

**PART A: THE CHEMICAL PHARMACOLOGY OF SOME  
2-PHENOXYCYCLOALKYLAMINES AND ANALOGS**

**PART B: THE APPLICATION OF CHLOROSULPHONYL ISOCYANATE  
IN THE SYNTHESIS OF CYCLIC SULPHAMYL UREAS**

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**by**

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**1962**

**.....Research Director**

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To Dr. Bernard Belleau, whose constant optimism and enthusiasm seemed to make the time pass so quickly, my respectful dedication.

For my wife Claire, who tolerated fluctuating moods and a multitude of lonely evenings, my deepest admiration and affection.

My gratitude is due also to Mr. A. Castagne of the National Research Council, for supplying many of the elemental analyses, to Dr. M. Pindell of Bristol-Myers, for providing most of the pharmacological assays, and to the National Cancer Institute of Canada, for a generous grant in support of this research.

## CONTENTS

### PART I: THE CHEMICAL PHARMACOLOGY OF SOME 2-PHENOXYCYCLOALKYLAMINES AND ANALOGS

|                                                                                               | Page |
|-----------------------------------------------------------------------------------------------|------|
| I. INTRODUCTION . . . . .                                                                     | 1    |
| Historical . . . . .                                                                          | 1    |
| Optical Isomerism . . . . .                                                                   | 3    |
| Geometrical Isomerism . . . . .                                                               | 3    |
| (a) <u>cis-trans</u> Olefins . . . . .                                                        | 3    |
| (b) Rotational and Diastereo-Isomerism . . . . .                                              | 5    |
| (c) Configurations Frozen by a Ring . . . . .                                                 | 8    |
| II. RESULTS AND DISCUSSION . . . . .                                                          | 18   |
| Introduction . . . . .                                                                        | 18   |
| 1. The Phenoxy-cyclopentane Series . . . . .                                                  | 21   |
| (a) N-Methyl- <u>cis</u> -2-Phenoxy-cyclopentylamine . . . . .                                | 21   |
| (b) N-Methyl-N-( $\beta$ -Chloroethyl- <u>cis</u> -2-Phenoxy-<br>cyclopentylamine . . . . .   | 22   |
| (c) <u>cis</u> -2-Phenoxy-cyclopentylamine . . . . .                                          | 23   |
| (d) <u>trans</u> -2-Phenoxy-cyclopentylamine . . . . .                                        | 26   |
| (e) N-Methyl- <u>trans</u> -2-Phenoxy-cyclopentylamine . . . . .                              | 29   |
| (f) N-Methyl-N-( $\beta$ -Chloroethyl- <u>trans</u> -2-Phenoxy-<br>cyclopentylamine . . . . . | 29   |
| 2. The Benzyl-cyclopentane Series . . . . .                                                   | 30   |
| (a) <u>trans</u> -2-Benzyl-cyclopentylamine . . . . .                                         | 30   |
| (b) The Reductive Amination of 2-Benzylcyclo-<br>pentanone . . . . .                          | 31   |
| (c) <u>trans</u> -1-Nitro-2-Benzylcyclopentane . . . . .                                      | 32   |
| (d) <u>2</u> -Benzylcyclopentanol . . . . .                                                   | 33   |
| (e) Some Anomalous Reactions . . . . .                                                        | 35   |
| 3. The Phenoxy-cyclobutane Series . . . . .                                                   | 37   |
| (a) <u>cis</u> -2-Phenoxy-cyclobutylamine . . . . .                                           | 37   |
| (b) <u>2</u> -Phenoxy-cyclobutanol . . . . .                                                  | 38   |

|                                                                                                                                   | Page |
|-----------------------------------------------------------------------------------------------------------------------------------|------|
| 4. The Phenoxycyclopropane Series . . . . .                                                                                       | 39   |
| (a) 2-Phenoxycyclopropane Carboxylic Acids . . . . .                                                                              | 39   |
| (b) <u>cis</u> - and <u>trans</u> -2-Phenoxycyclopropane<br>Intermediates . . . . .                                               | 41   |
| (c) The Reduction of 2-Phenoxycyclopropyl Methyl<br>Urethanes and of <u>trans</u> -2-Phenoxycyclo-<br>propyl Isocyanate . . . . . | 43   |
| (d) The Thermal Decomposition of <u>trans</u> -2-<br>-Phenoxycyclopropylamine . . . . .                                           | 44   |
| 5. The Base Strengths of the Amines . . . . .                                                                                     | 45   |
| 6. The Biochemical Implications of <u>cis-trans</u><br>Isomerism . . . . .                                                        | 48   |
| (a) Adrenergic Blocking Activity . . . . .                                                                                        | 48   |
| (b) Other Pharmacological Observations . . . . .                                                                                  | 55   |
| (c) The Monoamine Oxidase Inhibitors . . . . .                                                                                    | 56   |
| III. EXPERIMENTAL . . . . .                                                                                                       | 59   |
| 1. The Synthesis of <u>cis</u> -2-Phenoxycyclopentylamines . . . . .                                                              | 59   |
| (a) <u>trans</u> -2-Phenoxycyclopentyl Chloride . . . . .                                                                         | 59   |
| (b) <u>N</u> -Methyl- <u>cis</u> -2-Phenoxycyclopentylamine . . . . .                                                             | 60   |
| (c) <u>N</u> -( $\beta$ -Hydroxyethyl)- <u>cis</u> -2-Phenoxycyclopentyl-<br>amine . . . . .                                      | 60   |
| (d) <u>N</u> -Methyl- <u>N</u> -( $\beta$ -hydroxyethyl)- <u>cis</u> -2-<br>-Phenoxycyclopentylamine . . . . .                    | 61   |
| (e) <u>N</u> -Methyl- <u>N</u> -( $\beta$ -chloroethyl)- <u>cis</u> -2-<br>-Phenoxycyclopentylamine . . . . .                     | 62   |
| (f) The Synthesis of <u>cis</u> -2-Phenoxycyclopentyl-<br>amine . . . . .                                                         | 62   |
| 2. The Synthesis of <u>trans</u> -2-Phenoxycyclopentylamines . . . . .                                                            | 66   |
| (a) <u>cis</u> -2-Phenoxycyclopentanol . . . . .                                                                                  | 66   |
| (b) <u>trans</u> -2-Phenoxycyclopentanol . . . . .                                                                                | 68   |
| (c) <u>trans</u> -2-Phenoxycyclopentyl Azide . . . . .                                                                            | 69   |
| (d) <u>trans</u> -2-Phenoxycyclopentylamine . . . . .                                                                             | 69   |
| (e) <u>N</u> -Formyl- <u>trans</u> -2-Phenoxycyclopentylamine . . . . .                                                           | 70   |
| (f) <u>N</u> -Methyl- <u>trans</u> -2-Phenoxycyclopentylamine . . . . .                                                           | 70   |
| (g) <u>N</u> -Methyl- <u>N</u> -( $\beta$ -hydroxyethyl)- <u>trans</u> -2-<br>-Phenoxycyclopentylamine . . . . .                  | 71   |
| (h) <u>N</u> -Methyl- <u>N</u> -( $\beta$ -chloroethyl)- <u>trans</u> -2-<br>-Phenoxycyclopentylamine . . . . .                   | 72   |
| 3. The Synthesis of Benzylcyclopentylamines . . . . .                                                                             | 73   |
| (a) <u>trans</u> -2-Benzylcyclopentylamine . . . . .                                                                              | 73   |
| (b) The Reduction of 2-Benzylcyclopentanone<br>Oxime . . . . .                                                                    | 73   |

|                                                                                                          | Page |
|----------------------------------------------------------------------------------------------------------|------|
| 3. (c) The Reductive Amination of 2-Benzylcyclopentanone . . . . .                                       | 74   |
| (d) <u>trans</u> -1-Nitro-2-Benzylcyclopentane . . . . .                                                 | 74   |
| (e) The Reduction of <u>trans</u> -1-Nitro-2-Benzylcyclopentane . . . . .                                | 75   |
| (f) The Attempted Isomerization of <u>trans</u> -1-Nitro-2-Benzylcyclopentane . . . . .                  | 76   |
| (g) The Reduction of 2-Benzylcyclopentanone . . . . .                                                    | 76   |
| (h) The Reduction of 2-Benzylidenecyclopentanone Oxime . . . . .                                         | 77   |
| (i) The Lithium-tri- <i>t</i> -Butoxyaluminumhydride Reduction of 2-Benzylcyclopentanone Oxime . . . . . | 78   |
| 4. The Synthesis of 2-Phenoxycyclobutylamine . . . . .                                                   | 79   |
| (a) <u>cis</u> -Phenoxycyclobutylamine . . . . .                                                         | 79   |
| (b) <u>2</u> -Phenoxycyclobutanol . . . . .                                                              | 80   |
| 5. The Synthesis of 2-Phenoxycyclopropylamines . . . . .                                                 | 81   |
| (a) 2-Phenoxycyclopropane Carboxylic Acids . . . . .                                                     | 81   |
| (b) <u>trans</u> -2-Phenoxycyclopropyl Methyl Urethane . . . . .                                         | 82   |
| (c) <u>trans</u> -2-Phenoxycyclopropylamine . . . . .                                                    | 84   |
| (d) The Reduction of <u>trans</u> -2-Phenoxycyclopropyl Methyl Urethane . . . . .                        | 85   |
| (e) The Reduction of <u>trans</u> -2-Phenoxycyclopropyl Isocyanate . . . . .                             | 86   |
| (f) N-Methyl- <u>trans</u> -2-Phenoxycyclopropylamine . . . . .                                          | 86   |
| (g) <u>cis</u> -2-Phenoxycyclopropyl Methyl Urethane . . . . .                                           | 87   |
| (h) <u>cis</u> -2-Phenoxycyclopropylamine . . . . .                                                      | 88   |
| (i) The Reduction of <u>cis</u> -2-Phenoxycyclopropyl Methyl Urethane . . . . .                          | 88   |
| 6. Potentiometric Titrations . . . . .                                                                   | 89   |
| IV. CLAIMS TO ORIGINAL RESEARCH . . . . .                                                                | 91   |
| V. BIBLIOGRAPHY . . . . .                                                                                | 93   |
| PART B: THE APPLICATION OF CHLOROSULPHONYL ISOCYANATE IN THE SYNTHESIS OF CYCLIC SULPHAMYL UREAS         |      |
| I. INTRODUCTION . . . . .                                                                                | 97   |
| 1. The Chemistry of Sulphonyl Isocyanates . . . . .                                                      | 97   |
| (a) Chlorosulphonyl Isocyanate . . . . .                                                                 | 97   |
| (b) <i>p</i> -Toluenesulphonyl Isocyanate . . . . .                                                      | 101  |

|                                                                                                 | Page |
|-------------------------------------------------------------------------------------------------|------|
| 2. The Chemotherapeutic Significance of Some Sulphonamides . . . . .                            | 103  |
| (a) Antibacterials . . . . .                                                                    | 103  |
| (b) Anticancer Agents . . . . .                                                                 | 104  |
| (c) Diuretics . . . . .                                                                         | 105  |
| (d) Antidiabetic Drugs . . . . .                                                                | 105  |
| II. RESULTS AND DISCUSSION . . . . .                                                            | 106  |
| Introduction . . . . .                                                                          | 106  |
| 1. The Reaction of Chlorosulphonyl Isocyanate with 2-Aminopyridine . . . . .                    | 106  |
| (a) N-Chlorosulphonyl-N'-2-Pyridylurea . . . . .                                                | 106  |
| (b) 2, 4, 6-Pyridothiazine-3(2H)-one-1,1-Dioxide . . . . .                                      | 107  |
| (c) The Solvolysis of 2, 4, 6-Pyridothiazine-3(2H)-one-1,1-Dioxide . . . . .                    | 109  |
| (d) Potentiometric Titration of 2, 4, 6-Pyridothiazine-3(2H)-one-1,1-Dioxide . . . . .          | 110  |
| (e) The Reaction of 2-Pyridylurea Ethosulphate With Dehydrating Agents . . . . .                | 114  |
| (f) Physiological Data . . . . .                                                                | 115  |
| 2. N, N-Dimethylformamidine-N'-Sulphonic Acid . . . . .                                         | 115  |
| 3. The Attempted Synthesis of a Cyclic Sulphonyl Urethane . . . . .                             | 116  |
| III. EXPERIMENTAL . . . . .                                                                     | 118  |
| 1. The Reaction of Chlorosulphonyl Isocyanate with 2-Aminopyridine . . . . .                    | 118  |
| (a) N-Chlorosulphonyl-N'-2-Pyridylurea . . . . .                                                | 118  |
| (b) 2, 4, 6-Pyridothiazine-3(2H)-one-1,1-Dioxide . . . . .                                      | 119  |
| (c) The Acid-Catalysed Hydrolysis of 2, 4, 6-Pyridothiazine-3(2H)-one-1,1-Dioxide . . . . .     | 120  |
| (d) The Hydrolysis of 2, 4, 6-Pyridothiazine-3(2H)-one-1,1-Dioxide in Alkaline Medium . . . . . | 122  |
| (e) The Neutral Aqueous Hydrolysis of 2, 4, 6-Pyridothiazine-3(2H)-one-1,1-Dioxide . . . . .    | 122  |
| (f) The Methanolysis of 2, 4, 6-Pyridothiazine-3(2H)-one-1,1-Dioxide . . . . .                  | 123  |
| (g) The Methanolysis of 2-Pyridylurea Methosulphate . . . . .                                   | 124  |
| (h) The Ethanolysis of 2, 4, 6-Pyridothiazine-3(2H)-one-1,1-Dioxide . . . . .                   | 124  |
| (i) Potentiometric Titration of 2, 4, 6-Pyridothiazine-3(2H)-one-1,1-Dioxide . . . . .          | 125  |

|     |                                                                                                                                 |     |
|-----|---------------------------------------------------------------------------------------------------------------------------------|-----|
| 1.  | (j) Preparation of the Sodium Salts of 2, 4, 6-<br>-Pyridothiatriazine-3(2H)-one-1,1-Dioxide                                    | 125 |
|     | (k) Intramolecular Amidolysis of 2-Pyridylurea<br>Ethosulphate . . . . .                                                        | 127 |
| 2.  | The Reaction of Chlorosulphonyl Isocyanate with<br>Dimethylformamide: N, N-Dimethylformamidine-<br>-N'-Sulphonic Acid . . . . . | 128 |
| 3.  | The Reaction of Chlorosulphonyl Isocyanate with<br>Phenol and Aluminium Chloride: Phenyl Urethane                               | 128 |
| IV. | CLAIMS TO ORIGINAL RESEARCH . . . . .                                                                                           | 130 |
| V.  | BIBLIOGRAPHY . . . . .                                                                                                          | 131 |

PART A

THE CHEMICAL PHARMACOLOGY OF SOME  
2-PHENOXYCYCLOALKYLAMINES  
AND ANALOGUES



## I. INTRODUCTION

### Historical

The relationship between the chemical structure of a compound and its biological activity has been a subject of investigation since the late nineteenth century.

The development of this field of study has been marked by several transitions in the degree of sophistication that the structure-activity relationship (S. A. R.) assumed. For example, it soon became apparent that the type of molecule which constituted a hormone usually differed substantially both in skeletal and functional group characteristics from classes of compounds whose biological properties were generally associated with, say antibacterial, autonomic nervous, or analgesic activity.

From the inception of S. A. R. studies, all aspects, both subtle and generalized, were developed side by side up to the present day. A strictly chronological presentation of conceptual development in this field would therefore be misleading.

One of these early concepts, which is still undergoing modification and restatement, is the idea of a "lock-and-key" fit of a drug to its biological receptor. This viewpoint, which was independently enunciated by Erlich (1) and by Fischer (2), recognized several factors which determine the efficacy of this fit. Amongst these were surface shape and surface area of the molecule as well as the electronic nature of the functional groups involved.

When it was finally recognized that drastic alterations in chemical structure usually caused profound and unpredictable changes in the mode of action of a compound, S.A.R. studies were limited to restricted classes of chemicals. Structural variations within a class of compounds have, in general, been confined to observations of the effect on activity of positional isomerism (e.g., the dihydroxyphenols), homologation (e.g., the n-alkylresorcinols and the p-aminobenzoate esters), and isosteric changes (e.g., the sulphonamide antibacterials).

Stereoisomerism was early recognized as being a factor of considerable significance in this field. This realization initiated the investigation of molecular fine-structure as it pertains to biological activity.

Several fundamentals have been recognized as a result of the past sixty years of work in this field: the concept of the bio-receptor and its active sites, the kinetic and thermodynamic treatment of drug-receptor interaction (binding constants, reversibility, the nature of inhibition, etc.), the chemical classification of nervous transmission (adrenergic, cholinergic), and the correlation of physical properties (dissociation constants, surface activity, lipid solubility, etc.) with drug action.

The remainder of this survey will bear on stereoisomerism as it pertains to S.A.R., with particular emphasis on aspects which are more significant to the development of this part of the thesis. It is understood throughout this discussion that the bio-activity of a drug is determined by three distinct parameters, namely the selective permeability of all intervening anatomic structures, the compound's affinity

(binding ability) and its eventual efficacy (ability to initiate, at a receptor site, the appropriate molecular alteration which leads to a response).

### Optical Isomerism

The discovery by Pasteur (3) that ammonium tartrate exists in two forms which rotate the plane of polarized light in opposite directions was coupled with his finding that certain ferment enzymes can distinguish between the dextro- and levo- forms of tartaric acid.

Since that time, innumerable reports concerning biological specificity with respect to optical isomerism have been published (4-11). Two particularly thorough monographs in this field are that of Cushny (12), which deals with the alkaloids, and of a recent symposium (13) which covers many of the enzymic studies and their mechanistic implications.

We are not surprised, in retrospect, that this kind of specificity is existent in view of our present knowledge of the asymmetric nature of protein components which constitute the semipermeable membranes and postulated receptor sites.

### Geometrical Isomerism

#### a) Cis-trans Olefins

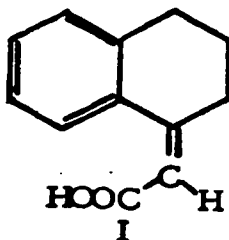
In 1922 Dakin (14) showed that the action of the enzyme, fumarase on fumaric acid yields malic acid whereas maleic acid is not a substrate for this enzyme.

Cooper and Edgar (15) investigated the respective physiological

properties of maleic and fumaric acids. They demonstrated that various biological systems exhibit a definite specificity for one or the other member of this pair of isomers. Still further work was done on these two acids by Fabisch (16) and by Steensholt (17).

Sistrone and Stanier (18) investigated muconate-lactonizing enzyme and showed that it produces carboxymethyl- $\gamma$ -butenolide from cis-cis-muconic acid at five thousand times the rate that it lactonizes cis-trans-muconic acid to the enantiomeric butenolide, whereas trans-trans-muconic acid is not lactonized at all by this enzyme.

Amongst the plant-growth stimulants, cis-cinnamic acid is active in this respect, whereas the trans isomer is inactive. Also, compound I is active, but its trans isomer is not (19).



A review article by Pitt and Morton (20) emphasizes the significance of cis-trans isomerism in the olefin, retinene as it pertains to the visual process.

It is expected, in general, that there will be greater differences in biological activity between double bond cis-trans isomers than there are between the members of a pair of enantiomers. Cis-trans isomers differ in their physical and chemical properties as well as in their spatial orientation whereas enantiomers differ only with respect to the latter aspect, and are of identical free energy content. For this reason, correlations between physico-chemical properties such as pKa, dipole moment, redox potential, etc., and the relative activity

of each member of a pair of geometric isomers can be undertaken, whereas a similar undertaking with enantiomers is meaningless.

Physico-chemical correlations have occasionally led to hypotheses of high predictive value, as has been amply illustrated with the acridine series (positional isomerism) where the bacteriostatic potencies and the base strengths of the members of the series rise together (21).

b) Rotational Isomerism and Diastereoisomerism

The non-bonded interactions between groups in an open-chain compound are known to introduce energy barriers to free rotation of these groups about the single bonds. The extent of these barriers for a given molecule depends on the electronic nature of the functional groups as well as on their size and interatomic distance.

It is of considerable importance, in the case of bio-active substances, to ascertain the nature and magnitude of these forces in order to correctly interpret S. A. R.: the nature of the ground-state conformation of a drug molecule ought frequently to determine the ease of its interaction with receptor groups. If this conformation is such that a receptor must overcome a considerable energy barrier at its substrate before it can form with it an effective complex, then the affinity of the drug will be reduced proportionately. If, on the other hand, suitable modifications are introduced in the molecular chain of the drug such that the ground state of the substance corresponds to a more favourable conformation with respect to its complementary receptor sites, then a corresponding increase in the affinity

of the drug should take place.

Ameliorative modifications of such a fundamental type facilitate the definition of receptor site requirements. They are therefore of the utmost significance to S.A.R. studies in general.

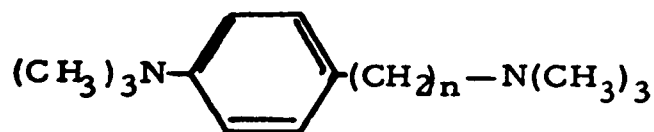
One of the more definitive attempts at the application of this kind of reasoning is the statistical analysis published by Gill (22) of the percentage of each conformation present in the ground state of the various members of a series of polymethylene bis-quaternary amines (II).



II

It was calculated that the probability that the inter-quaternary distance will lie between the postulated inter-receptor distance range of 6 - 7.8 Å (for the cholinergic sites in ganglia) reaches a maximum at  $n = 5$ , although observed maximum of activity comes at  $n = 6$  for compounds II.

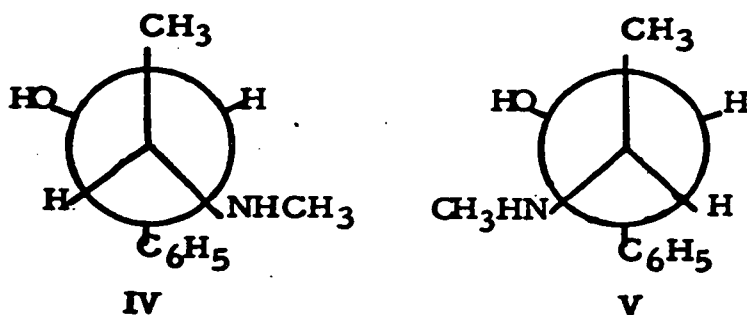
For the phenylalkane series (III), however, these calculations indicate a maximum inter-quaternary distance probability in the range of 6 - 7.8 Å at  $n = 2$ , which coincides with an observed maximum of ganglionic blocking activity at  $n = 2$  for compounds III.



III

For diastereoisomers, the most stable conformations of the threo, erythro and meso isomers of a compound will all be different. Again, one should observe corresponding differences in biological action, due both to the differences in rotational free energy barriers, as well as to the configurational differences between the asymmetric carbon atoms.

This aspect of S.A.R. is adequately exemplified with the ephedrines. Although (-)-ephedrine (IV) is only three times as active a pressor agent as is the (+) enantiomer, it is thirty-five times as potent as the (-)- $\psi$ -diastereoisomer (V) (23).

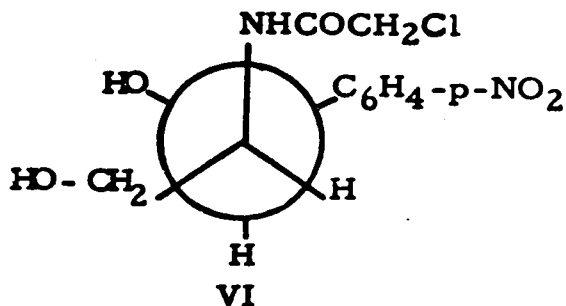


Furthermore, the rate of N-to-O acyl migration in N-benzoyl-(-)- $\psi$ -ephedrine is greater than the corresponding rate for N-benzoyl-(-)-ephedrine (24).  $\psi$ -Ephedrine must have a conformation in which the amino and hydroxyl groups are close, whereas the conformation of ephedrine must be one in which these two groups are relatively far apart.

The difference in activities between the two diastereoisomers must be due in part to a receptor requirement to which the conformation of IV is more complementary than is the conformation of V.

Similar observations have been made for chloramphenicol (VI), whose D(-)-threo isomer is a potent antibacterial while the L(+)-

-threo, L(+)-erythro, and D(-)-erythro isomers are inactive (25).



### c) Configurations Frozen by a Ring

Perhaps the most extensive investigations in this field have been undertaken with ring geometrical isomers. The steroids alone account for a vast number of S. A. R. studies with respect to this class of cis-trans isomerism.

The important factor requiring special consideration in this phase of the discussion is the nature of the alicyclic rings themselves. The results of conformational analyses of cyclohexane rings are well known. Very likely, the energy barriers separating the various conformations in such compounds are sufficiently low as to be overcome occasionally by a bio-receptor. The result would be a drug-receptor complex possessing a cyclohexane ring with a conformation different from that which it would possess in the unbound substrate. If suitable functional group modifications are made on a cyclohexyl compound of potential biological interest, and if such changes result in an abrupt increase in activity, then the possibility that the energy barrier to certain essential conformational transitions may have been lowered to a critical value must be accounted for in such S. A. R. studies. Of course, it is unlikely that a bio-receptor could force a cis or trans conformation



through binding since the energy barrier for such a transition is most likely too high. To a lesser degree, the same applies to rotational isomers, although the energy barriers are usually smaller and more difficult to estimate. This limitation may be circumvented by freezing the open-chain compound in alternative conformations through the construction of ring analogues.

The bulk of the ring itself might, of course, have a considerable influence on activity at all stages of transport, adsorption, and activation of receptor sites. Suitable theoretical allowances must be made for this when ring analogs of open-chain drugs are prepared and also when the ring size is changed.

Similar reasoning can be applied to drugs possessing the cyclopentane ring since this ring is flexible and non-planar (26). Standaert and Friess (27) failed to take this into account in their explanations of observed activity differences within pairs of cis-trans cyclopentane and cyclohexane congeners of cholinergic drugs.

The stereochemistry of disubstituted cis-trans cyclopentane isomers is controlled to a considerable degree by the size of their substituents (28). Spatial relationships between certain 1,2-disubstituted cis-trans cyclopentane compounds are therefore not nearly so different as one would visualize from a planar cyclopentane model. Consequently, such isomers permit the study of the susceptibility of a given bio-receptor to small changes in the relative orientation of prosthetic groups. Although the energy barrier for cis-to-trans transitions may be too large for the receptor to overcome, the receptor surface may be able to bring about an appreciable alteration of the interatomic distance

between substituents in a disubstituted cyclopentane compound.

In the cyclobutane ring, the degree of flexibility is very much reduced. Spatial differences between cis-trans disubstituted isomers therefore become quite appreciable (29). In addition, the free energy barrier to any significant alteration of interatomic distances between substituents is very likely beyond being overcome by any bio-receptor. If a receptor possesses rigid steric requirements, the cyclobutane isomers of a drug would accordingly be more likely to reflect such specificity than would the cyclopentane analogs.

Another factor may also be affected upon a transition from drugs containing rings of cyclopentane size and larger to congeners with cyclobutane rings. This is the relative resistance of attached groups toward displacement and elimination reactions. Solvolytic and other studies on cyclobutane compounds have indicated that displacements of both the bimolecular and unimolecular type, as well as elimination reactions, are considerably more difficult in the cyclobutane series than they are in the analagous larger ring compounds (30). If the process leading to a biological response at the receptor level involves such displacements or eliminations in the substrate, then the efficacy of a cyclobutyl compound should be lower than the efficacy of a corresponding cyclopentyl analog. Conversely, if a bio-response requires that the substrate be stable to such displacements or eliminations at the receptor level, then the substrate analogs with rings smaller than a cyclopentane ring should exhibit an enhanced or more prolonged activity.

In cyclopropane compounds, the spatial differences between cis and trans isomers attain a maximum. Furthermore, the reactivity of

many of the ring substituents is altered to such an extent that special considerations must be introduced in the S.A.R. theory to properly account for this characteristic.

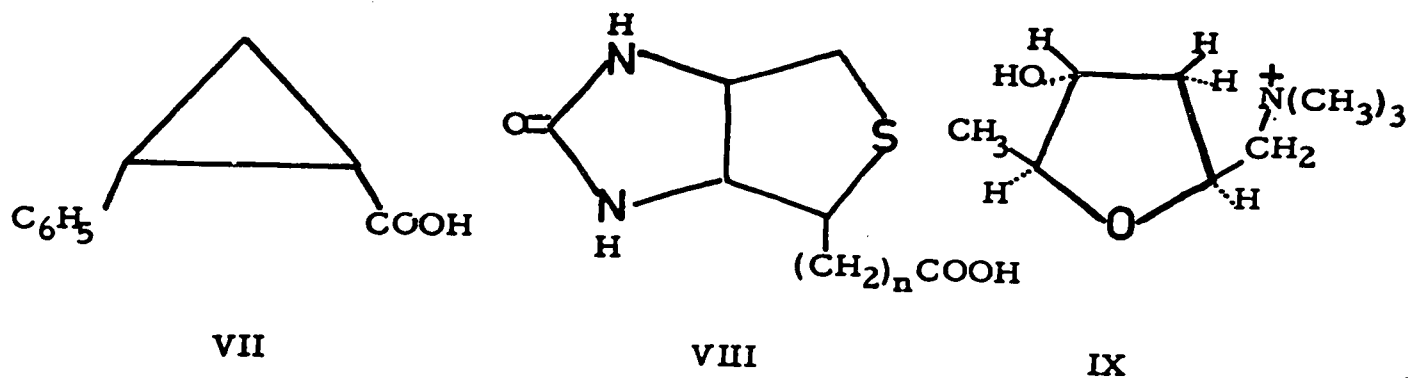
Another feature which is unique to the cyclopropane ring in the alicyclic series is its ability to enter into pseudo-conjugation with suitable groups (31a, b). Clearly, this property will profoundly influence the nature of the substituents if one or both of these are strongly inductive. Both the chemical and biological properties of such cyclopropyl compounds will reflect this phenomenon. A further complication is the degree to which this pseudo-conjugation is dependent on the geometric orientation of the functional groups (cis or trans).

Finally, the cyclopropane ring has a well-known propensity to undergo a wide variety of ring cleavage and rearrangement reactions (32). Whether or not this takes place during formation of the drug-receptor complex, must be carefully ascertained before any S.A.R. correlation is undertaken. If either of these reactions does take place under physiological conditions, it is possible that the actual active species is the product of the rearrangement or ring cleavage reaction rather than the starting substrate. This is a particularly important problem if steric factors favour the rearrangement in one isomer and not in the other.

A few interesting examples of cis-trans isomerism in alicyclic drugs are given in the forthcoming paragraphs.

The cis isomer of 2-phenylcyclopropane carboxylic acid (VII) is a plant growth stimulant, whereas the trans isomer is inactive in this respect (33). Optical isomerism is also significant in that there is a

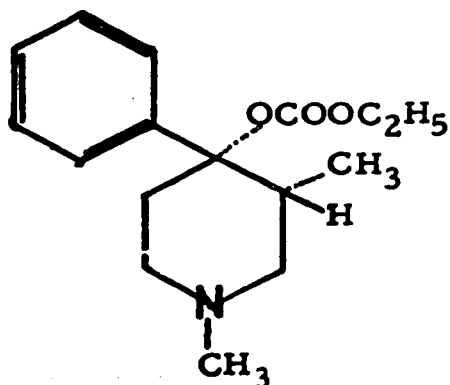
potency difference between the enantiomers of the cis isomer. This indicates that an  $\alpha$ -hydrogen is probably involved in the formation of the receptor-substrate complex as a third point of attachment.



Only the cis isomers of biotin (VIII) are growth factors for micro-organisms (34).

Barlow's review (35) of the pharmacology of muscarine (IX) reveals that, with respect to activity on frog heart, (+)muscarine has the greatest activity followed in descending order by ( $\pm$ )epiallo-muscarine, ( $\pm$ )allo-muscarine, ( $\pm$ )epi-muscarine and (-)muscarine. These findings indicate that the relative positions of the quaternary nitrogen, the hydroxyl group, the methyl group, and possibly the ether oxygen atom, determine the ease with which muscarine can interact with its receptor.

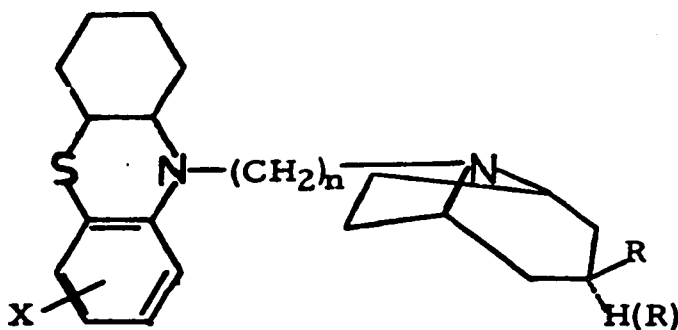
Zierling and Lee (36) investigated the stereochemistry of pethidine analogs and noted that the trans isomer of 1,3-dimethyl-4-phenyl-4-propionyloxypiperidine (X) had ten times the analgesic potency of the cis isomer.



X

They compared the conformation of the trans compound with that of the highly potent analgesic, dihydrodesoxynormorphine-D, in which the prethetic groups are also in a trans relationship.

Long, Lands and Zenitz (37) studied the pharmacology of some 8-(-10-phenothiazinyl)-substituted nortropanes (XI) where "n", "R", and "x" were varied independently for both the cis and the trans relationship between the "R" group and the nitrogen bridge.

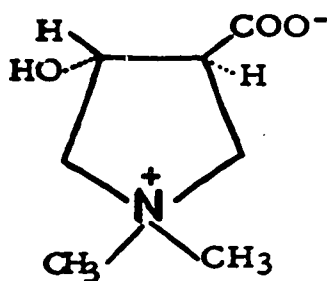


XI

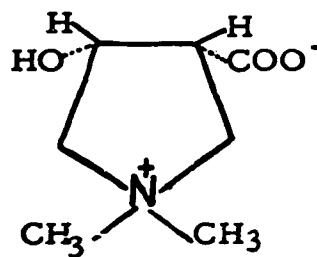
The trans isomers are all more potent than their respective cis isomers as both central nervous depressants and adrenolytics. The authors suggest that in the cis isomer, hydrogen bonding between the nitrogen atom and the "R" group (usually hydroxyl) probably hinders effective attachment of these groups to appropriate receptor sites. The general spatial differences would also be reflected in the adaptation

of each isomer to complex formation.

Friess, Patchett and Witkop (38) noted that L-betonicine (XII) inhibits acetylcholinesterase (Ach-ase) while neither the D nor the L isomer of turicine (XIII), the cis isomer of XII, is active in this respect.



XII



XIII

Friess and co-workers also investigated a series of cis-trans isomers of 2-hydroxycyclopentyl- and 2-hydroxycyclohexylamines and their analogues with regard to a variety of cholinergic and other responses which they elicited. This work will now be described in somewhat greater detail since the results have considerable bearing on the remainder of this part of the thesis.

With regard to:

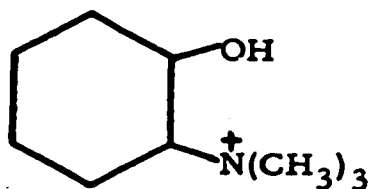
(a) acetylcholinesterase inhibition (39, 40),

(b) LD<sub>50</sub> (41),

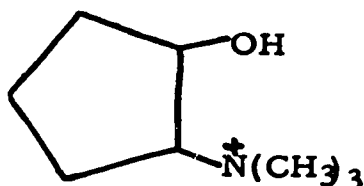
(c) convulsive action (41),

and (d) neuromuscular and phrenic nerve blockade (27),

the cis isomers of both the cyclohexyl (XIV) and the cyclopentyl (XV) compounds are more potent than the trans isomers by factors of two to ten.



XIV



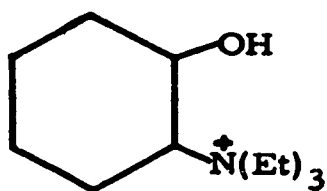
XV

For (a), the cis isomer of XV is more potent than the cis isomer of XIV, but by contrast, for (d), the order of potency of these two compounds is inverted.

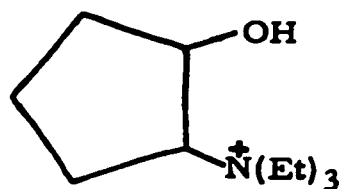
Also, for tests (b), (c), and (d), cis-trans mixtures of either XIV or XV show potentiation of effect, whereas if the trans isomers are administered prior to the cis isomers in each case, there is antagonism of effect.

For ganglionic blockade (42), the activity of the cis cyclopentyl compound (XV) is greater than that for the trans isomer, but the cis and trans isomers of the cyclohexyl analog (XIV) are equipotent. Although cis-trans mixtures of XV show neither antagonism nor potentiation in this test, a cis-trans mixture of XIV exhibits potentiation.

When the triethyl analogs, XVI and XVII were tested for convulsive potency and LD<sub>50</sub> (41), it was found that the cis isomers are each more potent than their respective trans isomers.



XVI



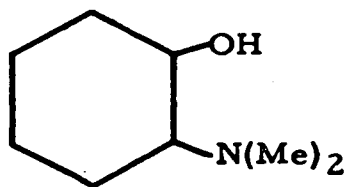
XVII

With the tertiary analogs of XIV (XVIII), the cis isomer has seventy times the Ach-ase inhibitory power of the trans isomer. Also, the potency of the cis isomer diminishes as the pH of the test medium is decreased below 8.1 (43). The trans isomer of XVIII is the more potent compound for depression of the fight reflex in Betta splendens (44).

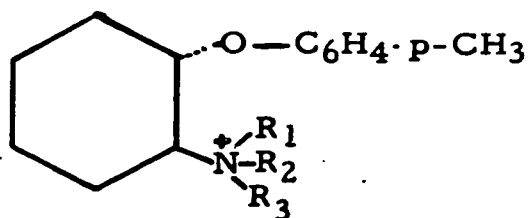
The diethyl analog of XVIII (XIX) was tested for (44):

- (a) Ach-ase inhibition,
  - (b) Betta fight reflex inhibition,
  - (c) convulsive power,
- and (d) sciatic nerve block.

The cis isomer of XIX is the more potent isomer for (b) and (c); the potency order of the isomers of XIX is reversed for both tests (a) and (d).



XVIII



XX



Other compounds in this series which were examined are the trans isomers of the ethers XX, for which the LD<sub>50</sub> rises with increasing substitution on the nitrogen atom ( $R = CH_3$ ), whereas the in vitro inhibition of Ach-ase falls in the order primary > quaternary > tertiary > secondary amine (45).

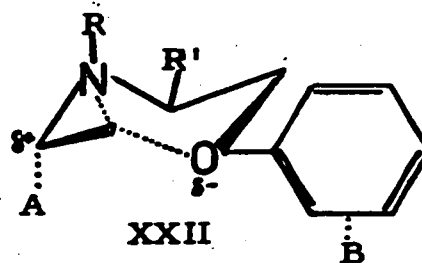
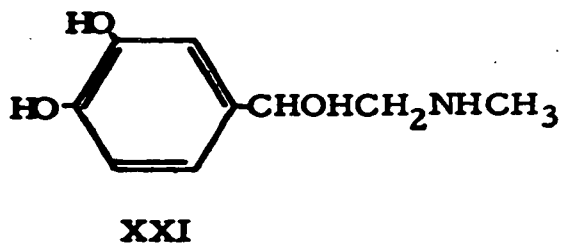
In addition, Friess et al. studied Ach-ase inhibition by several esters of XIV, XVI, and XVIII, as well as their ability to block sciatic nerve, and the subsequent wash-out recovery of the latter from these drugs (44).

We see that even when S.A.R. studies are limited to very closely related compounds, extensive and often unpredictable variations and inversions of potency often accompany seemingly minor structural modifications. In the above work of Friess, for example, the cis isomers of most of the substrates are the more active; however, a change in ring size, in degree or in type of nitrogen substitution, reverses this trend. Indeed, the order of activity within a single pair of geometric isomers is sometimes reversed on going from one bio-receptor to another.

## II. RESULTS AND DISCUSSION

### Introduction

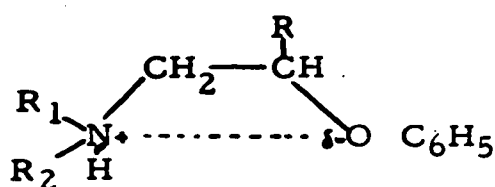
A number of observations on the mechanism of action of adreno-lytics and adrenergic blocking compounds have recently been incorporated into a comprehensive working hypothesis (46, 47, 48). Belleau assumes in this, that an adrenergic blocking compound (XXII) must have three characteristics in common with epinephrine (XXI) in order to inhibit the action of XXI in vivo.



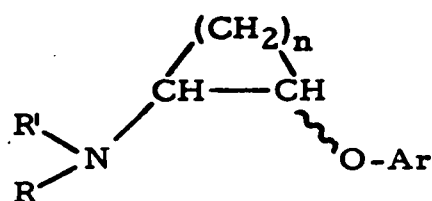
The first of these characteristics of the so-called "phenethylamine pattern" is an aromatic nucleus which is believed to be involved in aiding the binding of the drug, XXII to the receptor surface at site "B". The second is an ethyleneimmonium ion, which is the more important binding group; this is located at a postulated receptor site "A". The last of these prerequisites is an interjacency of approximately two bonding distances between the immonium ion and the aryl group. The last requirement is met only in one of the rotational modifications of open-chain aryloxyamines, that in which the ether oxygen

and the immonium ion are eclipsed, as illustrated in fig. XXII. The electrostatic interaction which aids this eclipsing is due to the partial negative charge on the oxygen atom. This, in fact, is the rationale for the function of the aryloxy group in compounds such as XXII.

A similar explanation is provided for the function of the aryloxy group in competitive adrenolytics such as XXIII, with the exception that an ammonium ion substitutes for the ethyleneimmonium ion.



XXIII



XXXIV

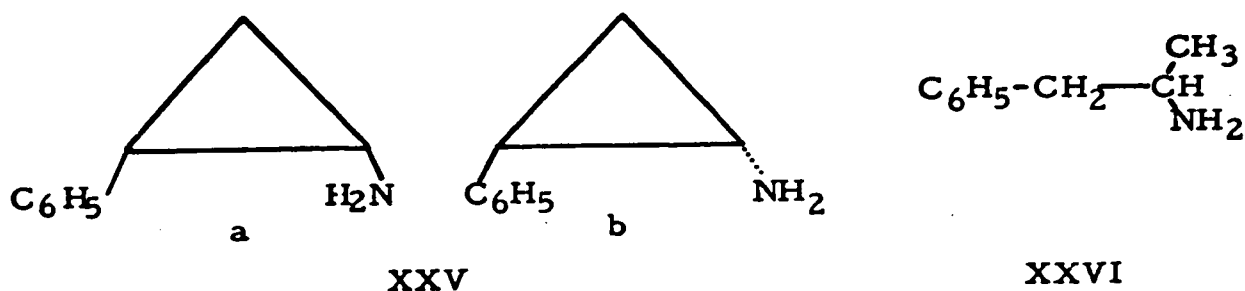
If the real function of the oxygen atom in aryloxyamines such as XXII and XXIII, is to allow the molecular conformation to adopt a "phenethylamine pattern", then this should be capable of verification by "freezing" the conformations of the open-chain adrenergic blocking and adrenolytic compounds into cis and trans conformations by introducing a ring in place of the ethylene linkage, as in compounds XXIV. Each isomer can be separately bio-assayed and the extent of the oxygen-to-nitrogen-interaction requirement can be estimated.

Toward this objective, it seemed profitable to prepare several compounds such as XXIV in which "n" was varied from three to one, the "R" groups being either methyl and hydrogen or methyl and  $\beta$ -chloroethyl. For each value of "n", an attempt was made to prepare both the cis and the trans isomers by unambiguous routes.

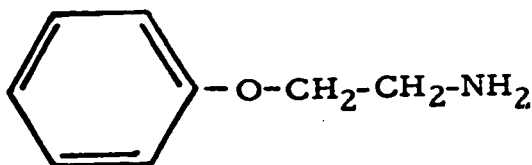
All of the intermediate primary amines (XXXIV,  $R = R' = H$ ) are

also of interest from an entirely divergent aspect.

In 1948, Burger and Yost (49) prepared cis- (XXVa) and trans- (XXVb) 2-phenylcyclopropylamines, the cyclic analogs of the prototype monoamine oxidase (MAO) inhibitor, amphetamine (XXVI).



Subsequent enzymological assays (50) of their MAO inhibitory power disclosed that although both isomers are very potent, the activity is independent of the relative orientation of the phenyl and amino groups.



XXVII

The phenoxyethylamine, XXVII is a sympathomimetic (51), unlike its N-alkylated derivatives, which are sympatholytics. The cyclic analogs (XXIV,  $\text{R} = \text{R}' = \text{H}$ ) of XXVII bear the same relationship to XXVII as do XXVa and b to the phenethylamine sympathomimetic, XXVI: the cyclic compounds possess only one  $\alpha$ -hydrogen. It is expected,

therefore, that the phenoxycycloalkylamines should possess MAO inhibiting activity. The effect of cis-trans isomerism and of the introduction of an oxygen atom between the aryl and the cycloalkyl groups can be investigated relative to this activity. If the potencies of XXVa and b are due mainly to the  $sp^2$  character of the cyclopropane bonds, as has been suggested by Belleau and Moran (72), then the phenoxy analogs should be less potent because the conjugation of the aryl and cyclopropyl rings is destroyed by insertion of the ether oxygen atom.

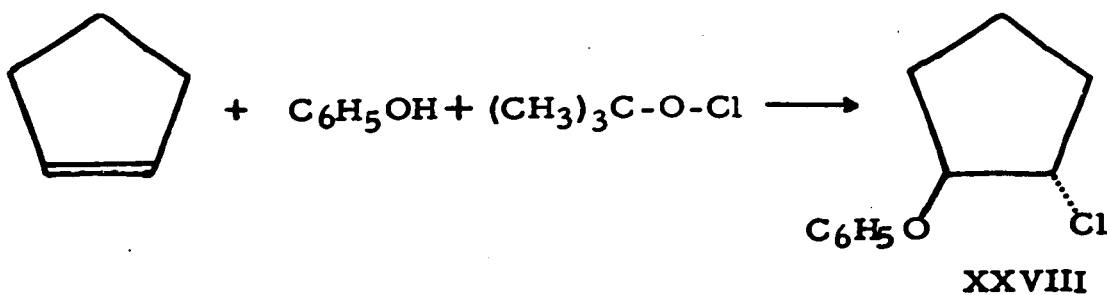
Finally, changes in MAO inhibitory activity can be correlated with alterations in the size of the cycloalkyl ring in XXIV and the effect of ring size on other molecular properties.

The following presentation embodies the results and suitable theoretical considerations of these investigations.

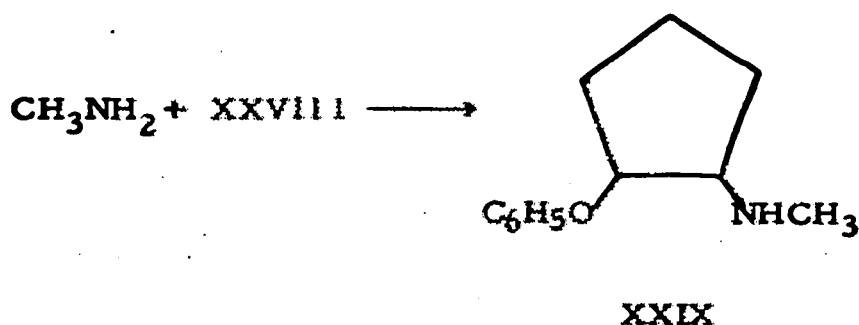
### 1. The Phenoxycyclopentane Series

#### a) N-Methyl-cis-2-Phenoxycyclopentylamine (XXIX)

The key starting material for the preparation of the cis isomers of 2-phenoxycyclopentylamines was trans-2-phenoxycyclopentyl chloride (XXVIII). This was prepared by the reaction of cyclopentene with phenol and t-butyl hypochlorite.

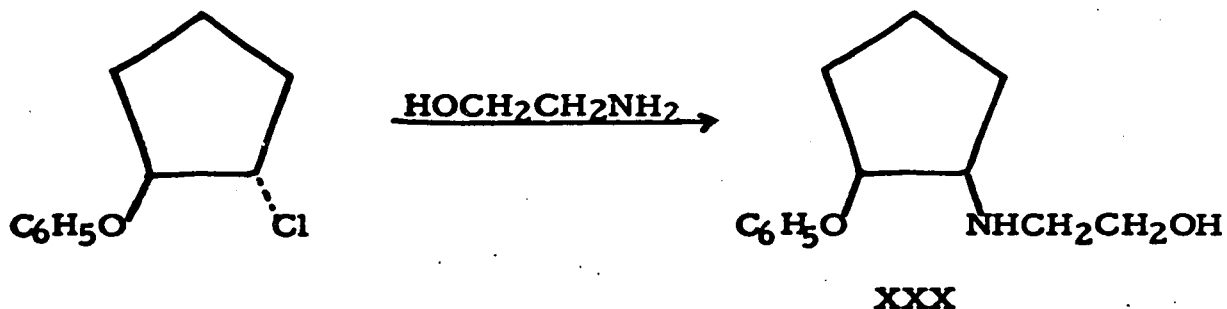


If the reaction proceeds via a chloronium ion, then the stereochemical assignment for XXVIII is correct. Furthermore, the reaction of the halide, XXVIII with methylamine produces only one isomeric amine, N-methyl-cis-2-phenoxy-cyclopentylamine (XXIX). Since the trans isomer of XXIX, which will be discussed later, was prepared by an unambiguous route, the conformational assignment of XXIX is absolute.



b) N-Methyl-N- $\beta$ -Chloroethyl-cis-2-Phenoxy-cyclopentylamine (XXXII)

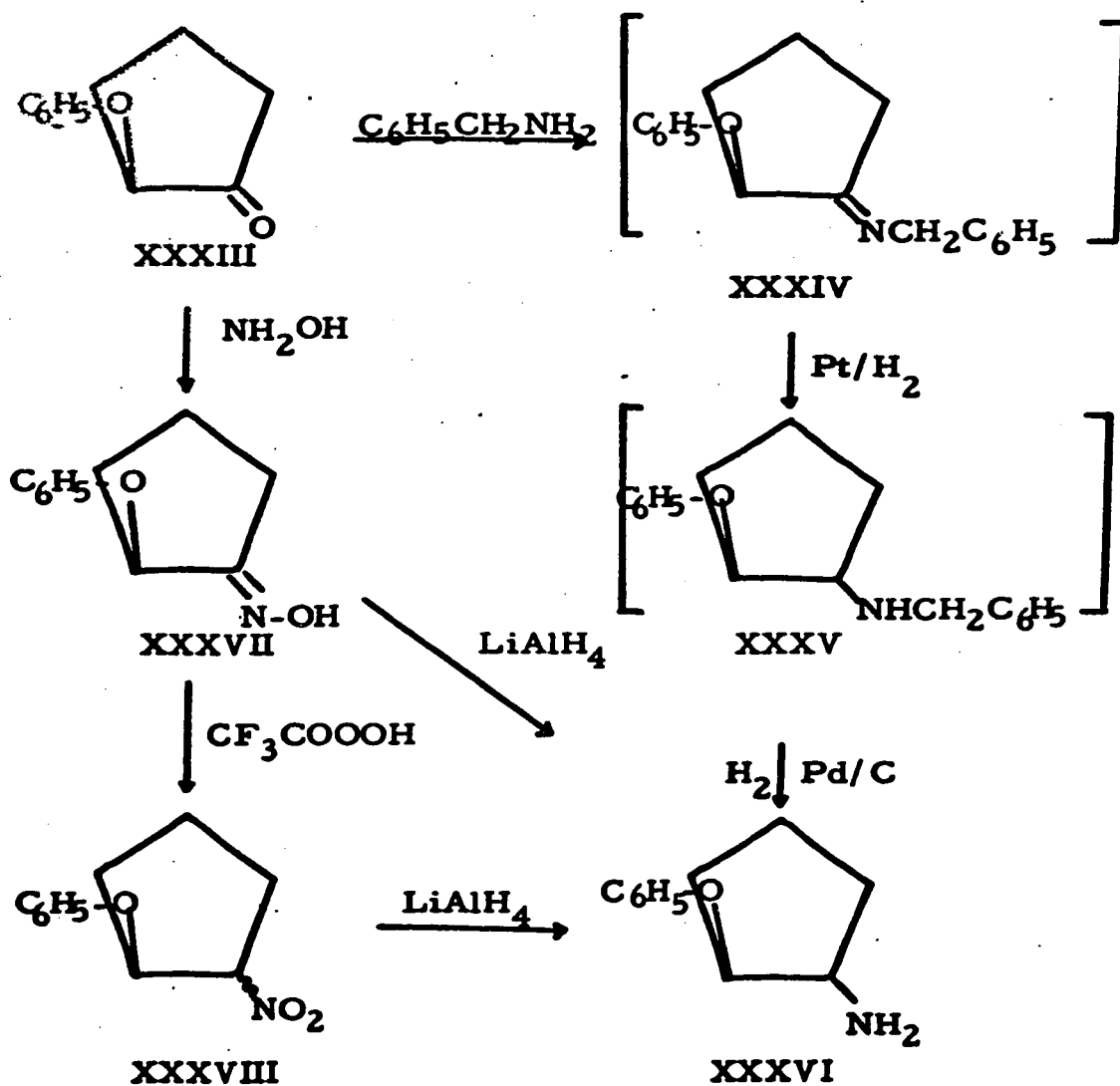
The following reaction sequence gave the tertiary haloamine, XXXII, which was required for biological testing.



**c) cis-2-Phenoxycyclopentylamine (XXXVI)**

**When 2-phenoxy-cyclopentanone (XXXII) was reductively aminated**

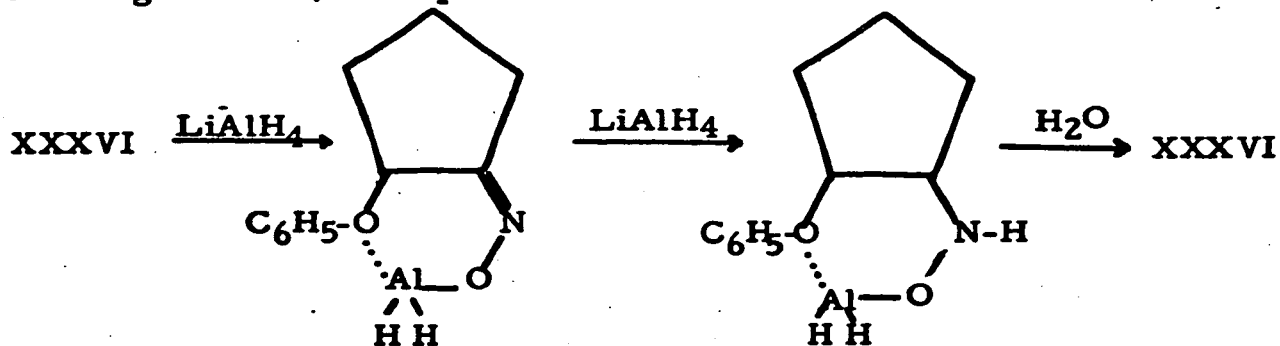
in the presence of benzylamine, cis-2-phenoxy-cyclopentylamine, XXXVI, was produced. The conformational assignment was verified by the synthesis of the trans isomer, which will shortly be discussed. The probable intermediates, benzylidene-2-phenoxy-cyclopentanone (XXXIV) and N-benzyl-2-phenoxy-cyclopentanone (XXXV), were not characterized. The formation of XXXVI in this reaction sequence can, however, be safely postulated as resulting from adsorption of "XXXIV" by the hydrogen-laden catalyst on the least hindered side of the ring, the side opposite that from which the phenoxy group projects, to yield cis-"XXXV", followed by catalytic debenzylation of "XXXV".





In view of the electrostatic repulsive forces between the ether oxygen atom and the nitrogen atom in XXXIV, the phenoxy group likely has a pseudo-axial orientation. The NMR study by Lemieux and Ch $\ddot{u}$  (52) on acetylated inositols has indicated that such electrostatic repulsions can cause deviations from Hassel's rules, so that the acetyl groups will adopt an axial orientation.

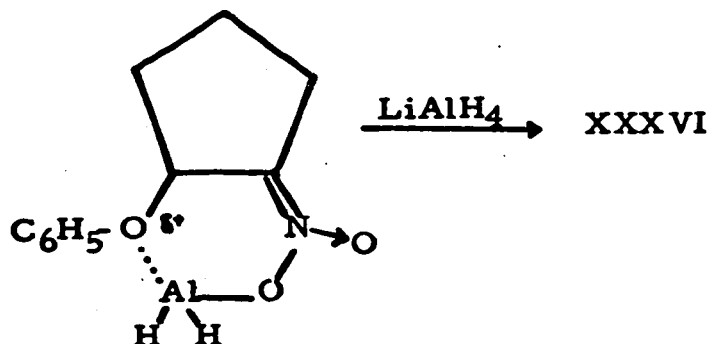
The reduction of 2-phenoxy-cyclopentanone oxime (XXXVII) with lithium aluminium hydride also gave the cis isomer of the amine, XXXVI. This result also can be considered to be the outcome of attack of the bulky, solvated hydride from the side of the ring opposite the phenoxy group. Kinetic control of the reduction might occur at a later stage, particularly if positive electrostatic interactions, such as are illustrated in fig. XXXIX, are operative.



Cram and Kopecky (53) have suggested that a similar directive influence is operative in the reaction of  $\beta$ -methoxyketones with methyl Grignard reagent.

We oxidized 2-phenoxy-cyclopentanone oxime (XXXVII) with pertrifluoroacetic acid and obtained a nitro compound (XXXVIII) which yields cis-2-phenoxy-cyclopentylamine (XXXVI) upon reduction with lithium aluminium hydride. Presumably, the first species formed

during the reduction is the aci-nitro salt, XL. For this reason, no stereochemical assignment can be made for XXXVIII on the basis of the reduction alone. In the intermediate, XL, coordination between the ether oxygen and the aluminium would direct the subsequent reduction step to yield the cis amine, XXXVI.



Good spectroscopic and chemical evidence for this type of interaction with the phenoxy oxygen will be presented in the section on cyclopropane compounds.

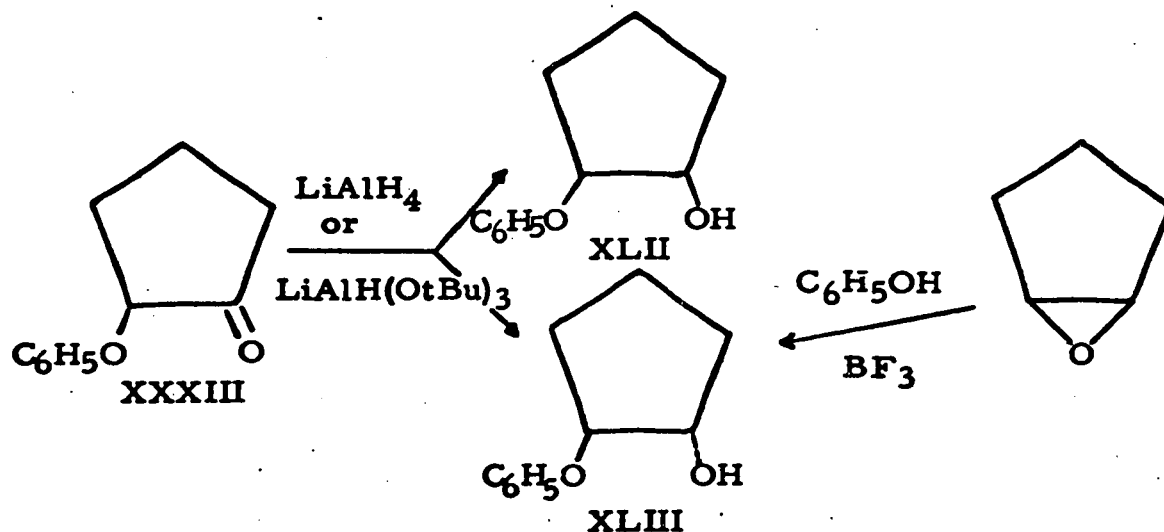
Our attempt to epimerize the nitro compound, XXXVIII, under alkaline conditions, resulted in the complete degradation of the starting material.

d) trans-2-Phenoxycyclopentylamine (L)

Entry into the trans series was made via cis-2-phenoxycyclopentanol (XLII). This was prepared by the reduction of 2-phenoxycyclopentanone (XXXIII) with lithium aluminium hydride, or better, with lithium tri-*t*-butoxyaluminium hydride.

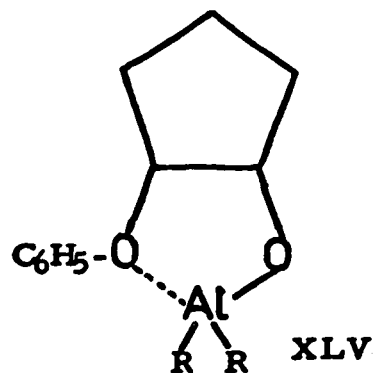
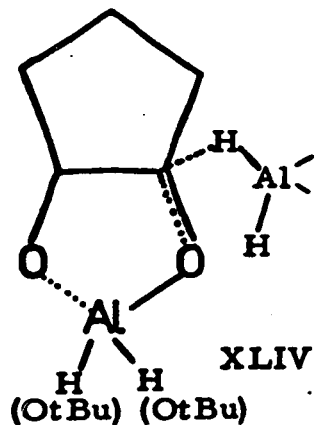
The simple hydride gives a mixture composed of sixty-six percent of XLII, the remainder being the trans isomer, XLIII. The complex hydride gives ninety-five percent of XLII, and only five percent of XLIII. Conformational assignments were made by comparing the reduction

products, XLII and XLIII, with an authentic sample of trans-2-phenoxy-cyclopentanol (XLIII), which was prepared by the reaction of cyclopentene oxide with phenol in the presence of boron trifluoride.

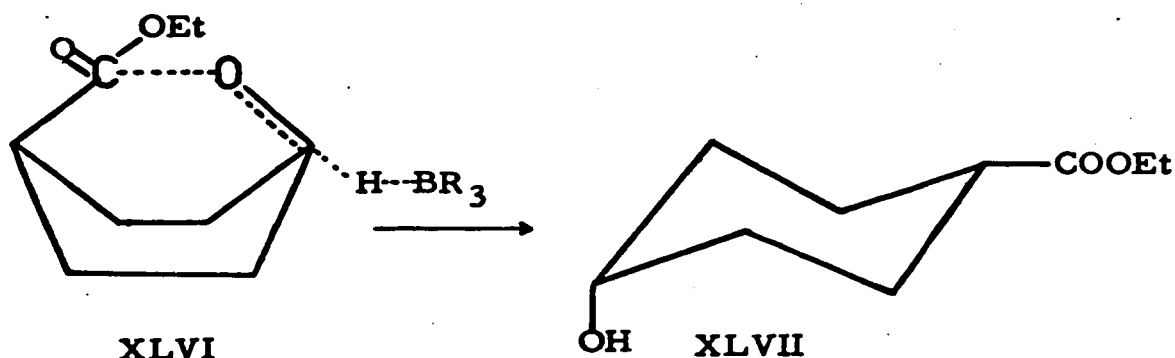


The work of Winstein and Henderson (54) and of Owens and Smith (55) confirms that this oxide is opened by nucleophiles to give trans-1, 2-disubstituted cyclopentanol.

Dipole-dipole interactions in the starting ketone (XXXIII) probably favour a pseudo-axial ether group, so that preferential attack of the simple hydride on the least hindered side of the ring results predominantly in formation of the cis alcohol. Use of the bulkier hydride, which is even more sensitive to steric hindrance to approach, produces almost entirely the cis isomer. It is also possible to invoke special interactions in an intermediate coordinate complex such as XLIV to explain these results.

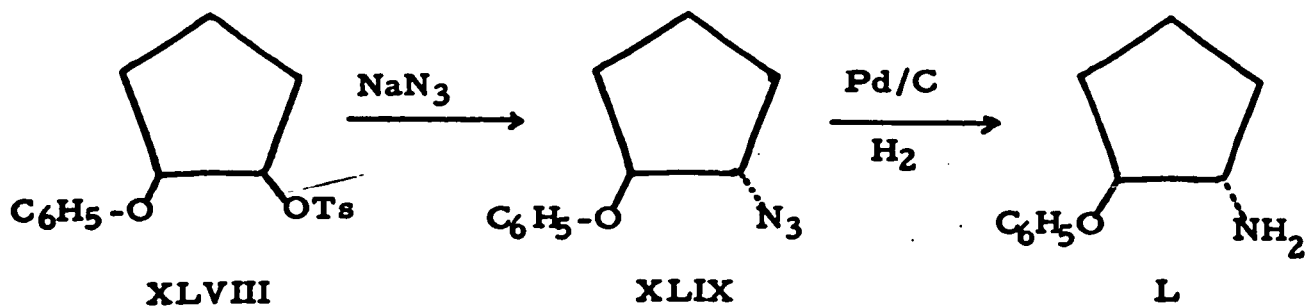


An interesting account of electrostatic interactions favouring the formation of cis-4-carboethoxycyclohexanol (XLVII) upon reduction of 4-carboethoxycyclohexanone (XLVI) with sodium borohydride is given by Kwart and Takeshita (56). They postulate that under suitable conditions, the interaction depicted in fig. XLVI can favour a cis transition state and can also accelerate the rate of the reduction.



However, it is not known whether or not thermodynamic control, rather than kinetic control, is operative in our example, since the actual product of our reaction is the cis alcoholate complex (XLV). The cis isomer, XLV, may be the thermodynamically more stable one due to the powerful coordinating ability of aluminium. In that case, the use of the complex hydride, which is less reactive than the simple hydride, permits a more complete equilibration.

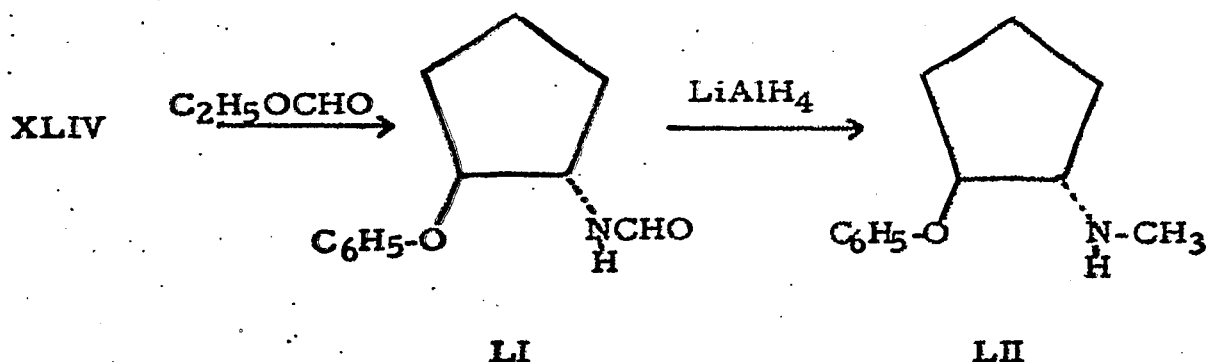
The tosylate (XLVIII) of the cis alcohol, XLII, gives upon reaction with sodium azide, trans-2-phenoxypropyl azide (XLIX).



Reduction of the azide over palladium and hydrogen gives trans-2-phenoxy-cyclopentylamine (L) which differs from the cis isomer (XXXVI) in its IR spectrum and in the melting point of a derivative.

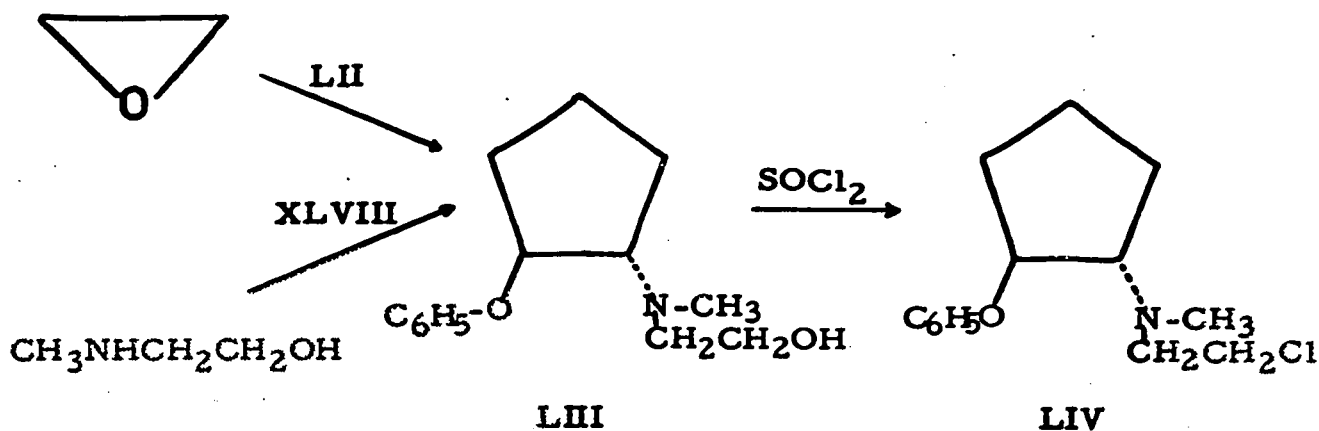
c) N-Methyl-trans-2-Phenoxy-cyclopentylamine (LII)

Formylation of the primary amine (L) followed by reduction of the N-formyl derivative (LI) with lithium aluminium hydride gives N-methyl-trans-2-phenoxy-cyclopentylamine (LII), which was distinguished from the cis isomer XXVI by the melting point of its hydrochloride salt.



f) N-Methyl-N-β-Chloroethyl-trans-2-Phenoxy-cyclopentylamine (LIV)

Treatment of LII with ethylene oxide gives N-methyl-N-β-hydroxyethyl-trans-2-phenoxy-cyclopentylamine (LIII), which could not be characterized as a solid derivative. Since none of the steps subsequent to the synthesis of the pure trans secondary amine, LII, could possibly have resulted in partial epimerization, the conformational purity of LIII is indisputable.



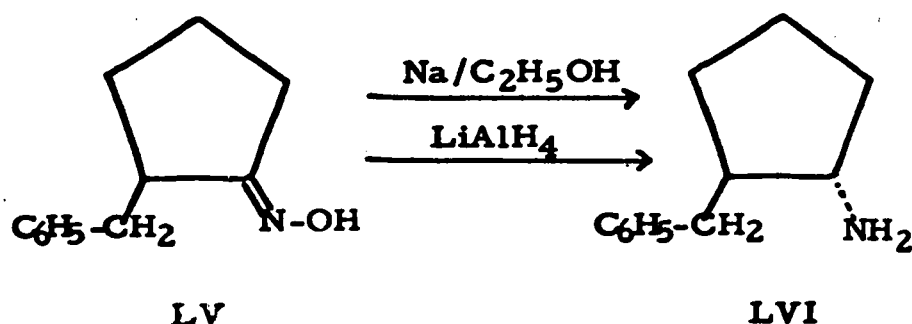
The reaction of the cis tosylate, XLVIII, with N-methylaminoethanol also gives LIII uncontaminated by the cis isomer. The tertiary amine, LIII gives, upon treatment with thionyl chloride, the desired N-methyl-N-(β-chloroethyl)-trans-2-phenoxy-cyclopentylamine (LIV).

## 2. The Benzylcyclopentane Series

In order to verify a number of assumptions which were made in explaining the results of the phenoxy-cyclopentane syntheses, and also to have cyclic analogs of sympathomimetics, we attempted to prepare cis- and trans-2-benzylcyclopentylamines. In view of the absence of electrostatic effects comparable to those in the phenoxy series, we expected that the stereochemical outcome of the reactions in the benzyl series would differ substantially from that of the reactions of phenoxy-cyclopentane analogs.

### a) trans-2-Benzylcyclopentylamine (LVI)

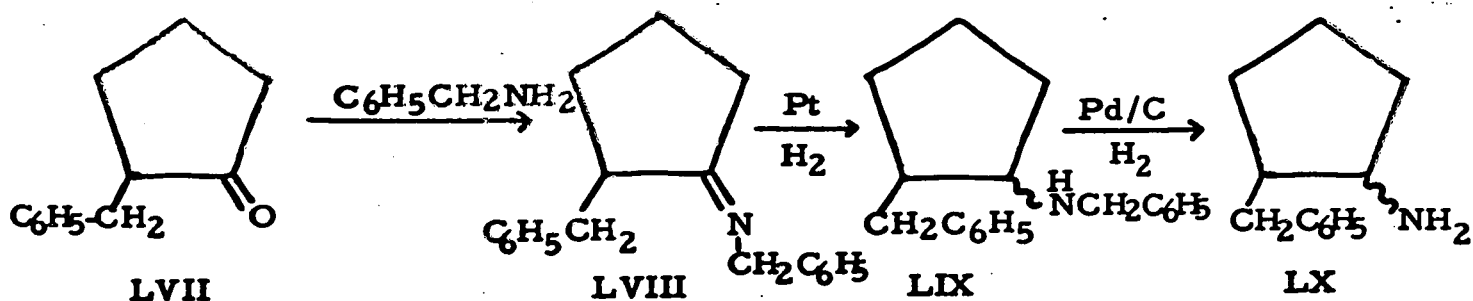
This compound was prepared by the reduction of 2-benzylcyclopentanone oxime (LV) with sodium and alcohol.



The same isomer is obtained by the action of lithium aluminium hydride on LV. This is anticipated when one considers that electrostatic interactions which favour the cis isomer, as is the case in the phenoxy series, are absent. The oximate salt of LV can be approached by the hydride from either side of the ring with about the same degree of ease since the benzyl group is probably pseudo-equatorial. The thermodynamically more stable trans product is therefore produced.

b) The Reductive Amination of 2-Benzylcyclopentanone (LVII)

The reductive amination of LVII in the presence of benzylamine gives N-benzyl-2-benzylcyclopentylamine (LIX). This was debenzylated to give a cis-trans mixture of isomers of 2-benzylcyclopentylamine (LX).



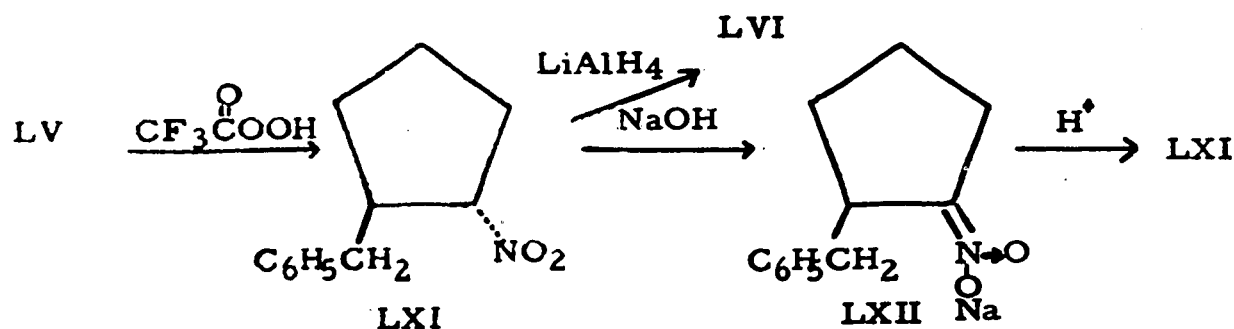
In this case, which again differs from that of the reduction of 2-phenoxy-cyclopentyl benzylamine (XXXIV), the intermediate Schiff base, LVIII, must offer about equal resistance to adsorption on the

hydrogenating catalyst from either side of the ring, resulting in a mixture of isomers.

c) trans-1-Nitro-2-Benzylcyclopentane (LXI)

The reaction of 2-benzylcyclopentanone oxime with pertrifluoroacetic acid gives a high yield of 1-benzyl-2-nitrocyclopentane (LXI).

The reduction of this material by lithium aluminium hydride gives trans-2-benzylcyclopentylamine (LVI).

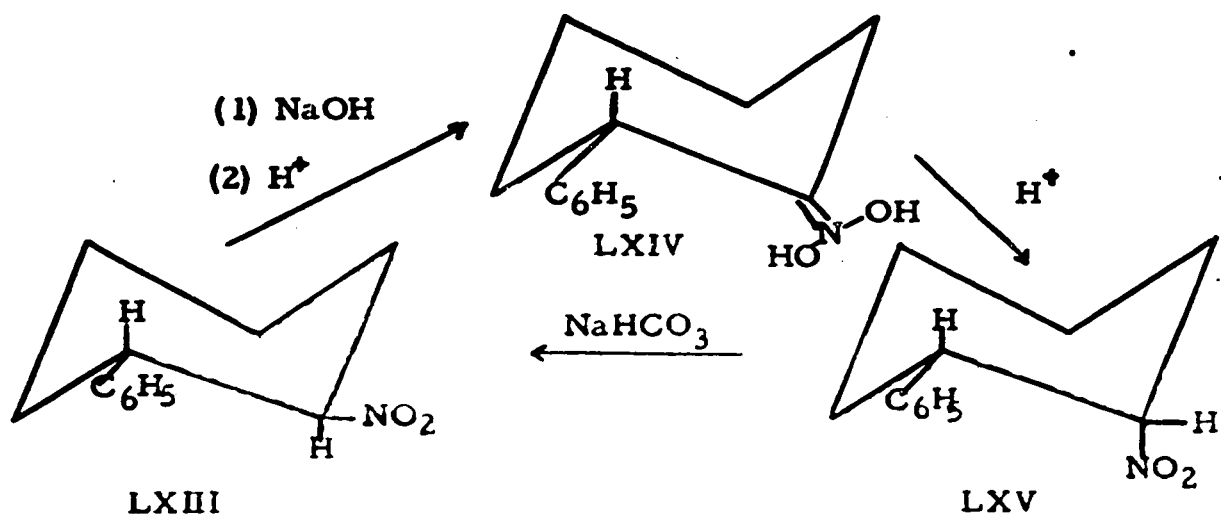


An attempt at the isomerization of LXI via its aci-nitro salt (LXII) results in the recovery of partially trans starting material.

The difference in results between the oxidation of the phenoxy- and the benzylcyclopentanone oximes can be rationalized by recognizing the absence of electrostatic orienting effects in the aci-nitro intermediate of LXI, which is formed both during the oxidation of LV as well as in the neutralization of LXII. In such circumstances, the outcome is thermodynamically, rather than kinetically controlled.

Zimmerman and Nevins (57) observed that the aci-nitro tautomer (LXIV) of trans-1-nitro-2-phenylcyclohexane (LXIII) reverts to cis-1-nitro-2-phenylcyclohexane (LXV) upon protonation. The equilibration of either LXIII or LXV with refluxing ethanolic sodium bicarbonate gives the pure trans isomer (LXIII).



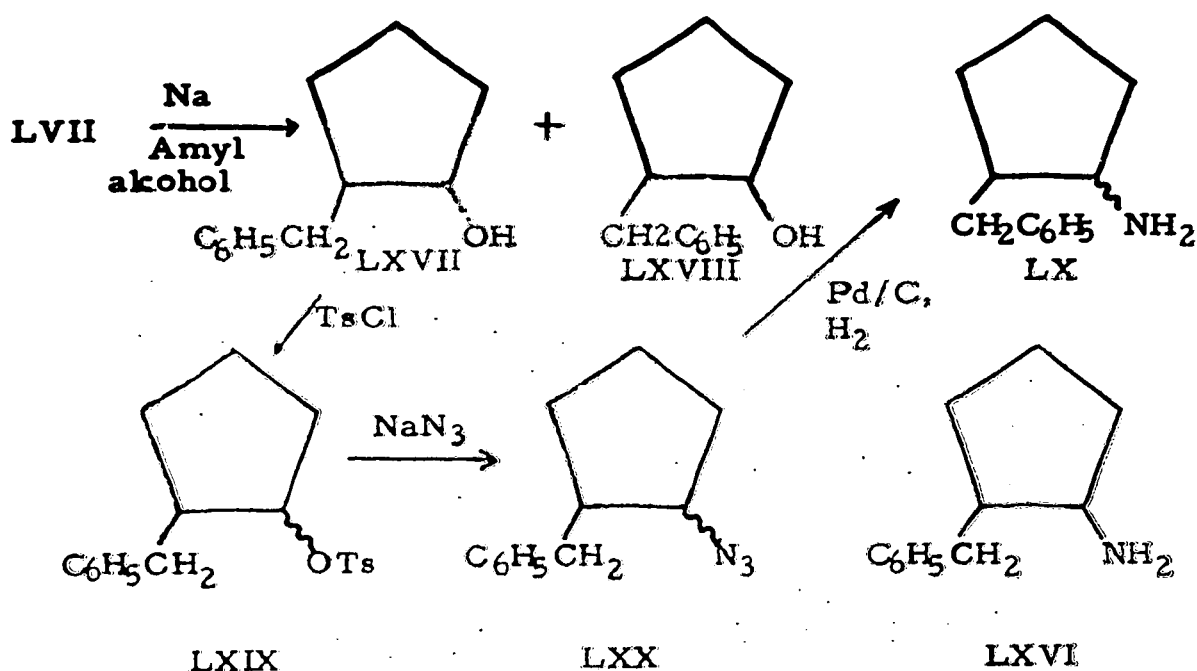


These workers proposed that the protonation of LXIV is rapid, taking place on the least hindered side of the ring, and therefore yielding the kinetic product. In the true equilibration, using sodium bicarbonate, the protonation is slow and the reaction is reversible, so that the thermodynamic product is formed.

General differences in the stereochemical make-up of cyclohexane and cyclopentane compounds as well, possibly, as the fact that the phenyl ring is one methylene group closer to the reaction site in LXIV than it is in LXI, would appear to be responsible for the deviation of our results from those of Zimmerman and Nevins.

#### d) 2-Benzylcyclopentanol (LXVII, LXVIII)

The synthesis of the desired cis-2-benzylcyclopentylamine (LXVI) was attempted via trans-2-benzylcyclopentanol (LXVII). The latter compound was obtained only as an admixture with the cis isomer (LXVIII) when 2-benzylcyclopentanone (LVII) was reduced with sodium and amyl alcohol.

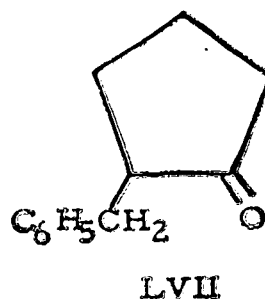
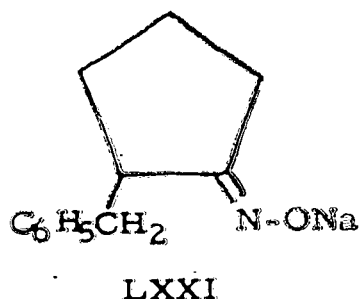


Tosylation of the mixture of alcohols gave a solid derivative (LXIX) which may be either a pure trans (or pure cis) tosylate, or a molecular complex. The reaction of LXIX with sodium azide is accompanied by extensive elimination. The small amount of 2-benzylcyclopentyl azide (LXX) thus obtained, yields a mixture of isomeric amines (LX) upon hydrogenation. It is likely that both elimination and ionization can compete with  $\text{S}_{\text{N}}2$  displacement of the tosyl group by azide ion in this case because of the absence of a relatively unhindered mode of approach, such as was present in cis-2-phenoxy-cyclopentyl tosylate (XLVIII).

The reduction of 2-benzylcyclopentanone by sodium and alcohol differs radically in stereochemical outcome from the similar reduction of its oxime. The following consideration may apply.

Since the oxime initially forms a sodio-salt (LXXI) the subsequent reduction of this complex may be sluggish by comparison with the reduction of the ketone; this introduces an element of thermodynamic control

in the reduction of the oxime which is absent in the reduction of the ketone, LVII.

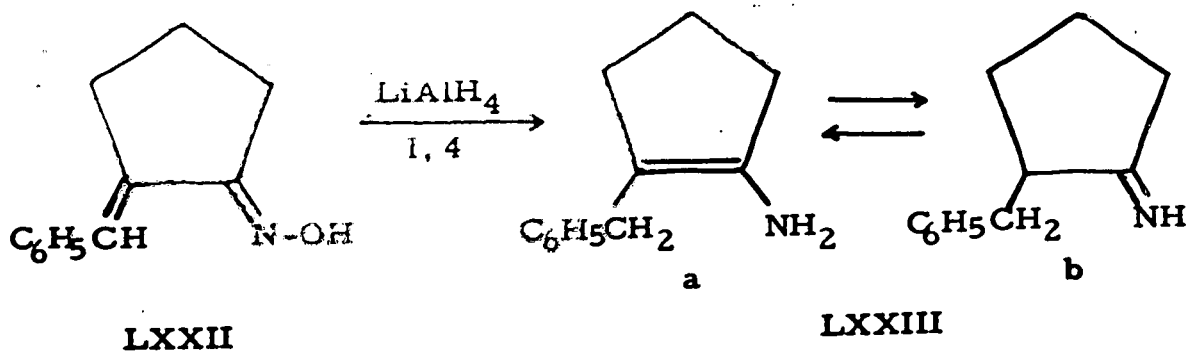


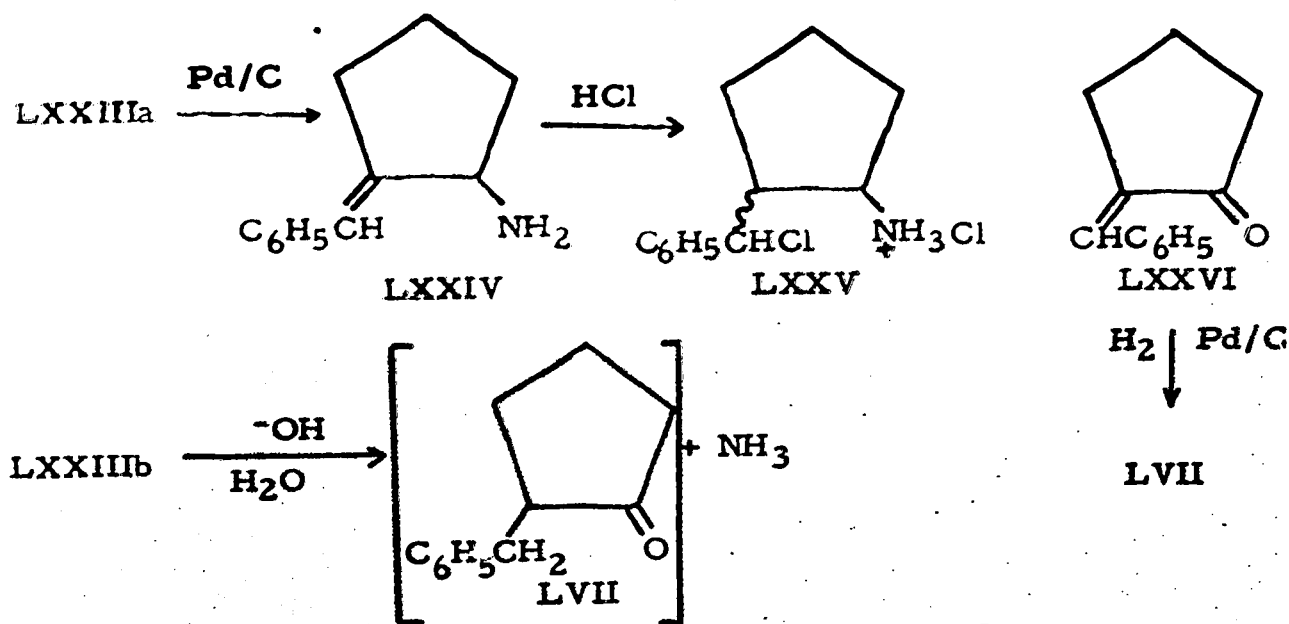
Since the orientation of the benzyl group in LVII does not impose any serious restriction on steric approach control, a mixture of alcohols results from its reduction.

#### e) Some Anomalous Reactions

While searching for a route to the cis isomer, LXVI, we encountered certain peculiar reactions which require comment.

The reduction of 2-benzylidene cyclopentanone oxime (LXXII) with lithium aluminium hydride leads to the formation of what appears to be 2-benzylcyclopentenamine (LXXIIIa). 2-Benzylcyclopentanone imine (LXXIIIb) is probably present as a tautomer, since the free base (LXXIII) slowly liberates ammonia on standing.





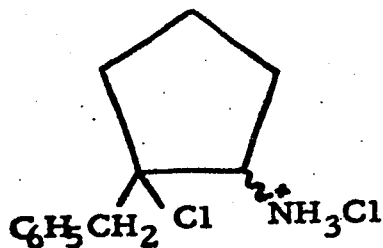
"Hydrogenation" of compound LXXIII over palladium on charcoal results in an incomplete uptake of hydrogen. The product (LXXIV) does not show the usual alicyclic olefinic double bond absorption in the infra-red. However, benzylidene cyclopentanone (LXXVI) shows a broadened aromatic band at  $1600\text{ cm}^{-1}$  but not an aliphatic double bond absorption. The conjugated double bond in LXXIV would therefore not be easily recognized in the infra-red spectrum.

Treatment of the "hydrogenation" product (LXXIV) with hydrogen chloride gave a compound containing both ionic and covalent chloride. Its elemental analysis corresponds to that for formulation LXXV.

We propose tentatively, that the palladium catalyst serves only to bring about double bond migration in the reaction under consideration, the driving force being an increased conjugation in LXXIV over that in LXXIII. Benzylidene cyclopentanone (LXXVI) gives benzylcyclopentanone (LVII) under identical conditions. However, whereas 2-phenoxy-cyclo-

pentanone(XXXIII) yields a completely saturated alcohol when it is hydrogenated over platinum, the Schiff base (XXXIV) of that ketone gives an aromatic compound (XXXV) upon treatment with hydrogen and platinum.. Possibly the amino group in LXXIIIa selectively poisons the hydrogenation catalyst so that it serves mainly as an isomerization surface. The stereochemistry and the precise location of the covalent chlorine in LXXV will have to be determined by further study.

The reaction of 2-benzylcyclopentanone oxime (LV) with lithium tri-*t*-butoxyaluminium hydride, followed by treatment of the liberated amine with hydrogen chloride, yields an amine salt (LXXVII) with the same elemental composition as LXXV, but whose admixture with LXXV gives a melting point depression.



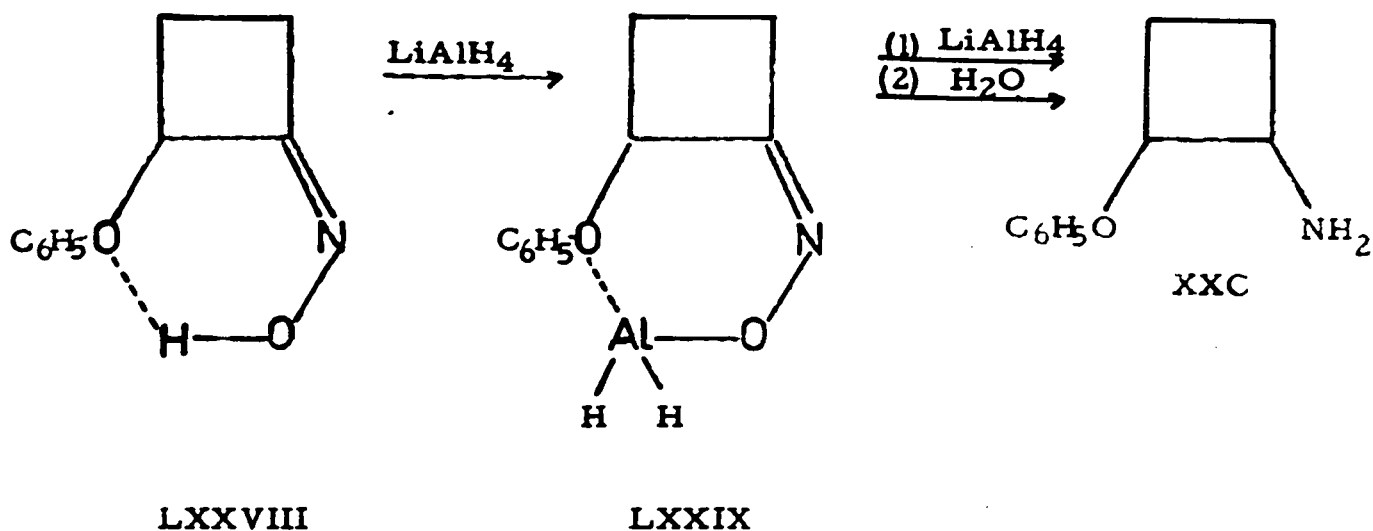
LXXVII

Unfortunately, none of the free base was isolated prior to the formation of LXXVII, so that the proposed structure is highly speculative, and no suitable mechanism can be offered at this time.

### 3. The Phenoxycyclobutane Series

#### a) cis-2-Phenoxycyclobutylamine (XXC)

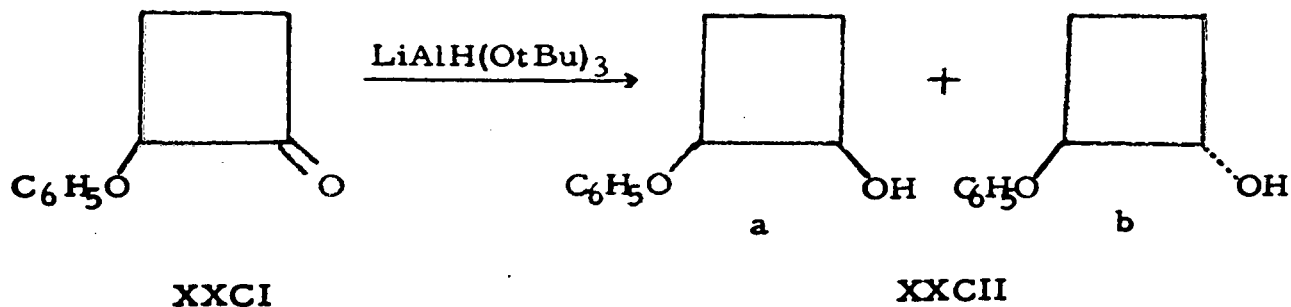
When 2-phenoxycyclobutanone oxime (LXXVIII) is reduced with lithium aluminium hydride, the resultant amine gives a well-defined salt which probably consists only of one isomer.



The same directing forces can be visualized operating here as were invoked for the cyclopentane analog of the intermediate LXXIX. In this case, the cis isomer (XXC) should be produced. However, since there is no reference compound of definite conformation, the assignment given to XXC is by analogy alone, and is open to some doubt.

b) 2-Phenoxycyclobutanol (XXCII)

The reduction of 2-phenoxycyclobutanone (XXCI) with lithium tri-*t*-butoxy aluminium hydride gives a mixture of roughly equal proportions of cis- (XXCIIa) and trans- (XXCIIb) 2-phenoxycyclobutanols.

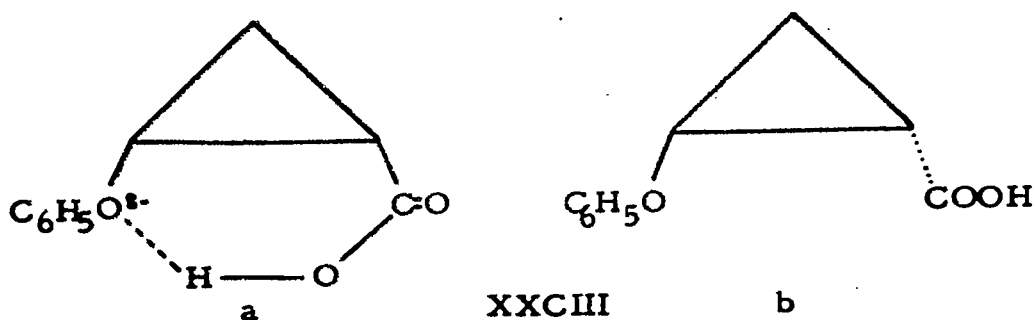


In the cyclobutane series, the aryloxy group cannot be displaced from its original position by electrostatic repulsions originating in the keto oxygen. In this respect, it differs from the cyclopentane congener of XXCI. The complex hydride can consequently approach almost equally well from either side of the ring of XXCI and yield a mixture of alcohols. The reduction of the oxime of XXCI can be stereospecific in spite of the rigidity imposed by the cyclobutane ring because the 1-6 interaction of the oximate salt (LXXIX) does not require a significant alteration of the orientation of the phenoxy group.

#### 4. The Phenoxycyclopropane Series

##### a) 2-Phenoxycyclopropane Carboxylic Acids (XXCIII)

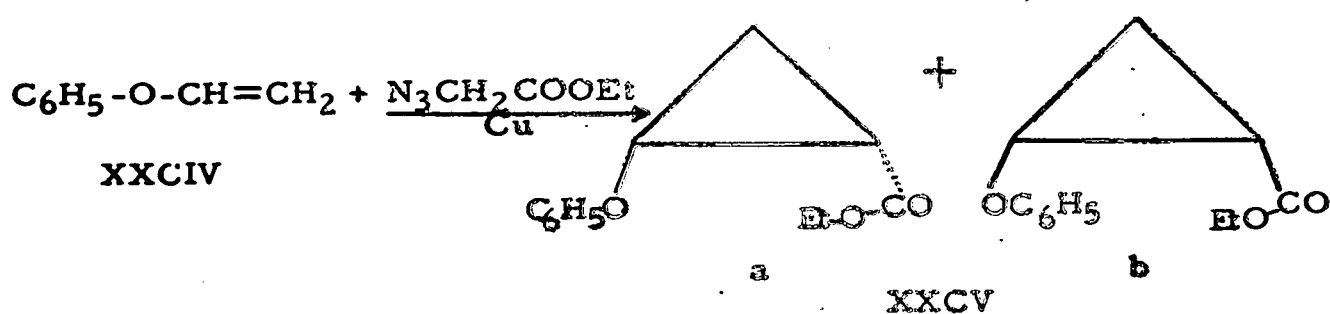
The work of Julia and Tchernoff (58), of Canonica and Fiechi (59) and of Looker and Braun (60) on the cis (XXCIIIa) and trans (XXCIIIb) isomers of 2-phenoxycyclopropane carboxylic acids has greatly simplified the preparation of amines in this series.



An interesting observation of Looker and Braun (60) that the carbonyl frequency of the cis isomer (XXCIIIa) is 15 to 20  $\text{cm}^{-1}$  higher than that of the trans isomer (XXCIIIb) has useful implications for the present investigation. Evidently, there must be considerable intramolecular hydrogen bonding in the cis isomer, as illustrated in

fig. XXCIIIa, which cannot take place in the trans isomer. This interaction dampens the mesomerism normally present in carboxyl groups, increasing the force constant of the carboxyl carbonyl group in the cis isomer relative to that in the trans isomer. Mohrbacher and Cromwell (61) have provided an intensive study along these lines.

In the present work, it was found that for the reaction of phenyl vinyl ether (XXCIV) with diazoacetic ester, the product ratio is two parts of trans-2-phenoxypropylene ethyl carboxylate (XXCVa) to one part of the cis isomer (XXCVb), regardless of whether the catalyst is copper powder or copper sulphate, or whether the reaction is carried out at ambient or elevated temperatures.



Other workers in this field (58, 59, 60) left some uncertainty in this regard because, in the past, the reported isomer ratio for this reaction was based on isolation procedures with the mixed carboxylic acids derived from the alkaline hydrolysis of the mixed esters. The establishment of the ratio reported here is based on a vapour phase chromatographic study of the reaction mixture.

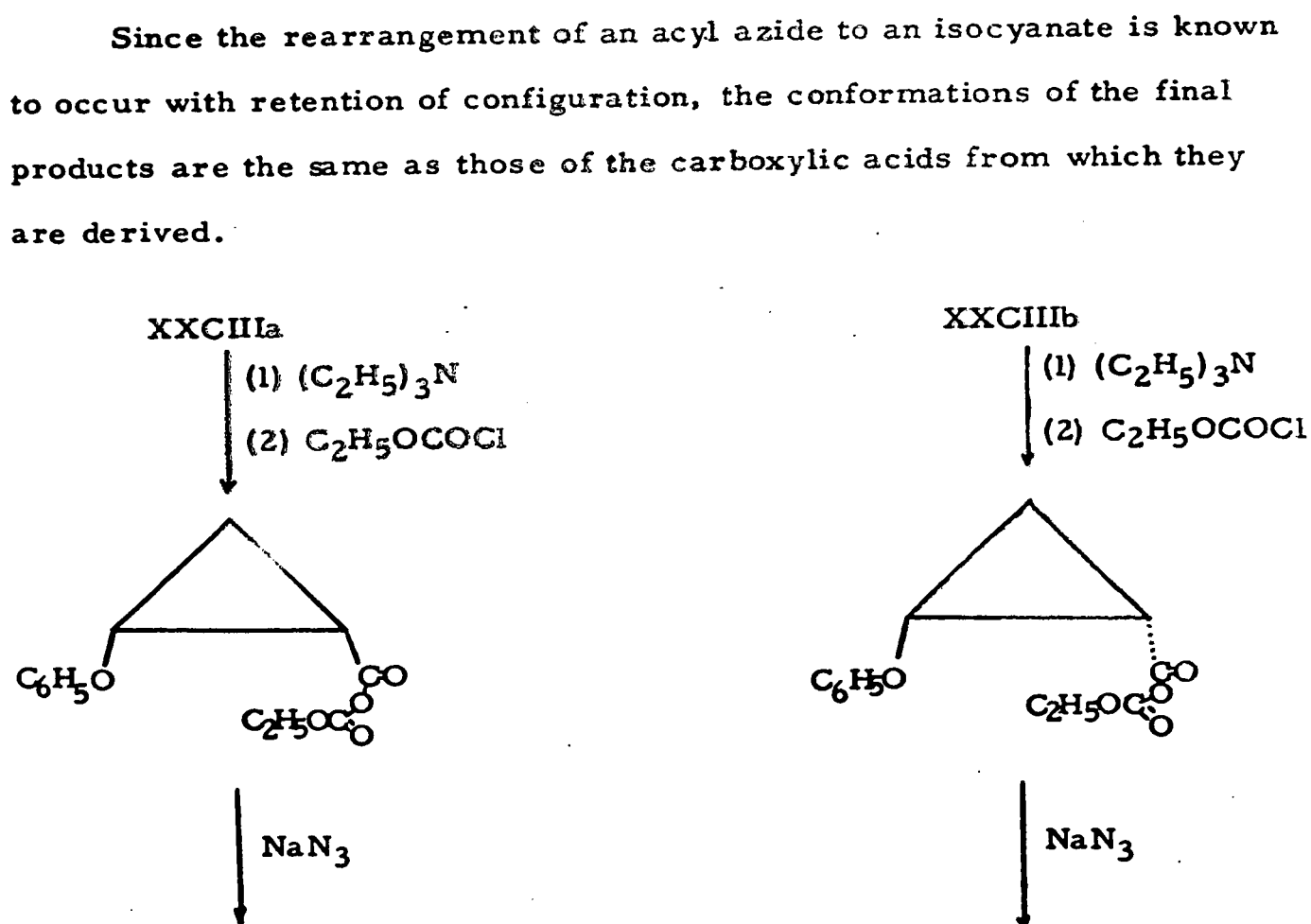
The isolation of the individual carboxylic acids was greatly simplified by an innovation developed in the present investigation. It involves the fractional precipitation of the acids from a solution of their

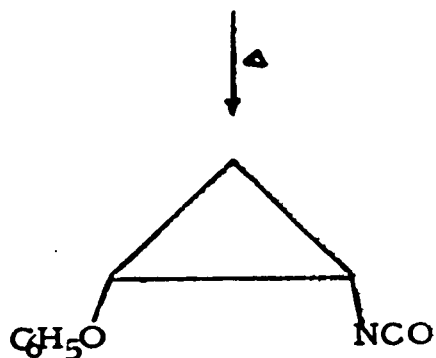
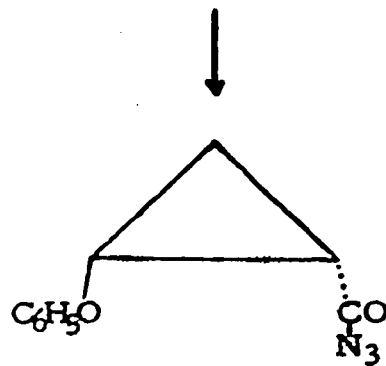
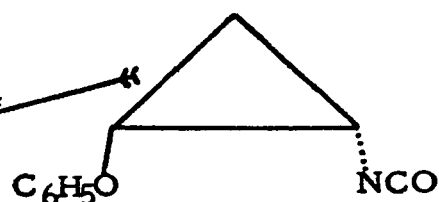
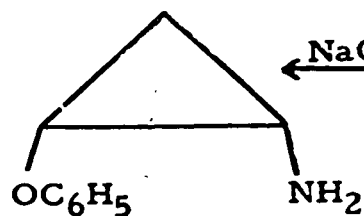
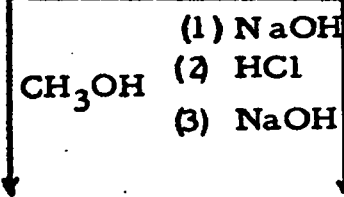
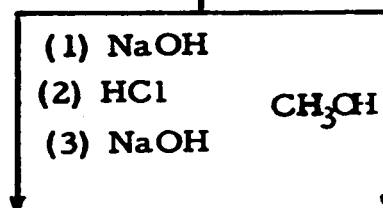


sodium salts by the addition of aliquots of mineral acid. A high degree of selectivity is operative, and considerable amounts of each of the pure isomeric carboxylic acids can rapidly be accumulated. The technique should also be applicable to similar systems.

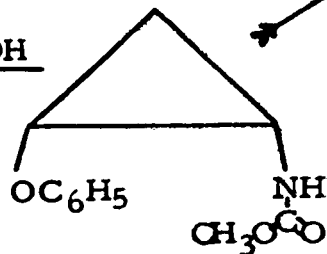
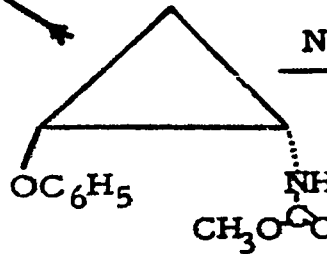
b) cis- and trans-2-Phenoxycyclopropane Intermediates

A recent modification (62) of the Curtius reaction was applied in this study for the synthesis of cis- (XXCVIa) and trans- (XXCVIb) 2-phenoxycyclopropyl isocyanates, cis- (XXCVIIa) and trans- (XXCVIIb) 2-phenoxycyclopropylamines, and cis- (XXCVIIIa) and trans- (XXCVIIIb) 2-phenoxycyclopropyl methyl urethanes from the corresponding cis- (XXCIIIa) and trans- (XXCIIIb) 2-phenoxycyclopropane carboxylic acids. The reaction sequence is illustrated in the following flow sheet.

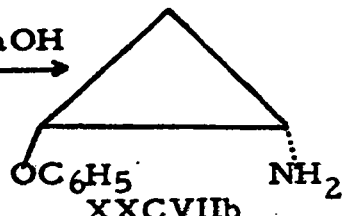



$$\text{LiAlH}_4$$

$$\begin{array}{c} \text{CH}_2=\text{CH}-\text{CH}_2\text{NHCH}_3 \\ + \\ \text{C}_6\text{H}_5\text{OH} \end{array}$$


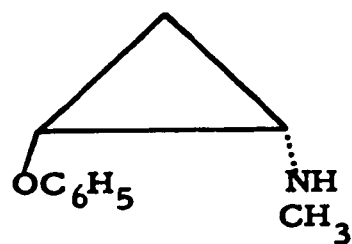
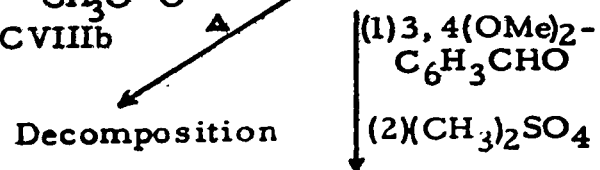
NaOH


$$\text{LiAlH}_4$$


**NaOH**



XXCVIIb

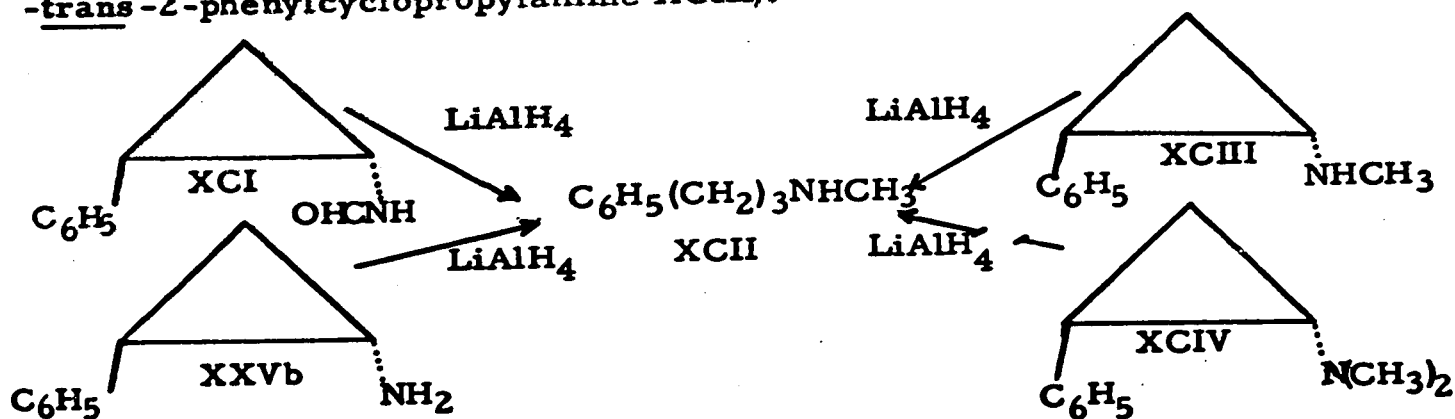


XC

c) The Reduction of 2-Phenoxycyclopropyl Methyl Urethanes (XXCVIII)  
and of trans-2-Phenoxycyclopropyl Isocyanate (XXCVIb)

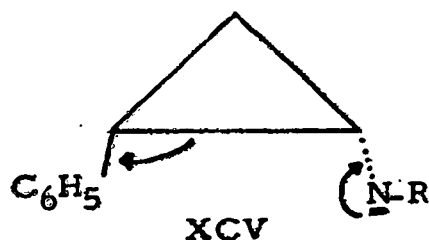
When either the trans isocyanate (XXCVIb) or the trans urethane (XXCVIIIb) is reduced with lithium aluminium hydride in attempts to prepare N-methyl-trans-2-phenoxycyclopropylamine (XC), an unusual ring cleavage and rearrangement reaction takes place. The products in both cases are phenol and N-methylallylamine (XXCIX). The same products are also obtained upon lithium aluminium hydride reduction of the cis urethane (XXCVIIIa). The reaction mechanism is therefore independent of configuration. (the desired N-methyl-trans-2-phenoxy-cyclopropylamine (XC) was ultimately prepared by the application of the Decker reaction to the primary amine, XXCVIb).

The recent observations of Burger and co-workers (63) have a bearing on these results. When they reduced N-formyl-trans-2-phenyl-cyclopropylamine (XCI) with lithium aluminium hydride, they obtained N-methyl-3-phenylpropylamine (XCII) rather than the expected N-methyl-trans-2-phenylcyclopropylamine XCIII).

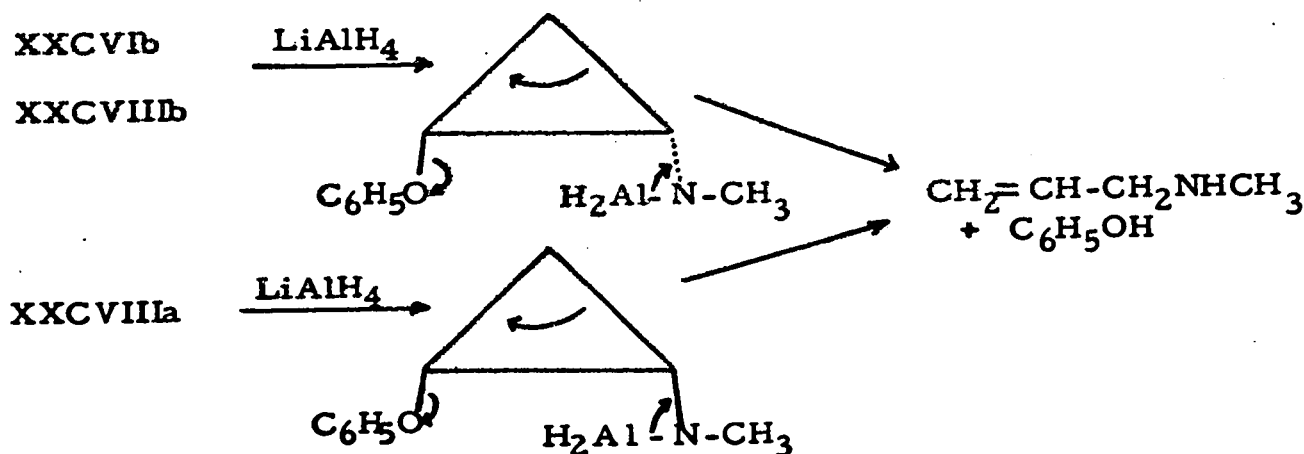


Although they also found that trans-2-phenylcyclopropylamine (XXVb) and N-methyl-trans-2-phenylcyclopropylamine (XCIII) both rearrange to XCII upon treatment with lithium aluminium hydride,

these workers noted that N, N-dimethyl-trans-2-phenylcyclopropylamine (XCIV) is stable to that reagent. From this evidence, they concluded that the rearrangement of XCI, XCIII, and XXVb centers about the preliminary formation of the anion, XCV.



The following analogous mechanism is proposed for the degradation of the urethanes XXCVIIIa and b, and of the isocyanate XXCVIb.



d) The Thermal Decomposition of trans-2-Phenoxycyclopropylamine (XXCVIIb)

When trans-2-phenoxycyclopropylamine (XXCVIIb) is heated to 100°, a violent decomposition ensues, with the formation of phenol and tars. This observation also has a parallel in the work of Burger and co-workers (63) who isolated phenylpropionaldehyde from the product of a similar thermal decomposition of trans-2-phenylcyclopropylamine (XXVb).

## 5. The Base Strengths of the Amines

Fig. 1 shows the relationship of the  $pK_a$ 's of the amine hydrochlorides in the 2-phenoxy- and 2-phenyl- cycloalkylamine series with the ring size.

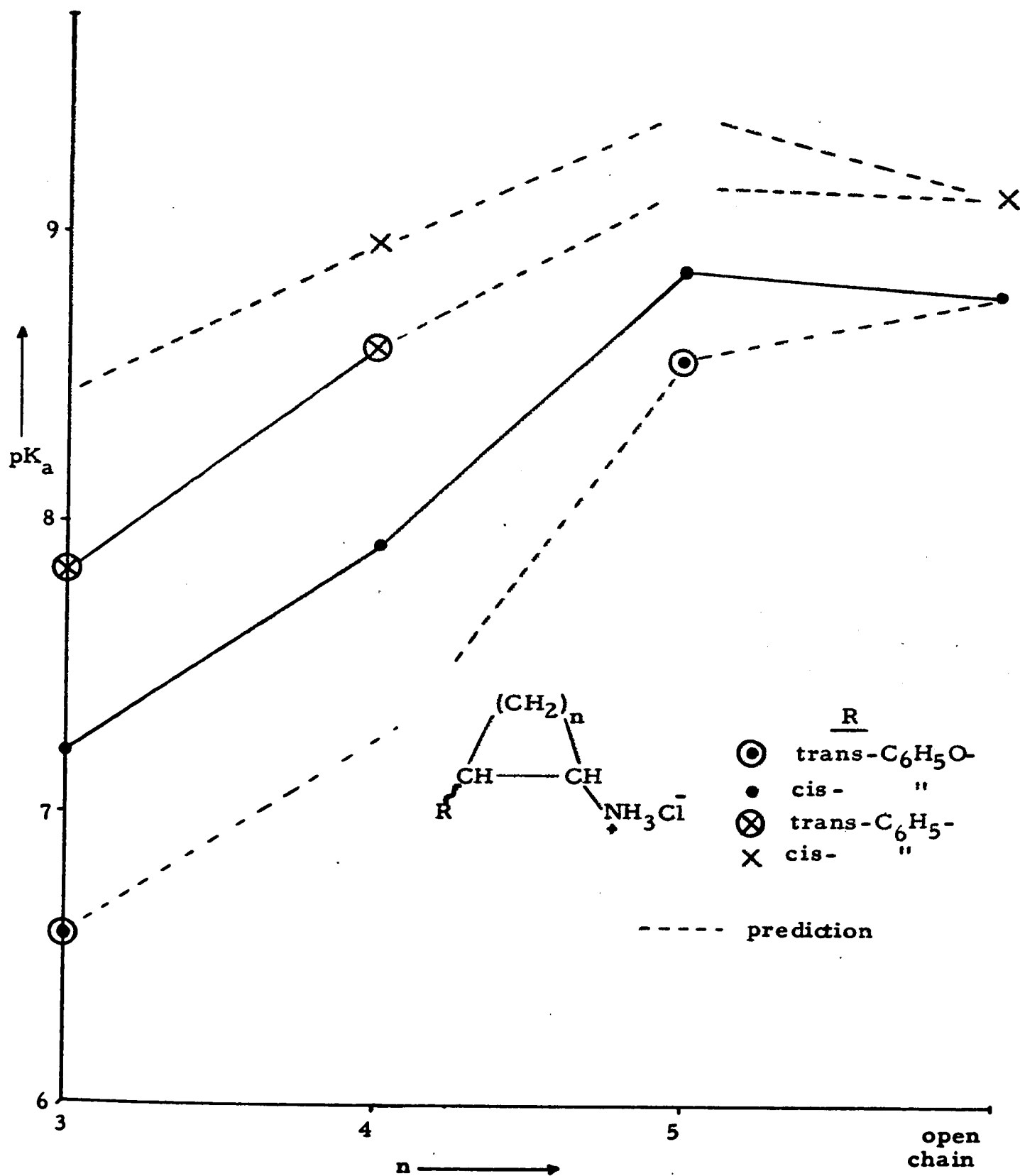
There are, unfortunately, a number of omissions; the general trend, however, is self-evident:

- (a) The basicities of the amines increase as the ring is enlarged, the open-chain phenyl analog (amphetamine) being the strongest base in the series.
- (b) The phenylcycloalkylamines are stronger bases than their corresponding phenoxycycloalkylamine analogs. This is also true for the open-chain analogs.
- (c) The cis isomers are stronger bases than the corresponding trans isomers for each ring size and for either a 2-phenyl or a 2-phenoxy substituent. In addition, cis-2-phenoxypropylamine carboxylic acid (XXCIIIa) is a weaker acid than the trans isomer (XXCIIIb).

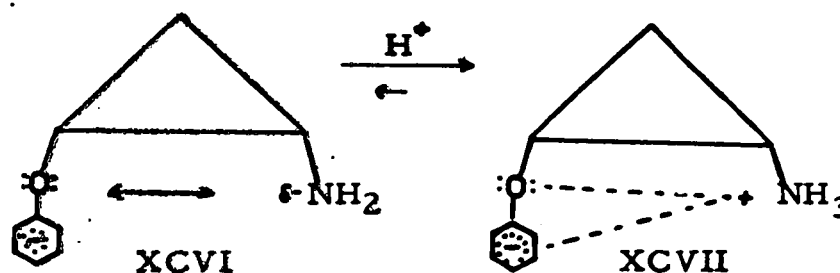
From observation (a), it can be concluded that the positive inductive effect of the aryl group diminishes with the size of the angle between alkyl substituents on the  $\alpha$ -carbon atom. This results in a more electrophilic  $\alpha$ -carbon atom and hence in a less basic amino group or a more acidic carboxyl group. This conclusion also explains, in part, the decreased reactivity of small-ring compounds toward nucleophilic attack.

The second observation (b) illustrates that the negative inductive effect of a phenoxy group is greater than that of a phenyl group.

Fig. I STERIC EFFECTS ON THE  $pK_a$ 's OF  
2-SUBSTITUTED CYCLOALKYLAMINES



The last observation (c) is a reflection of non-bonded electrostatic interactions. In the cis isomer of a 2-phenyl- or a 2-phenoxy- substituted cycloalkylamine, protonation is more favourable than in the corresponding trans isomer. In the cis isomer, electrostatic interaction reverts from a repulsive force in the free base (XCVI) to an attractive force in the protonated species (XCVII).



This particular incentive for protonation is, of course, absent in the trans isomer, where such intramolecular non-bonded interactions are impossible. It is to be noted that as the divergence between the stereochemistries of the cis-trans pairs of isomers diminishes (larger rings), the pKa difference also diminishes, because in such systems the electrostatic forces which we have been discussing are able to exert a more equal effect on each isomer.

If solvation effects are operative, as they likely are to some degree, their effect on pKa would be diametrically opposed to the electrostatic effect. Since solvation results in stabilization of the protonated form of the amine, it would tend to be more effective in the trans isomer, where steric crowding is not present to the same degree as it is in the cis isomer. The electrostatic effect must therefore be much more pronounced in the present cases than is the solvation stabilization.

The same factors differentiate the acidities of the two carboxylic acids, XXCIIIa and b. For the cis isomer, hydrogen bonding favours the free acid rather than its anion, in which an electrostatic repulsion is introduced. In this case, however, the solvation effect is in the same direction as is the electrostatic effect since it would be more effective in stabilizing the trans anion, making XXCIIIb the stronger acid. The infra-red study described on page 39 corroborates these assumptions in part.

In this connection, Trachtenberg and Odian (64) give the values 6.33 and 5.78 respectively, for the pK<sub>a</sub> values of cis- and of trans-2-phenylcyclopropane carboxylic acids. These results are in support of the conclusions drawn from observations (b) and (c) above, but the  $\Delta pK_a$  of 0.55 unit is the same as that for the phenoxy analogs (0.54). This may not be true for the corresponding amines.

## 6. The Biochemical Implications of cis-trans Isomerism

### a) Adrenergic Blocking Activity

Table I represents the pharmacological findings with the phenoxy-cyclopentylamines.

Perhaps the most salient feature of these assays is the difference in adrenolytic activity between the secondary amines, XXIX and LII, and their tertiary  $\beta$ -chloroethyl analogs, XXXII and LIV. It is appropriate to contemplate the disclosures of other workers in this field in order to properly appraise these findings.

Nickerson (65) found that Dibenamine (XCVIII) is several orders of magnitude more potent and more persistent in blocking the biological



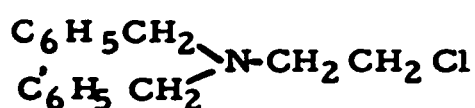
## 6. The Biochemical Implications of cis-trans Isomerism

Table I represents the pharmacological findings with the phenoxycyclopentylamines. The effects of intervenously (I. V.) injected amines on the blood pressure (B. P.) of normal dogs and of dogs treated with histamine (Hist.), acetylcholine (Ach.), epinephrine (Epin.), dimethylphenyl piperazinium (DMPP, a ganglionic stimulant which releases epinephrine and norepinephrine from the medulla) and norepinephrine (nor-Epin.) are recorded in percent change in blood pressure. Dibenzylamine (CI) is included for comparison in one test.

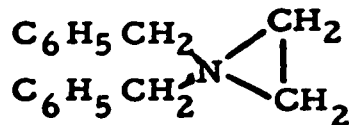
### a) Adrenergic Blocking Activity

Perhaps the most salient feature of these assays is the difference in adrenolytic activity between the secondary amines, XXIX and LII, and their tertiary -chloroethyl analogs, XXXII and LIV. It is appropriate to contemplate the disclosures of other workers in this field in order to properly appraise these findings.

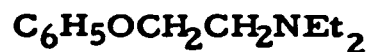
Nickerson (65) found that Dibenamine (XCVIII) is several orders of magnitude more potent and more persistent in blocking the biological responses to injected epinephrine than are most of the adrenolytics with structures based on the Fourneau compounds (C).



XCVIII



XCIX



C

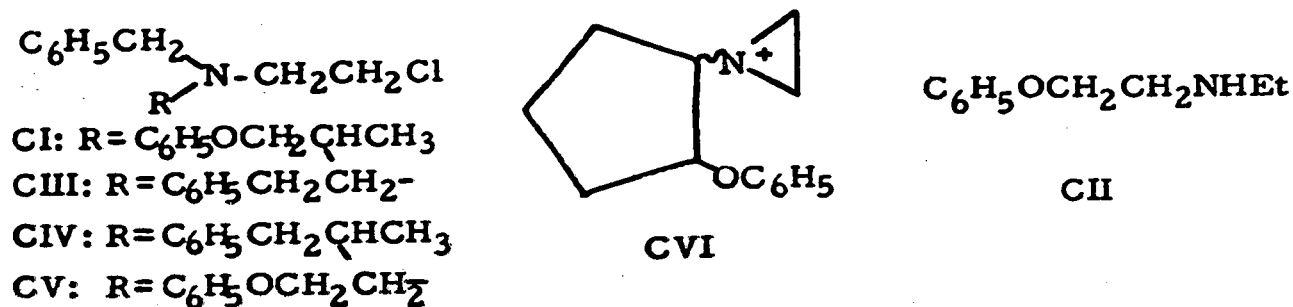
Speculations concerning this enhanced activity have centered about the ability of Dibenamine (XCVIII) and its congeners to produce ethylene-

TABLE I  
THE PHARMACOLOGICAL FINDINGS WITH  
ADRENERGIC BLOCKING AGENTS

| Compound | L. V. Dose<br>(mg/kg) | Percent<br>Change<br>in B. P.<br>(mm) | Percent Change in Response to<br>Injected |      |       |      |          |
|----------|-----------------------|---------------------------------------|-------------------------------------------|------|-------|------|----------|
|          |                       |                                       | Hist.                                     | Ach. | Epin. | DMPP | norEpin. |
| XXIX     | 0.1                   | -3                                    | -8                                        | -14  | 22    | -14  | --       |
|          | 0.5                   | 7                                     | -4                                        | -41  | 59    | 22   | --       |
|          | 1.0                   | -15/21                                | -6                                        | -60  | 60    | 53   | --       |
|          | 5.0                   | -25/16                                | -29                                       | -87  | 58    | 50   | --       |
|          | 10.0                  | -37                                   | -16                                       | -60  | -11   | -13  | --       |
| LII      | 0.1                   | 11                                    | 3                                         | -10  | 45    | 123  | --       |
|          | 0.5                   | -10/10                                | 3                                         | -10  | 57    | -91  | --       |
|          | 1.0                   | -23/13                                | 60                                        | -22  | 76    | 180  | --       |
|          | 10.0                  | -8/12                                 | 66                                        | -88  | 52    | 202  | --       |
| XXXII    | 1.0                   | --                                    | --                                        | --   | 40    | --   | 0        |
|          | 2.0                   | --                                    | --                                        | --   | 70    | --   | 50       |
| LIV      | 2.0                   | --                                    | --                                        | --   | 50    | --   | 0        |
|          | 4.0                   | --                                    | --                                        | --   | 100   | --   | 67       |
|          | 8.0                   | --                                    | --                                        | --   | 100   | --   | 75       |
| CI       | 8.0                   | --                                    |                                           | --   | 20    | --   | --       |

immonium ions (XCIX) at physiological pH. The interaction of this active species with the adrenergic receptor was postulated to give rise to a covalently bound drug-receptor complex (biological alkylation). This blockade is non-competitive by contrast with non-alkylating adrenolytics such as C and its congeners, which are presumed to interfere reversibly with the adsorption of adrenaline or noradrenaline on the adrenergic receptor.

The second, and more subtle characteristic of the results in Table I is that, although the secondary amines, XXIX and LII, are less potent than the analagous Fourneau compounds (C), the alkylating analogs, XXXI and LIV, are even more potent than Dibenzylamine (CI) which is one of the most powerful adrenergic blocking drugs in clinical use.



Relevant to this is the work of Polonovski and co-workers (66) who demonstrated that the introduction of an  $\alpha$ -methyl group into phenyl ethers such as CII is detrimental to antiadrenaline potency. However, Ulliot and co-workers (67) found that when an  $\alpha$ -methyl group was introduced into the feebly active Dibenamine analog, CIII, the resultant compound (CIV) is more potent than Dibenamine.

More significant was the observation that Dibenzylamine (CI) is more powerful than the analog, CV, by a factor of seven (68), and that CV is three times as potent as Dibenamine (69).

In this light, the potencies of the compounds, XXIX, LII, XXXII,

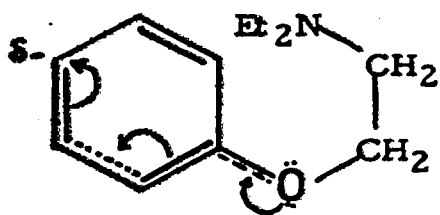
and LIV, relative to the potencies of their open-chain prototypes can be rationally accounted for. The secondary amines, XXIX and LII, are less potent than their prototype, CII, because the carbon atoms alpha to the nitrogen are alkylated, and are, in fact, in a cycle with the  $\beta$ -carbon atoms. That the ring itself may interfere with adsorption at the receptor surface is a possibility which will be minimized by other considerations to be presented shortly.

The tertiary amines, XXXII and LIV, resemble Dibenzyl line (CI) more closely than they resemble Dibenamine (XCVIII); they are thus expected to be more potent than Dibenamine. Also, the introduction of a cycle to bridge the alpha and beta carbon atoms results in an  $\alpha$ -alkylated analog of Dibenzyl line, so that the potency should be augmented just as it is in going from compound CIII to compound CIV. If the most important step in the sequence leading to a biological response is the formation of the ethyleneimmonium ion, CVI, then the alicyclic ring is not detrimental to potency because it would not impede this process through steric effects alone. Nonetheless, the second step, that of attachment of the active species, CVI, to the receptor, should be sensitive to the spatial restrictions imposed by the bulk of the alicyclic ring. Since there is no apparent deleterious effect on the potency of the cyclic analogs, XXXII and LIV, of Dibenzyl line, it can be concluded that the ring itself does not impose serious limitations on the binding of these cyclic alkylating agents. This probably applies to the competitive adrenolytics, XXIX and LII, as well, with some reservations to account for the different mechanism of action of the latter compounds.

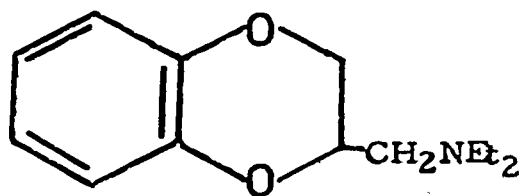
Finally, with regard to the pharmacological implications of cis-trans isomerism in these compounds, referring to adrenolytic and adrenergic blocking activity alone, it is well to present a rationale for the original purpose of this study.

On the basis of several pertinent facts, it was expected that within each pair of compounds, the cis isomers, XXIX and XXXII, would be more potent than their respective trans analogs, LII and LIV. The facts that led to this hypothesis are as follows:

1. The substitution of nitrogen or sulphur for the oxygen of the aryloxy group in either the open-chain aryloxyamines or in the benzodioxanes (CVII) does not abolish activity, whereas the substitution of a methylene group for the oxygen atom results in non-adrenolytic phenylpropylamines. This implicates the hetero atom of this class of adrenolytics in their mode of action.



CVIII



CVII

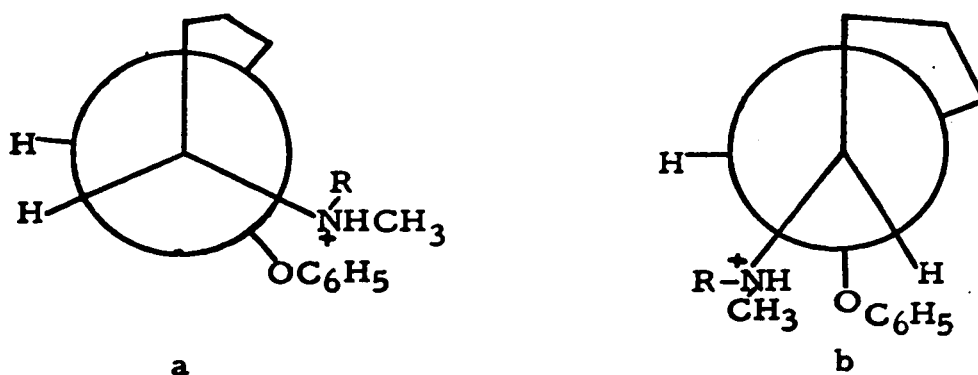
2. Early investigations by Bovet and Simon (70) showed that the incorporation in an adrenolytic agent, e.g. CVIII, of a second hetero atom in the form of a cyclic system (CVII), augments the potency of the compound by a considerable degree.

One aspect that may have some bearing on this amelioration of potency may be that a completely folded conformation such as is possible with CVIII, is excluded in the benzodioxane, CVII. The implication here is that the array of receptor groups cannot interact with a molecule in which the nitrogen and aryl groups are too proximal.

The other aspect is the greater electron density on the ether oxygen of compound CVII compared to that on compound CVIII, as a result of the damping of the mesomeric effect which is illustrated in fig. CVIII; corroboration of this idea comes from the well-known ability of ortho-methyl groups to augment the sympatholytic activity of phenoxyethylamines and Dibenzylamine analogs due to the positive inductive effect of the methyl group. Furthermore, in both compounds CVII and CVIII, the extra oxygen atom shares the demands of the aromatic electron sink, so that even compound CVIII is more potent an adrenolytic than the simple Fourneau compound, C. In the case of Dibenzylamine analogs, Belleau (48) has shown that the rate of ethylenimine ion formation increases with the positive electromeric effect of the aryl substituents.

These disclosures led to the postulates outlined in the introduction. The pKa study presented on page 45 et seq. indicates that there is an electrostatic interaction between the ether oxygen and the electrophilic ammonium or ethylenimine ion in the bio-active species of XXIX, LII, XXXII and LIV. It is therefore entirely reasonable to assume that this effect on molecular orientation, base strength, rate of ethylenimine ion formation, etc., should have its counterpart in the relative physiological activity of such compounds.

The expectation that the cis isomers, XXIX and XXXII, would be more active as adrenergic blocking agents than their respective trans analogs, LII and LIV, is not borne out by the present findings. It may be tentatively concluded that the difference in spatial orientation of cis and trans 1,2-disubstituted cyclopentanes are not sufficiently great to be reflected in terms of differences in adrenolytic potency. The flexibility of the cyclopentane ring permits of a considerable variation in interatomic distances between neighbouring substituents.

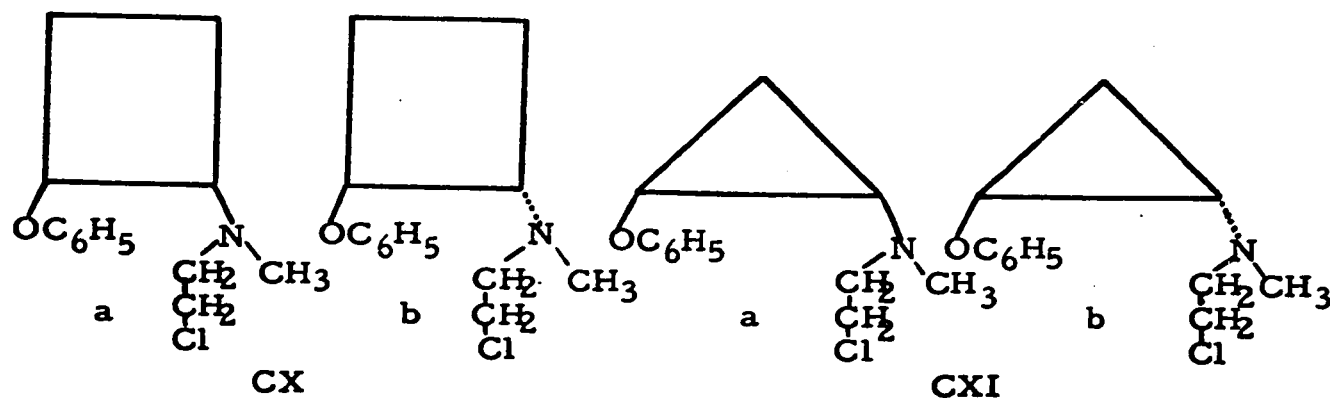


CIX

Complete eclipsing in the cis isomers (CIXa) would probably be energetically unfavourable due to a steric repulsion created by the hydrated ammonium ( $R = H$ ) or ethyleneimmonium ( $R = \text{CH}_2\text{-CH}_2$ ) ion. On the other hand, a pseudo-gauche conformation (CIXb) of the trans isomers is likely more favourable than a more extreme trans conformation because of the electrostatic attractive forces which have already been discussed and substantiated by pK<sub>a</sub> and infra-red studies.

The striking enhancement of potency of the β-chloroethylamino compounds, XXXII and LIV, over that of their simple open-chain analogs such as Dibenzylene (CI) and its congeners does seem to substantiate our hypothesis in part. The reasonable proximity of

the aryloxy oxygen atom to the ethyleneimmonium ion in either CIXa or CIXb ( $R = \text{CH}_2\text{-CH}_2$ ) assures a favourable entropy of binding whether the purpose of the aryloxy group is to serve as a second point of attachment to the receptor, to modify the basicity of the adjacent nitrogen function, or to maintain the "phenethylamine pattern" in the adrenergic blocking agent. Further proof of this proximity requirement will involve the synthesis and bio-assay of cyclobutyl or cyclopropyl analogs, CXa, b and CXIa, b respectively, where the stereochemistries are more rigidly defined and considerably more divergent than was the case with the cyclopentane compounds, XXXII and LIV.



#### b) Other Pharmacological Observations

With reference to other chemoreceptors (e.g. the acetylcholine receptor), there are marked differences in potency between the cis (XXIX) and the trans (XXXII) isomers of N-methyl-2-phenoxy-cyclopentylamine. This activity difference indicates a greater degree of stereospecificity of such receptors over that of the receptors involved in adrenergic blockade. Indeed, the work of Friess and his colleagues, which was discussed in the historical section of this part of the thesis,



adequately demonstrates the remarkable sensitivity of the acetylcholine and the acetylcholinesterase receptors to subtle alteration in the molecular geometry of substrates which are similar in structure to our own compounds.

c) The Monoamine Oxidase Inhibitors

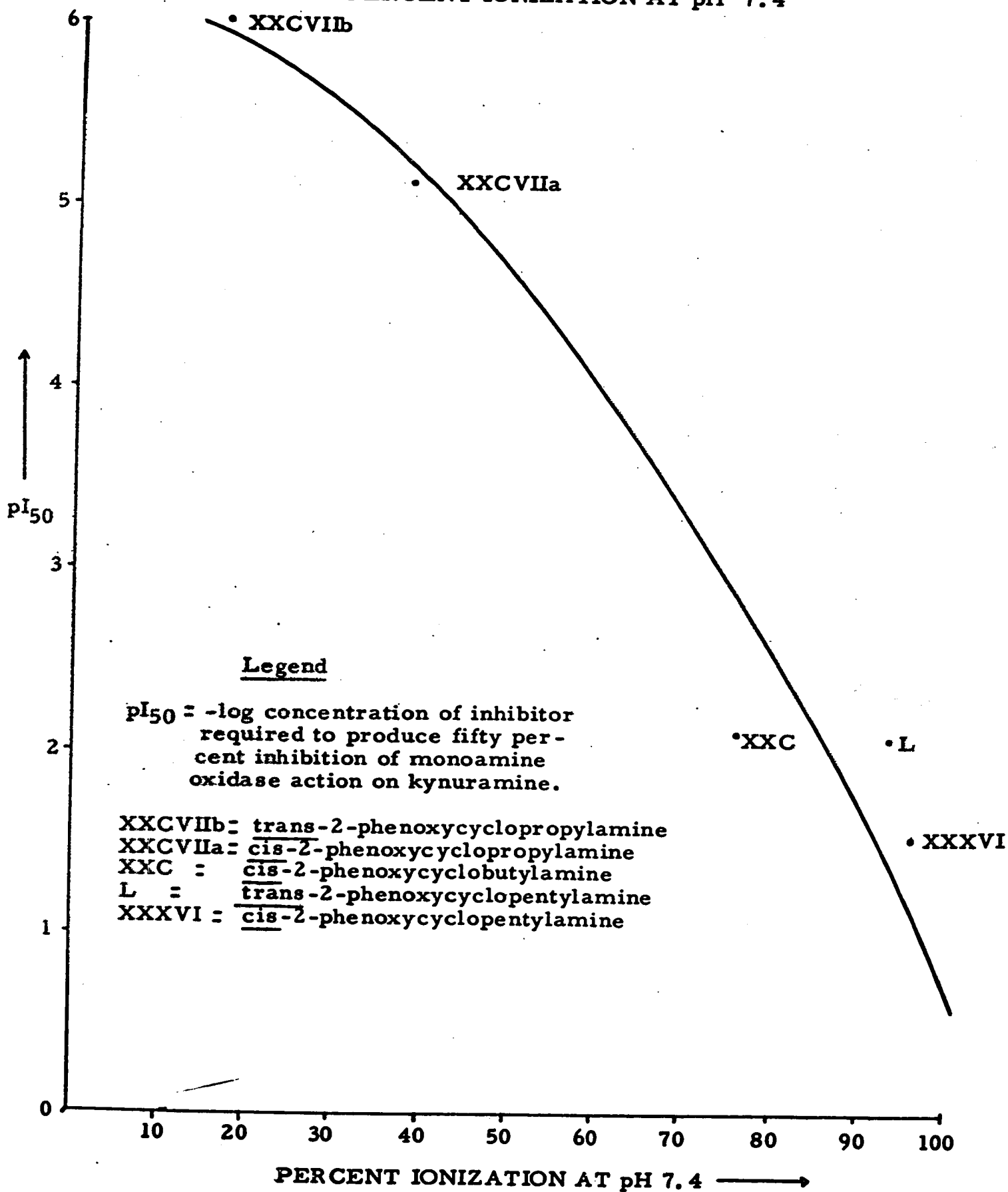
The monoamine oxidase preparation employed for these tests was one derived from rat liver homogenates by centrifugal fractionation. The disappearance of the substrate, kynuramine, was followed by ultraviolet spectrophotometry. Fig. II represents the results of monoamine oxidase (MAO) inhibition studies with the phenoxycycloalkyl primary amines. The MOA inhibitory strength varies inversely with the base strength of the amine.

Leffler, Spencer, and Burger (71) achieved a partial correlation between the  $pK_b$  values of a series of sympathomimetic amines and the pressor activities of the compounds. They observed that, providing the comparisons are limited to closely related structures, the pressor activity is inversely proportional to the base strength of the amine.

Apparently, the affinities of both the adrenergic receptor and the MAO receptor are dependant on the  $pK_b$  values of their respective substrates, and both receptors show a preference for the non-protonated form of the substrates. Although this is a significant limitation which one can impose when attempting to define the nature of the MAO receptor groups, it is premature to advance any suggestions in this regard.

The second result to be noted from fig. II is that the stereochem-

Fig. II MAO INHIBITORY STRENGTH VERSUS  
PERCENT IONIZATION AT pH 7.4



ical demands of the MAO receptor are not critical; the cis and trans isomers in each cycloalkyl pair are almost equipotent. The slight differences in potency can be accounted for solely on the basis of relative base strengths. This fact is in agreement with findings in the phenyl series of cyclopropylamine analogues (50).

Finally, the absolute potency values for the phenoxypropylamines (XXCVIIa, b) are about equal to those for the phenylcyclopropylamines. Belleau and Moran (72) have postulated from the results of deuterium isotope effects on MAO catalysed oxidations, that the potency of phenylcyclopropylamine (XXVb) may be due to the  $sp_2$  character of the cyclopropane bonds, which would reproduce the geometrical and electronic features of the transition state for oxidation by MAO. It appears that the present findings with the phenoxy analogs of XXV do not contradict this postulate. However, since the in vitro MAO inhibitory activity of the phenoxypropylamines with which we are presently concerned, increases with their diminishing base strength, it might be expected that the phenoxypropylamines would be more potent than their phenyl analogs. The presence, in the latter compounds, of a "conjugated" phenyl ring, by contrast with the phenoxy analogs, may have some significance which has not been taken into account.

In vivo studies on the reversal of epinephrine action in animals showed that trans-2-phenoxypropylamine (XXCVIIb) possesses only one-fifth of the potency of its phenyl analog (XXVb), as well as being slower in onset and more brief in duration of action.

### III. EXPERIMENTAL

All melting points were taken by the capillary technique and were corrected against reliable standards.

Infra-red (IR) spectra were taken on a Perkin-Elmer Infracord machine, employing liquid films (F), solutions (S, solvent), or Nujol mulls (NM).

Nuclear magnetic resonance (NMR) spectra were taken on a Varian Model V-4302 NMR Spectrometer at 60 Mc/sec.

Vapour phase chromatography (VPC) was performed on a Pye Argon VPC apparatus.

#### 1. The Synthesis of cis -2-Phenoxycyclopentylamines

##### a) trans -2-Phenoxycyclopentyl Chloride (XXVIII)

To a solution of 1.3 g. p-toluenesulphonic acid and 68 ml. (52.4 g, 0.77 mole) of cyclopentene in 100 ml. of dry benzene was added with stirring 20 g. (0.19 mole) of t-butyl hypochlorite. After the heat of reaction had subsided, a solution of 10 g. (0.10 mole) of reagent grade phenol in 10 ml. of dry benzene was added. The mixture was cooled to room temperature and a further 100 ml. (77 g, 1.13 mole) of cyclopentene was added followed by a solution of 117 g. (1.14 mole) of phenol in 150 ml. of benzene. Finally, there was added over three hours, with stirring, 126 g. (1.16 mole) of t-butyl hypochlorite. The mixture was then extracted with five 200 ml. portions of ten percent aqueous sodium hydroxide solution and then with five 200 ml. portions of water. The benzene solution was dried over sodium sulphate and then decanted. The solvent

was removed under reduced pressure and the residual oil was distilled in vacuo to yield 129 g. (34.7%) of colourless liquid, b.p. 59-64°/0.2mm,  $n_D^{25}$  1.5370, d. 1.12.

|       |                                 |                            |
|-------|---------------------------------|----------------------------|
| Anal. | Calc'd. for $C_{11}H_{13}OCl$ : | C, 67.7; H, 6.67; Cl, 18.0 |
|       | Found                           | C, 70.9; H, 6.64; Cl, 15.1 |

b) N-Methyl-cis-2-Phenoxycyclopentylamine (XXIX)

A solution of 7 g. (0.036 mole) of trans-2-phenoxycyclopentyl chloride (XXVIII) and 2.6 g. (0.084 mole) of methylamine in 10 ml of dioxane was heated in a Parr bomb at 180° for twenty hours. The bomb was cooled and opened, and the contents were taken up in 50 ml. of 10 percent aqueous hydrochloric acid. The mixture was extracted with ether and the ether extract was evaporated to leave 3.3 g. (47% recovery) of crude trans-2-phenoxycyclopentyl chloride.

The aqueous solution was made strongly alkaline with sodium hydroxide and was then extracted with ether. The ether extract gave, upon evaporation, 2.6 g. of oily brown residue. This was distilled under reduced pressure to yield 2.2 g. (32%) of N-methyl-cis-2-phenoxycyclopentylamine as a colourless liquid, b.p. 121-128°/9mm., picrate, m.p. 159.5-160.5° (s. 157°). Passage of dry hydrogen chloride through an ether solution of this amine gave an almost quantitative yield of the hydrochloride salt. Recrystallization of this salt from acetone-2-propanol gave a pure product, m.p. 134-136.5° (s. 131°).

|       |                                 |                            |
|-------|---------------------------------|----------------------------|
| Anal. | Calc'd for $C_{12}H_{18}NOCl$ : | C, 63.3; H, 7.97; N, 6.15. |
|       | Found:                          | C, 63.0; H, 7.89; N, 6.28  |

c) N- $\beta$ -Hydroxyethyl-cis-2-Phenoxycyclopentylamine (XXX)

A mixture of 28 g. (0.14 mole) of trans-2-phenoxycyclopentyl chloride and 28 g. (0.46 mole) of 2-aminoethanol was refluxed with stirring under nitrogen for twenty hours. The mixture was cooled and acidified with excess hydrochloric acid. The solution was extracted with ether, and the aqueous phase was then made strongly alkaline with sodium hydroxide. It was again extracted with ether and the ether extract was evaporated to leave an oily residue which solidified upon drying at 70°/10 mm. The solid, 4.5 g. (14.5%) was recrystallized from benzene to m.p. 66-68° (s. 65°).

Anal. Calc'd. for  $C_{13}H_{19}NO_2$ : C, 70.6; H, 8.68; N, 6.33.

Found: C, 70.6; H, 8.66; N, 6.17.

d) N-Methyl-N-( $\beta$ -hydroxyethyl)-cis-2-Phenoxycyclopentylamine (XXXI)

A mixture of 3 g. (0.013 mole) of N- $\beta$ -hydroxyethyl-cis-2-phenoxy-cyclopentylamine (XXX), 2.7 g. (0.052 mole) of 90 percent formic acid, and 2.4 ml. (0.032 mole) of 40 percent formalin was heated at 115° for twelve hours. An excess of 50 percent aqueous sodium hydroxide solution was then added. The mixture was shaken briefly, then extracted with chloroform, and the chloroform extract was evaporated to dryness. The residue was distilled under reduced pressure to yield 2.35 g. (77%) of colourless, viscous oil, b.p. 180°/0.2 mm.,  $n_D^{23}$  1.5405. Passage of hydrogen chloride through an ether solution of the amine gave the hydrochloride salt, m.p. 152-154° (s. 150°) from acetone-2-propanol.

Anal. Calc'd. for  $C_{14}H_{22}NO_2Cl$ : C, 61.8; H, 8.15; N, 5.16.

Found: C, 61.3; H, 8.22; N, 5.39.

e) N-Methyl-N-( $\beta$ )-chloroethyl)-cis-2-Phenoxycyclopentylamine Hydrochloride (XXXII)

To a solution of 0.5 g (0.002 mole) of N-methyl-N-( $\beta$ -hydroxyethyl)-cis-2-phenoxycyclopentylamine in 5 ml. of dry chloroform at 0° was added 5 ml. of chloroform saturated with dry hydrogen chloride. The mixture was maintained at 0° while 0.5 ml. (0.007 mole) of thionyl chloride was added with stirring over five minutes. The solution was stirred a further fifteen minutes at 0°, then stored one hour at room temperature, and finally refluxed for one hour. The solution was then evaporated in vacuo and the residue was taken up in hot acetone-ethyl acetate. The hydrochloride salt crystallized out after standing for several months at 25°. After repeated recrystallizations from acetone-2-propanol, the compound, ca 0.3 g. (49%), had mp 158-158.5° (sl 156°).

Anal. Calc'd. for  $C_{14}H_{21}NOCl_2$ : C, 57.8; H, 7.28; N, 4.82.

Found: C, 57.5; H, 7.60; N, 5.18.

f) The Synthesis of cis-2-Phenoxycyclopentylamine (XXXVI)

i) The Reductive Amination of 2-Phenoxycyclopentanone (XXXIII)

2-Phenoxycyclopentanone was prepared according to the method of Mousseron and co-workers (73).

A mixture of 2 g. (0.011 mole) of 2-phenoxycyclopentanone and 1.24 ml. (0.011 mole) of benzylamine was heated at 70° for three minutes. The resultant material was dissolved in 25 ml. of ethanol and the solution was hydrogenated over platinum oxide at 50 psi for three hours.

The mixture was then filtered and acidified with 10 ml. of concen-

trated hydrochloric acid. After a further hydrogenation over 10 per-cent palladium on charcoal for fifteen hours at 50 psi, the mixture was filtered and evaporated to dryness in vacuo. The residue was dissolved in water and extracted with ether. The aqueous phase was then made alkaline with sodium hydroxide and was extracted with ether. This ether extract was evaporated off and the residual oil was distilled to yield 0.75 g. (39%) of the primary amine, bp 220° (bath)/18 mm. The picrate had mp 210-212° from 2-propanol. The hydrochloride, prepared by passing dry hydrogen chloride through an ether solution of the amine, was recrystallized from methanol-acetone to constant mp 197-199°.

Anal. Calc'd. for  $C_{11}H_{16}NOCl$ : C, 61.8; H, 7.55; N, 6.56.

Found: C, 61.8; H, 7.51; N, 6.59.

The residue from the distilled primary amine was distilled at 180° (bath)/0.04 mm. to yield 1.32 g. (45%) of the intermediate, probably N-benzyl-cis-2-phenoxy-cyclopentylamine (XXXV).

ii) The Reduction of 2-Phenoxy-cyclopentanone Oxime (XXXVII)

2-Phenoxy-cyclopentanone was converted to the oxime by treating it with aqueous hydroxylamine hydrochloride and sodium acetate. After sublimation, it had mp 105-107°.

A solution of 1.3 g. (0.068 mole) of 2-phenoxy-cyclopentanone oxime in 20 ml. of dry ether was added over one hour to a stirred suspension of 0.5 g. (0.013 mole) of lithium aluminium hydride in 50 ml. of ether. The mixture was stirred and refluxed for a further hour and was then decomposed with water and aqueous sodium hydroxide solution.



Evaporation of the filtered ether solution followed by removal of the ether and vacuum distillation of the residual oil gave 1.06 g. (88%) of the amine, bp 170° (bath)/18 mm. The picrate had mp 200-203°. An admixture with the picrate from lf(i) gave mp 205-208°.

iii) 1-Nitro-2-Phenoxycyclopentane (XXXVIII)

The procedure used here was the general method of Emmons (74) for the oxidation of oximes to nitro compounds.

To a gently refluxing mixture of 5.15 g. (0.027 mole) of 2-phenoxycyclopentanone oxime, 0.55 g. of urea, and 21 g. of disodium hydrogen phosphate suspended in 50 ml. of acetonitrile was added over thirty minutes a mixture of 1.47 ml. (0.054 mole) of 90% hydrogen peroxide and 9.1 ml. (0.064 mole) of trifluoroacetic anhydride in 15 ml. of acetonitrile.

The mixture was refluxed a further hour and then most of the acetonitrile was removed in vacuo. The residual sludge was taken up in water, and the mixture was extracted with ether. The ether extract was washed with 25 ml. of water and then with 4x20 ml. of 10 percent aqueous sodium bicarbonate. Evaporation of the ether followed by distillation of the residue in vacuo gave 4.03 g. (72%) of 1-nitro-2-phenoxycyclopentane, b.p. 130° (bath)/0.05 mm.

A center cut of the distillate, which rapidly turned black on standing at 25°, was submitted for analysis.

Anal. Calc'd. for  $C_{11}H_{13}NO_3$ : C, 63.7; H, 6.32; N, 6.77.

Found: C, 63.5; H, 6.10; N, 8.54.

The IR spectrum (F) of this material showed an  $NO_2$  asymmetric stretch absorption at  $1530\text{ cm}^{-1}$  (strong) as well as a phenolic O-H

stretch at  $3550\text{ cm}^{-1}$  (weak) and a carbonyl band at  $1700\text{ cm}^{-1}$  (weak). The ether Ar-O stretch absorption was present at  $1225\text{ cm}^{-1}$  (strong).

iv) The Reduction of 1-Nitro-2-Phenoxycyclopentane (XXXVIII) with Lithium Aluminium Hydride

A solution of 3 g. (0.014 mole) of 1-nitro-2-phenoxycyclopentane in 30 ml. of dry ether was added over forty-five minutes to a suspension of 1.5 g. (0.037 mole) of lithium aluminium hydride in 75 ml. of ether. After the mixture was stirred for a further three hours, it was decomposed with water and alkali, and the inorganic salts were filtered off. The ether was removed from the filtrate and the residue was taken up in dilute hydrochloric acid. The aqueous phase, after being washed with ether, was made alkaline with sodium hydroxide and extracted with ether. Removal of the ether and distillation of the residue gave 1.1 g. (44%) of cis-2-phenoxycyclopentylamine, b.p.  $175^{\circ}$  (bath) at 19 mm. The hydrochloride, m.p.  $195-198^{\circ}$ , on admixture with a sample of the cis amine hydrochloride from 1f(i) gave m.m.p.  $196-199^{\circ}$ .

v) The Equilibration of 1-Nitro-2-Phenoxycyclopentane (XXXVIII)

The procedure employed here was the general method evolved by Zimmerman and Nevins (57) for the equilibration of 1-nitro-2-phenylcyclohexane (LXIII).

A solution of 0.7 g. of 1-nitro-2-phenoxycyclopentane in 300 ml. of 95 percent ethanol saturated with sodium bicarbonate was refluxed for four hours. The solution was then evaporated in vacuo to a 20 ml. volume, water was added, and the solution was then extracted with

ether. Removal of the ether gave a dark brown oil. Its IR spectrum showed that it contained much phenol.

Lithium aluminium hydride reduction of this material did not yield any amine.

## 2. The Synthesis of trans-2-Phenoxycyclopentylamines

### a) cis-2-Phenoxycyclopentanol (XLII)

#### i) The Reduction of 2-Phenoxycyclopentanone (XXXIII) with Lithium Aluminium Hydride

A solution of 5 g (0.028 mole) of 2-phenoxycyclopentanone in 60 ml of ether was added over one hour to a stirred suspension of 2 g (0.05 mole) of lithium aluminium hydride in 100 ml of ether. The mixture was refluxed for two hours and then decomposed with water and dilute hydrochloric acid. Filtration and removal of the ether from the filtrate gave 5 g (100%) of the alcohol. Its IR spectrum (F) showed no carbonyl peak. A VPC of this material on an Apiezon column at 167° / 40 ml/min. of argon showed that it consisted of a mixture of 66 percent of the cis alcohol (retention time, 18 min.) and 33 percent of the trans alcohol (retention time, 21 min.).

To a solution of 5 g (0.028 mole) of the mixed alcohols in 35 ml of dry pyridine at -10° was added 7 g of p-toluenesulphonyl chloride. The resultant solution was stored at 0° for two days and then at 22° for a further two days. It was then poured onto crushed ice and the solid precipitate was filtered off, washed thoroughly with water and dried. There was obtained 9 g (97%) of crude tosylate, mp 80-90°

(s36°). Upon recrystallization from 2-propanol there was obtained 6.3 g.(100%, based on VPC data) of pure cis tosylate, mp. 98-100°.

Anal. Calc'd. for  $C_{18}H_{20}O_4S$ : C, 65.2; H, 6.06.

Found: C, 65.1; H, 6.20.

From the mother liquors of the cis-tosylate was isolated 1.6 g. (66%) of the trans isomer, mp. 45-48° (s43°). An admixture with the trans-tosylate from 2b gave mmp 45-48° (s43°).

ii) The Lithium tri-t-Butoxyaluminumhydride Reduction of 2-Phenoxy-cyclopentanone

To a stirred suspension of 25 g.(0.1 mole) of lithium tri-t-butoxy-aluminumhydride in 50 ml. of dry Diglyme was added over forty minutes a solution of 8 g.(0.045 mole) of 2-phenoxy-cyclopentanone in 30 ml. of Diglyme. The mixture was stirred for a further two hours and was then poured onto crushed ice containing 15 ml. of concentrated hydrochloric acid. The mixture was extracted with ether and the ether extract was washed with water and then evaporated. The residue was dried at 85°/10 mm. to leave 8.7 g.(100%) of crude cis-2-phenoxy-cyclopentanol. Gas chromatography of a sample showed that it contained only ten percent of the trans alcohol. The mixture was dissolved in 50 ml of dry pyridine, cooled to 0°, and was treated with 11 g.(0.06 mole) of p-toluenesulphonyl chloride. The mixture was allowed to stand at 5° for two days, and then at 22° for an additional two days. It was then poured onto crushed ice, and the solid was filtered off and washed with water. Crystallization of this from 2-propanol gave 12 g.(80%) of pure cis-2-phenoxy-cyclopentyl tosylate (XLVIII), mp 98-99°.

iii) The Hydrogenation of 2-Phenoxycyclopentanone (XXXIII)

A solution of 5 g. (0.028 mole) of XXXIII in 50 ml. of ethanol was hydrogenated over 0.25 g. of platinum oxide at 50 psi. for two hours. The uptake of hydrogen was 0.12 mole (4 equiv.). The catalyst was filtered off and the solvent was removed in vacuo. The residue was distilled, bp  $80^{\circ}/18$  mm, yielding 3.2 g. (65%) of colourless oil, probably 2-cyclohexyloxycyclopentanol.

The infra-red spectrum (F) of this material showed a hydroxyl absorption band at  $3650\text{ cm}^{-1}$ , a carbonyl band at  $1770\text{ cm}^{-1}$ , and an aliphatic ether band at  $1125\text{ cm}^{-1}$ , but the aromatic absorptions at  $1600\text{ cm}^{-1}$ ,  $1500\text{ cm}^{-1}$ ,  $760\text{ cm}^{-1}$  and  $690\text{ cm}^{-1}$  were absent.

b) trans-2-Phenoxycyclopentanol (XLIII)

Cyclopentene oxide was prepared by adding 175 g. (1.07 mole) of cyclopentene bromhydrin in 690 ml. of benzene to 300 g. of powdered potassium hydroxide in 300 ml. of benzene. The solution thus obtained was filtered and distilled. The distillate, containing the cyclopentene oxide, was added dropwise over twenty minutes to a stirred solution of 140 g. (1.5 moles) of pure phenol in 200 ml. of benzene containing 10 ml. of boron trifluoride etherate. The solution was then extracted with eight 400 ml. portions of 5 percent aqueous sodium hydroxide solution and then with water until the washings were neutral. The benzene was evaporated and the residue was fractionated under reduced pressure to give 44 g. (25%) of colourless, viscous oil, bp  $78-95^{\circ}/5 \times 10^{-3}$  mm. Treatment of this trans-2-phenoxycyclopentanol with excess p-toluene-sulphonyl chloride and pyridine in the cold gave 60 g. (66%) of the crude

tosylate. Crystallization of this material from 2-propanol gave 47.4 g. of white crystals, mp 48-49.5°.

Anal. Calc'd. for  $C_{18}H_{20}O_4S$ : C, 65.2; H, 6.06.

Found: C, 65.0; H, 6.17.

c) trans-2-Phenoxycyclopentyl Azide (XLIX)

To a solution of 2.8 g. (0.043 mole) of sodium azide in 200 ml of Carbitol containing 35 ml. of water was added 6.65 g. (0.02 mole) of cis-2-phenoxycyclopentyl tosylate (XLVIII). The mixture was heated slowly to 95° and maintained at this temperature for twenty-four hours. It was then cooled to room temperature, poured onto crushed ice, and the mixture extracted with ether. The ether extract was washed with water and was then evaporated to dryness. The residual oil was distilled in vacuo to give 3.7 g. (90%) of oil, bp 100°/0.5 mm.

Anal. Calc'd. for  $C_{11}H_{13}N_3O$ : C, 65.0; H, 6.43; N, 20.8.

Found: C, 65.2; H, 6.34; N, 20.9.

An IR spectrum (F) of this compound showed an azide stretch absorption at  $2120\text{ cm}^{-1}$  (strong).

d) trans-2-Phenoxycyclopentylamine (L)

To a slurry of 1 g. of 10 percent palladium on charcoal in 100 ml. of methanol containing 3.5 ml. of concentrated hydrochloric acid was added 3.7 g. (0.018 mole) of trans-2-phenoxycyclopentyl azide. The mixture was hydrogenated at 45 psi. for twenty-four hours, filtered through Celite, and the filtrate evaporated. The solid residue was crystallized from 2-propanol to give 2.6 g. (66%) of trans-2-phenoxy-cyclopentylamine hydrochloride, mp 167-168° (sl 163°). An admixture

with cis-2-phenoxycyclopentylamine (XXXVI) hydrochloride gave mp 142-183° (sl15°).

Anal. Calc'd. for  $C_{11}H_{16}NOCl$ : C, 61.8; H, 7.55; N, 6.56.

Found: C, 61.6; H, 7.56; N, 6.51.

To a solution of 2.6 g. (0.012 mole) of the hydrochloride in 5 ml. of water was added 3 ml. of 20 percent aqueous sodium hydroxide solution. The mixture was extracted with ether and the ether extract was dried over sodium sulphate. The ether solution was decanted and evaporated to yield 2.16 g. (100%) of trans-2-phenoxycyclopentylamine.

e) N-Formyl-trans-2-Phenoxycyclopentylamine (LI)

A solution of 4 g. (0.018 mole) of trans-2-phenoxycyclopentylamine in 20 ml. of dry, acid-free ethyl formate containing one drop of ethylene glycol was heated in a bomb at 120° for forty-eight hours. The contents of the bomb were evaporated in vacuo almost to dryness and the residue was rinsed with ether. The solid was crystallized from acetone to give 3.65 g. (100%) of white needles, mp 104.5-108° (s99°).

Anal. Calc'd. for  $C_{12}H_{15}NO_2$ : C, 70.3; H, 7.41; N, 6.82.

Found: C, 70.2; H, 7.26; N, 6.82.

f) N-Methyl-trans-2-Phenoxycyclopentylamine (LII)

A solution of 3.3 g. (0.016 mole) of N-formyl-trans-2-phenoxycyclopentylamine in 500 ml. of dry ether was added slowly with stirring to a slurry of 4 g. (0.10 mole) of lithium aluminium hydride in 100 ml. of dry ether. The addition was complete after thirty minutes and the mixture was then stirred a further twelve hours. The slurry was then decomposed with aqueous sodium hydroxide solution, and the precipitated

inorganic salts filtered off and rinsed with several portions of ether. The combined filtrate and washings were dried over sodium sulphate, decanted and then evaporated. The oily residue was distilled in vacuo to give 2.85 g. (94%) of colourless oil, bp. 135°/20 mm. The hydrochloride of this base was prepared as described for the cis isomer. It was crystallized from boiling acetone to constant mp. 105-109° (sl 100°).

Anal. Calc'd. for  $C_{12}H_{18}NOCl$ : C, 63.3; H, 7.97; N, 6.15.

Found: C, 63.4; H, 7.91; N, 6.13.

g) N-Methyl-N-( $\beta$ -hydroxyethyl)-trans-2-Phenoxycyclopentylamine  
(LIII)

i) From cis-2-Phenoxycyclopentyl tosylate (XLVIII)

A solution of 1 g. (0.003 mole) of cis-2-phenoxycyclopentyl tosylate in 10 ml. (0.13 mole) of redistilled N-methyl-2-aminoethanol was heated at 65° for twenty-four hours, then at 125° for twenty-four hours and finally at 145° for twenty hours. The excess of N-methyl-2-aminoethanol was removed in vacuo and the residue was washed with 20 percent sodium hydroxide solution. The organic layer was distilled in vacuo to yield 0.4 g. (66%) of colourless oil, bp 180° (bath)/0.2 mm. The hydrochloride prepared from this amine never crystallized.

ii) From N-Methyl-trans-2-Phenoxycyclopentylamine (LII)

A mixture of 1.1 g. (0.0057 mole) of N-methyl-trans-2-phenoxy-cyclopentylamine, 0.3 g. (0.0071 mole) of ethylene oxide and a trace of phenol was heated in a sealed tube at 50° for twenty-four hours, then at 95° for a like period, and finally at 150° for the same time. Distillation of the product in vacuo gave 1 g. (90%) of the tertiary amine,



bp 114°/0.05 mm. Neither the picrate nor the hydrochloride of the base could be obtained as a solid. The free base was redistilled, a center cut being taken for analysis.

Anal. Calc'd. for  $C_{14}H_{21}NO_2 \cdot H_2O$ : C, 66.4; H, 9.17.

Found: C, 66.8; H, 8.74.

The IR spectra (F) of the products from 2g(i) and 2g(ii) were identical. The IR spectrum of the cis isomer (XXXI) was entirely different in the region 850-1000  $cm^{-1}$ .

h) N-Methyl-N-( $\beta$ -chloroethyl)-trans-2-Phenoxycyclopentylamine Hydrochloride (LIV)

A solution of 0.4 g. (0.0020 mole) of N-methyl-N-( $\beta$ )-hydroxyethyl)-trans-2-phenoxycyclopentylamine (LII) (prepared as in 2g(i)) in 10 ml. of dry chloroform was cooled to 0°. Dry hydrogen chloride was passed through the solution until it was acid to Congo Red paper. Then a solution of thionyl chloride, 0.26 g. (0.0022 mole) in 5 ml. of chloroform, was added over thirty minutes, maintaining the temperature of the mixture at 0°.

After the solution had stood for twelve hours at 0°, it was refluxed for thirty minutes, then decolorized with Norite, filtered, and evaporated to dryness in vacuo. The viscous, pale yellow residue failed to crystallize on treatment with a variety of solvents.

When the tertiary amino alcohol from 2g(ii) was treated in the same way as that from 2g(i), viz. hydrogen chloride and thionyl chloride at 0°, the produce could likewise not be made to solidify. It was therefore purified by molecular distillation at 75°/0.05 mm. in a microsublimation apparatus to give an almost colorless gum which

rapidly turned brown on standing.

Anal. Calc'd. for  $C_{14}H_{21}NOCl_2$ : C, 57.8; H, 7.28; N, 4.82.

Found: C, 57.4; H, 7.68; N, 5.62.

### 3. The Synthesis of 2-Benzylcyclopentylamines

#### a) trans-2-Benzylcyclopentylamine (LVI)

2-Benzylcyclopentanone (LVII) was prepared according to the method of Phillips and Mentha (75). The oxime had mp 119-121°, semicarbazone, mp 196-198° (reported for semicarbazone, 198-199°).

To a solution of 10 g. (0.0053 mole) of 2-benzylcyclopentanone oxime (LV) in 150 ml. of boiling absolute ethanol was added 23 g. (1.0 mole) of sodium metal in small pieces over ninety minutes.

The solution was evaporated to half volume, 100 ml. of water was added, and the mixture was extracted with ether. The ether extract was evaporated in vacuo and the residue was poured into 100 ml. of water containing 25 ml. of concentrated hydrochloric acid. The amine hydrochloride which precipitated was filtered off and dried to give 7.8 g. (70%) of white flakes, mp 204-206°. Recrystallization of this from 2-propanol gave pure material, mp 207-210°.

Anal. Calc'd. for  $C_{12}H_{18}NCl$ : C, 67.9; H, 8.55; N, 6.60.

Found: C, 67.9; H, 8.42; N, 6.74.

#### b) The Reduction of 2-Benzylcyclopentanone Oxime (LV)

A solution of 10 g. (0.0053 mole) of 2-benzylcyclopentanone oxime in 200 ml. of dry ether was added over twenty minutes to a stirred suspension of 2.5 g. (0.075 mole) of lithium aluminium hydride in 200 ml.

of ether. The mixture was stirred for a further twelve hours, then decomposed with water and alkali, the ether filtered and evaporated and the residue distilled in vacuo to obtain 4.1 g. (45%) of colourless oil, b.p.  $73^{\circ}/5 \times 10^{-3}$  mm.,  $n_D^{24}$  1.5379. The hydrochloride salt, m.p.  $203-206^{\circ}$  from 2-propanol-acetone was prepared in almost quantitative yield. An admixture with trans-2-benzylcyclopentylamine hydrochloride (LVI) gave m.m.p.  $202-210^{\circ}$ .

c) The Reductive Amination of 2-Benzylcyclopentanone (LVII)

A mixture of 8.7 g. (0.05 mole) of 2-benzylcyclopentanone and 5.3 g. (0.05 mole) of benzylamine was heated in vacuo until the water was removed. The residue, in 60 ml. of methanol, was hydrogenated over platinum oxide at 50 p.s.i. for 2 hours. The catalyst was removed and 4.1 ml. (0.05 mole) of concentrated hydrochloric acid was added. The solution was hydrogenated over 10 percent palladium on charcoal at 50 p.s.i. for 15 hours, the catalyst was removed, and the solution was evaporated to dryness. The free base, isolated from an aqueous alkaline solution of the residue, was distilled to yield 5.8 g. (67%) of material, b.p.  $130^{\circ}/10$  mm. Its infra-red spectrum was superimposable with that of LVI except for slight differences between 11 and  $15\mu$ . The hydrochloride salt was an intractable mixture from which only traces of LVI hydrochloride could be isolated.

d) 1-Nitro-2-Benzylcyclopentane (LXI)

To a gently refluxing mixture of 5.1 g. (0.025 mole) of 2-benzylcyclopentanone oxime, 0.55 g. of urea, and 21 g. of disodium hydrogen

phosphate in 50 ml of acetonitrile was added, with stirring, a mixture of 1.47 ml. (0.054 mole) of 90 percent hydrogen peroxide and 9.1 ml. (0.064 mole) of freshly distilled trifluoroacetic anhydride. The addition required one hour.

The mixture was refluxed a further two hours, then cooled, filtered, and the filtrate freed of solvent in vacuo. The residue was extracted with 4x50 ml of water and then distilled to yield 4.8 g. (94%) of the nitro compound.

Anal. Calc'd. for  $C_{12}H_{15}NO_2$ : C, 70.2; H, 7.37.

Found: C, 72.0; H, 7.58.

The IR spectrum (F) of this compound exhibited an asymmetric  $NO_2$  stretch band at  $1530\text{ cm}^{-1}$  (strong).

e) The Reduction of 1-Nitro-2-Benzylcyclopentane (LXI)

To a stirred suspension of 2 g. (0.02 mole) of lithium aluminium hydride in 75 ml. of ether was added over a period of thirty minutes, a solution of 3.6 g. (0.017 mole) of 1-nitro-2-benzylcyclopentane (LXI) in 40 ml. of ether.

The mixture was stirred for a further two hours, then decomposed with water and alkali, and finally filtered. The ether was removed from the filtrate and the residual oil was dried. The product was dissolved in dry ether and hydrogen chloride was passed through the solution. The solid was filtered off and dried to yield 2 g. (53%) of trans-2-benzylcyclopentylamine hydrochloride, mp 205-210° (from 2-propanol), undepressed by admixture with an authentic sample.

f) The Attempted Isomerization of LXI

The nitro compound was treated in a manner similar to that applied by Zimmerman and Nevins (57) to trans-2-phenyl-1-nitro-cyclohexane.

One g. (0.005 mole) of LXI was dissolved in 2.89 g. (0.01 mole) of 20 percent potassium hydroxide in ethanol. The solution was diluted with 60 ml. of water and cooled to  $-10^{\circ}$ . The mixture was stirred vigorously while it was acidified to Congo Red paper by the addition of 1:3 sulphuric acid:ethanol. The gum which separated was rinsed with water and was then added to 12 ml. of lithium acetate buffer. The gum solidified before dissolving. The solution was allowed to remain at  $25^{\circ}$  for fifteen minutes. It was then diluted with 20 ml. of water and the solution was extracted with ether. The ether extract was washed with aqueous bicarbonate solution and then with water. The solvent was removed from the ether solution to leave 0.93 g. (93%) of the nitro compound.

Reduction of this material with one g. of lithium aluminium hydride gave 0.90 g. (100%) of the amine. Passage of dry hydrogen chloride through an ether solution of this amine gave the hydrochloride salt in fifty percent yield, m.p.  $125-173^{\circ}$  (s.  $115^{\circ}$ ). Fractional crystallization from 2-propanol gave 0.12 g. (30%) of trans-2-benzylcyclopentylamine (LVI) hydrochloride.

g) The Reduction of 2-Benzylcyclopentanone (LVII)

To a refluxing solution of 12 g. (0.069 mole) of 2-benzylcyclopentanone in 100 ml. of anhydrous n-amyl alcohol was added, over thirty minutes, 5 g. (0.22 mole) of sodium cut into small pieces.

The solvent was stripped off and the residue was taken up in water. The suspension was extracted with ether and the ether was removed to leave an almost quantitative yield of the alcohol.

The IR spectrum (F) of the alcohol showed no carbonyl peak. The VPC data indicated that it was a mixture of about 40 percent cis alcohol (LXVIII) (ret. time, 19.3 min. at 185°/40 ml/min. argon on an Apiezon column) and 60% trans alcohol (LXVII) (ret. time, 18.4 min.).

The tosylate (LXIX) from this mixture was obtained in a 28 percent yield, mp 62-64° from 2-propanol. This material gave, on treatment with sodium azide followed by hydrogenation of the azide (LXX), 0.70 g. (6.6% overall) of a crude amine hydrochloride which could not be fractionated successfully.

h) The Reduction of 2-Benzylidenecyclopentanone Oxime (LXXII)

2-Benzylidenecyclopentanone was prepared according to the method of Phillips and Mentha (75). The oxime had mp. 130-132°.

A solution of 34.5 g. (0.18 mole) of 2-benzylidenecyclopentanone oxime in 700 ml. of ether was added to a stirred suspension of 10 g. (0.26 mole) of lithium aluminium hydride in 600 ml. of ether over a period of twenty minutes.

After it was stirred for a further fifteen minutes, the mixture was decomposed with water and alkali and the salts were filtered off. The ether solution evolved ammonia after standing at 25° for twelve hours. The solvent was stripped off and the residue was distilled to give 9.2 g. (30%) of yellow oil, bp 55°/10<sup>-3</sup> mm. From the undistilled residue was recovered 12 g. (35%) of unchanged starting material.

The amine was dissolved in dilute hydrochloric acid and the solution was extracted with ether. The aqueous phase was made alkaline with sodium hydroxide and extracted with ether. The ether extract was stripped of solvent and the residue was distilled in vacuo to yield 4.6 g. (50%) of chlorine-free amine, bp  $76^{\circ}/0.15$  mm. The IR spectrum (F) of this substance showed a strong double bond stretch absorption at  $1665\text{ cm}^{-1}$ .

A solution of 4.6 g of this amine in 100 ml of methanol was hydrogenated over 10 percent palladium on charcoal at 50 psi for fifteen minutes. The uptake was 0.8 lb. (calc. 2.2 lb.). The solution was filtered and evaporated in vacuo and the residue was distilled. The IR spectrum of the product was free of the absorption band at  $1665\text{ cm}^{-1}$ . An ether solution was treated with hydrogen chloride and the precipitated salt was recrystallized from 2-propanol to constant mp  $205^{\circ}$  (decomp.). An admixture with trans-2-benzylcyclopentylamine hydrochloride gave mp  $160^{\circ}$  (sl  $135^{\circ}$ ). An admixture with the product from 3(i) gave mp  $185-186^{\circ}$  (sl  $175^{\circ}$ ).

Anal. Calc'd. for  $\text{C}_{12}\text{H}_{17}\text{NCl}_2$ : C, 58.4; H, 6.94; N, 5.68; Cl, 28.6.

Found: C, 58.4; H, 6.83; N, 5.98; Cl, 27.9.

i) The Lithium tri-t-Butoxyaluminumhydride Reduction of 2-Benzylcyclopentanone Oxime (LV)

To a suspension of 50 g. (0.2 mole) of lithium tri-t-butoxyaluminumhydride in 30 ml. of Diglyme was added with stirring 10 g (0.05 mole) of 2-benzylcyclopentanone oxime dissolved in 30 ml. of Diglyme over one hour. The mixture was then stirred and heated at  $100^{\circ}$  for two days after which it was decomposed with water and alkali.

The solution was filtered off from inorganic salts, the water removed on a flash evaporator, and the organic solution finally saturated with hydrogen chloride. Ether was added, and the oil which separated was taken up in water. The aqueous solution was made alkaline with sodium hydroxide and extracted with ether.

The ether extract was evaporated to an oily residue, and this was distilled, bp 135°/12 mm. An ether solution of this distillate was saturated with hydrogen chloride and the precipitated amine hydrochloride was filtered off. After recrystallization from 2-propanol, it had mp 203-206° with decomp. An admixture with trans-2-benzylcyclopentylamine hydrochloride (LVI) had mmp 173-180° (s80°).

|        |                                   |                             |
|--------|-----------------------------------|-----------------------------|
| Anal.  | Calc'd. for $C_{12}H_{17}NCl_2$ : | C, 58.4; H, 6.94; N, 5.68;  |
|        |                                   | Cl, 28.6; Cl (ionic), 14.3. |
| Found: |                                   | C, 58.6; H, 7.02; N, 5.80;  |
|        |                                   | Cl, 27.5; Cl (ionic), 15.5. |

#### 4. The Synthesis of 2-Phenoxycyclobutylamine (XXC)

2-Phenoxycyclobutanone was prepared according to the procedure of Conia and Ripoli (76). The oxime had mp 101-105°.

##### a) cis-2-Phenoxycyclobutylamine (XXC)

A solution of 0.523 g (0.00295 mole) of dry 2-phenoxycyclobutanone oxime in 30 ml. of dry ether was added to a suspension of 0.6 g. (0.015 mole) of lithium aluminium hydride in 60 ml. of ether over thirty minutes.

The mixture was refluxed for one hour, and was then decomposed



with water and alkali. The filtered ether solution was stripped of solvent, and the residue was distilled in vacuo to yield 0.400 g. (83%) of the amine, b.p. 131°/15 mm.

The hydrochloride salt of this amine (452 mg., 92%) was purified by recrystallization from 2-propanol to constant m.p. 174-175° (s.171°).

Anal. Calc'd. for  $C_{10}H_{14}NOCl$ : C, 60.1; H, 7.01; N, 7.01.

Found: C, 59.9; H, 6.94; N, 7.09.

b) 2-Phenoxycyclobutanol (XXCII)

To a stirred suspension of 12.5 g. (0.05 mole) of lithium tri-*t*-butoxyaluminumhydride in 25 ml. of dry Diglyme was added, over forty minutes, a solution of 3.93 g. (0.024 mole) of 2-phenoxycyclobutanol in 15 ml. of Diglyme plus 2 ml. of ether.

The mixture was stirred for a further two hours and was then poured onto a mixture of 100 g. of crushed ice and 7 ml. of concentrated hydrochloric acid. The mixture was exhaustively extracted with ether, the ether extracts were combined, evaporated down, and the residue was distilled. There was obtained 3.2 g. (81%) of colourless oil, b.p. 68-80°/0.05 mm. A VPC run on an Apiezon column at 153° and 40 ml./min. of argon showed that this alcohol was a mixture of 55 percent of one isomer (ret. time, 16 min.) and 45 percent of the other isomer (ret. time, 21 min.). An infra-red spectrum showed that the mixture contained no ketone. The hydroxyl O-H stretch band was present at 3440  $cm^{-1}$ .

## 5. The Synthesis of 2-Phenoxycyclopropylamines

### a) 2-Phenoxycyclopropane Carboxylic Acids (XXCIII)

2-Phenoxycyclopropane ethyl carboxylate was prepared from phenyl vinyl ether and ethyl diazoacetate according to the procedure of Julia and Tchernoff (58). Vapour phase chromatography of the product on an Apiezon column at 180° and 30 ml/min. of argon showed that the material contained 66 percent of the trans ester (ret. time, 14.5 min.) and 33 percent of the cis ester (ret. time 15.2 min.). Identical results were obtained using copper sulphate in place of copper powder, or when the reaction was conducted at 25°.

The mixed esters were hydrolysed with boiling aqueous, ethanolic sodium hydroxide solution according to the method of Canonica and Fiechi (59). The hydrolysate was then freed of ethanol and the residual syrup was diluted with water and extracted with ether. Evaporation of the ether extract gave a small amount of unchanged ethyl ester. A VPC analysis of this material showed that it was the pure trans isomer.

The aqueous phase was freed of ether, cooled to 0° and neutralized fractionally by the addition of 5x0.2 equivalents of concentrated hydrochloric acid with vigorous stirring. The precipitated carboxylic acid was filtered off and rinsed with water after each 0.2 equivalent addition of hydrochloric acid. Each crop was analysed for the percentages of isomers by esterifying a trace of it with ethereal diazomethane and subjecting the resulting methyl ester to VPC separation (ret. time trans = 11.3 min. at 180°/30 ml.min.<sup>-1</sup> on Apiezon, ret. time cis isomer = 12 min.).

It was found that the isomer distribution was random rather than uniform throughout the fractions. A typical result is shown below for the fractional neutralization of the hydrolysate from 40 g. of the mixed ethyl esters with 4x0.25 equivalents of hydrochloric acid.

| <u>Fraction</u> | <u>Weight<br/>(g)</u> | <u>Percent <u>cis</u> Acid<br/>(XXCIIIa)</u> | <u>Percent <u>trans</u> Acid<br/>(XXCIIIb)</u> |
|-----------------|-----------------------|----------------------------------------------|------------------------------------------------|
| 1               | 9.3                   | 0                                            | 100                                            |
| 2               | 14.0                  | 45                                           | 55                                             |
| 3               | 6.3                   | 40                                           | 60                                             |
| 4               | 3.0                   | 90                                           | 10                                             |

Over several such runs, it was found that the order of separation was often inverted or even scrambled.

The purest fractions were separately recrystallized from carbon tetrachloride to give pure cis acid, mp 135° and pure trans acid, mp 115°. The mother liquors from these recrystallizations were combined and the solvent was stripped off. The residual acid was combined with the mixed fractions from the fractional neutralization above. The crude mixture was converted to the sodium salt by dissolving it in aqueous sodium bicarbonate, and the whole purification cycle was repeated.

b) trans-2-Phenoxycyclopropyl Methyl Urethane (XXCVIIIb)

The modified Curtius reaction employed here was similar to that applied by Weinstock (62) to 2-phenylcyclopropane carboxylic acids.

To a stirred solution of 7.7 g. (0.043 mole) of trans-2-phenoxy-cyclopropane carboxylic acid in 10 ml. of water plus 3 ml. of acetone at 0° was added dropwise with stirring, 7 ml. (5.0 g., 0.05 mole) of

triethylamine in 80 ml. of acetone.

The mixture was cooled to  $-5^{\circ}$  and maintained there while 5.5 ml. (6.25 g, 0.055 mole) of freshly distilled ethyl chloroformate in 20 ml. of acetone was added dropwise over thirty minutes. The mixture was stirred at  $0^{\circ}$  for a further thirty minutes after which a solution of 4.3 g. (0.065 mole) of sodium azide in 15 ml. of water was added dropwise over fifteen minutes.

The suspension was stirred for a further hour at  $0^{\circ}$  and the acetone was then removed at  $25^{\circ}/10$  mm. The residue was diluted with 25 ml. of water and then extracted with benzene. The benzene extract was dried over magnesium sulphate and then evaporated at  $25^{\circ}/10$  mm. to leave 10 g. of the crude acyl azide. The IR spectrum (F) of this material showed a strong azide band at  $2150\text{ cm}^{-1}$  as well as an intense carbonyl stretch absorption at  $1690\text{ cm}^{-1}$ . There was no isocyanate band at  $2250\text{ cm}^{-1}$ .

Thirty ml. of dry toluene and a boiling chip was added to the acyl azide, and the solution was gradually warmed on a steam bath until nitrogen evolution began. It was then heated at  $100^{\circ}$  until the decomposition was complete. The toluene was removed in vacuo to leave the crude isocyanate (XXCVIb). An IR spectrum (F) of this material showed an intense absorption at  $2250\text{ cm}^{-1}$  due to the isocyanate group, and no absorption peaks at  $2150\text{ cm}^{-1}$  or  $1690\text{ cm}^{-1}$ . The aryloxy-ether stretch absorption was present at  $1230\text{ cm}^{-1}$  (strong).

To 6 g. (0.034 mole) of the crude isocyanate was added 40 ml. of anhydrous methanol. After the solution had stood for twelve hours at

25° the excess methanol was removed in vacuo. There remained 5.8 g.(82%) of trans-2-phenoxypropyl methyl urethane (XXCVIIIb) which soon solidified, mp. 71.5-75° (s67°). Sublimation at 50°/0.05 mm. gave a pure sample, mp 74.5-75.5° (s71°).

Anal. Calc'd. for  $C_{11}H_{13}NO_3$ : C, 63.7; H, 6.32; N, 6.77.

Found: C, 63.7; H, 6.46; N, 6.47.

The IR spectrum of this urethane (S, chloroform) showed the amide N-H stretch absorption at  $3480\text{ cm}^{-1}$  (weak), the carbonyl stretch at  $1725\text{ cm}^{-1}$  (strong) and the aroxy ether band at  $1230\text{ cm}^{-1}$  (strong).

c) trans-2-Phenoxypropylamine (XXCVIIb)

i) From trans-2-Phenoxypropyl Isocyanate (XXCVIb)

To 1.0 g.(0.0057 mole) of the crude isocyanate from 4(b) was added 10 ml. of 50 percent aqueous sodium hydroxide solution. The mixture was stirred for five minutes and was then diluted with 5 ml. of cold water. The resultant suspension was added to an excess of cold, dilute hydrochloric acid and then the mixture was filtered to remove 0.20 g. of the urea.

The filtrate was made strongly alkaline with sodium hydroxide and extracted with ether. The ether solution was dried over calcium hydride and filtered. To the filtrate was added ethereal hydrogen chloride until the mixture was acid to Congo Red paper. The solid was filtered off to yield 0.60 g.(57%) of the amine hydrochloride, mp 219-220° with decomposition (from 2-propanol).

Anal. Calc'd. for  $C_9H_{12}NOCl$ : C, 58.2; H, 6.47; N, 7.53.

Found: C, 58.5; H, 6.72; N, 7.96.

When the free amine was distilled at 10 mm. under nitrogen and on an oil bath, a spontaneous violent decomposition ensued at 100-110°. Large amounts of volatile amine were rapidly evolved, and the pot residue suddenly foamed and then solidified.

The heavy brown oil which was entrained in the receiver was extracted with aqueous sodium hydroxide. The aqueous phase was back-extracted with ether, and then was acidified with hydrochloric acid. The mixture was extracted with ether and the ether was removed from the extract. The residue, in benzene, was treated with bromine. The benzene was evaporated off to leave tribromophenol, mp 94°.

ii) From trans-2-Phenoxycyclopropyl Methyl Urethane (XXCVIIIb)

A mixture of 0.80 g. (0.0039 mole) of the urethane, 0.5 g. of potassium hydroxide, 10 ml. of methanol and 5 ml. of water was refluxed on a steam bath for four hours. The methanol was distilled off and the distillate was treated with hydrogen chloride. The methanol was then removed, and the residue was washed into the aqueous, alkaline mixture in the reaction pot with a little water. The mixture was then extracted with ether and the ether was removed from the organic phase to leave 0.44 g. (75%) of the amine. A small amount of this was converted to the hydrochloride, mp 208-217°. An admixture of this with the hydrochloride obtained from 5c(i) gave mp 208-217°.

d) The Reduction of trans-2-Phenoxycyclopropyl Methyl Urethane (XXCVIIIb)

A solution of 5.75 g. (0.028 mole) of the urethane in 200 ml. of

ether was added dropwise to a stirred suspension of 4 g. (0.10 mole) of lithium aluminium hydride in 200 ml. of ether.

The mixture was stirred for twenty-four hours at 25° and was then decomposed with water and alkali and filtered. The ether filtrate after being dried over calcium hydride, was treated with an ether solution of anhydrous oxalic acid. The precipitate was filtered off to yield 2 g. (44%) of crude N-methylallylamine (XXCIX) oxalate, mp 140-160°. Several recrystallizations from ethanol gave a pure sample, mp 153-157°. An admixture of this with an authentic sample, mp 160°, gave mp 155-158°.

e) The Reduction of trans-2-Phenoxycyclopropyl Isocyanate (XXCVIb)

An ether solution of 5.9 g. (0.034 mole) of the isocyanate was reduced with 3 g. (0.075 mole) of lithium aluminium hydride by the same procedure as in 5 d. However, instead of precipitating the oxalate, the ether solution from the reduction was evaporated on a flash evaporator at 25°. Some of the N-methylallylamine was thus lost (bp. 67°/760 mm). There remained 1.5 g. (62%) of crude amine. An ether solution of this yielded crude N-methylallylamine oxalate on the addition of ethereal anhydrous oxalic acid.

f) N-Methyl-trans-2-Phenoxycyclopropylamine (XXCVIIb)

To 0.39 g. (0.0026 mole) of trans-2-phenoxycyclopropylamine was added 0.44 g. (0.0026 mole) of freshly distilled veratraldehyde and 20 ml. of benzene.

The mixture was refluxed for ten minutes and then heated at 110°/10 mm. on an oil bath until all of the water was removed. The

residue was dissolved in 5 ml. of benzene and 0.43 ml. (0.55 g, 0.0026 mole) of dimethyl sulphate was added. The solution was gently refluxed for twenty hours, then cooled and extracted first with 5 ml. of water and then with 5 ml. of 10 percent hydrochloric acid. The aqueous extracts were combined, washed with chloroform, evaporated to half volume at 10 mm, made alkaline with sodium hydroxide, and finally extracted with ether. The ether extract was dried over magnesium sulphate and was then acidified with ethereal hydrogen chloride. The oil which separated was taken up in chloroform from which solution a small amount of the primary amine (XXCVIIb) hydrochloride, mp. 208-210°, separated.

The chloroform filtrates from this salt were extracted with water, and the aqueous extract was back-extracted with chloroform. The aqueous phase was then made strongly alkaline and extracted with ether. The ether solution was dried over magnesium sulphate and then treated with ethereal picric acid. There was obtained 0.27 g. (26%) of yellow prisms, mp 137-140° (sl26°). Repeated recrystallization from isopropanol gave a pure sample of N-methyl-trans-2-phenoxypropylamine (XC) picrate, mp 141-142°.

Anal. Calc'd. for  $C_{16}H_{16}N_4O_8$ : C, 48.8; H, 4.11; N, 14.3.

Found: C, 48.6; H, 4.26; N, 14.3.

g) cis-2-Phenoxypropyl Methyl Urethane (XXCVIIIa)

A solution of 2 g. (0.0097 mole) of cis-2-phenoxypropylamine hydrochloride in 2 ml. of acetone plus 5 ml. of water was treated in the same way as was the trans isomer (part 5b) but using proportionately



smaller quantities of all of the reagents. The resultant acyl azide was decomposed by warming it in toluene on the steam bath.

To the isocyanate obtained in this way was added 25 ml. of anhydrous methanol. The solution was evaporated to dryness after twelve hours to yield 2.3 g. (100%) of cis-2-phenoxypropyl methyl urethane. A small amount was sublimed repeatedly to constant mp 85-86°.

Anal. Calc'd. for  $C_{11}H_{13}NO_3$ : C, 63.7; H, 6.32; N, 6.77.

Found: C, 63.6; H, 6.05; N, 6.55.

h) cis-2-Phenoxypropylamine (XXCVIIa)

The isocyanate obtained from 2 g. (0.0097 mole) of the cis acid was added to a stirred solution of 10 g. of 50 percent aqueous potassium hydroxide at 0°. The mixture was added to 18 ml. of cold, concentrated hydrochloric acid, and the solid was filtered off and rinsed with water. The aqueous filtrates were made strongly alkaline with sodium hydroxide and were extracted with ether. The ether extract was dried first over magnesium sulphate and then over calcium hydride. The filtered solution was then treated with hydrogen chloride. The precipitated salt was filtered off to yield 1.66 g. (75%) of cis-2-phenoxypropylamine hydrochloride. This was recrystallized from ethanol to constant mp 204-206° with decomp. An admixture with the trans isomer had mp 185-200°.

Anal. Calc'd. for  $C_9H_{12}NOCl$ : C, 58.2; H, 6.47; N, 7.53.

Found: C, 58.1; H, 6.38; N, 7.59.

i) The Reduction of cis-2-Phenoxypropyl Methyl Urethane (XXCVIIIa)

A solution of 0.4 g (0.002 mole) of the cis urethane in 20 ml. of

ether was added dropwise to 0.12 g. (0.003 mole) of lithium aluminium hydride in 10 ml of ether. After the solution had stirred for twenty hours, it was treated with water and alkali and worked up exactly as for the trans urethane.

There was obtained 0.095 g. (30%) of N-methylallylamine (XXCIX) oxalate, mp. 151-153°, undepressed by the addition of some of the authentic material. The filtrate from the oxalate was washed with water, dried over magnesium sulphate and then evaporated to give 0.16 g. (40%) of the starting urethane.

The inorganic lithium salts were dissolved in dilute hydrochloric acid and the solution was extracted with chloroform. Evaporation of the chloroform gave 0.045 g. (80% based on the yield of N-methylallylamine) of phenol.

## 6. Potentiometric Titrations

A Beckmann Model GS pH meter equipped with a calomel and hydrogen electrode was used for all titrations.

The amine hydrochloride, 6 to 12 mg, was dissolved in 5 ml of water plus 2 ml of ethanol. This solution was titrated with 0.109 N aqueous sodium hydroxide solution contained in a 1 ml microburette graduated in  $\text{ml} \times 10^{-3}$ . The solutions were stirred and protected from carbon dioxide by purging them with nitrogen throughout the titration. The same technique was employed for the two carboxylic acids. The  $\text{pK}_a$ s were determined from the pH at the half neutralization point. The results are tabulated below.

| <u>Compound</u>                                                 | <u>pK<sub>a</sub></u> |
|-----------------------------------------------------------------|-----------------------|
| <u>cis</u> -2-Phenoxycyclopropylamine (XXCVIIa) Hydrochloride   | 7.22                  |
| <u>trans</u> -2-Phenoxycyclopropylamine (XXCVIIb) Hydrochloride | 6.56                  |
| <u>cis</u> -2-Phenoxycyclobutylamine (XXC) Hydrochloride        | 7.91                  |
| <u>cis</u> -2-Phenoxycyclopentylamine (XXXVI) Hydrochloride     | 8.88                  |
| <u>trans</u> -2-Phenoxycyclopentylamine (L) Hydrochloride       | 8.53                  |
| * <u>trans</u> -2-Phenylcyclopropylamine (XXVb) Hydrochloride   | 7.85                  |
| * <u>cis</u> -2-Phenylcyclobutylamine Hydrochloride             | 8.97                  |
| * <u>trans</u> -2-Phenylcyclobutylamine Hydrochloride           | 8.60                  |
| 2-Phenylisopropylamine (XXVI) Sulphate                          | 9.16                  |
| 2-Phenoxyisopropylamine Hydrochloride                           | 8.78                  |
| <u>cis</u> -2-Phenoxycyclopropane Carboxylic Acid (XXCIIIa)     | 4.68                  |
| <u>trans</u> -2-Phenoxycyclopropane Carboxylic Acid (XXCIIIb)   | 4.14                  |

\*These compounds were kindly supplied by Dr. A. Burger.

#### IV. CLAIMS TO ORIGINAL RESEARCH

1. Twenty-five new small-ring alicyclic compounds, including eight pairs of cis-trans isomers, have been synthesized and characterized.
2. Several new synthetic approaches of wide applicability have been developed for the production of 2-phenoxyalkylamines.
3. The propensity of a 2-phenoxy group for promoting a cis orientation of certain functional groups during the trigonal-to-tetrahedral transition of the neighbouring carbon atom has been disclosed.
4. Variations in the size of the alicyclic rings in phenoxyalkylamines have been correlated with the relative ability of the phenoxy group to exert its electrostatic influence on the course of reactions and on the properties of the products.
5. An unusual rearrangement reaction of the cyclopropane ring has been demonstrated.
6. The pKa values of ten 2-substituted cycloalkylamine salts have been measured and correlated with the type and orientation of the 2-substituent and with the ring size.
7. Several biochemical assays are reported. A rationale for the biological results is presented in the light of physico-chemical evidence. The structure-activity relationship between the phenoxyalkylamines and their open-chain analogs has been developed.

8. N-methyl-N- $\beta$ -chloroethyl-cis- and trans- 2-phenoxy cyclopentyl- amines are exceedingly potent adrenergic blocking agents. This disclosure lends considerable support to our interpretation of the function of the aryloxy group in this class of biochemical alkylating agents.
9. It is shown that the stereochemical demands of the receptors which are blocked by both the competitive and the non-competitive adrenergic blocking agents are insufficient to differentiate between cis-trans analogs in the cyclopentane series. The same lack of specificity is observed with MAO toward cis- and trans-2-phenoxy cyclopropylamines. The latter two compounds, however, have in vitro MAO inhibitory activity approaching that of the clinically important trans-2-phenyl cyclopropylamine.

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**PART B**

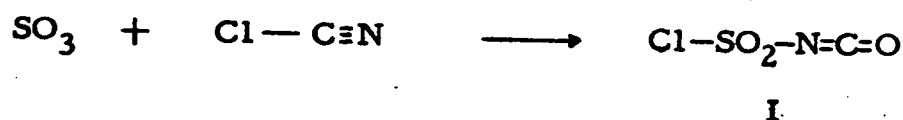
**THE APPLICATION OF CHLOROSULPHONYL  
ISOCYANATE IN THE SYNTHESIS OF  
CYCLIC SULPHAMYL UREAS**

## I. INTRODUCTION

### 1. The Chemistry of Sulphonyl Isocyanates

#### a) Chlorosulphonyl Isocyanate (I)

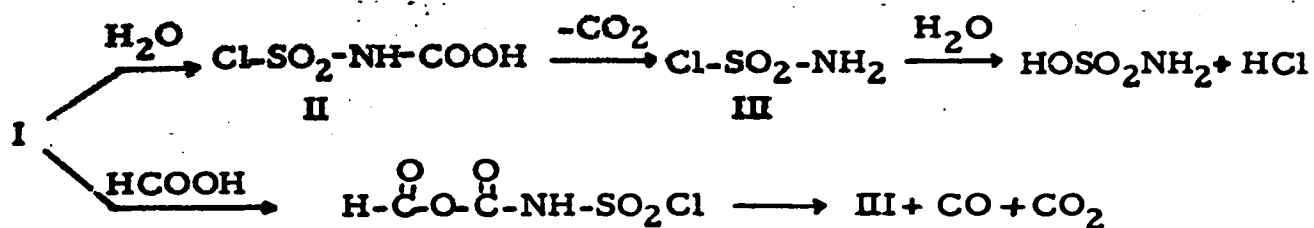
In 1956, Graf (1) reported the synthesis of an unusual isocyanate which was formed incidental to a project with another objective: the reaction of sulphur trioxide with cyanogen chloride gave high yields of a very reactive compound which was characterized as chlorosulphonyl isocyanate (I).



The reactivity of the isocyanate group in I is greatly enhanced over that of simple aliphatic and aromatic isocyanates due to the powerful electron-withdrawing character of the chlorosulphonyl group. This fact prompted several investigators (1-6) to examine the synthetic applications of chlorosulphonyl isocyanate.

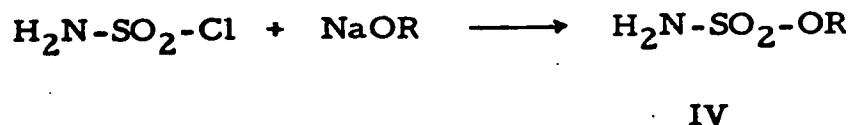
Aqueous hydrolysis of I gives first the unstable carbamic acid, II, which quickly decomposes to carbon dioxide and sulphamyl chloride (III). The latter intermediate is further hydrolysed to sulphamic acid (1).

Subsequently, it was found (4) that sulphamyl chloride (III) can be isolated if anhydrous formic acid is allowed to react with chlorosulphonyl isocyanate.



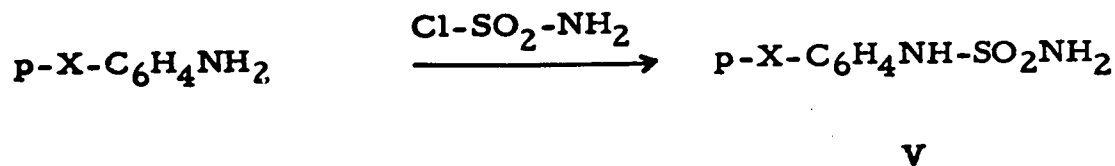
Numerous reactions of compound I with amines and with hydrazines have also been reported (2, 4).

The availability of sulphamyl chloride (III) for the first time as a result of the reaction just described, enabled Appel and Senkpiel (7) to prepare the hitherto unknown sulphamic esters, IV.

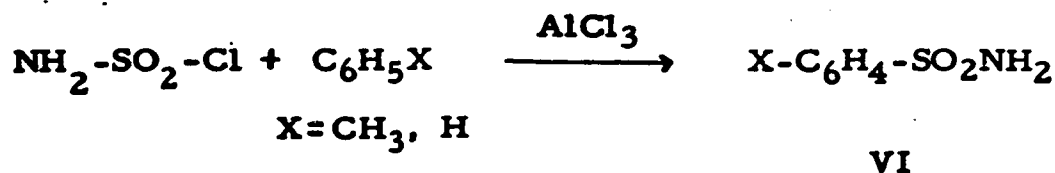


These esters are exceedingly labile; they readily undergo hydrolysis and ester interchange reactions.

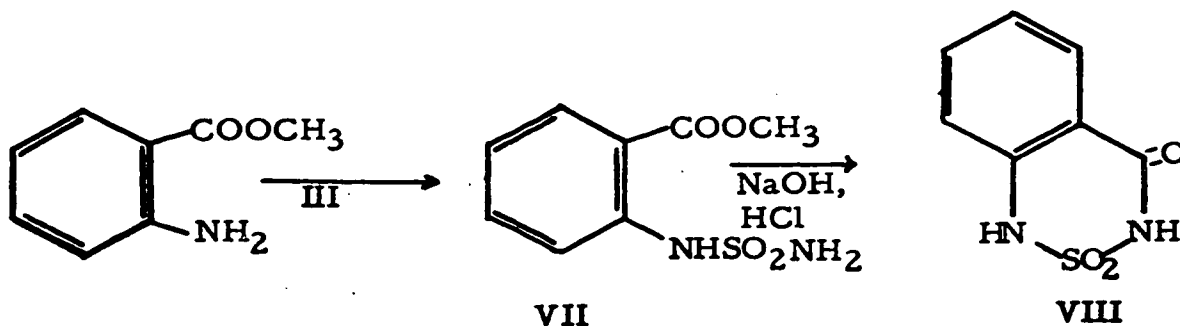
The reaction of sulphamyl chloride with para-substituted anilines gives the corresponding disulphonamides, V (8).



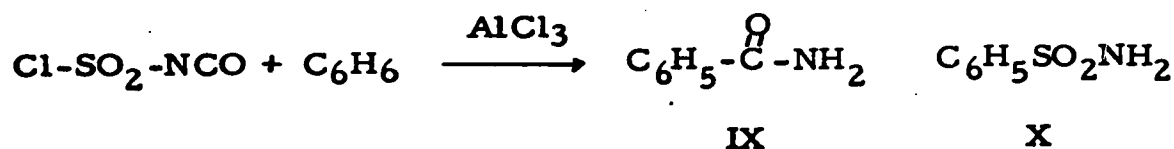
With benzene or toluene, sulphamyl chloride reacts under Friedel-Crafts conditions to give the sulphonamides, VI (8).



Methyl anthranilate and sulphamyl chloride gives the intermediate, VII, which is cyclized by alkali to the novel heterocycle, 1 H-2, 1, 3-benzothiadiazin-4(3H)-one 2, 2-dioxide (VIII) (9).

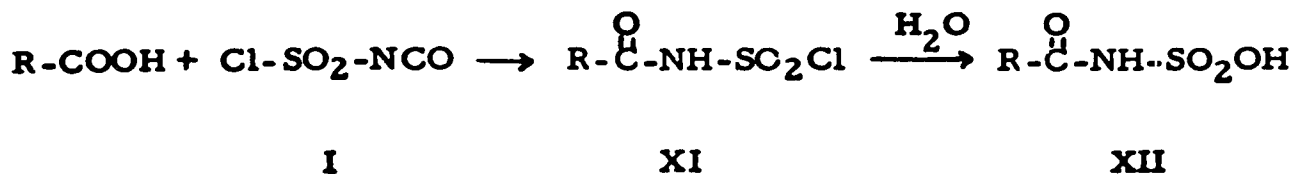


Chlorosulphonyl isocyanate reacts with benzene in the presence of aluminium chloride to give benzamide (IX) rather than the expected benzenesulphonamide (X) (8).

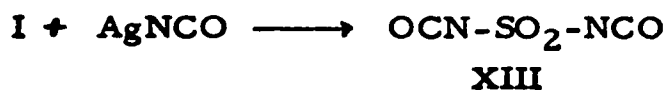


Although the Friedel-Crafts addition of benzene to isocyanates is not unprecedented (10), it is noteworthy that the chlorosulphonyl group in the novel isocyanate, I, does not react with the benzene ring, as in the case of sulphamyl chloride.

Chlorosulphonyl isocyanate also reacts with carboxylic acids other than formic acid to give the N-acyl chlorosulphonamides (XI) which are readily hydrolysed to N-acyl sulphamic acids (XII) (6).

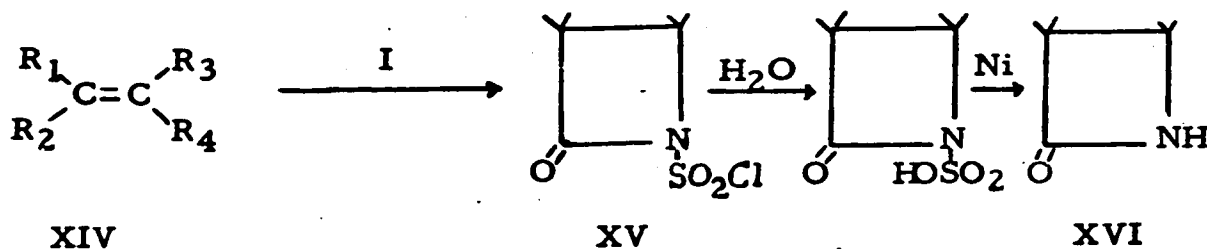


The preparation of sulphonyl diisocyanate (XIII) from chlorosulphonyl isocyanate has been reported (3).



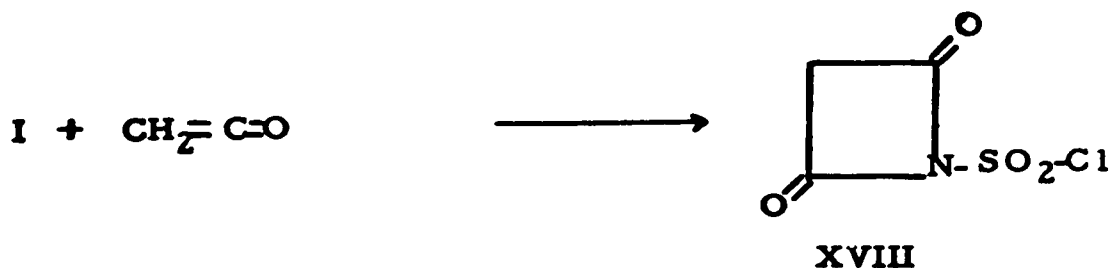
The reagent, XIII, should also be useful as a starting material in novel organic syntheses.

Olefins (XIV) react with chlorosulphonyl isocyanate to give  $\beta$ -lactams (XV) in high yields (11).

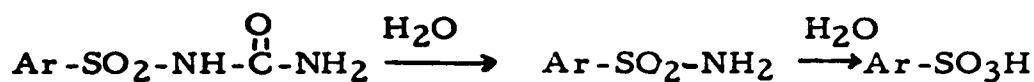
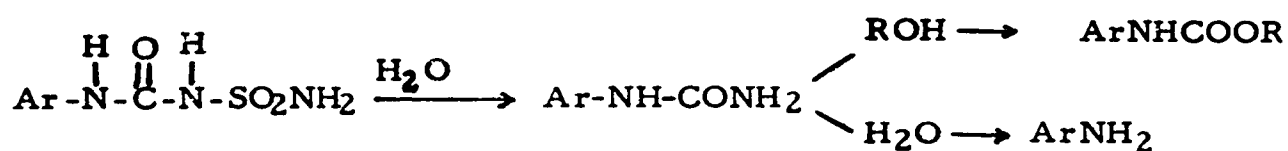


Subsequently (12), it was found that XV can be hydrolysed and then desulphurized by Raney nickel to give the  $\beta$ -lactams, XVI, so that a new synthesis of  $\beta$ -lactams and of  $\beta$ -amino acids and novel nylons derivable therefrom has been provided through the use of chlorosulphonyl isocyanate.

A ready synthesis of N-chlorosulphonyl azetidinediones (XVIII) has recently been reported (13), using chlorosulphonyl isocyanate and ketene.



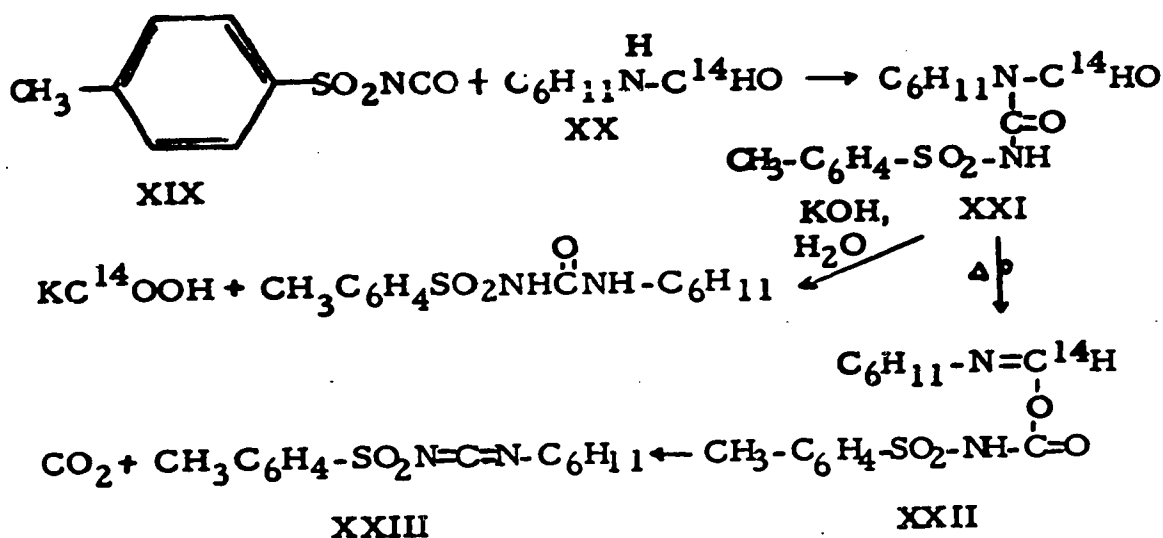
Finally, to illustrate the versatility of sulphonamide derivatives in syntheses, several degradative reactions involving sulphonamido-ureas obtained from chlorosulphonyl isocyanate are outlined below.



b) p-Toluenesulphonyl Isocyanate (XIX)

The reagent, p-toluenesulphonyl isocyanate (XIX) is another reactive isocyanate closely resembling chlorosulphonyl isocyanate. Several unusual reactions of XIX with a variety of compounds have recently been described.

Logemann and co-workers (14) observed that N-cyclohexylformamide (XX) reacts with XIX to give N-formyl-N-cyclohexyl-N'-p-toluenesulphonyl urea (XXI) which rearranges at 120-140° to an unstable intermediate which they postulate is the urethane, XXII.

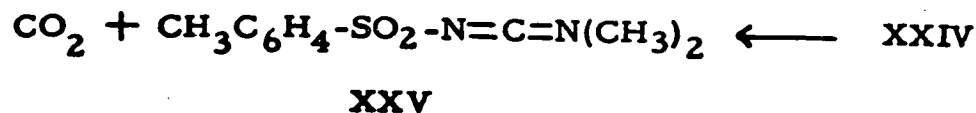
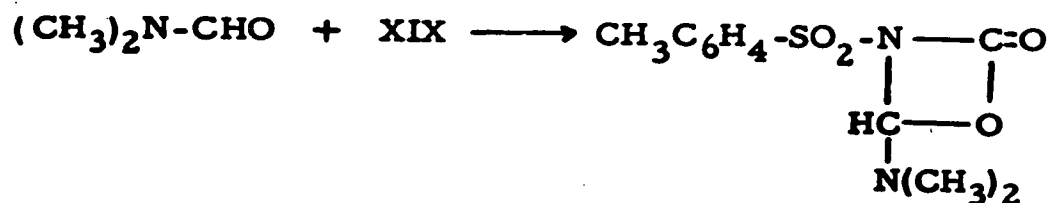


Compound XXII, in turn, undergoes decomposition and rearrangement to yield N-p-toluenesulphonyl-N'-cyclohexyl formamidine (XXIII) and carbon dioxide. The mechanism of this reaction was substantiated by carbon 14 tracer studies as indicated in the formulation.

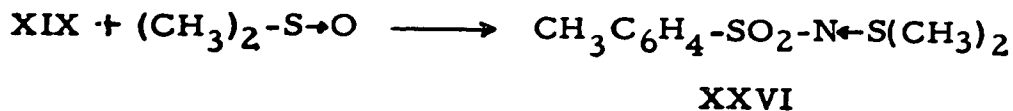
Similar results were obtained starting with N-phenylformamide, but N-butylformamide yields an analogue of XXI which does not rearrange to the corresponding formamidine on thermal decomposition. Logemann postulated on this basis, that the acyl migration in XXI is favourable only when both substituents are aromatic. This interpretation is questionable in view of the fact that a cyclohexyl moiety has no aromatic properties.

Furthermore, King (15) has shown that p-toluenesulphonyl isocyanate reacts with N,N-dimethyl formamide at room temperature to give N,N-dimethyl-N'-p-toluenesulphonyl formamidine (XXV) directly; the absence, therefore, of a second aryl group does not hinder the rearrangement. King postulated that the rearrangement proceeds via an unstable intermediate, XXIV, which was not isolated.





King also described several other reactions of XIX with secondary amides, with aldehydes, and with ketones. Dimethyl sulphoxide yields, with XIX, the sulphilimine, XXVI.



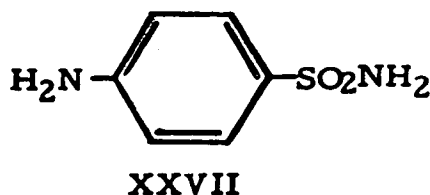
It is expected that the reactions of p-toluenesulphonyl isocyanate will have their counterparts in the reactions of chlorosulphonyl isocyanate.

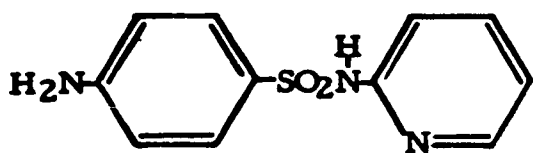
## 2. The Chemotherapeutic Significance of Some Sulphonamides

### a) Antibacterials

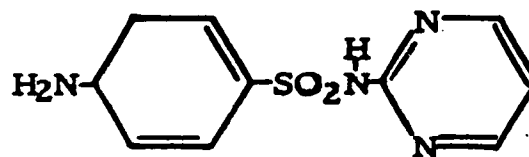
The antibacterial sulphonamides have contributed a voluminous literature to the chemistry and chemotherapy of sulphonamides in general.

Some of the best known representatives of this family of drugs, sulphanilamide (XXVII), sulphapyridine (XXVIII) and sulphadiazine (XXIX) are formulated below.





XXVIII

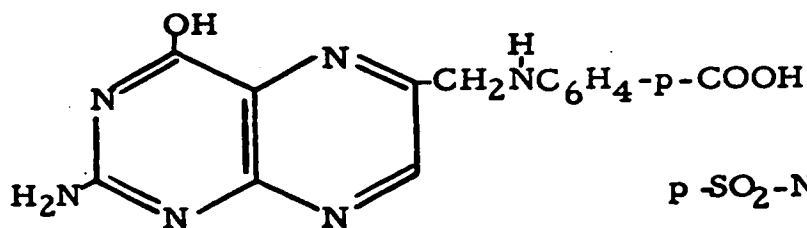


XXIX

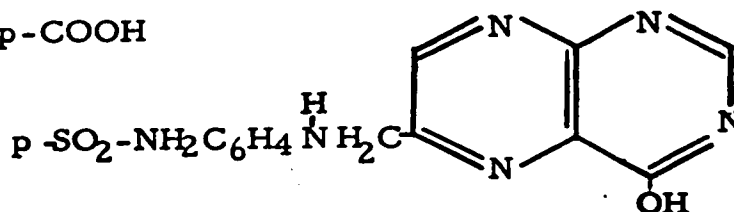
The antibacterial activity of such compounds rests with their ability to interfere with the reduction of folic acid by TPN.H (16).

#### b) Anticancer Agents

The sulphonamide analog, XXXI, of the growth-promoting and anti-anaemic factor, pterioic acid (XXX) also possesses antibacterial activity which is antagonized by folic acid.

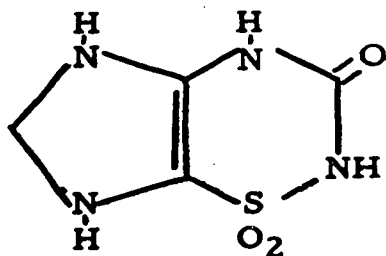


XXX

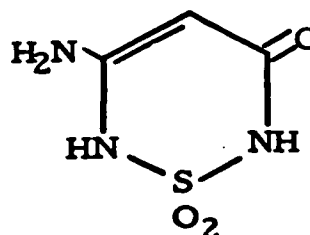


XXXI

Folic acid antagonists of all types have been receiving considerable attention because of their potential anticancer activity. Sulphonamide analogs of the purines (XXXII) and of the pyrimidines (XXXIII) should also be of interest in the study of cancer chemotherapy because of the possibility that they could interfere with the biogenesis of nucleic acids.



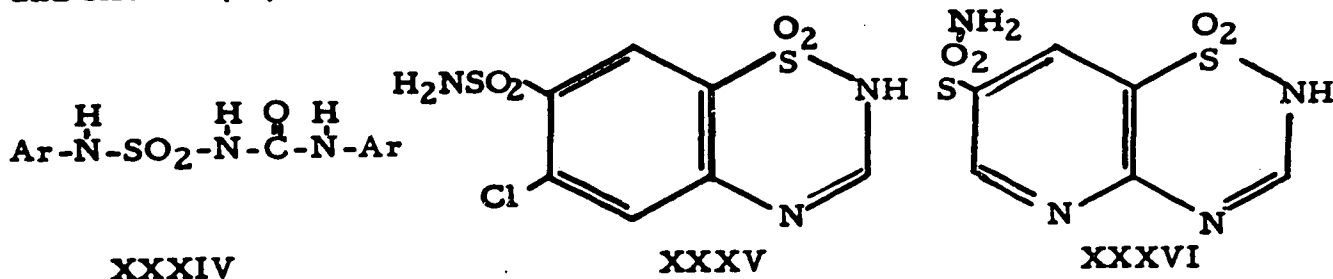
XXXII



XXXIII

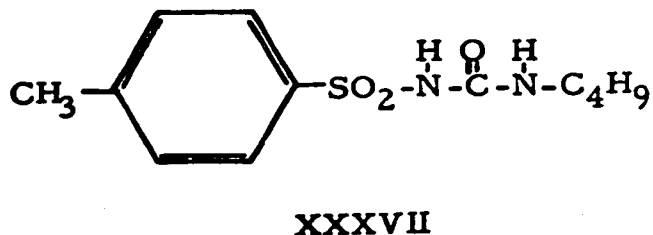
c) Diuretics

A host of diuretics have recently been developed along the structural lines of the sulphamyl urea, XXXIV, and the cyclic sulphonamides, XXXV and XXXVI (17).



d) Antidiabetic Drugs

"Tolbutamide", 1-n-butyl-3-p-toluenesulphonyl urea (XXXVII), is the prototype of a series of structurally related antidiabetic agents. The developments in the chemical and the clinical aspects of this new field have been extensively covered in reviews (18, 19). Wright and Willette (20) have recently presented their structure-activity findings with analogs of XXXVII.

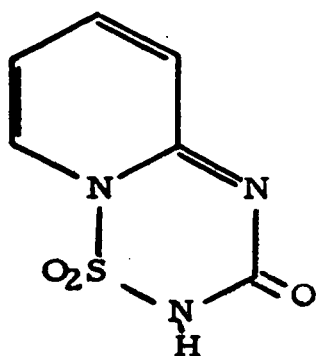


The few chemical and pharmaceutical examples cited here stress the merits of investigations into the synthetic routes to, and chemical and therapeutic properties of the sulphonamides and their derivatives. From both the chemical and the medicinal standpoints, sulphonamide chemistry is far from being exhausted.

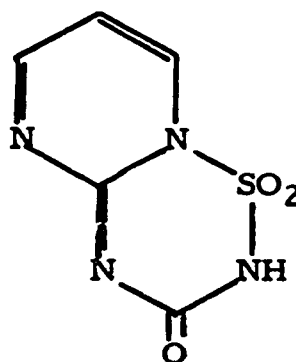
## II. RESULTS AND DISCUSSION

### Introduction

The dual functionality of chlorosulphonyl isocyanate prompted an investigation into its application for the synthesis of novel heterocycles such as XXXVIII and XXXIX. These structures, being improvisations around the pyrimidine nucleus, should be of interest in the chemotherapy of cancer.



XXXVIII



XXXIX

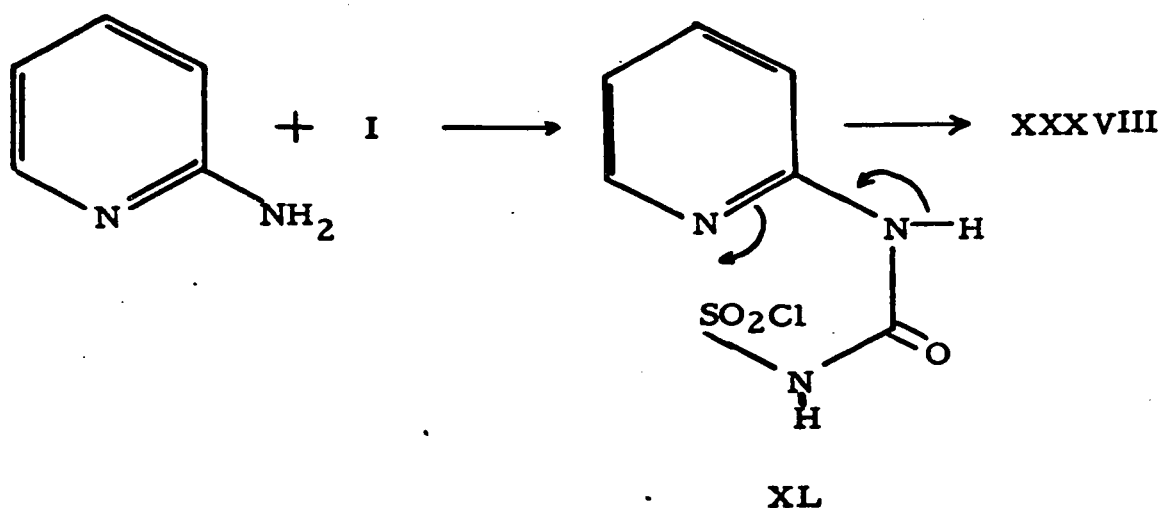
#### 1. The Reaction of Chlorosulphonyl Isocyanate with 2-Aminopyridine

##### a) N-Chlorosulphonyl-N'-2-Pyridylurea (XL)

The main investigation of the synthetic potentialities of chlorosulphonyl isocyanate centered around its reaction with 2-aminopyridine. It was anticipated that the product of this reaction would be the cyclic

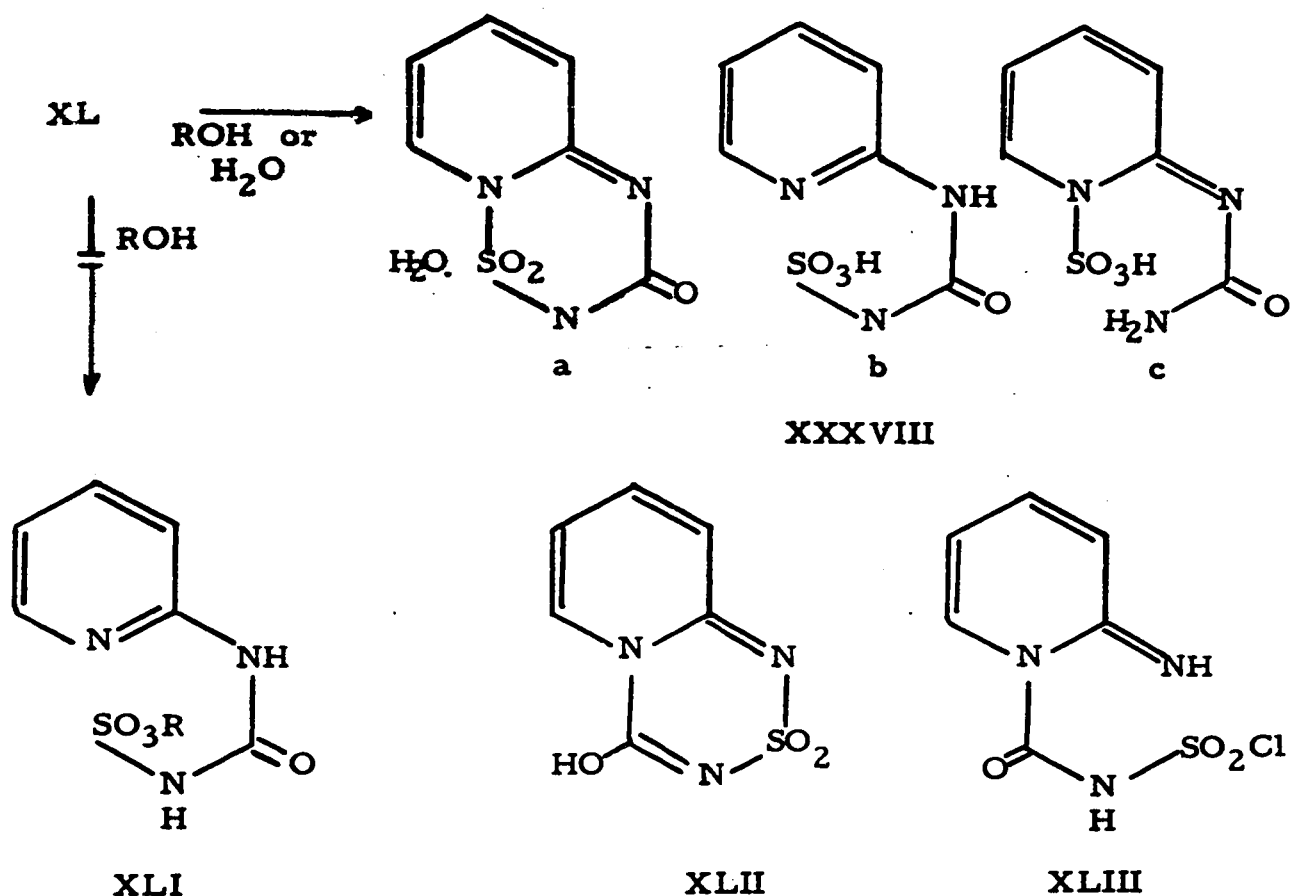
sulphamyl urea, 2,4,6-pyrido-thiatriazine-3(2H)-one-1,1-dioxide (XXXVIII).

When the reaction was carried out, the intermediate N-chloro-sulphonyl-N'-2-pyridylurea (XL) could be isolated.



b) 2,4,6-Pyridothiatriazine-3(2H)-one-1,1-Dioxide (XXXVIII)

The reaction of XL with a variety of hydroxylic solvents gave in every case the same halogen-free product. This at once suggests that the product is not a sulphonic ester such as XLI, in which case the products would differ since different alcohols were employed. The elemental analysis of this solvolysis product of XL corresponds to that of structure XXXVIII plus one molecule of water. We do not, however, imply that this is necessarily water of hydration. It is not known with any degree of certainty as yet, exactly what the mode of bonding is of this water molecule.

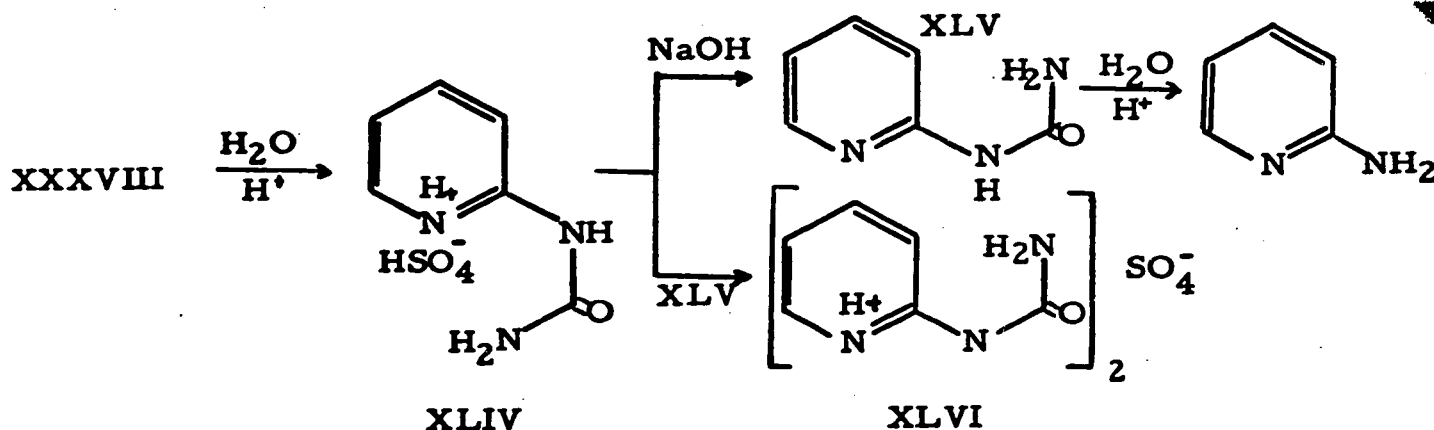


The alternative formulation, XLII, can safely be discarded in view of the fact that the isocyanate group in chlorosulphonyl isocyanate is more reactive towards amines than is the chlorosulphonyl group (1). Furthermore degradative studies which are described in this thesis, substantiate the rejection of XLII as an alternative formulation. The solvolysis product of an intermediate acid chloride would have to be XLIII rather than XL.

The treatment of XXXVIII with thionyl chloride resulted in the recovery of unchanged XXXVIII, a finding which is difficult to conciliate with any of the proposed formulations since XXXVIIIa should dehydrate under these conditions while the "b" and "c" structures should yield their corresponding sulphonyl chlorides.

### c) The Solvolysis of XXXVIII

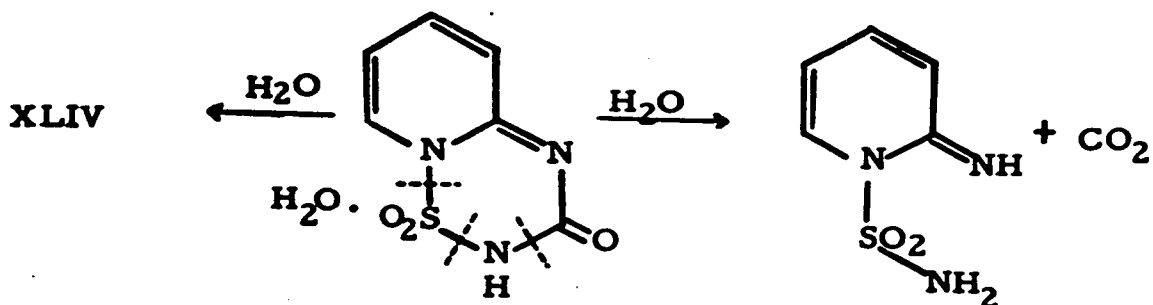
The acid-catalysed aqueous hydrolysis of XXXVIII was rapid and resulted in almost quantitative formation of 2-pyridylurea acid sulphate salt (XLIV), identified as the free base, XLV. The neutral sulphate, XLVI, can be prepared, and although it does not depress the melting point of XLIV, it has a different infra-red spectrum from that of XLIV.



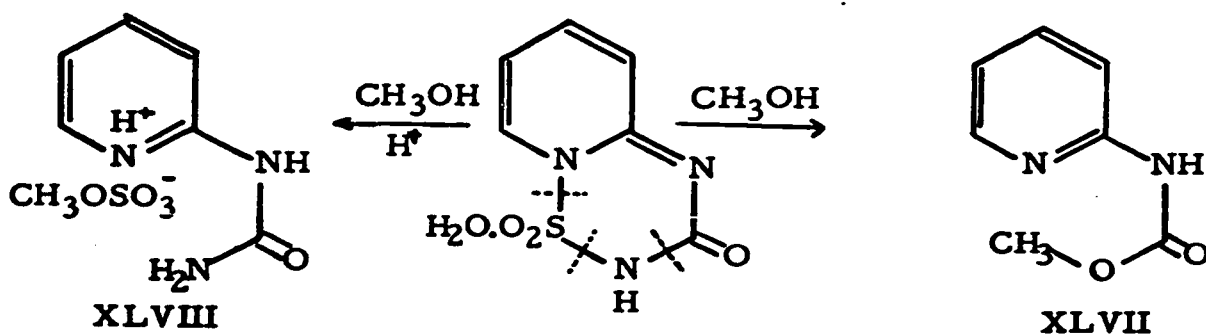
The formation of 2-pyridylurea in the solvolysis of XXXVIII confirms the formulation of the latter compound, since compound XLII could not give rise to XLV. Prolonged refluxing of 2-pyridylurea in aqueous acid medium gave 2-aminopyridine.

Compound XXXVIII, although soluble in aqueous alkaline medium by contrast with neutral or acidic media, is comparatively stable to hydrolysis under alkaline conditions. This is perhaps understandable since sulphonamides are known to be resistant to alkali and labile towards acid.

The neutral aqueous hydrolysis of XXXVIII is intermediate in efficiency, but other products besides XLIV appear to be formed. This would suggest that, in the absence of acid catalysis, an alternative mode of cleavage is possible, whereby an amide bond suffers rupture.



The methanolysis of XXXVIII gave evidence in support of this hypothesis. In the presence of traces of hydrogen chloride, refluxing methanol converted XXXVIII entirely to 2-pyridylurea methosulphate salt (XLVIII). This, on prolonged heating with methanol, yielded pyridyl methyl urethane (XLVII).



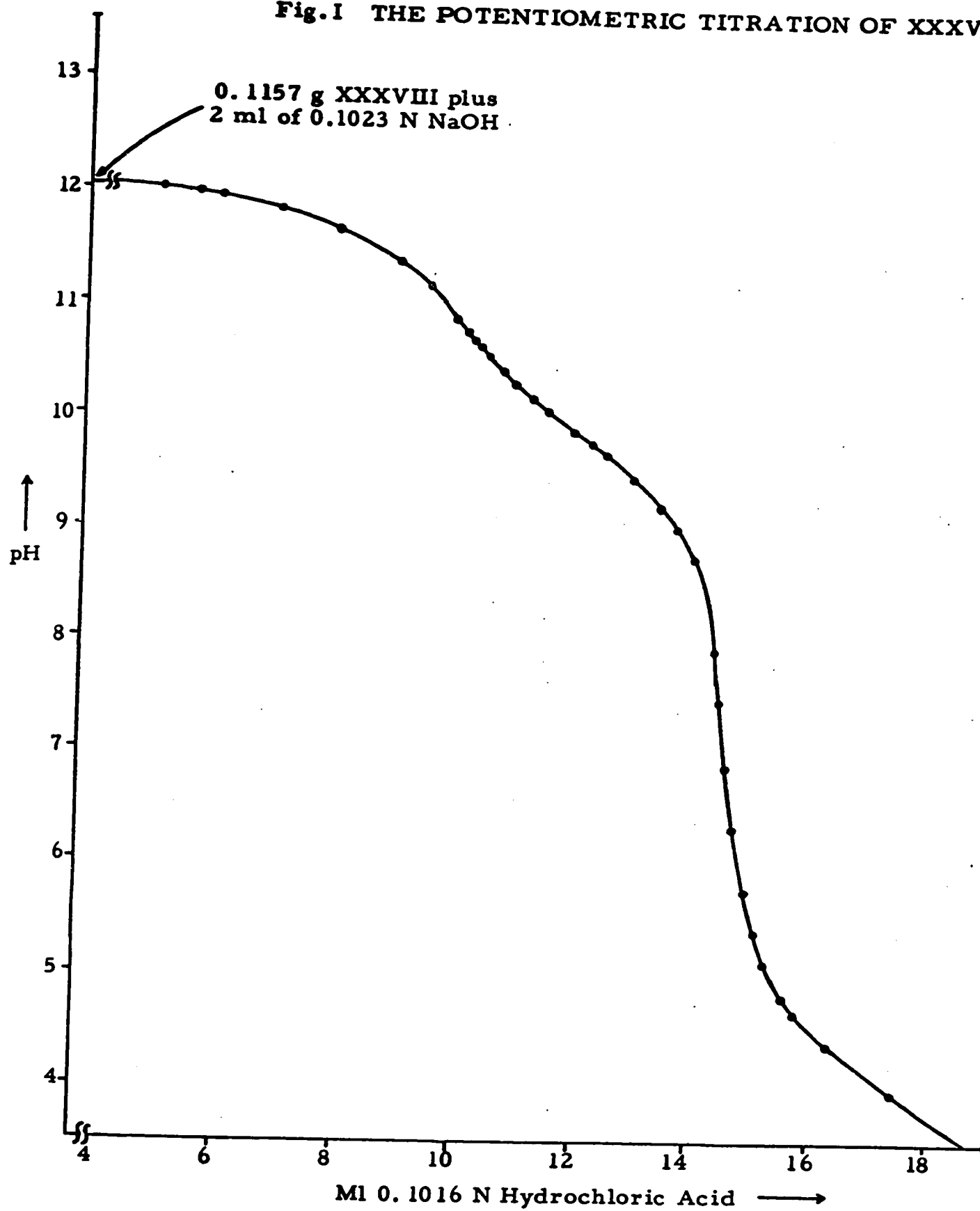
However, under neutral conditions, XXXVIII, upon treatment with hot methanol, yielded a considerable amount of pyridyl methyl urethane (XLVII) directly, as well as XLVIII and ammonium salts. Apparently the amide bond cleavage reaction can compete favourably with the sulphonamide bond cleavage reaction only in the absence of acid catalysis, which is more favourable to the latter reaction than to the former.

#### d) Potentiometric Titration of XXXVIII

The potentiometric titration (fig. 1) of compound XXXVIII indicated that the substance behaves like a dibasic acid with an estimated



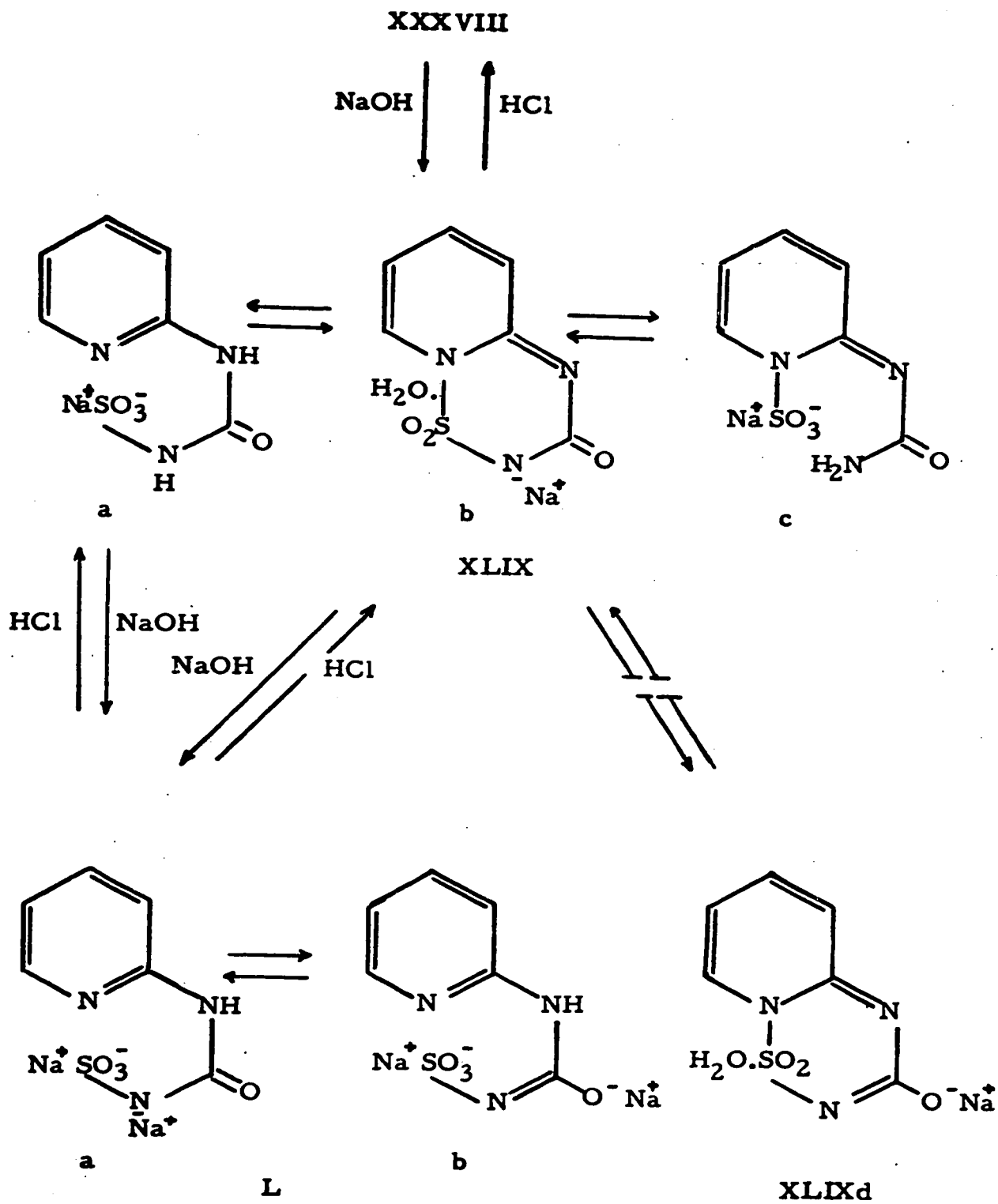
Fig. I THE POTENTIOMETRIC TITRATION OF XXXVIII



$pK_{a1}$  of 4.1 and a  $pK_{a2}$  of 6.4. Again, any one of the three formulations for XXXVIII, a, b, or c, could exhibit such behavior provided first that XXXVIIIa can undergo reversible ring opening in the presence of excess base, and second, that structures XLIXb and c are relatively stable towards aqueous hydrolysis. Formulation XLIXd is excluded as a possibility since the infra-red spectrum of the isolated monosodium salt of XXXVIII shows carbonyl absorption. Also, formulation La is excluded as the structure for the disodium salt because the isolated compound does not exhibit a carbonyl band in the infra-red. Furthermore, the electrostatic repulsion between vicinal like charges in structure La would favour its reversion to Lb..

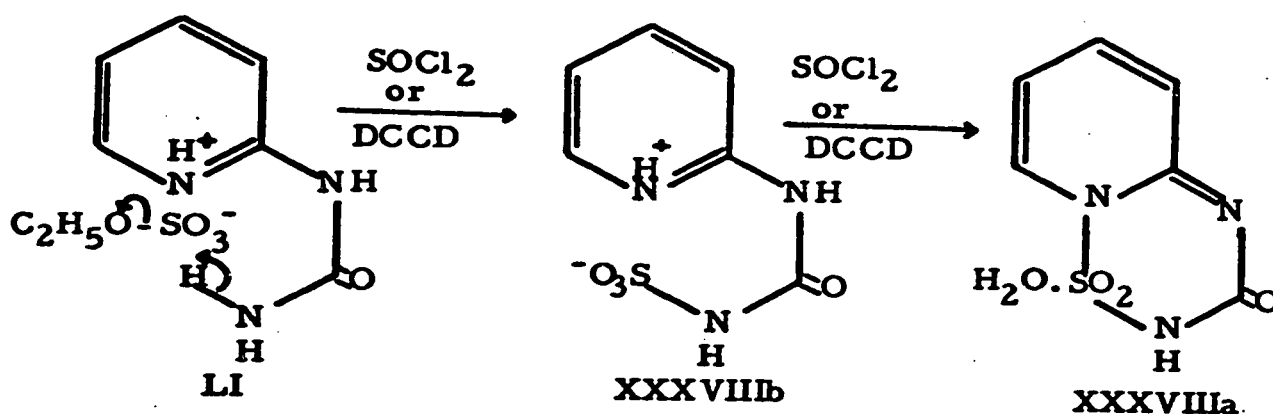
It is not possible at this time to select unambiguously any one of the formulations XLIXa, b, or c as representing the correct structure for the monosodium salt of XXXVIII. Although the alternatives, b and c would be expected to have a much lower  $pK$  than 4, mechanical difficulties (insolubility) in titrating below pH 6 renders the observed  $pK$  unreliable.

We also observed that there was a lack of reproducibility in the equivalent weight values obtained by titration. Since varying degrees of degradation can take place during the titration to yield sulphate ion, such difficulties were not unexpected. Furthermore, a hysteresis phenomenon made itself evident when the pH dropped below 6: a non-reproducible supersaturation phenomenon occurred. This would undoubtedly affect the pH curve seriously in that region of interest.

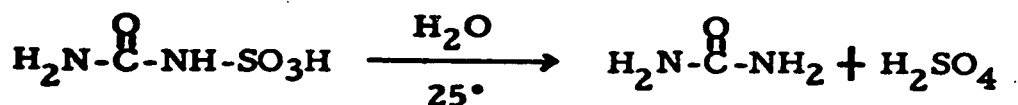


e) The Reaction of 2-Pyridylurea Ethosulphate (LI) With Dehydrating Agents

When 2-pyridylurea ethosulphate salt was treated with either thionyl chloride or dicyclohexylcarbodiimide (DCCD), the reaction product was XXXVIII. The application of heat alone did not result in the formation of XXXVIII. Therefore, the dehydration agents assist in the intramolecular amidolysis of LI.

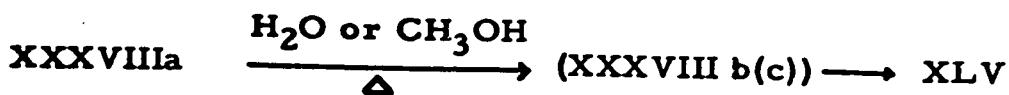


This finding would tend to favour the formulation of XXXVIII as XXXVIIIb. However, analogous compounds, such as LII, are known to be water-soluble and extremely labile towards hydroxylic solvents (21).



LII

Structure XXXVIIIc, being the imino analog of XXXVIIIb, would also be expected to have similar solubility properties and an equal reactivity toward hydroxylic solvents. Compound XXXVIIIa is labilized only under conditions in which one or both of structures XXXVIIIb and c are first produced (hot solvolytic media, for example).



f) Physiological Data

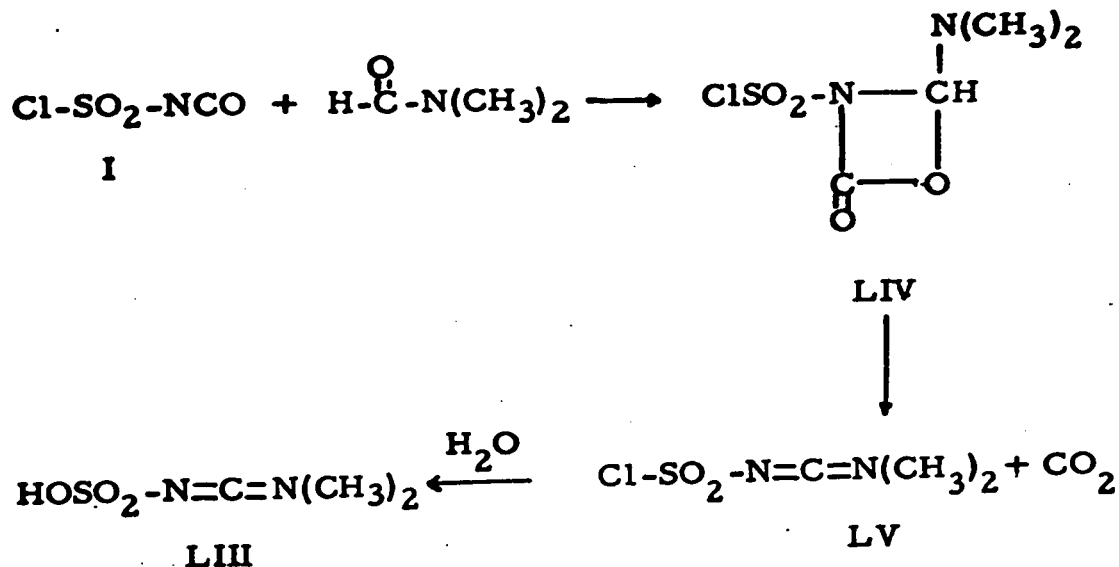
The cyclic sulphamyl urea, XXXVIII, was inactive in the following tests: diuretic, hypoglycemic, antibacterial, antispasmodic, anti-hypertensive, analgesic, psychosomimetic (CNS activity), cardiovascular.

However, the compound per se, was not necessarily prepared for chemotherapeutic purposes, but for use as a model for future synthetic work directed more precisely at a therapeutic target.

The unusual chemical properties of XXXVIII may open up new approaches to useful medicinal agents.

2. N, N-Dimethylformamidine-N'-Sulphonic Acid (LIII)

During the course of the investigation of the synthesis of XXXVIII we observed that when dimethylformamide was used as a solvent for the reaction of 2-aminopyridine with chlorosulphonyl isocyanate, another compound was isolated, which was formed in a side reaction of the isocyanate, I, with dimethylformamide. This by-product, which was subsequently prepared directly from I and dimethylformamide, corresponds in empirical composition and in chemical and spectroscopic properties to N, N-dimethylformamidine-N'-sulphonic acid (LIII).



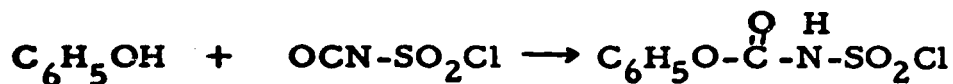
An analog of the cyclic urethane intermediate, LIV, has been postulated before (13) for the reaction of dimethyl formamide with p-toluenesulphonyl isocyanate.

The hydrolysis of the acid chloride, LV, must have occurred during isolation.

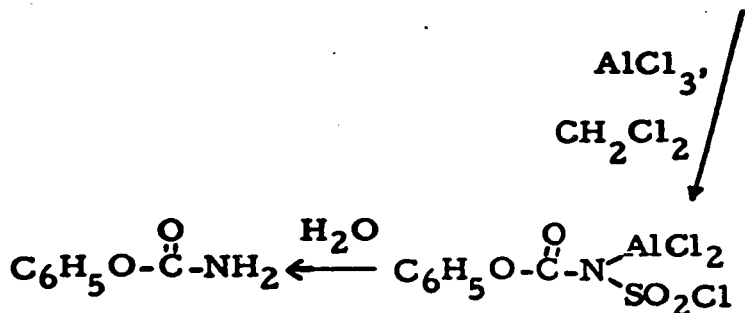
### 3. The Attempted Synthesis of a Cyclic Sulphonyl Urethane

In order to further demonstrate the versatility of chlorosulphonyl isocyanate, the synthesis of the sulphonyl urethane, LVI, was attempted

The reaction of phenol with chlorosulphonyl isocyanate gave the intermediate sulphamyl chloride, LVII, which, however, was not characterized.

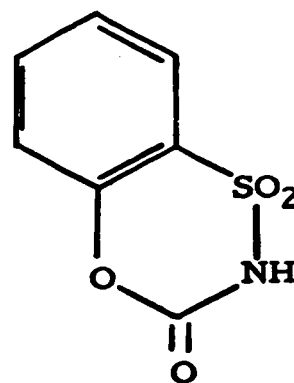


LVII



LVIII

LIX



LVI

When LVII was treated with aluminium chloride and methylene dichloride, hydrogen chloride was evolved during the course of the exothermic reaction. Decomposition of the reaction mixture with water gave only phenyl urethane ( LVIII ).

Since hydrogen chloride was evolved without ring closure having concomitantly taken place, the reaction of LVII with aluminium chloride may be pictured as a neutralization reaction rather than a typical Friedel-Crafts reaction. The salt, LIX, may be postulated as the intermediate which suffers hydrolysis to give the urethane, LVIII.

### III. EXPERIMENTAL

Chlorosulphonyl isocyanate was prepared from cyanogen chloride and sulphur trioxide by the method of Graf (1). It was stored in 5 g. ampules, so that the bulk of the reagent was never exposed to air, water vapour, or temperatures in excess of 5°.

All melting points were taken by the capillary technique, and were corrected against reliable standards.

Infra-red (IR) spectra were taken on a Perkin-Elmer Infracord machine employing liquid films (F), solutions (S, solvent), or Nujol mulls (NM). Intensities are indicated as strong (s), medium (m), or weak (w), and band positions are in  $\text{cm}^{-1}$ .

Nuclear magnetic resonance (NMR) spectra were taken on a Varian Model V-4302 Spectrometer at 60 Mc/sec.

#### 1. The Reaction of Chlorosulphonyl Isocyanate With 2-Aminopyridine

##### a) N-Chlorosulphonyl-N'-2-Pyridylurea (XL)

To a stirred solution of 4.28 g.(0.030 mole) of chlorosulphonyl isocyanate in 20 ml. of dry methylene dichloride at -50° was added over a period of one minute, 2.76 g.(0.029 mole) of freshly distilled 2-aminopyridine dissolved in 20 ml. of dry methylene dichloride. The mixture was stirred vigorously while it was allowed to reach room temperature. The yellow oil which separated soon solidified. The material was broken up and transferred rapidly to a Buchner funnel where it was washed thoroughly with dry methylene dichloride. After the solid was dried briefly



at 25°/10 mm, there remained 6.35 g.(92%) of pale yellow solid, mp 170-190° with gaseous decomposition (sl40°). The compound was insoluble in all organic solvents and slowly underwent decomposition with evolution of hydrogen chloride.

Anal. Calc'd. for  $C_6H_6N_2O_3SCl$ : C, 30.6; H, 2.57; Cl, 15.

Found: C, 30.3; H, 3.32; Cl, 11.

IR (NM): 3350(m), 3150(m), N-H str.; 1700(m), C = O str.;

1650(m), 1620 (m), amide I, II; 1340(s), asym. SO<sub>2</sub> str.;

1290(m), sym. SO<sub>2</sub> str.

b) 2, 4, 6-Pyridothiatriazine-3(2H)-one-1,1-dioxide (XXXVIII)

i) To 7.4 g.(0.031 mole) of XL was added 20 ml.of cold, absolute methanol. The mixture was shaken for ten minutes during which time heat and hydrogen chloride were evolved.

The resultant solid was filtered off and washed with methanol. The dry solid weighed 5.9 g.(87%), mp 238° with gaseous decomp. (s235). It was soluble only in alkaline solutions.

A solution of 1.5 g. of XXXVIII in 0.6 ml. of 30% aqueous ammonium hydroxide was filtered and cooled to 0°. The solid was filtered off to yield 0.8 g.(50%) of the ammonium salt. This, after two recrystallizations from warm water, melted at 115.5-118° with decomp. at 120° (sl12°). An aqueous solution of this salt was acidified with acetic acid. The precipitated solid was filtered off and washed with water. After it was dried at 45°/0.05 mm, it melted at 233-235° with decomp. (s228°). Admixture with XXXVIII gave no melting point depression.

Anal. Calc'd. for  $C_6H_7N_3O_4S$ : C, 33.2; H, 3.26; N, 19.4;  
O, 29.3; S, 14.8.

Found: C, 33.5; H, 3.39; N, 19.1;  
O, 29.4; S, 14.7.

IR (NM): 3300(m), 3180(m), N-H str.; 1700(m), C = O str.;  
1655(m), 1630(m), amide I, II; 1350(w), asym.  $SO_2$  str.;  
1290(m), sym.  $SO_2$  str.

The combined filtrates from the ammonium salt were evaporated to dryness, the residue was dissolved in water, and the solution was acidified with acetic acid. The precipitated solid was filtered off and washed with water to yield 0.55 g. of recovered XXXVIII (36.6%).

ii) A small amount of XL was treated in the cold with excess absolute ethanol until no further heat was evolved. The resultant solid was filtered off and washed with ethanol. The dry material had mp 223-225° (dec.) (s205°). An admixture with XXXVIII had mp 223-225°.

The identical compound was obtained using water in place of the ethanol.

iii) A suspension of 0.200 g. of XXXVIII was refluxed with 2 ml. of thionyl chloride in a dry atmosphere for twenty-four hours. The mixture was then evaporated and the residue stirred with dry chloroform, filtered, and the solid washed with chloroform. The dry material had mp 226-228° (dec.), undepressed by admixture with starting XXXVIII.

c) The Acid-Catalysed Hydrolysis of XXXVIII

i) To 0.59 g. (0.0027 mole) of XXXVIII suspended in 25 ml. of water

was added 0.5 ml. of concentrated hydrochloric acid. The mixture was heated to 90° for ten minutes and was then cooled and filtered. The filtrate was evaporated to dryness and the residual solid was crystallized from ethanol. There was obtained 0.40 g. (62.6%) of 2-pyridyl urea acid sulphate (XLIV), mp 180-181.5° with decomp. (sl 178°). An authentic sample of this salt (from 2-pyridyl urea prepared according to Gerchuk and Tafts (22)) had mp 173-175° (sl 170°) with decomp. An admixture of the two samples gave mp 176-177° with decomp. (sl 175°).

To a small amount of the acid sulphate dissolved in water was added excess 2-pyridyl urea. After a brief stirring, the mixture was filtered free of solid and the filtrate was poured into excess acetone. The precipitated neutral sulphate, XLVI was filtered off and dried, mp 178-180° (sl 140°) with decomp. An admixture with the acid sulphate salt gave no melting point depression; however the infra-red spectra of the two salts were entirely different in the region 800 to 1300  $\text{cm}^{-1}$ .

ii) To a solution of 27 mg. of the acid sulphate in 0.5 ml. of water was added excess 10% aqueous sodium hydroxide. The precipitate was filtered off, washed with water and dried to yield 5 mg. of 2-pyridyl urea, mp 175-177°. Recrystallization from ethanol gave material mp 175-176° (sl 171°). Admixture with an authentic sample gave no depression.

iii) A solution of 0.096 g. (0.00077 mole) of 2-pyridyl urea in 5 ml of 2N aqueous hydrochloric acid was refluxed for twenty-two hours. The solution was then evaporated in vacuo until crystallization commenced. The residue was dissolved in 2 ml. of water and was then treated with

0.8 ml. of 20% aqueous sodium hydroxide solution. Ammonia was evolved. The solution was saturated with potassium carbonate and then extracted with benzene. The benzene extract was dried over potassium carbonate and then evaporated to leave 0.0652 g. (88%) of 2-aminopyridine, mp 57-62°.

d) The Hydrolysis of XXXVIII in Alkaline Medium

A solution of 0.32 g. of XXXVIII in 10 ml. of 2.6N sodium hydroxide solution was refluxed for ninety minutes and then evaporated in vacuo to half volume. To the residue was added 4.4 ml. of acetic acid and 5 ml. of water. The precipitate was filtered off and washed with water to yield 0.27 g. (84%) of starting material, mp 234°. No cleavage products could be isolated from the filtrates.

e) The Neutral Aqueous Hydrolysis of XXXVIII

Suspensions of pure XXXVIII in water were refluxed for various periods of time. The results are tabulated below:

| <u>Wt. of XXXVIII</u><br><u>(g)</u> | <u>Reflux Time</u><br><u>(hrs.)</u> | <u>Homogeneity Time</u><br><u>(hrs.)</u> |
|-------------------------------------|-------------------------------------|------------------------------------------|
| 0.025                               | 0.50                                | --                                       |
| 0.025                               | 0.66                                | 0.66                                     |
| 0.025                               | 1.00                                | 0.66                                     |
| 0.026                               | 1.00                                | 0.66                                     |

When 0.67 g. of XXXVIII was refluxed in 8 ml. of water for one hour followed by evaporation of the resultant solution to dryness in vacuo, there was obtained by treatment of the residual syrup with methanol,

380 mg.(52%) of 2-pyridyl urea acid sulphate, mp 160-170°. No crystalline products could be isolated from the methanolic mother liquors.

f) The Methanolysis of XXXVIII

i) A suspension of 2.54 g.(0.0117 mole) of XXXVIII containing traces of XL in 30 ml. of methanol was refluxed for sixteen hours. The solution was filtered and the filtrate was evaporated in vacuo until there remained a crystalline sludge. This was filtered off and rinsed with methanol to yield 1.85 g.(68%) of 2-pyridyl urea methosulphate (XLVIII). Recrystallization of this from methanol gave a pure sample, mp 178-180°.

Anal. Calc'd. for  $C_7H_{11}N_3O_5S$ : C, 33.7; H, 4.43.

Found: C, 33.6; H, 4.82.

An NMR spectrum of this salt taken in water showed a methyl peak at -4.4 ppm.(TMS as a reference).

The addition of 0.33 ml. of 29% aqueous ammonium hydroxide to a solution of 1 g. of this salt in a minimum of water gave an immediate precipitate of 0.54 g.(100%) of 2-pyridyl urea. Evaporation of the aqueous filtrate yielded ammonium methosulphate, mp 130°.

ii) A suspension of 2.1 g.(0.0097 mole) of pure, dry XXXVIII in 4 g. of absolute methanol was heated in a Parr bomb at 100° for forty-eight hours. The solution was cooled, filtered and evaporated to dryness in vacuo. The residue was extracted with acetone to leave 0.75 g.(47%) of water-soluble solid, which contained ammonium salts and 2-pyridyl urea methosulphate but which was free of sulphate and sulphamate ions.

The acetone extract yielded upon evaporation, 0.80 g.(50%) of 2-pyridyl methyl urethane (XLVII), mp.(from methanol) 126.5-128°.

Sublimation of this material at 45°/0.1 mm. gave long needles, mp. 128-129° (reported for 2-pyridyl methyl urethane 128-129° (23)).

Anal. Calc'd. for  $C_7H_8N_2O_2$ : C, 55.4; H, 5.23; N, 18.3.

Found: C, 55.8; H, 5.32; N, 18.5.

An NMR spectrum of the compound showed the methyl peak at -4.1 ppm. from TMS.

When 100 mg. of the urethane was refluxed with 5 ml. of 2N aqueous hydrochloric acid for twenty-two hours, there was obtained from the hydrolysate, 53 mg. (86%) of 2-aminopyridine and 14 mg. (14%) of recovered urethane.

g) The Methanolysis of 2-Pyridylurea Methosulphate (XLVIII)

A mixture of 0.33 g. (0.0013 mole) of XLVIII and 0.80 g. of absolute methanol was heated in a sealed tube at 100° for forty-eight hours. The residue obtained by evaporation of this solution in vacuo was extracted with acetone to leave 0.25 g. of solid consisting of unchanged starting material as well as other water soluble salts. The acetone extract gave upon evaporation, 0.07 g. (38%) of 2-pyridyl methyl urethane.

h) The Ethanolysis of XXXVIII

A small amount of XXXVIII was refluxed with ethanol for sixteen hours. The resultant solution was evaporated to dryness and the residual solid was rinsed with acetone. The solid that remained gave a negative sulphate test and had mp 122-130°. Several recrystallizations from ethanol gave pure 2-pyridylurea ethosulphate, (LI) m.p. 127-130°.

Anal. Calc'd. for  $C_8H_{12}N_3O_5S$ : C, 36.5; H, 4.97; S, 12.2.

Found: C, 36.6; H, 5.00; S, 12.1.

An NMR spectrum showed the methylene protons at -3.8 ppm., and the methyl protons at -1.7 ppm. (TMS as a reference).

i) Potentiometric Titration of XXXVIII

A Beckmann Model GS pH Meter was used for all titrations. The compound XXXVIII was dissolved in 0. 1N aqueous sodium hydroxide solution and the volume was brought to 15 ml. with water. This was titrated with 0. 1N aqueous hydrochloric acid employing a nitrogen bubbler for agitation and exclusion of carbon dioxide. The following is a tabulation of the results:

| Moles XXXVIII<br>( $\times 10^3$ ) | Moles Base<br>( $\times 10^3$ ) | Equivalence Points<br>(equiv. HCl) |        | Equivalent of (II)<br>( $\times 10^3$ ) |
|------------------------------------|---------------------------------|------------------------------------|--------|-----------------------------------------|
|                                    |                                 | pH 10.4                            | pH 7.3 |                                         |
| 0.242                              | 1.023(NaOH)                     | 0.548                              | 0.807  | 0.216                                   |
| 0.527                              | 1.023 "                         | --                                 | 0.548  | 0.475                                   |
| 0.298                              | 2.046 "                         | 1.48                               | 1.73   | 0.316                                   |
| 0.533                              | 2.046 "                         | 1.06                               | 1.47   | 0.576                                   |
| 0.213                              | 0.993(NH <sub>4</sub> OH)       | --                                 | 0.818  | 0.175                                   |
| 0.467                              | 0.993 "                         | --                                 | 0.585  | 0.408                                   |
| 0.526                              | 0.993 "                         | --                                 | 0.492  | 0.501                                   |

The  $pK_b$  corresponding to the end point at pH 10.4 was 11.9 as determined by the pH at half neutralization of the disodium salt. The  $pK_b$  corresponding to the end point at pH 7.3 was 9.6.

j) Preparation of the Sodium Salts of XXXVIII

i) The Monosodium Salt

To a 2N methanolic solution of sodium methoxide was added an

excess of XXXVIII. The mixture was shaken for ten minutes and the undissolved material was then filtered off. The filtrate was evaporated in vacuo and the residual solid was repeatedly recrystallized from hot methanol-water. The dry solid had mp. 174-180° (gas evolved at 123°).

Anal. Calc'd. for  $C_6H_6N_3O_4SNa \cdot CH_3OH$ :

C, 31.0; H, 3.69; N, 15.5; S, 11.8; Na, 8.5.

Found: C, 29.7; H, 3.54; N, 15.8; S, 11.9; Na, 9.6.

When this material was dried at 137°/0.5 mm. for eight hours, the constant-weight sample that resulted had lost 7.3% (calc. 11.8%) of its weight and had mp 172-178° (no gassing).

The pH of a solution of 50 mg. of the salt in 5 ml. of water was 6.08 at 20°.

The IR spectrum (NM) showed a hydroxyl O-H stretch band at 3650  $cm^{-1}$  and small peaks at 1500 and 1427  $cm^{-1}$  which were absent from the free acid (XXXVIII).

When saturated aqueous solutions of the sodium salt were acidified with hydrochloric or acetic acids, there was obtained the starting acid, XXXVIII in from 56 - 79% yields.

## ii) The Disodium Salt, (L)

To a solution of the monosodium salt, (XLIX) in methanol was added excess sodium methoxide in methanol. The gelatinous precipitate was filtered off and washed with methanol. After it was recrystallized from warm methanol-water, the solid had a melting point above 300° (sinter 275°).

Anal. Calc'd. for  $C_6H_5N_3O_4SNa_2 \cdot 3/2CH_3OH$ : Na, 14.5.

Found: Na, 14.6.



The pH of a solution of 0.061 g. of this salt in 10 ml. of water was 10.7 at 20°.

When a solution of 0.15 g. of the salt in water was acidified with excess acetic acid, there was obtained 0.09 g. (72%) of XXXVIII.

The IR spectrum (NM) of the material showed an O-H stretch absorption at  $3400\text{ cm}^{-1}$ . There was no absorption between  $1600\text{ cm}^{-1}$  and  $2900\text{ cm}^{-1}$ .

k) Intramolecular Amidolysis of 2-Pyridylurea Ethosulphate (LI)

i) A mixture of 0.55 g. (0.0021 mole) of LI and 1 ml. of thionyl chloride was refluxed for ninety minutes. It was then cooled and was allowed to stand for two hours. The mixture was evaporated and the residue was rinsed with chloroform and then with water. There remained 0.21 g. (48%) of XXXVIII, m.p. 230° with decomposition (sl95°). An admixture with a sample of XXXVIII prepared as in section 1b(i) gave m.m.p. 230°.

ii) A small amount of LI and an excess of dicyclohexylcarbodiimide was heated at 100° for ninety minutes. The mixture was then cooled and rinsed first with acetone, then with water, ether and finally with acetone again. There remained a white solid, m.p. 232° with decomposition (s. 215°), undepressed by the addition of XXXVIII.

iii) One half g. of LI was heated to 140° for three and one half hours, during which time 2-aminopyridine was liberated. The residue remained molten. At the end of this time, the mixture was cooled. It was entirely water-soluble

2. The Reaction of Chlorosulphonyl Isocyanate With Dimethylformamide:  
N,N-Dimethylformamidine-N'-Sulphonic Acid (LIII)

To 5 ml. (0.06 mole) of dimethylformamide was added slowly, 2 g. (0.014 mole) of chlorosulphonyl isocyanate. There was an exothermic reaction accompanied by the evolution of carbon dioxide. No hydrogen chloride was produced. After the solution had cooled, the excess of dimethylformamide was removed in vacuo, and the crystalline residue was rinsed with 2-propanol. There remained 1.25 g. (59%) of water-soluble, chloride-free, acidic solid, m.p. 238-239° with decomposition.

|       |                               |                                     |
|-------|-------------------------------|-------------------------------------|
| Anal. | Calc'd. for $C_3H_8N_2O_3S$ : | C, 23.8; H, 5.27; N, 18.4; S, 21.1. |
|       | Found:                        | C, 24.5; H, 5.19; N, 18.3; S, 21.1. |

A potentiometric titration of this material with 0.104N aqueous sodium hydroxide solution gave an equivalent weight value of  $151 \pm 0.5$  (calc'd. 152). The  $pK_a$  was 3.51.

The IR spectrum (KBr pellet) showed a free O-H stretch band at  $3480\text{ cm}^{-1}$ , a bonded O-H stretch band (strong) at  $3150\text{ cm}^{-1}$ , and an intense band at  $1680\text{ cm}^{-1}$  corresponding to the C = N stretch frequency.

3. The Reaction of Chlorosulphonyl Isocyanate With Phenol  
and Aluminium Chloride: Phenyl Urethane (LVIII)

To a solution of 0.94 g. (0.01 mole) of phenol in 25 ml. of dry methylene dichloride was added 1.41 g. (0.01 mole) of chlorosulphonyl isocyanate. After two days, 0.25 g. of boron trifluoride etherate was added.

After the mixture had stood at room temperature for a further nine days, it was evaporated in vacuo to leave an oil which soon solidified. Aluminium chloride, 1.33 g. (0.01 mole) was added, and the mixture was gently heated to effect fusion. It was then cooled and 20 ml. of methylene dichloride was added. Upon agitation, an exothermic reaction took place, accompanied by the evolution of hydrogen chloride and by dissolution of the aluminium chloride.

After one hour, 50 ml. of cold water was added with external cooling and agitation. The suspension was then extracted with benzene, the benzene extract was dried over sodium sulphate, and the solvent was evaporated off to leave a small amount of brown oil.

The aqueous phase deposited white plates upon standing over night. These were filtered off and rinsed with water to leave 0.35 g. (25%) of phenyl urethane, m.p. 139-140° (s. 136°). An authentic sample which was prepared from phenol, potassium cyanate and hydrochloric acid, had m.p. 143-145°. An admixture of the two samples gave m.m.p. 143-145°.

#### IV. CLAIMS TO ORIGINAL RESEARCH

1. A new heterocycle, 2, 4, 6-pyridothiatriazine-3(2H)-one-1, 1-dioxide (XXXVIII), has been conveniently synthesized using chlorosulphonyl isocyanate.
2. The unusual anhydride-like properties of this cyclic sulphonyl urea have been outlined, and the structure has been almost completely established by a sequence of step-wise degradation reactions as well as by synthesis by a second, independent route.
3. The order and rate of bond cleavage in the novel heterocyclic ring has been shown to be dependent on the pH of the solvolytic medium.
4. N, N-Dimethyl-N'-chlorosulphonyl-formamidine (LV) is shown to be the end product in the reaction of dimethylformamide with chlorosulphonyl isocyanate.

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