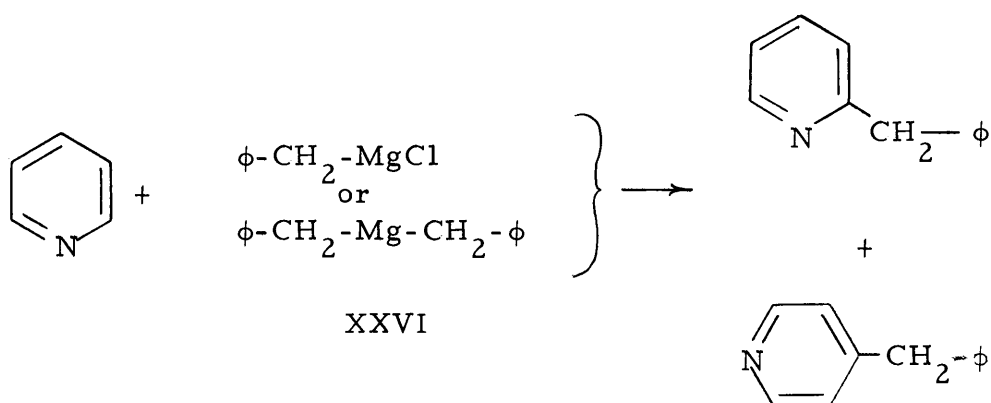
Scheme 10



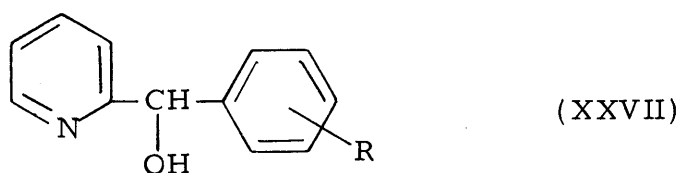
Overhoff and Proost (81) prepared 2-pyridylmagnesium bromide in about 40-55% yields by reaction of magnesium metal with 2-bromopyridine (III) in the presence of another organic bromide, without an ether solvent. Addition of an aromatic aldehyde to the Grignard reagent gave the aryl-2-pyridylcarbinol (XXV) (Scheme 11). This

Scheme 11

method was found to be superior to that where an ether solvent is used in the presence of methyl iodide, aluminum, and dibromomethylene. Benkeser and Holton (6) showed that a mixture of 2- and 4-benzylpyridines was formed on reacting pyridine with either benzylmagnesium chloride or dibenzylmagnesium (XXVI) (Scheme 12). The yields of the 2-isomer were about 2% with benzylmagnesium chloride and about 6% with dibenzylmagnesium.

Scheme 12

All the methods discussed above generally gave unsatisfactory yields or used inaccessible reagents. Yields may be improved by the use of more reactive organometallic compounds, namely 2-pyridyllithium (V) (90). The preparation of phenyl-2-pyridylcarbinols (VIII) using the reactive lithium intermediate has been accomplished by several researchers (42, 90). Alkylpyridylcarbinols have been produced by similar methods (1, 66). The reactive 2-pyridyllithium is formed from the reaction of 2-bromopyridine (III) with *n*-butyllithium (IV). The properly substituted benzaldehyde (VI) is reacted with the 2-pyridyllithium, and the product is hydrolyzed to yield the phenyl-2-pyridylcarbinol. Sperber *et al.* (90) have reported excellent yields (70-90%) of various phenyl-2-pyridylcarbinols (XXVII), obtained by reaction of 2-pyridyllithium with the proper benzaldehydes.



They also reported "good" yields for the conversion of the carbinols to the corresponding 2-benzylpyridines, by treating XXVII with thionyl chloride in benzene and then dechlorinating with zinc and acetic acid. Table 3<sup>11</sup> shows the yields they obtained for the p-substituted-2-benzylpyridines that were prepared.

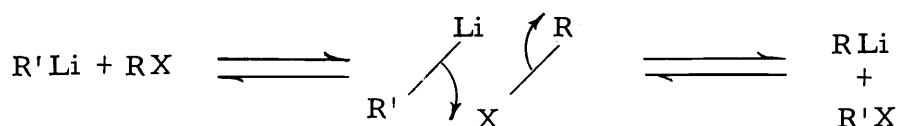
Table 3. Reported Yields of p-Substituted-2-benzylpyridines

R (in the <u>p</u> - position)	Percent Yield
CH <sub>3</sub> -	82
(CH <sub>3</sub> ) <sub>2</sub> CH -	75
CH <sub>3</sub> O -	45
Cl -	77
H -	71

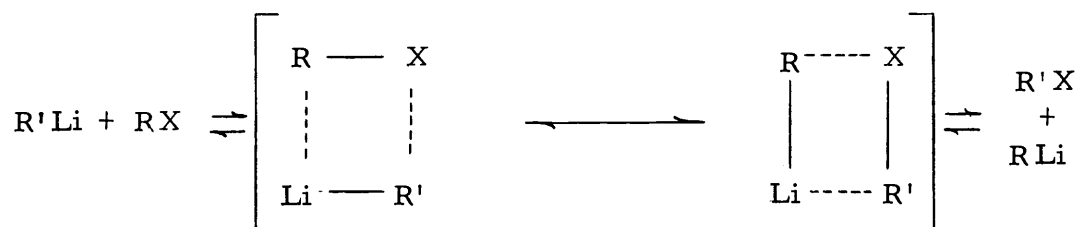
<sup>11</sup> The yields in Table 3 are those reported by Sperber et al. (90). They did not specifically state how these yields were calculated; however, they seem to be for the conversion of the carbinols to the benzylpyridines.

The formation of 2-pyridyllithium is an example of the well-established halogen-metal interconversion reaction. *n*-Butyllithium is the reagent of choice for halogen-lithium exchange because of its relative stability, reactivity, and ease of preparation (60). The reaction is an equilibrium process (112) but often goes to near completion in non-polar solvents due to the low solubility of the aryllithiums produced (97). The halogen-lithium exchange reaction is thought to occur via a "four-center" mechanism (Scheme 13) (112), which may originate by nucleophilic attack of the carbanion on positively charged halogen (60) with simultaneous electrophilic attack of lithium on carbon (112). The ease of exchange is directly related to the degree

Scheme 13



[Perhaps a better representation of this reaction would be as follows.]

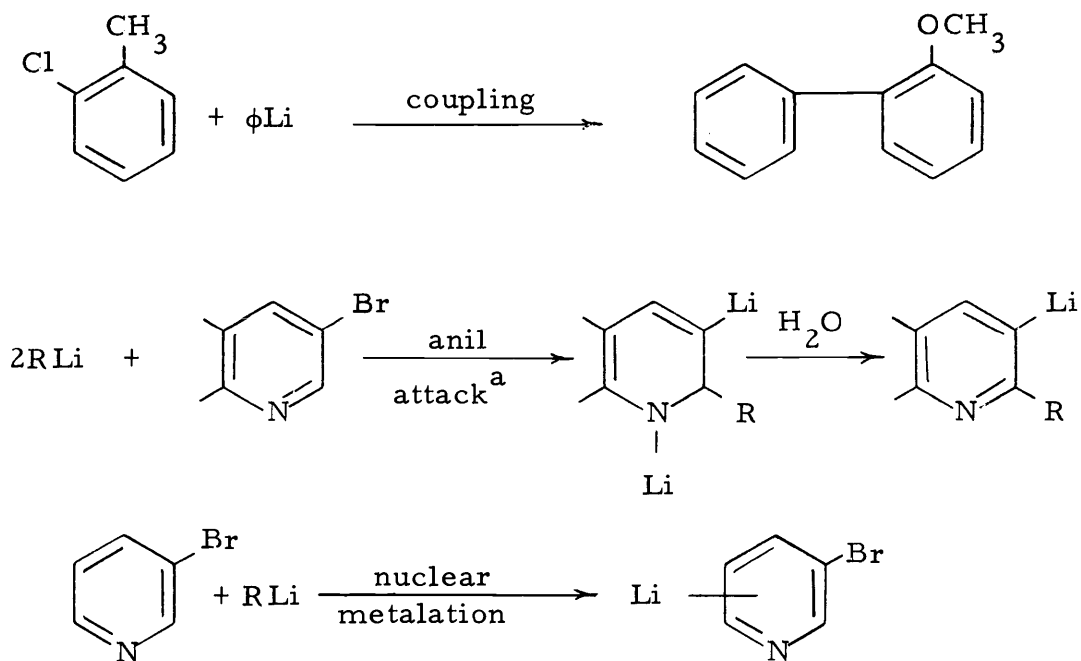


of positive polarization of the halogen involved. Accordingly, fluorine compounds generally do not undergo interconversion reactions,

and iodine compounds react most readily (60). Nucleophilic attack on carbon does not seem to occur (112).

Halogen-lithium interconversions are best conducted in ethereal solvents at low temperatures (about  $-35^{\circ}$ ). Reactions have been conducted in mixtures of ether and benzene at  $60-65^{\circ}$ , but side reactions occur to a greater extent (60). Some possible side reactions occurring in halogen-lithium exchange reactions are coupling reactions (60), attack of anil linkages (42), and metalation at other positions on the molecule (60). Scheme 14 illustrates examples of these reactions.

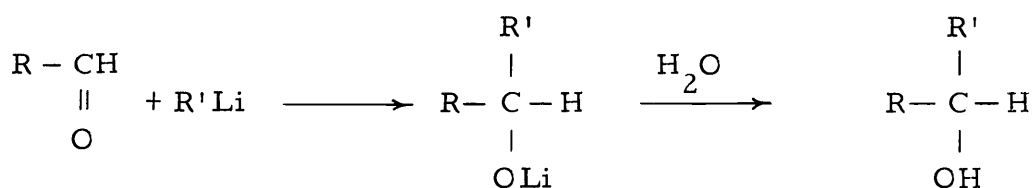
Scheme 14



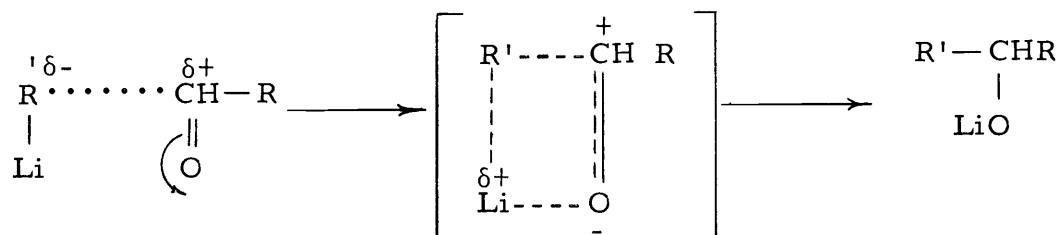
<sup>a</sup>Anil bonds of 2-halopyridines are less vulnerable, due to electron-withdrawing and steric effects.

Changing the solvent system in a given halogen-lithium interconversion may have significant effects on the rate (113), yields (41), and/or course (36) of the reaction. The relative ion-solvating power of the solvent is thought to be responsible. Winkler and Winkler (113), noted an increased rate of exchange between phenyllithium and aryl bromides in tetrahydrofuran as compared to diethylether. It is interesting to note that their kinetic data suggested a build up of negative charge in the transition state. Such a charged transition state would be favored by solvents of relatively high dielectric constant. Tetrahydrofuran would therefore be expected to accelerate the reaction relative to diethylether. In the reaction of n-butyllithium with benzyl chloride in tetrahydrofuran at  $-100^{\circ}$ , Hoeg and Lusk (54) have suggested an  $\alpha$ -hydrogen-lithium interconversion rather than a halogen-lithium interconversion. They feel that tetrahydrofuran solvates lithium cations well enough to produce dissociated butyllithium (i. e. butyl carbanion) in solution.

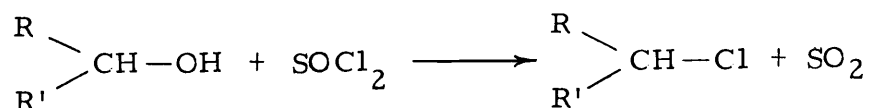
2-Pyridyllithium reacts with benzaldehydes to form phenyl-2-pyridylcarbinols. This reaction may be illustrated as:



No discussion of the mechanism involved could be found in the literature; however, nucleophilic attack of R' on the carbonyl carbon seems reasonable.

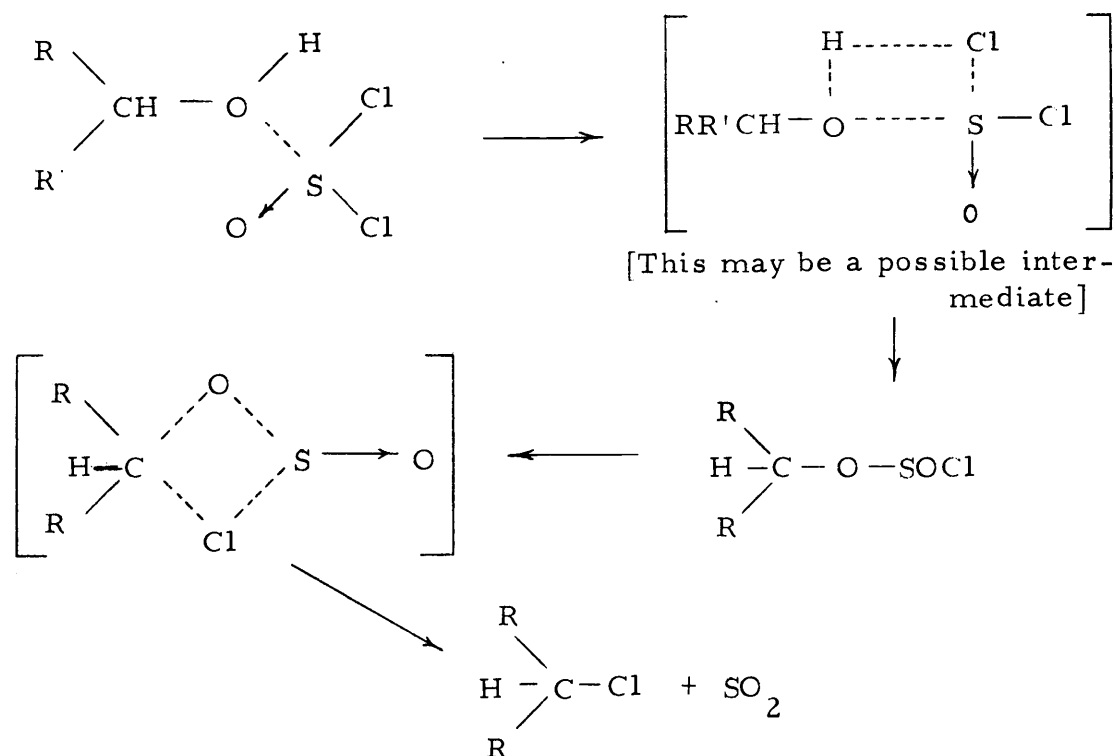


The chlorination of the carbinol (VIII) may be represented by the general reaction:



The mechanism of this reaction is not via direct chlorination by a chloride nucleophile (i.e. not S<sub>N</sub>2). Rather (73, p. 269), the first step in the overall reaction is the formation of sulfate ester by nucleophilic attack of the oxygen atom of the alcohol on the sulfur of thionyl chloride. The alcohol retains its configuration (68, p. 305). The ester then undergoes internal nucleophilic substitution (S<sub>N</sub>i) (48, p. 295). This results in retention of configuration also. If an S<sub>N</sub>2 reaction were responsible, inversion would be expected. This sequence of reactions is illustrated below.





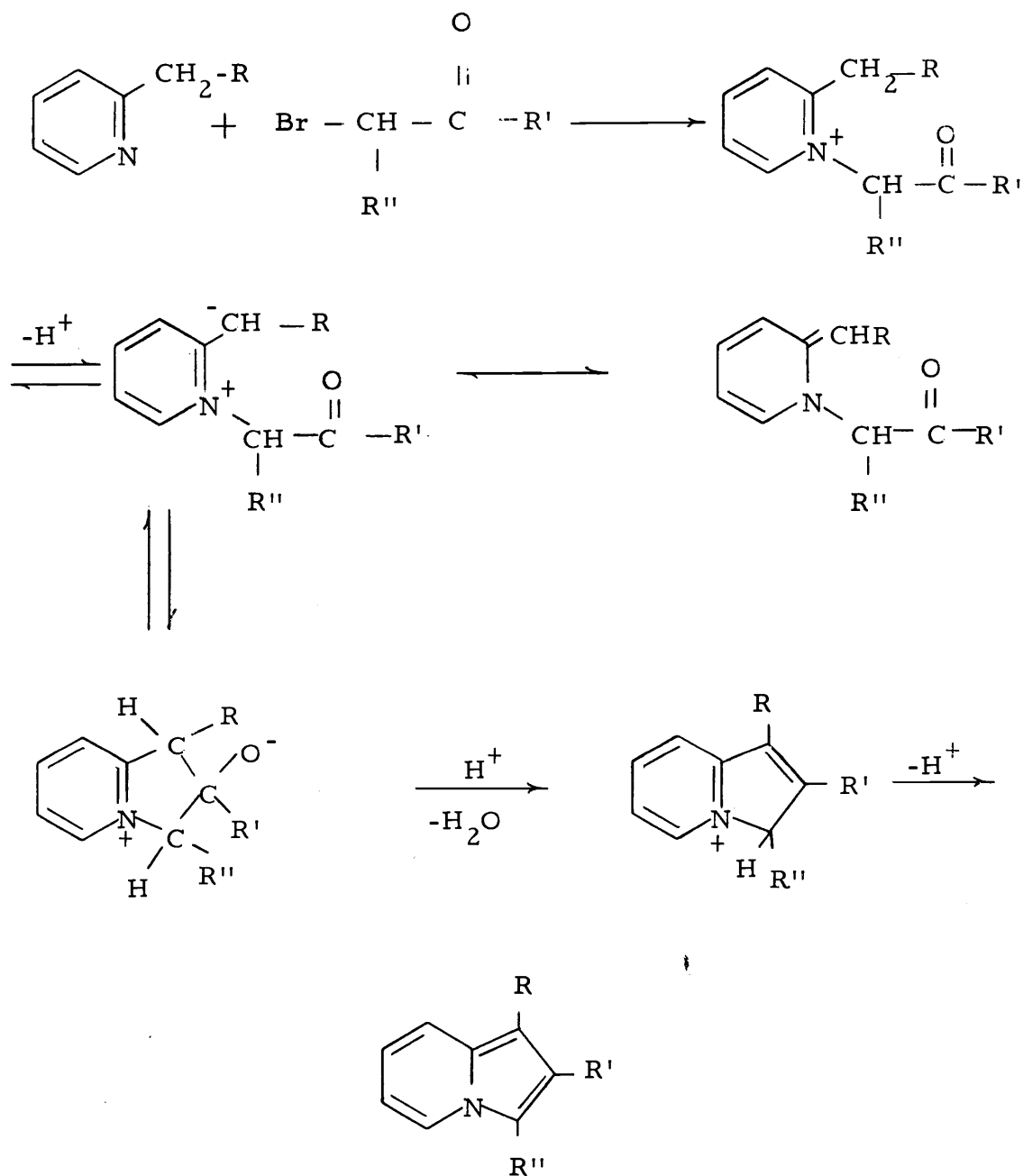
The use of zinc and acetic acid as a hydrogenating agent for alkyl halides has been known for some time (108). Nascent hydrogen is said to be involved in the reaction (104); however, a detailed discussion of the mechanism could not be found in the literature.

### The Preparation of the Indolizines

The indolizines were synthesized from the properly substituted 2-benzylpyridines (X) and phenacyl bromides (II) using the Chichibabin synthesis (27). This series of reactions involves the formation of a quaternary nitrogen salt (XI) which is cyclized using a mild base such as bicarbonate. In all cases the phenacyl halide was a bromide. Phenacyl chlorides have been shown to give substantially lower yields

of the pyridinium intermediates (10, 101). A mechanism for the Chichibabin synthesis has been postulated by Bragg and Wibberly (11) (Scheme 15).

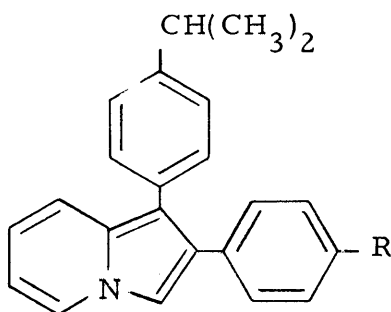
Scheme 15



The experimental techniques employed in the present study were similar to those used by Venturella (100, 101) in his preparation of analogous p-substituted-1,2-diphenylindolizines. A few of the pyridinium salts were readily converted to the corresponding indolizine in hot aqueous bicarbonate. Most, however, formed extremely impure products or tars under these conditions. An alternate method was cyclization in hot pyridine. In this case, the indolizine which forms remains in solution and may be retrieved easily and in a relatively pure form by removing the pyridine under reduced pressure. Kappe (61) and Bragg and Wibberly (12) have used pyridine(s) in acetone solvent to cyclize pyridinium salts.

Purification of the indolizines was extremely difficult in many cases. Often, merely addition of solvent resulted in tar formation. Chloroform, in the presence of light, caused decomposition of all indolizines, usually within about a half hour. Generally, the relatively pure indolizines were most easily recrystallized. Treating solutions with activated charcoal was seldom useful. Simple chromatographic procedures were useless.

When possible, recrystallization from petroleum ether was attempted, since impurities were nearly always less soluble than the indolizine in this solvent. A notable exception to this rule was the group:



This series of compounds was not only very soluble in petroleum ether but in other commonly used solvents as well. Impurities in this series had very similar solubilities. Therefore, only one compound out of five could be isolated in pure form. The indolizine analog of Indoxol, 1,2-bis(p-methoxyphenyl)indolizine, was extremely unstable, especially in ethanol. A ridiculous number of attempts to purify the compound were made, all to no avail.

Similar purification problems were encountered by Venturella (101). He noted that the purity of the 2-benzylpyridines greatly affected the ease of isolation of subsequently prepared indolizines. The difficulties in isolation were attributed to the concomitant formation of an uncharacterized "green indolizine" and the desired compound. In view of the fact that another indolizine was a contaminant (as may have been the case in this investigation), it seems reasonable to expect purification difficulties. This is borne out by the work of Choulis and Harrell (28). They attempted to characterize a group of seven Mannich bases, derived from 1,2-diphenylindolizine, by

thin-layer chromatographic procedures, using silica gel, alumina, and cellulose as layers. For any given compound, the  $R_f$  value varied with the nature of the layer used; however, for any given layer and solvent system, the  $R_f$  values for all seven indolizines were identical. Nineteen different solvent systems were employed.

Table 4. p-Substituted-1, 2-diphenylindolizines Reported in the Literature

Empirical Formula	Indolizine	Melting Point (°C)	Reference
$C_{20}H_{13}BrClN$	2-( <u>p</u> -Bromophenyl)-1- ( <u>p</u> -chlorophenyl)-	178-180° (decomp.)	(100)
$C_{20}H_{13}ClN_2O_2$	1-( <u>p</u> -Chlorophenyl)-2- ( <u>p</u> -nitrophenyl)-	214-216°	(100)
$C_{20}H_{14}BrN$	2-( <u>p</u> -Bromophenyl)-1- phenyl	138-139.5° 143-145	(64) (100)
$C_{20}H_{14}ClN$	1-( <u>p</u> -Chlorophenyl)-2- phenyl-	118°	(4)
$C_{20}H_{14}ClNO$	1-( <u>p</u> -Chlorophenyl)-2- ( <u>p</u> -hydroxyphenyl)-	130-131°	(101)
$C_{20}H_{14}N_2O_2$	2-( <u>p</u> -Nitrophenyl)-1 phenyl-	158-160° 166-167° (decomp.)	(56) (100)
$C_{20}H_{15}NO$	2-( <u>p</u> -Hydroxyphenyl)- 1-phenyl-	156-157°	(101)
$C_{20}H_{16}N_2$	2-( <u>p</u> -Aminophenyl)-1- phenyl-	153-154.5°	(100)
$C_{21}H_{16}ClNO$	1-( <u>p</u> -Chlorophenyl)-2- ( <u>p</u> -methoxyphenyl)-	118.5-119.5°	(101)
$C_{21}H_{17}NO$	2-( <u>p</u> -Methoxyphenyl)- 1-phenyl	97-98°	(101)

Table 5. Summary of New Compounds Prepared in this Research

Empirical Formula	Compound	Melting Point
$C_{20}H_{13}Cl_2N$	1, 2-Bis(p-chlorophenyl)indolizine	165-168° (decomp.)
$C_{20}H_{16}BrCl_2NO$	2-(p-Chlorobenzyl)-1-(p-chlorophenacyl)- pyridinium Bromide	207-209° (decomp.)
$C_{21}H_{16}BrNO$	2-(p-Bromophenyl)-1-(p-methoxyphenyl)- indolizine	138-140° (decomp.)
$C_{21}H_{16}ClN$	1-(p-Chlorophenyl)-2-(p-methylphenyl)- indolizine	130-133° (decomp.)
$C_{21}H_{16}ClNO$	2-(p-Chlorophenyl)-1-(p-methoxyphenyl)- indolizine	125-126°
$C_{21}H_{17}N$	2-(p-Methylphenyl)-1-phenyl- indolizine	120-121°
$C_{21}H_{17}NO$	1-(p-Methoxyphenyl)-2-phenyl- indolizine	94-95° (decomp.)
$C_{21}H_{19}BrClNO$	2-(p-Chlorobenzyl)-1-(p-methylphenacyl)- pyridinium Bromide	220-221° (decomp.)
$C_{21}H_{19}BrClNO_2$	1-(p-Chlorophenacyl)-2-(p-methoxybenzyl)- pyridinium Bromide	210-212° (decomp.)
$C_{21}H_{19}Br_2NO_2$	1-(p-Bromophenacyl)-2-(p-methoxybenzyl)- pyridinium Bromide	196-197° (decomp.)
$C_{21}H_{20}BrNO$	2-Benzyl-1-(p-methylphenacyl)pyridinium Bromide	184-186° (decomp.)
$C_{21}H_{20}BrNO_2$	2-(p-Methoxybenzyl)-1-phenacylpyridinium Bromide	186-187° (decomp.)
$C_{22}H_{19}NO$	1-(p-Methoxyphenyl)-2-(p-methylphenyl)- indolizine	103-104° (decomp.)
$C_{22}H_{22}BrNO_2$	2-(p-Methoxybenzyl)-1-(p-methylphenacyl)- pyridinium Bromide	199-201° (decomp.)
$C_{22}H_{22}BrNO_3$	2-(p-Methoxybenzyl)-1-(p-methoxyphenacyl)- pyridinium Bromide	179-181°

Table 5. Continued

Empirical Formula	Compound	Melting Point
$C_{23}H_{23}BrClNO$	1-( <u>p</u> -Chlorophenacyl)-2-( <u>p</u> -isopropylbenzyl)- pyridinium Bromide	221-222° (dec omp. )
$C_{23}H_{23}Br_2NO$	1-( <u>p</u> -Bromophenacyl)-2-( <u>p</u> -isopropylbenzyl)- pyridinium Bromide	229-230° (dec omp. )
$C_{24}H_{23}NO$	1-( <u>p</u> -Isopropylphenyl)-2-( <u>p</u> -methoxyphenyl)- indolizine	151-152°
$C_{24}H_{26}BrNO_2$	2-( <u>p</u> -Isopropylbenzyl)-1-( <u>p</u> -methoxyphenacyl)- pyridinium Bromide	124-125°



## EXPERIMENTAL

All melting points were taken on the Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra (results listed in Appendix A) were taken on the Beckman IR-8 spectrophotometer. Nuclear magnetic resonance spectra (Appendix B) were taken on the Varian HA-100 spectrometer, through the services of the Department of Chemistry, School of Science, Oregon State University. Elemental analyses were obtained from the Strauss Microanalytical Laboratory, Oxford, England, and the Spang Microanalytical Laboratory, Ann Arbor, Michigan.

Unless otherwise specified, all solvents were analytical reagent grade quality. The manufacturers of the solvents and reagents used are listed below.

Allied Chemical Corporation

Ammonium Hydroxide Solution (28%)

J. T. Baker Chemical Company

Zinc Metal Dust

Dupont; Dyes and Chemical Division

Glacial Acetic Acid

Hydrochloric Acid (36% )

Eastman Organic Chemicals

p-Bromoacetophenone

p-Chloroacetophenone

p-Methylacetophenone

Foote Mineral Company

n-Butyllithium, 15% in hexane solution

Mallinckrodt Chemical Works

Acetone

Benzene

Ether, anhydrous

Methanol, anhydrous

Petroleum Ether, boiling range 30-70°

Pyridine

Tetrahydrofuran, anhydrous and stabilized

Matheson, Coleman, and Bell; Division of the Matheson  
Company, Inc.

Acetophenone

2-Benzylpyridine

2-Bromopyridine

n-Butyllithium, 15% in hexane solution

p-Chlorobenzaldehyde

p-Isopropylbenzaldehyde

p-Methoxyacetophenone

p-Methoxybenzaldehyde

Sodium Sulfate, anhydrous

Thionyl Chloride

### Preparation of the p-Substituted Phenacyl Bromides

A 250 ml., three neck, round bottom flask was equipped with a water cooled reflux condenser, mechanical stirrer, and dropping funnel. About 0.25 mole of the properly substituted acetophenone, dissolved in 90 ml. of methanol, was poured into the reaction flask, stirred, and cooled to about 15°. A solution of 0.25 mole of bromine in about 50 ml. of ice-cold methanol<sup>12</sup> was then added, dropwise with stirring, to the cooled acetophenone solution, until the mixture took on a deep red color. At this point, the ice bath was removed and replaced with a hot water bath at about 40°. The reaction mixture soon decolorized. The water bath was removed, and the bromine solution added dropwise, at a rate that allowed the reaction mixture to clear up completely between drops. The temperature of the reaction mixture was held below 40°. In most cases a precipitate of the phenacyl bromide formed near the end of the reaction. To avoid this, more methanol solvent and/or slight warming of the reaction vessel could be employed. After all the bromine was

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<sup>12</sup>The methanol must be ice-cold, since there is a danger of overheating and "bumping" if the bromine is mixed with the methanol at room temperature.

added, stirring was continued for about 15 minutes. Then the solution was slowly poured into a 250 ml. beaker filled with crushed ice. This was done with vigorous stirring. The resulting precipitate (usually white) was suction filtered, washed with 100 ml. of cold water, and dried under reduced pressure over anhydrous calcium chloride. Recrystallization was usually not necessary but could be accomplished with methanol.

With the possible exception of *p*-methoxyphenacyl bromide, all the dried phenacyl bromides could be stored for over a year with minimal decomposition, if kept in tight, opaque containers, under an atmosphere of dry nitrogen and at 5°.

### Preparation of the Phenyl-2-pyridylcarbinols

#### *p*-Methoxyphenyl-2-pyridylcarbinol

A dry, 500 ml., three-neck, round-bottom flask was equipped with a mechanical stirrer, air condenser with calcium chloride tube, and a dropping funnel. The assembly was flushed with dry nitrogen for about five minutes; and then, while maintaining a slight positive pressure of nitrogen, 100 ml. of anhydrous ether was poured into the flask. The reaction vessel was then slowly immersed in a Dry Ice-acetone bath (-60°). After about five minutes of cooling, 85 ml. (0.136 mole) of *n*-butyllithium (15% in hexane) was added, with

stirring, using a 50 ml. syringe fitted with a six-inch needle.<sup>13</sup> The ether solution occasionally turned milky if it was not extremely dry; however, normally, this was not a problem. Next, with the bath temperature maintained at  $-50^{\circ}$ , 65 ml. of a solution of 2-bromopyridine (24.9 g., 0.158 mole, in 50 ml. anhydrous, stabilized tetrahydrofuran) was added, dropwise, during 15 minutes, with moderate stirring. The reaction mixture became deep red, and then almost black, after the addition was completed. Within five minutes, 110 ml. of a solution of p-methoxybenzaldehyde (30.6 g., 0.225 mole, in 80 ml. anhydrous, stabilized tetrahydrofuran and about 30 ml. anhydrous ether) was added dropwise and with efficient stirring. The addition required 30 minutes and the temperature of the cold bath was maintained between  $-45^{\circ}$  and  $-35^{\circ}$ . As the solution was added, the reaction mixture became more viscid and went through color changes from black, to tan, to blue-green, and, finally, to green. Moderate stirring was continued for approximately 45 minutes, until the bath temperature reached  $-10^{\circ}$ . The reaction

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<sup>13</sup>Because n-butyllithium solutions are highly unstable in air, they are commercially packaged in containers with an air-tight, rubber diaphragm seal. The solution must therefore be withdrawn from the container using a syringe and needle. The syringe barrel must be lightly lubricated with mineral oil to maintain a seal between the barrel and the cylinder wall. The diaphragm is punctured with the needle; and the proper amount of solution is drawn up, while maintaining a positive pressure in the reagent bottle, by passing a very slow stream of dry nitrogen into it via another hypodermic needle.

mixture was then poured onto a slush of about 400 g. of ice in about 350 ml. of aqueous hydrochloric acid (10%). This mixture was stirred until the ice melted. It was then well agitated in a separatory funnel for about three minutes. The organic layer was extracted with an equal volume of aqueous hydrochloric acid (10%) and then discarded. The deep red acid extracts were washed three times with an equal volume of ether and then basified with a slight excess of aqueous ammonia (28% w/w). The resulting mixture was milky, opaque, and orange in color. A brown, cloudy oil separated from the mixture. The oil was removed from the aqueous solution and the latter extracted three times with an equal volume of ether. The combined ether extracts were washed twice with an equal volume of distilled water and added to the oil previously removed. The resulting ethereal solution was dried for 24 hours over anhydrous sodium sulfate, and the ether was then removed under reduced pressure to yield a dark oil and a powdery tan precipitate.

This and all other pyridylcarbinols prepared in this research were used in subsequent steps without further purification. Also, yields were not calculated at this stage in the synthetic sequence.

#### p-Chlorophenyl-2-pyridylcarbinol

The preparation of p-chlorophenyl-2-pyridylcarbinol was accomplished by procedures identical to those for the preparation of

p-methoxyphenyl-2-pyridylcarbinol, with the following exceptions.

Tetrahydrofuran was not used as a solvent in this reaction and was replaced with an equal volume of anhydrous ether. Also, the 2-bromopyridine solution was added at  $-45^{\circ}$  to  $-40^{\circ}$ ; and the p-chlorobenzaldehyde solution (32.0 g., 0.228 mole) was added at  $-35^{\circ}$  to  $-25^{\circ}$ .

The observations during this reaction were also similar to those seen in the preparation of p-methoxyphenyl-2-pyridylcarbinol, with the following exception. Color changes were less evident. The 2-bromopyridine did not produce such a dark coloration; and, when the aldehyde was added, the reaction mixture never reached a green coloration.

#### p-Isopropylphenyl-2-pyridylcarbinol

The preparation of p-isopropylphenyl-2-pyridylcarbinol was accomplished by procedures identical to those for the preparation of p-chlorophenyl-2-pyridylcarbinol. The aldehyde used in this case was p-isopropylbenzaldehyde (33.5 g., 0.225 mole).

The observations during this reaction were also very similar to those seen in the preparation of p-chlorophenyl-2-pyridylcarbinol.

## Preparation of the Phenyl-2-pyridylchloromethanes

### p-Methoxyphenyl-2-pyridylchloromethane

The impure p-methoxyphenyl-2-pyridylcarbinol<sup>14</sup> was dispersed in about 300 ml. of benzene in a four-neck, two liter, round-bottom flask, equipped with a mechanical stirrer, thermometer, water reflux condenser, and dropping funnel. The mixture was cooled to about 10° using an ice-salt bath. At this point, thionyl chloride<sup>15</sup> was added dropwise and with moderate stirring. The temperature of the reaction mixture was kept below 25°. During the addition, the initially brown reaction mixture became yellow and then red and very viscous. After all the thionyl chloride had been added, stirring was continued for one hour at room temperature. Then the temperature of the mixture was brought down to 5°; and aqueous sodium

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<sup>14</sup>Usually, the carbinol formed in three or four runs was combined for this reaction. It was more convenient to synthesize the carbinols on a small scale, so this was necessary. This was also true for the formation of p-chlorophenyl-2-pyridylchloromethane and p-isopropylphenyl-2-pyridylchloromethane.

<sup>15</sup>The amount of thionyl chloride was determined by assuming there was a 45% yield of the carbinol (90) in the previous step. Then a 3:2 molar ratio of thionyl chloride to carbinol was used.



hydroxide (25% w/v)<sup>16</sup> was added dropwise, over about a one hour period, with vigorous stirring. The temperature was maintained below 30° during the addition. The completely neutralized solution was deep red, and a large amount of gummy, red sediment was present. The aqueous layer was extracted twice with about 350 ml. of benzene and combined with the benzene of the reaction mixture. This mixture was washed once with an equal volume of water and dried over anhydrous sodium sulfate. The benzene was removed under reduced pressure, leaving a deep red to brown, viscid residue. This was used without further purification for the next step. The yield was not calculated.

#### p-Chlorophenyl-2-pyridylchloromethane

The p-chlorophenyl-2-pyridylchloromethane was prepared by the same method used to obtain p-methoxyphenyl-2-pyridylchloromethane. The amount of thionyl chloride used was determined by assuming a 75% yield for the carbinol. Again, a 50% excess of thionyl chloride was used.

Observations during this reaction were as follows. After about 5 ml. of thionyl chloride was added, a tan precipitate formed.

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<sup>16</sup> The amount of sodium hydroxide solution needed varied somewhat in different runs. Generally, about 500 ml were needed. The base was added until the reaction mixture gave an alkaline reaction to litmus.

As the addition continued, the reaction mixture became darker and distinct foaming was usually evident. About one-half way through the addition the foaming ceased, and the temperature began to rise much more quickly. The mixture finally turned brown to black in color, and bits of sediment were present. After extraction with benzene the remaining aqueous layer was deep red in color. The benzene mixture was dried and concentrated as before, leaving a brown oil, which was not further purified for the next step. The yield was not calculated.

#### p-Isopropylphenyl-2-pyridylchloromethane

The p-isopropylphenyl-2-pyridylchloromethane was prepared by the same method used to obtain p-methoxyphenyl-2-pyridylchloromethane. The amount of thionyl chloride used was determined by assuming a 75% yield for the carbinol. Here too, a 50% excess of thionyl chloride was used.

Observations during this reaction were as follows. The reaction mixture darkened as the thionyl chloride was added. Later, the color became lighter, and the solution became more viscid. The benzene mixture was dried and concentrated as before, leaving a dark brown oil, which was not further purified for the next step. The yield was not calculated.

## Preparation of the 2-Benzylpyridines

### 2-(p-Methoxybenzyl)pyridine

The crude p-methoxyphenyl-2-pyridylchloromethane previously prepared was dissolved in about 350 ml. of glacial acetic acid in a 500 ml., three-neck, round-bottom flask, equipped with a mechanical stirrer and water cooled condenser. The dark brown mixture was heated on a steam bath, with moderate stirring. Zinc metal dust was added in small increments (about 0.5 g.) every one-half to one hour. The mixture gradually became a deep yellow color. After eight hours, the remaining zinc and zinc salts were filtered from the hot reaction mixture. The acetic acid solvent was removed under reduced pressure, using a boiling water bath. The remaining, very viscid, brown residue was liquified on a steam bath, and about 600 ml. of hot aqueous sodium hydroxide (25% w/v) was added in increments. The mixture was vigorously agitated after each addition until the residue was completely dispersed and an oil began to separate from the aqueous suspension. This mixture was cooled to room temperature and extracted with ether until the aqueous layer was clear and nearly colorless. Some solid matter formed during the extraction. It was collected and leached with about 200 ml. of ether. The extracts were combined and dried over anhydrous sodium sulfate. The ether

solvent was removed under reduced pressure, and the remaining oil was distilled using a four-inch Bantamware<sup>R</sup> fractionating column. The fraction boiling at 135° to 180° (5 mm Hg) was collected (90). The yield<sup>17</sup> was 16%<sup>18</sup>, as calculated from the amount of butyllithium used in the synthesis of the carbinol precursor. The final product was a clear yellow oil.

### 2-(p-Chlorobenzyl)pyridine

The reduction and isolation procedures leading to 2-(p-chlorobenzyl)pyridine were identical to those for 2-(p-methoxybenzyl)pyridine. The observations were also much the same. The crude 2-(p-chlorobenzyl)pyridine was distilled in a like manner, and the fraction boiling from 125° to 140° (1.5 mm Hg) was collected (90). The yield<sup>19</sup> was 56%, as calculated from the amount of butyllithium used in the synthesis of the carbinol precursor. The final product was a clear, light yellow oil.

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<sup>17</sup> This yield represents an average derived from the conversion of five lots of p-methoxyphenyl-2-pyridylcarbinol, which were prepared as previously described.

<sup>18</sup> It is interesting to note that when the tetrahydrofuran was replaced by ether in the preparation of the carbinol, the final yield for five runs was on the order of 35%.

<sup>19</sup> This yield represents an average derived from the conversion of four lots of p-chlorophenyl-2-pyridylcarbinol, which were prepared as previously described.

### 2-(p-Isopropylbenzyl)pyridine

The reduction and isolation procedures leading to 2-(p-isopropylbenzyl)pyridine were identical to those for 2-(p-methoxybenzyl)pyridine. The observations were also much the same. The crude 2-(p-isopropylbenzyl)pyridine was distilled in a like manner, and the fraction boiling from 135° to 165° (5 mm Hg) was collected (90). The yield<sup>20</sup> was 40%, as calculated from the amount of butyllithium used in the synthesis of the carbinol precursor. The final product was a clear, light yellow oil.

### Preparation of the Pyridinium Salts

#### 1-(p-Chlorophenacyl)-2-(p-methoxybenzyl)pyridinium Bromide

Seventeen grams (0.085 mole) of 2-(p-methoxybenzyl)pyridine and 17.5 g. (0.075 mole) of p-chlorophenacyl bromide were mixed together in a 250 ml. beaker and partially liquified by heating to 40° for ten minutes. Five milliliters of acetone and three milliliters of 95% ethanol were added to the mixture, and it was heated to 80° for a minute. At this stage, only a little undissolved matter remained. After about one-half hour at room temperature, needle-like crystals began to form. After another 18 hours, the solution began to darken

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<sup>20</sup>

Ibid., for p-isopropylphenyl-2-pyridylcarbinol.

and was then refrigerated at  $-5^{\circ}$  for two days. The resulting, mushy mixture was dissolved in an excess of hot, 95% methanol, concentrated to about 150 ml., and allowed to stand at  $-5^{\circ}$  for four days. A sparse, yellow powder was removed by suction filtration and recrystallized from boiling acetone, to yield 0.5 g. of a white powder, m.p.  $195-200^{\circ}$  (decomp.). The filtrate was diluted with 75 ml. of acetone and 225 ml. of ether and refrigerated at  $-5^{\circ}$  for six days to give 7.65 g. of additional salt. This filtrate was concentrated to one-quarter volume, stored at  $-5^{\circ}$  for four days, and filtered to yield 0.95 g. more of the white crystalline salt. The total yield of crude product was 9.1 g., (28%). All three collections were combined, pulverized, and leached twice with 150 ml. of acidified acetone.<sup>21</sup> The resulting white powder melted at  $210-212^{\circ}$  (decomp.), as did a portion of this salt which was recrystallized from a sufficient amount of boiling acetone. The conversion of this salt to the proper corresponding indolizine was used as the basis for identification.

#### 2-(p-Methoxybenzyl)-1-(p-methylphenacyl)pyridinium Bromide

Seventeen grams (0.085 mole) of 2-(p-methoxybenzyl)pyridine and 15.9 g. (0.076 mole) of p-methylphenacyl bromide were mixed

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<sup>21</sup> Two to five drops of 10% aqueous hydrochloric acid were added to one pint of analytical reagent acetone. This was done to avoid cyclization of the salt to the indolizine during purification procedures using the acetone solvent.

together in a 250 ml. beaker and liquified by heating in a 40° water bath for ten minutes. The mixture was allowed to stand 18 hours at room temperature and then refrigerated (-5°) for 72 hours. One-hundred and seventy-five milliliters of 95% methanol were mixed with the viscid, brown mass; and the solution was refrigerated (-5°) for 20 hours, resulting in no noticeable changes. The methanol solvent was then removed under reduced pressure leaving a gummy, dark brown residue. This material was triturated with 100 ml. of anhydrous ether for a few minutes and then replaced at -5° for two hours. White crystals were then noted on the walls of the container. After six days of standing at this temperature, nearly all of the residue had changed to off-white crystals. These were suction filtered and washed with 10 ml. of ice-cold acetone. The yield of crude product was 9.75 g. The filtrate was mixed with an equal volume of ether and refrigerated (-5°) for one day to give 0.6 g. of additional salt. Both collections were combined and pulverized to give a white powder, m.p. 188-193° (decomp.). The total yield of crude product was 10.3 g. (32.9%). The powder was leached twice with 200 ml. of boiling, acidified acetone. The resulting white powder melted at 199-201° (decomp.). A small amount of this powder was recrystallized from sufficient, acidified acetone and gave a white powder, m.p. 199-201° (decomp.). The conversion of this salt to the proper corresponding indolizine was used as the basis for

identification.

2-Benzyl-1-(p-methylphenacyl)pyridinium Bromide

Twenty grams (0.118 mole) of 2-benzylpyridine and 26.0 (0.114 mole) of p-methylphenacyl bromide were mixed together in a 250 ml. beaker and liquified on a steam bath. The mixture was refrigerated ( $-5^{\circ}$ ) for three days and the solid tan cake which had formed was dissolved in 200 ml. of hot 95% methanol on a steam bath. This solution was allowed to stand three days at  $-5^{\circ}$ . At this time, the resulting white powder was suction filtered, washed with 10 ml. of ice-cold acetone, and air dried. The yield was 16.6 g. The filtrate was concentrated to one-half the original volume and stored at  $-5^{\circ}$  for three days to yield 0.23 g. Reconcentration of the mother liquor, again by one-half, and refrigeration ( $-5^{\circ}$ ) for seven days gave 0.3 g. of additional salt. The three collections were combined and pulverized, m.p.  $175-180^{\circ}$  (decomp.). The total yield of crude product was 17.1 g. (39.3%). The resulting powder was leached twice with boiling acetone for ten minutes. The remaining white powder melted at  $184-186^{\circ}$  (decomp.), as did a portion of the salt which was recrystallized from sufficient, boiling, acidified acetone. Analysis, calc. for  $C_{21}H_{20}BrNO$ : C, 65.98; H, 5.27; N, 3.66. Found: C, 66.08; H, 5.36; N, 3.62.



2-(p-Chlorobenzyl)-1-(p-methylphenacyl)pyridinium Bromide

Seventeen grams (0.084 mole) of p-chlorobenzylpyridine and 16.9 g. (0.079 mole) of p-methylphenacyl bromide were mixed together in a 250 ml. beaker, liquified on a steam bath, and allowed to stand under a dry nitrogen atmosphere at  $-5^{\circ}$  for three days. The resulting brown cake was dissolved in hot 95% methanol and allowed to stand at  $-5^{\circ}$  for three days to give a fluffy, white powder. The powder was suction filtered and washed with 10 ml. of ice-cold acetone. The yield was 6.82 g., m.p.  $220^{\circ}$  (decomp.). Refrigeration of the filtrate for three days at  $-5^{\circ}$  gave 2.3 g. of additional salt. The total yield of crude product was 9.2 g. (27.8%). The two collections of salt were combined, pulverized, and leached twice with 200 ml. of boiling acetone for ten minutes to give a white powder, m.p.  $220-221^{\circ}$  (decomp.). The conversion of this salt to the proper corresponding indolizine was used as the basis for identification.

2-(p-Chlorobenzyl)-1-(p-chlorophenacyl)pyridinium Bromide

Thirteen grams (0.064 mole) of 2-(p-chlorobenzyl)pyridine and 13.7 g. (0.059 mole) of p-chlorophenacyl bromide were mixed together in a 250 ml. beaker and liquified on a steam bath. The resulting solution was refrigerated for three days at  $-5^{\circ}$ . The resulting cake was dissolved in 100 ml. of hot 95% methanol and allowed to

stand at  $-5^{\circ}$  for three days to give a white solid. The methanol was decanted and the solid dispersed in acetone at room temperature. The resulting white powder was suction filtered and air dried. The yield was 6.0 g., m.p.  $209-210^{\circ}$  (decomp.). Refrigeration ( $-5^{\circ}$ ) of the acetone filtrate gave 5.9 g. of additional salt, m.p.  $207-209^{\circ}$  (decomp.). The total yield of crude product was 11.9 g. (46.3%). Recrystallization of a portion of the salt from boiling acetone gave a white powder, m.p.  $210-211^{\circ}$  (decomp.). The conversion of this salt to the proper corresponding indolizine was used as the basis for identification.

#### 1-(p-Bromophenacyl)-2-(p-isopropylbenzyl)pyridinium Bromide

Eight grams (0.038 mole) of 2-(p-isopropylbenzyl)pyridine and 9.8 g. (0.035 mole) of p-bromophenacyl bromide were mixed together in a 250 ml. beaker and liquified on a steam bath. The resulting tan solution was refrigerated ( $-5^{\circ}$ ) for three days, and the resulting dark brown, transparent cake was dissolved in 75 ml. boiling 95% methanol. The solution was refrigerated ( $-5^{\circ}$ ) for four days. All but about 10 ml. of the methanol was removed under reduced pressure; and the remaining solution refrigerated ( $-5^{\circ}$ ) for three hours, but still no crystals had formed. Twenty milliliters of acetone were added, and about 200 ml. of ether were then slowly poured onto the acetone:methanol solution. A cloudy, white, opaque layer formed

initially; but, after eight hours of standing ( $5^{\circ}$ ), a gummy precipitate remained. The precipitate was filtered and washed with about 25 ml. of methanol to yield 7.26 g. (42%) of off-white powder. The product was recrystallized twice from acidified acetone. The melting point was difficult to determine, since decomposition occurred before any true melting took place. Discoloration began at  $216^{\circ}$  and the final black substance melted at  $229-230^{\circ}$ . Analysis, calc. for  $C_{23}H_{23}Br_2NO$ : C, 56.46; H, 4.74; N, 2.86. Found: C, 56.42; H, 4.77; N, 2.82.

1-(p-Chlorophenacyl)-2-(p-isopropylbenzyl)pyridinium Bromide

Eight grams (0.038 mole) of 2-(p-isopropylbenzyl)pyridine and 8.2 g. (0.035 mole) of p-chlorophenacyl bromide were mixed together in a 250 ml. beaker and liquified on a steam bath. The brown solution was refrigerated ( $-5^{\circ}$ ) for three days, and the resulting dark, crystalline cake was dissolved in about 60 ml. of hot 95% methanol. After refrigeration ( $-5^{\circ}$ ) for two days, no crystals had formed; so the methanol solvent was removed under reduced pressure. The resulting dark brown residue was refrigerated ( $-5^{\circ}$ ) for 24 hours. The residue was then triturated with a few milliliters of acetone and refrigerated ( $-5^{\circ}$ ) for 18 hours, to give some crystals of the salt. At this point, about 75 ml. of anhydrous ether were added until a cloudy white mixture formed over the crystals. Within a

few minutes, a gummy brown residue also formed. This mixture was allowed to stand ( $-5^{\circ}$ ) for eight days to give a gummy, white substance, which, when washed with acetone, yielded 3.5 g. of white powder, m.p.  $183^{\circ}$  (decomp.). An excess of anhydrous ether was added to the filtrate and the mixture was refrigerated ( $-5^{\circ}$ ) for four days to give 1.5 g. of additional white powder. The total yield of crude product was 5.0 g. (32%). The product was recrystallized twice from acidified acetone to yield a white powder, which began to decompose at  $189^{\circ}$ . The resulting black substance melted at  $221-222^{\circ}$ . Analysis, calc. for  $C_{23}H_{23}BrClNO$ : C, 62.11, H, 5.21; N, 3.15. Found: C, 62.00; H, 5.21; N, 3.17.

2-(p-Isopropylbenzyl)-1-(p-methoxyphenacyl)pyridinium Bromide

Eight grams (0.038 mole) of 2-(p-isopropylbenzyl)pyridine and 8.8 g. (0.038 mole) of p-methoxyphenacyl bromide were mixed together in a 250 ml. beaker and liquified on a steam bath. The nearly colorless solution was refrigerated ( $-5^{\circ}$ ) for three days, and the resulting, light, crystalline cake was dissolved in 40 ml. of 95% methanol at room temperature. After four days of refrigeration ( $-5^{\circ}$ ), the methanolic solution showed no sign of crystals. The methanol was therefore removed under reduced pressure. The residue was dissolved in 20 ml. of acetone, and 200 ml. of anhydrous ether were poured onto the solution until the usual cloudy, white

solution formed. After six days at  $-5^{\circ}$ , no crystals had formed so the ether:acetone solvent was removed under reduced pressure. The gummy brown residue was triturated for a few minutes with acetone, and then a large excess of anhydrous ether was added. This mixture was allowed to stand ( $-5^{\circ}$ ) for ten days to yield 10.4 g. (62%) of yellow powder, m.p.  $107-110^{\circ}$ . The product was recrystallized twice from acetone to yield clear, needle-like crystals, m.p.  $124-125^{\circ}$ . Conversion of the salt to the proper indolizine was used as the basis for identification.

2-(p-Methoxybenzyl)-1-(p-methoxyphenacyl)pyridinium Bromide

Four grams (0.02 mole) of 2-(p-methoxybenzyl)pyridine and 4.0 g. (0.018 mole) of p-methoxyphenacyl bromide were mixed together in a 250 ml. beaker and the mixture liquified on a steam bath. The mixture was allowed to stand in a dry nitrogen atmosphere at  $-5^{\circ}$  for three days. The resulting hard brown cake was converted to a powder by adding about 150 ml. of ice-cold acetone to the beaker and "scraping" the surface (of the cake) with a slowly rotating, magnetic stirring bar. The acetone and suspended powder were decanted when about one-half of the cake had been converted; and 150 ml. of fresh, cold acetone was added to repeat the process. The two acetone suspensions were combined and about 300 ml. of ether was slowly added. The resulting mixture had a cloudy white upper layer

and was refrigerated ( $5^{\circ}$ ) for two days to yield 2.0 g. (27%) of a yellow powder, m.p.  $175^{\circ}$  (decomp.). This powder was leached three times with acidified acetone, yielding a white powder, m.p.  $179-181^{\circ}$ . Analysis, calc. for  $C_{22}H_{22}BrNO_3$ : C, 61.69; H, 5.18; N, 3.27. Found: C, 61.64; H, 5.15; N, 3.31.

1-(p-Bromophenacyl)-2-(p-methoxybenzyl)pyridinium Bromide

Eight grams (0.04 mole) of 2-(p-methoxybenzyl)pyridine and 9.5 g. (0.034 mole) of p-bromophenacyl bromide were mixed together in a 250 ml. beaker and the mixture liquified on a steam bath. This mixture was converted to a white powder by the procedures used in the preparation of 2-(p-methoxybenzyl)-1-(p-methoxyphenacyl) bromide. The yield was a coarse, white powder of 9.6 g. (59%), m.p.  $170-175^{\circ}$  (decomp.). This powder was ground to a fine consistency and leached twice with acidified acetone to give a fine white powder, m.p.  $196-197^{\circ}$  (decomp.). The conversion of this salt to the proper corresponding indolizine was used as the basis for identification.

2-(p-Methoxybenzyl)-1-phenacylpyridinium Bromide

Ten grams (0.05 mole) of 2-(p-methoxybenzyl)pyridine and 8.0 g. (0.04 mole) of phenacyl bromide were mixed together in a 250 ml. beaker and liquified on a steam bath. This mixture was

converted to a powder by procedures used in the preparation of 2-(p-methoxybenzyl)-1-(p-methoxyphenacyl)pyridinium bromide. The yield was 12.7 g. (80%) of white powder, m.p. 184-185° (decomp.). This powder was leached twice with acidified acetone, to give a fine white powder, m.p. 186-187° (decomp.). The conversion of this salt to the proper corresponding indolizine was used as the basis for identification.

#### Preparation of the Indolizines

##### 2-(p-Methylphenyl)-1-phenylindolizine

Five grams (0.013 mole) of 2-benzyl-1-(p-methylphenacyl)-pyridinium bromide was suspended in 200 ml. of pyridine. The solution became cloudy during this time and was stirred occasionally until it was completely clear and homogenous. The pyridine solvent was removed under reduced pressure, leaving a yellow crystalline solid. The crude indolizine was immediately recrystallized from methanol: acetone (4:1). After 24 hours at 5°, the resulting yellow crystals were suction filtered and dried in air. The yield was 2.5 g., m.p. 119-121°. Water was added to the mother liquor until cloudy, and the suspension was allowed to stand at -5° for one day to give 0.8 g. of additional indolizine, m.p. 118-121°. The total yield of crude product was 3.3 g. (90%). Two recrystallizations from petroleum

ether:acetone (3:1) gave clear, yellow crystals, m.p. 120-121°.

Analysis, calc. for  $C_{21}H_{17}N$ : C, 89.01; H, 6.05; N, 4.94. Found: C, 89.09; H, 6.02; N, 4.82.

2-(p-Chlorophenyl)-1-(p-methoxyphenyl)indolizine

Three grams (6.9 millimoles) of 1-(p-chlorophenacyl)-2-(p-methoxybenzyl)pyridinium bromide was added to approximately 200 ml. of hot pyridine. The solution took on the normal yellow coloration, became cloudy, and finally cleared after being heated and stirred on a steam bath for about 15 minutes. The pyridine solution was concentrated to 100 ml. under reduced pressure and refrigerated (-5°) for three hours. No crystals formed, so the remaining solvent was likewise removed to give a gummy, yellow crystalline mass. This was agitated with 200 ml of 95% ethanol on a steam bath; and after about two minutes, a heavy, flocculant precipitate formed throughout the ethanolic solution. About 100 ml. of additional 95% ethanol and 25 ml. of acetone were added and heating was continued until solution was affected. The solution was filtered and refrigerated (5°) for two hours to yield a dense, fluffy, off-white precipitate, which was suction filtered and air dried. The yield was 1.82 g. (79%), m.p. 122-126°. Recrystallization from, first, petroleum ether:acetone (3:1) and, then, just petroleum ether gave fluffy yellow to off-white crystals, m.p. 125-126°. Analysis, calc.



for  $C_{22}H_{15}ClNO$ : C, 75.56; H, 4.83; N, 4.20; Cl, 10.62. Found: C, 75.68; H, 4.90; N, 4.25; Cl, 10.85.

1-(p-Methoxyphenyl)-2-(p-methylphenyl)indolizine

Three grams (7.3 millimoles) of 2-(p-methoxybenzyl)-1-(p-methylphenacyl)pyridinium bromide was added to about 200 ml. of pyridine. The solution immediately turned the usual yellow color and cleared after 15 minutes of heating on the steam bath. The pyridine solvent was removed under reduced pressure, and the remaining yellow crystals were dissolved in a minimum amount of hot methanol. The solution was refrigerated for 3 days at  $5^{\circ}$ , but no crystals formed. Water was then added to the solution, dropwise, until it became cloudy. Refrigeration ( $5^{\circ}$ ) of this suspension gave an oily residue after one hour. The methanol solvent was removed under reduced pressure, and the gummy matter remaining was dissolved in a minimum amount of hot 95% ethanol. The solution was filtered and refrigerated ( $5^{\circ}$ ). Within about a half hour crystals began to form; and three hours later, they were collected by suction filtration and washed with 5 ml. of ice-cold 95% ethanol. The total yield of crude product was 1.5 g. (63), m.p.  $95-98^{\circ}$  (decomp.). Recrystallization from, first, 95% ethanol and then petroleum ether gave fluffy, yellow to orange crystals, m.p.  $103-104^{\circ}$  (decomp.). Analysis, calc. for  $C_{22}H_{19}NO$ : C, 84.32; H, 6.11; N, 4.47.

Found: C, 84.26; H, 6.14; N, 4.49.

1-(p-Chlorophenyl)-2-(p-methylphenyl)indolizine

Two grams (4.8 millimoles) of 2-(p-chlorobenzyl)-1-(p-methylphenacyl)pyridinium bromide was added to 200 ml. of pyridine. The usual yellow coloration occurred. The cloudy solution cleared after about 15 minutes on a steam bath, and the pyridine solvent was removed under reduced pressure to yield yellow-green crystals. These were recrystallized twice from ethanol:acetone (3:1) to give 0.6 g. of tan crystals, m.p. 132-133° (decomp.). The mother liquor was evaporated to one-half its original volume, seeded, and stored at -5° for three days to yield 0.65 g. of indolizine, m.p. 132-133° (decomp.). Evaporation of the remaining solvent gave 0.7 g. of residue, m.p. 130-133° (decomp.). The total yield of crude product was 1.05 g. (69%). Analysis, calc. for  $C_{21}H_{16}ClN$ : C, 79.36; H, 5.07; N, 4.41; Cl, 11.16. Found: C, 79.56; H, 4.98; N, 4.40; Cl, 11.37.

1,2-Bis(p-chlorophenyl)indolizine

Two grams (4.6 millimoles) of 2-(p-chlorobenzyl)-1-(p-chlorophenacyl)pyridinium bromide was added to 200 ml. of pyridine. The solution turned pink initially; and, when heated and stirred on a steam bath, changed to a yellow cloudy mixture. Heating was

continued for 20 minutes until the usual clear homogenous solution was obtained. The pyridine was removed under reduced pressure, leaving off-white crystals, which were recrystallized twice from ethanol:acetone (3:1). The yield was 0.8 g. of light green crystals, m.p. 168-169° (decomp.). The mother liquors were combined, reduced to one-half their original volume, seeded, and refrigerated (-5°) for three days. The resulting light green crystals weighed 0.70 g. The filtrate was evaporated to give 0.5 g. of residue, m.p. 165-168° (decomp.). The total yield of crude product was 1.45 g. (93%). Analysis, calc. for  $C_{20}H_{13}Cl_2N$ : C, 71.02; H, 3.87; N, 4.14; Cl, 20.96. Found: C, 70.87; H, 3.91; N, 4.15; Cl, 21.15.

1-(p-Isopropylphenyl)-2-(p-methoxyphenyl)indolizine

Nine-hundred milligrams (2 millimoles) of 2-(p-isopropylbenzyl)-1-(p-methoxyphenacyl)pyridinium bromide was added to 100 ml. of warmed (about 40°), aqueous sodium bicarbonate (10%). This mixture was stirred at the same temperature for about 15 minutes, giving a cloudy yellow solution containing a sparse, curdy, yellow precipitate. The mixture was then refrigerated (5°) for about three hours and filtered with suction to yield a brittle, yellow solid. The crude indolizine was pulverized, leached with about 100 ml. of warm water and air dried. The total yield of crude product was 500 mg. (73%). Recrystallization from 95% ethanol gave a tan

powder, m.p. 148-150° (decomp.). This product was recrystallized twice from petroleum ether to give light yellow crystals, m.p. 151-152°. Analysis, calc. for  $C_{24}H_{26}NO$ : C, 84.42; H, 6.79; N, 4.10. Found: C, 84.22; H, 6.78; N, 4.10.

2-(p-Bromophenyl)-1-(p-methoxyphenyl)indolizine

One and one-half gram (3 millimoles) of 1-(p-bromophenacyl)-2-(p-methoxybenzyl)pyridinium bromide was heated on a steam bath with about 75 ml. of pyridine. The solution first turned yellow and then changed to deep brown after about five minutes. The pyridine solvent was then removed under reduced pressure, and the gummy brown residue was dispersed in cold methanol. Solution was incomplete and 0.5 g. of a flakey brown solid, m.p. 131-133° (decomp.), remained undissolved after about 20 minutes. The remaining solution was evaporated to dryness in a stream of air to give 0.2 g. of a dry brown solid, m.p. 138-140° (decomp.). The total yield of crude product was 62%. The collected solids were combined, pulverized, and recrystallized twice from petroleum ether to give a brown, fluffy crystalline solid, m.p. 138-139° (decomp.). Analysis, calc. for  $C_{21}H_{16}BrNO$ : C, 66.68; H, 4.26; N, 3.70. Found: C, 66.54; H, 4.18; N, 3.71.

1-(p-Methoxyphenyl)-2-phenylindolizine

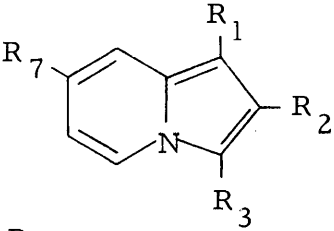
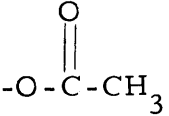
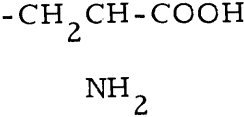
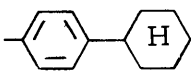
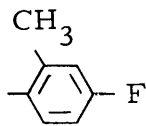
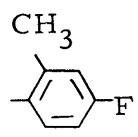
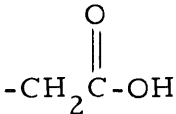
One and one-half gram (3.8 millimoles) of 2-(p-methoxybenzyl)-1-phenacylpyridinium bromide was heated on a steam bath with about 100 ml. of pyridine. The solution became clear yellow and was heated for an additional 20 minutes. The pyridine solvent was removed under reduced pressure and the gummy residue dissolved in methanol:acetone (6:1). The solvent was evaporated in a stream of air to yield 0.7 g. of a yellow-brown solid, m.p. 92-95° (decomp.). The total yield of crude product was 62%. Two recrystallizations from petroleum ether gave small, yellow-green, nugget-like crystals, m.p. 94-95° (decomp.). Analysis, calc. for  $C_{21}H_{17}NO$ : C, 84.25; H, 5.72; N, 4.68. Found: C, 84.19; H, 5.68; N, 4.71.

## DISCUSSION OF PHARMACOLOGY

Summary of Literature Reports Concerning  
Indolizine Pharmacology

The literature contains only a few reports of the biological activity of indolizines. No systematic study has been reported. Hirose (52) showed that 2-methylindolizine (XXVIII) and 1-acetyl-2-methyl-3-aminoindolizine (XXIX) produced convulsions, motor paralysis and respiratory paralysis in mice, frogs, and rabbits. It has been noted that 1-indolizinealanine (XXX) is active in vitro as a feedback inhibitor of indole synthesis in the indole accumulating mutant of Salmonella typhimurium (69). This is thought to be due to this indolizine's similarity to tryptophan. Accordingly, Carbon and Brehm (25) have also considered 1-indolizinealanine as a tryptophan antimetabolite. Buu-Hoï et al. (23) and Buu-Hoï and Xuong (22) have considered 2-(p-cyclohexylphenyl)indolizine (XXXI), 2-(4-fluoromethylphenyl)indolizine (XXXII), and 2-(4-fluoro-2-methylphenyl)-7-methylindolizine (XXXIII) as carcinogens; but they failed to mention whether these compounds are carcinogenic. As was mentioned earlier, indolizine-1-acetic acid (XXXIV) (79) was found to have analgesic and anti-inflammatory activity. Table 6 lists these indolizines, which have been considered for biological activity.

Table 6. Biologically Active Indolizines Reported in the Literature

				
Compound	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>7</sub>
XXVIII	H	CH <sub>3</sub>	H	H
XXIX		CH <sub>3</sub>	NH <sub>2</sub>	H
XXX		H	H	H
XXXI <sup>a</sup>	H		H	H
XXXII <sup>a</sup>	H		H	H
XXXIII <sup>a</sup>	H		H	CH <sub>3</sub>
XXXIV		H	H	H

<sup>a</sup>Biological activity has not been fully substantiated for this compound.

To date, the only p-substituted 1, 2-diphenylindolizines prepared for potential biological activity have been synthesized by Venturella (100, 101, 102). These compounds were under investigation for psychotropic activity in 1964 (101); however, as yet, no reports have appeared in the literature.

#### Results of Pharmacological Screening of Some of the Indolizines Prepared in This Investigation

Through the courtesy of Smith, Kline, and French Laboratories, several of the compounds were tested for anti-inflammatory activity.<sup>22</sup> In the adjuvant induced arthritis screen on rats, 2-(p-methylphenyl)-1-phenylindolizine and 2-(p-bromophenyl)-1-(p-methoxyphenyl)indolizine ". . . were ineffective in reducing the paw swelling produced by a standard injection of mycobacterium." (110), as compared to Indoxol, which gave significant results. The compounds were administered orally in tragacanth suspension, once a day for 16 days. It should be noted here that factors such as route of administration, dose, and test animal are often critical with respect to a drug's observed activity. Therefore, these parameters should be varied before any definite conclusions are drawn about the anti-inflammatory activity of these indolizines.

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<sup>22</sup>Other tests (e.g. anti-viral screening) are being conducted presently.



At present, an overall pharmacological study of 2-(p-methyl-phenyl)-1-phenylindolizine is being conducted by Dr. Robert Larson, Professor of Pharmacology, Oregon State University, School of Pharmacy. Preliminary results of tests with 2-(p-chlorophenyl)-1-(p-methoxyphenyl)indolizine are not promising. Severe liver damage and death occur in mice, usually within several days after intraperitoneal administration of 100  $\mu$ g to 1 mg./kg. in dimethylsulfoxide vehicle.

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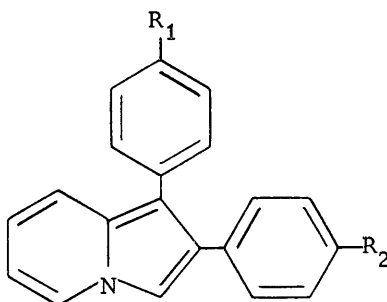
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## APPENDICES

APPENDIX A  
INFRARED DATA

Some Characteristic Infrared Absorbances of the Indolizines  
and Pyridinium Bromides Prepared<sup>a, b</sup>

Indolizines



$R_1$	$R_2$	Location of Major Absorbptions ( $\text{cm}^{-1}$ )
$-\text{OCH}_3$	$-\text{H}$	1605, 1308, 1287, 1248, 1182, 1032, 966, 843, 752, 735, 701, 612
$-\text{OCH}_3$	$-\text{CH}_3$	1609, 1304, 1284, 1245, 1175, 1035, 829, 754, 734
$-\text{OCH}_3$	$-\text{Br}$	1610, 1311, 1286, 1245, 1178, 1036, 1014, 965, 835, 756, 735, 706
$-\text{OCH}_3$	$-\text{Cl}$	1604, 1286, 1249, 1176, 1037, 1018, 836, 755, 733
$-\text{Cl}$	$-\text{CH}_3$	1621, 1305, 1224, 1092, 1017, 965, 844, 825, 752
$-\text{Cl}$	$-\text{Cl}$	1627, 1372, 1310, 1223, 1094, 1019, 964, 833, 814, 753, 663
$-\text{iPr}$	$-\text{OCH}_3$	1610, 1287, 1247, 1178, 1033, 836, 758
$-\text{H}$	$-\text{CH}_3$	1596, 1304, 829, 769, 743, 705, 665

<sup>a</sup> All spectra were obtained from samples imbedded in potassium bromide discs made with the Wilks Mini-Press.

<sup>b</sup> These data are presented as a partial description of the infrared spectrum of the given compound. Only some of the major absorbptions are listed. No attempt is made to present all the distinguishable absorbptions.

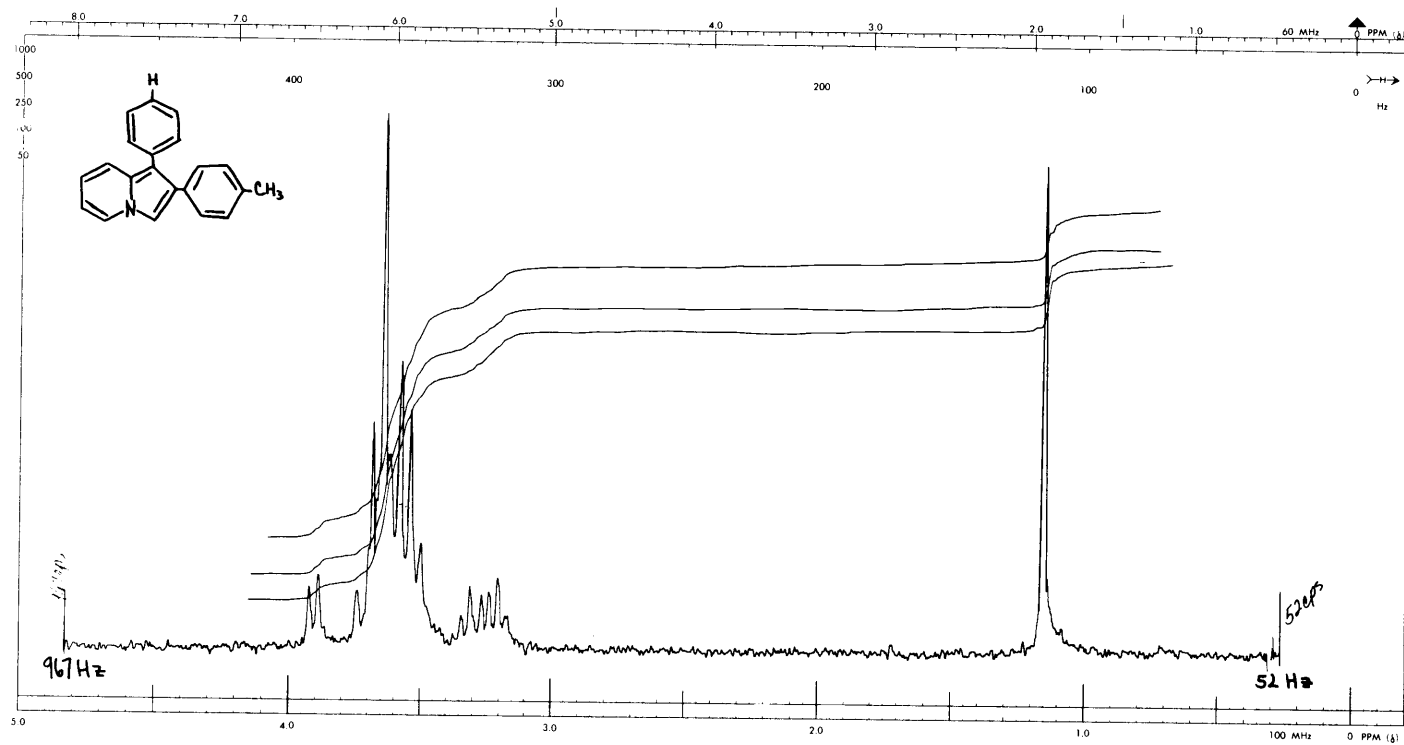




## APPENDIX B

## NUCLEAR MAGNETIC RESONANCE SPECTRA

All spectra were obtained from an approximately 10% (w/v) solution of the sample in deuterated chloroform (Stohler Isotope Chemicals), containing 1% tetramethylsilane as the internal standard.



NAME SPECTRUM  
 DATE *Oct 27-70* SPECTRUM NO. *1452*  
 NUCLEUS  $^1\text{H}$  INSTRUMENT *HA-100*  
 OPERATOR *CJB* FREQUENCY *100* MHz  
 SAMPLE *C-1*  
**2-(2-Methylphenyl)-1-phenyl indolizine**

SOLVENT \_\_\_\_\_ CONCENTRATION \_\_\_\_\_ REFERENCE *TMS*  
 TEMPERATURE \_\_\_\_\_ °C (LOCK SIGNAL) *TMS*  
 SWEEP MODE *333* FREQ SWEEP ☐ Hz  
 WIDTH *333* \_\_\_\_\_ Hz  
 TIME \_\_\_\_\_ sec  
 OFFSET \_\_\_\_\_ Hz

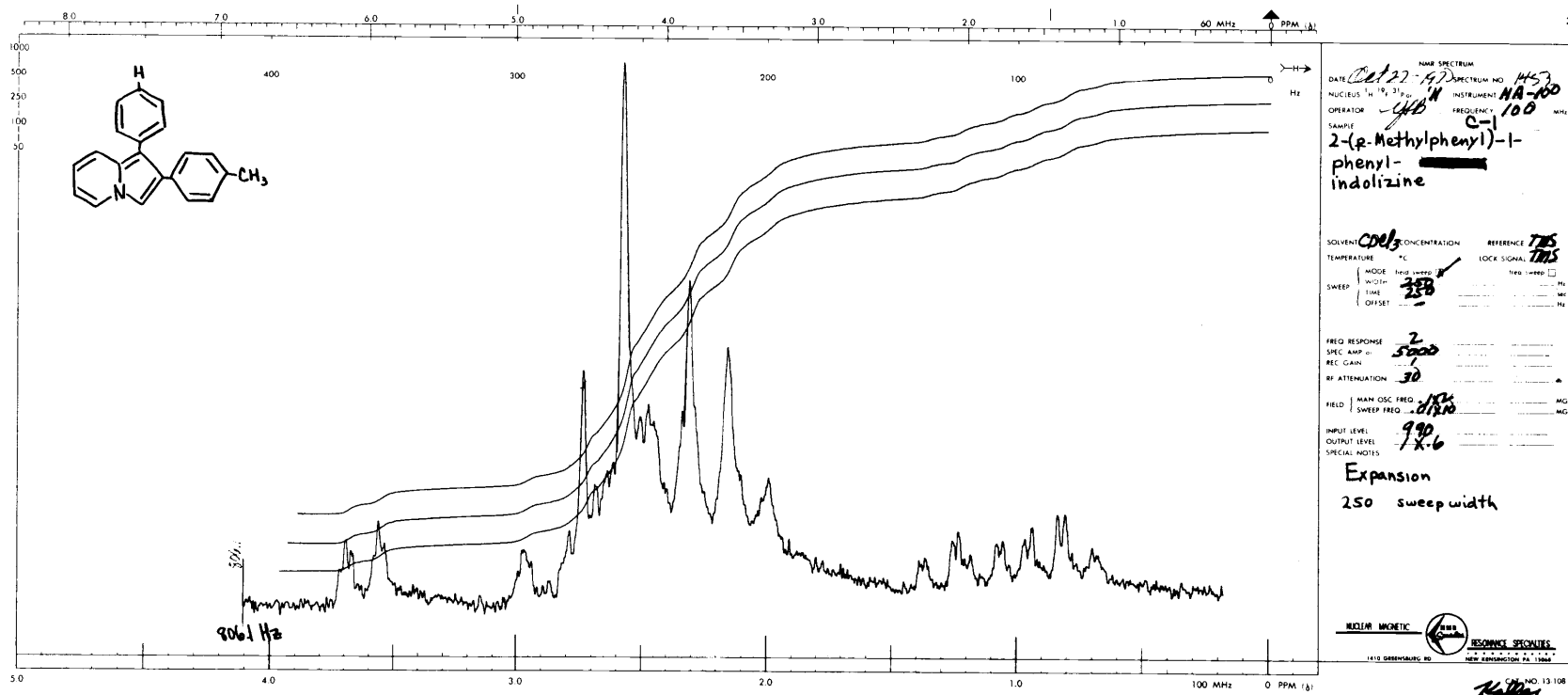
FREQ RESPONSE *5000* \_\_\_\_\_  
 SPEC AMP or \_\_\_\_\_  
 REC GAIN \_\_\_\_\_  
 RF ATTENUATION *30* \_\_\_\_\_ dB

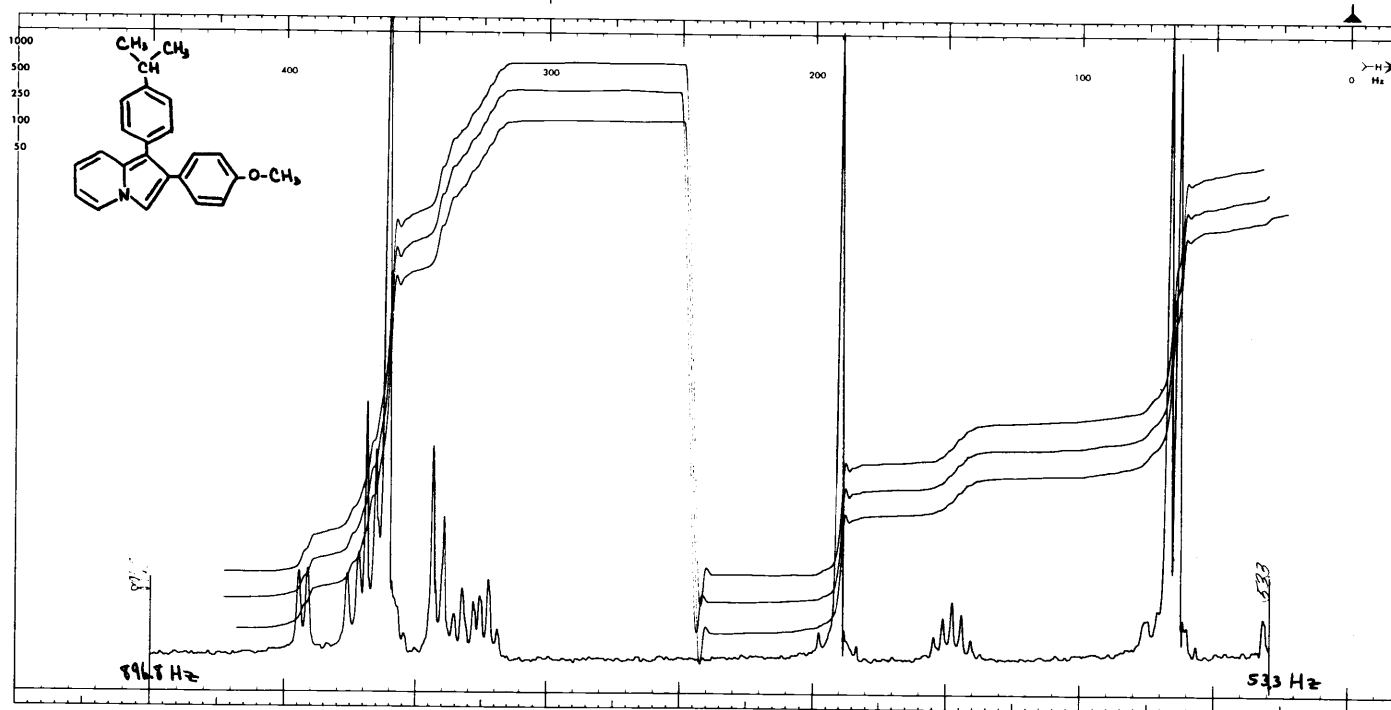
FIELD | MAIN OSC FREQ *100* \_\_\_\_\_ MHz  
 SWEEP FREQ *100* \_\_\_\_\_ MHz

INPUT LEVEL *9.0* \_\_\_\_\_  
 OUTPUT LEVEL *10.4* \_\_\_\_\_  
 SPECIAL NOTES \_\_\_\_\_

NUCLEAR MAGNETIC  
 RESONANCE SYSTEMS  
 1410 GREENBURG RD.  
 NEW BRUNSWICK, N.J. 08901

*Kallos*





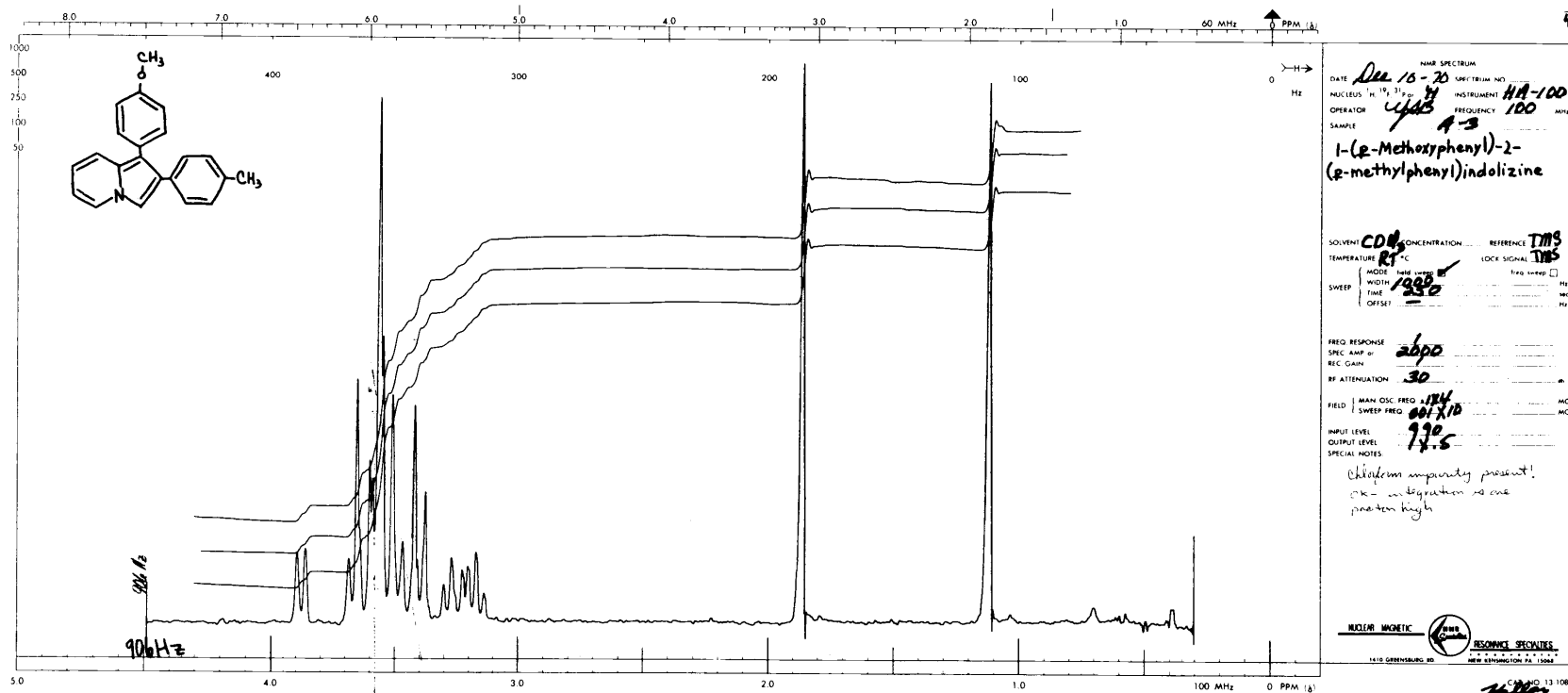
HA-100 SPECTRUM 3

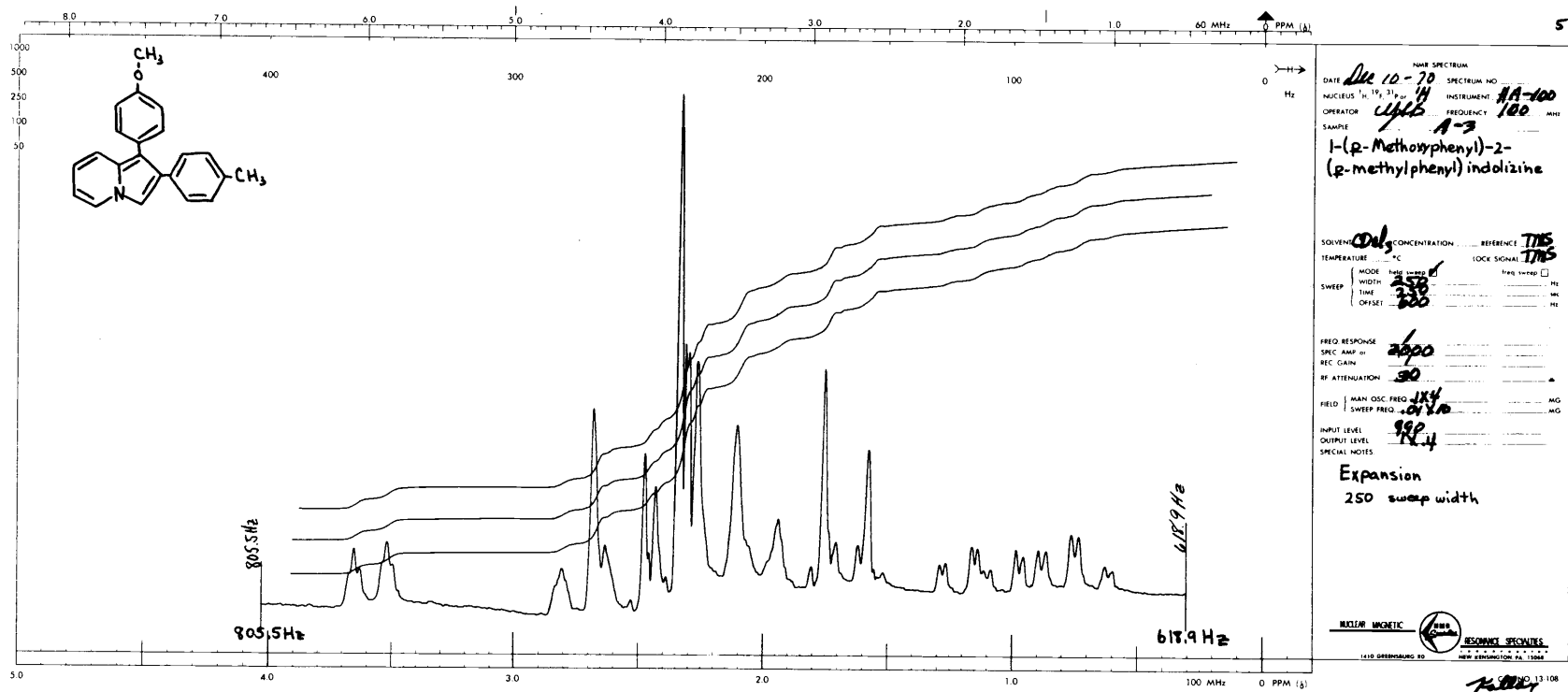
100 MHz NMR  
SPECTRUM NO. 448  
OPERATOR: JHB DATE 2-25-77  
SAMPLE: 1  
D-5  
1-(2-Isopropylphenyl)-2-(p-methoxyphenyl)indolizine

SOLVENT CDCl<sub>3</sub>  
TEMPERATURE RT °C  
FREQ. RESPONSE 1 Hz  
R. F. ATTENUATOR 30 db  
SWEEP TIME 250 sec  
SWEEP WIDTH 1000 Hz  
SWEEP OFFSET - Hz  
SPECTRUM AMP. 2000  
OUTPUT 12.5  
LOCK SIGNAL 775  
MANUAL OSC. 12.5 m gauss  
SWEEP OSC. 12.5 m gauss  
EXT. OSC. FREQ. - Hz  
EXT. OSC. AMP. - PP mV  
R. F. REF. PHASE 264  
FIELD SWEEP ☒  
FREQ. SWEEP ☐

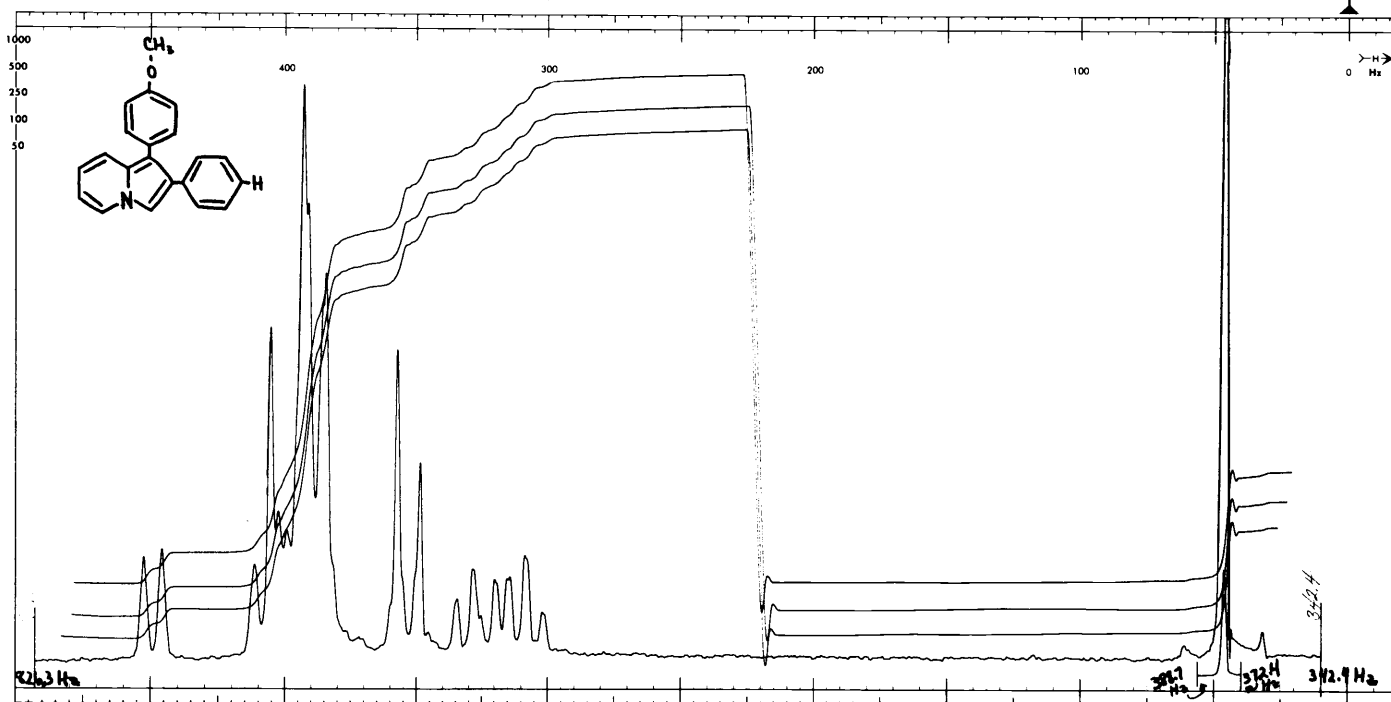
RECEIVED CHART  
GRAPHIC: 100 MHz NMR  
NO. VN 1000  
10-1000

Keller





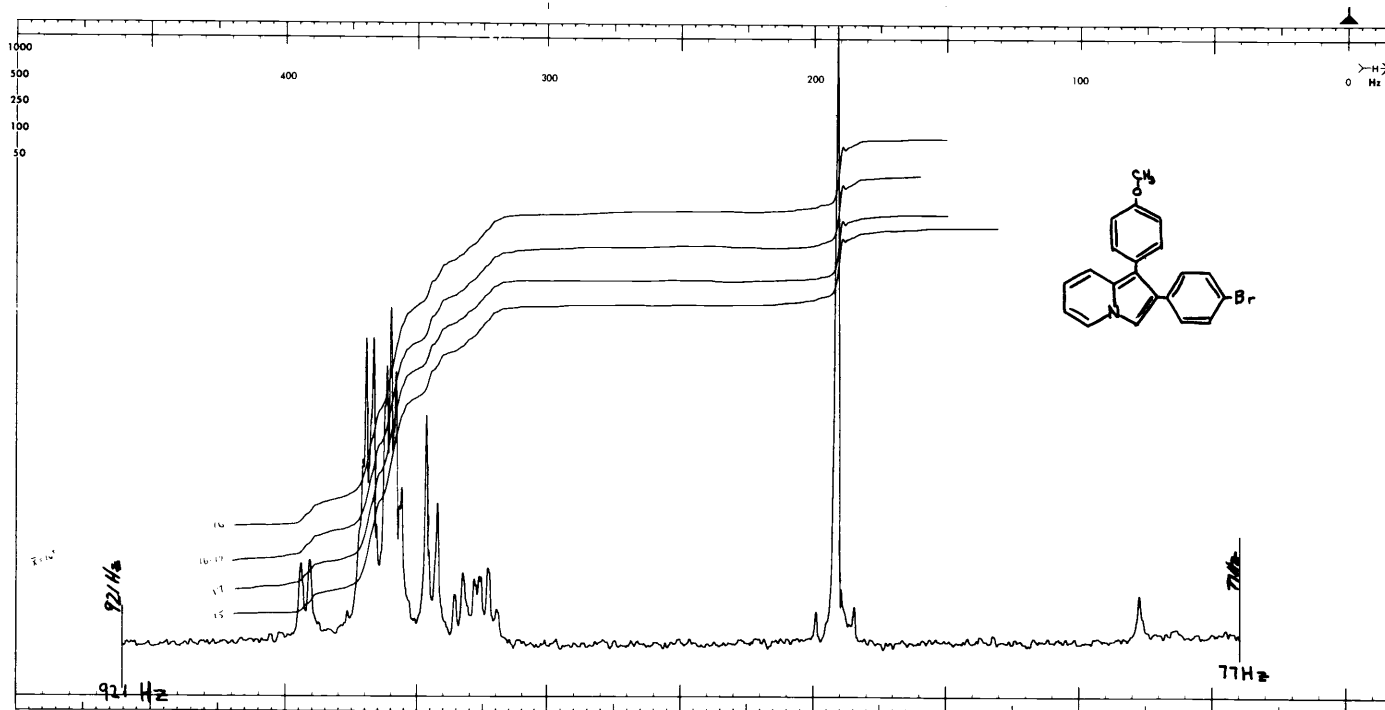




HA-100 SPECTRUM  
 100 MHZ NMR  
 SPECTRUM NO. *446*  
 OPERATOR: *YJB* DATE *Feb 25*  
 SAMPLE: *A-5*  
**1-(2-Methoxyphenyl)-2-phenylindoline**

SOLVENT	<i>CDCl<sub>3</sub></i>	
TEMPERATURE	<i>RT</i>	°C
FREQ. RESPONSE	<i>30</i>	Hz
R. F. ATTENUATOR	<i>20</i>	dB
SWEEP TIME	<i>250</i>	sec
SWEEP WIDTH	<i>100</i>	Hz
SWEEP OFFSET	<i>340</i>	Hz
SPECTRUM AMP.	<i>200</i>	
OUTPUT	<i>12.4</i>	
LOCK SIGNAL	<i>17.5</i>	m gauss
MANUAL OSC.	<i>.01X</i>	m gauss
SWEEP OSC.	<i>.01X</i>	Hz
EXT. OSC. FREQ.	<i>-</i>	Hz
EXT. OSC. AMP.	<i>-</i>	mV
R. F. REF. PHASE	<i>-</i>	
FIELD SWEEP	<input checked="" type="checkbox"/>	
FREQ. SWEEP	<input type="checkbox"/>	

RECORDED BY *Kaller*  
 GRAPHIC CONTROL CORPORATION  
 BUFFALO, NEW YORK  
 NO. VN 1006  
 (8-10061)



HA-100 SPECTRUM  
100 MHz NMR  
SPECTRUM NO. 1033  
OPERATOR: JBS DATE Jan 19-71  
SAMPLE: A-4

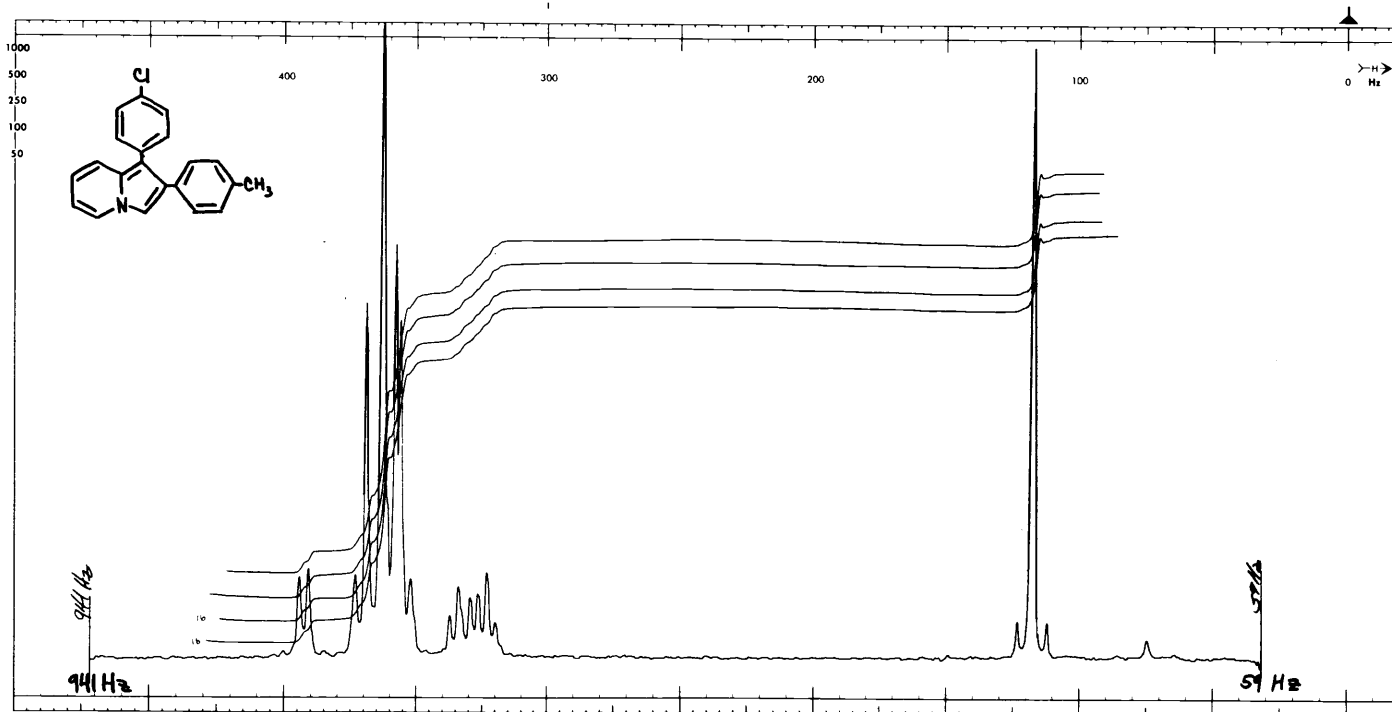
2-(p-Bromophenyl)-1-(p-methoxyphenyl)indoline

SOLVENT CDCl<sub>3</sub>  
TEMPERATURE RT  
FREQ. RESPONSE 1  
R. F. ATTENUATOR 30  
SWEEP TIME 250  
SWEEP WIDTH 1000  
SWEEP OFFSET -  
SPECTRUM AMP. 5000  
OUTPUT 12.5  
LOCK SIGNAL 12.5  
MANUAL OSC. 12.5  
SWEEP OSC. 0.1 Hz  
EXT. OSC. FREQ. -  
EXT. OSC. AMP. -  
R. F. REF. PHASE -  
FIELD SWEEP ☒  
FREQ. SWEEP ☐

°C  
Hz  
db  
sec  
Hz  
Hz  
m gauss  
m gauss  
Hz  
PP mV

RECORDED BY: CHART  
GRAPHIC CONTROL CORPORATION  
BURLINGTON, MASS. 01803  
NO. VN 1006  
(3-10041)





HA-100 SPECTRUM  
100 MHZ NMR  
SPECTRUM NO.  
OPERATOR: *yhb* DATE: *Jan 15-77*  
SAMPLE: *B-2*

1-(p-chlorophenyl)-2-(p-methylphenyl)indolizine

SOLVENT: *CDCl<sub>3</sub>*  
TEMPERATURE: *RT* °C  
FREQ. RESPONSE: *10* Hz  
R. F. ATTENUATOR: *10* dB  
SWEEP TIME: *25.0* sec  
SWEEP WIDTH: *1000* Hz  
SWEEP OFFSET: *-* Hz  
SPECTRUM AMP.: *3000*  
OUTPUT: *15.4*  
LOCK SIGNAL: *7.15*  
MANUAL OSC.: *.1X5* m gauss  
SWEEP OSC.: *.01X10* m gauss  
EXT. OSC. FREQ.: *-* Hz  
EXT. OSC. AMP.: *-* mV  
R. F. REF. PHASE: *28.1*  
FIELD SWEEP: ☒  
FREQ. SWEEP: ☐

RECORDED ON CHART  
GRAPHIC CORPORATION  
BOSTON, MASS 02108  
NO. VN 1006  
(5-100A)

*Kelly*

