6-15-1971

The Synthesis of Some New Condensed Pyridazines, Pyridazine N-Oxides and Pyrimidines as Potential Chemotherapeutic Agents

Donald E. Pichler

SYNTHESIS OF SOME NEW CONDENSED PYRIDAZINES, PYRIDAZINE N-OXIDES AND PYRIMIDINES

PICHLER

THE UNIVERSITY OF NEW MEXICO
ALBUQUERQUE, NEW MEXICO 87106

Policy on Use of Theses and Dissertations

Unpublished theses and dissertations accepted for master's and doctor's degrees and deposited in the University of New Mexico Library are open to the public for inspection and reference work. *They are to be used only with due regard to the rights of the authors.* The work of other authors should always be given full credit. Avoid quoting in amounts, over and beyond scholarly needs, such as might impair or destroy the property rights and financial benefits of another author.

To afford reasonable safeguards to authors, and consistent with the above principles, anyone quoting from theses and dissertations must observe the following conditions:

1. Direct quotations during the first two years after completion may be made only with the written permission of the author.

2. After a lapse of two years, theses and dissertations may be quoted without specific prior permission in works of original scholarship provided appropriate credit is given in the case of each quotation.

3. Quotations that are complete units in themselves (e.g., complete chapters or sections) in whatever form they may be reproduced and quotations of whatever length presented as primary material for their own sake (as in anthologies or books of readings) ALWAYS require consent of the authors.

4. The quoting author is responsible for determining "fair use" of material he uses.

This thesis/dissertation by Donald E. Pichler has been used by the following persons whose signatures attest their acceptance of the above conditions. (A library which borrows this thesis/dissertation for use by its patrons is expected to secure the signature of each user.)

NAME AND ADDRESS	DATE

July 1971—1,000—GS

This dissertation, directed and approved by the candidate's committee, has been accepted by the Graduate Committee of The University of New Mexico in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY IN CHEMISTRY

THE SYNTHESIS OF SOME NEW CONDENSED PYRIDAZINES, PYRIDAZINE N-OXIDES AND PYRIMIDINES AS POTENTIAL CHEMOTHERAPEUTIC AGENTS

Donald E. Pichler
Candidate

Chemistry
Department

David T. Bendiner
Dean

June 15, 1971
Date

Committee

Raymond N. Castle
Chairman

Terence J. Scallen

Roy D. Eaton, Jr.

Milton Kahn

E. Papadopoulos

THE SYNTHESIS OF SOME NEW CONDENSED PYRIDAZINES, PYRIDAZINE N-OXIDES AND PYRIMIDINES AS POTENTIAL CHEMOTHERAPEUTIC AGENTS

BY
Donald E. Pichler

DISSERTATION

Submitted in Partial Fulfillment of the
Requirements for the Degree of
Doctor of Philosophy in Chemistry
in the Graduate School of
The University of New Mexico
Albuquerque, New Mexico
1971

UNIVERSITY OF NEW MEXICO LIBRARY

DEDICATION

TO

BRENDA

ACKNOWLEDGEMENT

The author wishes to express his sincere appreciation to Professor Raymond N. Castle for his advisement, encouragement, understanding and help during the accomplishment of this work.

My sincerest thanks are also extended to the faculty and the graduate students in the Department of Chemistry for their helpful suggestions and discussions during my stay at the university.

Special thanks go to the following students who worked diligently as undergraduate research students in preparing some of the synthetic intermediates for this research:

Kane Gross, Linda Thorne, Floyd Braaten, Gregory Dohrer, James Clark, Steve Heilman, Roberta Sparks.

To the Graduate School of the University of New Mexico, my gratitude for a teaching assistantship during the years 1966-1970 which made my way possible.

THE SYNTHESIS OF SOME NEW CONDENSED PYRIDAZINES, PYRIDAZINE N-OXIDES AND PYRIMIDINES AS POTENTIAL CHEMOTHERAPEUTIC AGENTS

BY
Donald E. Pichler

ABSTRACT OF DISSERTATION

Submitted in Partial Fulfillment of the
Requirements for the Degree of
Doctor of Philosophy in Chemistry
in the Graduate School of
The University of New Mexico
Albuquerque, New Mexico
1971

ABSTRACT

The need for new antimicrobial and antifungal agents as well as medicinals possessing antiprotozoal activity against special strains of malaria resistant to most synthetic antimalarials prompted the synthesis of new compounds that may have the desired antimetabolite properties. The structural similarities of the 1,2,5-thiadiazolo[3,4-d] pyridazines and the v-triazolo[4,5-d]pyridazines with the biologically important purines prompted the synthesis of members of these ring systems. The 1,2,5-thiadiazoles synthesized as intermediates were also screened as potential chemotherapeutic agents. Similarly, the pyridazine N-oxides and the 5-nitro substituted pyrimidines are structurally similar to the pyrazine N-oxides and the pyridine N-oxides, which are known to possess a broad spectrum inhibition against bacteria and fungi in a very low concentration.[77,112]

A series of 4,7-disubstituted and 4-monosubstituted 1,2,5-thiadiazolo[3,4-d]pyridazines, 4-substituted 7-methyl-v-triazolo[4,5-d]pyridazines, some 6-aminopyridazine 1-oxides substituted in the 3 position and several 5-nitropyrimidines substituted in the 4,6 positions were prepared. Ultraviolet and infrared spectra were reported for all compounds, while nuclear magnetic resonance spectra were measured only for certain select compounds. A number of these compounds were screened for their inhibitory action against several bacterial and fungal species.

TABLE OF CONTENTS

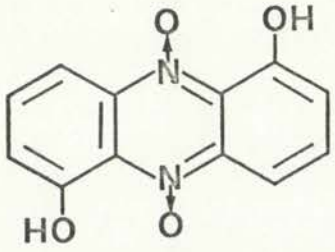
LIST of TABLES

I. Introduction and Review of the Literature

Antibacterial and Antifungal Agents

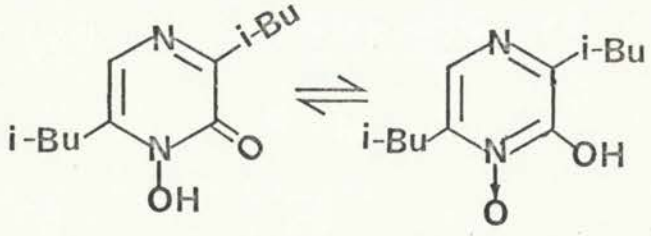
I. Introduction

Chemical history indicates that perhaps the first interest in the biological properties of aromatic amine oxides most probably came with the isolation, in 1938, from Chromobacterium Iodinum of iodenin,[27] a substance having a strong antibacterial activity and structurally elucidated as 1,6-dihydroxyphenazine-5,10-dioxide (I).



I

In 1943, White and Hill[134] discovered an antibiotic with marked bacteriostatic action. The antibiotic, named aspergillic acid and produced by Aspergillus flavus, was shown to be a derivative of 2-hydroxypyrazine 1-oxide (II). Aspergillic acid inhibits the growth of



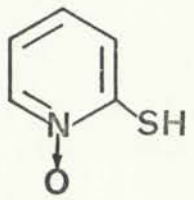
II

a large number of gram-negative and gram-positive microorganisms. Aspergillic acid can be represented by either 2-hydroxy-3,6-diisobutyl-pyrazine 1-oxide (II) or 1-hydroxy-3,6-diisobutyl-2-pyrazinone. Removal

of the N-oxide function results in weaker antibacterial activity.[88]

In subsequent years a considerable number of aromatic amine oxides were synthesized with the skeleton of these antibiotics as models and their action on microorganisms examined.[112,91]

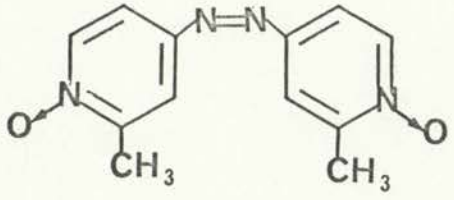
One outcome of these studies is that 2-mercaptopyridine 1-oxide (III)



III

shows a strong antifungal activity[91] and a variety of its derivatives are used as pesticides and preservatives.[91] When the mercapto-hydrogen of 2-mercaptopyridine 1-oxide is substituted with N- heterocyclic groups such as imidazolinyl and tetrahydropyrimidinyl, they function as active antiinfective agents for treatment of superficial mycoses.[30]

In 1961, Itai and Kamiya[63] reported that the 4-azido derivatives of pyridine, and 2,2'-dimethyl-4,4'-azopyridine-1,1'-dioxide (IV) had a

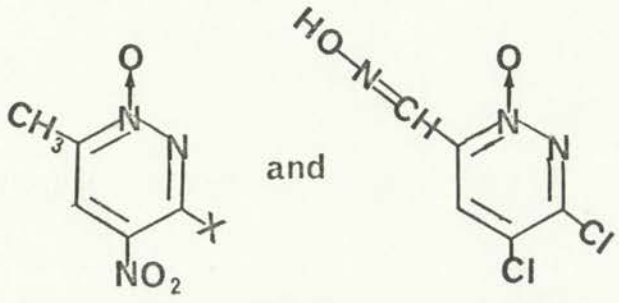


IV

strong bacteriostatic activity against Staphylococcus aureus, Escherichia coli, and Candida albicans.

Attention was first directed to the pyridazine and pyridazine 1-oxide derivatives in the early 1960's as possible chemotherapeutic agents.[64,89] In 1963, Takanobu and Kamiya[64] synthesized azidopyridazine derivatives in order to examine their anticancer and bacteriostatic actions. This work also dealt with the synthesis and reactions of 3- and 6-azidopyridazine 1-oxides, as well as some related compounds.

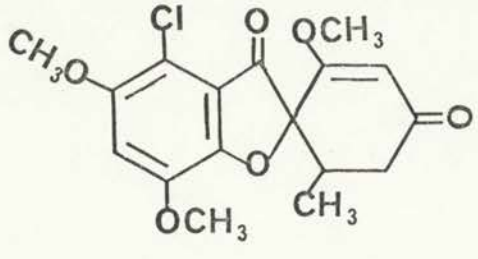
However, the most productive of investigations which pointed to the usefulness of some pyridazine N-oxides was the work of Nishimura, Kano and their associates,[89] who examined the antimicrobial activity of pyridazine 1-oxide derivatives and stated that some of the 3,6-di-substituted 4-nitro and 4-chloro derivaties (Va, b) had a strong



Va and Vb

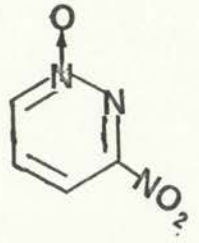
antifungal activity <u>in vitro</u>.

Most noteworthy of these compounds were the following: it was found that the antitrichophyton activity of 3-halogeno-6-methyl-4-nitropyridazine 1-oxides and 3,4-dichloro-6-(hydroxyiminomethyl) pyridazine 1-oxide is stronger than that of griseofulvin (VI).[89]



VI

In 1963, Itai and Natsume[67] synthesized the 3-nitro derivative of pyridazine 1-oxide (VII) as a potential anticancer agent. This



VII

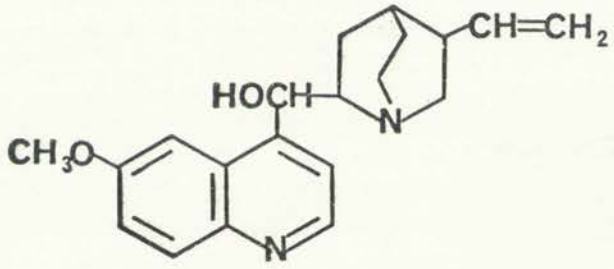
compound, however, showed no activity against Ehrlich ascites carcinoma in vivo, but did show strong activity against Staphylococcus aureus, Escherichia coli, Shigella flexneri, and Candida albicans in vitro.

Part of this present investigation was done to synthesize some new pyridazine N-oxides and test them for antibacterial and antifungal activity in vitro.

Antimalarial Agents

Malaria is perhaps the most widespread of all human diseases, for there is little doubt that in terms of morbidity, malaria is one of the most important of all the ills that beset mankind.[107] It is caused by protozoa of the genus Plasmodium. These protozoa are transmitted by infected Anopheles mosquitoes. At least four different species of Plasmodium can infect the human host. They are P. vivax, P. falciparum, P. malariae and P. ovale.[111]

Man, in his search for an effective remedy to suppress malaria, found only one herbal remedy, quinine (VIII) which was the first alkaloid isolated from cinchona bark, and its dominant position and use in the

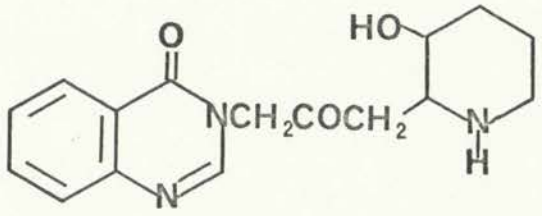


VIII

treatment of malaria is due to this fact. The alkaloid quinine (VIII) is effective as a suppressive in the control of overt attacks of malaria due to P. falciparum, P. vivax, and P. malariae.[111] In general, quinine is neither as active nor as

well tolerated as most of the newer synthetic antimalarials.[69,9,15]

In China, the drug Ch'ang Shan has been used as a remedy for malaria. The drug consists of the powdered roots of Dichroa febrifuga. The therapeutically active alkaloid febrifugine (IX) was isolated from this root and its structure elucidated shortly after World War II.[26,73,74,62]



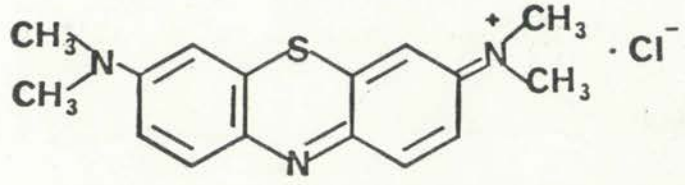
IX

Febrifugine (IX) has some effect against the asexual forms of P. falciparum and P. vivax but its value is limited by the fact that it is also a powerful emetic.[40]

The investigations of compounds related to quinine have not produced a useful antimalarial compound. The original ideas that eventually led to synthetic chemotherapeutic agents came from an entirely different direction. Ehrlich and Guttman[54] in 1891 observed that the dyestuff methylene blue (X) had some beneficial effects on patients suffering from malaria.[54] During World War I, the Germans, finding themselves cut

off from the main world supply of quinine, began to consider the possibilities of preparing synthetic antimalarials. Since it was essential that they should achieve independence of the world quinine supply, attention was focused on the production of a synthetic antimalarial.

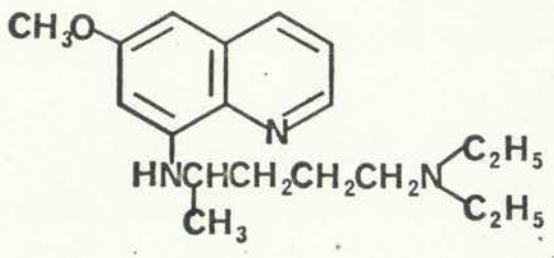
Schuleman and coworkers[115] first directed their attention to the thiazine derivatives related to methylene blue (X). They prepared



X

several compounds which were more active than methylene blue (X) in which one of the methyl groups on the nitrogen atom was replaced by a dialkylaminoalkylamino group.[115] These observations of Schuleman led to the belief that the dialkylaminoalkylamino side chain, "the basic side chain," was essential for high antimalarial activity.[115] Attempts were made to combine this basic side chain with a whole range of heterocyclic ring systems and in the course of time this led to most of the synthetic antimalarials now used.

Consequently, quinoline was one of the most useful heterocyclic ring systems. The combination of the basic side chain and a 6-methoxyquinoline was attempted first because the quinoline nucleus is present in the cinchona alkaloids. In 1924 this line of research led to the first synthetic antimalarial compound,[115] pamaquine (XI). Other 8-amino-



XI

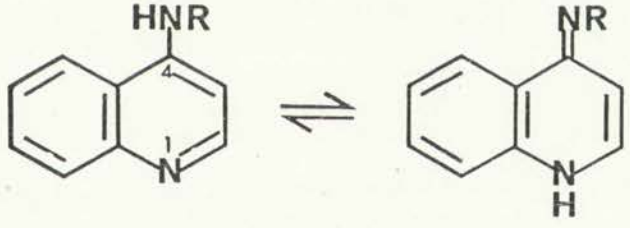
quinoline derivatives were soon prepared. However, the chief disadvantage of pamaquine (XI) and the other 8-aminoquinolines[41,42] was their toxicity which prohibits their being used in doses large enough to effect a radical cure.[50]

During the pre- and post-World War II period, several attempts were made to correlate the relationship between chemical constitution and antimalarial activity in the quinine series.

Perhaps the most significant pre-war observation of the effect of chemical constitution on antimalarial activity in this series concerns

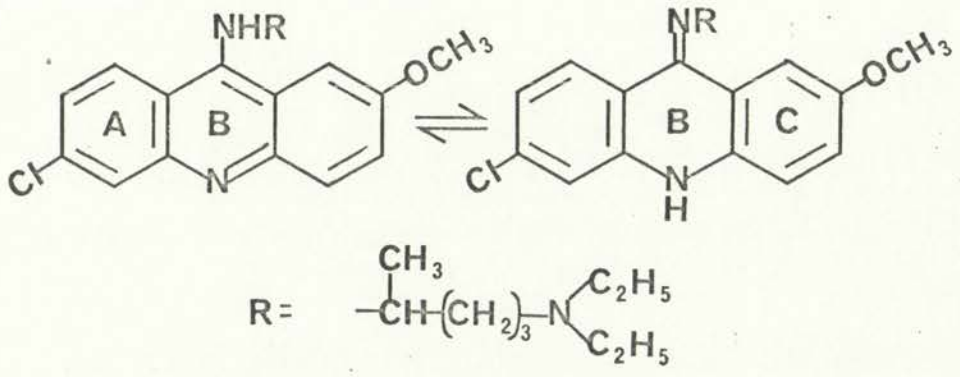
changes in the quinunclidine nucleus. Ainley and King[1] showed that the (-CHOH-CH-N-) grouping arising from oxidative cleavage of the quinunclidine nucleus is in reality the basic side chain and a main reason for the activity of quinine (VIII).

Of the possible positions of the basic side chain in the quinoline nucleus, only the 4-, 6-, and 8-positions seem to give rise to active antimalarials. Since the 6- and 8- positions are para and ortho to the heterocyclic nitrogen atom, respectively, quinone formation between these positions could be visualized after oxidation. The 4- position differs from either the 6- or 8- position in that an imino compound can be formed by simple prototropy (XII). Such tautomerism can be viewed as



XII

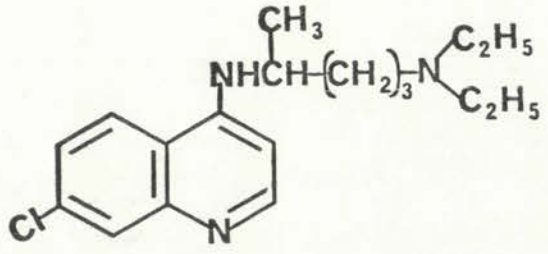
existing in the acridine antimalarial, quinacrine (XIII).



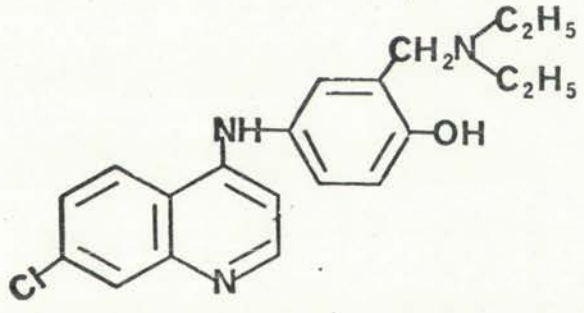
XIII

This compound can in fact be regarded as being made up of two 4-aminoquinolines, one containing rings A and B, the other B and C. It was these observations that led Schonhofer[114] in 1942 to postulate that tautomerism of this type was necessary, or at least desirable for high antimalarial activity.

As a result of these early views not based on modern comparative biochemistry, many quinoline derivatives substituted in the 4- position with the basic side chain were prepared. The most useful of the 4-aminoquinolines are chloroquine (XIV)[126] and amodiaquine (XV)[19]. The value of the 4-aminoquinolines rests upon their outstanding activity against the asexual blood forms of all species of malaria. They will produce a clinical cure in all types of human malaria and eradicate falciparum infections.[80,61] They are excellent suppressive agents



XIV



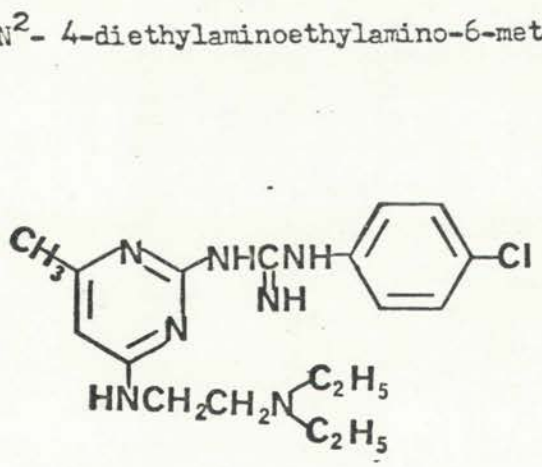
XV

against all species of malaria and at doses of 300-400 mg./week for from 3-4 weeks, give suppressive cures of falciparum malaria. Their

very rapid activity and low toxicity makes them most useful as drugs for acute attacks of malaria.[31,92]

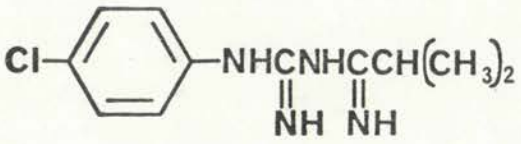
The early success of the Japanese in Southeast Asia in 1941 denied the Allies access to the main quinine-producing areas of the world. Yet it was essential that the Allies maintained large armies in areas where malaria was endemic. In Britain, as well as the United States, attention was turned to the study of synthetic antimalarials.

After the development of the 4-, 8- aminoquinolines in the United States, a completely new kind of antimalarial drug was developed in Great Britain based on a pyrimidine nucleus.[33] In parallel with Schonhofer's hypothesis[114] suitably substituted aminopyrimidines would be capable of tautomerism. It was decided to make the pyrimidine system the central nucleus around which certain pendant groups would be attached to confer the correct pharmacological properties on the compound. A series of compounds of this type were prepared, the most useful of which contained a guanidine linkage between the aryl and pyrimidine groups, such as N^1- p-chlorophenyl -N^2- 4-diethylaminoethylamino-6-methyl-2-pyrimidyl - guanidine (XVI).



XVI

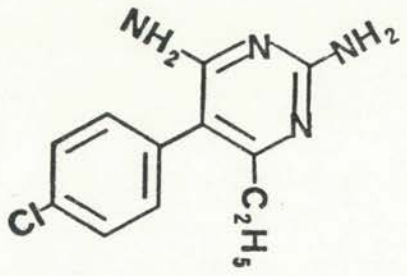
Simplified structures based upon the above structure resulted in the discovery of chloroguanide (XVII). Chloroguanide (XVII) is highly



XVII

active against the primary exoerythrocytic forms of P. falciparum and is therefore a powerful drug for the causal prophylaxis of malignant tertian malaria.[31,48,26]

Associated with the investigations of pyrimidine antimalarials was the discovery of pyrimethamine (Daraprim) (XVIII). Pyrimethamine



XVIII

is highly active against all experimental malarias. It is most active against the asexual blood forms of all human malarias. It will produce a clinical cure in all and a radical cure in most cases of P. falciparum infection.[32] Pyrimethamine is the most powerful suppressive known.

Post World War II research has done much to shed a new light on the structure activity relationships of these antimalarials.

The ability of chloroquine and some of its congeners to form molecular complexes with DNA was known in the early 1950's.[93] In 1965, O'Brien and Hahn[90] postulated that this ability is closely correlated with antimalarial activity. They postulated that the quinoline ring becomes horizontally inserted between the bases of the DNA double helix involving electrostatic forces and probably London-Eisenschitz-Wang forces and the side chain diagonally spans the minor groove of DNA and electrostatically binds to DNA phosphates.[90] The chlorine atom, attached to the 7- position of the quinoline ring in chloroquine (XIV) becomes superimposed over a DNA base pair with the 7- chloro group in proximity to the 2-amino group of guanine. Alterations in the substituent in position -7 result in reduced antimalarial activity, through differences in electronegativity as well as in volume, which affect the affinity for the 2-amino group of guanine or affect steric hindrance to intercalation.[90] Alterations in the heterocyclic ring structure also influence antimalarial activity by changing the electronic configuration of the ring structurein ways which alter the ring-ring interaction between DNA bases and chloroquine.[90] The length of the side chain, (the basic dialkylaminoalkylamino group) is critical, optimum binding to DNA occurring when the distance between the two amino groups spans that

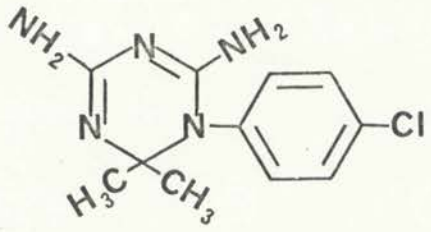
between the two DNA phosphates across the minor groove, which is 10.5 Å. If the ionic radii of the non-primary amines in the side chain of chloroquine (XIV) and the phosphates of DNA are considered, the ideal distance between side chain nitrogens is approximately 7.5 Å. This distance is attained between the amino groups in chloroquine (XIV) and certain of its analogs which have comparable antimalarial activity.[90] The importance for binding of DNA to each of the functional segments of the 4-aminoquinoline molecule has been defined and the proposed hypothetical model of the DNA-Chloroquine complex of O'Brien and Hahn[90] is acceptable from the standpoint of the available biophysical data.

In 1970, investigations into the mode of antimalarial activity for chloroquine and its analogs were carried out by Purcell.[100] Through the use of molecular orbital calculations and mathematical models, the mechanism of DNA intercalation for these analogs was in agreement with the postulates of previous investigators.[90,93]

Estensen, Krey and Hahn[47] reported that a DNA-quinine complex formed with double-helical calf thymus DNA as shown by changes in the UV absorbtion spectrum of quinine (VIII), however, single stranded DNA did not complex with quinine.[47] Spectral changes caused by the complexing of quinine with DNA were reversed by thermal strand separation, and by sodium and magnesium ions.[47] Spectrophotometric titrations of quinine with calf thymus DNA showed that quinine (VIII) binds to more than one class of sites in DNA.[47]

Early members of the chloroguanide (XVII) series were synthesized as pyrimidine derivatives (XVI) because of the known importance of pyrimidine

containing compounds in cell metabolism.[108] Later members of the series, of which chloroguanide (XVII) is one, were simplified by opening the pyrimidine ring to give a biguanide, which is converted in vivo via metabolic processes to a triazine (XIX) 2,4-diamino-5-(p-chlorophenyl)-6, 6-dimethyl-5,6-dihydro-1,3-5-triazine, the active form of the drug.[113]

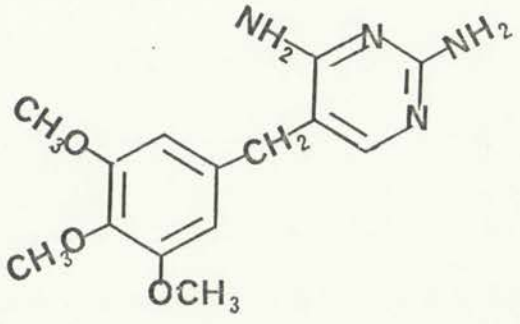


XIX

In exploring the mode of action of diaminopyrimidines, in particular pyrimethamine (XVIII), Hitchings[59] showed that in Streptococcus faecalis growth occurred normally in the presence of folic acid. However, when a small concentration of pyrimethamine was introduced to the organism, growth with folic acid was completely blocked.[59]

Recent work, carried out with dihydrofolate reductases[17] isolated from several mammalian and bacterial sources has shown that there is a strong correlation between the binding of a drug by a particular dihydrofolate reductase and the capactiy of that drug to inhibit the source organism.[17]

Pyrimethamine has been shown [59] to penetrate cells by simple diffusion and its entrance is unrelated to the ability of the cell to assimilate folic acid. The question one asks is, "Why then is pyrimethamine selectively toxic to the malaria parasite, leaving untouched the cells of the host?" The answer can be drawn by inference. A close structural analog of pyrimethamine, timethoprim (XX) produces 50% inhibition



XX

of bacterial dihydrofolate reductase (XX) at concentrations ca. 5×10^{-9} molar, while similar inhibition of mammalian liver reductase requires concentrations of the order of 3×10^{-4} molar.[81] Presumably, a similar difference accounts for the selective toxicity of pyrimethamine and the structurally similar triazine (XIX), metabolite of chloroguanide in malarial infection.[113,109]

By 1950, the arsenal of antimalarial drugs seemed to be complete; however, this triumph was short-lived. Reports of resistant strains

began to appear. These reports did not attract much attention until the United States became involved in Vietnam. Reports of chloroquine,[51,52,97,99] and pyrimethamine[20,9,15] "multiple resistance" strains of Plasmodium falciparum had come from Malayia,[28,35] Thailand,[137] and Vietnam.[98,20,29] These drug-resistant strains soon began to appear among the United States troops sent to South Vietnam.[20,29]

As a consequence, interest was revived for the development of additional synthetic antimalarials. It was in response to this need that part of this present work was undertaken.

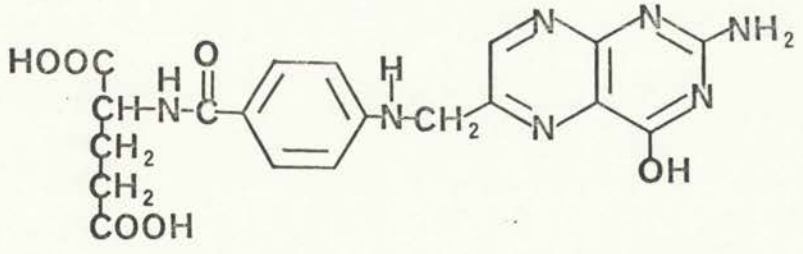
Anticancer Agents

Cancer chemotherapy has a simple goal, to discover compounds that will control the growth of cancer cells or destroy them completely without serious damage to the normal tissues of the host.[37]

In order for the cells to proliferate, nucleic acid precursors are necessary for the synthesis of DNA and RNA, and certain coenzymes.[94,70] A number of analogs structurally related to nucleic acid precursors and the purine and pyrimidine bases and their nucleosides have been discovered, which interferewith the biosynthesis of these essential substances. These antimetabolites are structurally similar to the normal metabolites.[53,7,43,57,58]

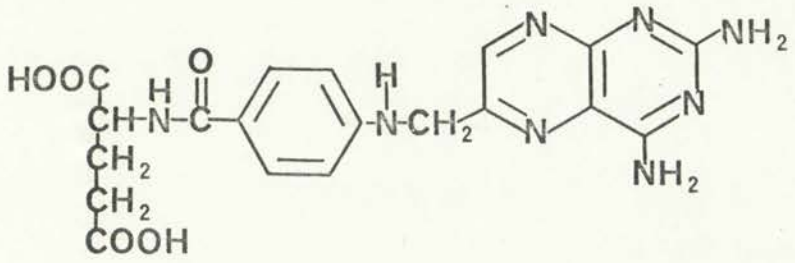
Two general classes of antagonists have received a large share of the attention given to antimetabolites in the treatment of cancer. These are the folic acid antagonists and the purine and pyrimidine antagonists.

Folic acid (XXI), known to be an essential growth factor for cells,[60]



XXI

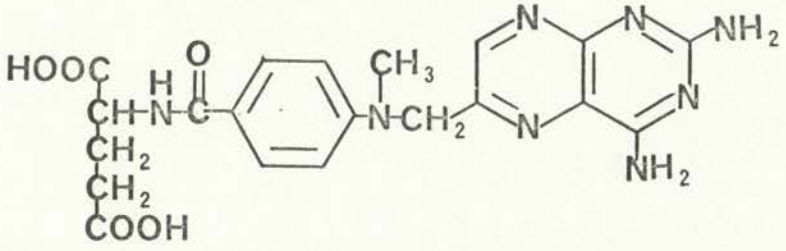
was characterized and synthesized by Walker and coworkers[129] in 1946. A year later, the 4-amino analog of folic acid (Aminopterin) (XXIIa),[116] was described. Soon afterward, the first successful demonstration of the usefulness of the antimetabolite aminopterin was shown by Farber



XXIIa

and associates,[49] who by administration of this drug, clinically produced temporary remissions of acute leukemia in children. Since then, many related compounds to folic acid have been synthesized. The most widely used antimetabolite of folic acid is 4-amino-N^{10}-methylpteroylglutamic acid (Methotrexate) (XXIIb).

In order to exert its biological effect, folic acid must be reduced to its active coenzyme form, 5,6,7,8-tetrahydrofolic acid. This occurs in two steps. The first step to 7,8-dihydrofolic acid and secondly, the reduction of 7,8-dihydrofolic acid to 5,6,7,8-tetrahydrofolic acid.[79] Folic acid reductases are necessary for catalyzing



XXIIb

both of these reactions. The 5,6,7,8-tetrahydrofolic acid thus formed is of critical importance in the metabolic transfer of one-carbon units in a variety of biochemical reactions.[79]

Subcellularly, methotrexate competitively inhibits dihydrofolate reductase, thus restricting the availability of tetrahydrofolic acid to cells.[11,130] In human leukocytes, the synthesis of DNA appears to be more sensitive than that of RNA to inhibition by methotrexate,[132] suggesting that the most important effect of methotrexate is on thymidylate synthesis. It had been shown by Roberts,[103] that in mouse leukemias methotrexate can block the <u>in vivo</u> incorporation of deoxyuridine into DNA; therefore, cellularly, methotrexate prevents cell replication by inhibiting DNA synthesis.[103]

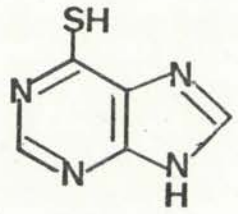
However, both aminopterin and methotrexate still have serious

limitations to their usefulness, their toxicity at theraputic levels[128] and the rapid development of resistance to them.[55,72,125,122]

In spite of their disadvantages, folic acid antagonists are very effective drugs, particularly in certain forms of leukemia,[125,121] and have also produced improvement in several other forms of human cancer.[136,131,85]

Large numbers of purines, pyrimidines and related compounds have been tested for anticancer activity in experimental systems.[18,110]

6-Mercaptopurine (XXIII), the first of the purine antagonists



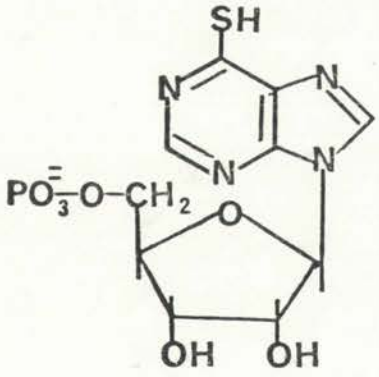
XXIII

to be available,[18] has been used effectively in producing remissions of acute leukemia in man.[45,75,78] The mechanism of action of this antimetabolite is shown metabolically in that 6-mercaptopurine must be converted intracellularly to its corresponding ribonucleotide (XXIV), the thio analog of inosinic acid to exert its biological effect.[14] Once

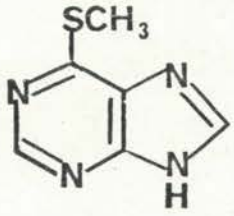
this ribonucleotide is formed, it can: (1) suppress purine biosynthesis via "pseudofeedback inhibition" of the formation of ribosylamine-5-phosphate from glutamine and 5-phosphoribosyl-1-pyrophosphate[44,83]; (2) inhibit the formation of adenylic and guanylic acid from inosinic acid,[44] and (3) inhibit interconversion reactions among intermediate compounds in purine metabolism.[44]

As with other antimetabolites, clinical usage of 6-mercaptopurine warrants caution for toxic effects.[101] Resistance eventually develops to its inhibition.[14,86]

A number of S-alkyl derivatives of 6-mercaptopurine show activity of the type exhibited by the parent compound.[44] One of them, 6-methylthiopurine (XXV), which <u>in vivo</u> is incorporated as 6-methylthiopurine-ribonucleotide,[3] had just recently been shown to be a metabolite of 6-mercaptopurine in human <u>Epidermoid Carcinoma</u>,[4] and most probably is responsible for the inhibition of purine synthesis <u>de novo</u> produced by the administration of 6-mercaptopurine.[8]

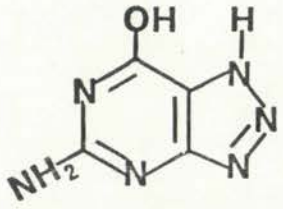


XXIV



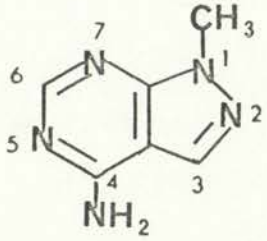
XXV

Alterations of the purine ring system have led to a series of compounds which show some antitumor activity. The first of these modifications involves the substitution of nitrogen for the carbon in the 8- position to give the so-called 8-azapurines or v-triazolo[d]pyrimidines. The best-known member of this group is 8-azaguanine (XXVI), which was originally prepared and tested as an antibacterial agent.[106]

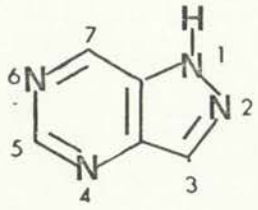


XXVI

Another series of purine analogs are the pyrazolopyrimidines[23,104,105] which are active in tumors usually susceptible to purine antagonists.[123] Two compounds showing activity in preliminary tests were 4-amino- and 4-amino-1-methylpyrazolo[3,4-d]pyrimidine (XXVII). In subsequent tests with over 140 pyrazolo[3,4-d]pyrimidines, the 4-alkylamino derivatives also showed activity, whereas twelve members of the alternate pyrazolo-[4,3-d]pyrimidine (XXVIII) series were inactive.[124]



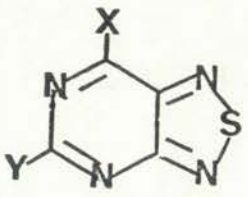
XXVII



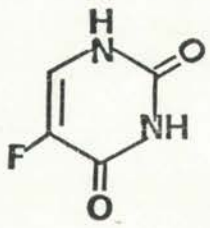
XXVIII

References to a number of other ring systems analogous to the purines with reports of antitumor activity may be found in a review by Timmis.[127] He reported that the 1,2,5-thiadiazolo [3,4-d] pyrimidines (8-thiapurines)(XXIX) may be considered analogs of two biologically important heterocyclic ring systems. They are analogs to the purines by virtue of the [3,4-d] fusion of the five-membered ring to the pyrimidine ring, and they are also iso π electronic with the pteridines.[127]

As compared to the purine antagonists, the pyrimidine antagonists have had much less success in the control of neoplastic diseases.[56,6] 5-Fluorouracil (XXX) was found to be at present the most effective single chemotherapeutic agent in the treatment of carcinomas of the colon[84] and rectum.[84] The biological mechanism of action of fluorouracil subcellularly, is its conversion in vivo to the



XXIX



XXX

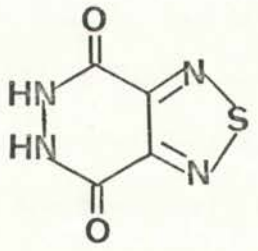
5-fluorouracildeoxyribonucleotide which has an affinity for thymidylate synthetase, thus preventing the methylation of deoxyuridylic acid to deoxythymidylic acid.[22,13] The thymidine definciency produced causes cellular injury and death ("thymineless death").[24]

However, sensitivity to 5-fluorouracil develops after prolonged treatment, and cases both in experimental[71] and human[5,86] cancers of resistance to this drug have been observed.

There is an everpresent need for new drugs to eradicate the many forms of cancer. In response to this need, part of this investigation was the synthesis of some new chemotherapeutic agents for cancer.

Literature Review for the 1,2,5-thiadiazolo [3,4-d] pyridazine Ring System

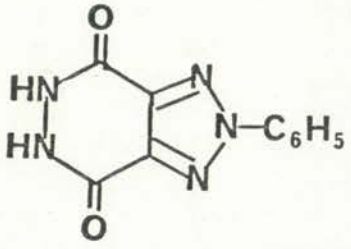
The first and only compound prepared in this ring system, 1,2,5-thiadiazolo [3,4-d] pyridazine-4,7-dione (XXXI), was reported by



XXXI

Sekikawa[120] in 1969 from the facile ring closure of 1,2,5-thiadiazole-3,4-dicarboxylic acid bishydrazide when treated with hydrochloric acid.

In 1931 Seka and Preissecker[117] described the synthesis of a derivative of 2H-v-triazolo [4,5-d] pyridazine (XXXIII) from 2-phenyl-1,2,3-triazole-4,5-dicarboxylic acid dihydrazide.

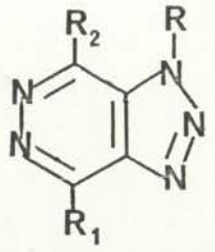


XXXIII

Erichomovitch and Chubb[46] converted 1-phenyl-1,2,3-triazole-4,5-dicarboxylic acid dihydrazide in the presence of 2N hydrochloric to structure XXXIV, R_1 = R_2-OH; R-Phenyl. From this starting material seven more derivatives of 1H-v-triazolo [4,5-d] pyridazine were synthesized.

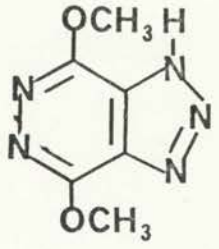
The first demonstration that the appropriate pyridazines could be converted into the v-triazolo [4,5-d] pyridazines was shown by Itai and Suzuki.[68] They treated a solution of 3,5-dimethoxy-4,5-diaminopyridazine in acetic acid dropwise with a solution of sodium nitrate to obtain 4,7-dimethoxy-v-triazolo [4,5-d] pyridazine (XXXV). This reaction was extended by Aldous and Castle[2] to synthesize 4-methoxy-7-methyl-v-triazolo [4,5-d] pyridazine (XXXVI).

The most recent work in the v-triazolo [4,5-d] pyridazines was published by Martin and Castle[82] in 1969, who converted 4,5-diamino-pyridazin-3-one with nitrous acid to give v-triazolo [4,5-d] pyridazin-

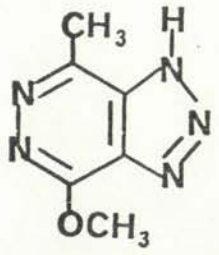


XXXIV (a-g)

	R	R_1	R_2
a.	phenyl	chloro	chloro
b.	phenyl	methoxy	methoxy
c.	phenyl	methylthio	methylthio
d.	phenyl	OH($Me_2NCH_2CH_2O$)	$Me_2NCH_2CH_2O$(OH)
e.	phenyl	$Me_2NCH_2CH_2O$	$Me_2NCH_2CH_2O$
f.	phenyl	OH(Cl)	Cl(OH)
g.	phenyl	$NHNH_2$(MeS)	MeS($NHNH_2$)

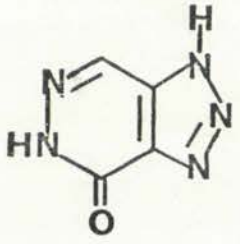


XXXV



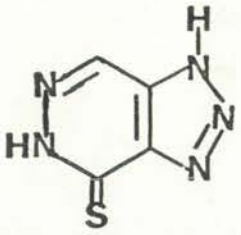
XXXVI

4-one (XXXVII). Martin and Castle[82] allowed phosphorus pentasulfide to react with XXXVII and were able to obtain v-triazolo [4,5-d] pyridazine-

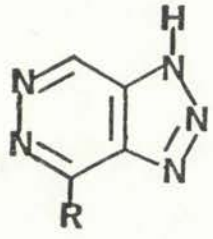


XXXVII

4-thione (XXXVIII). With this compound (XXXVIII) as the starting material, six more v-triazolo [4,5-d] pyridazines (XXXIXa-f) were prepared.



XXXVIII



XXXIX(a-f)

R =

a. $-S-CH_2-\phi$

b. $-S-CH_3$

c. $-NH-NH_2$

d. $-NH_2$

e. $-HN-(CH_2)_3-N(ET)_2$

f. $-HN-(CH_2)_2-N(Me)_2$

At the beginning of the present research only twenty-one 1H-v-triazolo-[4,5-d]pyridazines had been prepared.

Literature Review for the Pyrimidines and Pyridazines

Since an enormous amount of work has been done in these two systems, the author cites three reviews which contain the vast majority of published work:

1. "The Pyrimidines," D. J. Brown, Interscience Publisher (1962).

2. "Advances in Heterocyclic Chemistry," A. R. Katritzky, Vol. 9:211(1968). Chapter 5 'Pyridazines.'

3. "On the Chemistry of Pyridazine N-Oxides," T. Itai, Eisei Shikensho Hokuku (Bulletin of the National Institute of Hygenic Sciences) 82:1 (1964). In Japanese.

4. A comprehensive volume on the pyridazines and their derivatives will be published in the Spring of 1972 with Dr. Raymond N. Castle as editor.

II. Discussion

Discussion

Synthesis of 1,2,5-thiadiazolo [3,4-d] pyridazines

2,1,3-Benzothiadiazole (XLI) was prepared by the method of Pesin and Khaletskii,[95,96] by the reaction of o-phenylenediamine (XL) with thionyl chloride. Ring oxidation of 2,1,3-benzothiadiazole (XLI) with potassium permanganate to 1,2,5-thiadiazole-3-dicarboxylic acid (XLII) followed by esterification with absolute ethanol in sulfuric acid. Diethyl 1,2,5-thiadiazole-3,4-dicarboxylate (XLIII) was the product. This was the method of Sekikawa.[118,119] 1,2,5-Thiadiazole-3,4-dicarboxamide was prepared by the ammonolysis of the diethyl ester (XLIII). Dehydration of the diamide (XLIV) with phosphorus oxychloride proceeded smoothly to give the dinitrile (XLV), by the procedure of Wen.[133] The bishydrazide of 1,2,5-thiadiazole (XLIX) was prepared from the diester (XLIII) by the reaction of XLIII with hydrazine by the method of Sekikawa.[118] This was converted into 4,7-dihydroxy-1,2,5-thiadiazolo [3,4-d] pyridazine (L) by the method of Sekikawa.[120]

The reaction of 3,4-dicyano-1,2,5-thiadiazole (XLV) with methylhydrazine gave 4,7-diamino-5-methyl-1,2,5-thiadiazolo [3,4-d] pyridazine (XLVI). Similarly, the dinitrile (XLV) was converted into 4,7-diamino-5-phenyl-1,2,5-thiadiazolo [3,4-d] pyridazine (XLVII) with phenylhydrazine. Two separate methods were employed for the synthesis of 4,7-diamino-1,2,5-thiadiazolo [3,4-d] pyridazine (XLVIII). The first was the reaction of 3,4-dicyano-1,2,5-thiadiazole (XLV) with hydrazine and the second

method was the reaction of 4,7-bis(methylthio)-1,2,5-thiadiazolo[3,4-d]-pyridazine (LIII) with absolute ethanol saturated with ammonia in a pressure bottle.

The reaction of 4,7-dihydroxy-1,2,5-thiadiazolo[3,4-d]pyridazine (L) with phosphorus pentasulfide in anhydrous pyridine in equimolar amounts gave 4-hydroxy-1,2,5-thidiazolo[3,4-d]pyridazine-7-thione (LI); however, using 2 moles of phosphorus pentasulfide in anhydrous pyridine 1,2,5-thiadiazolo[3,4-d]pyridazine-4,7-dithione (LII) was obtained. Methylation of LIII gave 4,7-bis(methylthio)-1,2,5-thiadiazolo[3,4-d]pyridazine (LIII).

The last series of reactions of this series of compounds generated not only some new mono-substituted 1,2,5-thiadiazolo[3,4-d]pyridazines; a new pyridazine was obtained by cleavage of the thiadiazole ring. The reaction of phosphorus oxychloride in α-picoline with 1,2,5-thiadiazolo-[3,4-d]pyridazine-4,7-dione gave 7-chloro-1,2,5-thiadiazolo[3,4-d]pyridazin-4-one (LVIII). Attempts to isolate and prepare the 4,7-dichloro derivative failed. Reaction of LVIII with sodium hydroxide generated the new pyridazine which was identified as 4,5-diamino-6-chloropyridazine-3-one (LIX).

The method of Reicheneder and Dury,[102] was used to synthesize the starting material 4,5-diaminopyridazin-3-one (LIV). The reaction of thionyl chloride and pyridine with 4,5-diaminopyridazin-3-one (LIV) led to the formation of 1,2,5-thiadiazolo[3,4-d]pyridazin-3-one (LV), which was also synthesized *via* the catalytic dechlorination of LVIII with hydrogen over palladium on carbon. The reaction of LV with phosphorus pentasulfide in anhydrous pyridine led to the synthesis of 1,2,5-thiadiazolo[3,4-d]pyridazine-3-thione (LVI). Finally methylation of

LVI with methyl iodide and base gave 4-methylthio-1,2,5-thiadiazolo [3,4-d]-pyridazine (LVII).

Synthesis of v-Triazolo [4,5-d] pyridazines

Compounds LX-LXVIII were synthesized by the method of Aldous and Castle.[2] 4-Methoxy-7-methyl-v-triazolo [4,5-d] pyridazine (LXVIII) was allowed to react with the appropriate ω-dialkylaminoalkylamines to yield the appropriately substituted compounds (LXIXa-d). 4-(3-Dimethyl-aminopropylamino)-7-methyl-v-triazolo [4,5-d] pyridazine (LXIXb) was the only one isolated as the dihydrochloride; the other compounds were isolated as the free bases. When 4-methoxy-7-methyl-v-triazolo [4,5-d] pyridazine (LXVIII) was allowed to react with ammonia under pressure and heat; 4-amino-7-methyl-v-triazolo [4,5-d] pyridazine (LXX) was formed. Compound LXVIII was also hydrolyzed with acetic acid/hydrochloric acid to give 4-hydroxy-7-methyl-v-triazolo [4,5-d] pyridazine (LXXI). When compound LXVIII was refluxed with phosphorus pentasulfide in anhydrous pyridine, 7-methyl-v-triazolo [4,5-d] pyridazine-4-thione (LXXII) was obtained. The final reaction in this series was the methylation of LXXII with methyl iodide to give 4-methylthio-7-methyl-v-triazolo [4,5-d] pyridazine (LXXIII).

Synthesis of Pyrimidines

Uracil (LXXX) (2,4-pyrimidinedione) was converted into the 5-nitro derivative (LXXXI) by boiling LXXX in fuming nitric acid by the method of Brown.[16] Compound LXXXI was converted to 2,4-dichloro-5-nitropyrimidine by the action of phosphorus oxychloride in accordance with the method of

Whittaker.[135] Refluxing LXXXII with two moles of aniline gave 2,4-dianilino-5-nitropyrimidine in accordance with the procedure of Dille.[36] However, when one mole of aniline was used a new pyrimidine, 2-hydroxy-4-anilino-5-nitropyrimidine (LXXXIII) was formed. Nitration of 2,4-dianilino-5-nitropyrimidine proceeded smoothly to give 2,4-bis(p-nitroanilino)-5-nitropyrimidine (LXXXV).

The compound LXXIV, 4,6-dihydroxy-5-nitropyrimidine was prepared by the method of Daly,[34] by allowing 4,6-dihydroxypyrimidine to react with nitric acid. Refluxing LXXIV with phosphorus oxychloride in accordance with the method of Boon[12] led to the synthesis of 4,6-dichloro-5-nitropyrimidine (LXXV).

When two moles of aniline were reacted with LXXV, 4,6-dianilino-5-nitropyrimidine (LXXVIII) was formed. Nitration of LXXVIII with concentrated nitric acid gave 4,6-bis(p-nitroanilino)-5-nitropyrimidine (LXXVII). N-oxidation of LXXVIII with trifluoroperacetic acid led to the synthesis of 4,6-bis(anilino)-5-nitropyrimidine 1-oxide (LXXIX).

The reaction of 4,6-dichloro-5-nitropyrimidine (LXXVI) with the appropriate ω-dialkylaminoalkylamines gave the corresponding 4,6-bis-(dialkylaminoalkylamino)-5-nitropyrimidine dihydrochlorides (LXXVIa-e). The dihydrochloride salts of these amine derivatives were generated as the reaction proceeded in the flask and the product directly isolated as the dihydrochloride salt.

Tetrachloropyrimidine (LXXXVI) was prepared by the method of Childress and McKee.[25] Compound LXXXVI was reacted with sodium azide in anhydrous dimethylsulfoxide to give compound LXXXVII. The structure

of 2,4,6-triazido-5-chloropyrimidine (LXXXVII) has not been determined. It may have one or more of the azide groups cyclized to a tetrazolo structure. Infrared spectra of LXXXVII indicate the presence of azido group(s) at 2150 cm^{-1} and 2090 cm^{-1}. The reaction of 2,4,6-triaminopyridine (LXXXVIII) with picryl fluoride in anhydrous dimethylsulfoxide led to the isolation of 2,4,6-tripicrylaminopyrimidine (LXXXIX).

Synthesis of Pyridazines and Pyridazine N-Oxides

6-Amino-3-chloropyridazine (XCIII) was synthesized by the action of ammonia on 3,6-dichloropyridazine (XC) in accordance with the procedure of Druey and Meier.[38] The action of 3,6-dichloropyridazine with aniline led to the synthesis of 3,6-dianilinopyridazine (XCI) following the procedure of Kumagai.[76] Compound XCI was nitrated with concentrated nitric acid to give 3,6-dipicrylaminopyridazine (XCII).

By the procedure of Itai and Nakashima[65,66] 3-chloro-6-aminopyridazine 1-oxide (XCIV) was prepared. Reaction of XCIV with benzyl mercaptan in base afforded 6-amino-3-benzylthiopyridazine 1-oxide (XCV). With sodium ethoxide, 3-chloro-6-aminopyridazine 1-oxide (XCIV) was smoothly converted into 6-amino-3-ethoxypyridazine 1-oxide (XCVI). The reaction of XCIV with hydrazine led to the preparation of 6-amino-3-hydrazinopyridazine 1-oxide (XCVII).

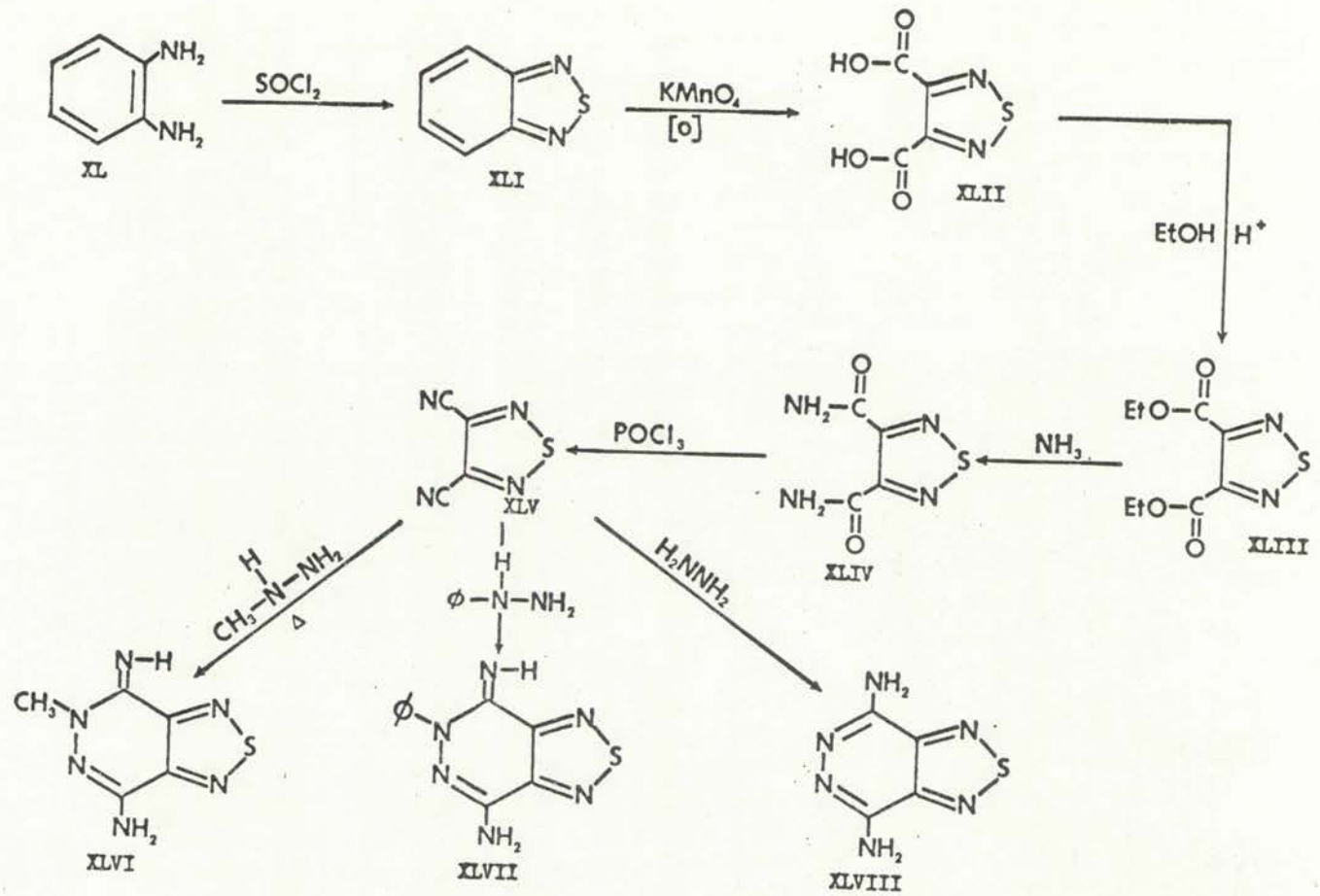
Reaction of 6-amino-3-hydrazinopyridazine 1-oxide (XCVII) with m-nitroacetophenone, o-nitroacetophenone, acetophenone, and benzaldehyde gave the appropriately substituted benzylidenehydrazino derivatives C, CI, CII, and XCVIII. The reaction of 6-amino-3-(benzylidenehydrazino)-

pyridazine 1-oxide with 2,4-dinitrofluorobenzene gave 6-(2,4-nitroanilino)-3-(benzylidenehydrazino)pyridazine 1-oxide)(XCIX).

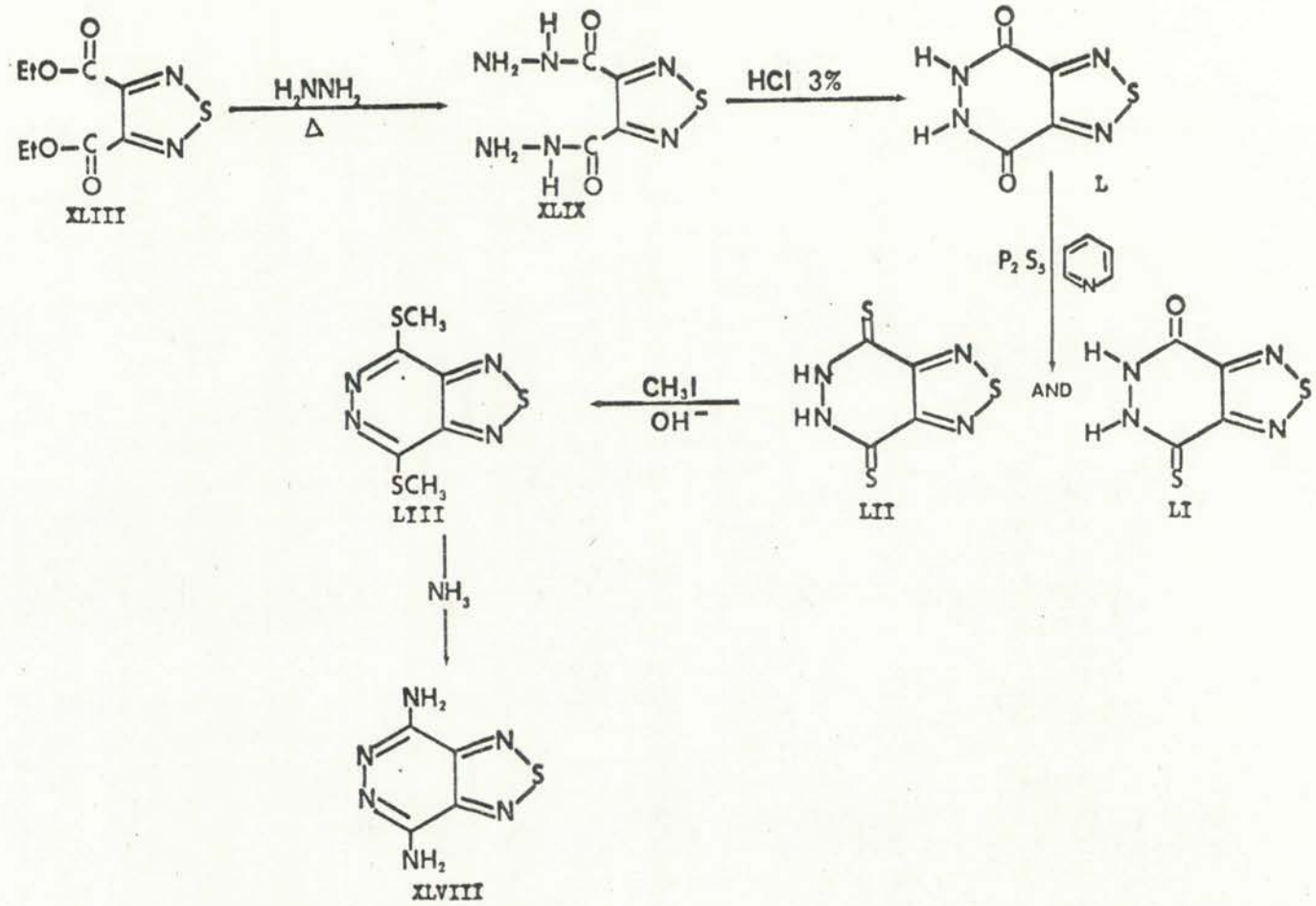
Reaction of 4,5-diaminopyridazin-3-one (LIV) with 2,3-butanedione gave 2,3-dimethylpyrazino [2,3-d] pyridazin-5-one (CIII). The reaction of 5-hydrazino-4-chloropyridazin-3-one (CIV) with acetophenone gave 4-chloro-5-(@-nitrobenzylidenehydrazino)pyridazin-3-one (CV). 3,6-Dimethyl-4-amino-pyridazine 1-oxide (CVI) was prepared by the method of Nakagome.[87] Compound CVI was allowed to react with dilute nitric acid followed by basic oxidation with permanganate to give 6,6',2,2'-tetramethyl-4,4'-azo-pyridazine 1,1'-dioxide (CVII). Cleavage of 7-chloro-1,2,5-thiadiazolo-[3,4-d] pyridazine with 5% sodium hydroxide led to the synthesis and isolation of the new pyridazine 4,5-diamino-6-chloropyridazin-3-one (LIX).

The synthetic routes are shown in Section III. Antibacterial and antifungal activities are shown in the tables of Section V.

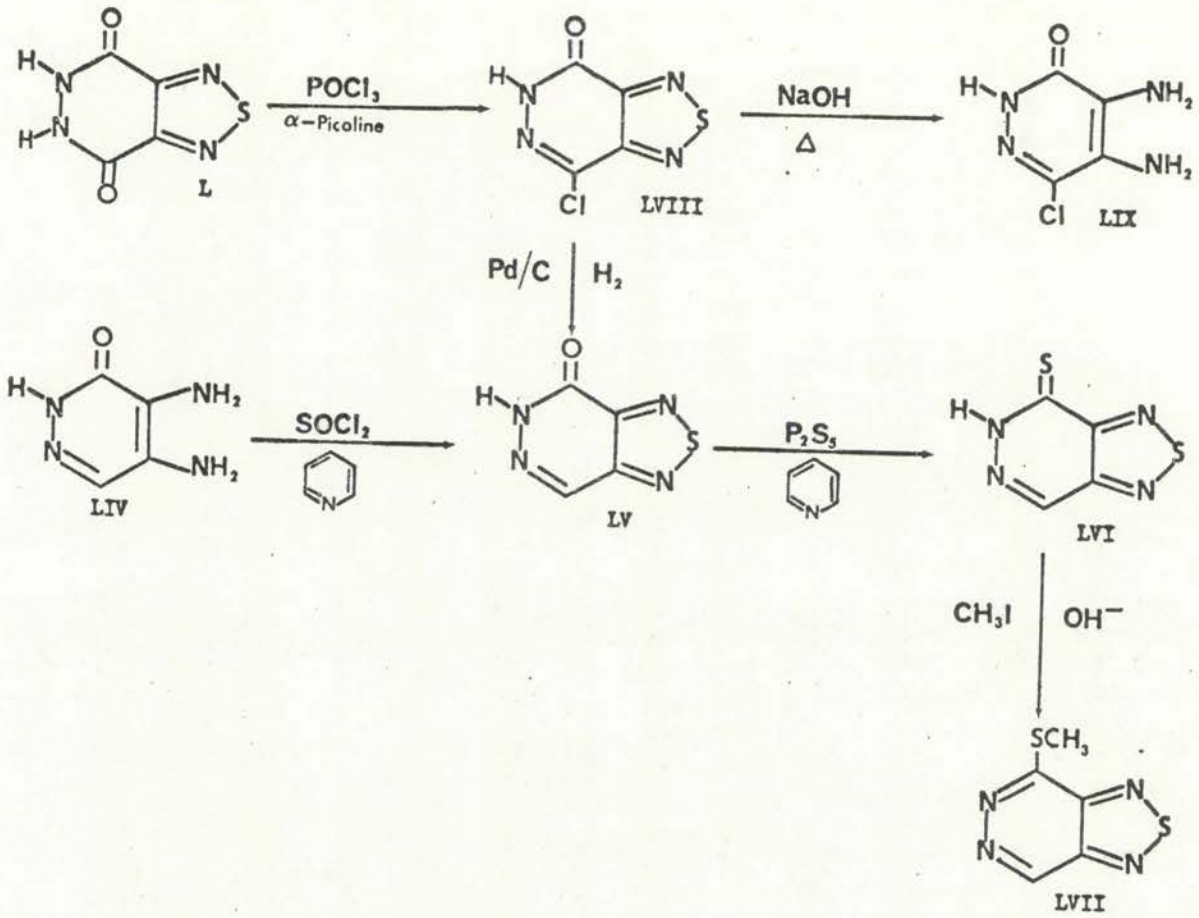
III. Synthetic Routes

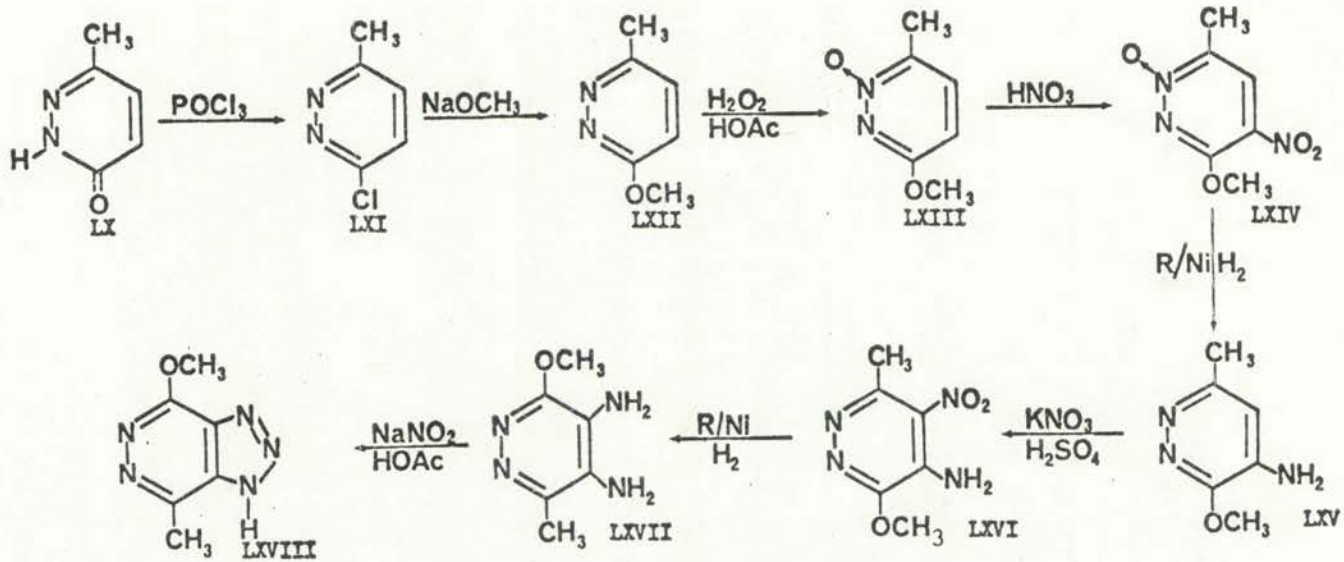


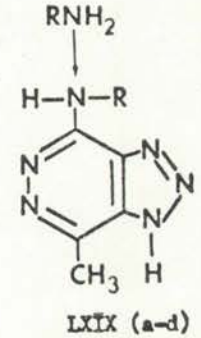
III. SYNTHETIC ROUTES



XLIII XLIX L LII LI LIII XLVIII


POCl3
α–Picoline
NaOH
Δ
Pd/C
H2
SOCl2
P2S5
CH3I
OH−
L
LVIII
LIX
LIV
LV
LVI
LVII





LXIX (a-d)

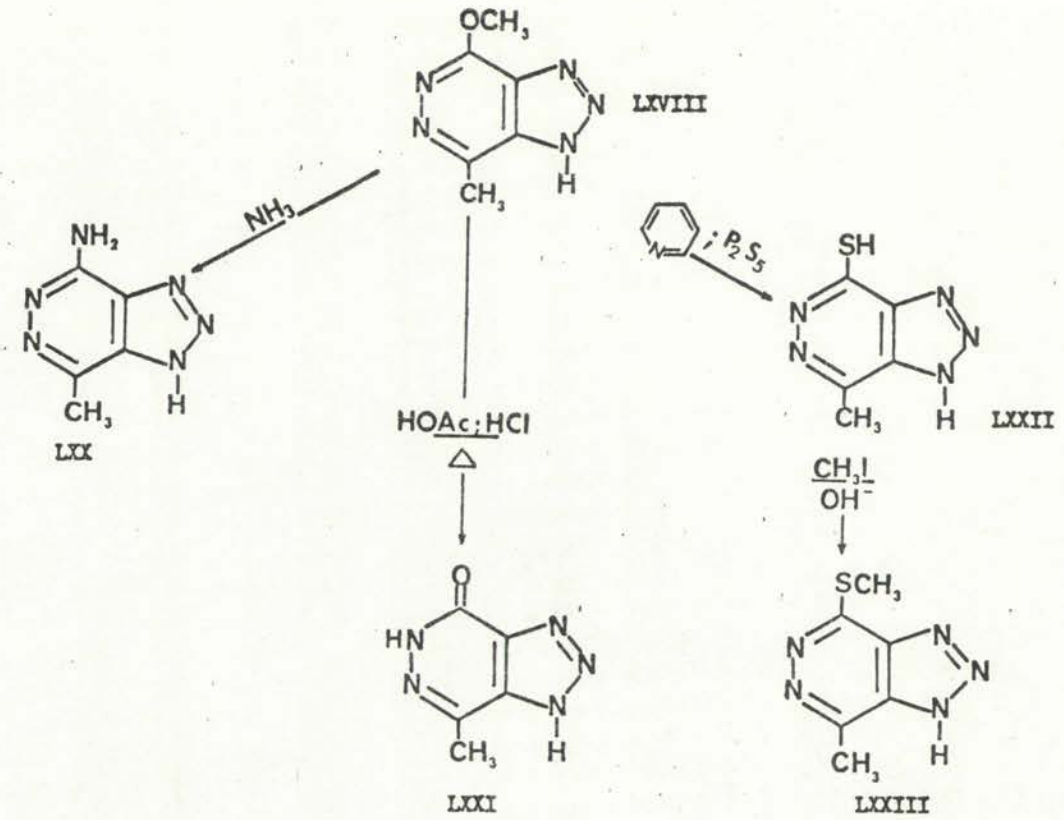
R =

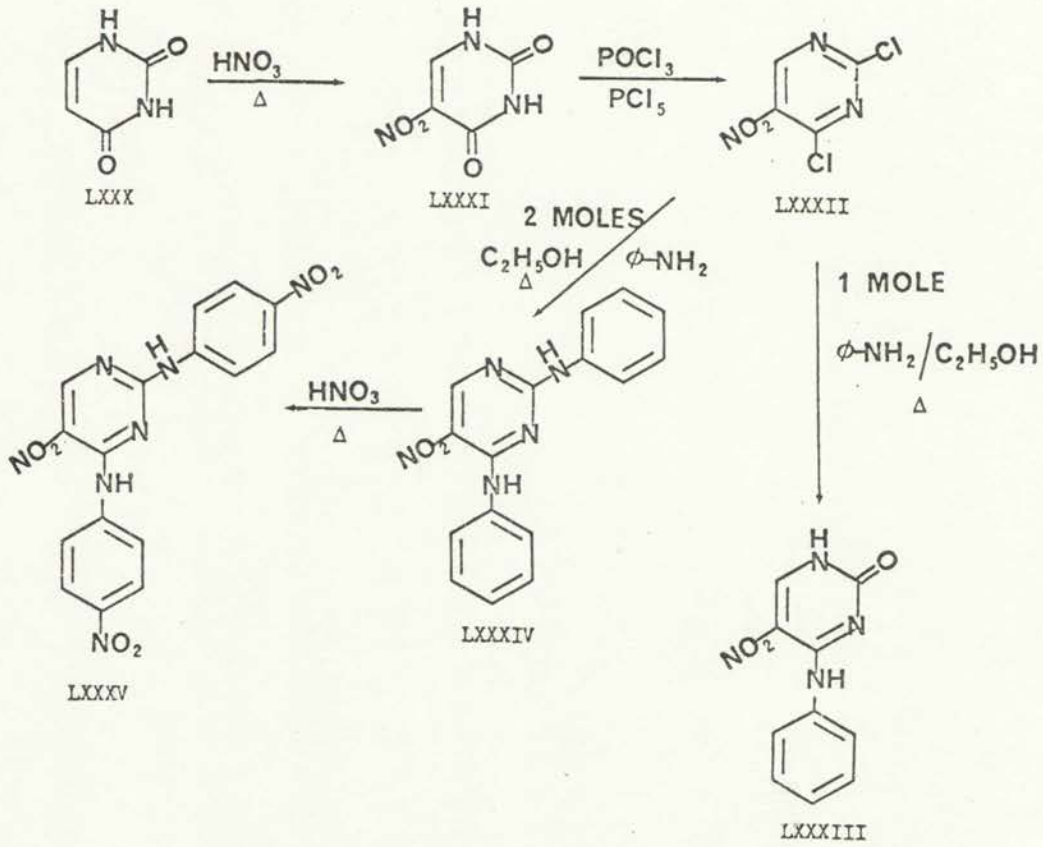
a. $-(CH_2)_2-N-(CH_3)_2$

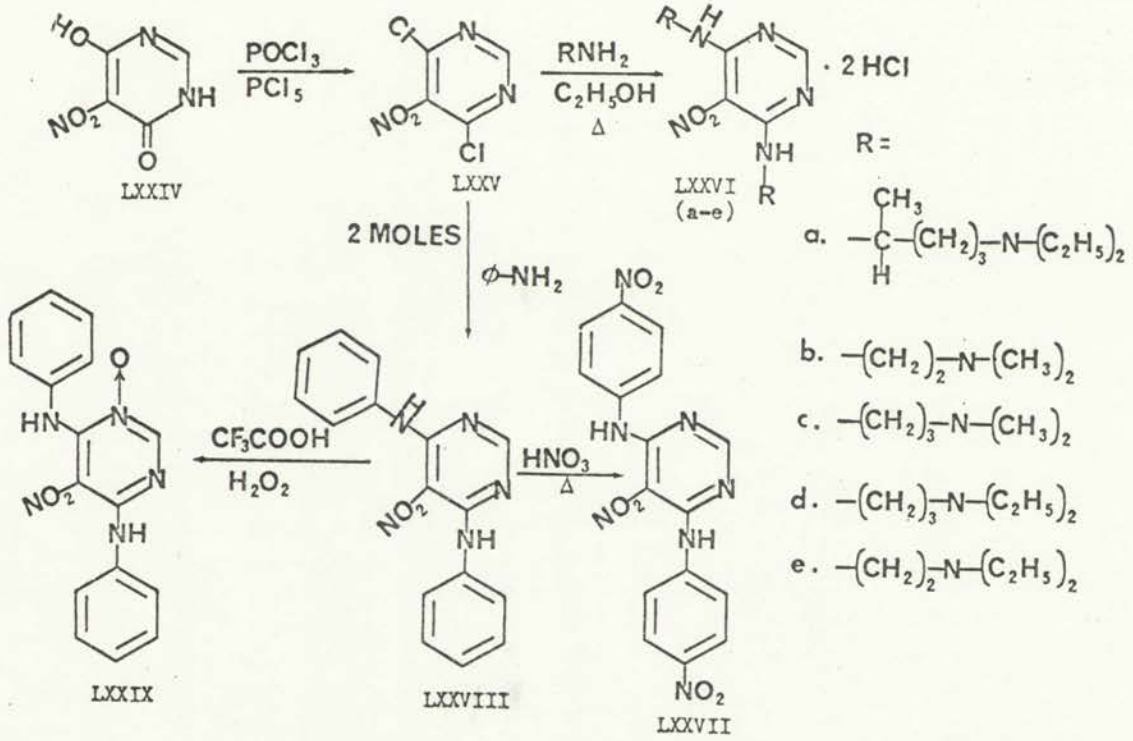
b. $-(CH_2)_3-N-(CH_3)_2$ (di-HCl)

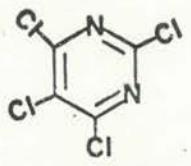
c. $-(CH_2)_3-N-(CH_2CH_3)_2$

d. $-(CH_2)_2-N-(CH_2CH_3)_2$


OCH3
LXVIII
NH3
NH2
CH3
LXX
HOAc:HCl
P2S5
SH
CH3
H
LXXII
CH3I
OH⁻
SCH3
LXXI
LXXIII

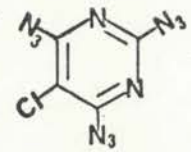

HNO3
Δ
POCl3
PCl5
2 MOLES
C2H5OH
Δ
Φ-NH2
1 MOLE
Φ-NH2/C2H5OH
Δ
HNO3
Δ
LXXX
LXXXI
LXXXII
LXXXIII
LXXXIV
LXXXV


POCl3
PCl5
RNH2
C2H5OH
Δ
· 2 HCl
R =
LXXIV
LXXV
LXXVI
(a-e)
2 MOLES
ØNH2
a. –C(CH3)H–(CH2)3–N–(C2H5)2
b. –(CH2)2–N–(CH3)2
c. –(CH2)3–N–(CH3)2
d. –(CH2)3–N–(C2H5)2
e. –(CH2)2–N–(C2H5)2
CF3COOH
H2O2
HNO3
Δ
LXXIX
LXXVIII
LXXVII

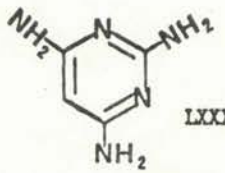


LXXXVI

NaN_3
DMSO

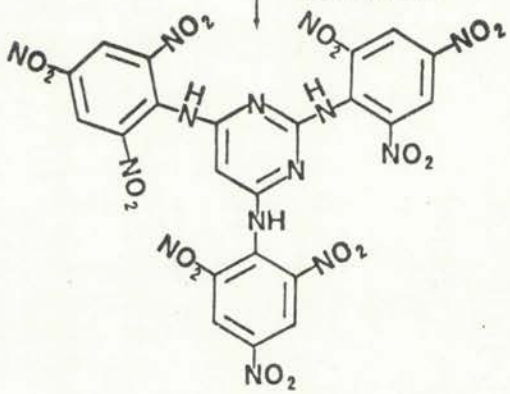


LXXXVII

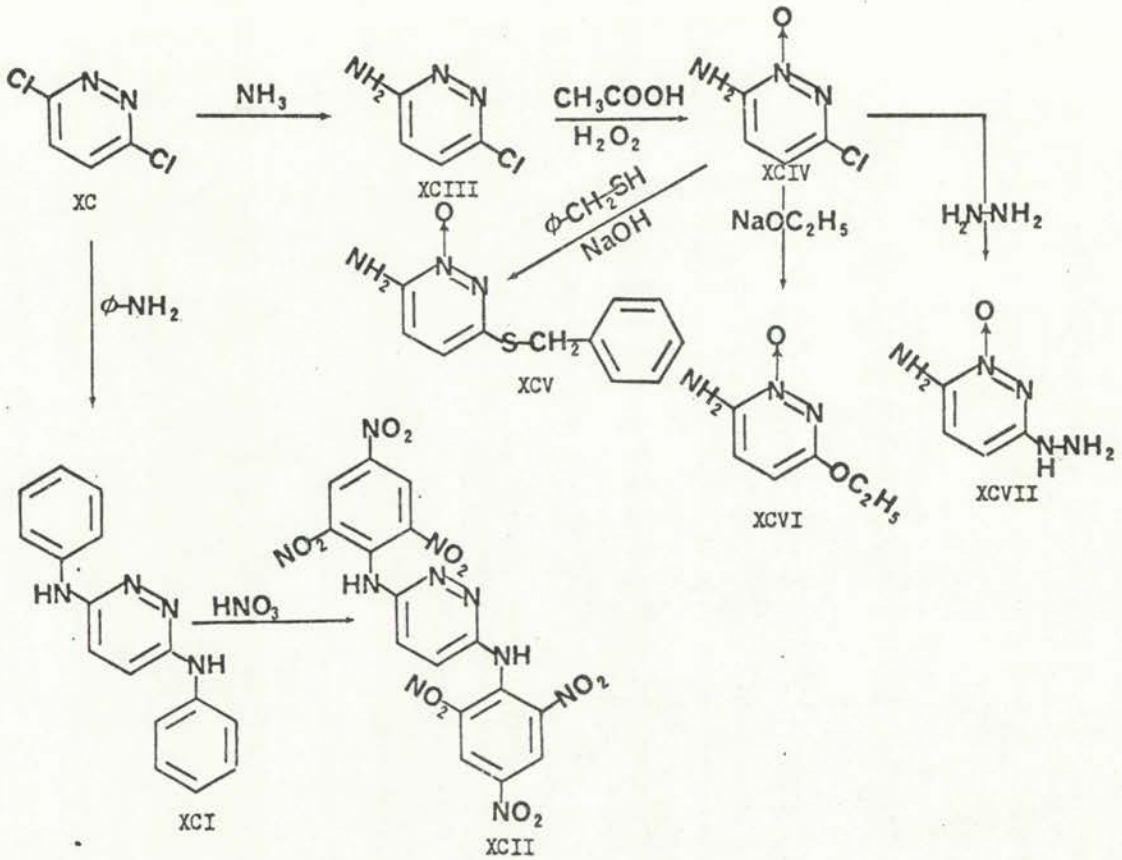


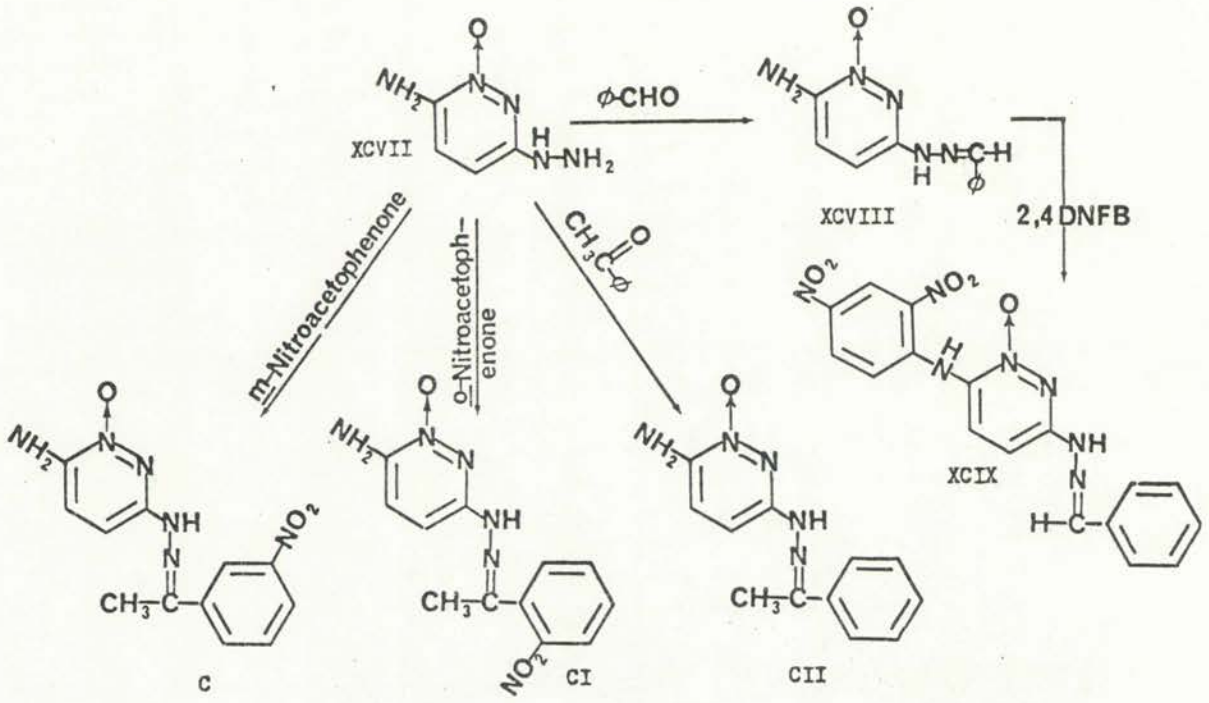
LXXXVIII

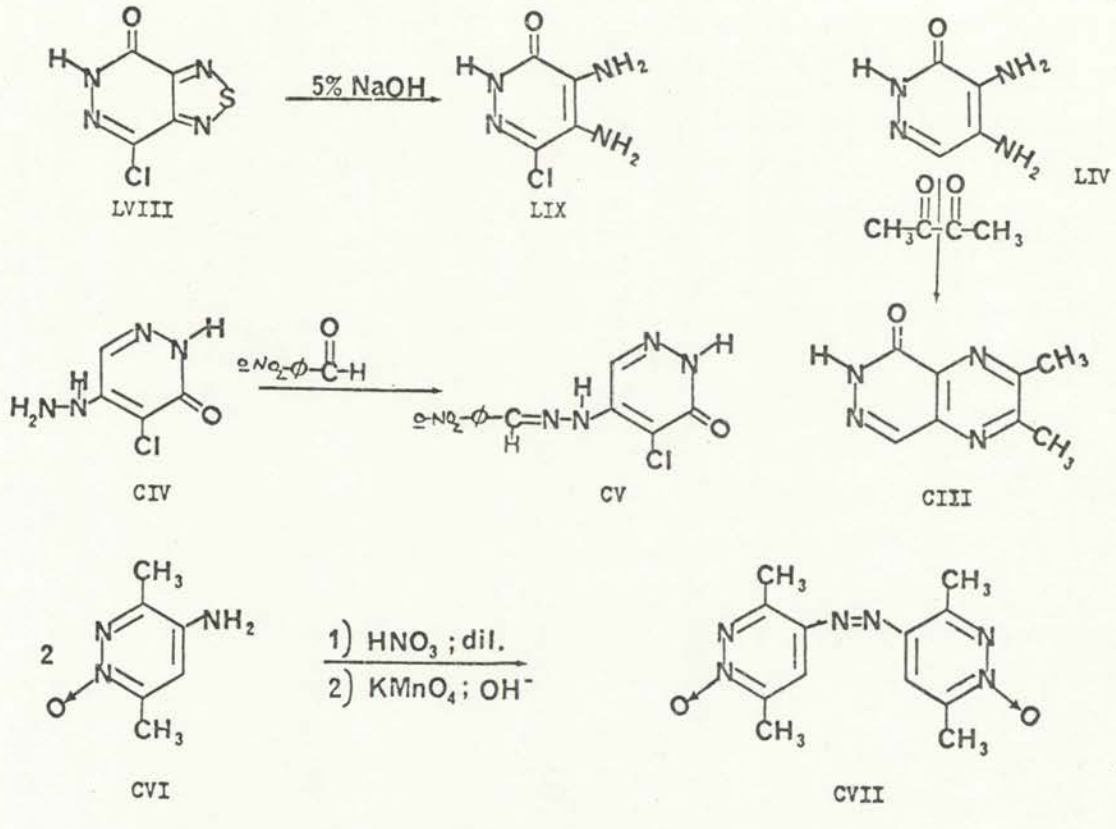
PICRYL
FLOURIDE



LXXXIX


XC
XCIII
XCIV
XCV
XCVI
XCVII
XCI
XCII
NH3
CH3COOH
H2O2
NaOC2H5
H2N-NH2
NaOH
HNO3


XCVII
ϕCHO
XCVIII
2,4 DNFB
m-Nitroacetophenone
o-Nitroacetophenone
CH3C(=O)ϕ
XCIX
C
CI
CII


5% NaOH
LVIII
LIX
LIV
CIV
CV
CIII
2
1) HNO3 ; dil.
2) KMnO4 ; OH-
CVI
CVII

IV. Experimental

EXPERIMENTAL

All melting points were recorded on a Thomas-Hoover melting point apparatus and are uncorrected. The nmr were recorded on a Varian H-60-A with the standard and conditions indicated for each compound. The ir spectra were recorded in potassium bromide discs with a Perkin-Elmer 337 spectrophotometer. The uv spectra were determined with a Cary 14R spectrophotometer in the solvent indicated.

7-Chloro-1,2,5-thiadiazolo [3,4-d] pyridazin-4-one (LVIII)

To a mixture of 5.0 g. (0.294 mole) of 1,2,5-thiadiazolo [3,4-d]-pyridazine-4,7-dione (L) and 150 ml. of phosphorus oxychloride was added slowly 20 ml. of freshly distilled α-picoline at room temperature. The mixture was heated under reflux for three hours. During the early stages of reflux, the white solid dissolved and the solution became cherry red. About 90% of the excess phosphorus oxychloride was then removed under reduced pressure and the dark syrup was allowed to stand overnight in a desiccator over phosphorus pentoxide. The mixture was then poured cautiously into 150 g. of crushed ice, maintaining the temperature near 0°. The beige-colored solid which separated was filtered quickly from the acid solution, washed thoroughly with chilled water and air dried, giving 3.75 g. (yield 67%) of crude product. Repeated recrystallization from petroleum ether (90°-120°) gave white needles m.p. 214-215°; uv λ max (95% ethanol), 202 (ε, 22,100) 248 (ε, 13,500), 267 (sh) (ε, 5,400), 276 (sh) (ε, 3,900), 327 nm (ε, 6,200); ir cm^{-1}: 3435(m), 3250(m), 3190(m),

3160(m), 3075(m), 2975(m), 2940(m), 2890(m), 2860(m), 1695(s), 1675(m), 1560(m), 1490(m), 1450(m), 1420(s), 1350(m), 1340(m), 1290(s), 1170(s), 1125(m), 995(s), 855(s), 840(m), 820(m), 785(m), 610(m), 605(m), 560(w), 510(m), 505(s).

Anal. Calcd. for $C_4H\,ClN_4OS$: C, 25.47; H, 0.54; N, 29.71. Found: C, 25.85; H, 0.52; N, 29.57.

1,2,5-Thiadiazolo [3,4-d] pyridazin-4-one (LV)

Method A.

4,5-Diamino-3-pyridazin-one (LIV) (1.0 g., 0.013 mole) was added slowly to 20 ml. of thionyl chloride at room temperature. After the addition of the pyridazone was complete, 2 ml. of dry pyridine was added to the reaction mixture. The resulting mixture was then refluxed overnight and an aliquot was subjected to tlc with ethyl acetate-silica gel in order to monitor the progress of the reaction. The reaction mixture was then evaporated to dryness under reduced pressure, followed by boiling for 10 minutes with 25 ml. of a 1% sodium hydroxide solution to remove residual pyridine. Glacial acetic acid was added dropwise until the solution was neutral to universal indicator paper, then evaporated to dryness on a rotary evaporator. The yellow powder was dissolved in a minimum amount of 70% ethanol and allowed to stand overnight in the refrigerator. Filtration and drying gave 0.985 g. (50%) of crude product. Recrystallization from 95% ethanol (Norite) gave white fluffy needles, m.p. 218-219°; uv λ max (95% ethanol), 243 (ε, 10,600), 267 (sh) (ε, 2,400), 327 nm (ε, 4,500); ir cm^{-1}: 3450(m), 3210(m),

3060(m), 2975(m), 1675(s), 1480(m), 1440(w), 1400(m), 1360(m), 1275(s), 1150(m), 1070(m), 910(s), 840(m), 830(s), 790(m), 625(m), 585(s), 560(w), 560(s), 460(m); nmr spectrum (deuterium oxide/sodium deuteroxide/DDS) δ 8.90 (singlet C_7H).

Anal. Calcd. for $C_4H_2N_4OS$: C, 31.17; H, 1.31; N, 36.37. Found: C, 31.41; H, 1.37; N, 36.23.

Method B.

7-Chloro-1,2,5-thiadiazolo[3,4-d]pyridazin-4-one (LVIII) (1.0 g., 0.0058 mole) 150 ml. of methanol and 1 ml. of concentrated ammonium hydroxide were mixed together. To this was added 0.50 g. of 10% palladium on charcoal. The solution was hydrogenated at room temperature under atmospheric pressure for 14 hours. The solution was warmed, filtered and evaporated to dryness to give 0.628 g., (77%) of a yellow compound. Repeated recrystallization from 95% ethanol gave white fluffy needles, m.p. 218-219°. No depression of m.p. was observed upon admixture with the product obtained from Method A. The ir and uv spectra were identical with those of the compound synthesized by Method A.

1,2,5-Thiadiazolo[3,4-d]pyridazine-4-thione (LVI)

1,2,5-Thiadiazolo[3,4-d]pyridazin-4-one (LV) (3.0 g., 0.02 mole) was dissolved in 150 ml. of dry pyridine and the mixture was heated under reflux with stirring. Phosphorus pentasulfide (6.33 g., 0.029 mole) was added slowly and the mixture heated in an oil bath at 125-130° for six hours. The excess pyridine was removed under reduced pressure and 150 ml. of ice water was added to replace the pyridine. The mixture was warmed on

a steam bath for 30 minutes and a small amount of ammonium hydroxide (28%) was added to dissolve the suspended solids. The solution was then heated to boiling, treated with Norite, and filtered. The dark red filtrate was acidified with concentrated hydrochloric acid to pH 1 and allowed to cool in the refrigerator overnight. After subsequent filtration and drying, the solid residue amounted to 1.06 g. (32%), m.p. 180-182° dec. Purification of a sample for analysis was accomplished by acid-base precipitation. A pumpkin-yellow powder was obtained; uv λ max (95% ethanol) 204 (ε, 13,800), 210 (sh) (ε, 13,300), 324 nm (ε, 5,700); ir cm^{-1}: 3415(s), 3330(s), 3200(s), 2980(m), 2960(s), 1650(s), 1595(s), 1590(m), 1490(s), 1385(m), 1315(w), 1295(m), 1250(s), 1170(m), 1070(s), 935(m), 885(m), 745(m), 675(m), 610(w), 470(w), 425(w); nmr (deuterium oxide/sodium deuteroxide/DDS) δ 8.15 (singlet C_7H).

Anal. Calcd. for $C_4H_2N_4S_2 \cdot H_2O$: C, 25.54; H, 2.14; N, 29.79. Found: C, 25.67; H, 1.93; N, 29.91.

4-Methylthio-1,2,5-thiadiazolo[3,4-d]pyridazine (LVII)

Methyl iodide (4.26 g., 0.003 mole) in 10 ml. of ethanol wad added in portions to 0.5 g. (0.0029 mole) of 1,2,5-thiadiazolo[3,4-d]pyridazine-4-thione (LVI) dissolved in a mixture of 10 ml. of 10% potassium hydroxide and 5 ml. of 28% ammonium hydroxide. The mixture was stirred for five-hours at room temperature, cooled in ice, and the product was collected by filtration, washed with ice water and dried over phosphorus pentoxide in a desiccator. The yield of crude product was 0.345 g. (64%). The product was recrystallized from ethanol-water (Norite), light tan crystals, m.p. 148-150°; uv λ max (95% ethanol) 218 (ε, 9,300),

238 (sh) (ε, 6,400), 260 (ε, 3,700), 301 nm (ε, 1,300); ir cm^{-1}: 3340(s), 3270(s), 3195(s), 1655(s), 1620(s), 1590(s), 1575(s), 1540(m), 1520(w), 1475(m), 1445(w), 1420(s), 1390(w), 1375(m), 1355(m), 1260(m), 1185(m), 1115(s), 1045(m), 970(m), 900(s), 855(m), 805(s), 670(m), 590(m), 555(s); nmr (deuterium oxide/sodium deuteroxide/DDS) δ 8.32 (singlet C_7H), δ 2.64 (singlet-SCH_3).

Anal. Calcd. for $C_5H_4N_4S_2$: C, 32.61; H, 2.19; N, 30.44. Found: C, 32.62; H, 2.44; N, 30.64.

1,2,5-Thiadiazolo [3,4-d] pyridazin-4-one-7-thione (LI)

1,2,5-Thiadizolo [3,4-d] pyridazine-4,7-dione (L) (4.13 g., 0.024 mole) was added to 200 ml. of dry pyridine and the mixture was heated under reflux. Phosphorus pentasulfide (7.33 g., 0.033 mole) was added slowly (Caution! Frothing occurs.) in small portions to the boiling solution. The mixture was then heated for four hours and allowed to cool several degrees. The excess pyridine was removed under reduced pressure. The black, syrupy residue was added to 250 ml. of ice and water. The mixture was digested on a steam bath for one hour, followed by the addition of a few sodium hydroxide pellets to bring all the solids into solution. The solution was treated with Norite and the volume reduced to 60 ml. by rotary evaporation. The solution was then acidified with concentrated hydrochloric acid to pH 1, and allowed to stand in the refrigerator overnight. The orange-colored compound was filtered and dried to give 3.4 g. (76%) of crude product, m.p. 238-239°dec. An analytical sample was prepared by acid-base (Norite) precipitation; uv λ max (0.1 N-

sodium hydroxide) 266 nm (ε, 19,100); ir cm^{-1}: 3400(s), 3325(s), 3245(m), 3000(m), 2950(m), 2875(m), 1630(s), 1550(s), 1470(s), 1380(m), 1355(m), 1295(s), 1050(m), 990(m), 960(w), 855(s), 845(m), 640(m), 545(m), 510(s).

Anal. Calcd. for $C_4H_2N_4OS_2 \cdot \frac{1}{2}H_2O$: C, 24.62; H, 1.55; N, 28.72. Found: C, 24.40; H, 1.37; N, 28.38.

1,2,5-Thiadiazolo [3,4-d] pyridazine-4,7-dithione (LII)

1,2,5-Thiadiazolo [3,4-d] pyridazine-4,7-dione (L) (7.88 g., 0.0463 mole) was heated with 200 ml. of dry pyridine while stirring. To the refluxing solution was added slowly (Caution! Frothing occurs.) in small portions 20.67 g. (0.093 mole) of phosphorus pentasulfide. The solution was heated under reflux for six hours. The excess pyridine was removed by distillation under reduced pressure. The black tar-like residue was added slowly to 200 ml. of ice and water. The solution was digested on a steam bath for one hour, followed by the addition of a few pellets of sodium hydroxide to dissolve the few remaining suspended solids. The dark solution was treated with Norite, filtered, and acidified to pH 1 with hydrochloric acid. The dark red product was refrigerated overnight, filtered and dried over phosphorus pentoxide, giving 5.78 g. (62%) of crude material, m.p. 224° dec. An analytical sample was prepared by repeated reprecipitation (acid-base)(Norite), to give a dark red powder; uv λ max (0.1 N-sodium hydroxide) 256 (ε, 25,700), 292 (sh) nm (ε, 5,300); ir cm^{-1}: 3380(s), 3320(s), 3235(m), 3125(m), 3010(w), 1625(s), 1530(s), 1475(s), 1375(m), 1350(m), 1300(s), 1250(s), 1190(w), 1120(s), 990(w), 960(w), 915(m), 860(m), 620(w), 505(w).

Anal. Calcd. for $C_4H_2N_4S_3$: C, 23.75; H, 1.00; N, 27.70. Found: C, 23.53; H, 0.89; N, 28.04.

4,7-Bis(methylthio)-1,2,5-thiadiazolo [3,4-d] pyridazine (LIII)

Methyl iodide (9.94 g., 0.07 mole) in 50 ml. of ethanol was added portionwise to 6.85 g. (0.034 mole) of 1,2,5-thiadiazolo [3,4-d] pyridazine-4,7-dithione (LII) dissolved in a mixture of 20 ml. of 10% potassium hydroxide and 10 ml. of 28% ammonium hydroxide. During the addition, a yellow-green precipitate began to separate. Stirring was continued for 12 hours at room temperature. The reaction mixture was cooled in ice, the solid was collected, washed with 30 ml. of cold ethanol, dried in a vacuum desiccator and recrystallized from 95% ethanol to give 4.57 g. (59%) of prisms (yellow) m.p. 220-221°. An analytical sample was recrystallized from petroleum ether (90°-120°); uv λ max (95% ethanol) 238 (ε, 15,900), 302 nm (ε, 3,000); ir cm^{-1}: 1625(m), 1500(w), 1425(m), 1400(m), 1385(s), 1350(m), 1335(w), 1290(s), 1050(m), 990(m), 950(w), 860(s), 845(m), 640(m), 545(m), 510(s); nmr (deuteriochloroform-TMS) δ 2.80 ($S-CH_3$ singlet).

Anal. Calcd. for $C_6H_6N_4S_3$: C, 31.28; H, 2.63; N, 24.33. Found: C, 31.64; H, 2.75; N, 24.27.

4,7-Diamino-1,2,5-thiadiazolo [3,4-d] pyridazine (XLVIII)

Method A.

To a solution of 4,5-dicyano-1,2,5-thiadiazole (XLV) (1.5 g., 0.0110 mole) in 50 ml. of 95% ethanol was added slowly, 15 ml. of hydrazine hydrate, while cooling the reaction mixture in ice. After refluxing the mixture for six hours, the product was obtained by evaporating the solvent under reduced pressure. Upon drying overnight in a vacuum desiccator over

sodium hydroxide, 1.28 g. (69%) of a bright red product was obtained. Further recrystallization from 95% ethanol gave an analytical sample (pale orange) m.p. 268°dec; uv λ max (95% ethanol), 206 (ε, 11,400), 259 nm (ε, 13,000); ir cm^{-1}: 3445(m), 3290(m), 3050(m), 1675(m), 1630(s), 1480(s), 1400(w), 1350(m), 1280(m), 1150(m), 1020(w), 870(s), 840(m), 805(w), 740(w), 715(w), 670(w), 620(w), 560(w), 525(w), 520(m), 475(m).

Anal. Calcd. for $C_4H_4N_6S$: C, 28.57; H, 2.40; N, 50.00. Found: C, 28.14; H, 2.23; N, 49.86.

Method B.

A mixture containing 0.250 g. (0.0011 mole) of 4,7-bis(methylthio)-1,2,5-thiadiazolo[3,4-d]pyridazine (LIII) in 50 ml. of absolute ethanol saturated with ammonia at 0-5° was heated in a glass pressure bottle at 150° for 16 hours. The orange solution was evaporated to dryness giving 0.102 g. (56%) of a pale orange residue. The residue was recrystallized from 95% ethanol to give pale orange crystals of 4,7-diamino-1,2,5-thiadiazolo[3,4-d]pyridazine, m.p. 268°dec; with the product prepared via Method A as shown by a comparison of the melting point and the uv and ir spectra.

7-Amino-4-imino-5-methyl-1,2,5-thiadiazolo[3,4-d]pyridazine (XLVI)

3,4-Dicyano-1,2,5-thiadiazole (LXV) (1.0 g., 0.0073 mole) was dissolved in 50 ml. of absolute ethanol. To this rapidly stirred and cooled mixture was added dropwise, 15 ml. of methylhydrazine reagent. The reaction mixture was refluxed for five hours. The black solution

was evaporated to dryness under reduced pressure to give a black powder, 1,32 g. (85%). Repeated recrystallization from 95% ethanol (Norite) gave a black crystalline product, m.p. 209-210°dec; uv λ max (95% ethanol), 210 (ε, 10,000), 268 nm (ε, 11,900); ir cm^{-1}: 3425(m), 3320(m), 3200(m), 1655(m), 1610(s), 1560(m), 1525(m), 1400(m), 1340(m), 1280(m), 1155(m), 1020(w), 960(m), 850(s), 705(m), 670(w), 630(w), 575(w), 555(w), 515(m).

Anal. Calcd. for $C_5H_6N_6S$: C, 32.96: H, 3.33; N, 46.14. Found: C, 33.11; H, 3.14; N, 46.09.

7-Amino-4-imino-5-phenyl-1,2,5-thiadiazolo[3,4-d]pyridazine (XLVII)

To a solution of (1.2 g., 0.0088 mole) of 3,4-dicyano-1,2,5-thiadiazole (XLV) in 50 ml. of absolute ethanol was added dropwise 10 ml. of phenylhydrazine reagent with stirring and cooling on ice. The reaction mixture was refluxed for four hours. This was followed by evaporation to dryness in a rotary evaporator to give a deep red powder, 1.98 g. (92%). The analytical sample was prepared by repeated recrystallization from 95% ethanol (Norite) to give an orange-red crystalline compound, m.p. 204-205°dec.; uv λ max (95% ethanol), 204 (ε, 20,800), 258 nm (ε, 13,400); ir cm^{-1}: 3430(m), 3335(m), 3300(m), 1600(m), 1550(s), 1485(m), 1445(s), 1395(m), 1335(w), 1280(m), 1250(w), 1160(m), 1125(m), 1080(w), 1050(w), 990(w), 960(w), 850(m), 845(m), 750(m), 705(m), 685(m), 600(w), 535(w), 500(w), 450(m).

Anal. Calcd. for $C_{10}H_8N_6S$: C, 49,15; H, 3.31; N, 34.43. Found: C, 49.31; H, 3.40; N, 34.30.

v-Triazolo[4,5-*d*]pyridazines

7-Methyl-v-triazolo[4,5-d]pyridazine-4-thione (LXXII)

4-Methoxy-7-methyl-v-triazolo[4,5-d]pyridazine (LXXVIII) (3.0 g., 0.0182-mole) was added to 125 ml. of dry pyridine and the mixture was heated to reflux temperature. Phosphorus pentasulfide (9.0 g., 0.025 mole) was added slowly, (caution, frothing occurs), to the refluxing mixture. The solution was heated under reflux for 6 hours. The excess pyridine was removed by evaporation under reduced pressure. The black, syrupy residue was poured into 250 ml. of ice-water mixture. The mixture was heated on a steam cone, and a few sodium hydroxide pellets were added to bring all the suspended solids into solution. The solution was treated with Norite, filtered, and concentrated down to 50 ml. by boiling on a hot plate. The solution was then acidified to pH 1, and allowed to cool in the refrigerator overnight to give 1.65 g. (54%) crude material. The product was purified by acid-base precipitation (Norite), m.p. 285° dec.; uv λ max (0.1N NaOH) 226 (ε, 14,700), 266 nm (ε, 3,700); ir cm^{-1}: 3520(m), 3450(m), 3150(s), 3040(s), 2855(s), 2125(w), 1850(m), 1700(w), 1590(m), 1575(m), 1510(m), 1460(m), 1450(s), 1435(m), 1410(s), 1385(s), 1340(m), 1280(s), 1180(m), 1140(s), 1105(m), 1075(s), 1090(m), 1070(m), 1050(m), 970(s), 960(m), 730(s), 625(w), 585(s), 525(w); nmr spectrum (D_2O/NaOD/DDS) δ 2.45 (singlet C_7-CH_3).

Anal. Calcd. for $C_5H_5N_5S$: C, 35.91; H, 3.02; N, 41.90. Found: C, 35.77; H, 3.01; N, 41.47.

4-Methylthio-7-methyl-v-triazolo[4,5-d]pyridazine (LXXIII)

7-Methyl-v-triazolo[4,5-d]pyridazine-4-thione (LXXII) (0.150 g.,

0.0009 mole) was added to 15 ml. of a 1.5 N potassium hydroxide solution. To this mixture 1 ml. of methyl iodide dissolved in 10 ml. of ethanol was added slowly. The reaction mixture was stirred at room temperature for eight hours, cooled, and the product collected by filtration, washed with 10 ml. of ice water and dried, crude yield 0.130 g. (80%). The product was recrystallized from 70% ethanol (Norite) m.p. 260°dec., as white crystalline needles; uv λ max (95% ethanol) 214 (ε, 20,200), 241 (ε, 9,300), 275 (ε, 6,000), 301 nm (ε, 6,000); ir cm^{-1}: 3440(s), 3000(m), 2915(m), 2555(s), 2000(s), 1705(w), 1625(m), 1550(w), 1530(s), 1425(s), 1375(s), 1350(s), 1330(s), 1170(m), 1160(m), 1140(w), 1050(s), 1015(m), 975(m), 720(m), 705(s), 620(s), 525(m); nmr spectrum (D_2O/NaOD/DDS) δ 2.78 (singlet C_4-SC$\underline{H}_3$); δ 2.40 (singlet C_7-C$\underline{H}_3$).

Anal. Calcd. for $C_6H_7N_5S$: C, 39.77; H, 3.90; N, 38.66. Found: C, 39.74; H, 3.81; N, 38.57.

4-Hydroxy-7-methyl-v-triazolo[4,5-d]pyridazine (LXXI)

4-Methoxy-7-methyl-v-triazolo[4,5-d]pyridazine (LXVIII)(0.500 g., 0.003 mole) was added to 0.3 ml. of glacial acetic acid mixed with 3 ml. of 10% hydrochloric acid and heated at reflux for one hour. The reaction was brought to 65° and stirred at this temperature overnight. The mixture was cooled to room temperature, neutralized with saturated sodium bicarbonate, to give a white precipitate. The product was filtered and dried to give 0.350 g. (77%) of white crystalline material. The sample submitted for analysis was purified by sublimation at 0.025mm/300°, m.p. 355°dec.; uv λ max (0.1N NaOH) 216 (ε, 17,200),

264 nm (ε, 3,300); ir cm^{-1}: 3440(m), 3150(m), 1675(s), 1580(m), 1500(w), 1450(w), 1400(w), 1310(m), 1240(m), 1200(s), 1130(m), 1090(m), 1010(m), 980(w), 900(m), 780(s), 640(m), 605(w), 550(m), 480(m); nmr spectrum (D_2O/NaOD/DDS) δ 2.62 (singlet C_7-CH_3).

Anal. Calcd. for $C_5H_5N_5O$: C, 39.74; H, 3.33; N, 46.34. Found: C, 39.64; H, 3.34; N, 46.38.

4-Amino-7-methyl-v-triazolo[4,5-d]pyridazine (LXX)

4-Methoxy-7-methyl-v-triazolo[4,5-d]pyridazine (LXVIII)(1.0 g., 0.006 mole) was dissolved in 40 ml. of 28% ammonium hydroxide and this solution was heated with stirring in a glass bottle at 100° overnight. The pressure bottle was allowed to cool, was opened, and the contents were evaporated to dryness on a rotary evaporator. The solid was collected and recrystallized from dilute ammonium hydroxide (Norite) and neutralized with dilute hydrochloric acid. The crystals separated giving 0.84 g. (92%) m.p. 375°dec.; uv λ max (95% ethanol) 204 (ε, 27,300), 286 (sh) (ε, 6,700), 268 nm (ε, 9,800); ir cm^{-1}: 3150(s), 3100(m), 2965(s), 1660(s), 1580(m), 1540(m), 1495(m), 1450(m), 1410(m), 1380(m), 1270(m), 1180(m), 1160(m), 1110(m), 1055(m), 1025(m), 965(w), 840(m), 780(m), 645(s), 600(m), 545(m), 470(m); nmr spectrum (D_2O/NaOD/DDS) δ 2.47 (singlet C_7-CH_3).

Anal. Calcd. for $C_5H_6N_6$: C, 39.99; H, 4.03; N, 55.97. Found: C, 40.02; H, 4.10; N, 55.92.

4-(Dimethylaminoethylamino)-7-methyl-v-triazolo[4,5-d]pyridazine (LXIXa)

To a solution of 0.495 g. of 4-methoxy-7-methyl-v-triazolo[4,5-d]-

pyridazine (LXVIII)(0.003 mole) in 50 ml. of absolute ethanol was added dropwise 0.270 g. (0.003 mole) of dimethylaminoethylamine. The mixture was refluxed in an oil bath for 16 hours, then the solvent was removed by evaporation under reduced pressure. The viscous semi-solid residue was triturated with 50 ml. of anhydrous ether, followed by vigorous scratching and cooling of the flask on ice to yield a white precipitate. This was filtered, washed with cold ether and dried in a vacuum desiccator over phosphorus pentoxide to give 0.41 g. of product in 62% yield. An analytical sample was prepared by repeated recrystallization from absolute ethanol - anhydrous (Norite) ether, m.p. 262-263°; uv λ max (95% ethanol) 221 (ε, 15,600), 274 nm (ε, 6,600); ir cm^{-1}: 3450(s), 3250(s), 2950(s), 1650(m), 1600(s), 1470(s), 1375(m), 1350(w), 1325(m), 1250(s), 1175(m), 1140(s), 1105(m), 1075(m), 780(m), 745(m), 680(w), 655(m), 615(m), 525(s), 430(m); nmr spectrum (D_2O/DDS) δ 3.86 (H-N-$\underline{CH_2}$-CH_2 triplet), δ 3.48 (-CH_2-$\underline{CH_2}$-N triplet), δ 3.07 -N-($\underline{CH_3}$)$_2$ singlet , δ 2.64 (C_7-$\underline{CH_3}$ singlet).

Anal. Calcd. for $C_9H_{15}N_7$: C, 48.84; H, 6.85; N, 44.31. Found: C, 48.78; H, 6.43; N, 44.09.

4-(3-Dimethylaminopropylamino)-7-methyl-v-triazolo[4,5-d]pyridazine Dihydrochloride (LXIXb)

4-Methoxy-7-methyl-v-triazolo[4,5-d]pyridazine (LXVIII)(0.495 g., 0.003 mole) was dissolved in 50 ml. of absolute ethanol and to this mixture was added 0.414 g. (0.003 mole) of 3-dimethylaminopropylamine. The mixture was refluxed in an oil bath for 16 hours, then the solvent was removed by evaporation under reduced pressure. The residue was

dissolved in water made slightly basic with potassium hydroxide and extracted 4 times with 25 ml. portions of chloroform. The chloroform solution was dried with magnesium sulfate, filtered, and evaporated under reduced pressure to a semi-solid residue. The dihydrochloride salt was prepared by dissolving the residue in anhydrous ether and passing dry hydrogen chloride through the solution. It was purified by solution in absolute ethanol and precipitation by the addition of anhydrous ether to give 0.73 g. (79%) of the dihydrochloride salt, m.p. 255-257°; uv λ max (95% ethanol) 205 (ε, 17,700), 225 (ε, 15,900), 263 nm (ε, 6,200); ir cm^{-1}: 3430(m), 3190(m), 3125(s), 3060(s), 2965(s), 2900(s), 2680(s), 1810(m), 1670(s), 1590(s), 1500(m), 1460(s), 1410(s), 1320(m), 1285(w), 1235(m), 1215(m), 1175(m), 1050(s), 1030(m), 1000(m), 975(s), 945(m), 930(m), 905(w), 880(w), 825(w), 800(w), 775(m), 745(m), 700(m), 685(m), 650(m), 580(w); nmr spectrum (D_2O/DDS) δ 3.87 (H-N-$\underline{CH_2}$-C triplet), δ 3.46 (H-N-CH_2-CH_2-$\underline{CH_2}$-N multiplet), δ 3.00 -N-$(\underline{CH_3})_2$ singlet, δ 2.84 (C_7-$\underline{CH_3}$ singlet), δ 2.40 (-N-CH_2-$\underline{CH_2}$-CH_2-N multiplet).

Anal. Calcd. for $C_{10}H_{19}Cl_2N_7$: C, 38.95; H, 6.21; N, 31.81. Found: C, 38.88; H, 6.43; N, 31.79.

4-(3-Diethylaminopropylamino)-7-methyl-v-triazolo[4,5-d]pyridazine (LXIXc)

To a solution of 0.495 g. of 4-methoxy-7-methyl-v-triazolo[4,5-d]-pyridazine (LXVIII)(0.003 mole) in 50 ml. of absolute ethanol was added dropwise 0.489 g. (0.003 mole) of 3-diethylaminopropylamine. The mixture was refluxed in an oil bath for 16 hours, then the solvent was removed by evaporation on a rotary evaporator. To the semi-solid

material was added 50 ml. of anhydrous ether, and with vigorous scratching and cooling of the flask in ice, a white precipitate was obtained. This was filtered, washed with cold ether and dried in a vacuum desiccator over phosphorus pentoxide to give 0.56 g. of product in 71% yield. An analytical sample was prepared by repeated recrystallization from absolute ethanol-ether (anhydrous) (Norite), m.p. 268°dec.; uv λ max (95% ethanol) 202 (ε, 19,100), 221 (ε, 17,100), 277 nm (ε, 7,800); ir cm^{-1}: 3430(m), 3245(m), 2965(s), 2920(m), 2810(m), 1660(s), 1600(m), 1535(w), 1505(w), 1470(m), 1375(m), 1325(s), 1235(s), 1205(w), 1180(m), 1145(m), 1110(s), 1075(s), 765(m), 655(s), 615(m), 570(w); nmr spectrum (D_2O/DDS) δ 3.75 (H-N-$\underline{CH_2}$-triplet), δ 3.37 -CH_2-N-$(CH_2)_2$ -multiplet, δ 2.85 (C_7-$\underline{CH_3}$singlet), δ 2.20 (C-$\underline{CH_2}$-C multiplet), δ 1.43 (-CH_2-$\underline{CH_3}$-triplet).

Anal. Calcd. for $C_{12}H_{21}N_7$: C, 54.73; H, 8.04; N, 37.23. Found: C, 54.65; H, 7.95; N, 37.25.

4-(Diethylaminoethylamino)-7-methyl-v-triazolo[4,5-d]pyridazine (LXIXd)

To a solution of 0.495 g. of 4-methoxy-7-methyl-v-triazolo[4,5-d]-pyridazine (LXVIII)(0.003 mole) in 50 ml. of absolute ethanol was added dropwise 0.420 g. (0.003 mole) of 3-diethylaminoethylamine. The mixture was refluxed in an oil bath for 16 hours, then the solvent was removed by evaporation under reduced pressure. To the residue was added 50 ml. of anhydrous ether, and with vigorous scratching and cooling of the flask on ice, a white precipitate was obtained. This was filtered, washed with cold ether and dried in a vacuum desiccator

over phosphorus pentoxide to give 0.51 g. of product in 68% yield. An analytical sample was prepared by repeated recrystallization from absolute ethanol-anhydrous ether (Norite), m.p. 275°; uv λ max (95% ethanol) 220 (ε, 17,500), 276 nm (ε, 7,500); ir cm^{-1}, 3425(m), 3245(m), 2975(s), 2925(m), 1665(s), 1595(s), 1545(m), 1495(m), 1455(s), 1365(s), 1325(s), 1245(s), 1200(m), 1190(w), 1150(m), 1070(m), 1040(s), 860(m), 750(s), 680(m), 660(m), 615(m), 560(w), 535(m), 520(w), 470(w); nmr spectrum (D_2O/DDS) δ 3.84 (H-N-$\underline{CH_2}$-CH_2-triplet), δ 3.33 -CH_2N-(CH_2)-multiplet, δ2.74 (C_7-$\underline{CH_3}$ singlet), δ 1.37 (-C-$\underline{CH_3}$ triplet).

Anal. Calcd. for $C_{11}H_{19}N_7$: C, 52.91; H, 7.70; N, 39.32. Found: C, 52.79; H, 7.56; N, 39.36.

Pyrimidines

4,6-bis(5-Diethylamino-2-pentylamino)-5-nitropyrimidine Dihydrochloride (LXXVIa)

To a stirred solution of 1.93 g. of 4,6-dichloro-5-nitropyrimidine (LXXV) (0.01 mole) in 50 ml. of absolute ethanol was added dropwise 3.16 g. of 5-diethylamino-2-pentylamine (0.02 mole). The mixture was refluxed for three hours, then the solvent was removed under reduced pressure to give the yellow dihydrochloride salt (1.65 g., 33%). It was purified by solution in absolute ethanol and precipitation by the addition of petroleum ether (90°-120°) to give a pale yellow solid, m.p. 182° dec.; uv λ max (95% ethanol) 217 (ε, 34,700), 233(sh) nm (ε, 15,300); ir cm^{-1}: 3340(s), 2975(s), 2950(s), 2630(s), 2475(s), 1575(s), 1525(s), 1460(m), 1375(m), 1345(m), 1300(m), 1255(s), 1230(m), 1190(s), 1160(m), 1140(m), 1100(w), 1075(m), 1050(m), 955(w), 965(w), 925(w), 885(m), 850(m), 830(m), 795(s), 755(m), 665(m), 565(w), 550(w), 575(m); nmr spectrum (D_2O/DDS) δ 8.04 (C_2-H pyrimidine ring proton singlet), δ 3.72 $-\underset{H}{\overset{CH_3}{C}}-\underline{CH_2}CH_2-$multiplet, δ 3.21 $CH_2-N-(CH_2)_2-$multiplet, δ 2.95 ($CH_2-\underline{CH_2}-CH_2-N$ multiplet), δ 1.97 $-\underset{CH_2}{\overset{CH_3}{C}}-\underline{H}$ methine and methyl protons broad envelope), δ 1.33 ($-CH_2-\underline{CH_3}$ multiplet).

Anal. Calcd. for $C_{22}H_{45}Cl_2N_7O_2$: C, 51.75; H, 8.88; N, 19.22. Found: C, 51.45; H, 9.07; N, 19.41.

4,6-bis(Dimethylaminoethylamino)-5-nitropyrimidine Dihydrochloride (LXXVIb)

To a stirred solution of 1.93 g. of 4,6-dichloro-5-nitropyrimidine (LXXV) (0.01 mole) in 50 ml. of absolute ethanol was added dropwise 1.76 g. of

dimethylaminoethylamine (0.02 mole). The mixture was refluxed for three hours, then the solvent was removed under reduced pressure to give the yellow dihydrochloride salt (2.67 g., 73%). It was purified by solution in absolute ethanol and precipitation by the addition of petroleum ether (90°-120°) to give a pale yellow solid, m.p. 259° dec.; uv λ max (95% ethanol) 215 (ε, 25,900), 235(sh) (ε, 14,800), 343 nm (ε, 10,300); ir cm^{-1}: 3450(m), 3370(s), 3320(s), 3010(m), 2950(s), 2660(s), 2575(m), 2450(s), 1575(s), 1525(s), 1460(m), 1360(m), 1310(m), 1260(s), 1220(s), 1190(m), 1100(m), 1060(m), 1025(m), 995(m), 980(m), 920(w), 870(m), 825(m), 800(s), 670(m), 580(w), 480(m), nmr spectrum (D_2O/DDS) δ8.18 (C_2-H pyrimidine ring proton singlet), δ 4.05 (H-N-$C\underline{H}_2$-CH_2-triplet), δ3.50 (H-N-CH_2-$C\underline{H}_2$-N triplet), δ 3.03 -N-$(C\underline{H}_3)_2$ singlet.

Anal. Calcd. for $C_{12}H_{25}Cl_2N_7O_2$: C, 38.94; H, 6.80; N, 26.47. Found: C, 38.86; H, 6.85; N, 26.30.

4,6-bis(3-Dimethylaminopropylamino)-5-nitropyrimidine Dihydrochloride (LXXVIc)

To a stirred solution of 1.93 g. of 4,6-dichloro-5-nitropyrimidine (LXXV) (0.01 mole) in 50 ml. of absolute ethanol was added dropwise 2.76 g. of 3-dimethylaminopropylamine (0.02 mole). The mixture was refluxed for three hours, then the solvent was removed under reduced pressure to give the yellow dihydrochloride salt (1.81 g., 46%). It was purified by solution in absolute ehtanol and precipitation by the addition of petroleum ether (90°-120°) to give a pale yellow solid, m.p. 254° dec.; uv λ max (95% ethanol) 216 (ε, 34,000), 233 nm (ε, 16,700); ir cm^{-1}: 3440(m), 3325(m), 2940(m), 2575(m), 2470(m), 1590(s), 1525(m), 1460(m),

1360(m), 1350(m), 1280(m), 1245(s), 1190(s), 1100(m), 1070(w), 1055(w), 1005(w), 970(m), 935(w), 875(w), 820(w), 790(s), 665(m), 630(m), 500(w), 475(w); nmr spectrum (D_2O/DDS) δ 8.09 (C_2-H pyrimidine ring proton-singlet), δ 3.72 (H-N-CH_2-CH_2-triplet), δ 3.28 (H-N-CH_2-CH_2-CH_2-N multiplet), δ 2.98 -N-$(CH_3)_2$ singlet , δ 2.15 (-CH_2-CH_2-CH_2-N multiplet).

Anal. Calcd. for $C_{14}H_{29}Cl_2N_7O_2$: C, 42.19; H, 7.35; N, 24.61. Found: C, 42.18; H, 7.37; N, 24.46.

4,6-bis(Diethylaminoethylamino)-5-nitropyrimidine Dihydrochloride (LXXVIe)

To a stirred solution of 1.93 g. of 4,6-dichloro-5-nitropyrimidine (LXXV) (0.01 mole) in 50 ml. of absolute ethanol was added dropwise 2.80 g. of diethylaminoethylamine (0.02 mole). The mixture was refluxed for three hours, then the solvent was removed under reduced pressure to give the yellow dihydrochloride salt (2.45 g., 57%). It was purified by solution in absolute ethanol and precipitation by the addition of petroleum ether (90°-120°) to give a pale yellow solid, m.p. 256-257°dec.; uv λ max (95% ethanol) 214 (ε, 33,200), 230(sh) nm (ε, 18,400); ir cm^{-1}: 3450(m), 3300(s), 2975(s), 2930(s), 2770(m), 2590(s), 2450(s), 1575(s), 1520(m), 1460(m), 1410(w), 1395(m), 1275(s), 1255(s), 1220(s), 1185(m), 1160(m), 1100(m), 1080(m), 1050(m), 1030(m), 970(m), 885(w), 835(s), 795(s), 715(m), 700(m), 665(w), 620(w), 485(s), 450(m); nmr spectrum (D_2O/DDS) δ 8.24 (C_2-H pyrimidine ring proton-singlet), δ 4.07 (H-N-CH_2-CH_2-triplet), δ 3.45 -CH_2-N-(CH_2)-multiplet , δ1.38 (-CH_2-CH_3 triplet).

Anal. Calcd. for $C_{16}H_{33}Cl_2N_7O_2$: C, 45.05; H, 7.81; N, 22.99. Found: C, 45.26; H, 7.86; N, 22.94.

4,6-bis-(3-Diethylaminopropylamino)-5-nitropyrimidine Dihydrochloride (LXXVId)

To a stirred solution of 1.93 g. of 4,6-dichloro-5-nitropyrimidine (LXXV) (0.01 mole) in 50 ml. of absolute ethanol was added dropwise 3.36 g. of 3-diethylaminopropylamine (0.02 mole). The mixture was refluxed for three hours, then the solvent was removed under reduced pressure to give the yellow dihydrochloride salt (2.31 g., 51%). An analytical sample of the salt was obtained by solution in absolute ethanol and precipitation by the addition of petroleum ether (90°-120°), m.p. 217-218°; uv λ max (95% ethanol) 216 (ε, 35,500), 232(sh) nm (ε, 17,700); ir cm^{-1}: 3450(m), 3325(s), 3290(s), 2975(s), 2940(s), 2580(s), 2475(s), 1575(s), 1520(s), 1470(m), 1425(m), 1360(s), 1285(s), 1235(s), 1200(s), 1155(w), 1080(m), 1060(m), 1040(m), 1020(m), 960(w), 880(w), 830(m), 795(s), 755(w), 720(m), 625(m), 555(w), 475(m); nmr spectrum (D_2O/DDS) δ 8.05 (C_2-H pyrimidine ring-proton singlet), δ3.72 (H-N-$C\underline{H}_2$-CH_2-triplet), δ 3.34 $C\underline{H}_2$-N-$(CH_2)_2$- multiplet , δ 2.17 (-CH_2-$C\underline{H}_2$-CH_2-N multiplet), δ 1.38 -N-$(CH_2C\underline{H}_3)_2$-triplet.

Anal. Calcd. for $C_{18}H_{37}Cl_2N_7O_2$: C, 47.55; H, 8.22; N, 21.57. Found: C, 47.70; H, 8.20; N, 21.68.

4,6-bis(p-Nitroanilino)-5-nitropyrimidine (LXXVII)

4,6-Dianilino-5-nitropyrimidine (LXVIII) (1.0 g.,0.0033 mole) was added slowly to 20 ml. of precooled 70% nitric acid solution kept at 0°. The mixture was brought to room temperature and then heated at 50° for ½ hour. At the end of this time the solution was brought to 85° for two hours, cooled, then poured over 75 g. of crushed ice, and the yellow compound which separated was stirred vigorously for 30 minutes. The

product was filtered, washed three times with small portions of ice water, dried over phosphorus pentoxide in a vacuum desiccator to give 1.1 g. (85%) of crude product. An analytical sample was prepared by recrystallizing the product from acetonitrile-ethanol (1:1) as yellow needles, m.p. 262-263°; uv λ max (95% ethanol) 227 (ε, 29,300), 327 nm (ε, 24,400); ir cm^{-1}, 3440(s), 1610(m), 1560(s), 1525(w), 1495(s), 1330(s), 1265(s), 1190(m), 1120(m), 860(m), 790(m), 745(m).

Anal. Calcd. for $C_{16}H_{11}O_6N_7$: C, 48.36; H, 2.80; N, 24.68. Found: C, 48.31; H, 2.81; N, 24.72.

4,6-bis(Anilino)-5-nitropyrimidine (LXXVIII)

To a stirred solution of 1.0 g. of 4,6-dichloro-5-nitropyrimidine (LXXV) (0.0052 mole) in 25 ml. of absolute ethanol was added 1.15 g. of freshly distilled aniline (0.0125 mole). A yellow-orange precipitate formed immediately, and the mixture was refluxed for 1 hour, cooled, filtered, washed with cold benzene, and dried in a vacuum desiccator over anhydrous magnesium sulfate to give 1.4 g. (89%) of crude material. Recrystallization of the product from absolute ethanol (Norite) gave analytically pure, yellow-orange needles, m.p. 167-168°; uv λ max (95% ethanol) 205 (ε, 28,900), 267 nm (ε, 27,600); ir cm^{-1}: 3450(m), 3275(m), 3050(w), 1600(s), 1565(s), 1500(s), 1450(m), 1360(w), 1310(w), 1265(s), 1235(w), 1180(s), 1090(w), 1030(w), 905(m), 840(w), 780(s), 755(s), 710(m), 685(m), 615(w), 560(m), 520(w), 500(m), 470(m).

Anal. Calcd. for $C_{16}H_{13}N_5O_2$: C, 62.53; H, 4.26; N, 22.79. Found: C, 62.56; H, 4.34; N, 22.87.

4,6-bis(Anilino)-5-nitropyrimidine 1-Oxide (LXXIX)

To a solution of 1.15 g. of 4,6-dianilino-5-nitropyrimidine (LXXVIII) (0.0037 mole) in 10 ml. of trifluoroacetic acid (cooled to 5°) was added 10 ml. of 50% hydrogen peroxide dropwise, being careful to maintain the reaction temperature below 40°. The resulting mixture was allowed to stir at room temperature overnight, chilled in the refrigerator, followed by trituration with 55 ml. of ice water, to precipitate out the yellow product. The crude material (0.405 g., 33%) was purified by dissolving in chloroform and passing through a silica gel column, followed by evaporation of the eluant and recrystallization of the product from ethanol to give yellow needles, m.p. 284-285°; uv λ max (95% ethanol) 208 (ε, 22,100), 265 nm (ε, 28,500); ir cm^{-1}: 3425(s), 1655(m), 1605(s), 1575(s), 1540(s), 1480(m), 1440(m), 1400(w), 1350(m), 1295(s), 1230(m), 1195(m), 1150(s), 1110(w), 1080(w), 1025(w), 865(w), 775(s), 710(w), 690(w), 550(w), 490(m).

Anal. Calcd. for $C_{16}H_{13}N_5O_3$: C, 59.44; H, 4.05; N, 21.66. Found: C, 59.42; H, 3.98; N, 21.89.

2-Hydroxy-4-anilino-5-nitropyrimidine (LXXXIII)

To a stirred solution of 5.0 g. of 2,4-dichloro-5-nitropyrimidine (LXXXII) (0.0253 mole) in 20 ml. of absolute ethanol was added dropwise 2.30 g. of freshly distilled aniline (0.025 mole). A yellow precipitate formed immediately, and the mixture was refluxed for 45 minutes, cooled, filtered, washed with cold ethanol, and dried in a vacuum oven over phosphorus pentoxide to give 4.5 g. (75%) of crude product. An analytical sample was prepared by recrystallization from benzene

(Norite) to give yellow fluffy needles, m.p. 234-245°; uv λ max (95% ethanol) 204 (ε, 27,000), 245 nm (ε, 17,700); ir cm^{-1}: 3475(s), 3340(s), 3275(s), 3060(m), 1620(s), 1575(s), 1545(s), 1485(m), 1460(m), 1440(s), 1400(m), 1350(m), 1315(s), 1285(s), 1250(s), 1180(w), 1075(m), 1030(w), 955(w), 905(w), 875(w), 840(w), 785(s), 750(s), 700(m), 685(m), 570(w), 500(w), 440(w).

Anal. Calcd. for $C_{10}H_8N_4O_3$: C, 51.72; H, 3.48; N, 24.13. Found: C, 51.61; H, 3.78; N, 24.30.

2,4-bis(p-Nitroanilino)-5-nitropyrimidine (LXXXV)

2,4-Dianilino-5-nitropyrimidine (LXXXIV) (1.0 g., 0.0033 mole) was added slowly to 35 ml. of a 70% nitric acid solution cooled to 0°. The mixture was then heated at 85° for two hours, followed by additional heating for one hour at 100°. The solution was cooled, poured over 50 g. of crushed ice. The yellow precipitate was vigorously stirred until the ice melted, filtered, and washed twice with 20 ml. of cold distilled water. The product was dried in a vacuum oven over phosphorus pentoxide at 80° to give 0.900 g. (70%) of crude material. The analytical sample was recrystallized from acetone-acetonitrile (1:1) as pale yellow needles, m.p. > 300°; uv λ max (95% ethanol) 203 (ε, 41,900, 227(sh) nm (ε, 27,100); ir cm^{-1}: 3440(s), 1610(s), 1575(s), 1500(s), 1460(w), 1410(m), 1325(s), 1330(s), 1285(s), 1225(s), 1185(m), 1165(m), 1025(w), 850(m), 785(m), 750(m), 685(w), 495(w).

Anal. Calcd. for $C_{16}H_{11}O_6N_7$: C, 48.36; H, 2.80; N, 24.68. Found: C, 48.17; H, 3.02; N, 24.70.

2,4,6-Triazido-5-chloropyrimidine (LXXXVII)

Tetrachloropyrimidine (LXXXVI) (0.200 g., 0.0009 mole) was intimately mixed with 0.240 g. of sodium azide (0.0037 mole). To this mixture was added slowly, while cooling and stirring, 5 ml. of anhydrous dimethylsulfoxide and the reaction allowed to reach room temperature, followed by stirring and heating in an oil bath at 55° for an additional two hours. Then crushed ice was added to the reaction flask and the pale yellow precipitate was filtered, washed with water, dried over phosphorus pentoxide in a vacuum dessicator to give 0.125 g. (60%) of crude product, m.p. 89°-91°. The product was subsequently purified for analysis by dissolution in hot ethanol (Norite), to give white needles, m.p. 90.0-91.5°. A Beilstein test was positive; uv λ max (95% ethanol) 239 (ε, 34,800), 311(sh) (ε, 14,200), 319 nm (ε, 14,900); ir cm^{-1}: 3450(m), 2325(m), 2150(s), 2090(m), 1575(s), 1540(s), 1360(s), 1235(s), 1210(s), 1155(m), 1070(m), 1005(m), 955(w), 800(w), 770(s), 735(m), 590(w), 540(m).

Anal. Calcd. for $C_4N_{11}Cl$: C, 20.21; N, 64.84. Found: C, 20.53; N, 64.93.

2,4,6-Tripicrylaminopyrimidine (LXXXIX)

To a stirred solution of .500 g. of 2,4,6-triaminopyrimidine (LXXXVIII) (0.0040 mole) in a mixture of 5 ml. of anhydrous dimethylsulfoxide and 0.5 ml. of triethylamine was added portionwise 2.76 g. of picryl fluoride (0.0174 mole). The red solution was heated at 78° for one hour, then cooled to 50° and stirred at this temperature overnight under anhydrous conditions. The reaction contents were poured into a mixture of 50 ml. of 95% ethanol and 50 g. of ice, which resulted in the formation of a red-colored precipitate that was stirred vigorously until all the ice

melted. The red precipitate was filtered and washed with ice cold distilled water, dried in a vacuum oven at 80° over phosphorus pentoxide to give 1.2 g. (40%) of crude material. Purification was effected by passing the crude product through a neutral alumina column using acetone as the eluant, evaporation of the acetone to dryness and recrystallization of the product from acetone-acetic acid (3:1) yielded yellow crystals, m.p. > 300°; uv λmax (95% ethanol) 216 nm (ε, 14,500); ir cm^{-1}: 3440(m), 3470(m), 3090(w), 1610(s), 1590(s), 1530(s), 1490(m), 1440(s), 1390(w), 1360(w), 1330(s), 1310(s), 1275(m), 1175(s), 1095(m), 945(w), 925(m), 830(m), 810(w), 760(w), 725(s), 670(w).

Anal. Calcd. for $C_{22}H_{10}N_{14}O_{18}$: C, 34.84; H, 1.33; N, 25.86. Found: C, 34.98; H, 1.43; N, 25.61.

Pyridazines

3,6-Dipicrylaminopyridazine (XCII)

3,6-Dianilinopyridazine (XCI) (2.0 g., 0.008 mole) was added slowly to 30 ml. of concentrated nitric acid that had been precooled to 15°; care was taken to maintain the temperature below 20° during the addition. The mixture was brought to room temperature, followed by heating and stirring at 85° for 1½ hours. The reaction mixture was poured over 15 g. of ice, and the yellow precipitate was filtered, washed with water, and dried in a dessicator oven to give 3.4 g. (84%) of crude product. Recrystallization of the product from acetone-ethanol (Norite) solvent pair (3:1) gave straw-colored needles of pure material, m.p. 254°dec.; uv λ max (95% ethanol) 205 nm (ε, 33,100); ir cm^{-1}: 3440(s), 1620(s), 1600(s), 1450(s), 1480(s), 1445(s), 1340(s), 1310(s), 1255(m), 1175(m), 1090(m), 1040(w), 930(m), 880(w), 850(w), 820(w), 770(w), 720(m).

Anal. Calcd. for $C_{16}H_8N_{10}O_{12}$: C, 36.10; H, 1.51; N, 26.32. Found: C, 36.22; H, 1.47; N, 26.39.

6-Amino-3-ethoxypyridazine 1-Oxide (XCVI)

To a stirred solution of 3.0 g. (0.13 g.-atom) of sodium metal in 40 ml. of absolute ethanol was added 1.05 g. (0.007 mole) of 6-amino-3-chloropyridazine 1-oxide (XCIV) and the mixture heated in an oil bath at 80° for three hours. The reaction mixture was cooled, and filtered to give a clear filtrate. To the filtrate was added 20 ml. of tetrahydrofuran and the resulting solution extracted four times with 25 ml. portions of petroleum ether (30°-60°). The petroleum

ether fractions were combined and evaporated to dryness to give 0.51 g. (48%) of a yellow material. The product was recrystallized from benzene (Norite) as white needles, m.p. 149-150°; uv λ max (95% ethanol) 228 (ε, 7,100), 249(sh) nm (ε, 3,800); ir cm^{-1}: 3460(s), 3400(s), 3245(s), 3080(s), 2980(m), 2945(w), 2900(w), 1635(s), 1590(s), 1560(s), 1495(s), 1475(s), 1410(m), 1380(s), 1340(s), 1315(s), 1275(s), 1200(s), 1140(m), 1115(m), 1045(s), 1010(m), 960(w), 900(m), 835(m), 830(s), 740(m), 710(m), 635(w), 600(m), 570(m), 560(m), 500(w), 455(w).

Anal. Calcd. for $C_6H_9N_3O_2$: C, 46.44; H, 5.86; N, 27.08. Found: C, 46.54; H, 5.67; N, 27.36.

3-Chloro-4,5-diaminopyridazine-6-one(LIX)

A solution containing 1.69 g. (0.00895 mole) of 4-chloro-1,2,5-thiadiazolo [3,4-d]pyridazine-7-one (LVIII) and 50 ml. of 5% aqueous sodium hydroxide was heated in a pressure bottle at 80° for one hour. After cooling, the solution was neutralized with glacial acetic acid and the white crystalline solid that separated was filtered and dried to give 1.25 g. (86%) of crude product. Recrystallization from dilute ammonium hydroxide (Norite) gave the purified compound in the form of white fluffy needles, m.p. 336°. A Beilstein test was positive; uv λ max (95% ethanol) 209 (ε, 12,600), 232(ε, 18,600), 278(sh) (ε, 3,100), 316 nm (ε, 7,800); ir cm^{-1}: 3450(s), 3360(s), 3010(m), 2950(m), 2880(m), 1620(s), 1590(s), 1520(m), 1390(s), 1310(m), 1255(m), 1190(m), 1115(m), 1025(m), 905(s), 745(s), 635(s), 640(w), 495(w); nmr (DMSO-d_6/ext. TMS) δ12.36 (N_1-H singlet), δ5.28 (C_4-NH_2-broad singlet), δ5.07 (C_5-NH_2-broad singlet).

Anal. Calcd. for $C_4H_5ClN_4O$: C, 29.91; H, 3.14; N, 34.62. Found: C, 30.04; H, 3.03; N, 34.89.

6-Amino-3-benzylthiopyridazine 1-Oxide (XCV)

To a solution of 6-amino-3-chlorpyridazine 1-oxide (XCIV) (2.0 g., 0.014 mole) in a 40 ml. of ethanol was added a mixture of 20 ml. of 5% aqueous sodium hydroxide, 15 ml. of 28% ammonium hydroxide, 15 ml. of ethanol and 1.65 ml. (0.014 mole) of benzylmercaptan. The resulting mixture was heated and stirred magnetically at 80° for six hours; the solution evaporated on a rotary evaporator and the solid residue triturated with water (50 ml.) to dissolve the salts. The yellow precipitate was filtered and dried to give 1.45 g. (45%) of crude product. The compound was recrystallized from benzene as yellow needles, m.p. 116-117°; uv λ max (95% ethanol) 218 (ε, 8,600), 238 (ε, 7,700), 272 nm (ε, 6,300); ir cm^{-1}: 3345(m), 3260(m), 3100(m), 1620(s), 1550(w), 1520(m), 1480(m), 1460(s), 1350(w), 1285(s), 1195(w), 1150(w), 1110(m), 1070(w), 1040(w), 935(m), 865(m), 770(w), 700(s), 665(m), 585(w), 555(w); nmr spectrum ($CDCl_3$/TMS), 7.2-7.3 δ (phenyl protons - multiplet), 6.87 δ (C_5-ring proton), 6.73 δ (C_4-ring proton), 6.4 δ ($-NH_2$-broad), 4.49 δ (benzylic CH_2-singlet).

Anal. Calcd. for $C_{11}H_{11}N_3OS$: C, 56.60; H, 4.73; N, 18.00. Found: C, 56.81; H, 4.79; N, 18.18.

6-Amino-3-hydrazinopyridazine 1-Oxide (XCVII)

6-Amino-3-chloropyridazine 1-Oxide (XCIV) (2.0 g., 0.014 mole) was

mixed with 50 ml. of 95% ethanol and to this mixture was added 20 ml. of hydrazine hydrate. The reaction mixture was heated in a pressure bottle on a steam bath for 24 hours. After cooling and opening, the yellow product was filtered and washed with cold absolute ethanol to give 1.6 g. (83%) of the crude product. The product was recrystallized from ethanol-water 25/75, to give pale yellow needles, m.p. 218-219°. A ferric chloride-absolute ethanol test for the N-oxide function was positive, and a Beilstein test was negative; uv λ max (95% ethanol) 230 (ε, 14,000), 264 nm (ε, 9,300); ir cm^{-1}: 3410(s), 3245(s), 3125(s), 3055(s), 2820(w), 1660(s), 1610(s), 1505(s), 1400(m), 1340(s), 1255(s), 1200(s), 1155(m), 1135(m), 1030(m), 950(m), 820(s), 745(s), 685(m), 610(m), 575(w), 535(w), 430(m).

Anal. Calcd. for $C_4H_7N_5O$: C, 34.03; H, 5.01; N, 49.62. Found: C, 34.26; H, 4.97; N, 49.73.

6-Amino-3-(benzylidenehydrazino)pyridazine 1-Oxide (XCVIII)

To a stirred solution of 6-Amino-3-hydrazinopyridazine 1-oxide (XCVII) (0.120 g., 0.00085 mole) in 50 ml. of ethanol was added (0.9 g., 0.0085 mole) of benzaldehyde in 10 ml. of ethanol to which a few drops of 1N HCl were added. Almost immediately a yellow precipitate appeared and stirring was continued at room temperature for a few minutes. The product was filtered, washed three times with 3 ml. of absolute ethanol followed by a final washing with anhydrous ether, dried in a vacuum oven at 80° to give 0.183 g. (94%) of crude material. An analytical sample was recrystallized from water-acetic acid (Norite) to give amber needles, m.p. 273-274°. A ferric chloride

test for the N-oxide function was positive; uv λ max (95% ethanol) 237 (ε, 20,700), 325 nm (ε, 20,800); ir cm^{-1}: 3420(m), 3350(m), 3260(m), 3150(m), 3050(m), 1625(w), 1590(s), 1560(s), 1535(s), 1480(m), 1450(s), 1445(s), 1400(s), 1355(m), 1320(m), 1265(s), 1240(m), 1200(s), 1140(s), 1075(m), 1030(w), 985(m), 940(m), 885(w), 780(w), 755(m), 690(m), 630(w), 645(m), 585(m).

Anal. Calcd. for $C_{11}H_{11}N_5O$: C, 57.62; H, 4.85; N, 30.55. Found: C, 57.37; H, 4.80; N, 30.74.

6-(2,4-Dinitroanilino)-3-(benzylidenehydrazino)pyridazine 1-Oxide(XCIX)

To a solution of 6-amino-3-(benzylidenehydrazino)pyridazine 1-oxide (XCVIII) (0.500 g., 0.0022 mole) in a mixture of 2 ml. of anhydrous dimethylsulfoxide and 0.5 ml. of triethylamine was added 0.27 ml. of 2,4-dinitrofluorobenzene and the reaction mixture was magnetically stirred at 70° for 24 hours. Ice was then added to the mixture and the red product was filtered and air-dried to give 0.650 g. (76%) of crude material. Recrystallization from 95% ethanol (Norite) gave an analytically pure sample, m.p. 264°; uv λ max (95% ethanol) 205 (ε, 25,700), 236 (ε, 31,000), 253 (ε, 30,500), 318 nm (ε, 19,300); ir cm^{-1}: 3430(s), 3270(m), 3050(w), 1615(m), 1580(m), 1510(m), 1460(s), 1390(w), 1325(s), 1235(m), 1195(m), 1130(m).

Anal. Calcd. for $C_{17}H_{13}N_7O_5$: C, 51.64; H, 3.32; N, 24.81. Found: C, 51.51; H, 3.23; N, 24.78.

6-Amino-3-(o-nitro-α-methylbenzylidenehydrazino)pyridazine 1-Oxide (CI)

To a stirred solution of 6-amino-3-hydrazinopyridazine 1-oxide (XCVII)

(0.250 g., 0.0018 mole) in 15 ml. of methanol was added (0.339 g., 0.002-mole) of o-nitroacetophenone in 5 ml. of methanol to which a few drops of glacial acetic acid were added. The solution was refluxed for 30 minutes, cooled, and the product filtered, washed with anhydrous ether, dried in a vacuum desiccator over phosphorus pentoxide to give 0.45 g. (88%) of crude product. Recrystallization from methanol-aceitc acid (Norite) in a (10:1) solvent pair yielded yellow crystals, m.p. 206-207°. A ferric chloride test for the N-oxide function was positive; uv λ max (95% ethanol) 205 (ε, 19,900), 232 (ε, 25,200), 280 nm (ε, 19,000); ir cm^{-1}, 3425(s), 1625(m), 1575(m), 1520(s), 1450(m), 1400(m), 1375(w), 1335(m), 1310(m), 1220(m), 1195(m), 1130(m), 855(w), 820(w), 750(m), 665(w).

Anal. Calcd. for $C_{12}H_{12}N_6O_3$: C, 49.99; H, 4.20; N, 29.16. Found: C, 49.71; H, 4.27; N, 28.96.

6-Amino-3-(m-nitro-α-methylbenzylidenehydrazino)pyridazine 1-Oxide (C)

To a stirred solution of 6-amino-3-hydrazinopyridazine 1-oxide (XCVII) (0.250 g., 0.0018 mole) in 15 ml. of methanol was added (0.33 g., 0.002-mole) of m-nitroacetophenone in 5 ml. of methanol to which a few drops of glacial acetic acid were added. The solution was refluxed for 30 minutes, cooled, and the product filtered, washed with anhydrous ether, dried in a vacuum dessicator over phosphorus pentoxide to give 0.50 g. (98%) of crude product. Recrystallization from methanol-acetic acid (Norite) in a (10:1) solvent pair, yielded orange fluffy needles, m.p. 269-270°. A ferric chloride test for the N-oxide function was positive; uv λ max (95% ethanol) 241 (ε, 24,000), 323 nm (ε, 21,300); ir cm^{-1},

3420(m), 3260(m), 1570(m), 1510(s), 1465(w), 1440(m), 1390(s), 1340(s), 1315(m), 1285(m), 1270(m),1195(m), 1155(m), 1130(m), 880(w), 810(m), 765(m), 740(m), 680(m), 650(w).

Anal. Calcd. for $C_{12}H_{12}N_6O_3$: C, 49.99; H, 4.20; N, 29.16. Found: C, 49.84; H, 4.02; N, 28.98.

6-Amino-3-(α-methylbenzylidenehydrazino)pyridazine 1-Oxide (CII)

To a stirred solution of 6-amino-3-hydrazinopyridazine 1-oxide (XCVII) (0.250 g., 0.0018 mole) in 25 ml. of methanol was added (0.24 g., 0.002-mole) of acetophenone in 5 ml. of methanol to which a few drops of 1N HCl were added. The solution was refluxed for 30 minutes, cooled, and triturated with 30 ml. of water, whereupon a precipitate appeared. The product was filtered, washed several times with anhydrous ether, dried under vacuum in a desiccator over phosphorus pentoxide to give 0.352 g. (82%) of crude material. A pure sample was prepared by dissolution in a methanol-acetic acid (Norite) solvent pair (10:1) and crystallization to give needles, m.p. 228-230°. A ferric chloride test in absolute ethanol for the N-oxide function was positive; uv λ max (95% ethanol) 235 (ε, 21,100), 251(sh) (ε, 15,200), 313 nm (ε, 20,900); ir cm^{-1}, 3400(m), 3275(s), 2900(w), 1625(w), 1570(s), 1510(s), 1485(s), 1445(m), 1395(s), 1355(w), 1310(s), 1270(s), 1195(s), 1135(s), 1075(m), 1030(w), 995(w), 960(w), 910(w), 870(m), 760(s), 745(m), 690(s), 650(w), 590(w).

Anal. Calcd. for $C_{12}H_{13}N_5O$: C, 59.23; H, 5.40; N, 28.79. Found: C, 59.03; H, 5.53; N, 28.95.

4-Chloro-5-(o-nitrobenzylidenehydrazino)pyridazine-3-one (CV)

To a solution of 4-chloro-5-hydrazinopyridazine-3-one (CIV) (1.0 g., 0.0062 mole) in 50 ml. of acetic acid was added 0.92 g. (0.0062 mole) of o-nitrobenzaldehyde in 10 ml. of ethanol and the reaction was brought to 80° with heating and stirring for 20 minutes. After cooling the reaction mixture over ice, a yellow precipitate was obtained which was filtered and dried to give 1.92 g. (93%) of crude material. The compound was purified by recrystallization from methanol-acetic acid (Norite) solvent pair (10:1) to give brilliant yellow needles, m.p. 304-305°. A Beilstein test was positive; uv λ max (95% ethanol) 206 (ε, 57,100), 279 nm (ε, 17,400); ir cm^{-1}: 3350(m), 3280(m), 3140(m), 2875(m), 1650(s), 1605(s), 1555(w), 1510(s), 1480(w), 1440(m), 1395(s), 1335(s), 1265(s), 1240(m), 1200(s), 1140(s), 1080(m), 1030(w),985(m), 940(m), 885(w), 820(w), 780(w), 755(m), 690(m), 640(w), 595(m), 510(m).

Anal. Calcd. for $C_{11}H_8ClN_5O_3$: C, 44.98; H, 2.75; N, 23.85. Found: C, 45.32; H, 2.45; N, 24.14.

2,3-Dimethylpyrazino[2,3-d]pyridazine-5-one (CIII)

To a solution of 4,5-diaminopyridazine-3-one (LIV) (2.0 g., 0.015-mole) in 25 ml. of methanol was added a solution of 1.29 g. (0.015 mole) 2,3-butanedione in 25 ml. of glacial acetic acid. The mixture was refluxed for 12 hours, cooled and the white floculant precipitate filtered, and dried to give 1.6 g. (57%) of impure material. The product was recrystallized from ethanol (Norite) to give white needles, m.p. 321°; uv λ max (95% ethanol) 205 (ε, 18,400), 235(sh) (ε, 8.500), 250 (ε, 12,500),

306 nm (ε, 5,900); ir cm^{-1}, 3440(s), 3195(m), 3125(m), 3040(m), 2945(m), 1680(s), 1590(w), 1550(m), 1440(m), 1400(m), 1385(s), 1350(s), 1310(w), 1280(s), 1260(m), 1220(m), 1205(w), 1110(s), 1080(w), 1020(m), 995(w), 930(m), 900(s), 845(m), 810(m), 775(w), 770(w), 755(w), 660(s), 580(m), 560(m), 500(m), 495(m), 490(m).

Anal. Calcd. for $C_8H_8N_4O$: C, 54.53; H, 4.59; N, 31.80. Found: C, 54.78; H, 4.85; N, 31.95.

6,6',3,3'Tetramethyl-4,4'-azopyridazine 1,1'-dioxide (CVII)

3,6-Dimethyl-4-aminopyridazine 1-oxide (CVI) (5.0 g., 0.036 mole) was slowly added to 75 ml. of a refluxing 30% nitric acid solution. Heating was continued for 15 minutes after the addition, and this was followed by the addition of a basic 5% potassium permaganate solution until no more manganese dioxide formed. Then the hot solution was filtered and concentrated down to one-fourth of its volume and placed in a refrigerator overnight. The product of the reaction was filtered, dried in a vacuum desiccator over sodium hydroxide to give 0.945 g. (19%) of a red compound. Recrystallization from ethanol (Norite) gave red needles, m.p. 280° dec.; uv λ max (95% ethanol) 202 (ε, 6,900), 242 (ε, 11,100), 308 nm (ε, 5,000); ir cm^{-1}: 3440(s), 3255(m), 1625(m), 1600(m), 1530(w), 1405(m), 1390(m), 1355(w), 1325(s), 1240(s), 1080(w), 1010(w), 740(w), 720(w), 530(w), 450(m).

Anal. Calcd. for $C_{12}H_{14}N_6O_2$: C, 52.55; H, 5.14; N, 30.64. Found: C, 52.64; H, 5.18; N, 30.58.

V. Antibacterial and Antifungal Activity

Antibacterial and Antifungal Activity

Tables I-IV are a compilation of screening data on all the compounds that showed some activity when evaluated by ICN Nucleic Acid Institute.

In this testing, the disk test was used. The test organism is first grown on uniformly seeded agar and incubated for 24 hours. Then a minute quantity of compound is applied to the infected agar plate and it is allowed to incubate for a short period of time. Following this incubation, the diameters of the zones of inhibition are measured.

The following test organisms were used: Pseudomonas aeruginoisa; Staphylococcus aureus; Escherichia coli; Streptococcus faecalis; Bacillus subtilis; Aspergillus niger; Candida albicans; Cryptococcus diffluens; Neurospora crassa; Streptomyces grisens; Saccharomyces cerevisiae; Serratia marcescens; Microsporim fulvum; Trichophyton mentagrophytes; Trichophyton tonsurans.

The symbols used in the tables are the following:

The notations of 0 to ++++++ indicate the relative size of the zone of inhibition.

0 = no inhibition

± = 0.25 cm. zone

\+ = 0.5 cm. zone

++ = 0.75 cm. zone

+++ = 1.0 cm. zone

++++ = 1.5 cm. zone

+++++ = 2.5 cm. zone

++++++ = zone approximately $\frac{1}{2}$ of the plate

[ ] = zone size, but slight growth is observed.

The most active compound screened was 6-amino-3-hydrazinopyridazine 1-oxide (XCVII). This compound exhibited activity toward seven out of the fourteen organisms tested.

Antimalarial and antitumor screening on all the compounds synthesized in this investigation will be done at a later date.

The screening data were supplied by Drs. Darrell O'Brien and Roland K. Robins of ICN Nucleic Acid Institute, 2727 Campus Drive, Irvine, California, 92664.

TABLE I

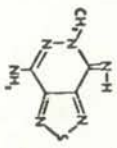
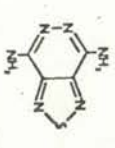
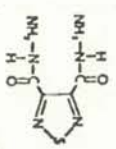
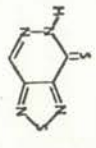
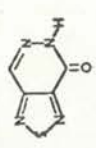
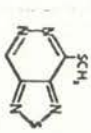
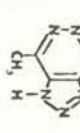
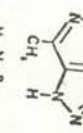
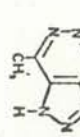
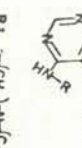
					
0	0	+	0	0	Pseudomonas aeruginosa
[+]	0	[+]	+	0	Staphylococcus aureus
0	[+]	[+]	+	0	Escherichia coli
0	+-	0	[+]	0	Streptococcus faecalis
0	0	0	+-	0	Bacillus subtilis
0	+	0	‡	‡‡	Aspergillus niger
0	+-	0	+-	0	Candida albicans
0	+	0	[+++]	+	Cryptococcus diffluens
0	0	0	0	‡	Neurospora crassa
0	0	0	0	‡‡	Streptomyces grisens
0	+-	0	[++]	+	Saccharomyces cerevisiae
0	0	[+]	0	0	Serratia marcescens
0	0	0	0	0	Microsporum fulvum
0	‡	0	0	0	Trichophyton rentagrophytes
0	+	0	0	0	Trichophyton tonsurans

TABLE II

					
				R = $-(CH_2)_2-N-(C_2H_5)_2$	
0	+	0	+	0	Pseudomonas aeruginosa
+	0	[+]	+	0	Staphylococcus aureus
+/-	+/-	0	+/-	0	Escherichia coli
+/-	0	0	+	0	Streptococcus faecalis
0	0	0	+	0	Bacillus subtilis
0	0	0	0	0	Aspergillus niger
0	0	0	0	0	Candida albicans
0	0	0	0	0	Cryptococcus diffluens
0	0	0	0	0	Neurospora crassa
0	0	0	0	0	Streptomyces grisens
0	0	0	0	+/-	Saccharomyces cerevisiae
0	+/-	0	0	0	Serratia marcescens
0	0	0	0	0	Microsporum fulvum
0	0	0	0	0	Trichophyton mentagrophytes
0	0	0	0	0	Trichophyton tonsurans

R = $-(CH_2)_2-N-(CH_3)_2$ (di-HCl)

TABLE III

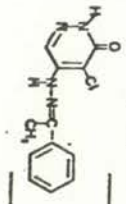
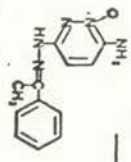
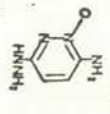
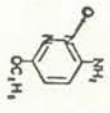
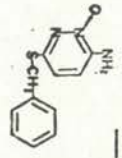
					
o	o	[++++]	+	o	Pseudomonas aeruginosa
o	o	++	o	++	Staphylococcus aureus
o	o	++++	++	o	Escherichia coli
o	o	++	o	o	Streptococcus faecalis
o	o	+++	+	o	Bacillus subtilis
o	+	o	o	o	Aspergillus niger
o	[++]	o	o	o	Candida albicans
+	+	o	o	o	Cryptococcus diffluens
o	+++	o	o	o	Neurospora crassa
o	o	+++	++	o	Streptomyces griseus
o	+	[++]	[++]	o	Saccharomyces cerevisiae
o	o	o	o	o	Serratia marcescens
o	o	o	o	o	Microsporum fulvum
o	o	o	o	o	Trichophyton mentagrophytes

TABLE IV

Pseudomonas aeruginosa	o	o	o	o	o
Staphylococcus aureus	o	[+]	o	o	o
Escherichia coli	o	o	o	o	o
Streptococcus faecalis	o	o	o	o	o
Bacillus subtilis	o	o	o	o	o
Aspergillus niger	o	o	o	+	o
Candida albicans	o	+!	+!	+!	+!
Cryptococcus diffluens	[+]	o	o	+!	o
Neurospora crassa	o	o	o	o	o
Streptomyces grisens	‡	o	o	o	o
Saccharomyces cerevisiae	+!	+!	o	+!	+!
Serratia marcescens	o	o	o	o	o
Microsporum fulvum	o	[+]	o	o	o
Trichophyton mentagrophytes	o	+!	o	o	o
Trichophyton tonsurans	o	+!	o	o	o

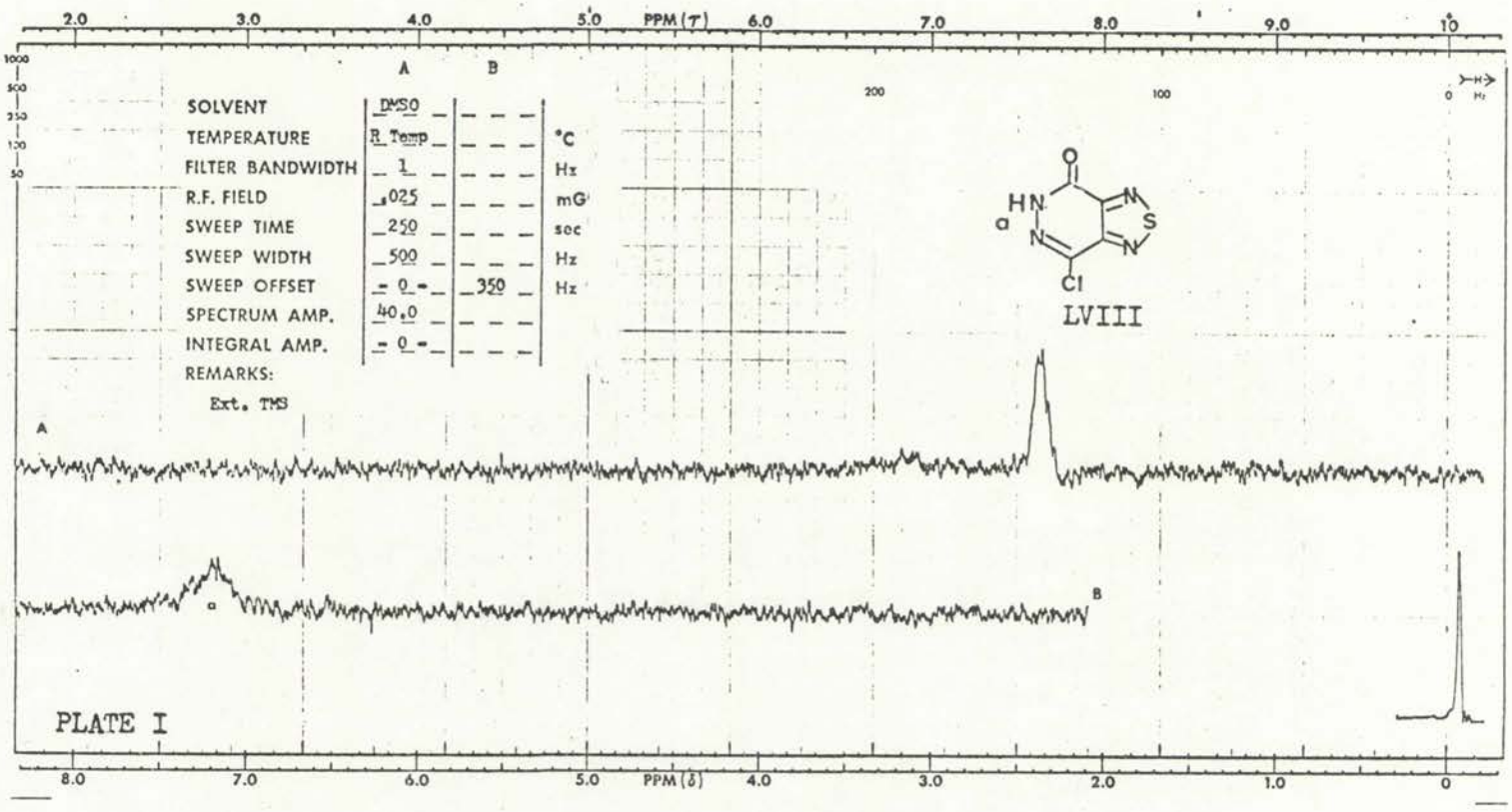
R=

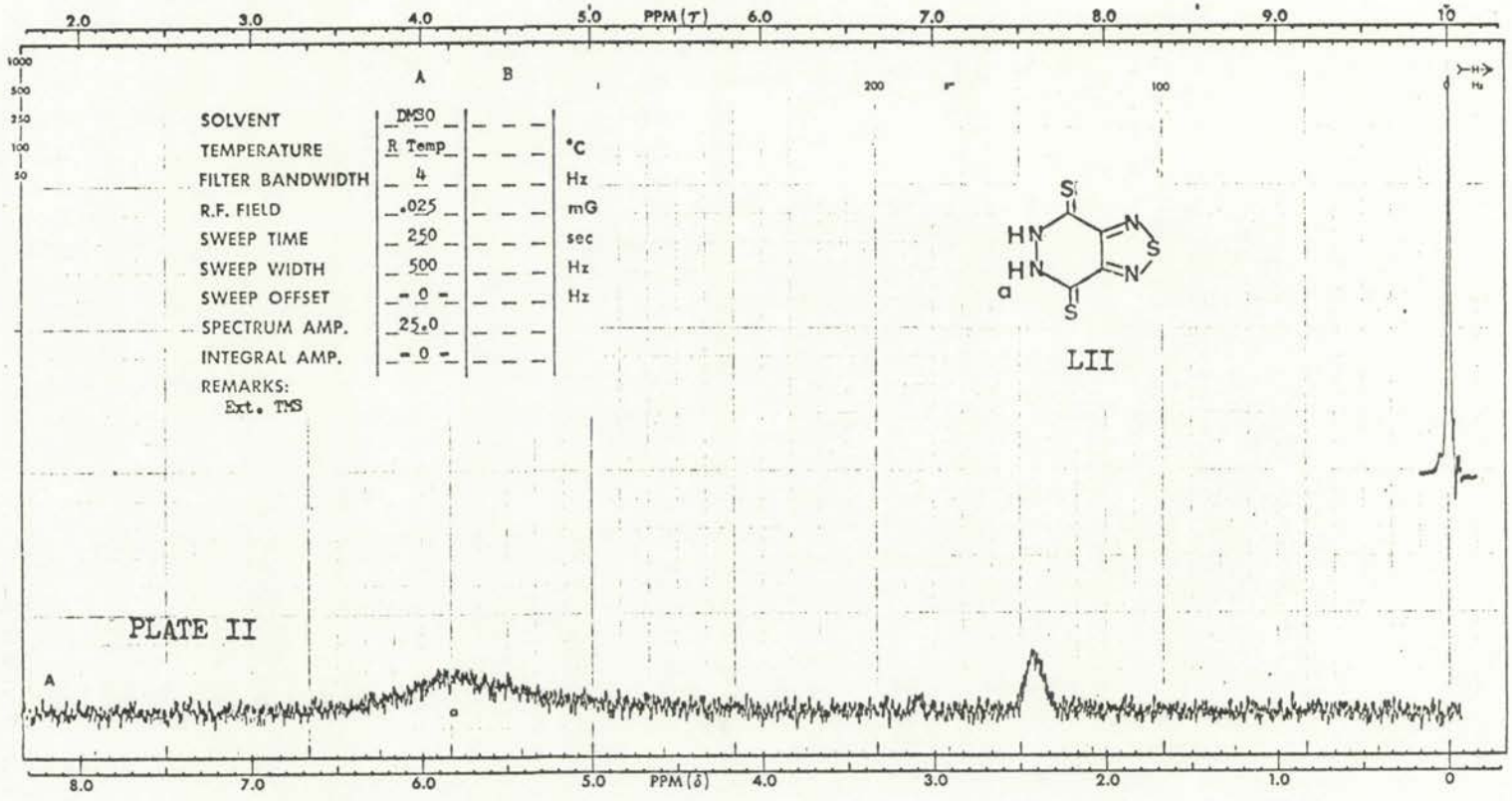
$-(CH_2)_2-N-(C_2H_5)_2$

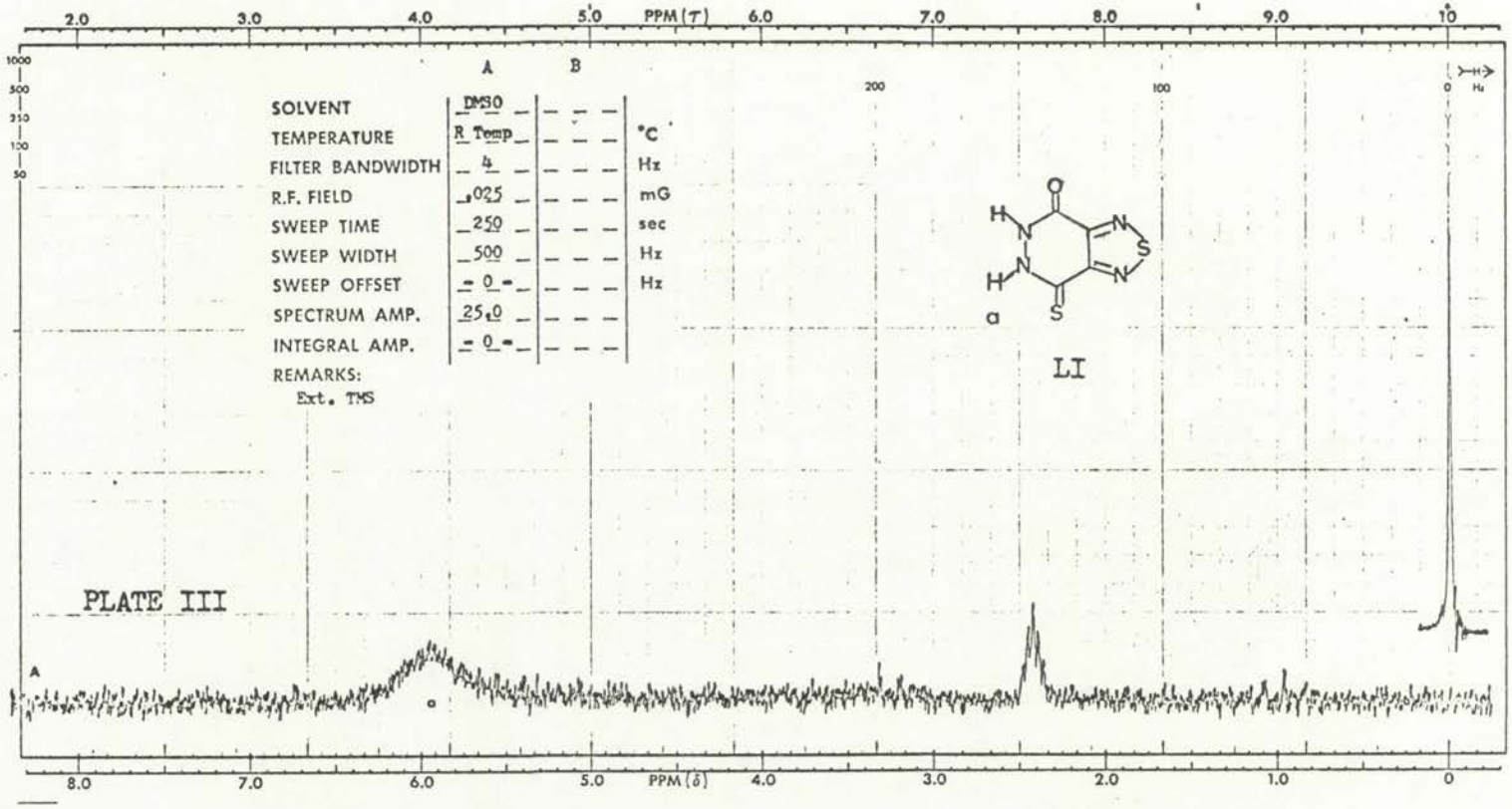
$-(CH_2)_2-N-(CH_3)_2$

$-(CH_2)_2-N-(CH_2)_2$

VI. Nuclear Magnetic Resonance Spectra


2.0
3.0
4.0
5.0
PPM(τ)
6.0
7.0
8.0
9.0
10
A
B
SOLVENT DMSO
TEMPERATURE R. Temp °C
FILTER BANDWIDTH 1 Hz
R.F. FIELD .025 mG
SWEEP TIME 250 sec
SWEEP WIDTH 500 Hz
SWEEP OFFSET 0 350 Hz
SPECTRUM AMP. 40.0
INTEGRAL AMP. 0
REMARKS:
Ext. TMS
a
LVIII
PLATE I
8.0
7.0
6.0
5.0
PPM(δ)
4.0
3.0
2.0
1.0
0


2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
A
B
SOLVENT
DMSO
TEMPERATURE
R Temp
°C
FILTER BANDWIDTH
4
Hz
R.F. FIELD
.025
mG
SWEEP TIME
250
sec
SWEEP WIDTH
500
Hz
SWEEP OFFSET
0
Hz
SPECTRUM AMP.
25.0
INTEGRAL AMP.
0
REMARKS:
Ext. TMS
LII
PLATE II
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0


2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
A
B
SOLVENT
DMSO
TEMPERATURE
R Temp
°C
FILTER BANDWIDTH
4
Hz
R.F. FIELD
.025
mG
SWEEP TIME
250
sec
SWEEP WIDTH
500
Hz
SWEEP OFFSET
- 0 -
Hz
SPECTRUM AMP.
25.0
INTEGRAL AMP.
- 0 -
REMARKS:
Ext. TMS
PLATE III
LI
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

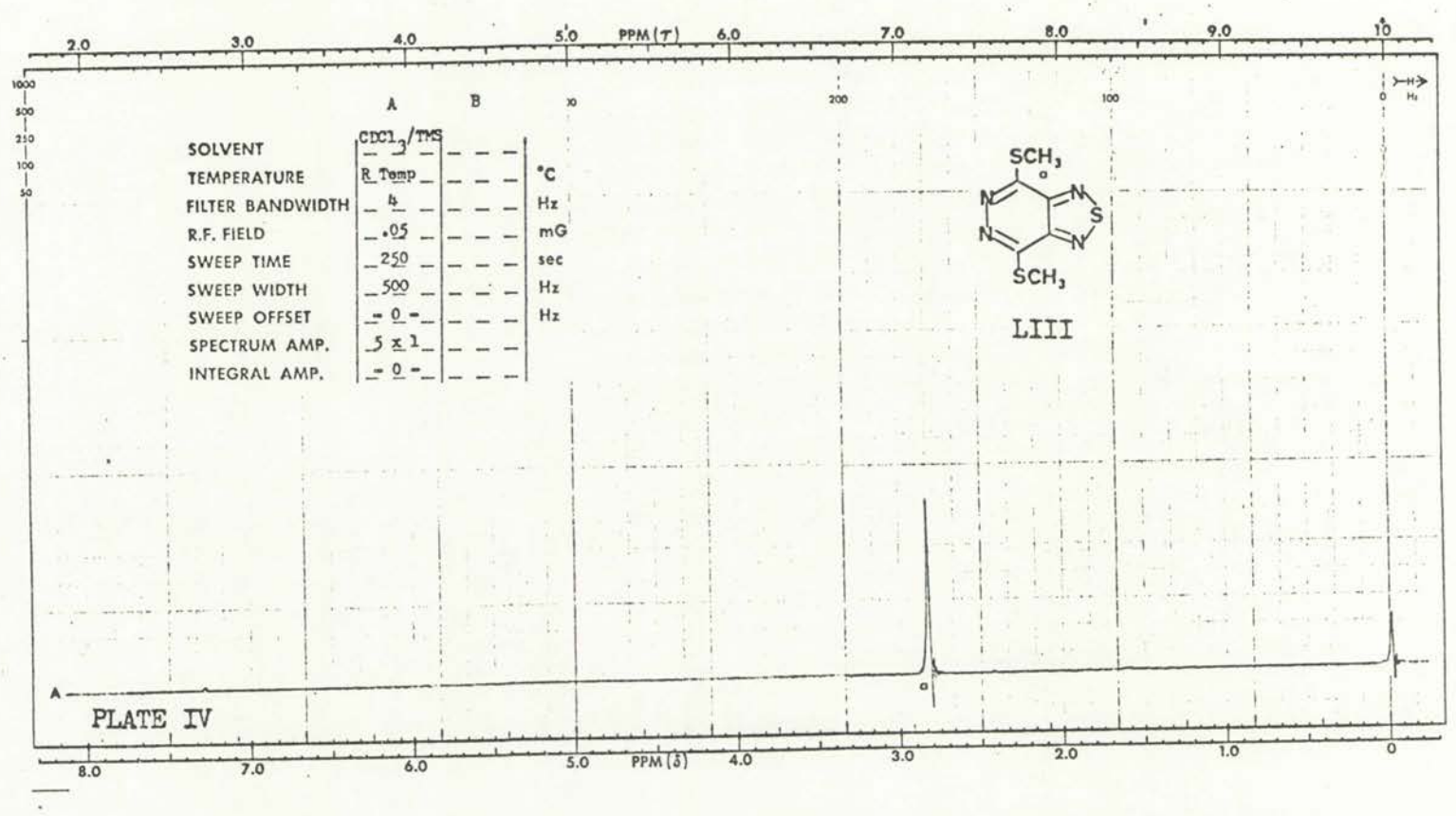

2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
1000
500
250
100
50
200
100
0
Hz
A
B
SOLVENT
CDCl3/TMS
TEMPERATURE
R Temp
°C
FILTER BANDWIDTH
4
Hz
R.F. FIELD
.05
mG
SWEEP TIME
250
sec
SWEEP WIDTH
500
Hz
SWEEP OFFSET
0
Hz
SPECTRUM AMP.
5 x 1
INTEGRAL AMP.
0
SCH3
a
N
N
S
N
N
SCH3
LIII
A
a
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

PLATE IV

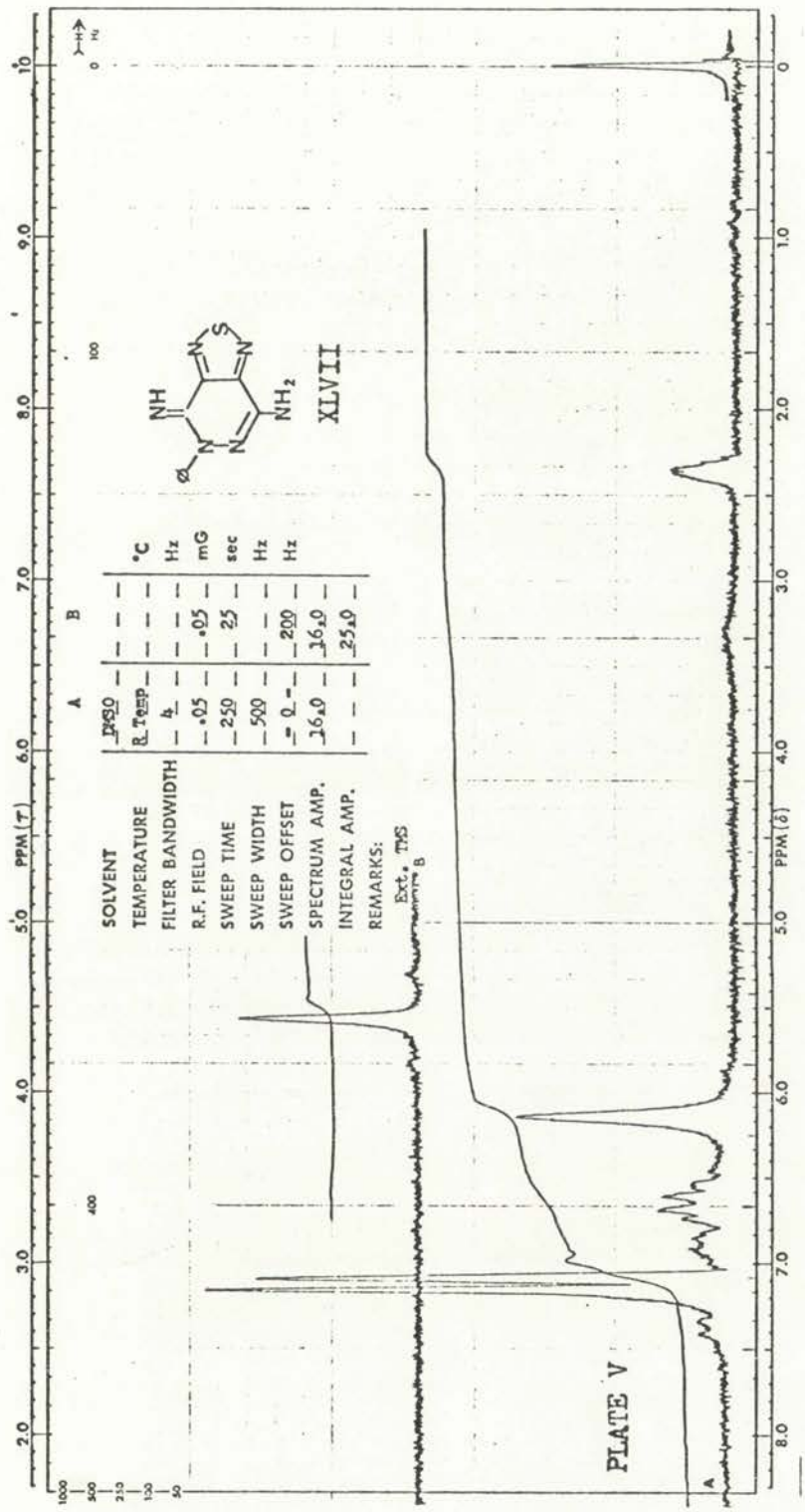
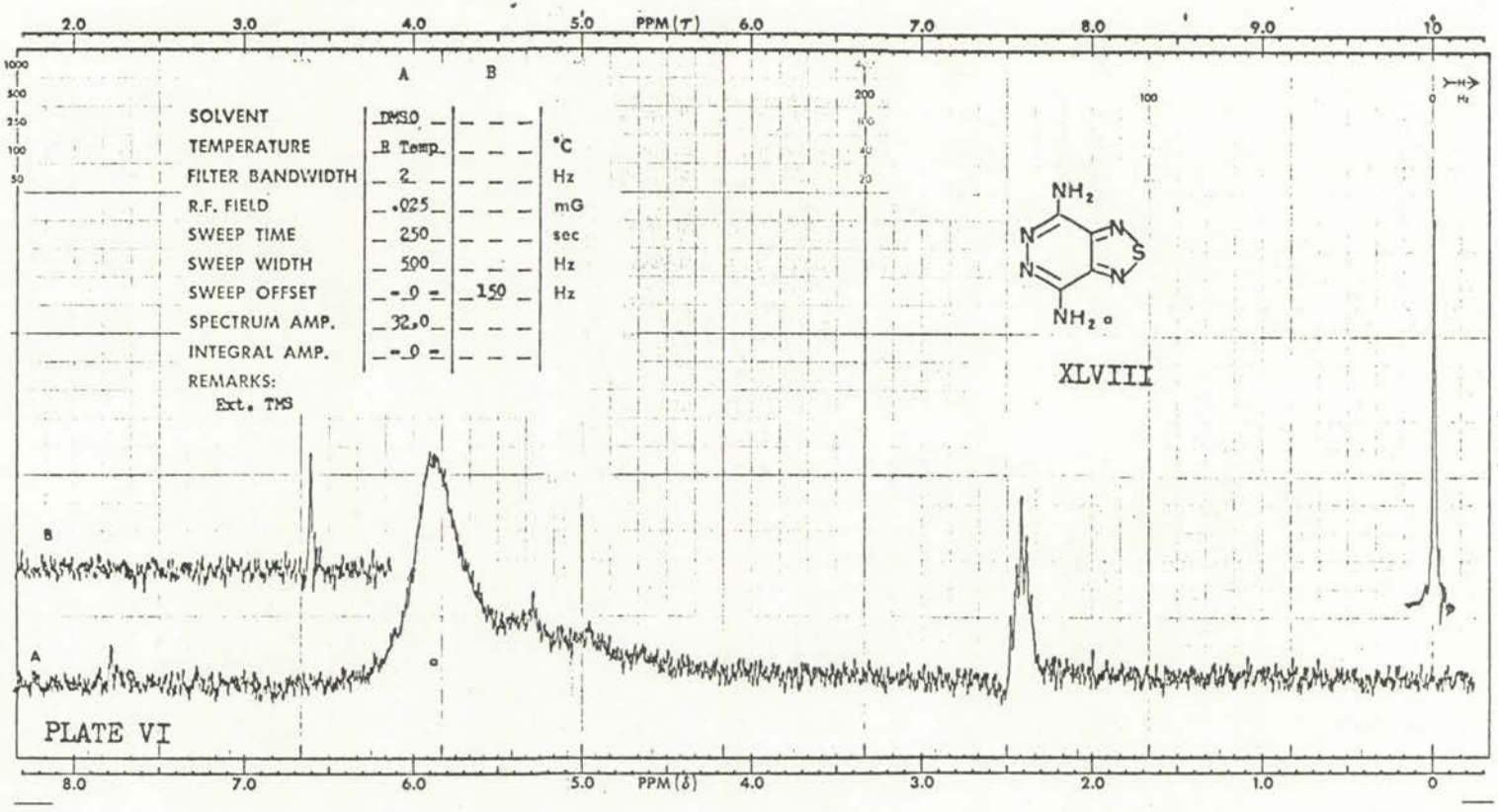
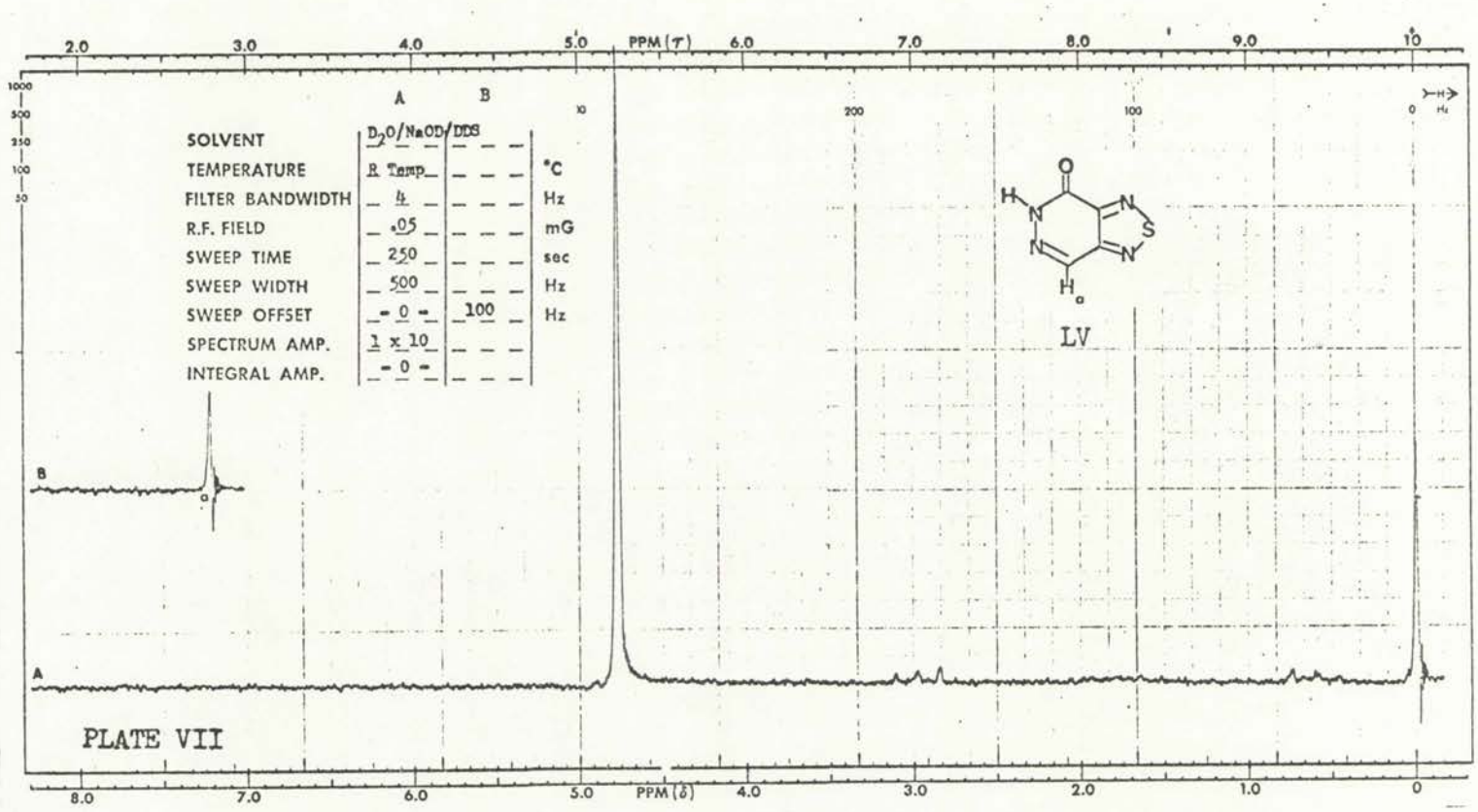
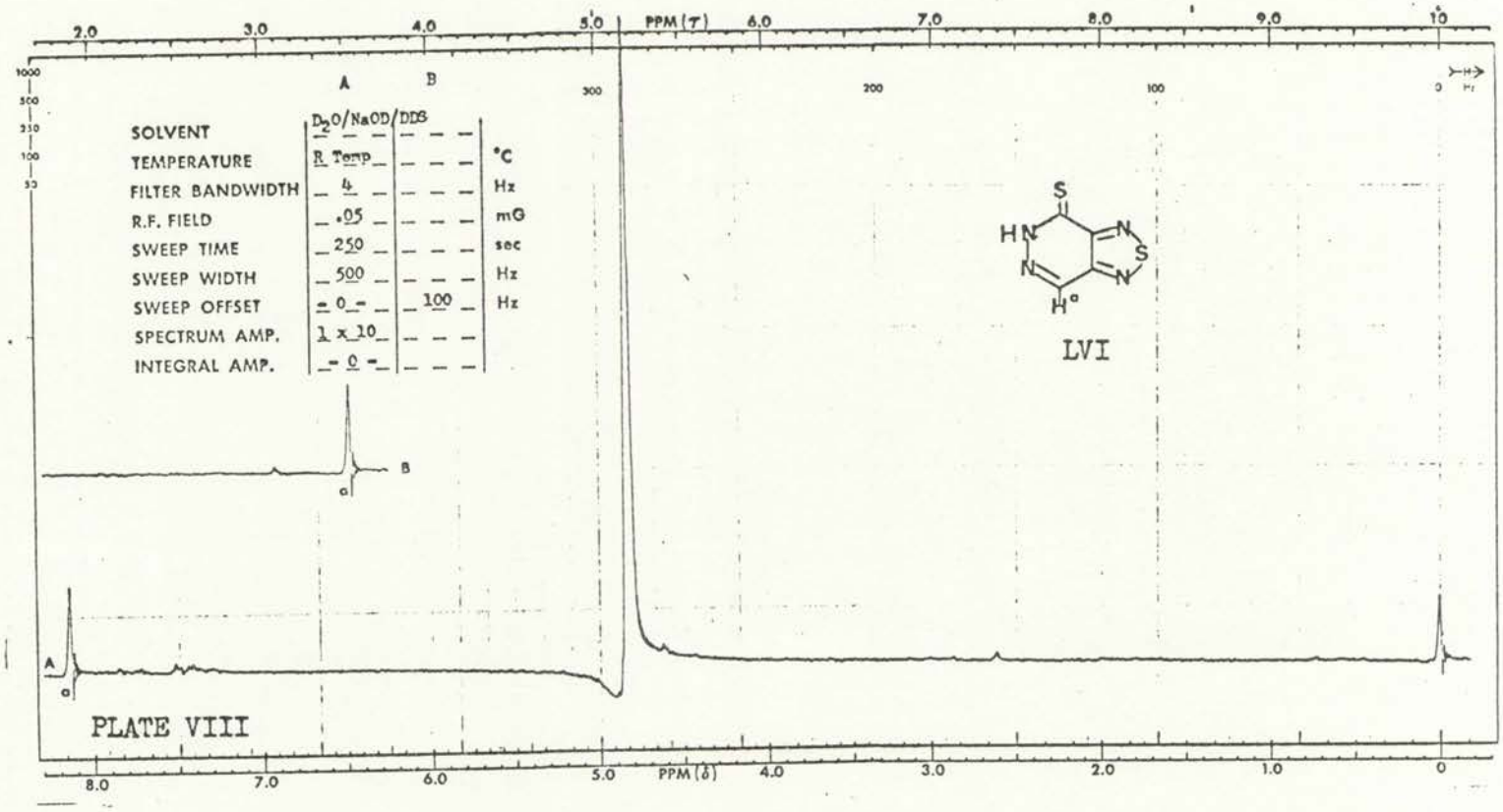

PPM(τ)
PPM(δ)
SOLVENT
TEMPERATURE
FILTER BANDWIDTH
R.F. FIELD
SWEEP TIME
SWEEP WIDTH
SWEEP OFFSET
SPECTRUM AMP.
INTEGRAL AMP.
REMARKS:
Ext. TMS
A
B
°C
Hz
mG
sec
Hz
Hz
NH
NH2
XLVII

PLATE V

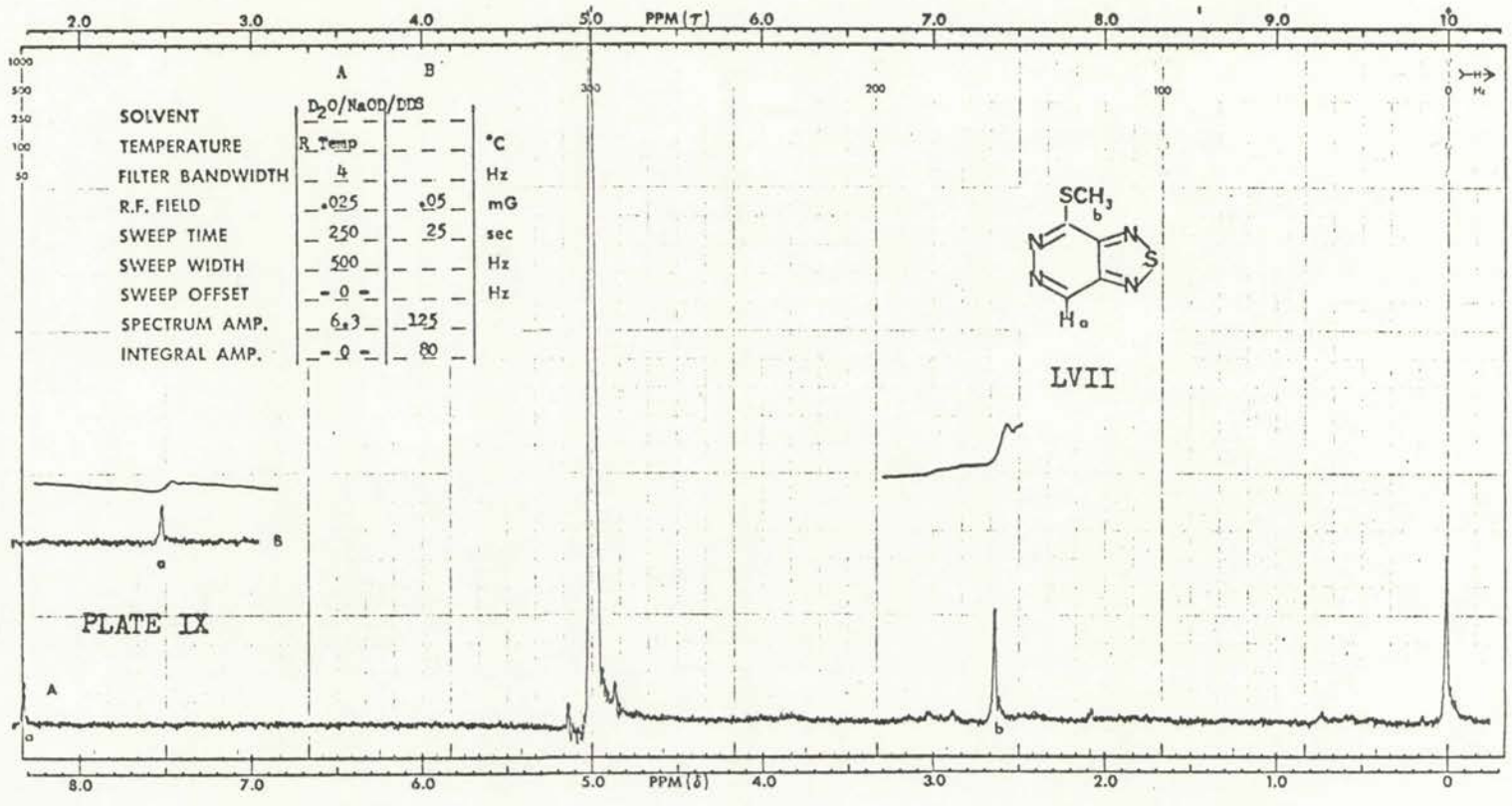

2.0
3.0
4.0
5.0
PPM(τ)
6.0
7.0
8.0
9.0
10
A
B
SOLVENT
DMSO
TEMPERATURE
R Temp.
°C
FILTER BANDWIDTH
2
Hz
R.F. FIELD
.025
mG
SWEEP TIME
250
sec
SWEEP WIDTH
500
Hz
SWEEP OFFSET
0
150
Hz
SPECTRUM AMP.
32.0
INTEGRAL AMP.
0
REMARKS:
Ext. TMS
NH2
NH2
XLVIII
PLATE VI
8.0
7.0
6.0
5.0
PPM(δ)
4.0
3.0
2.0
1.0
0

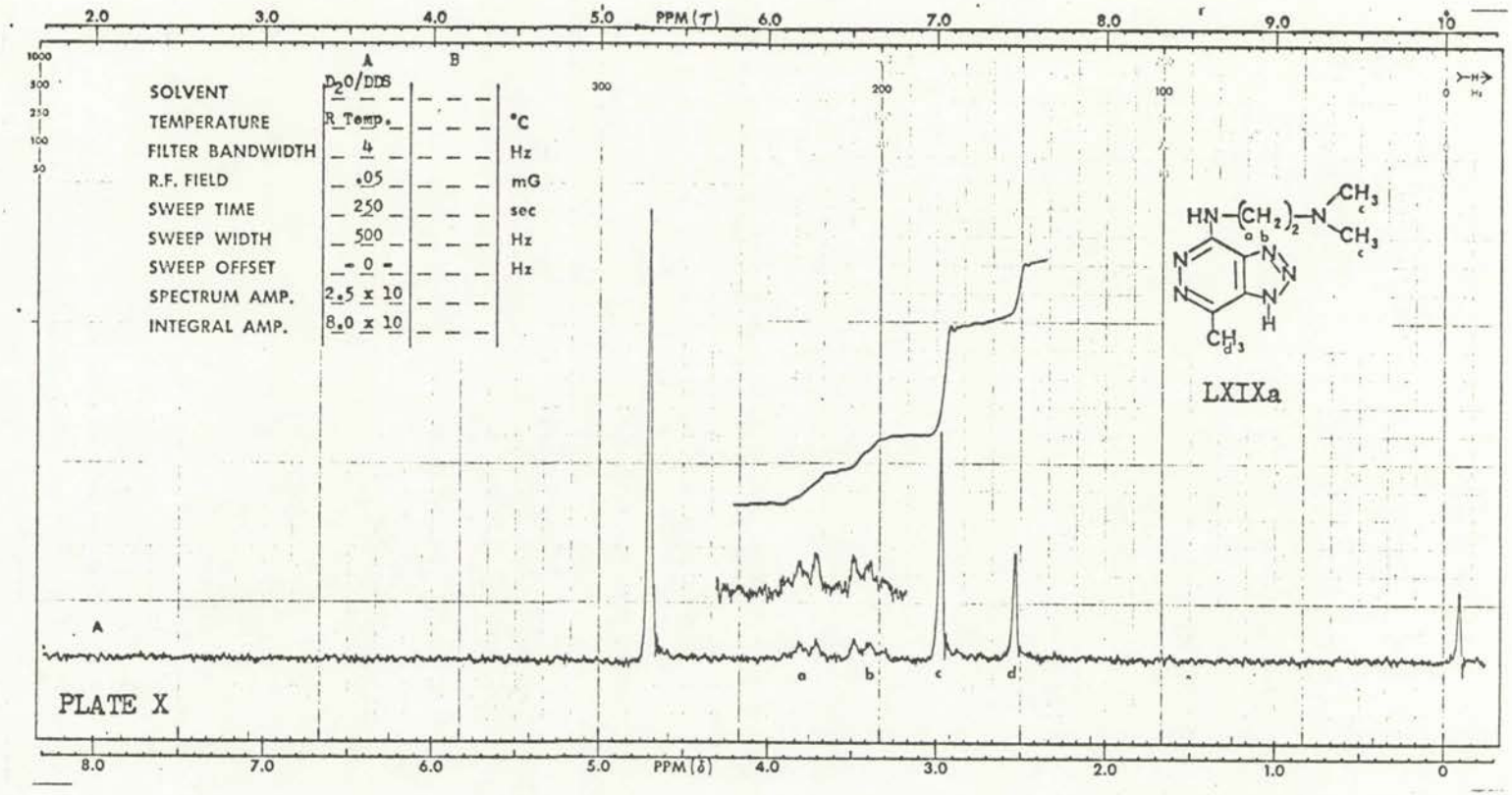

2.0
3.0
4.0
5.0
PPM(τ)
6.0
7.0
8.0
9.0
10
A
B
SOLVENT
D2O/NaOD/DDS
TEMPERATURE
R Temp
°C
FILTER BANDWIDTH
4
Hz
R.F. FIELD
.05
mG
SWEEP TIME
250
sec
SWEEP WIDTH
500
Hz
SWEEP OFFSET
0
100
Hz
SPECTRUM AMP.
1 x 10
INTEGRAL AMP.
0
LV
PLATE VII
8.0
7.0
6.0
5.0
PPM(δ)
4.0
3.0
2.0
1.0
0

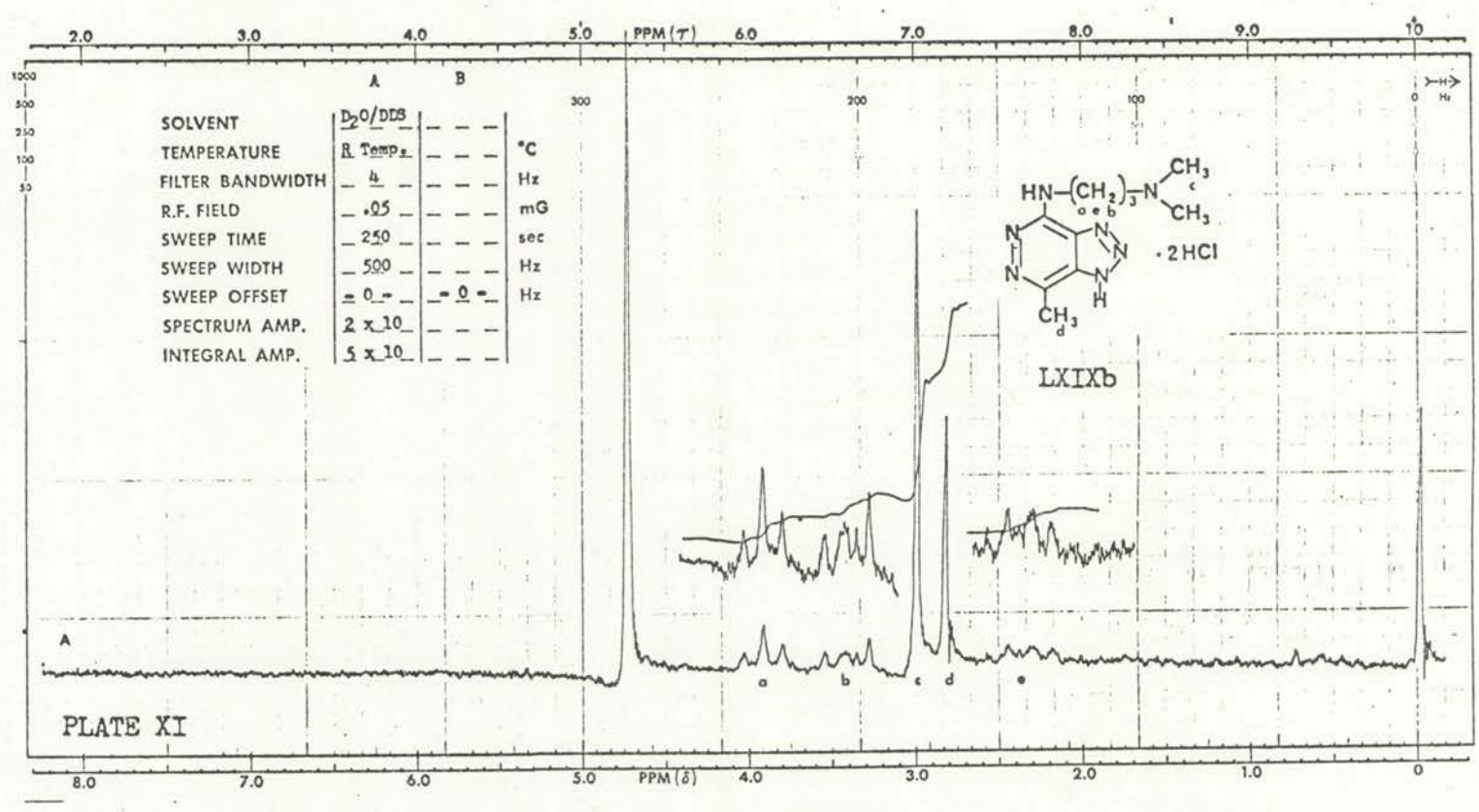


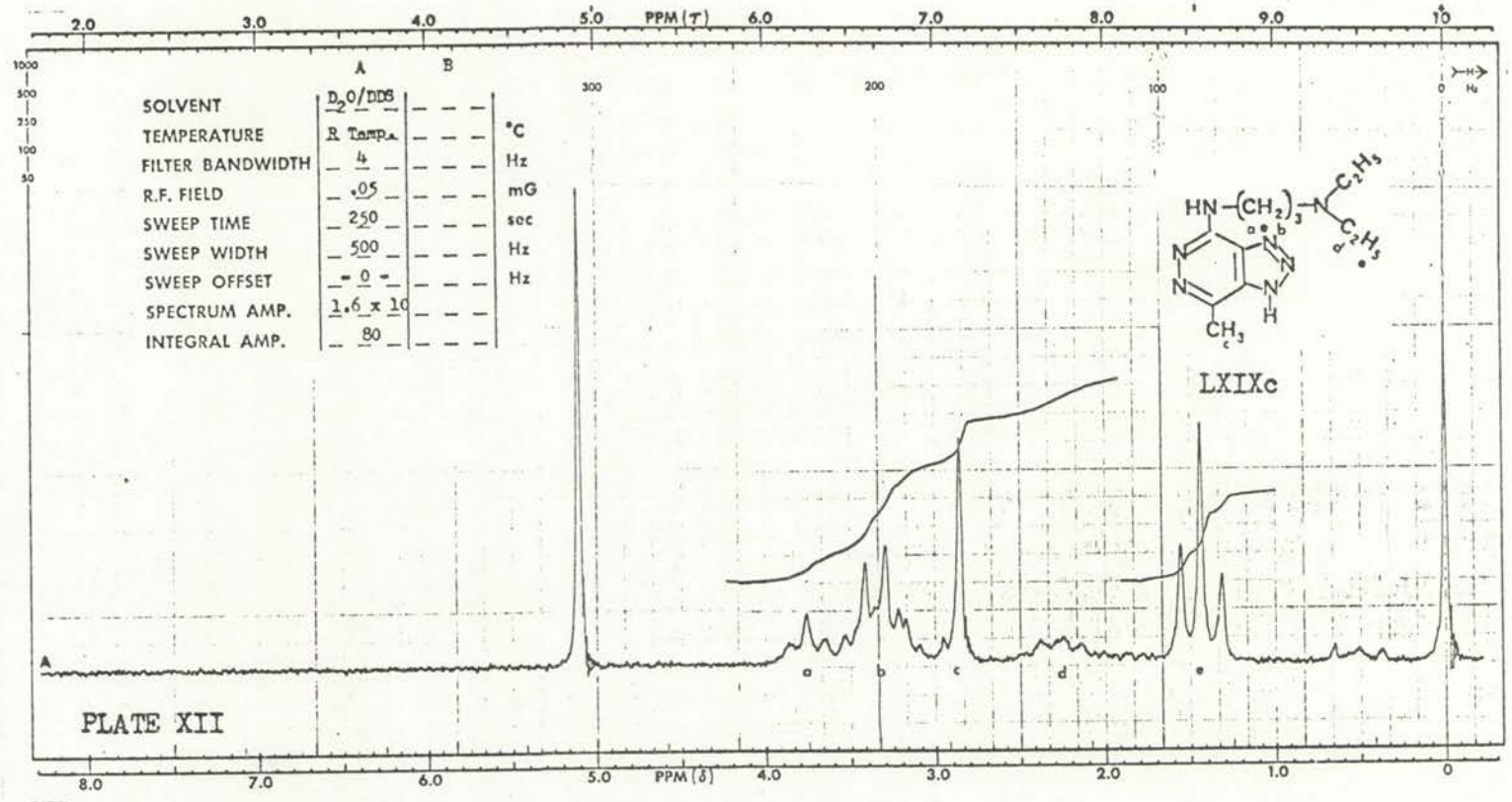
LVI

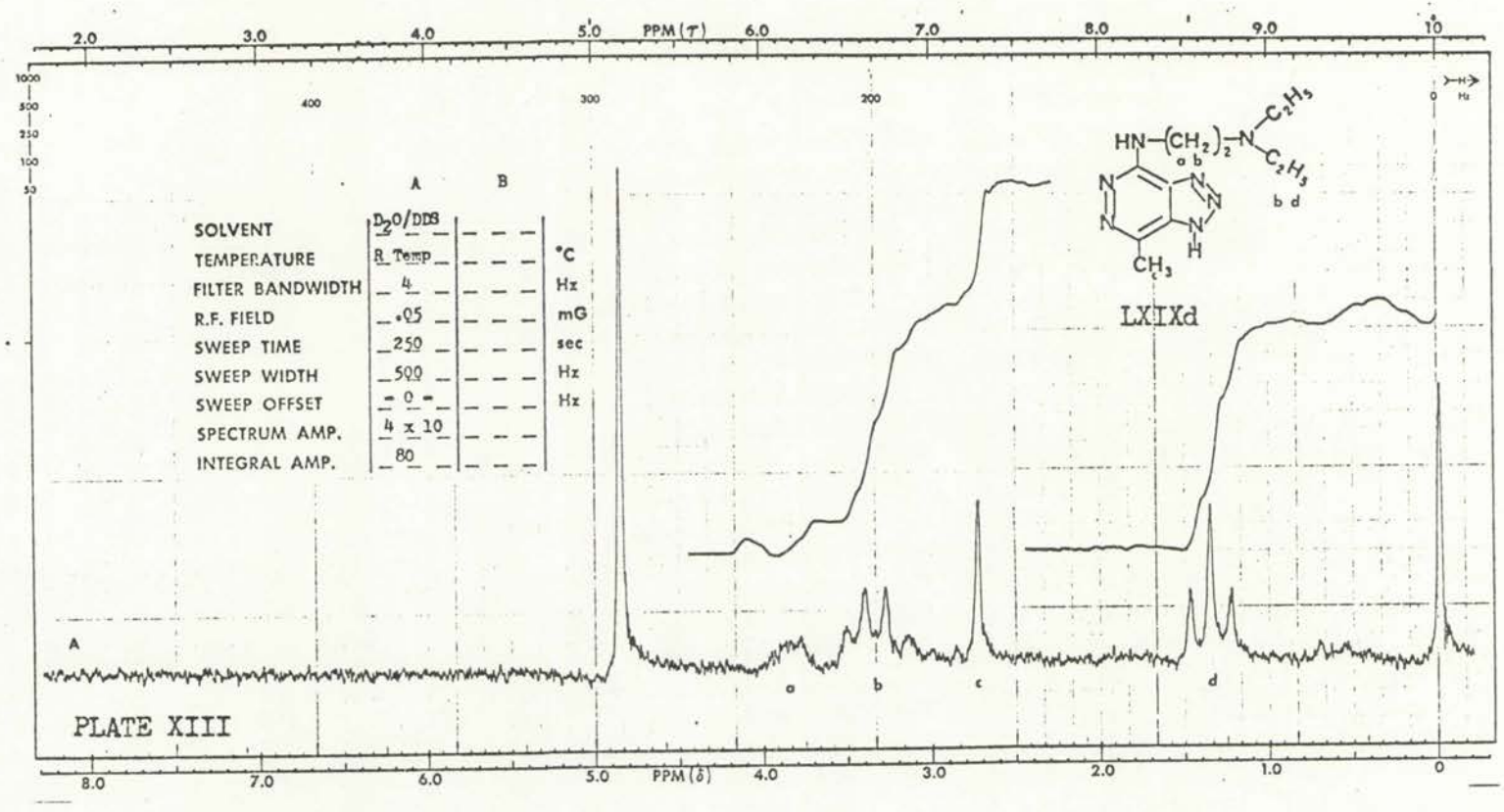
PLATE VIII

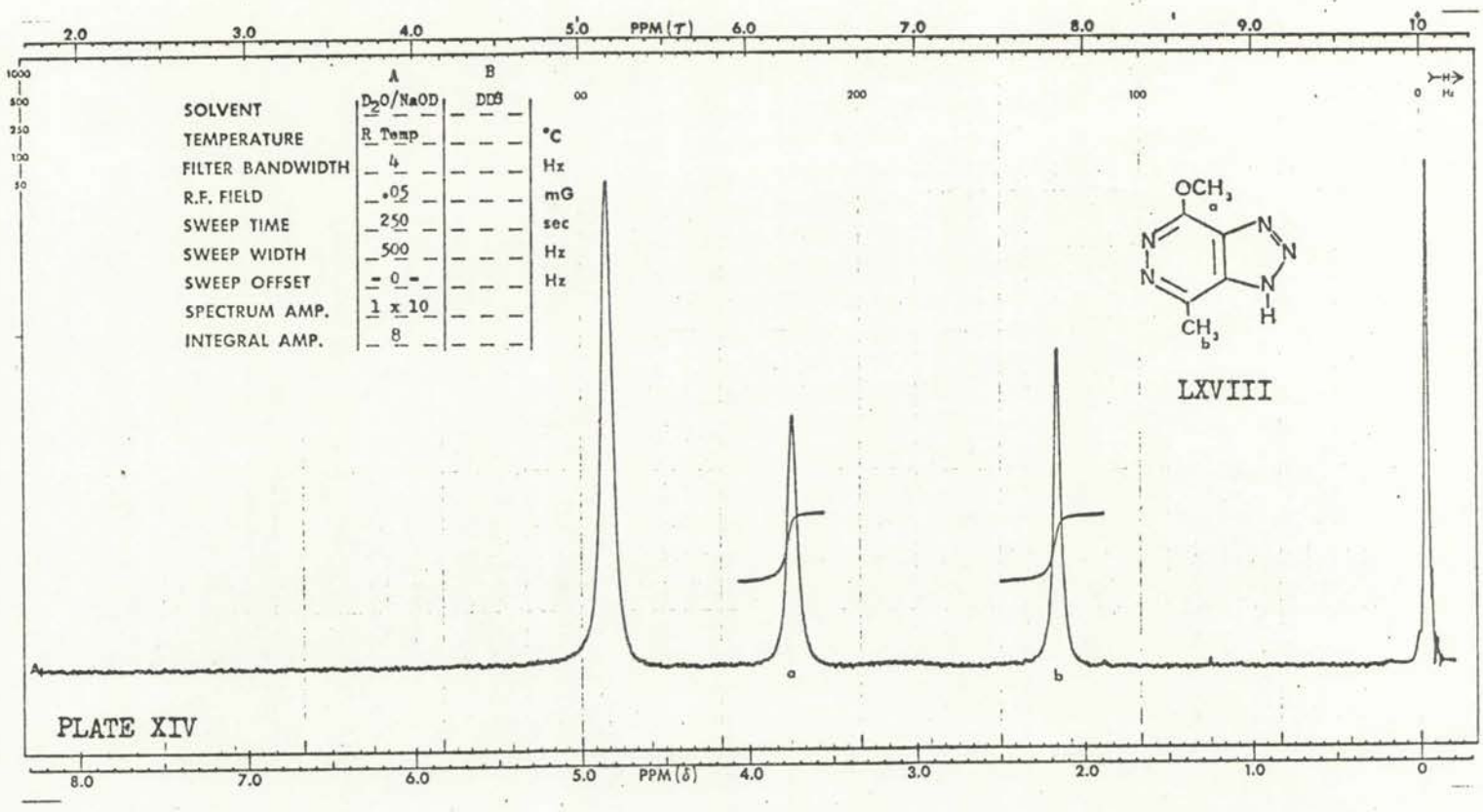

2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
A
B
SOLVENT
D2O/NaOD/DDS
TEMPERATURE
R. Temp
°C
FILTER BANDWIDTH
4
Hz
R.F. FIELD
.025
.05
mG
SWEEP TIME
250
25
sec
SWEEP WIDTH
500
Hz
SWEEP OFFSET
0
Hz
SPECTRUM AMP.
6.3
125
INTEGRAL AMP.
0
80
SCH3
b
Ha
LVII
PLATE IX
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

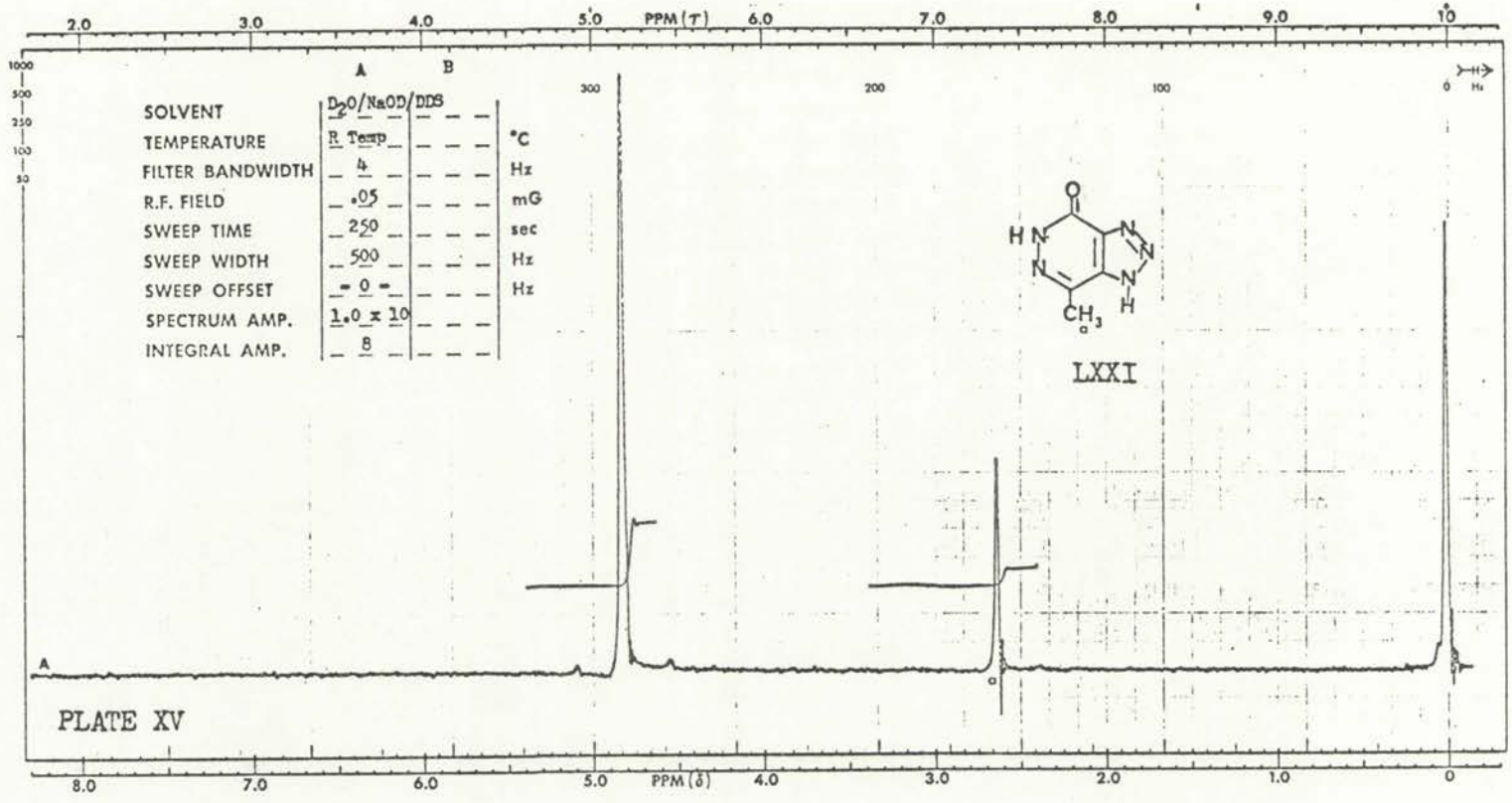

2.0
3.0
4.0
5.0
PPM(τ)
6.0
7.0
8.0
9.0
10
A
B
SOLVENT
D2O/DDS
TEMPERATURE
R Temp.
°C
FILTER BANDWIDTH
4
Hz
R.F. FIELD
.05
mG
SWEEP TIME
250
sec
SWEEP WIDTH
500
Hz
SWEEP OFFSET
0
Hz
SPECTRUM AMP.
2.5 x 10
INTEGRAL AMP.
8.0 x 10
HN
CH3
CH3
CH3
LXIXa
a
b
c
d
PLATE X
8.0
7.0
6.0
5.0
PPM(δ)
4.0
3.0
2.0
1.0
0

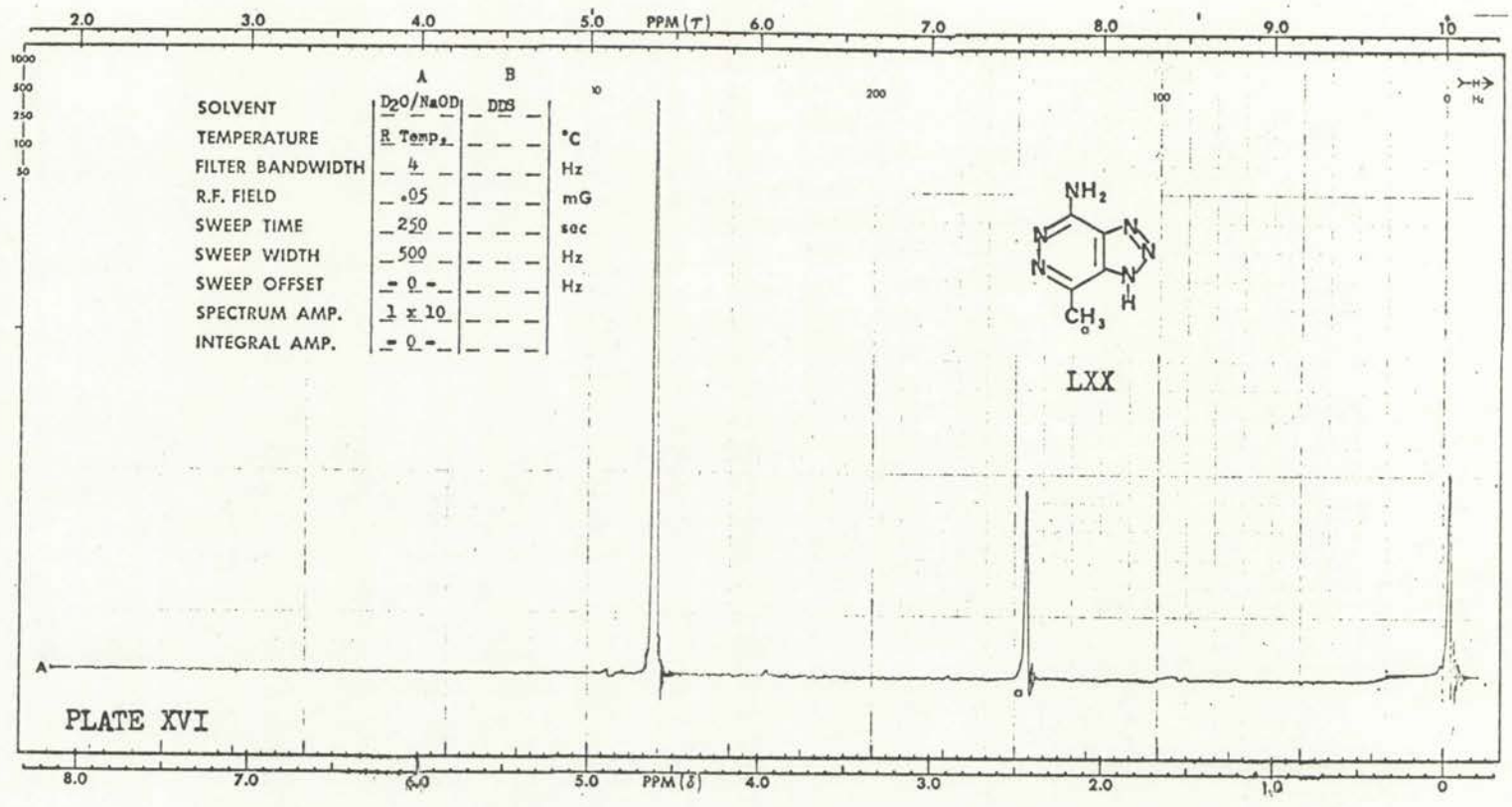

2.0
3.0
4.0
5.0
PPM(τ)
6.0
7.0
8.0
9.0
10
A
B
SOLVENT
D2O/DIS
TEMPERATURE
R. Temp.
°C
FILTER BANDWIDTH
4
Hz
R.F. FIELD
.05
mG
SWEEP TIME
250
sec
SWEEP WIDTH
500
Hz
SWEEP OFFSET
0
0
Hz
SPECTRUM AMP.
2 x 10
INTEGRAL AMP.
5 x 10
LXIXb
·2HCl
PLATE XI
PPM(δ)

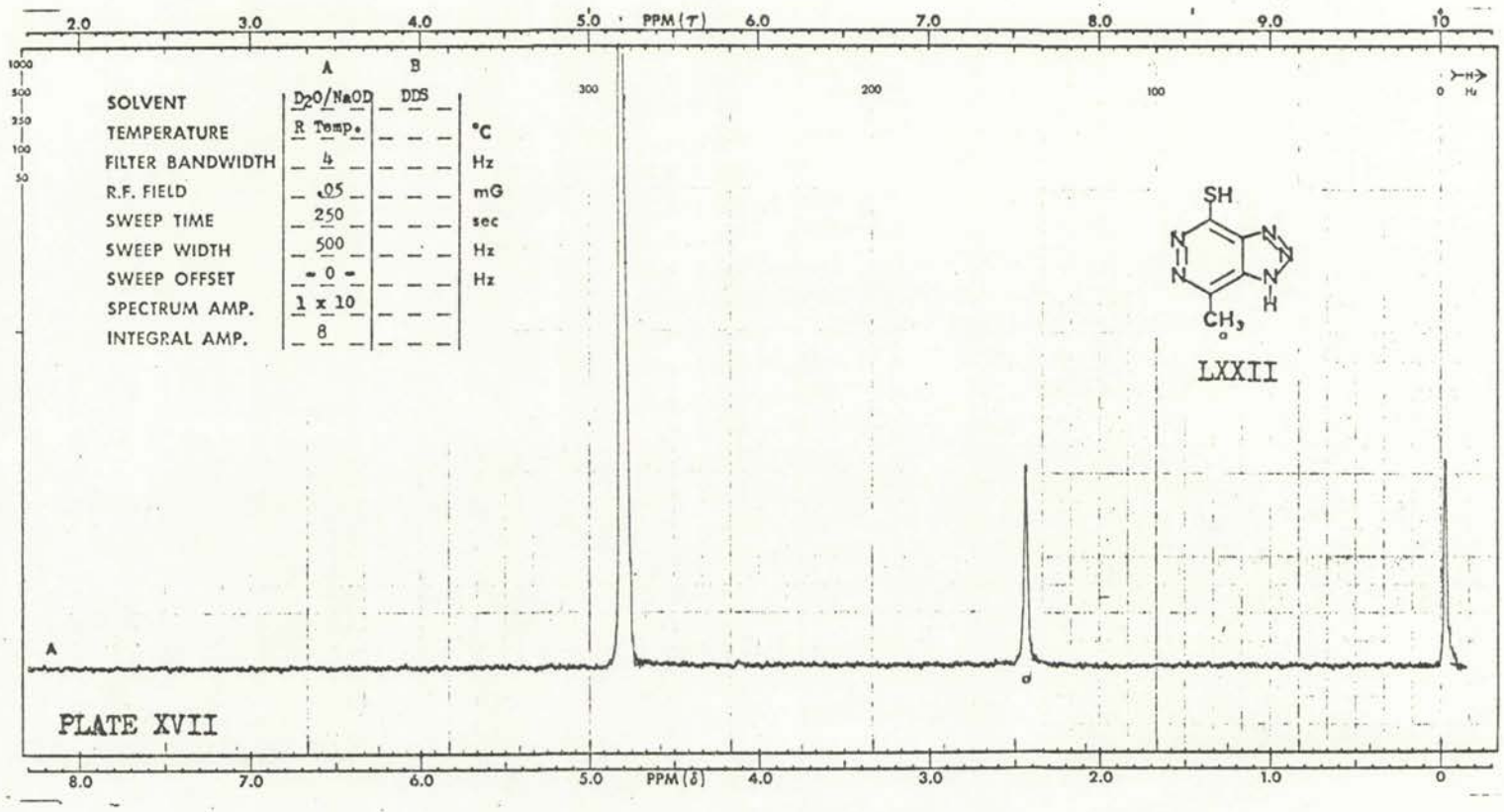

2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
A
B
SOLVENT
D2O/DDS
TEMPERATURE
R Temp.
°C
FILTER BANDWIDTH
4
Hz
R.F. FIELD
.05
mG
SWEEP TIME
250
sec
SWEEP WIDTH
500
Hz
SWEEP OFFSET
0
Hz
SPECTRUM AMP.
1.6 x 10
INTEGRAL AMP.
80
LXIXc
a
b
c
d
e
PLATE XII
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

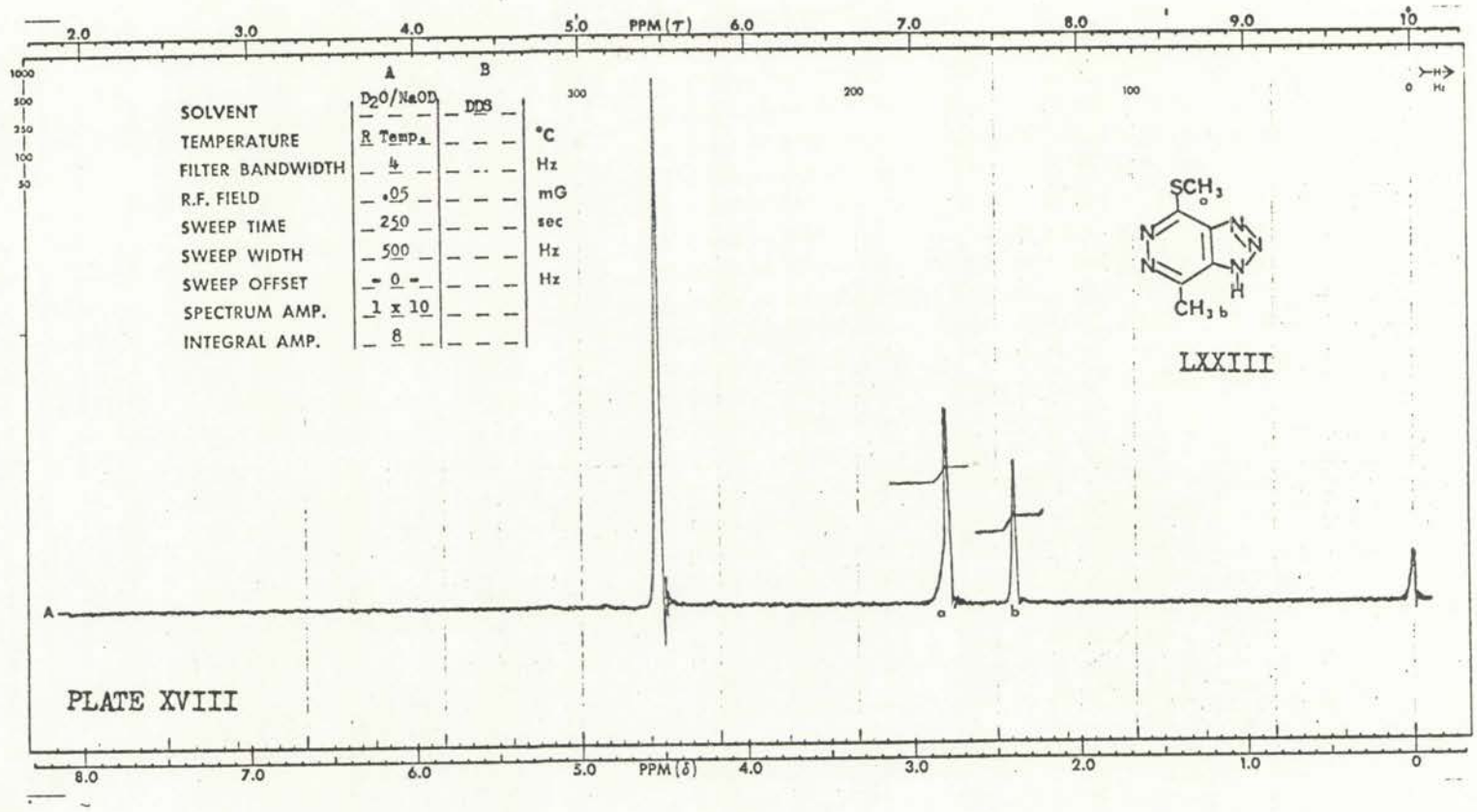

2.0
3.0
4.0
5.0
PPM(τ)
6.0
7.0
8.0
9.0
10
1000
500
250
100
50
400
300
200
0
Hz
A
B
SOLVENT
D2O/DDS
TEMPERATURE
R Temp
°C
FILTER BANDWIDTH
4
Hz
R.F. FIELD
.05
mG
SWEEP TIME
250
sec
SWEEP WIDTH
500
Hz
SWEEP OFFSET
- 0 -
Hz
SPECTRUM AMP.
4 x 10
INTEGRAL AMP.
80
HN-(CH2)2-N
C2H5
C2H5
a b
b d
CH3
H
LXIXd
A
a
b
c
d
PLATE XIII
8.0
7.0
6.0
5.0
PPM(δ)
4.0
3.0
2.0
1.0
0

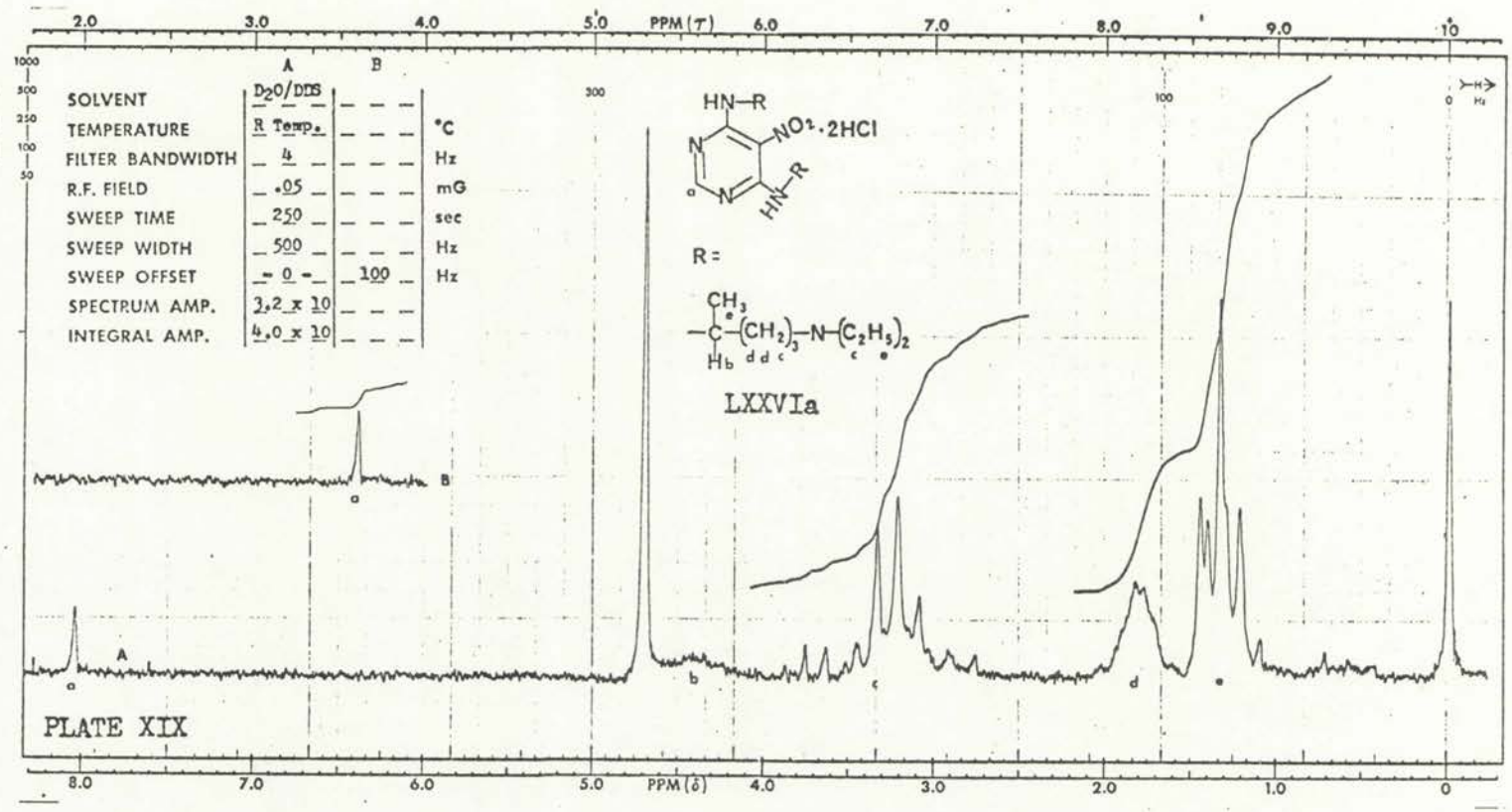

2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
A
B
SOLVENT
D2O/NaOD
DDB
TEMPERATURE
R Temp
°C
FILTER BANDWIDTH
4
Hz
R.F. FIELD
.05
mG
SWEEP TIME
250
sec
SWEEP WIDTH
500
Hz
SWEEP OFFSET
0
Hz
SPECTRUM AMP.
1 x 10
INTEGRAL AMP.
8
OCH3
a
CH3
b
LXVIII
a
b
PLATE XIV
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

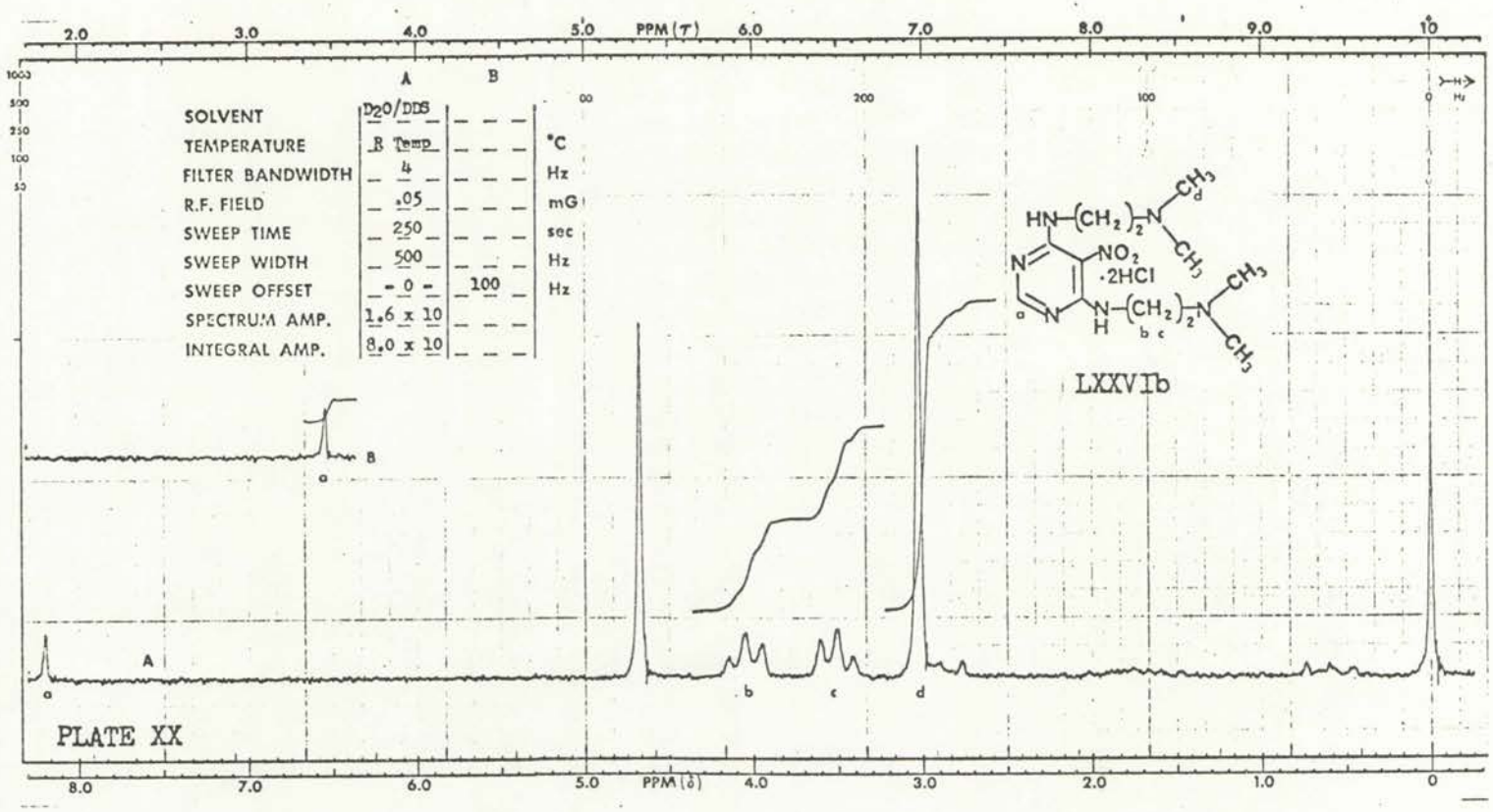

2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
A
B
SOLVENT
D2O/NaOD/DDS
TEMPERATURE
R Temp
°C
FILTER BANDWIDTH
4
Hz
R.F. FIELD
.05
mG
SWEEP TIME
250
sec
SWEEP WIDTH
500
Hz
SWEEP OFFSET
0
Hz
SPECTRUM AMP.
1.0 x 10
INTEGRAL AMP.
8
LXXI
PLATE XV
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

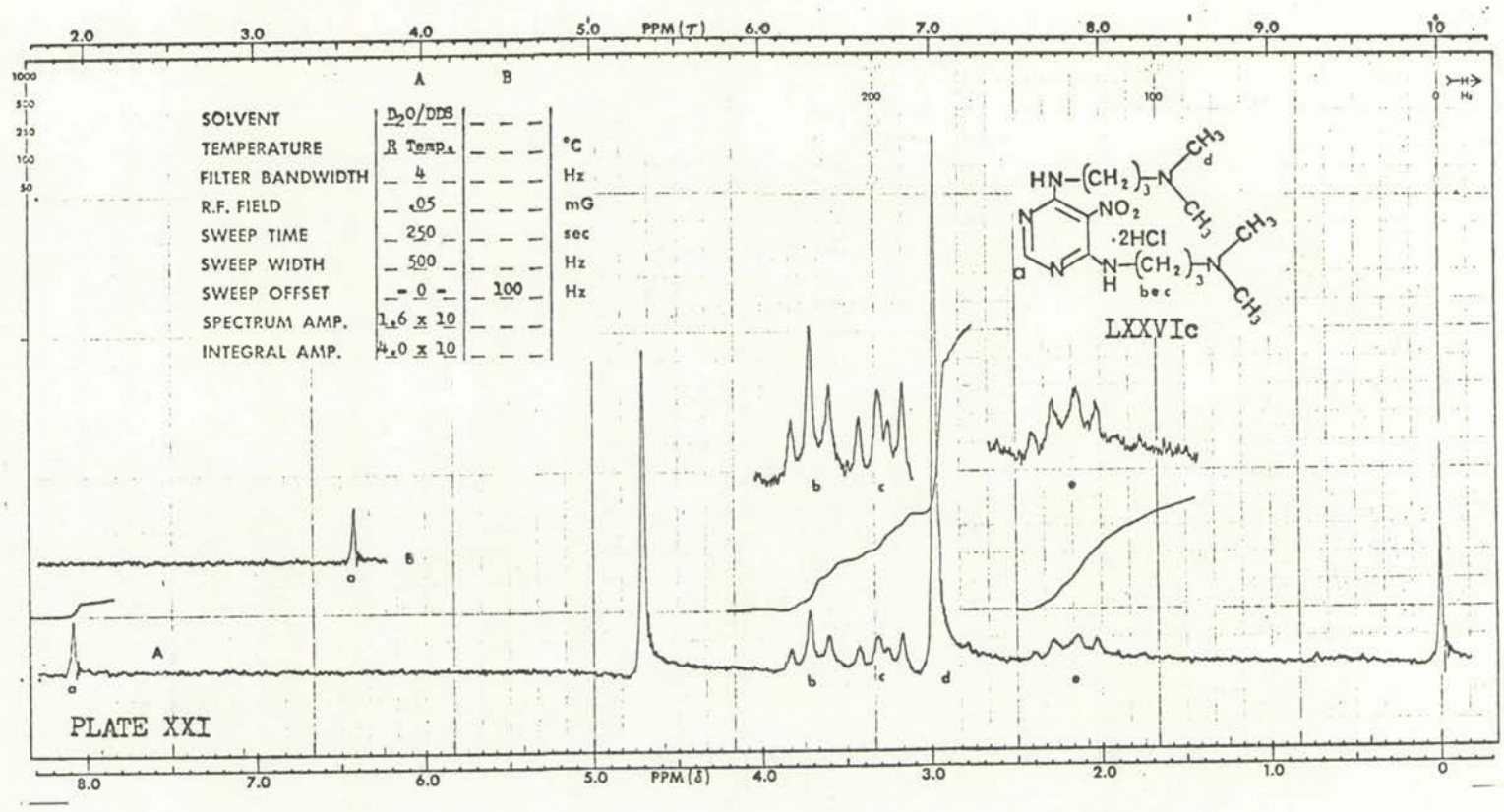

2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
1000
500
250
100
50
A
B
SOLVENT
D2O/NaOD
DDS
TEMPERATURE
R Temp.
°C
FILTER BANDWIDTH
4
Hz
R.F. FIELD
.05
mG
SWEEP TIME
250
sec
SWEEP WIDTH
500
Hz
SWEEP OFFSET
0
Hz
SPECTRUM AMP.
1 x 10
INTEGRAL AMP.
0
10
200
100
0
Hz
NH2
N
N
N
N
N
H
CH3
LXX
A
PLATE XVI
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

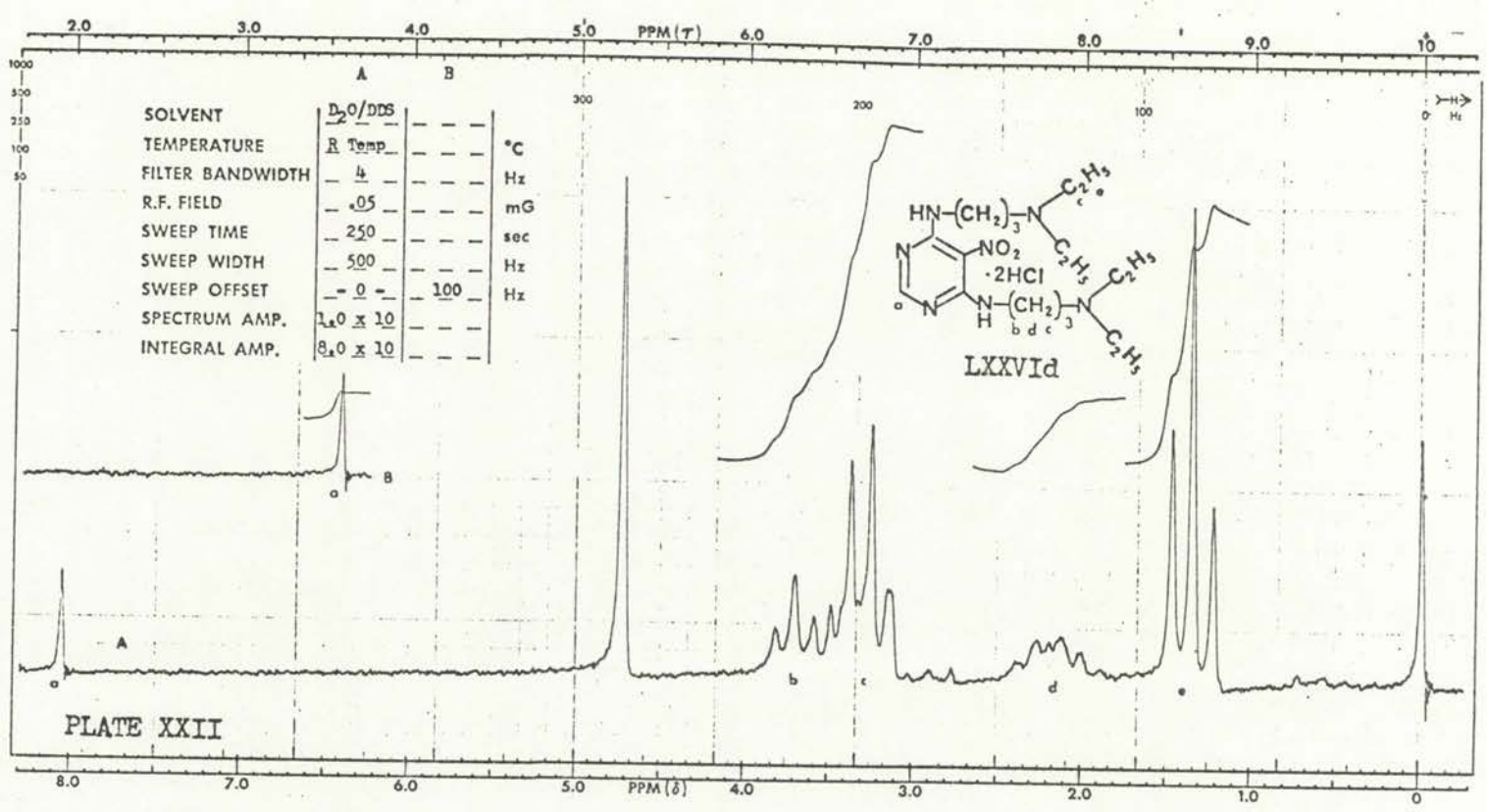

2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
A
B
SOLVENT
D2O/NaOD
DDS
TEMPERATURE
R Temp.
°C
FILTER BANDWIDTH
4
Hz
R.F. FIELD
.05
mG
SWEEP TIME
250
sec
SWEEP WIDTH
500
Hz
SWEEP OFFSET
0
Hz
SPECTRUM AMP.
1 x 10
INTEGRAL AMP.
8
SH
CH3
a
H
LXXII
A
a
PLATE XVII
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

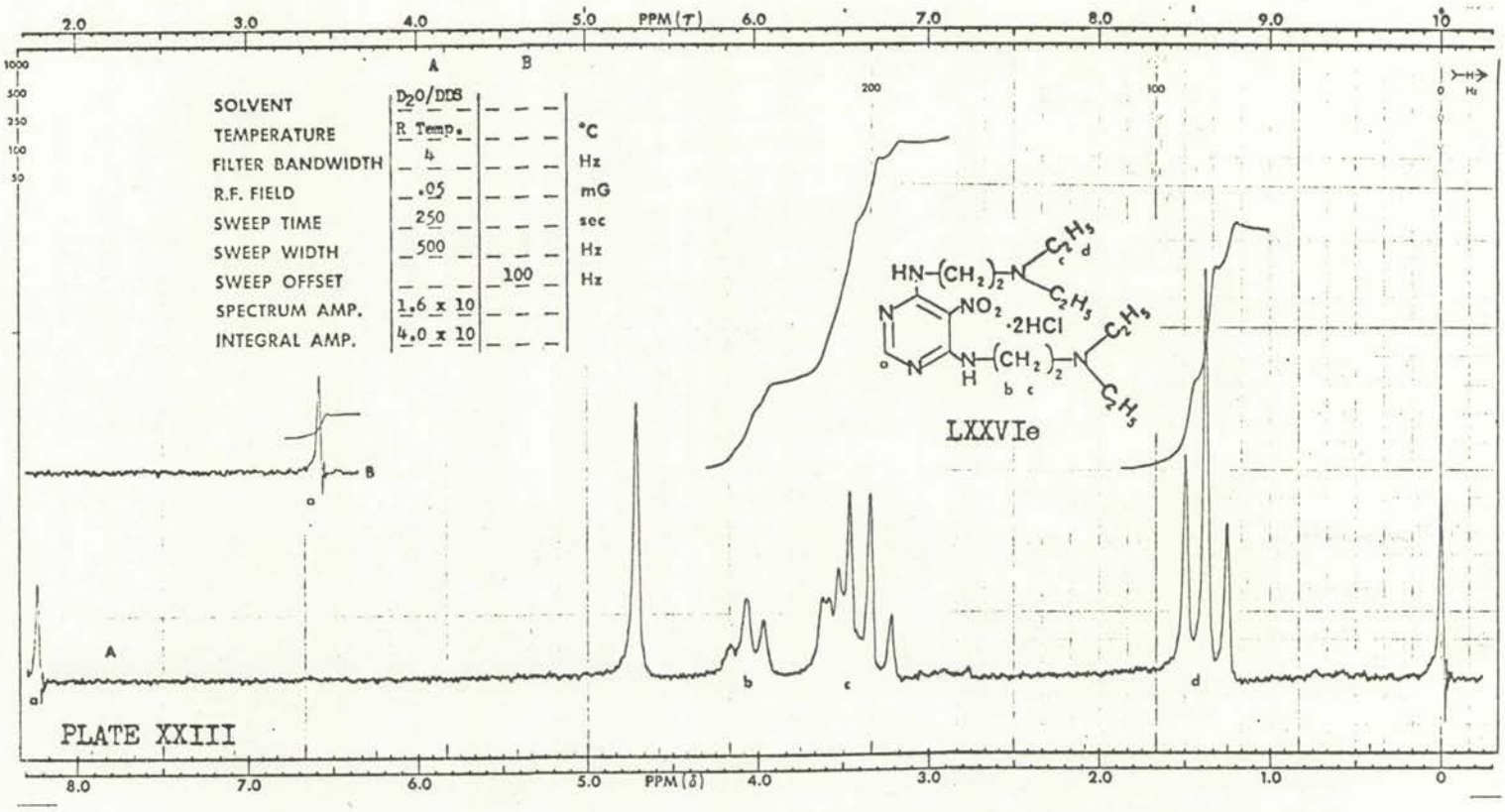

2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
A
B
SOLVENT
D2O/NaOD
DDS
TEMPERATURE
R Temp.
°C
FILTER BANDWIDTH
4
Hz
R.F. FIELD
.05
mG
SWEEP TIME
250
sec
SWEEP WIDTH
500
Hz
SWEEP OFFSET
0
Hz
SPECTRUM AMP.
1 x 10
INTEGRAL AMP.
8
SCH3
CH3 b
H
LXXIII
a
b
PLATE XVIII
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

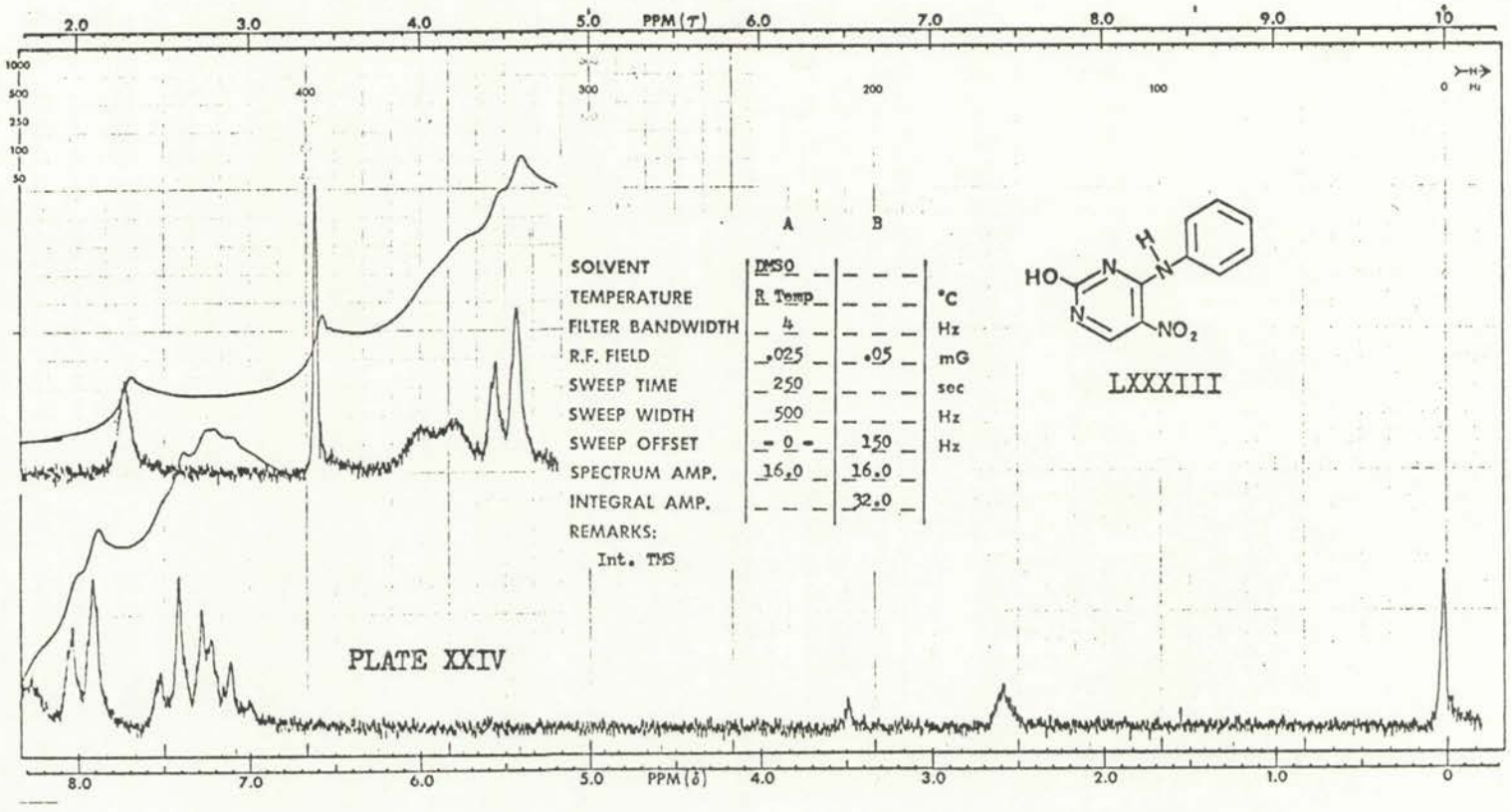

2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
A
B
SOLVENT
D2O/DMS
TEMPERATURE
R Temp.
°C
FILTER BANDWIDTH
4
Hz
R.F. FIELD
.05
mG
SWEEP TIME
250
sec
SWEEP WIDTH
500
Hz
SWEEP OFFSET
0
100
Hz
SPECTRUM AMP.
3.2 x 10
INTEGRAL AMP.
4.0 x 10
HN—R
NO2·2HCl
HN—R
R =
CH3
Hb d d c
LXXVIa
PLATE XIX
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

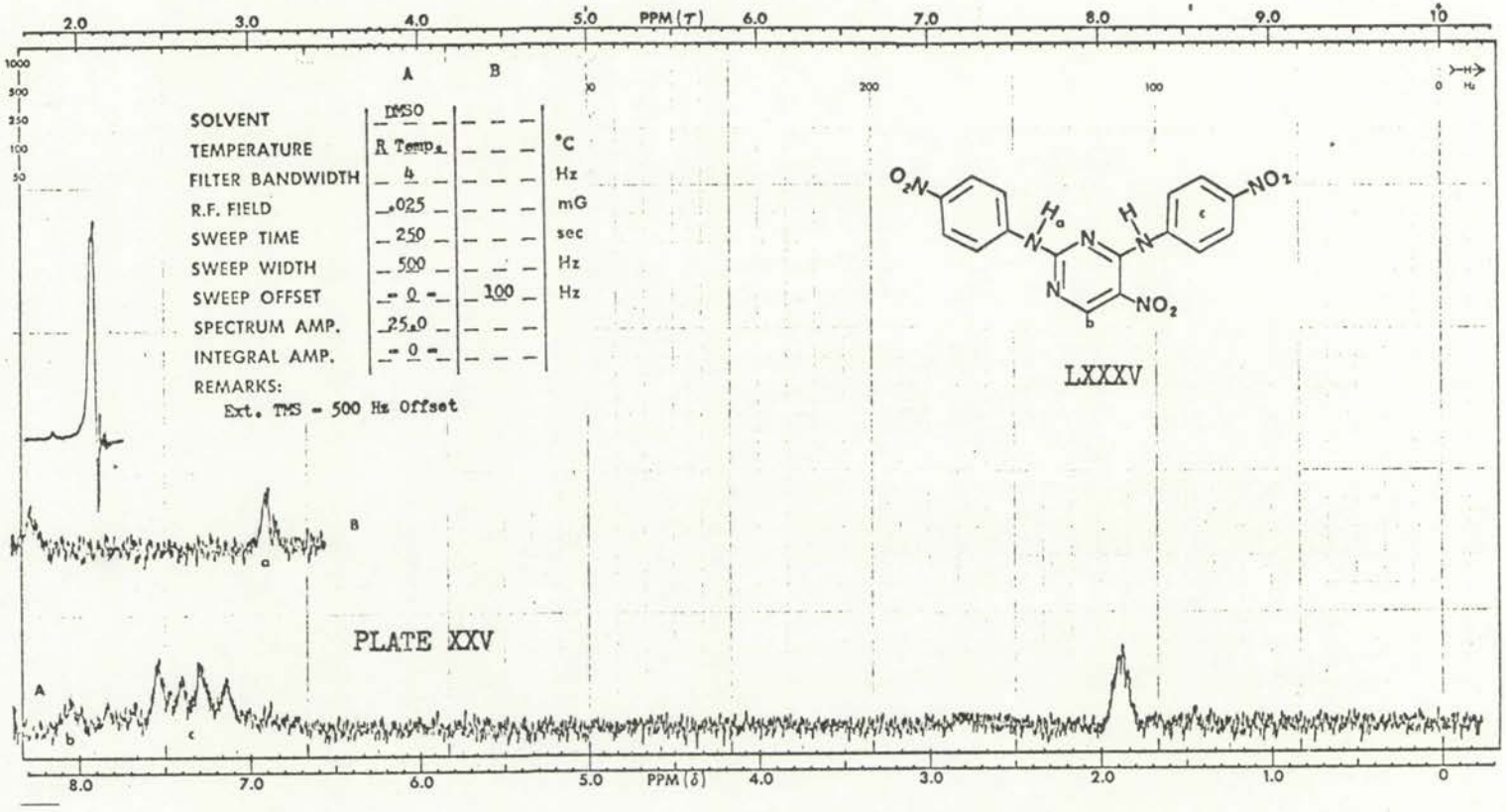

2.0
3.0
4.0
5.0
PPM(τ)
6.0
7.0
8.0
9.0
10
A
B
SOLVENT D2O/DDS
TEMPERATURE R Temp °C
FILTER BANDWIDTH 4 Hz
R.F. FIELD .05 mG
SWEEP TIME 250 sec
SWEEP WIDTH 500 Hz
SWEEP OFFSET -0- 100 Hz
SPECTRUM AMP. 1.6 x 10
INTEGRAL AMP. 8.0 x 10
LXXVIb
PLATE XX
8.0
7.0
6.0
5.0
PPM(δ)
4.0
3.0
2.0
1.0
0

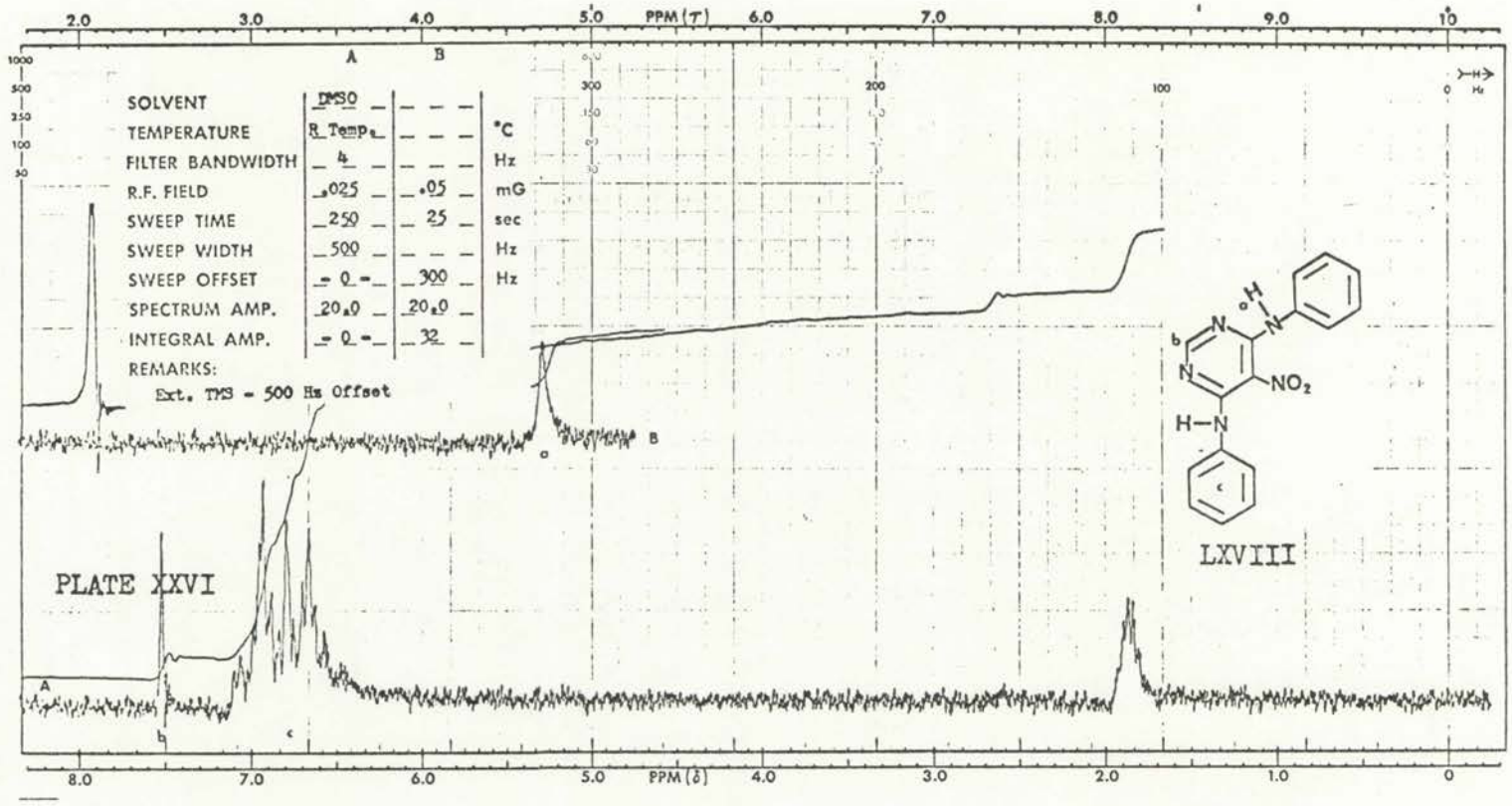

2.0
3.0
4.0
5.0
PPM(τ)
6.0
7.0
8.0
9.0
10
A
B
SOLVENT
D2O/DDS
TEMPERATURE
R Temp.
°C
FILTER BANDWIDTH
4
Hz
R.F. FIELD
.05
mG
SWEEP TIME
250
sec
SWEEP WIDTH
500
Hz
SWEEP OFFSET
0
100
Hz
SPECTRUM AMP.
1.6 x 10
INTEGRAL AMP.
4.0 x 10
HN-(CH2)3-N
CH3
d
NO2
·2HCl
N
H
bec
LXXVIc
PLATE XXI
8.0
7.0
6.0
5.0
PPM(δ)
4.0
3.0
2.0
1.0
0

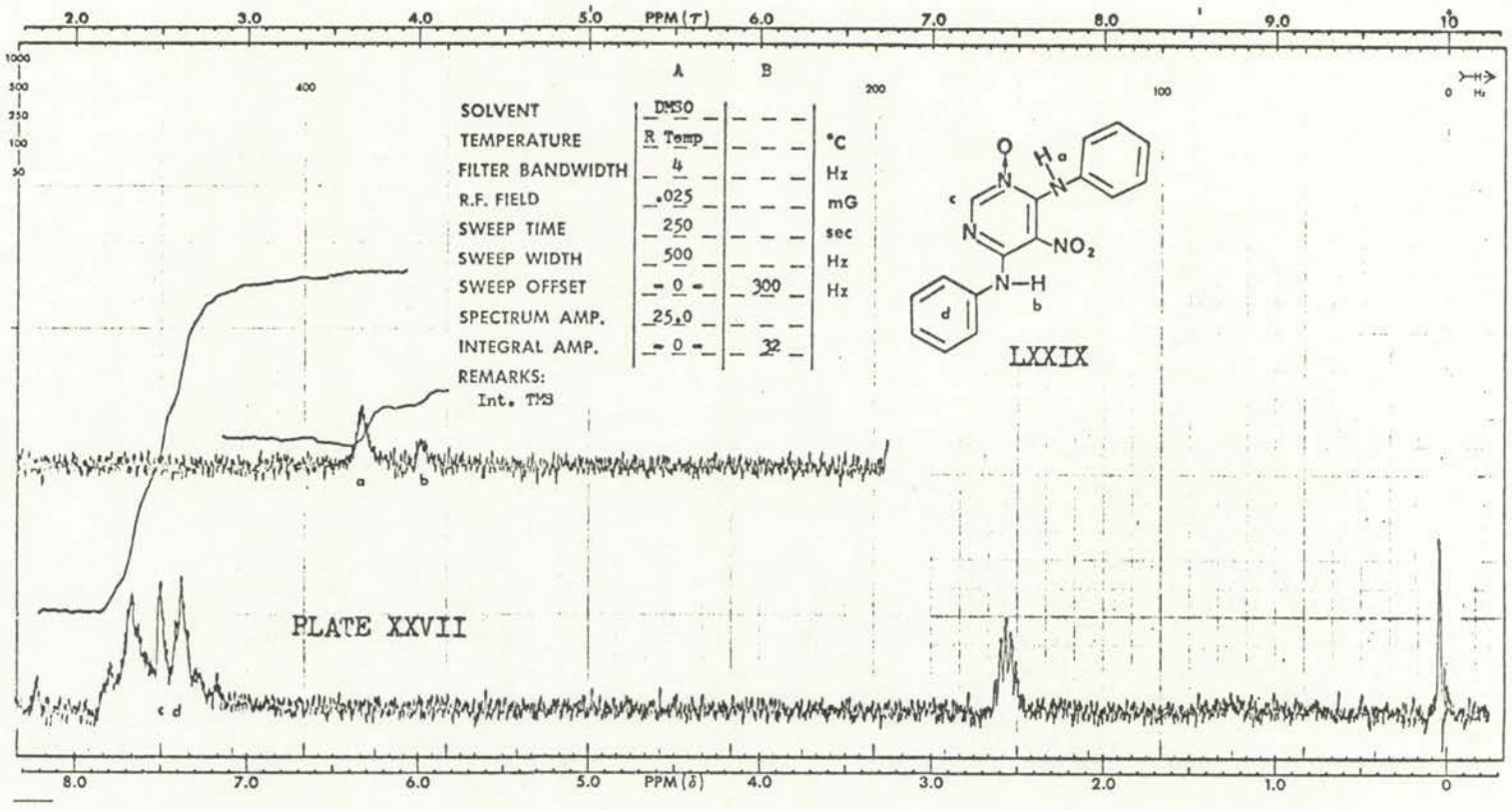

2.0
3.0
4.0
5.0
PPM(τ)
6.0
7.0
8.0
9.0
10
A
B
SOLVENT D2O/DDS
TEMPERATURE R Temp °C
FILTER BANDWIDTH 4 Hz
R.F. FIELD .05 mG
SWEEP TIME 250 sec
SWEEP WIDTH 500 Hz
SWEEP OFFSET -0- 100 Hz
SPECTRUM AMP. 1.0 x 10
INTEGRAL AMP. 8.0 x 10
LXXVId
PLATE XXII
8.0
7.0
6.0
5.0
PPM(δ)
4.0
3.0
2.0
1.0
0

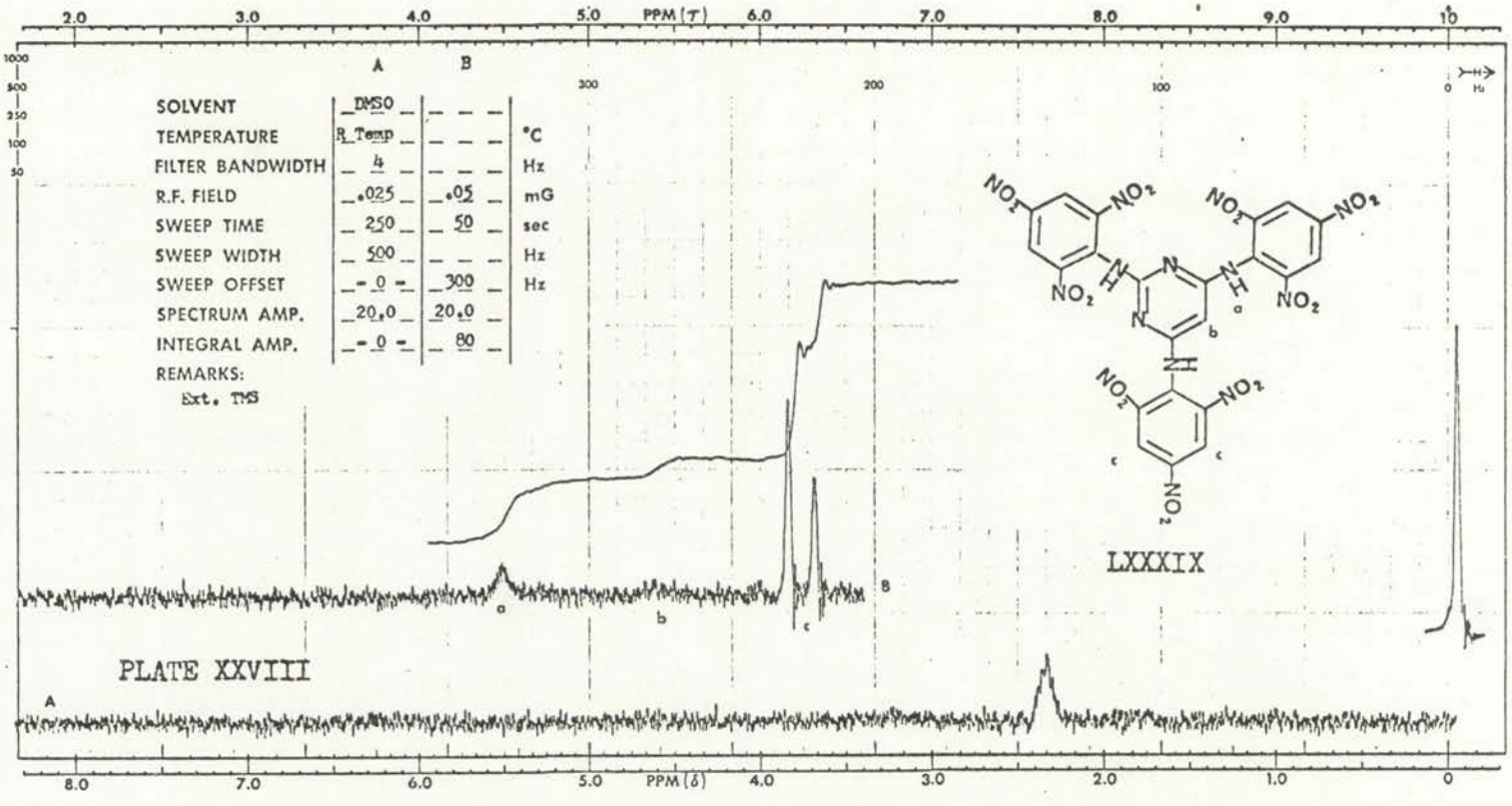

2.0
3.0
4.0
5.0
PPM(τ)
6.0
7.0
8.0
9.0
10
A
B
SOLVENT D2O/DDS
TEMPERATURE R Temp.
FILTER BANDWIDTH 4 Hz
R.F. FIELD .05 mG
SWEEP TIME 250 sec
SWEEP WIDTH 500 Hz
SWEEP OFFSET 100 Hz
SPECTRUM AMP. 1.6 x 10
INTEGRAL AMP. 4.0 x 10
°C
LXXVIe
PLATE XXIII
8.0
7.0
6.0
5.0
PPM(δ)
4.0
3.0
2.0
1.0
0

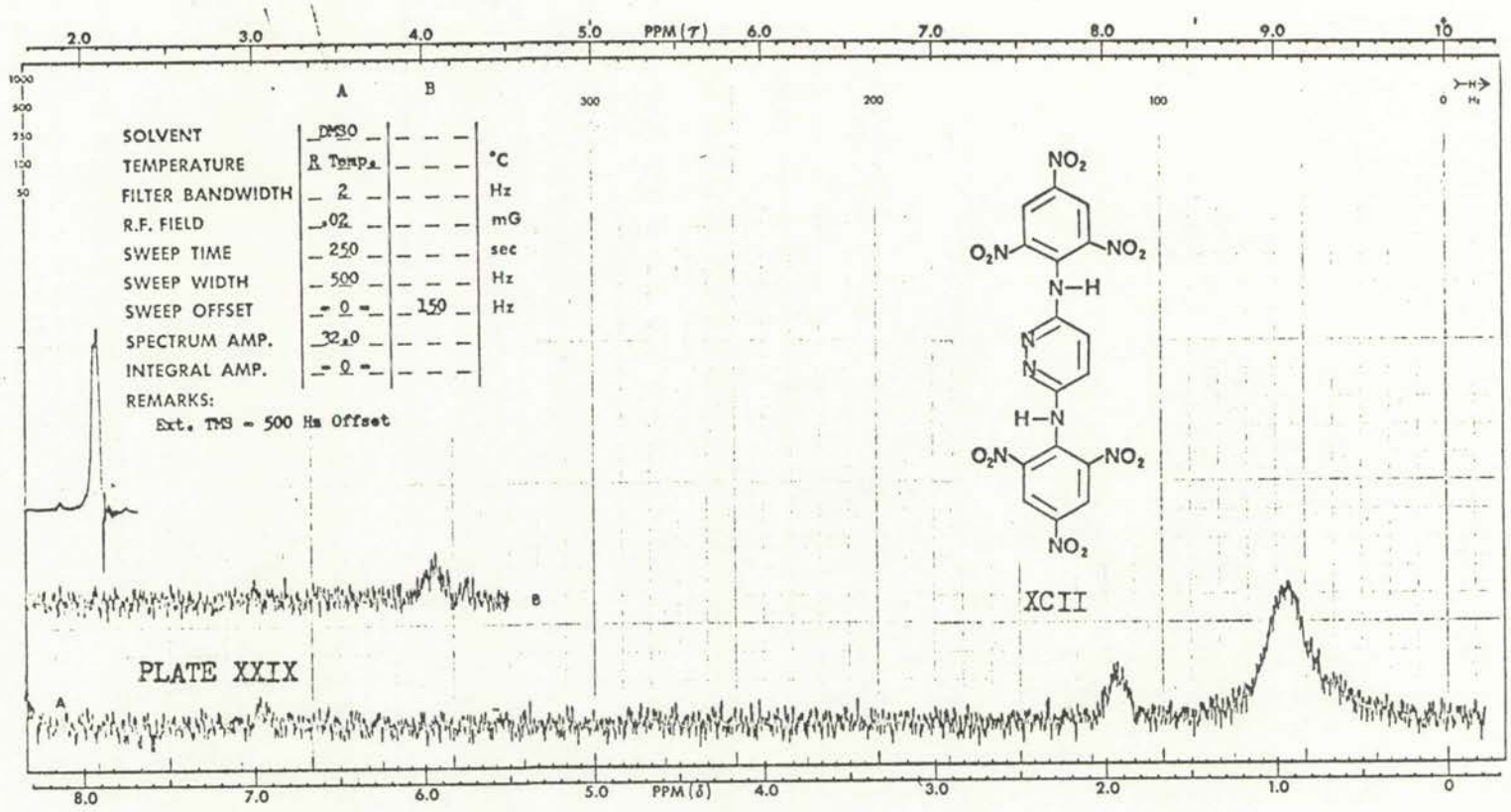

2.0
3.0
4.0
5.0 PPM (τ)
6.0
7.0
8.0
9.0
10
1000
500
250
100
50
400
300
200
100
0 Hz
A
B
SOLVENT DMSO °C
TEMPERATURE R. Temp
FILTER BANDWIDTH 4 Hz
R.F. FIELD .025 .05 mG
SWEEP TIME 250 sec
SWEEP WIDTH 500 Hz
SWEEP OFFSET 0 150 Hz
SPECTRUM AMP. 16.0 16.0
INTEGRAL AMP. 32.0
REMARKS:
Int. TMS
HO
N
H
N
N
NO2
LXXXIII
PLATE XXIV
8.0
7.0
6.0
5.0 PPM (δ)
4.0
3.0
2.0
1.0
0


2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
A
B
SOLVENT DMSO
TEMPERATURE R Temp. °C
FILTER BANDWIDTH 4 Hz
R.F. FIELD .025 mG
SWEEP TIME 250 sec
SWEEP WIDTH 500 Hz
SWEEP OFFSET 0 100 Hz
SPECTRUM AMP. 25.0
INTEGRAL AMP. 0
REMARKS:
Ext. TMS - 500 Hz Offset
LXXXV
PLATE XXV
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0


2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
A
B
SOLVENT DMSO
TEMPERATURE R Temp.
°C
FILTER BANDWIDTH 4 Hz
R.F. FIELD .025 .05 mG
SWEEP TIME 250 25 sec
SWEEP WIDTH 500 Hz
SWEEP OFFSET 0 300 Hz
SPECTRUM AMP. 20.0 20.0
INTEGRAL AMP. 0 32
REMARKS:
Ext. TMS - 500 Hz Offset
PLATE XXVI
LXVIII
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0


2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
A
B
SOLVENT DMSO
TEMPERATURE R Temp °C
FILTER BANDWIDTH 4 Hz
R.F. FIELD .025 mG
SWEEP TIME 250 sec
SWEEP WIDTH 500 Hz
SWEEP OFFSET 0 300 Hz
SPECTRUM AMP. 25.0
INTEGRAL AMP. 0 32
REMARKS:
Int. TMS
LXXIX
PLATE XXVII
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0


2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
A
B
SOLVENT
DMSO
TEMPERATURE
R. Temp
°C
FILTER BANDWIDTH
4
Hz
R.F. FIELD
.025
.05
mG
SWEEP TIME
250
50
sec
SWEEP WIDTH
500
Hz
SWEEP OFFSET
0
300
Hz
SPECTRUM AMP.
20.0
20.0
INTEGRAL AMP.
0
80
REMARKS:
Ext. TMS
LXXXIX
PLATE XXVIII
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0


2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
A
B
SOLVENT DMSO
TEMPERATURE R Temp. °C
FILTER BANDWIDTH 2 Hz
R.F. FIELD .02 mG
SWEEP TIME 250 sec
SWEEP WIDTH 500 Hz
SWEEP OFFSET - 0 - 150 Hz
SPECTRUM AMP. 32.0
INTEGRAL AMP. - 0 -
REMARKS:
Ext. TMS - 500 Hz Offset
PLATE XXIX
XCII
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

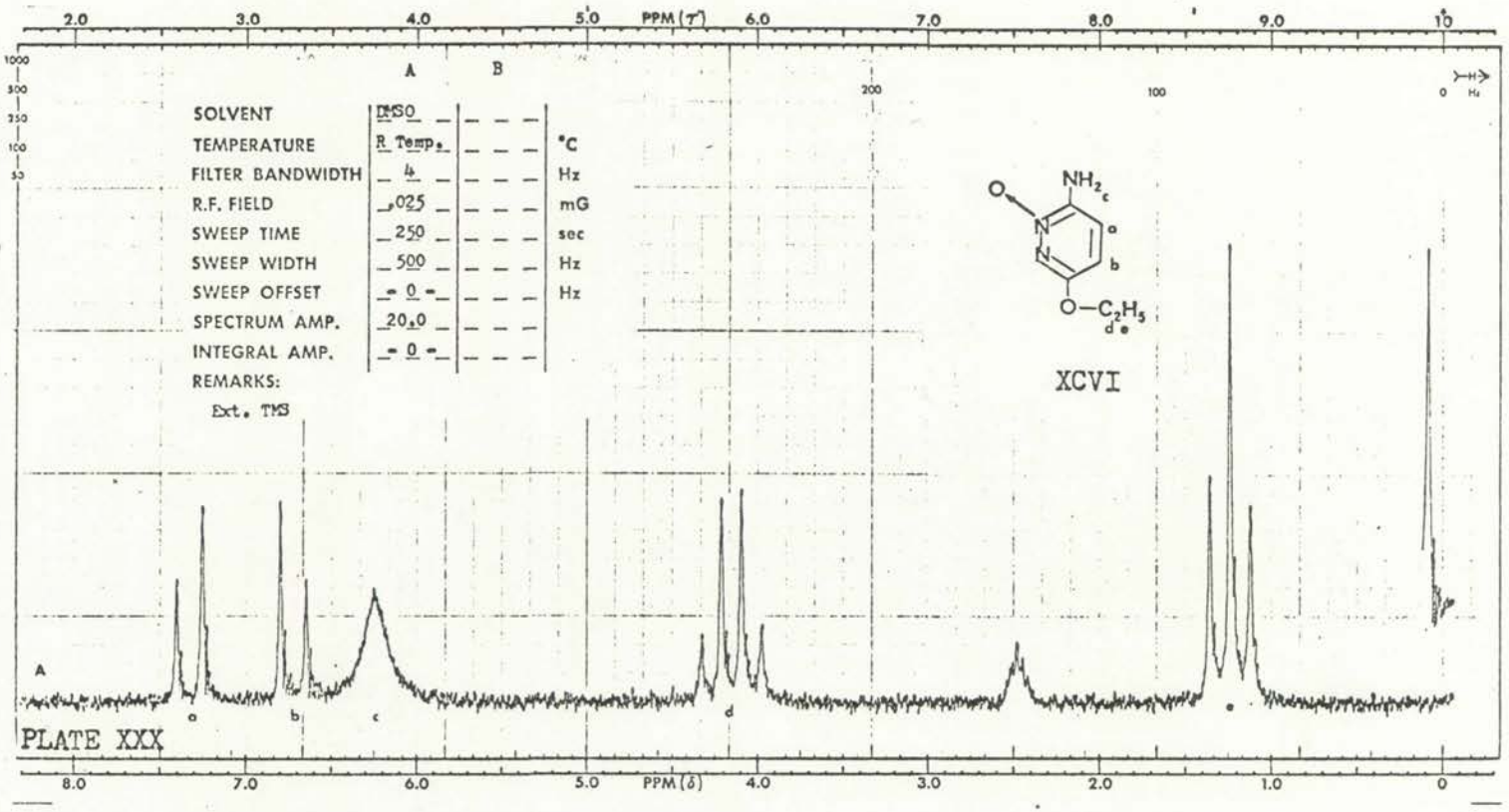

2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
A
B
SOLVENT DMSO
TEMPERATURE R Temp. °C
FILTER BANDWIDTH 4 Hz
R.F. FIELD .025 mG
SWEEP TIME 250 sec
SWEEP WIDTH 500 Hz
SWEEP OFFSET - 0 - Hz
SPECTRUM AMP. 20.0
INTEGRAL AMP. - 0 -
REMARKS:
Ext. TMS
XCVI
PPM (δ)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0

PLATE XXX

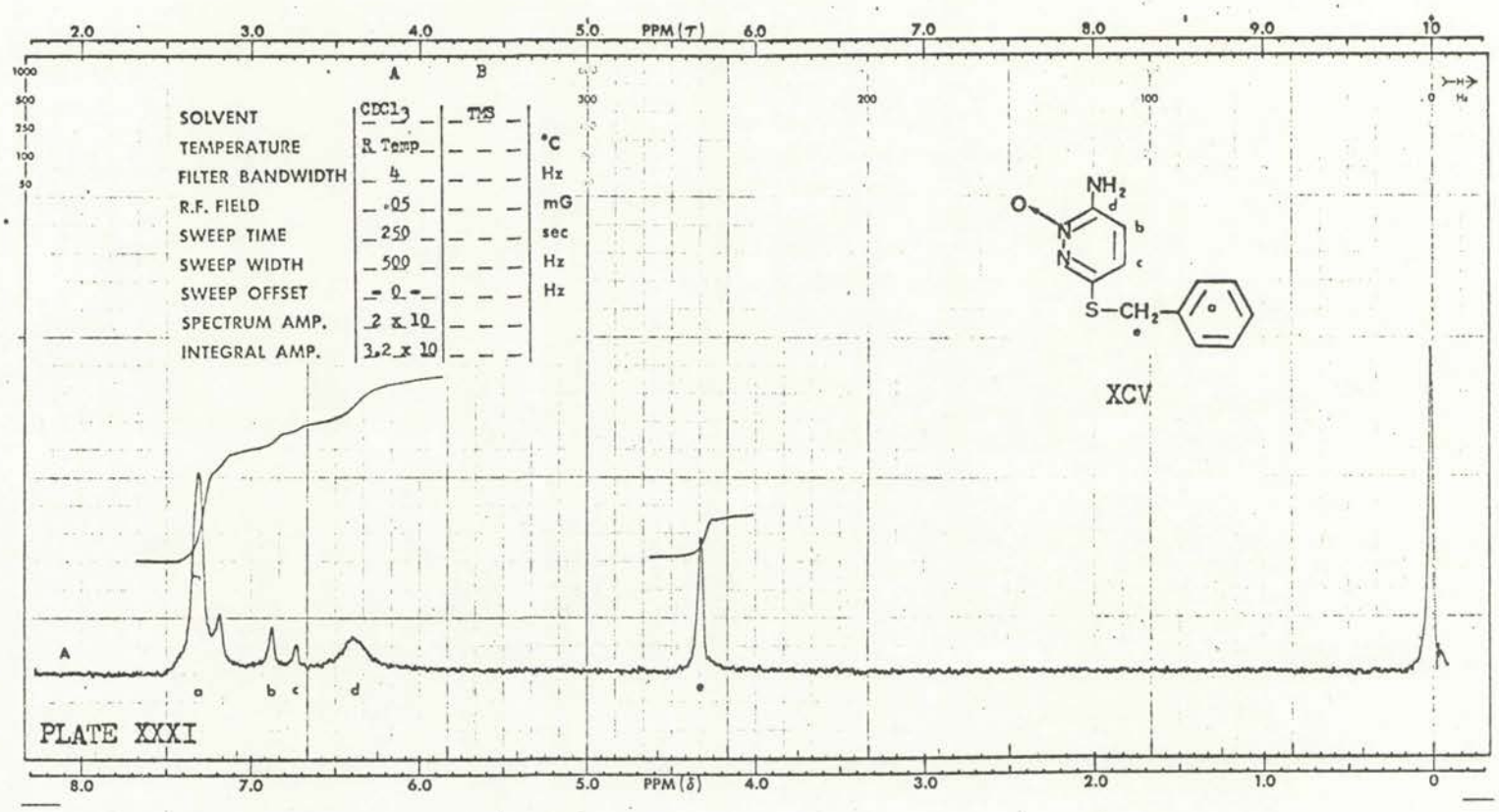
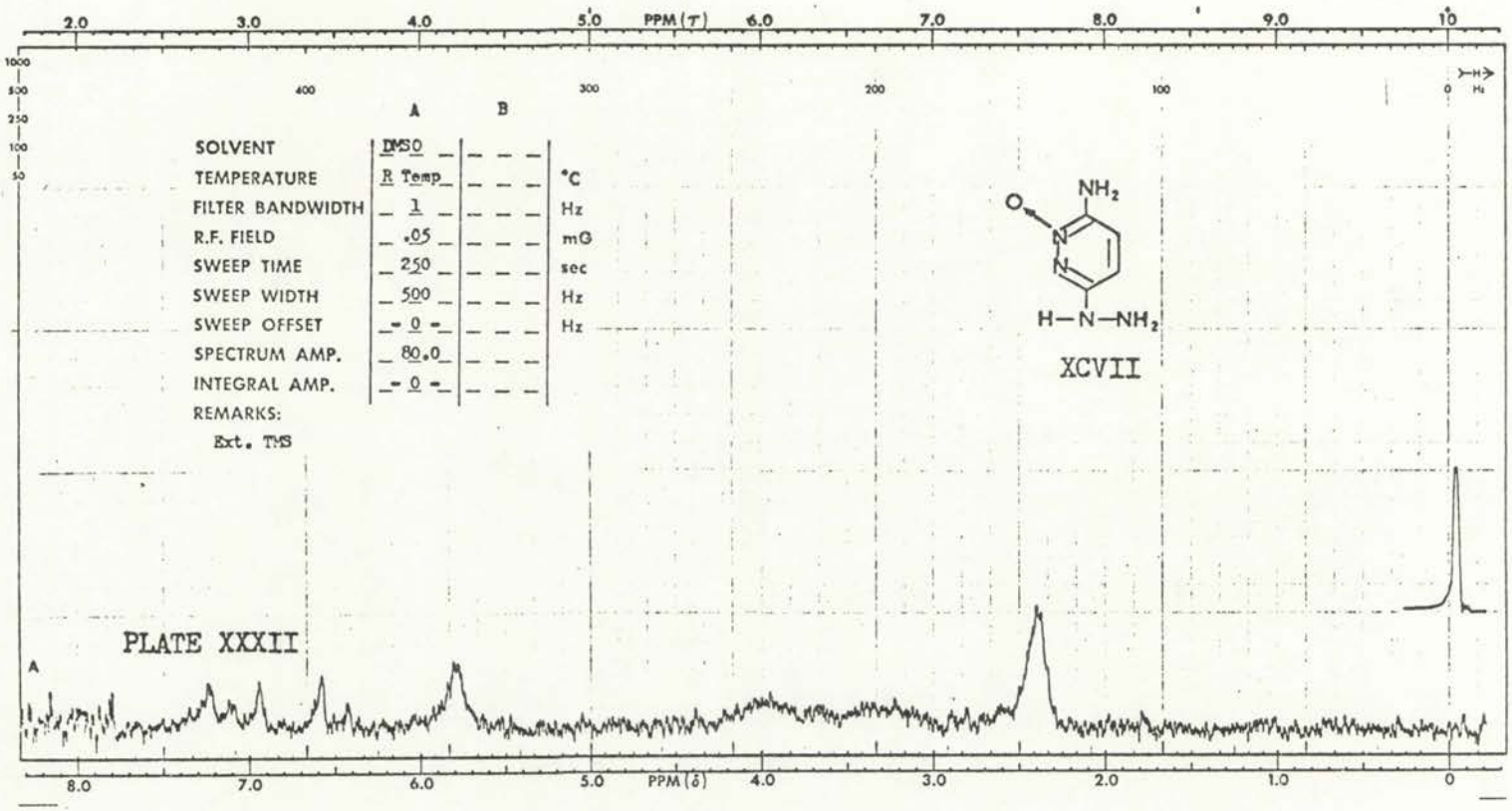
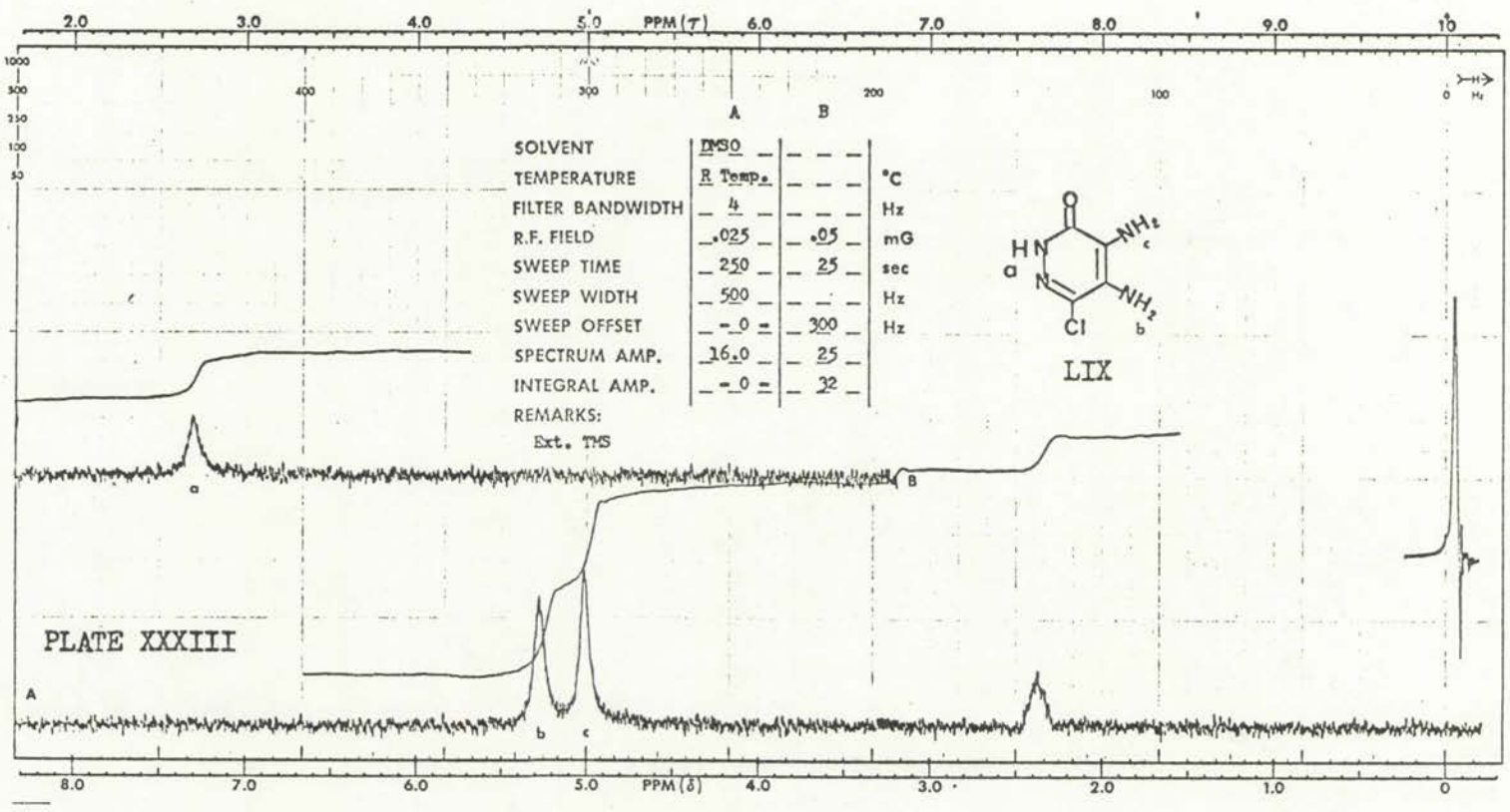
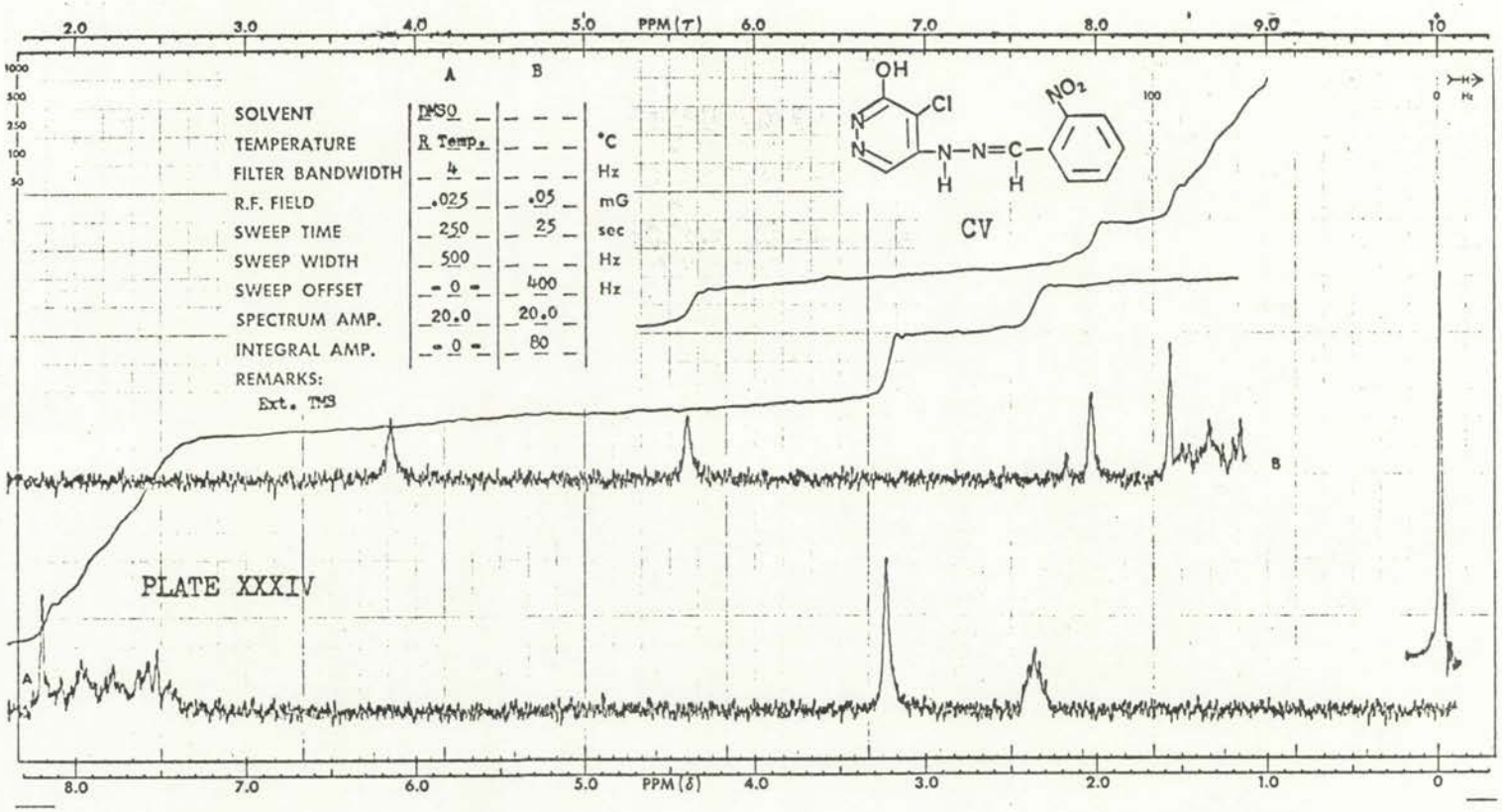
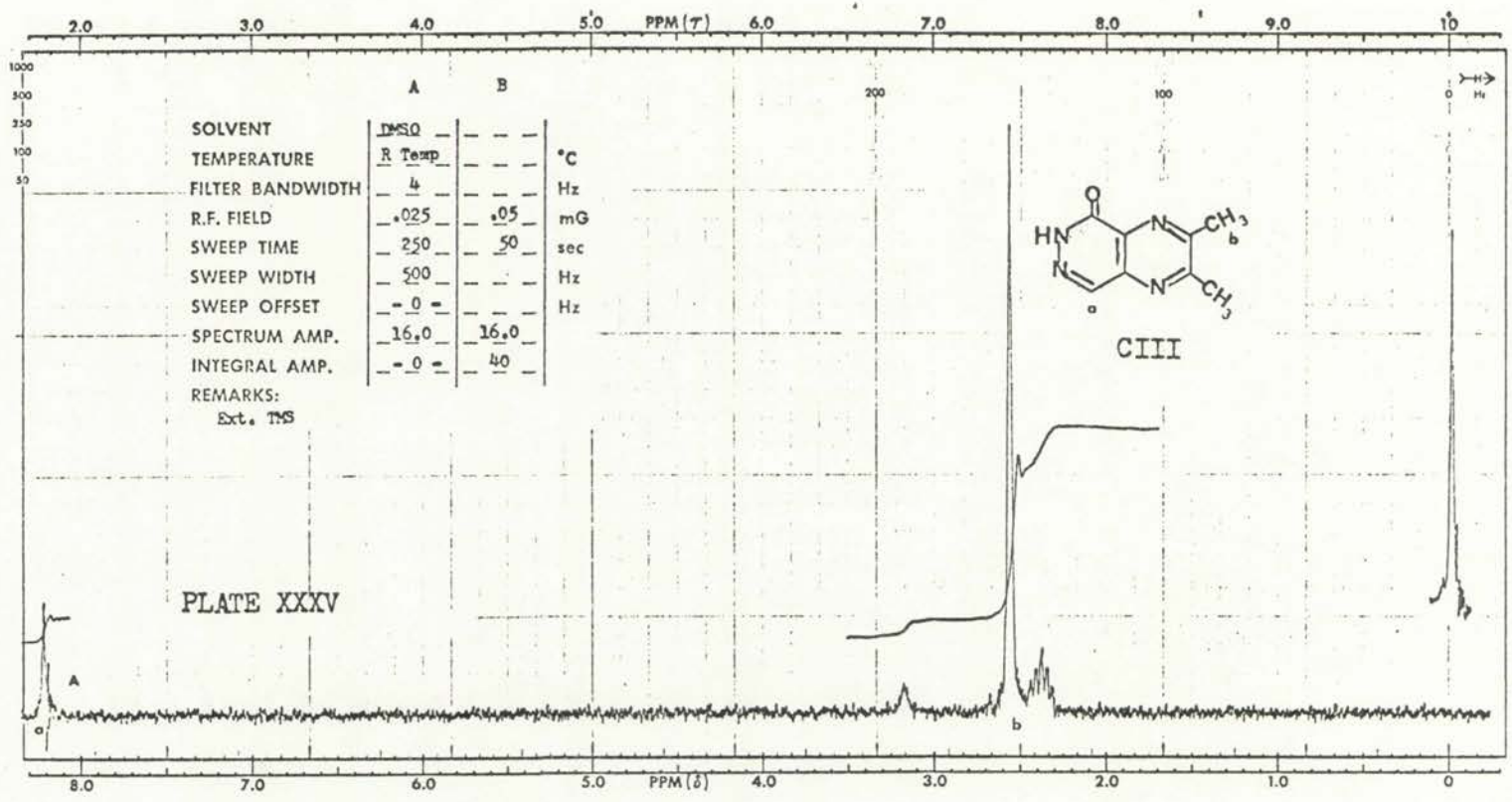

2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
A
B
SOLVENT
CDCl3
TMS
TEMPERATURE
R. Temp.
°C
FILTER BANDWIDTH
4
Hz
R.F. FIELD
.05
mG
SWEEP TIME
250
sec
SWEEP WIDTH
500
Hz
SWEEP OFFSET
0
Hz
SPECTRUM AMP.
2 x 10
INTEGRAL AMP.
3.2 x 10
NH2
O
N
N
S—CH2
a
b
c
d
XCV
A
a
b c
d
PPM (δ)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0

PLATE XXXI

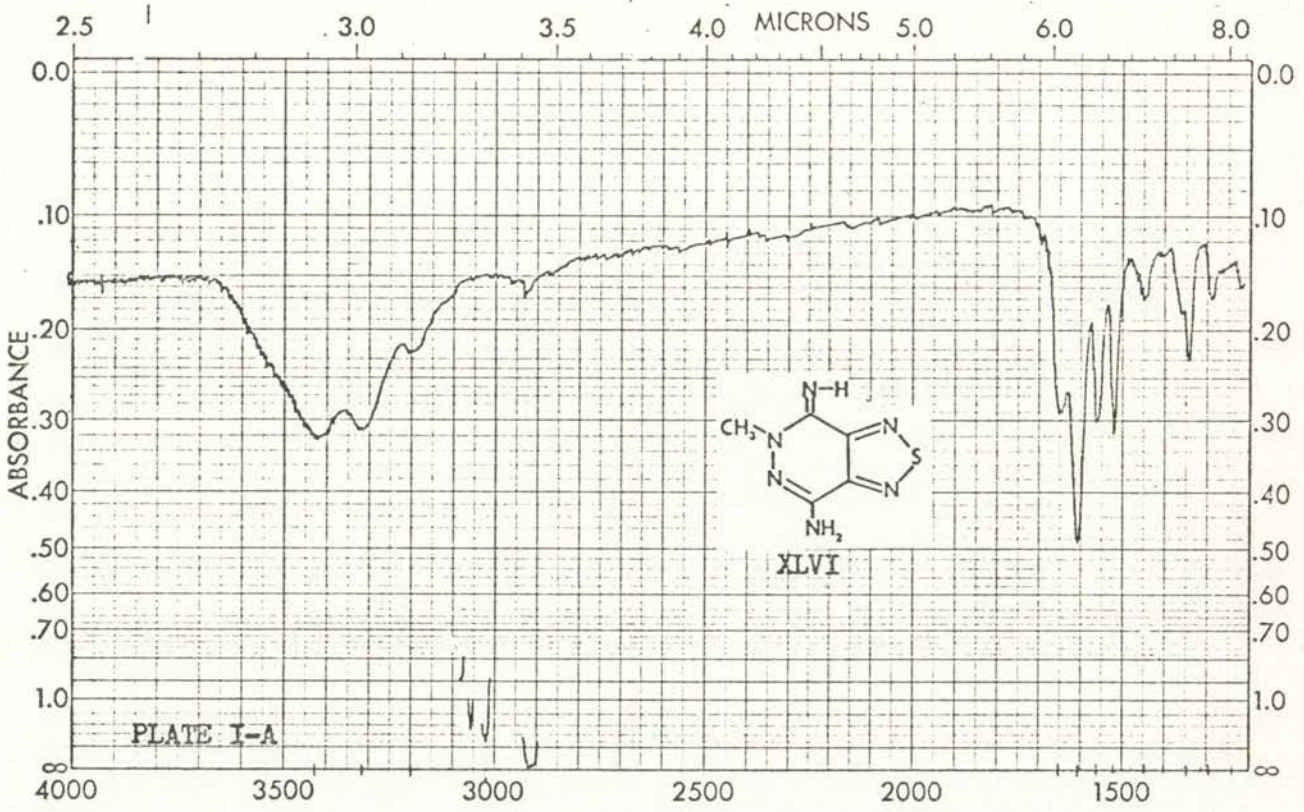

2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
1000
500
250
100
50
400
300
200
100
0
H
Hz
A
B
SOLVENT | DMSO
TEMPERATURE | R Temp | °C
FILTER BANDWIDTH | 1 | Hz
R.F. FIELD | .05 | mG
SWEEP TIME | 250 | sec
SWEEP WIDTH | 500 | Hz
SWEEP OFFSET | 0 | Hz
SPECTRUM AMP. | 80.0
INTEGRAL AMP. | 0
REMARKS:
Ext. TMS
NH2
O
N
N
H—N—NH2
XCVII
PLATE XXXII
A
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0


2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
A
B
SOLVENT DMSO
TEMPERATURE R Temp. °C
FILTER BANDWIDTH 4 Hz
R.F. FIELD .025 .05 mG
SWEEP TIME 250 25 sec
SWEEP WIDTH 500 Hz
SWEEP OFFSET -0- 300 Hz
SPECTRUM AMP. 16.0 25
INTEGRAL AMP. -0- 32
REMARKS:
Ext. TMS
LIX
PLATE XXXIII
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

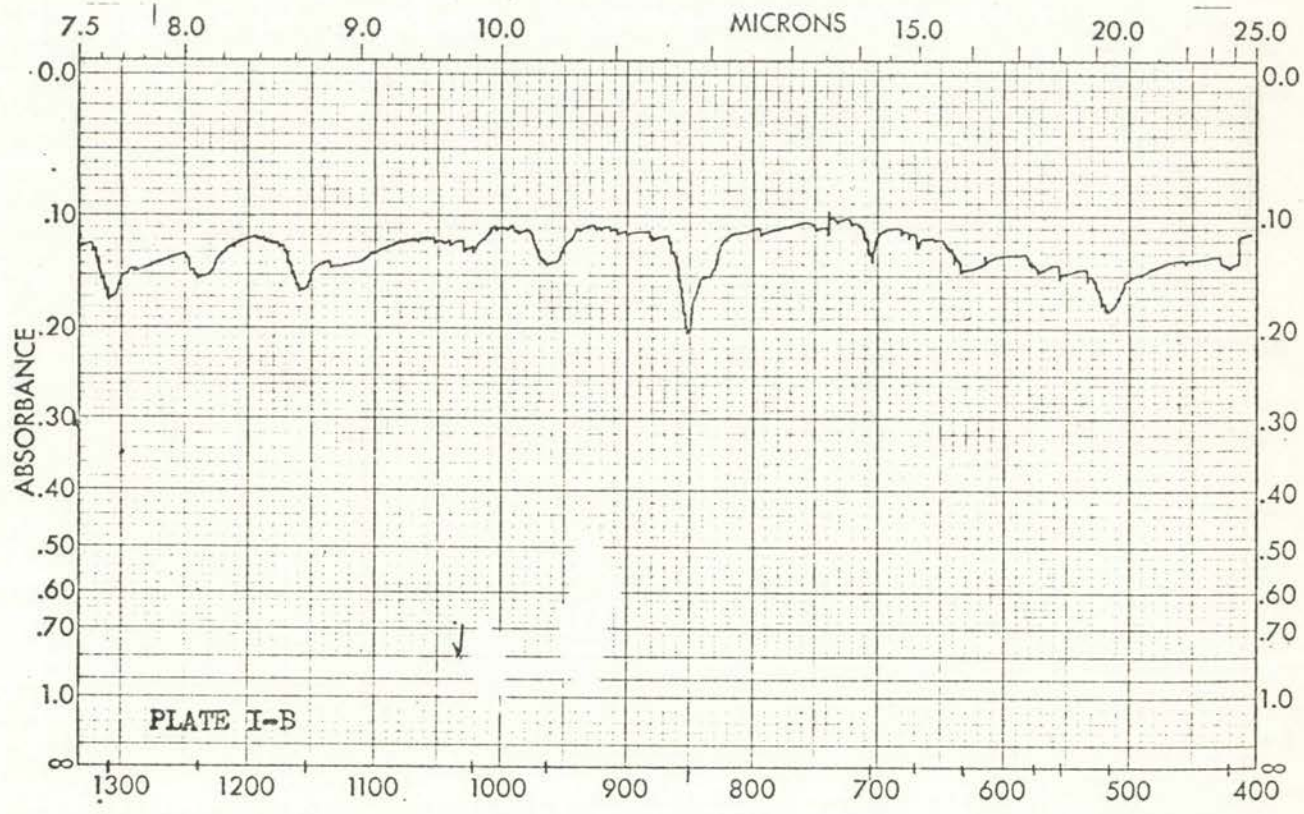

2.0
3.0
4.0
5.0
PPM (τ)
6.0
7.0
8.0
9.0
10
A
B
SOLVENT
TEMPERATURE
FILTER BANDWIDTH
R.F. FIELD
SWEEP TIME
SWEEP WIDTH
SWEEP OFFSET
SPECTRUM AMP.
INTEGRAL AMP.
REMARKS:
Ext. TMS
DMSO
R Temp.
4
.025
250
500
0
20.0
0
.05
25
400
20.0
80
°C
Hz
mG
sec
Hz
Hz
OH
Cl
NO2
N
H
H
CV
PLATE XXXIV
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

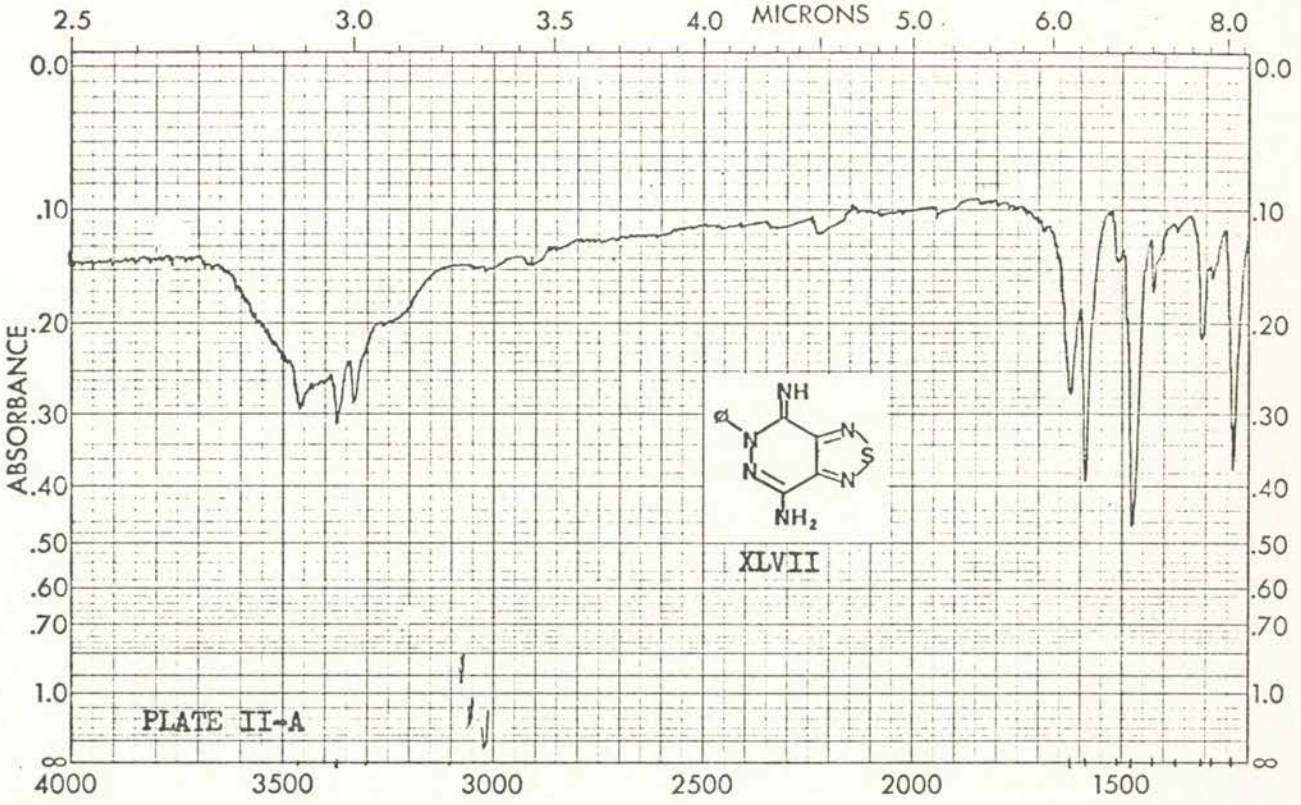

2.0
3.0
4.0
5.0
PPM(τ)
6.0
7.0
8.0
9.0
10
A
B
SOLVENT
DMSO
TEMPERATURE
R Temp
°C
FILTER BANDWIDTH
4
Hz
R.F. FIELD
.025
.05
mG
SWEEP TIME
250
50
sec
SWEEP WIDTH
500
Hz
SWEEP OFFSET
0
Hz
SPECTRUM AMP.
16.0
16.0
INTEGRAL AMP.
0
40
REMARKS:
Ext. TMS
CIII
PLATE XXXV
8.0
7.0
6.0
5.0
PPM(δ)
4.0
3.0
2.0
1.0
0

VII. Infra Red Spectra

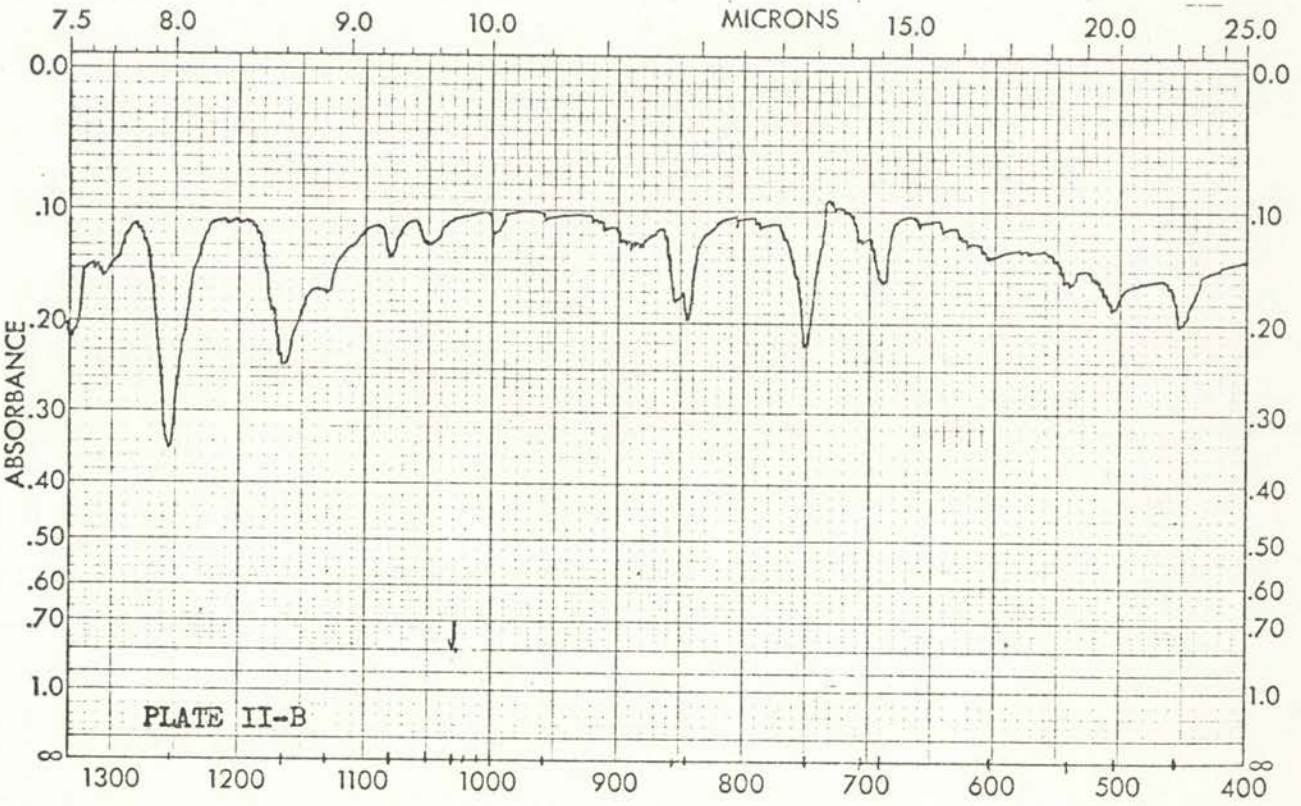

2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
ABSORBANCE
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
4000
3500
3000
2500
2000
1500
PLATE I-A
N–H
CH₃
NH₂

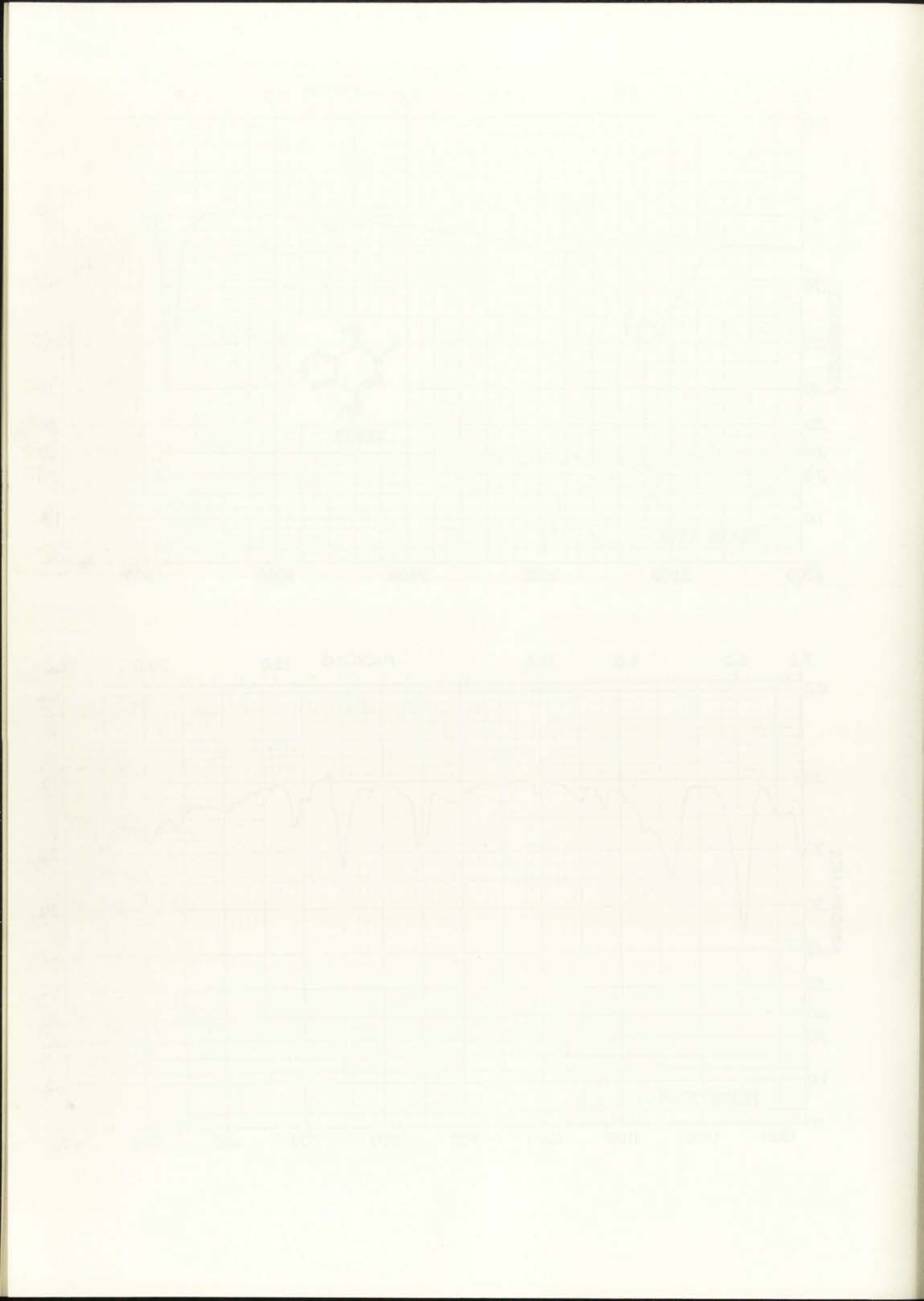
XLVI

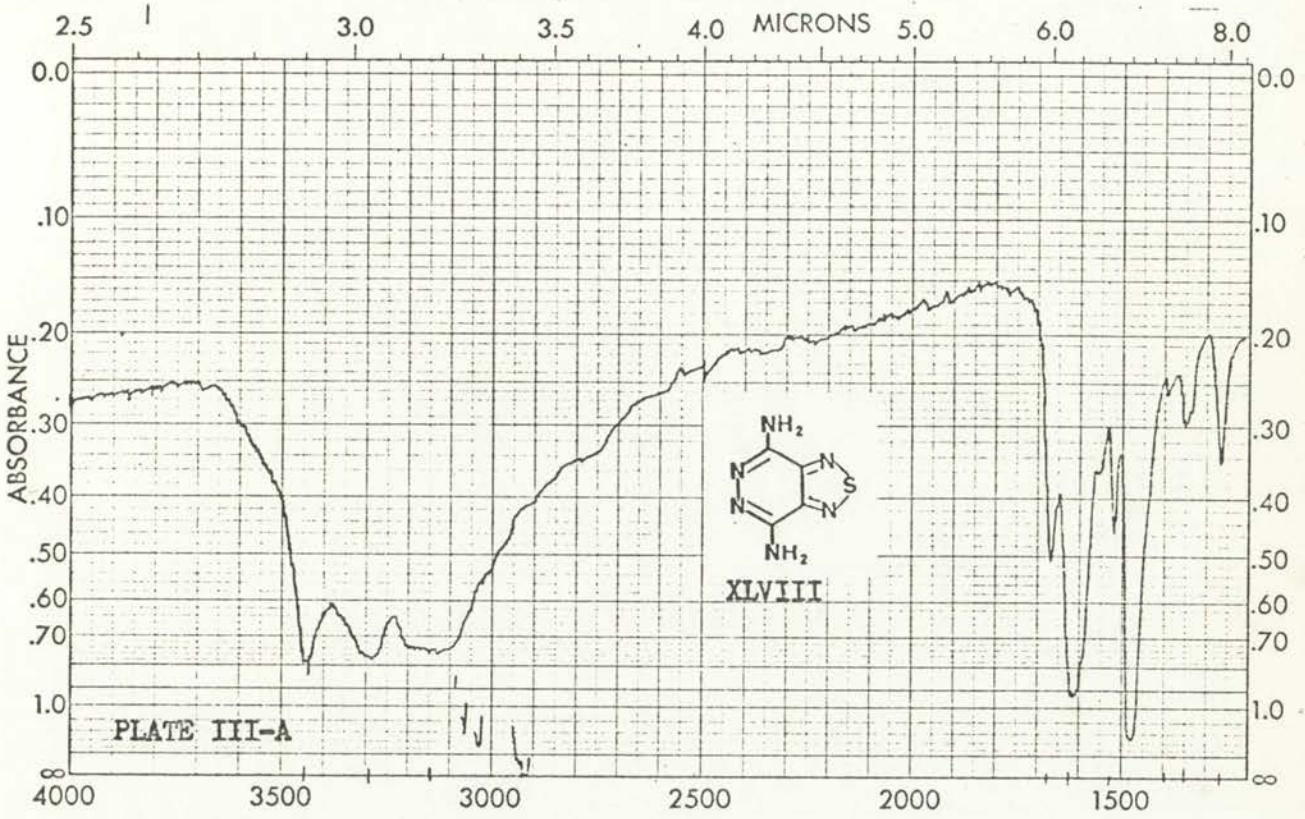

7.5
8.0
9.0
10.0
MICRONS
15.0
20.0
25.0
ABSORBANCE
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
1300
1200
1100
1000
900
800
700
600
500
400
PLATE I-B

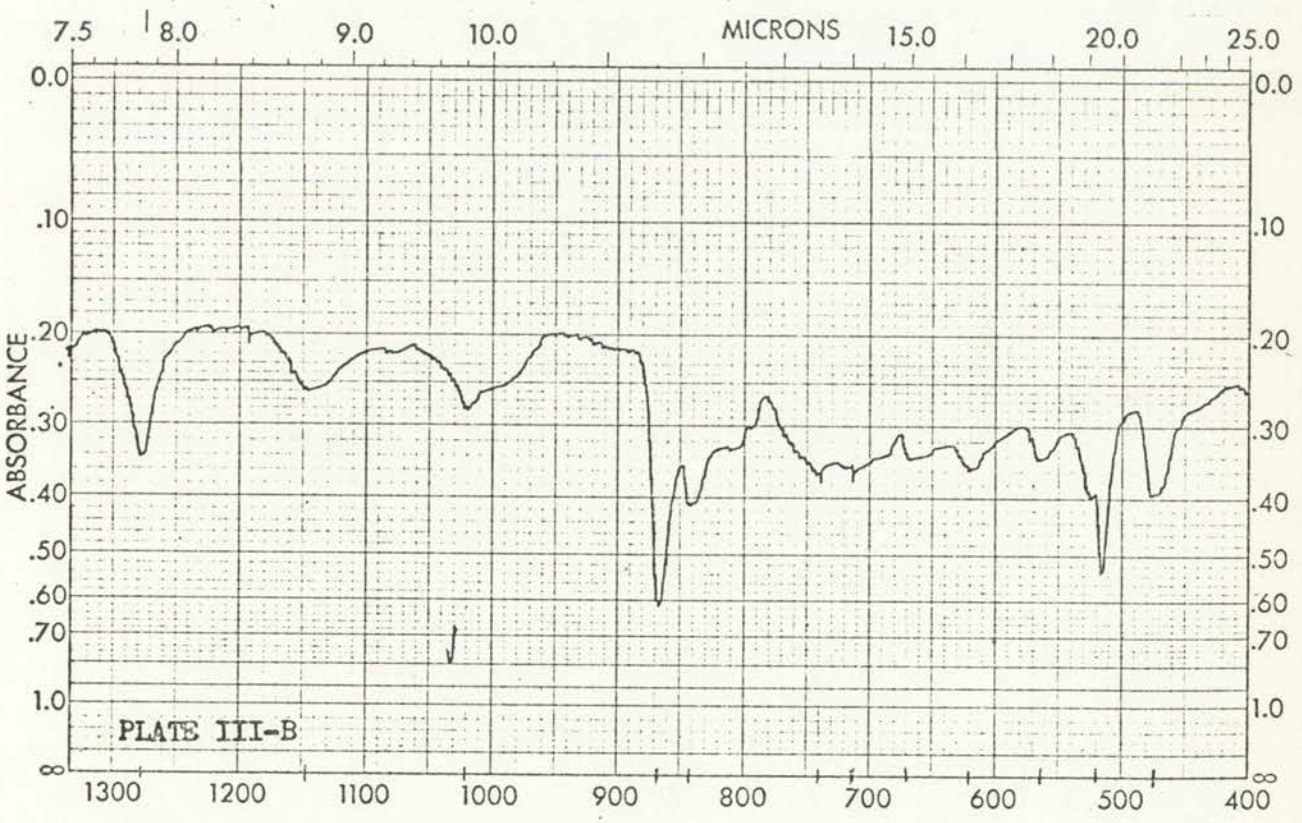

2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
ABSORBANCE
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
4000
3500
3000
2500
2000
1500
NH
N
S
NH2
PLATE II-A

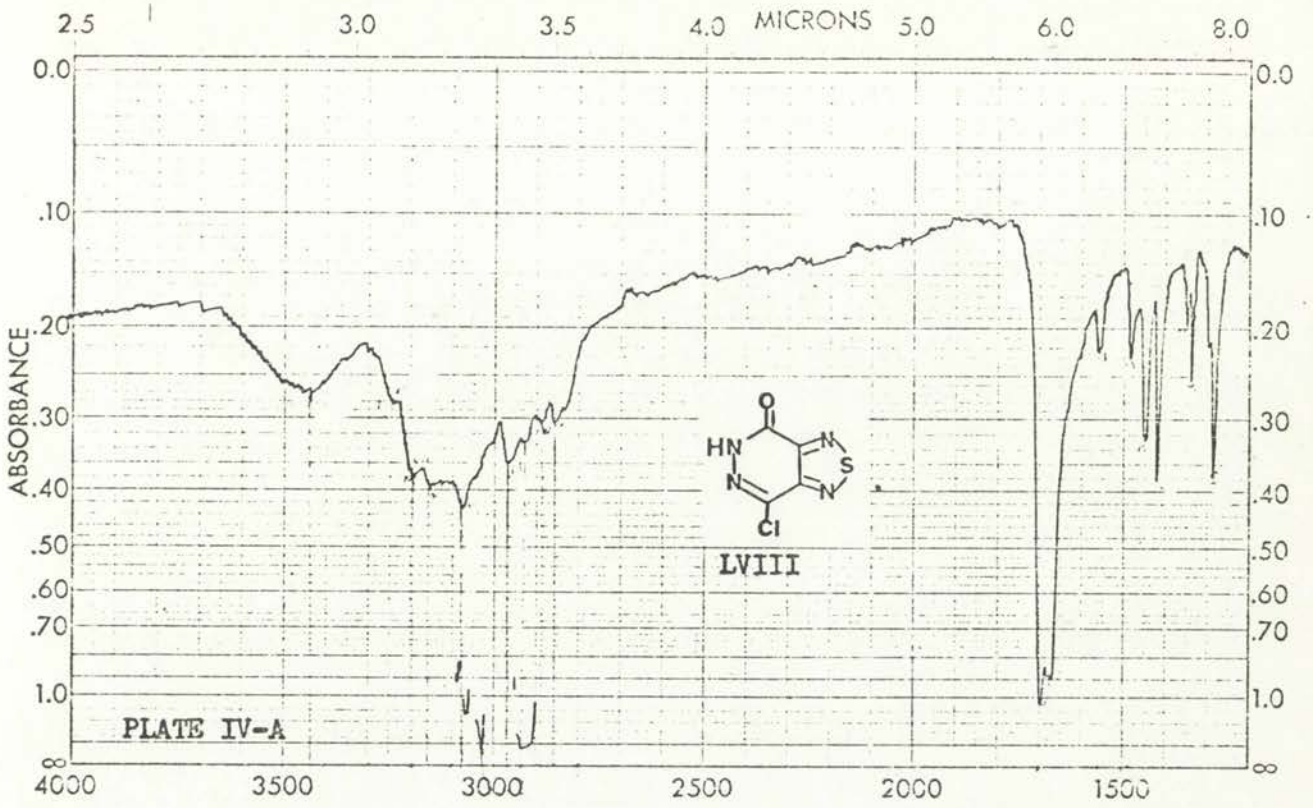
XLVII

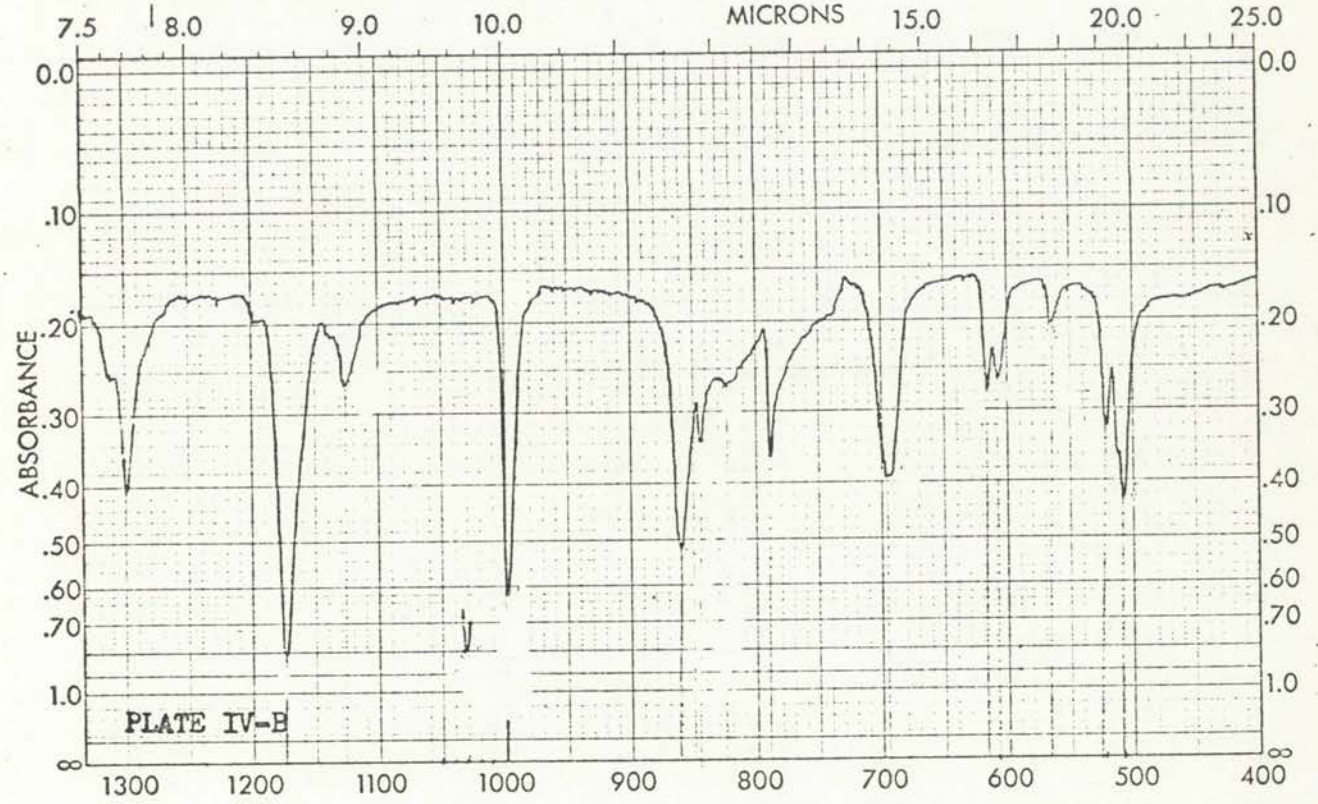

7.5
8.0
9.0
10.0
MICRONS
15.0
20.0
25.0
ABSORBANCE
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
1300
1200
1100
1000
900
800
700
600
500
400
PLATE II-B

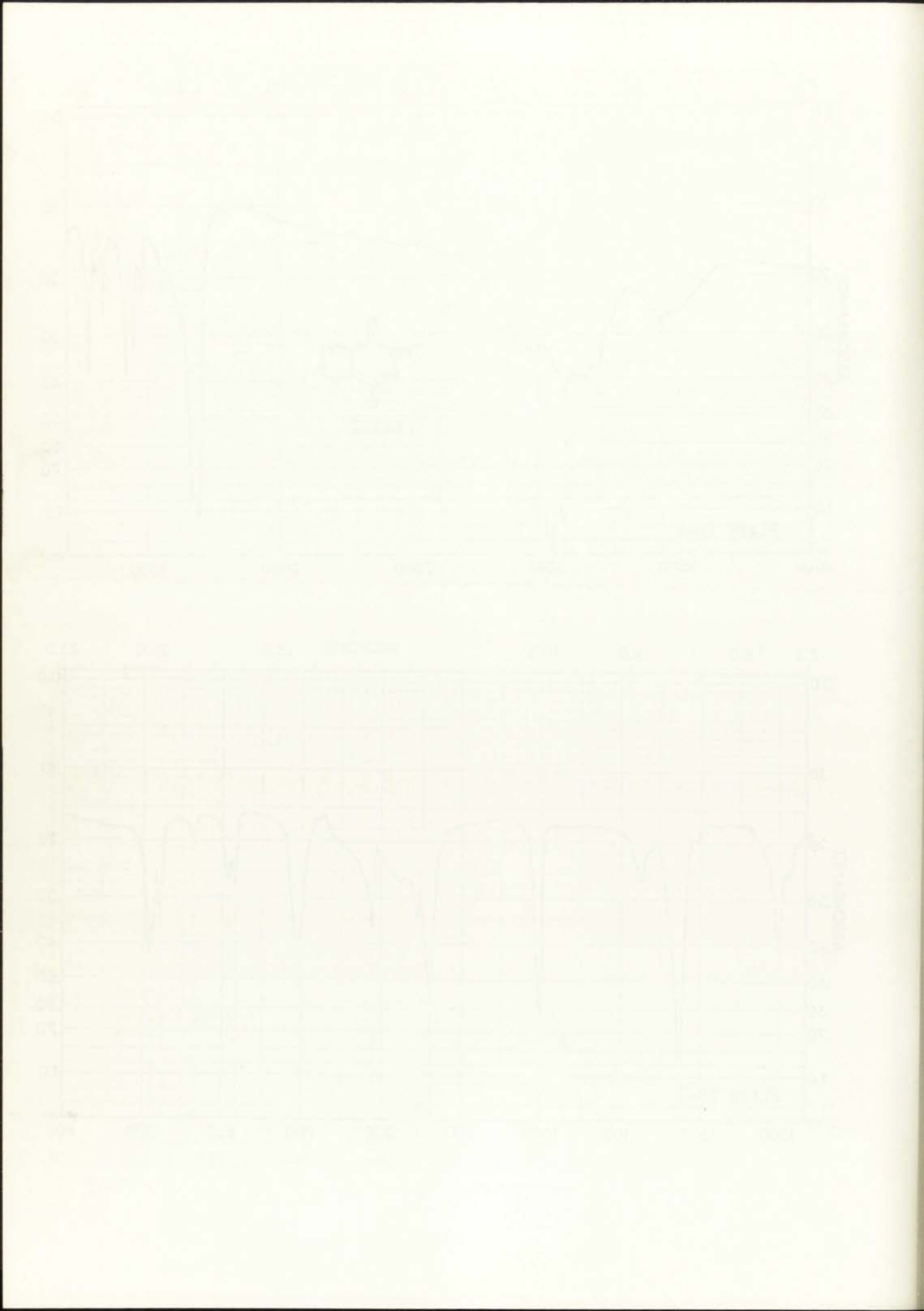


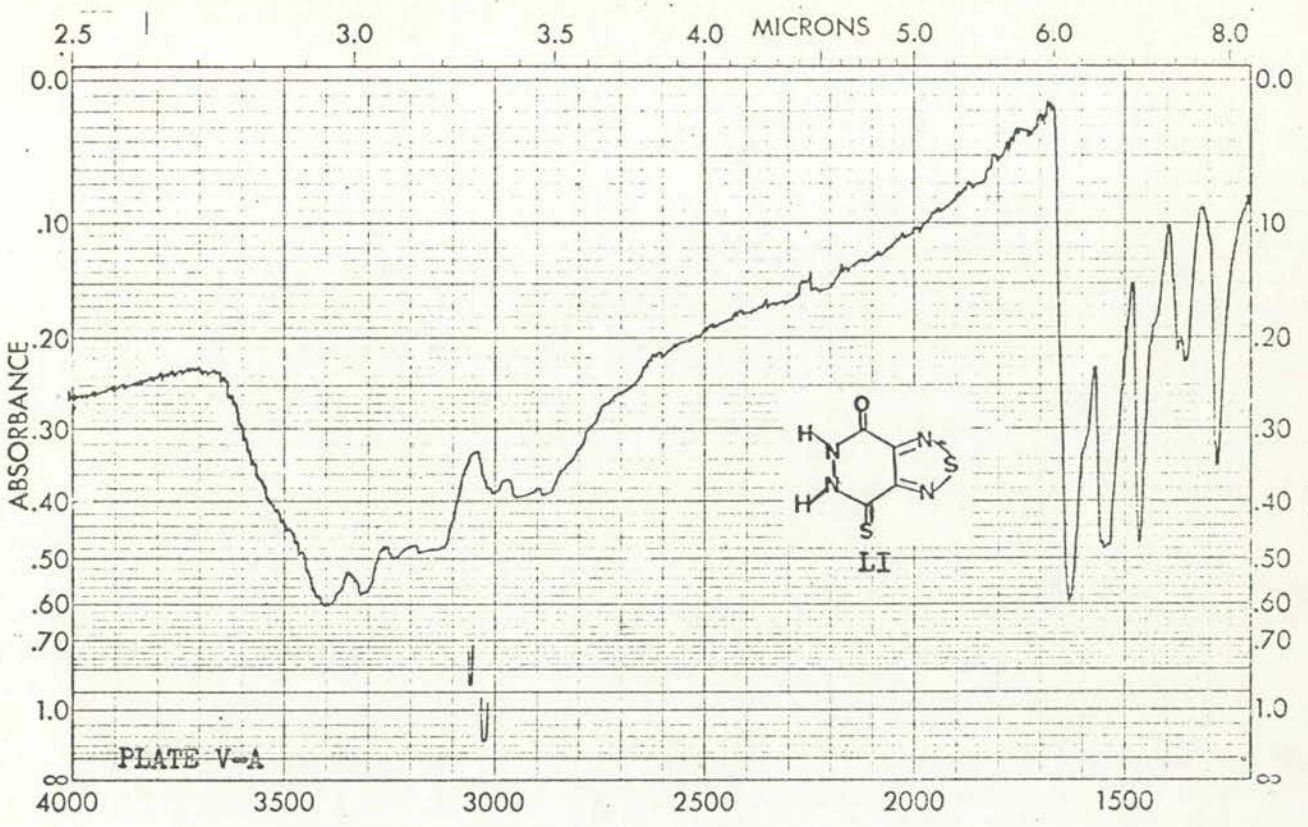

2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
ABSORBANCE
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
4000
3500
3000
2500
2000
1500
NH2
N
N
N
S
N
NH2
XLVIII
PLATE III-A


7.5
8.0
9.0
10.0
MICRONS
15.0
20.0
25.0
ABSORBANCE
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
1300
1200
1100
1000
900
800
700
600
500
400
PLATE III-B

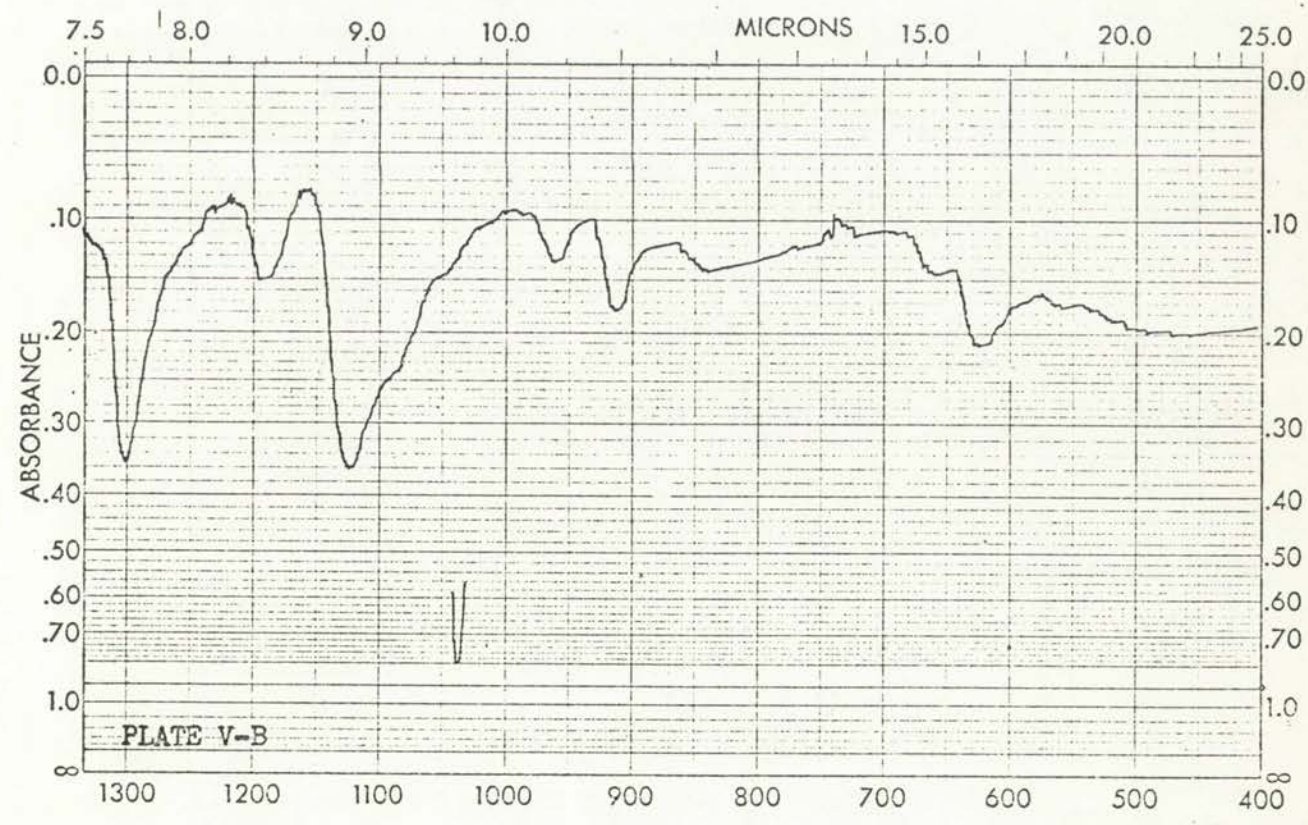

2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
ABSORBANCE
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
4000
3500
3000
2500
2000
1500
HN
N
N
S
N
Cl
O
LVIII
PLATE IV-A

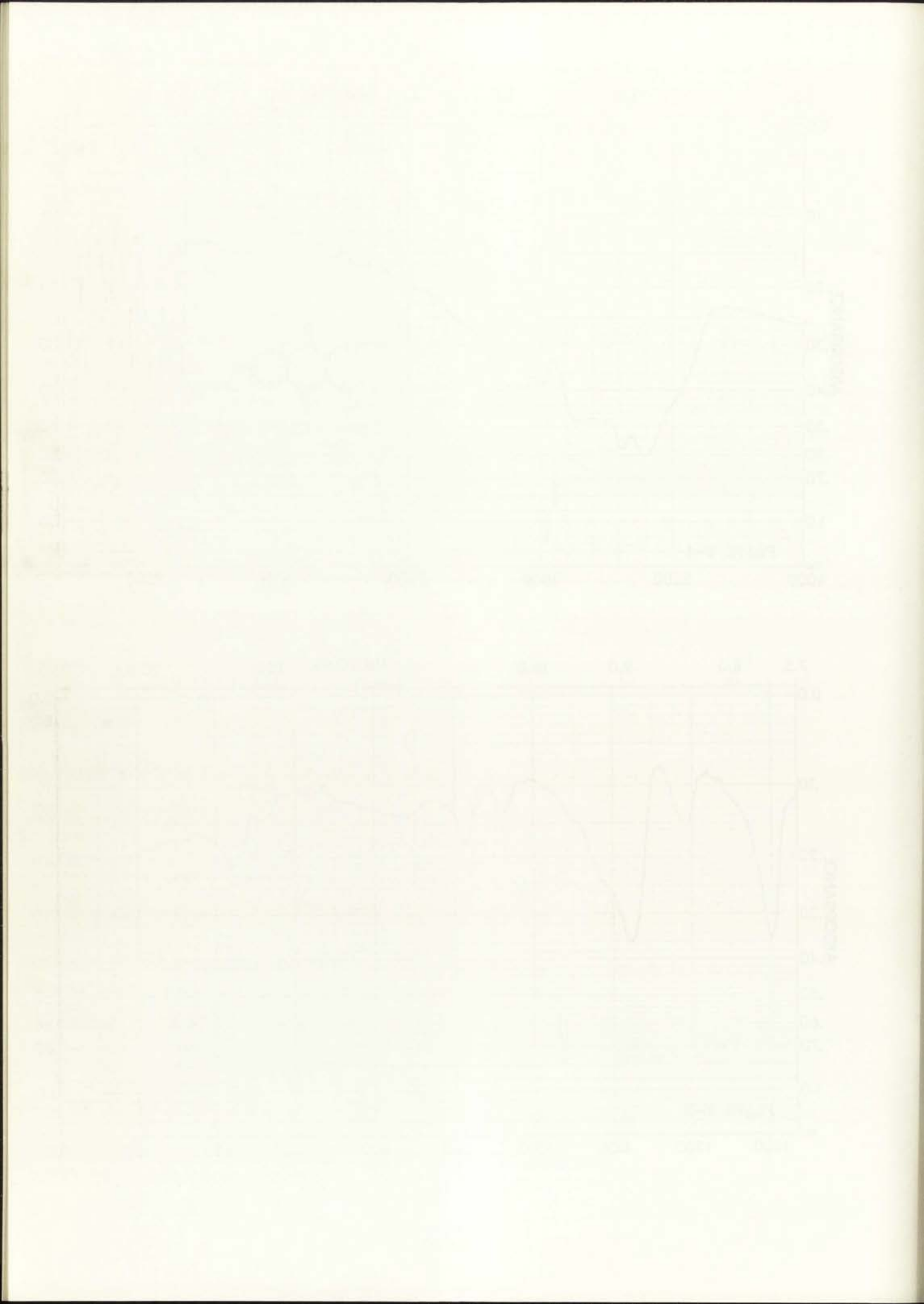

7.5
8.0
9.0
10.0
MICRONS
15.0
20.0
25.0
ABSORBANCE
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
1300
1200
1100
1000
900
800
700
600
500
400
PLATE IV-B

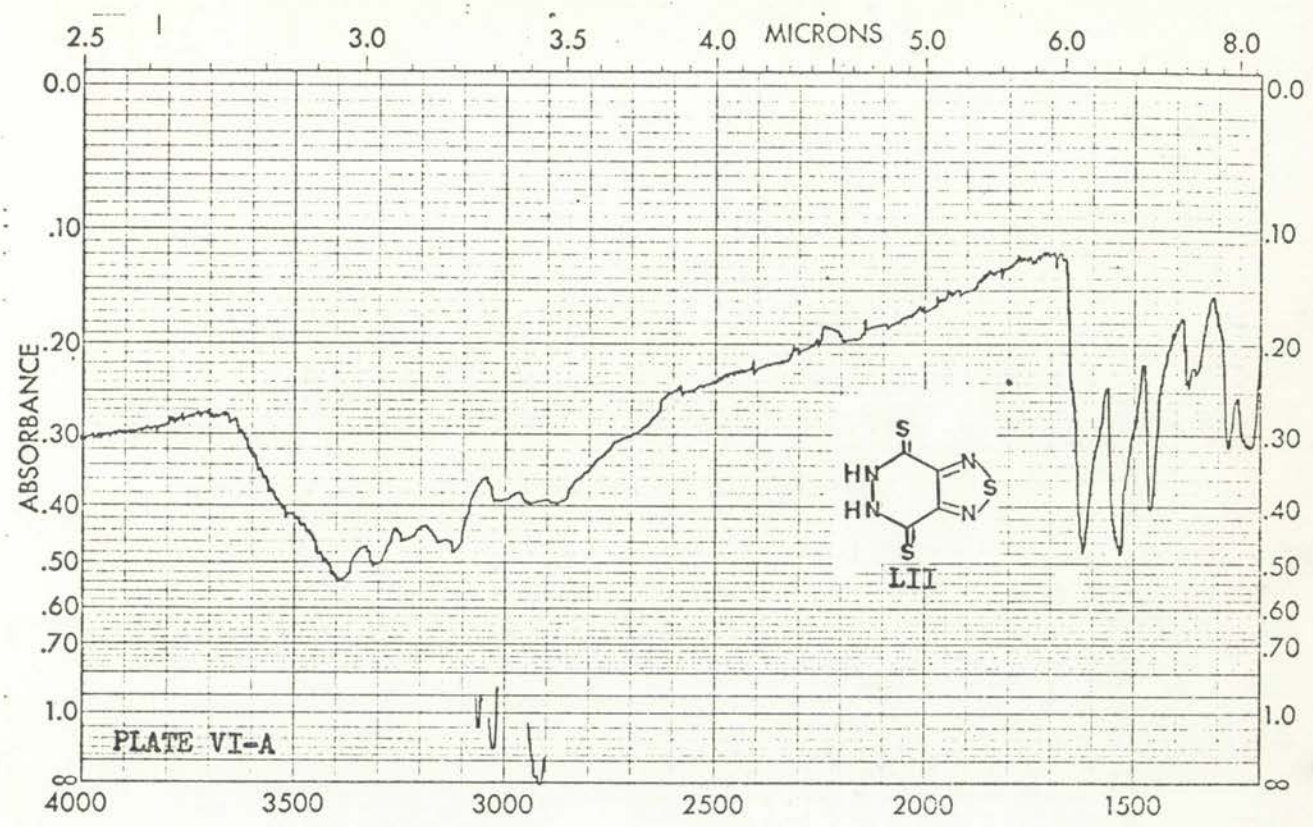


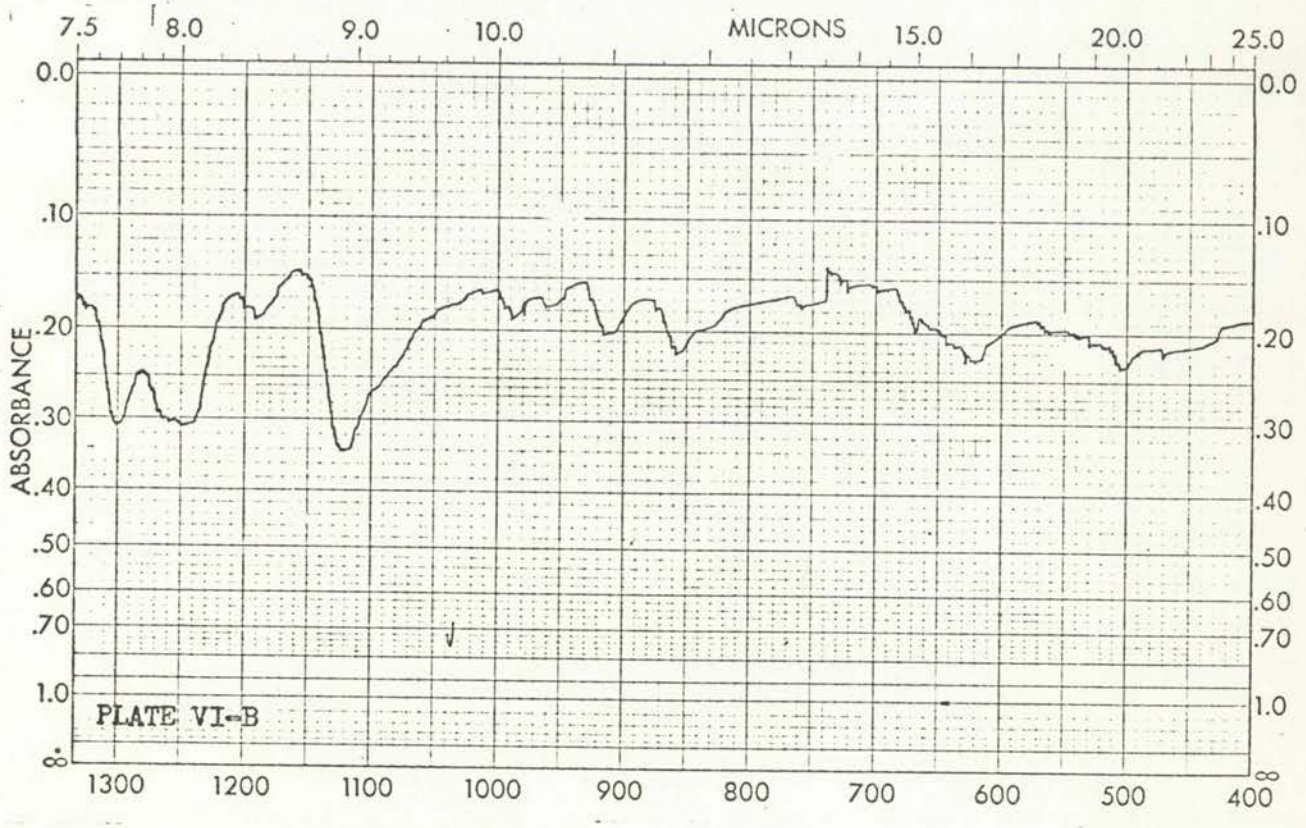

2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
ABSORBANCE
PLATE V-A
4000
3500
3000
2500
2000
1500

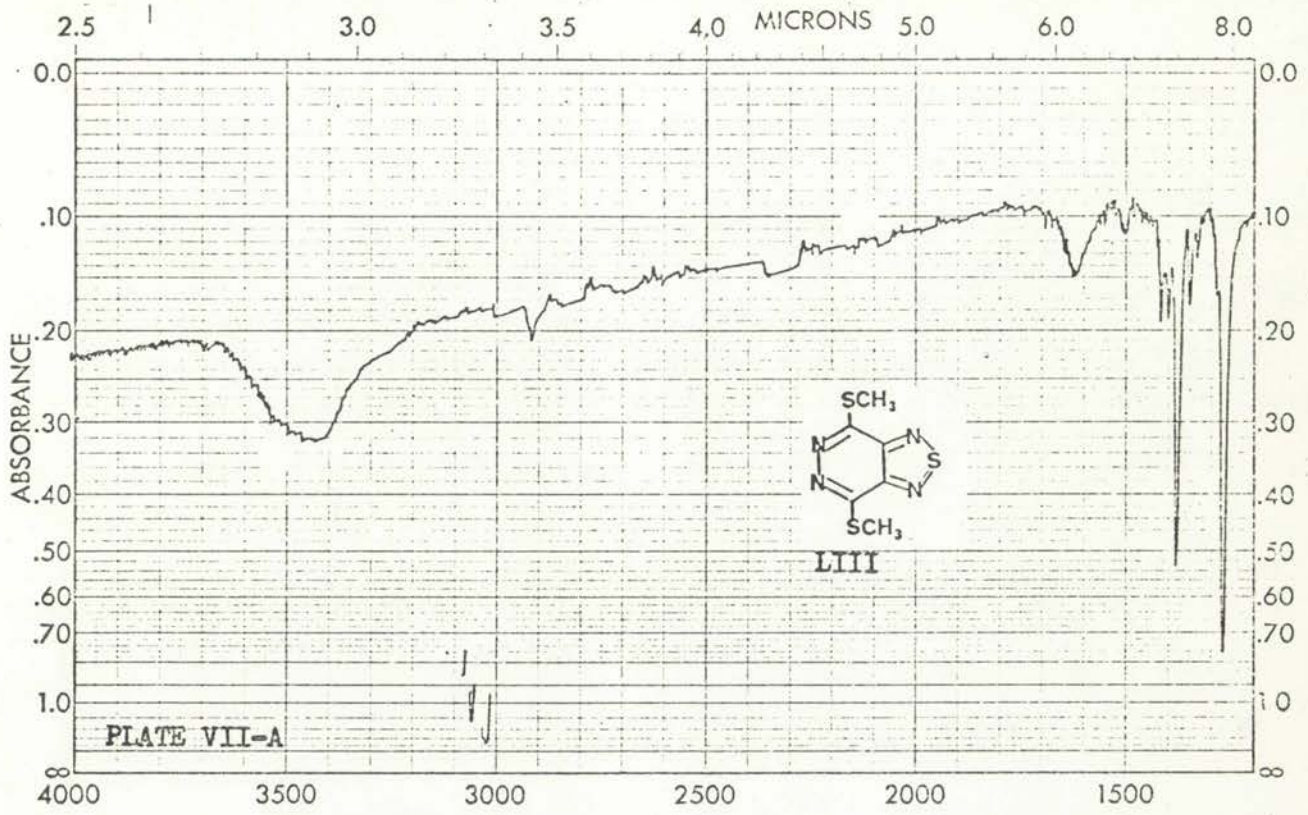
LI

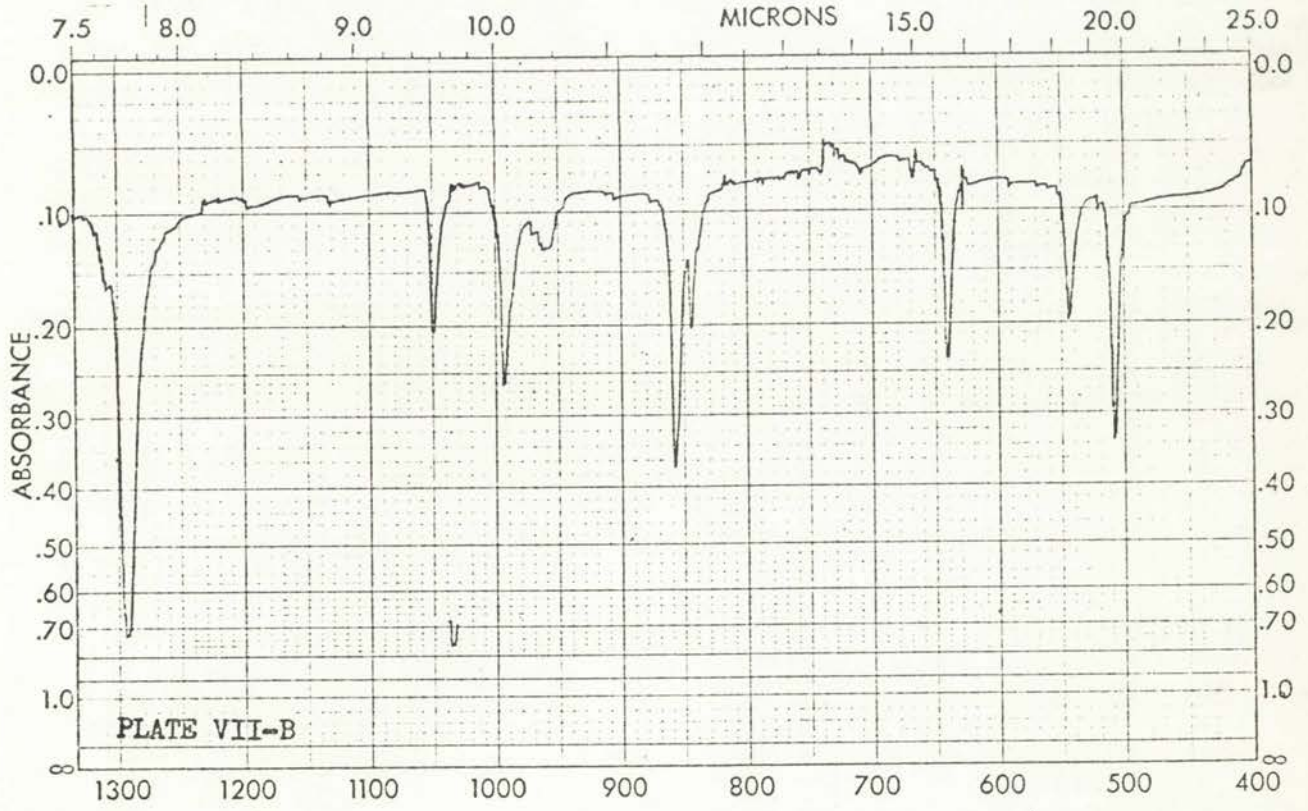

7.5
8.0
9.0
10.0
MICRONS
15.0
20.0
25.0
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
ABSORBANCE
PLATE V-B
1300
1200
1100
1000
900
800
700
600
500
400

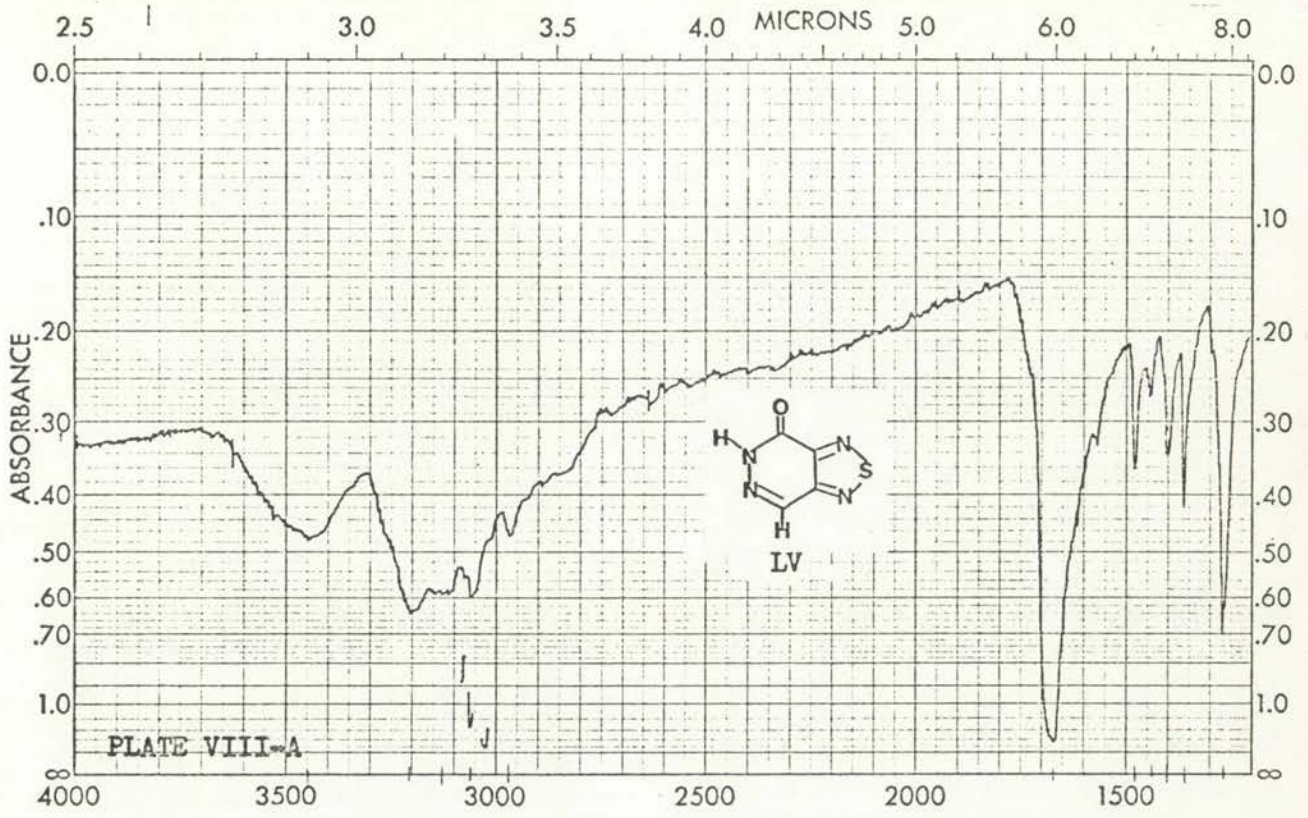



2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
ABSORBANCE
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
4000
3500
3000
2500
2000
1500
HN
HN
S
N
S
N
S
LII
PLATE VI-A

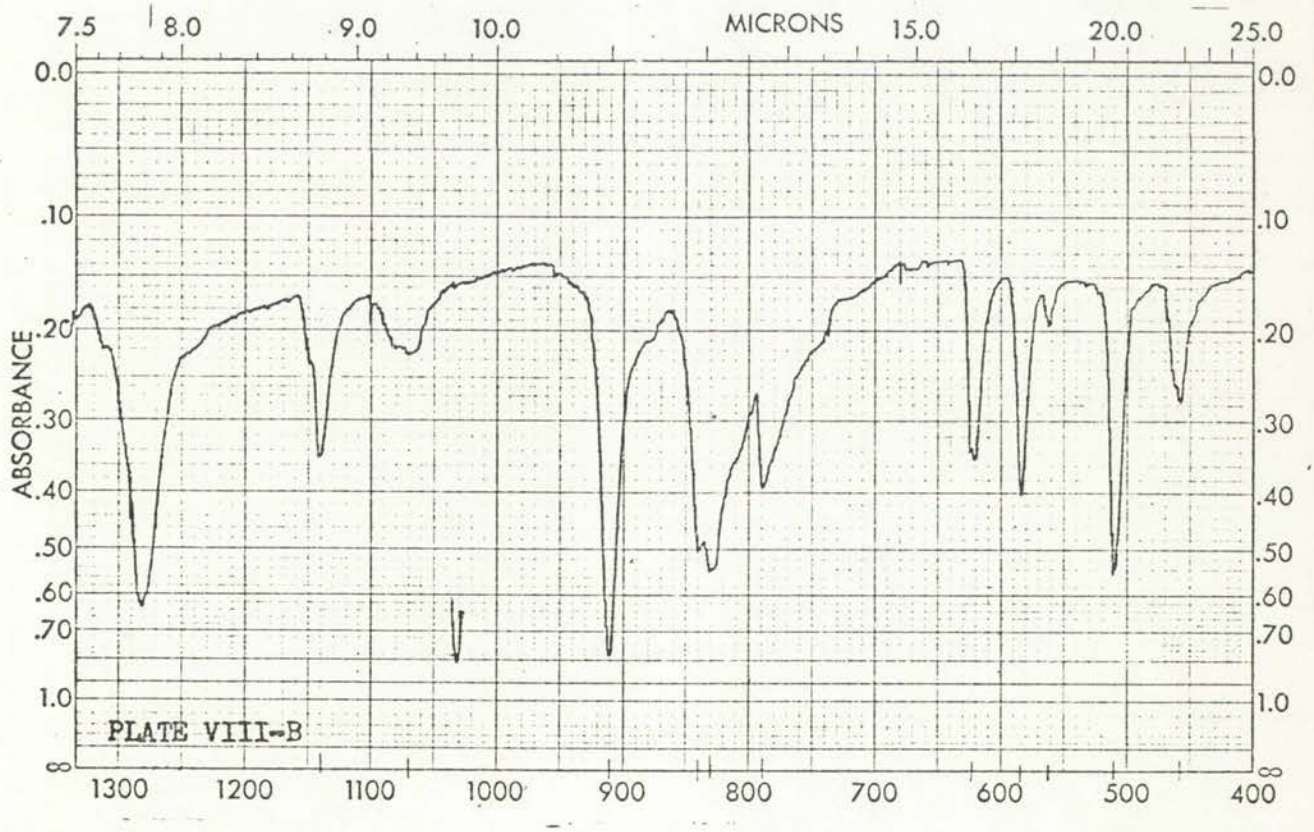

7.5
8.0
9.0
10.0
MICRONS
15.0
20.0
25.0
ABSORBANCE
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
1300
1200
1100
1000
900
800
700
600
500
400
PLATE VI-B

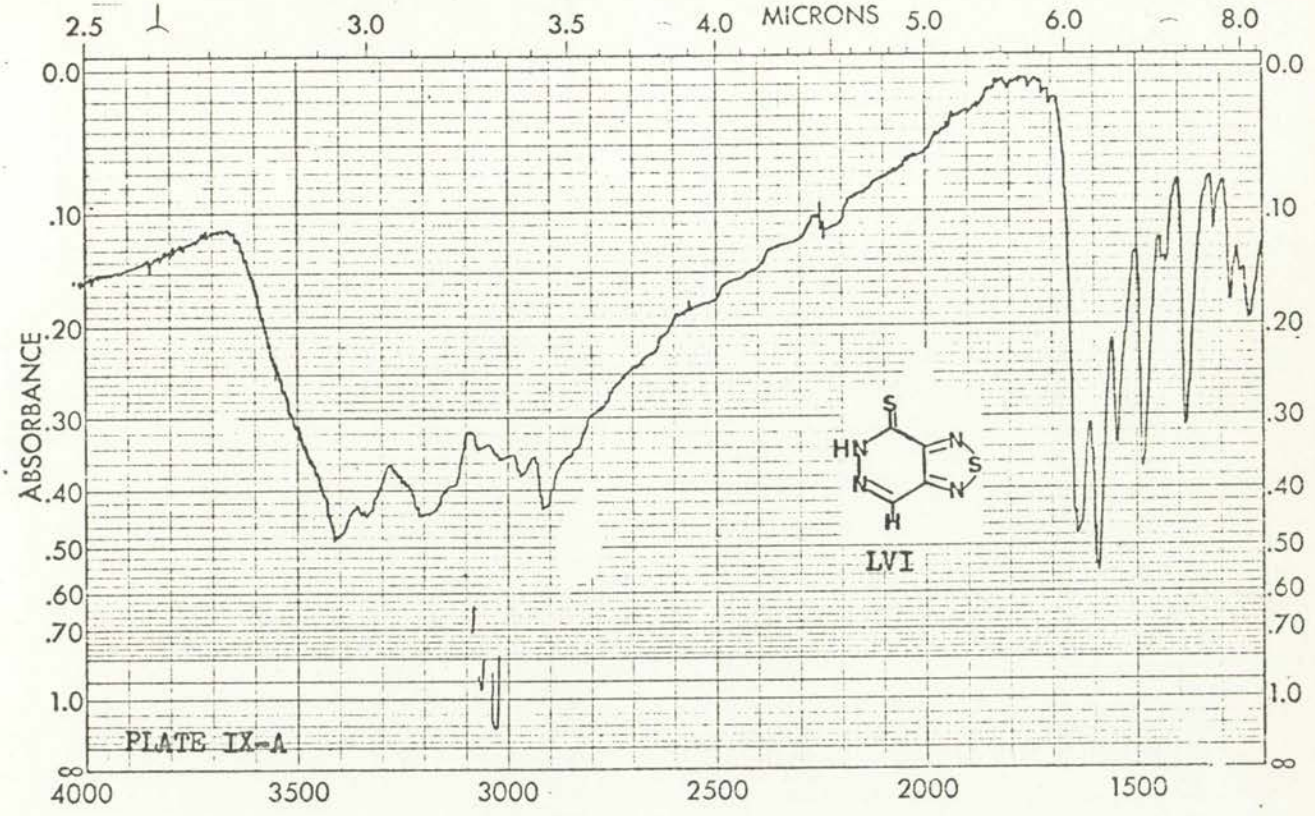

2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
ABSORBANCE
SCH3
SCH3
LIII
PLATE VII-A
4000
3500
3000
2500
2000
1500


7.5
8.0
9.0
10.0
MICRONS
15.0
20.0
25.0
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
ABSORBANCE
PLATE VII-B
1300
1200
1100
1000
900
800
700
600
500
400

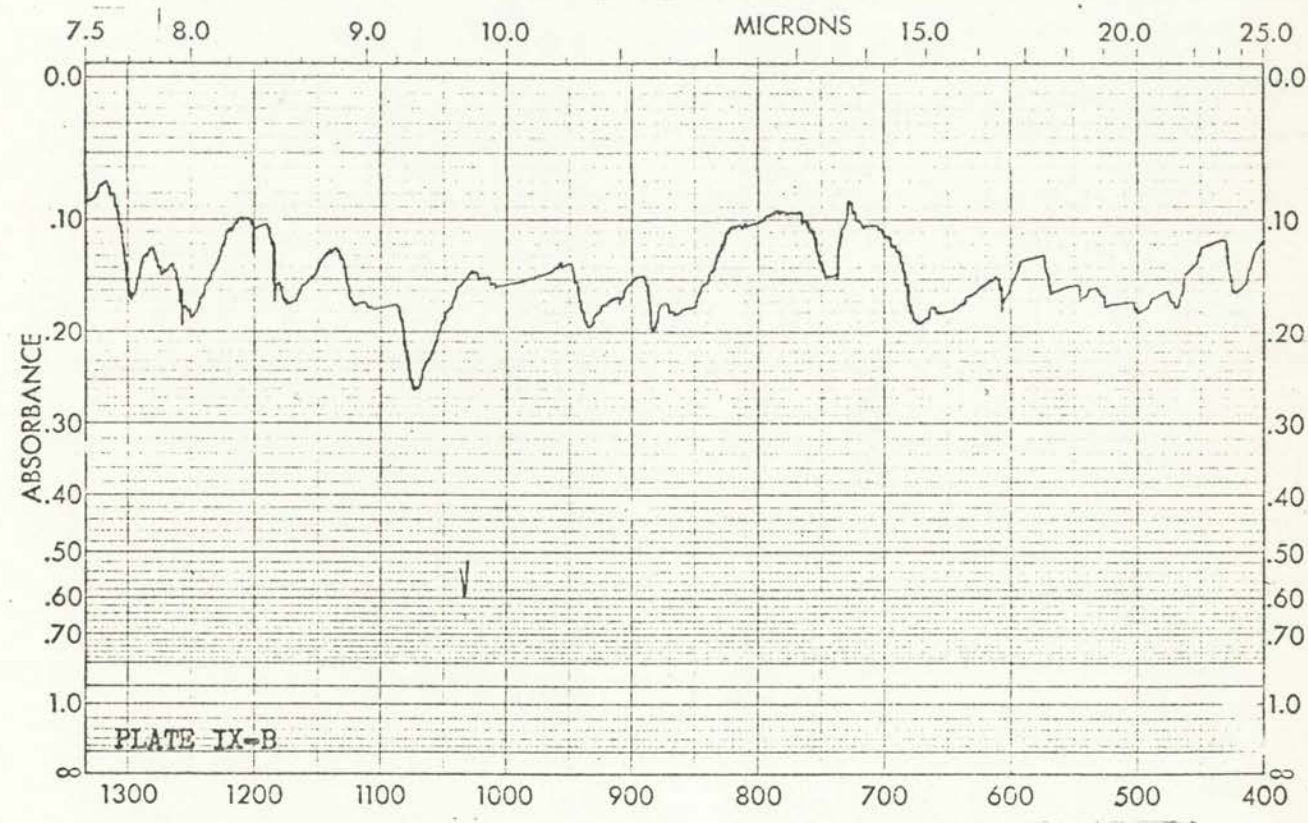

2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
ABSORBANCE
4000
3500
3000
2500
2000
1500
PLATE VIII-A

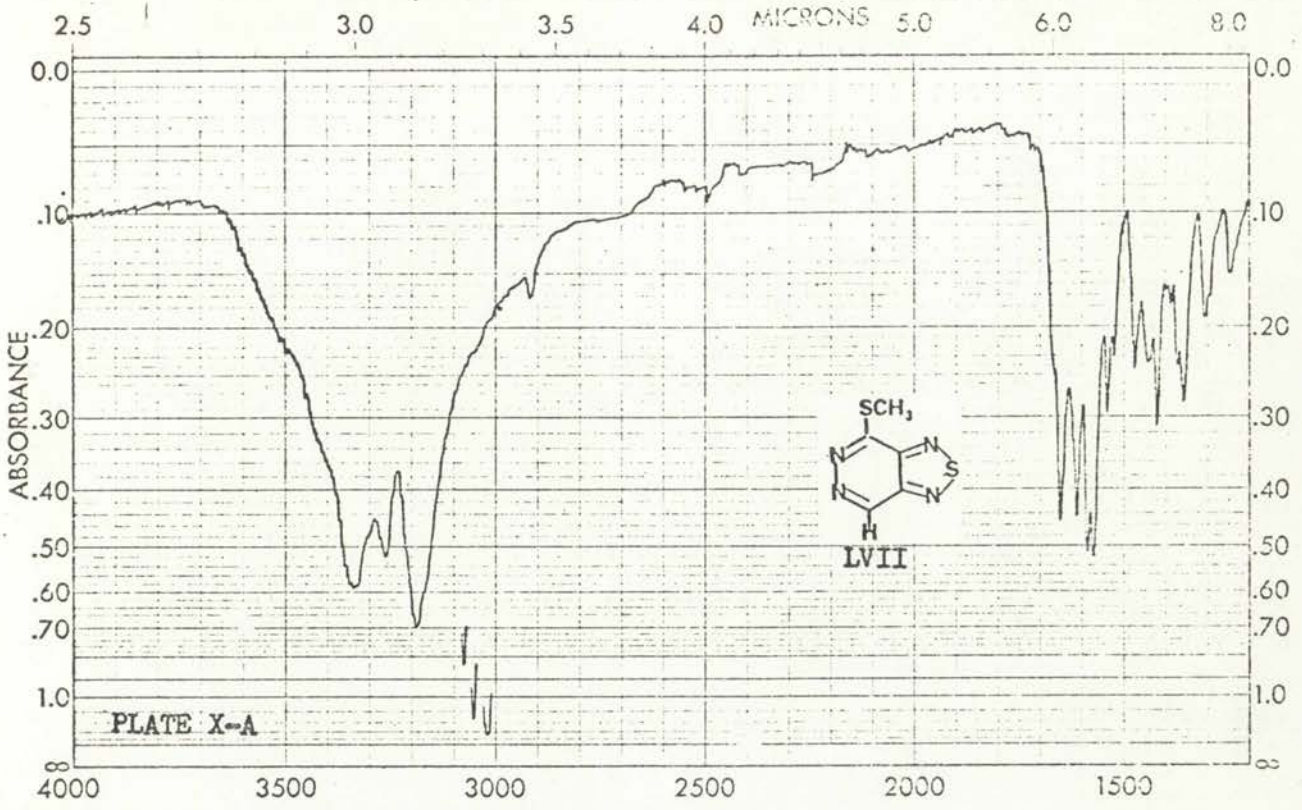
LV

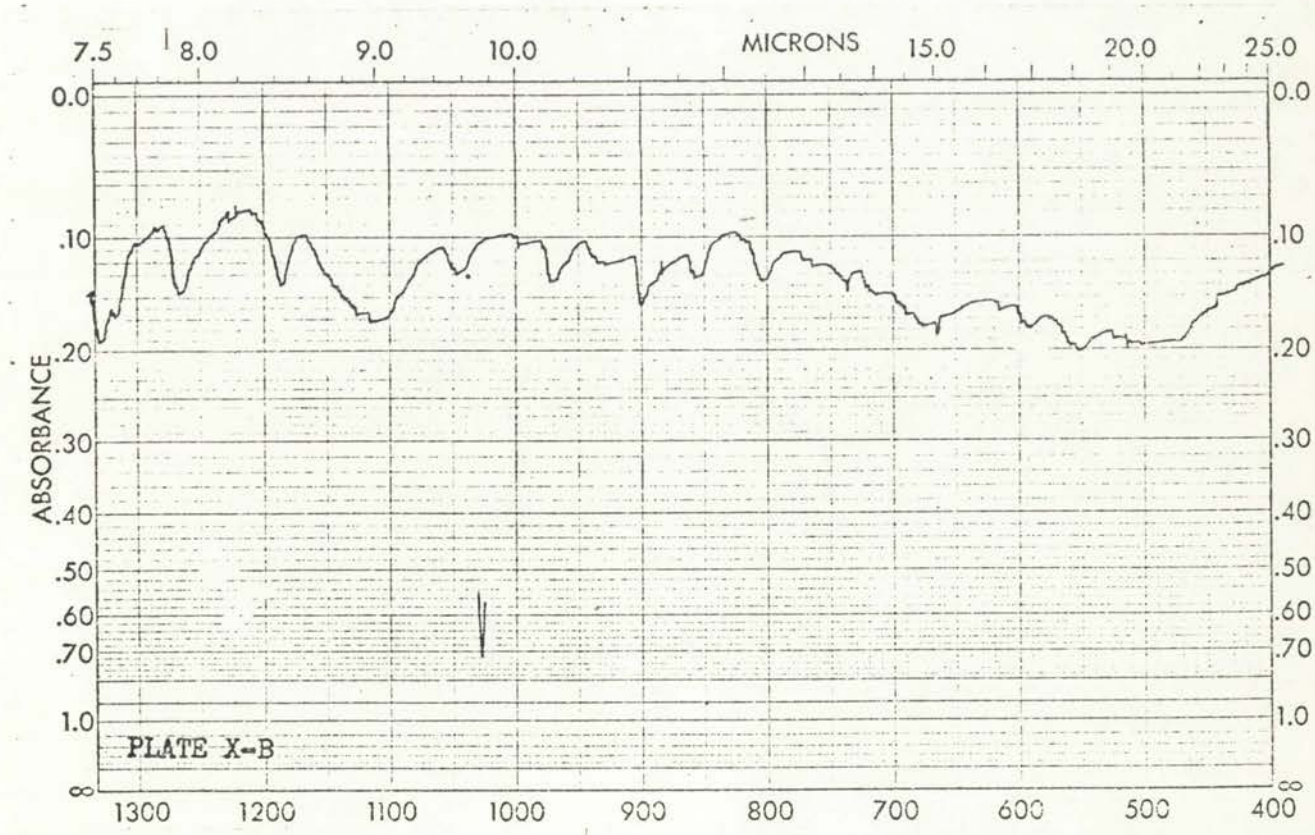

7.5
8.0
9.0
10.0
MICRONS
15.0
20.0
25.0
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
ABSORBANCE
1300
1200
1100
1000
900
800
700
600
500
400
PLATE VIII-B

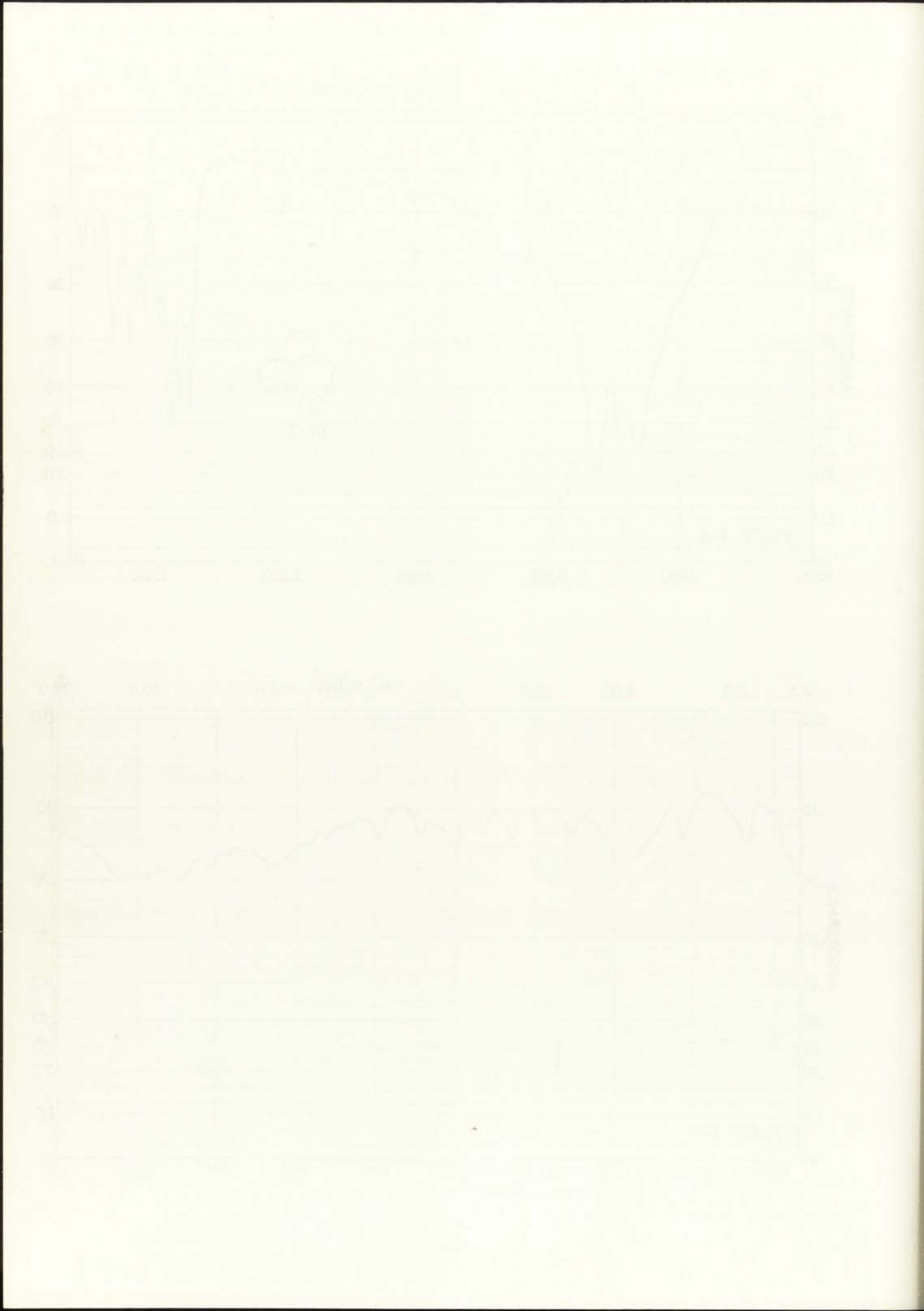

2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
ABSORBANCE
4000
3500
3000
2500
2000
1500
PLATE IX-A

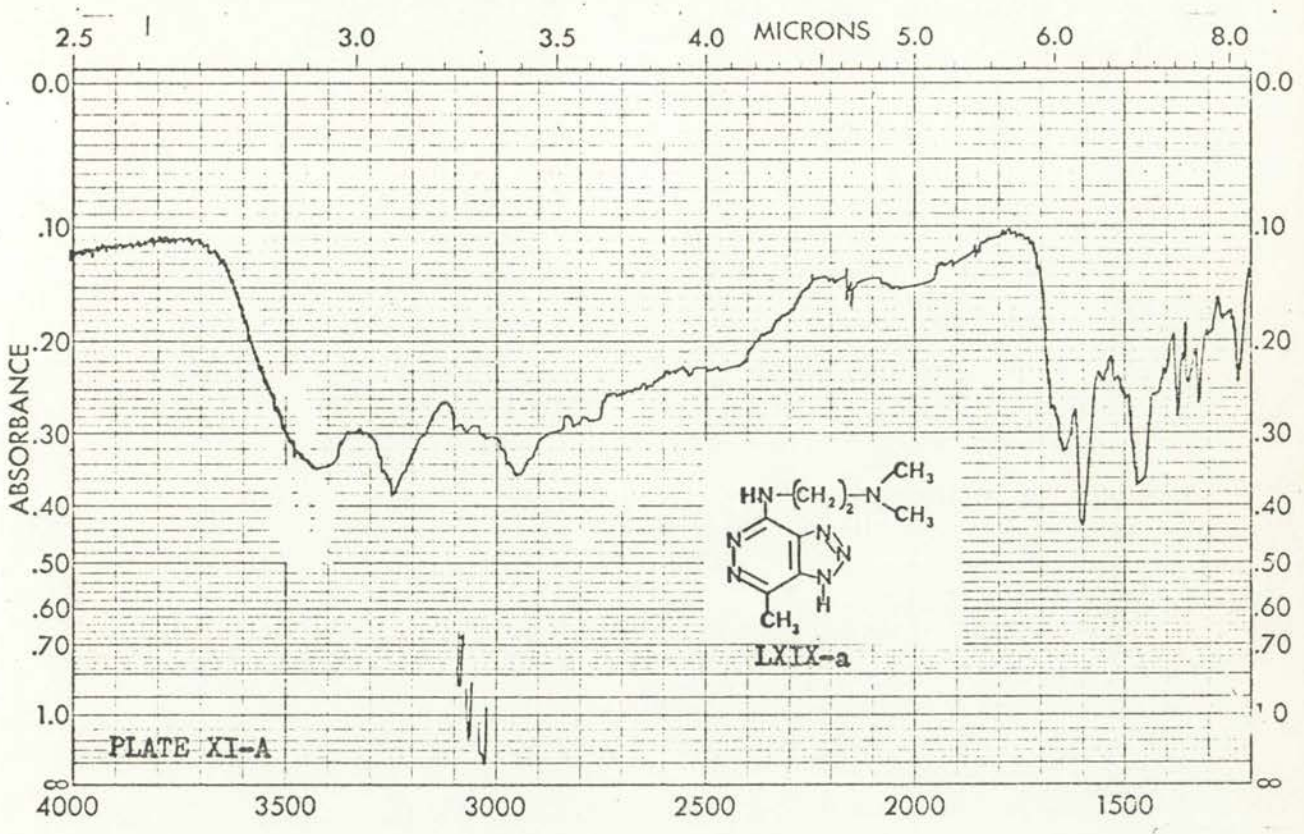
LVI


7.5
8.0
9.0
10.0
MICRONS
15.0
20.0
25.0
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
ABSORBANCE
1300
1200
1100
1000
900
800
700
600
500
400
PLATE IX-B

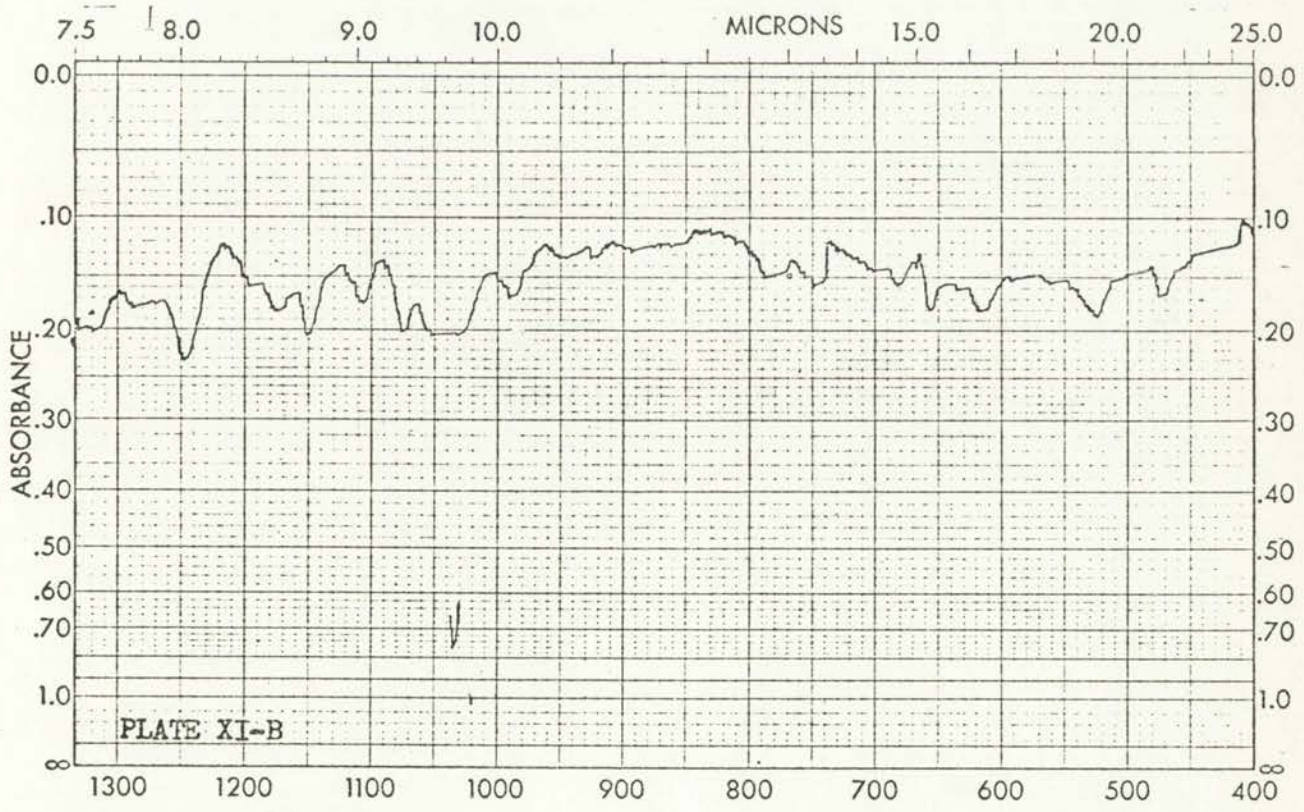

2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
ABSORBANCE
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
SCH3
N
S
H
LVII
PLATE X-A
4000
3500
3000
2500
2000
1500

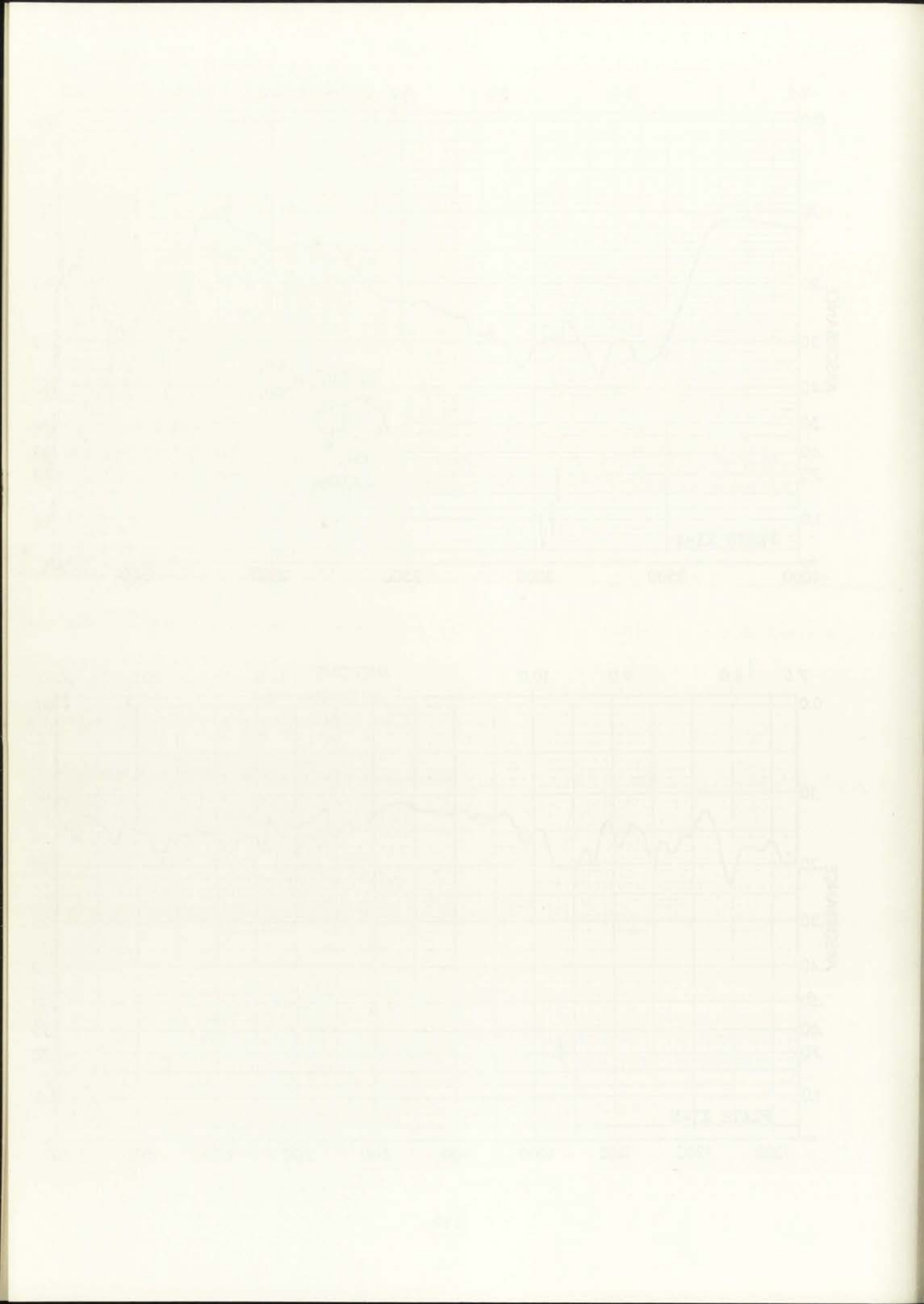

7.5
8.0
9.0
10.0
MICRONS
15.0
20.0
25.0
ABSORBANCE
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
PLATE X-B
1300
1200
1100
1000
900
800
700
600
500
400

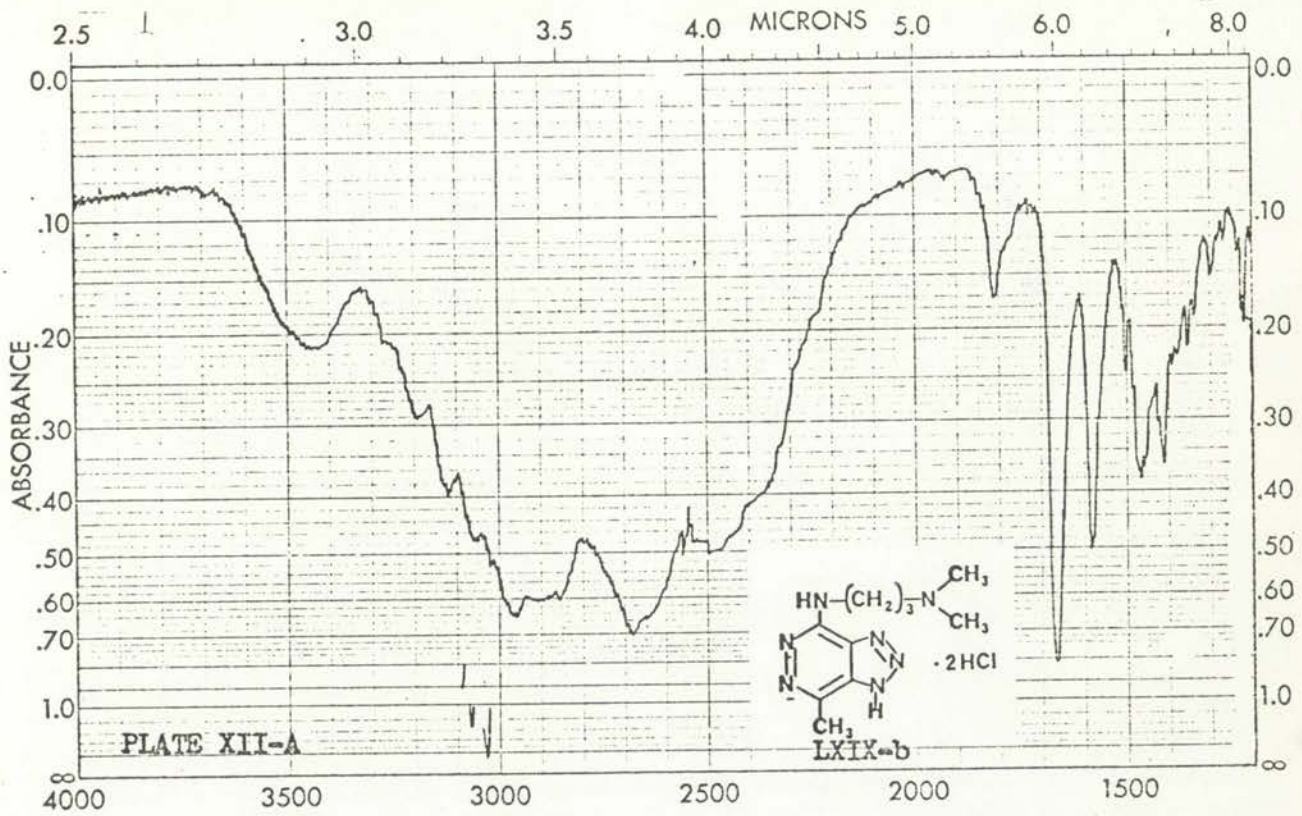


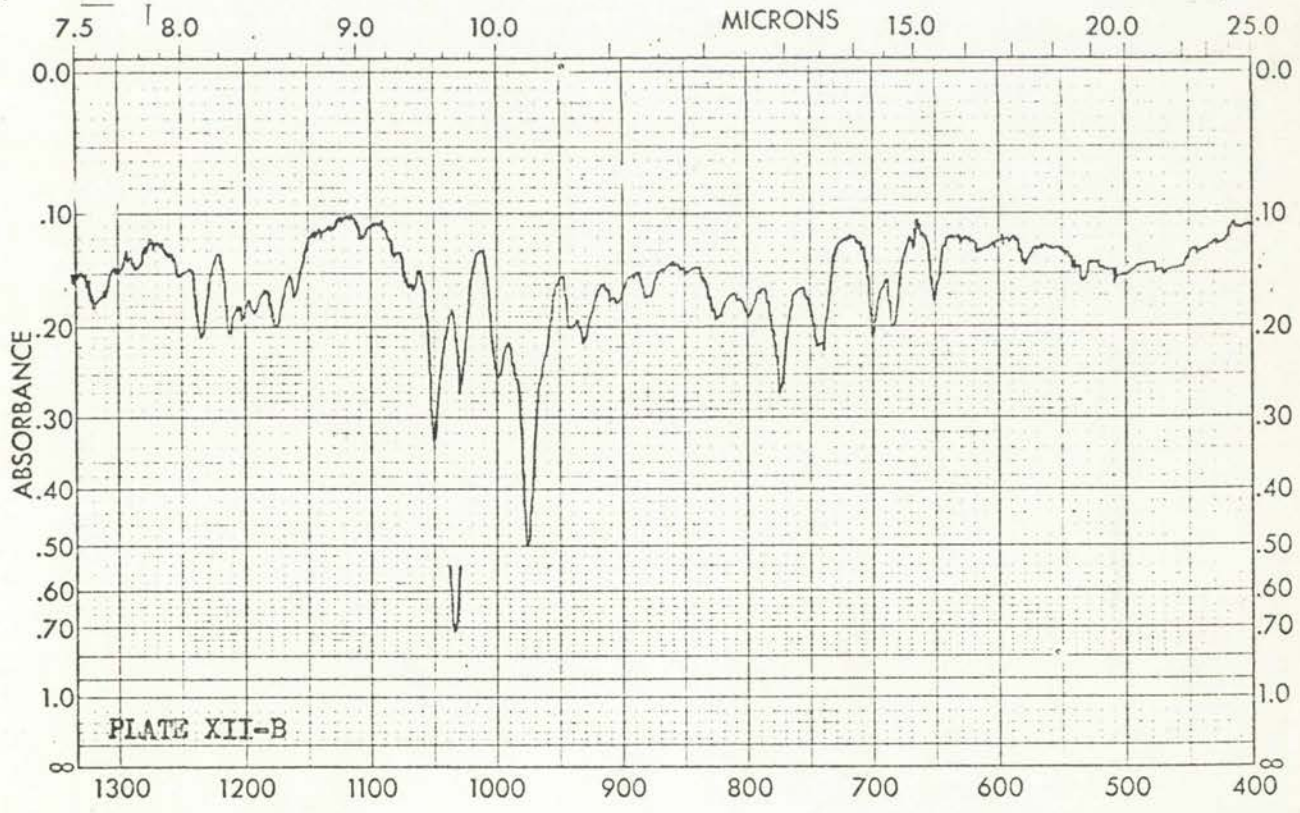

2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
ABSORBANCE
PLATE XI-A
4000
3500
3000
2500
2000
1500

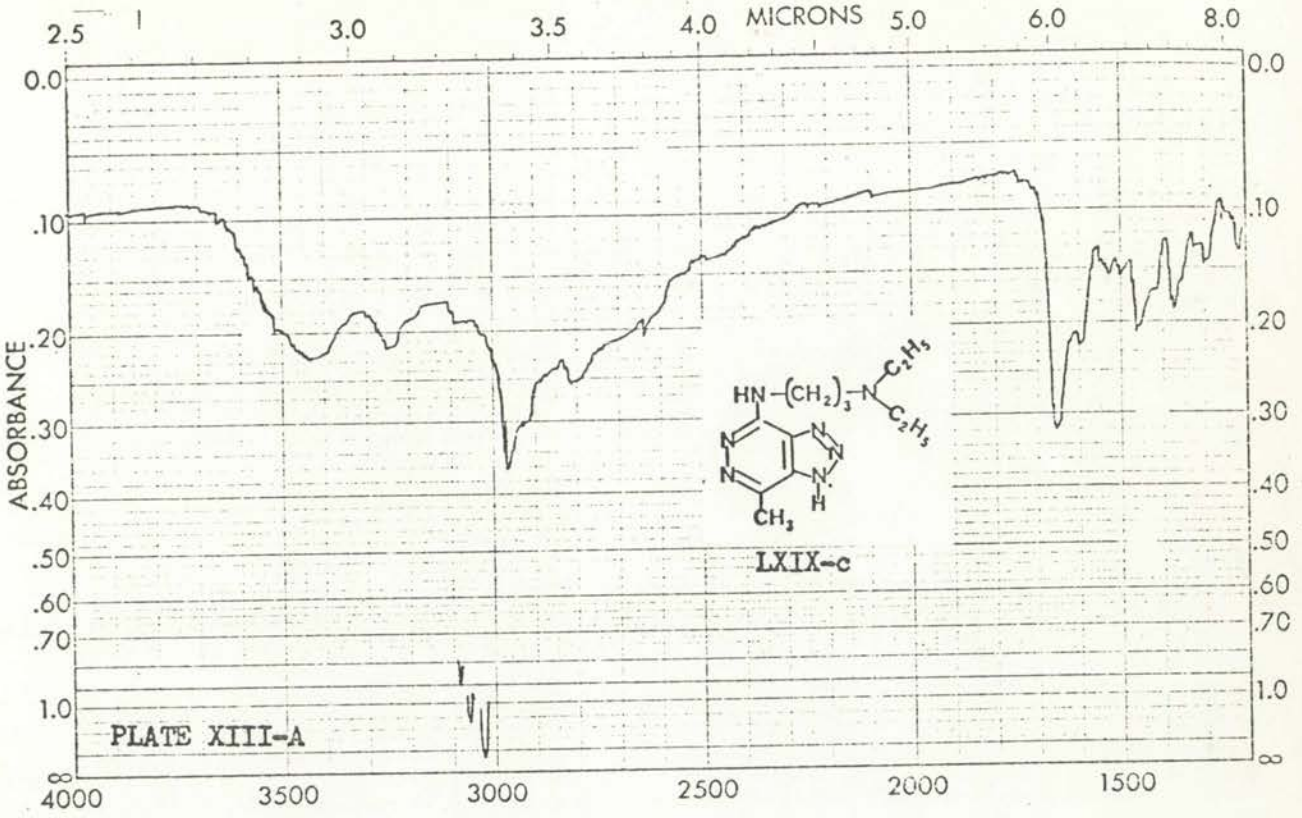
LXIX-a

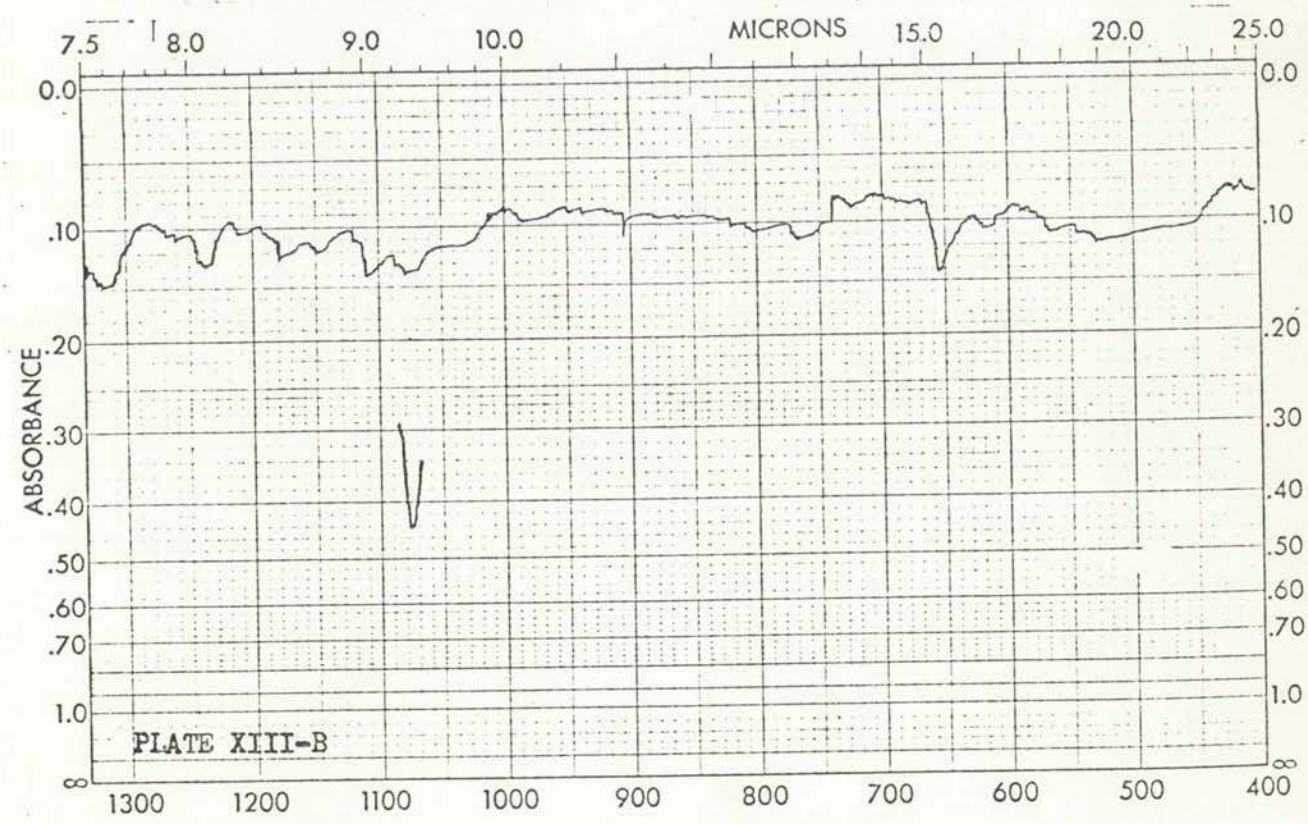

7.5
8.0
9.0
10.0
MICRONS
15.0
20.0
25.0
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
ABSORBANCE
PLATE XI-B
1300
1200
1100
1000
900
800
700
600
500
400

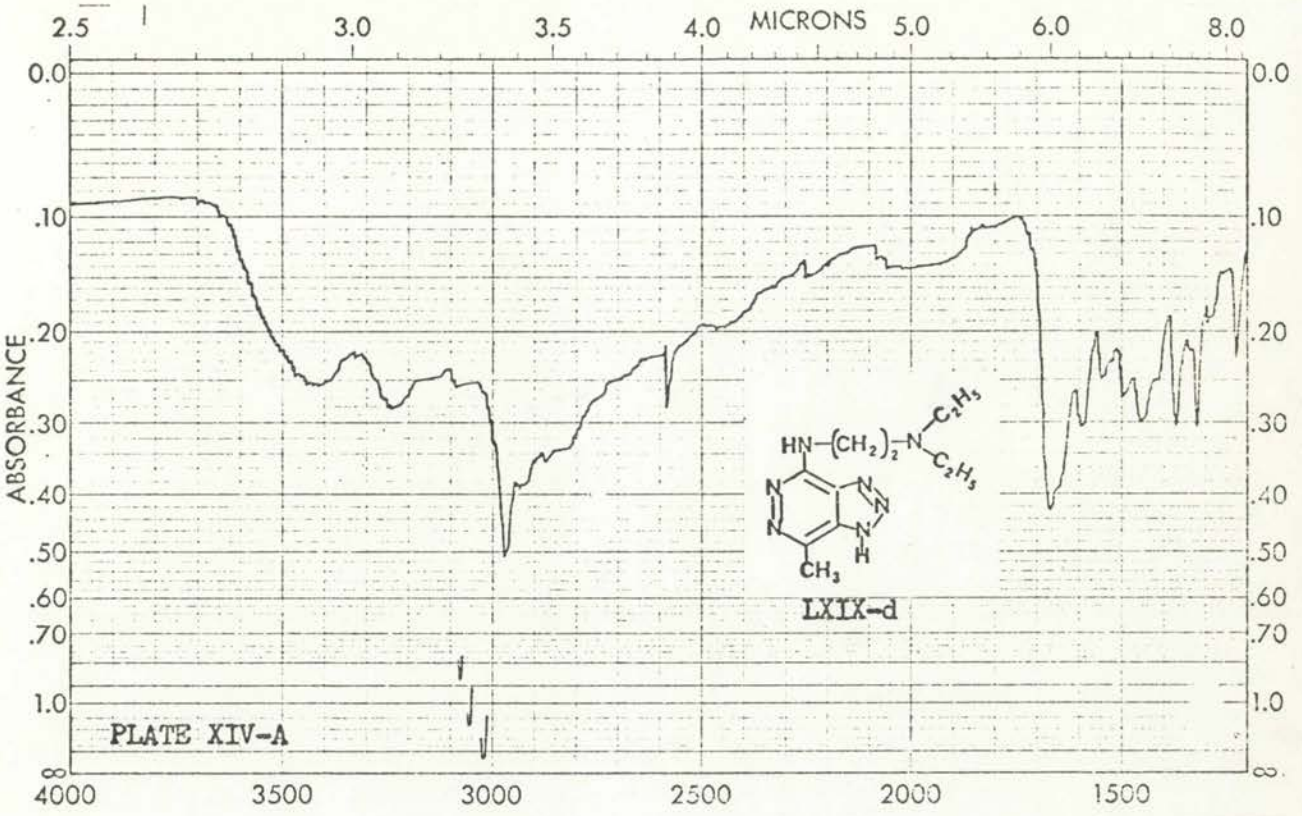


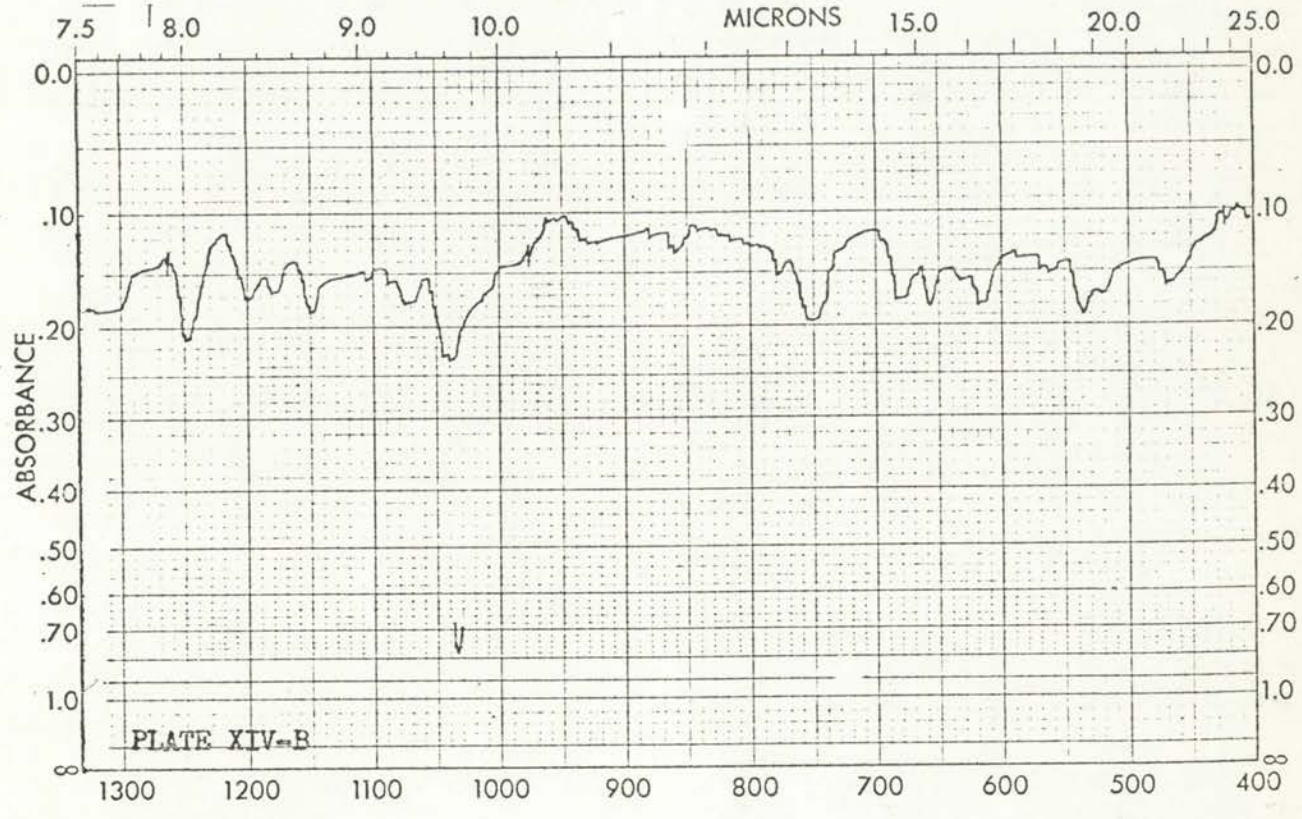

2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
ABSORBANCE
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
4000
3500
3000
2500
2000
1500
HN–(CH2)3–N
CH3
CH3
· 2HCl
CH3
PLATE XII-A
LXIX-b

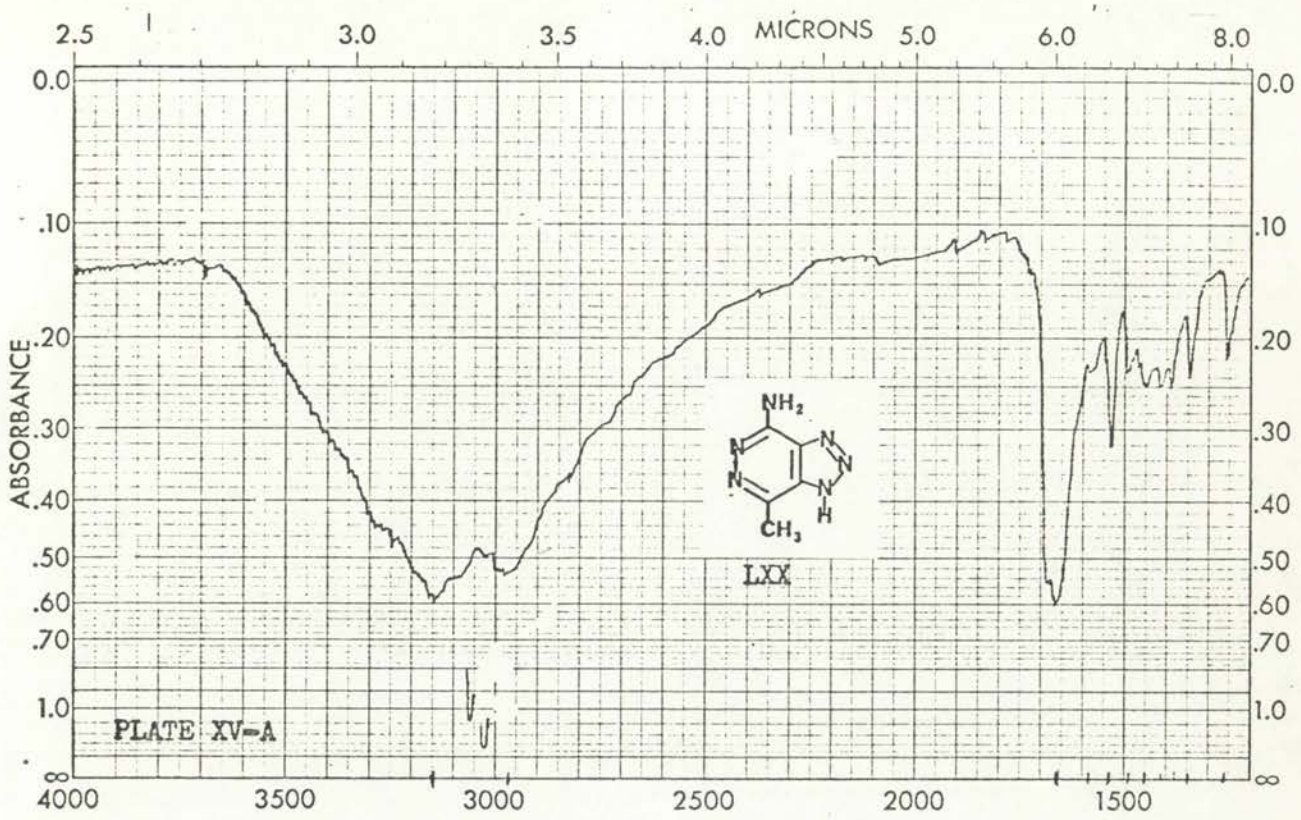

7.5
8.0
9.0
10.0
MICRONS
15.0
20.0
25.0
ABSORBANCE
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
1300
1200
1100
1000
900
800
700
600
500
400
PLATE XII-B

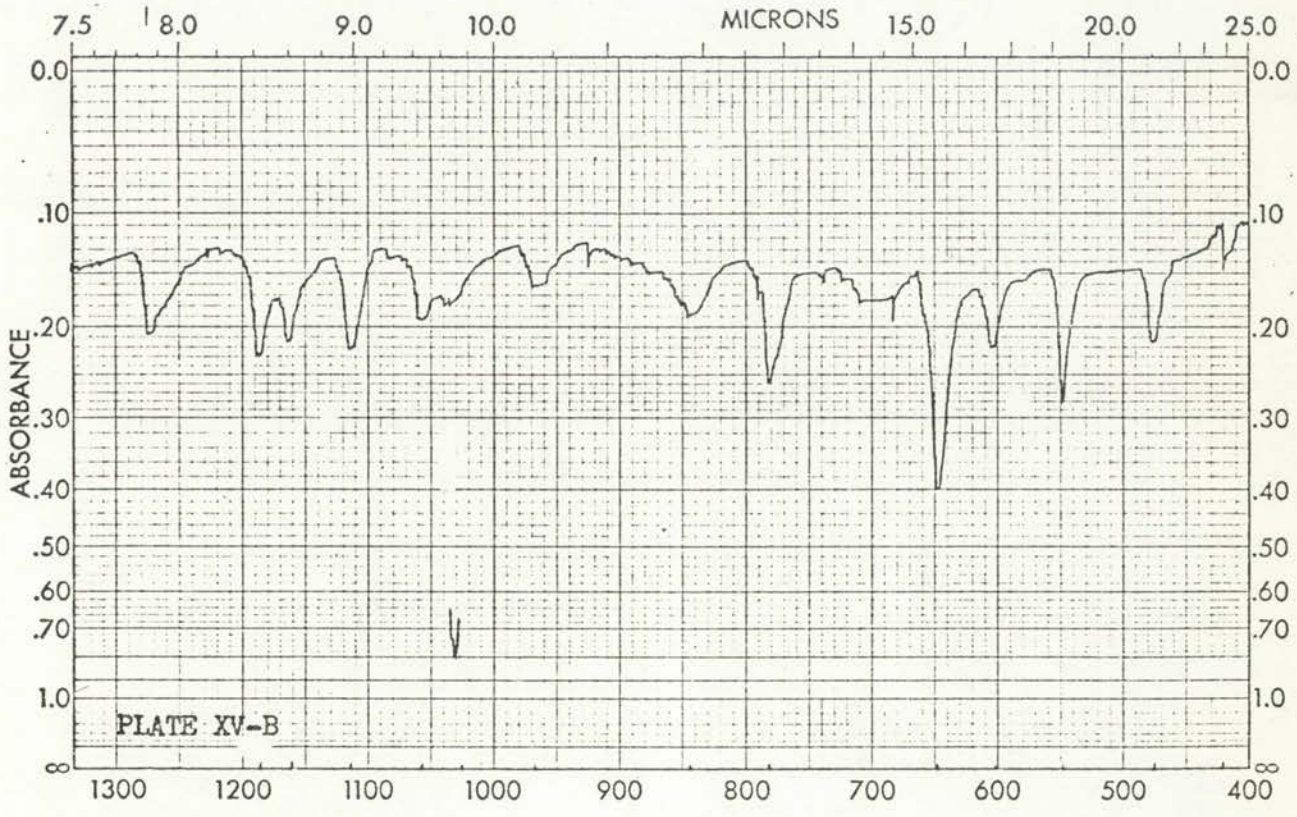

2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
ABSORBANCE
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
4000
3500
3000
2500
2000
1500
PLATE XIII-A
LXIX-c

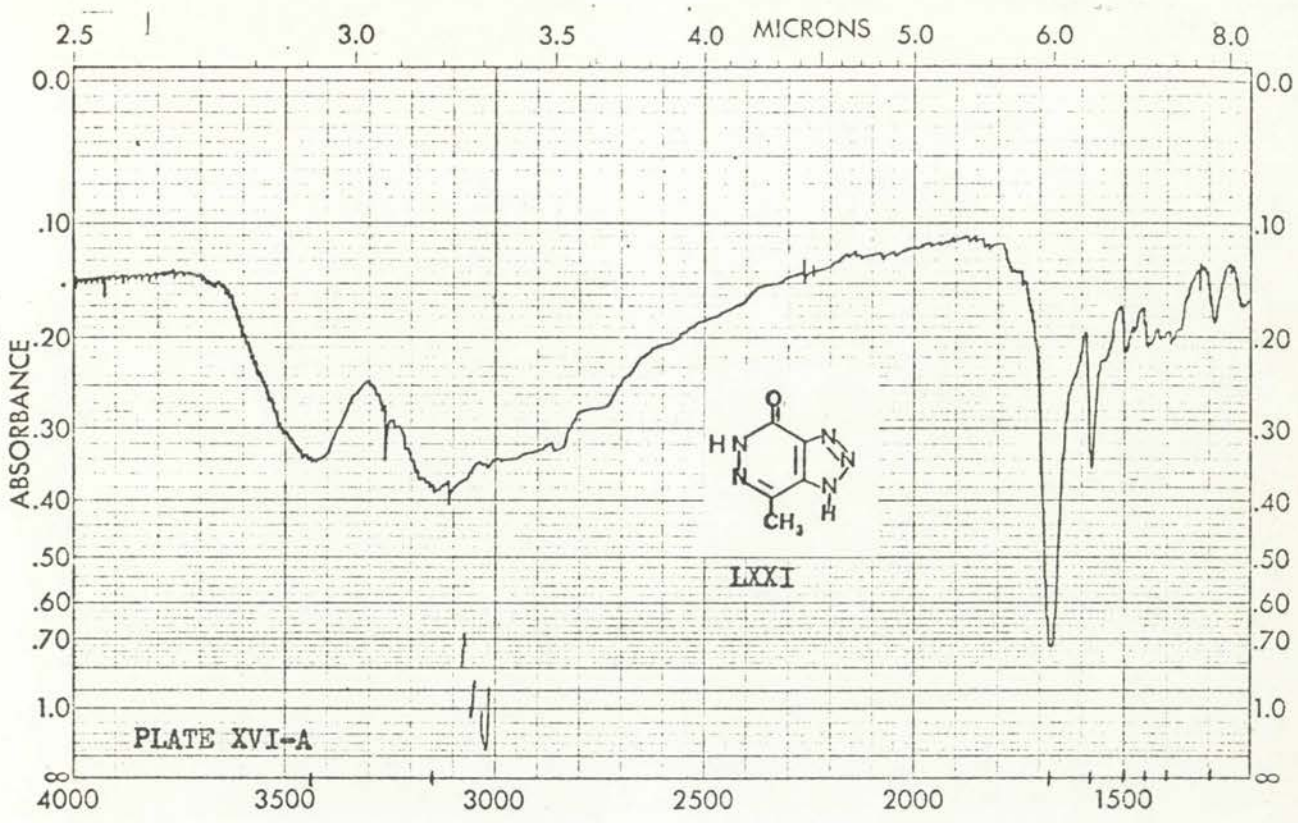

7.5
8.0
9.0
10.0
MICRONS
15.0
20.0
25.0
ABSORBANCE
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
1300
1200
1100
1000
900
800
700
600
500
400
PLATE XIII-B


2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
ABSORBANCE
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
4000
3500
3000
2500
2000
1500
HN–(CH2)2–N
C2H5
C2H5
N
N
N
N
H
CH3
LXIX–d
PLATE XIV–A

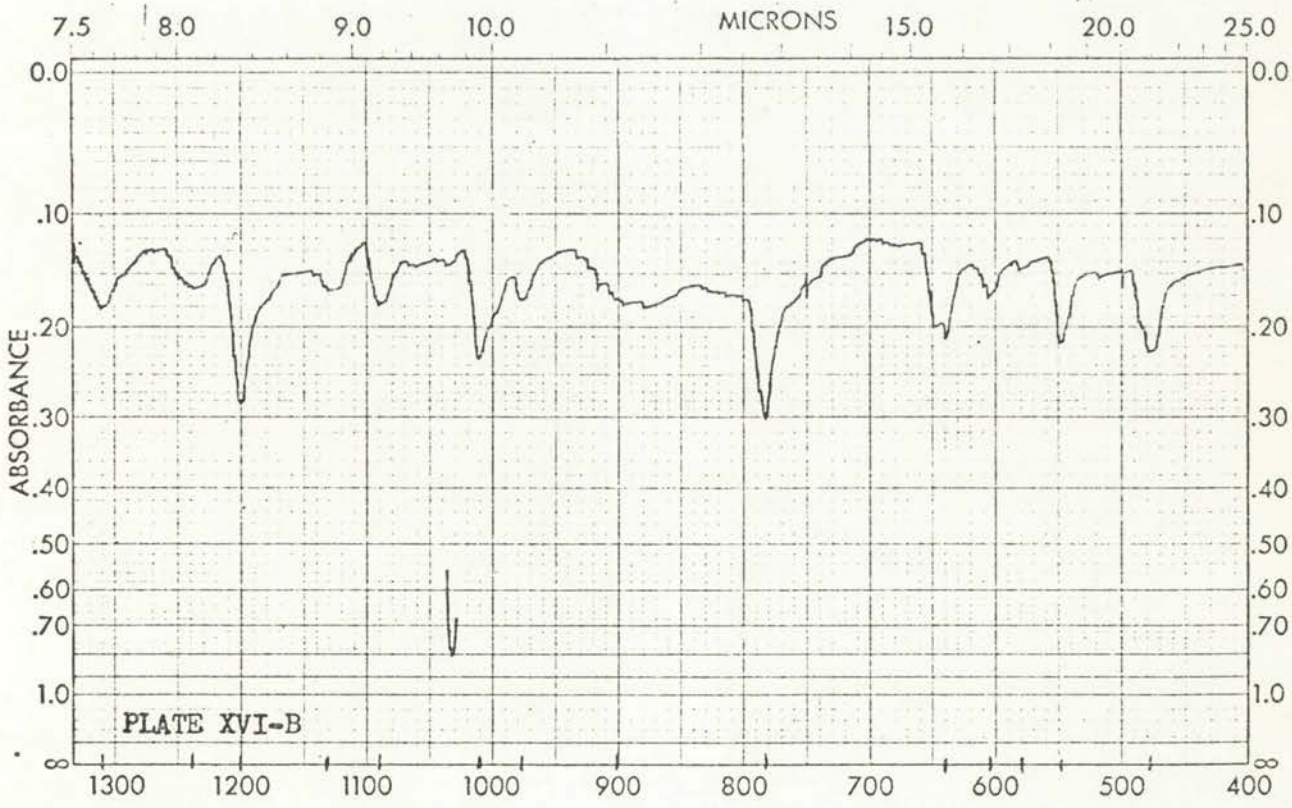

7.5
8.0
9.0
10.0
MICRONS
15.0
20.0
25.0
ABSORBANCE
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
1300
1200
1100
1000
900
800
700
600
500
400
PLATE XIV–B

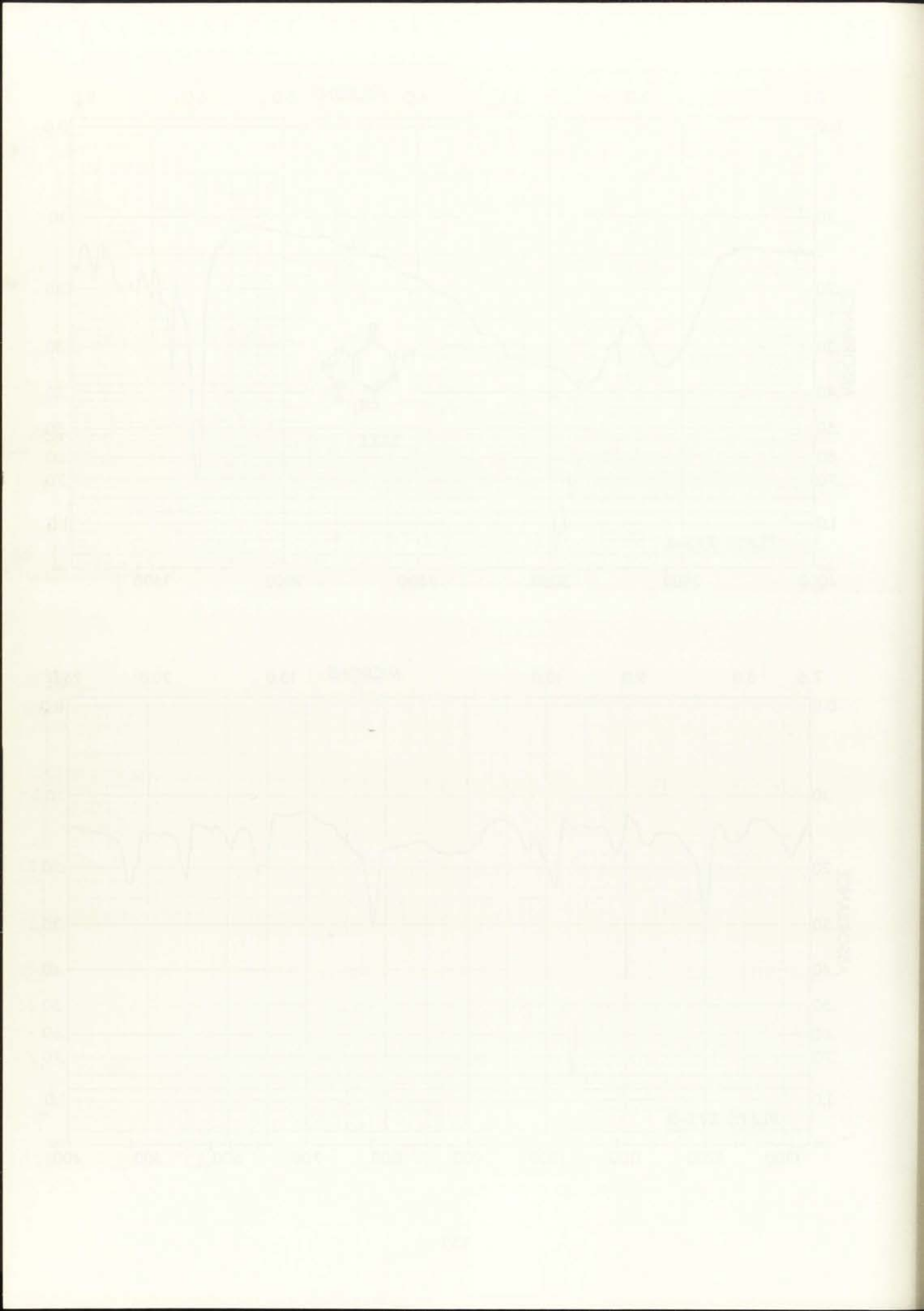

2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
ABSORBANCE
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
4000
3500
3000
2500
2000
1500
PLATE XV-A
LXX

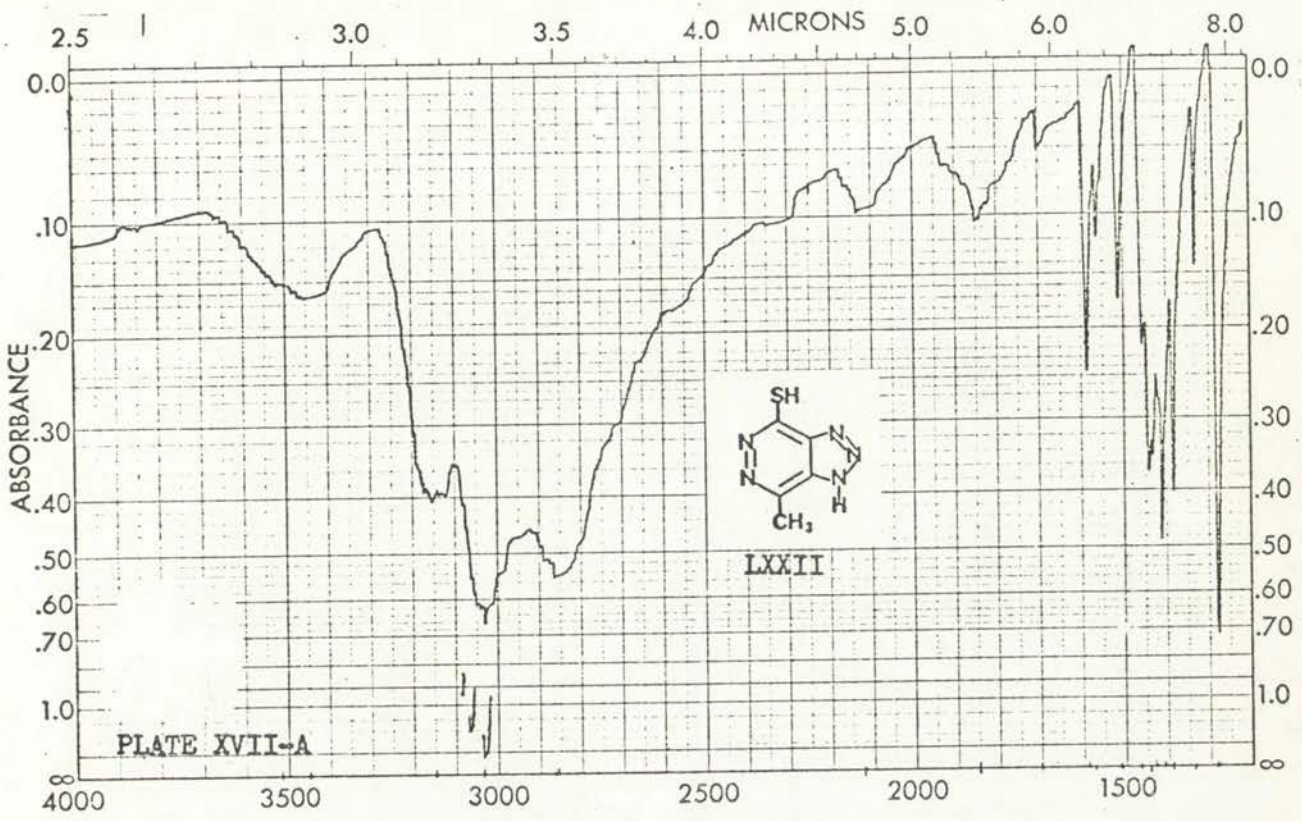

7.5
8.0
9.0
10.0
MICRONS
15.0
20.0
25.0
ABSORBANCE
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
1300
1200
1100
1000
900
800
700
600
500
400
PLATE XV-B

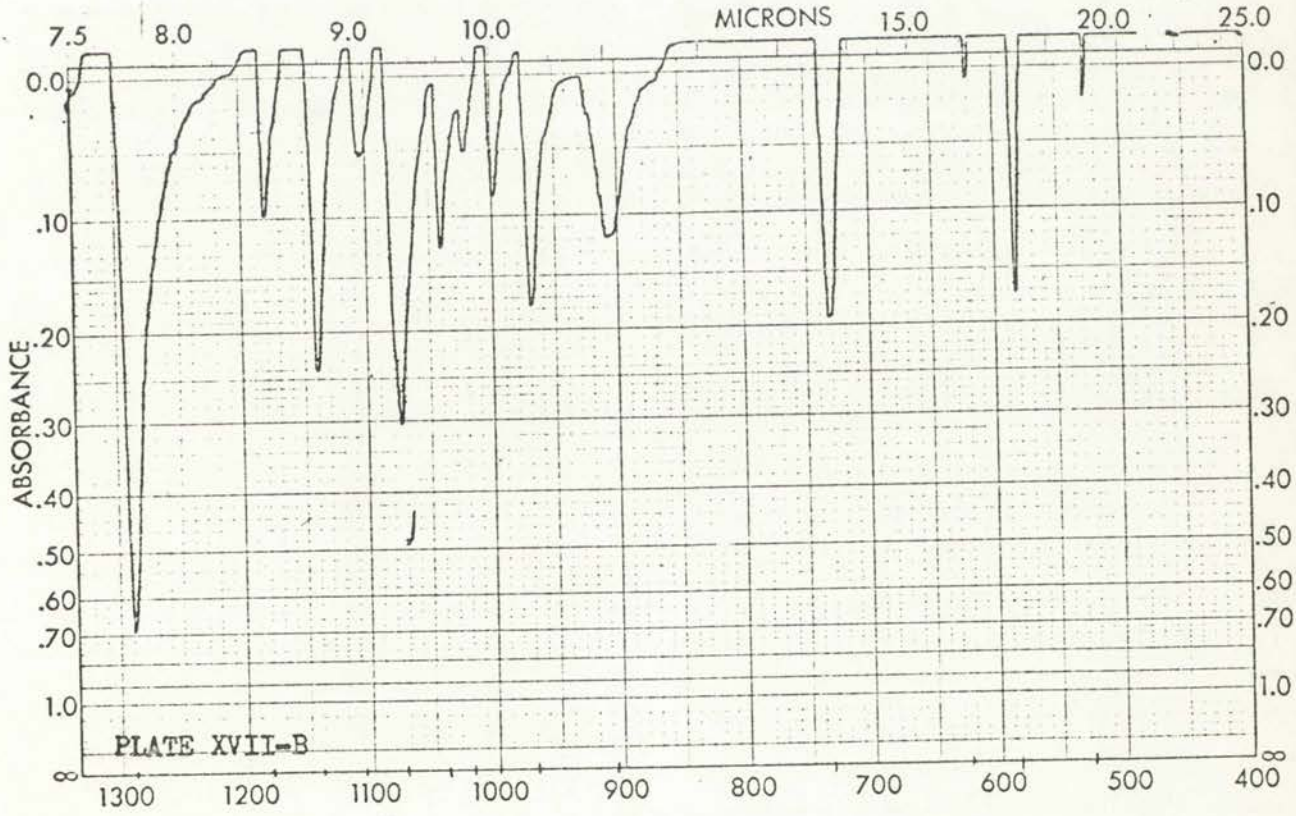

2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
ABSORBANCE
4000
3500
3000
2500
2000
1500
PLATE XVI-A

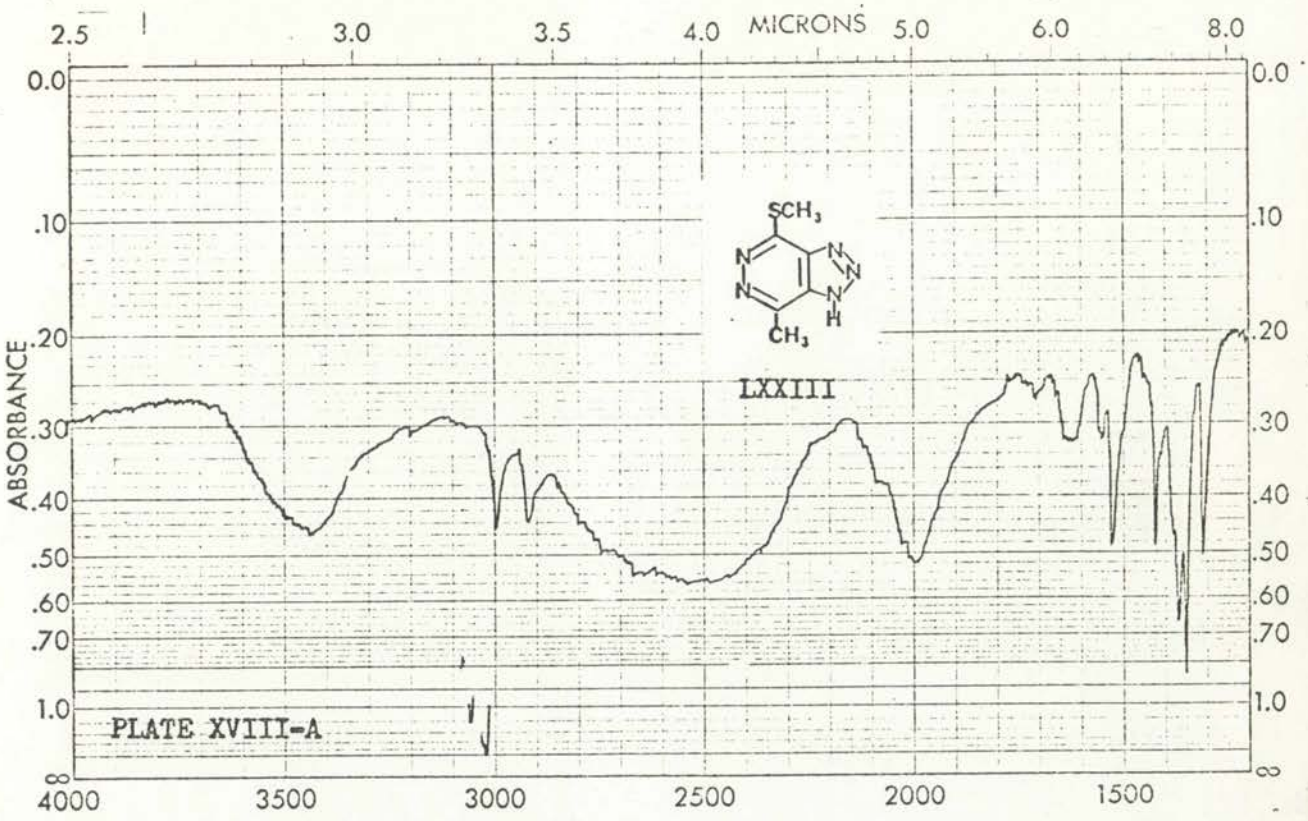
LXXI

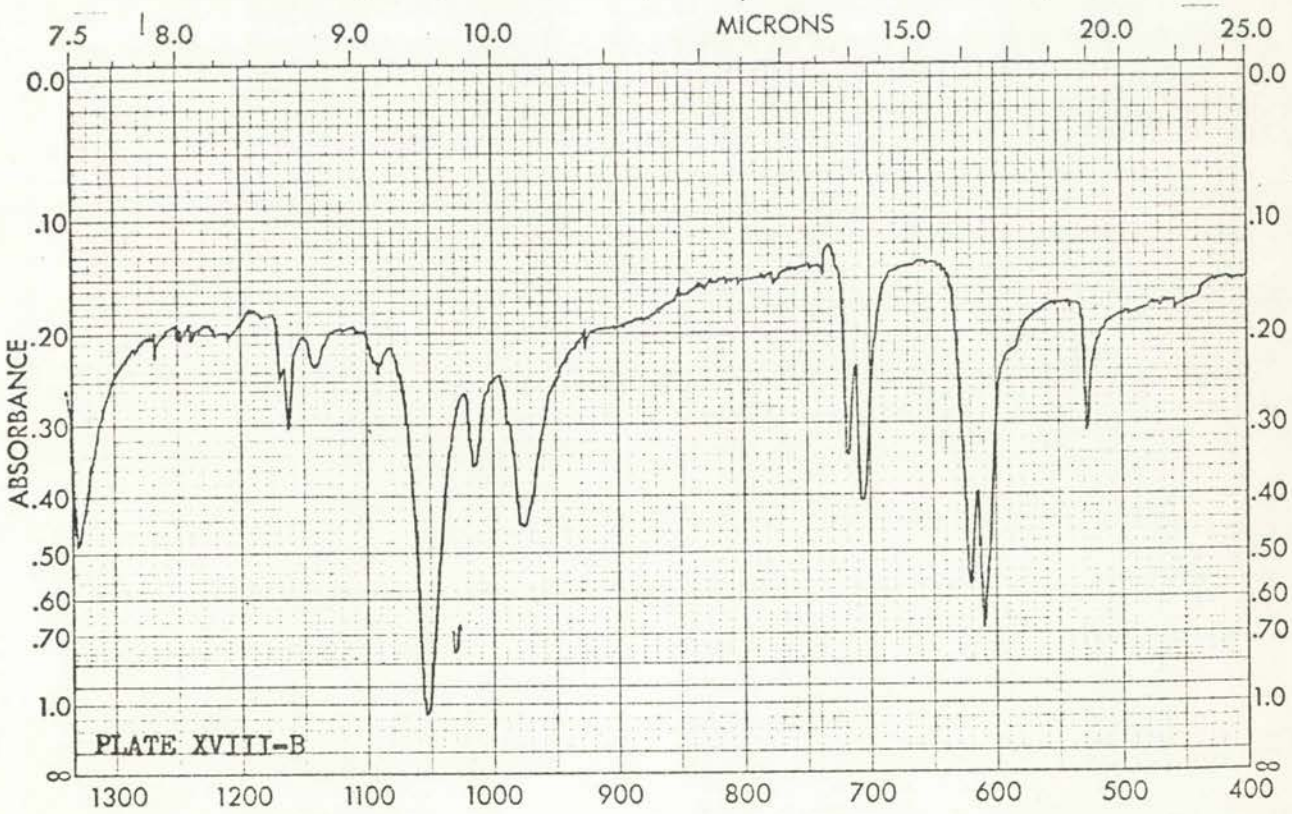

7.5
8.0
9.0
10.0
MICRONS
15.0
20.0
25.0
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
ABSORBANCE
1300
1200
1100
1000
900
800
700
600
500
400
PLATE XVI-B

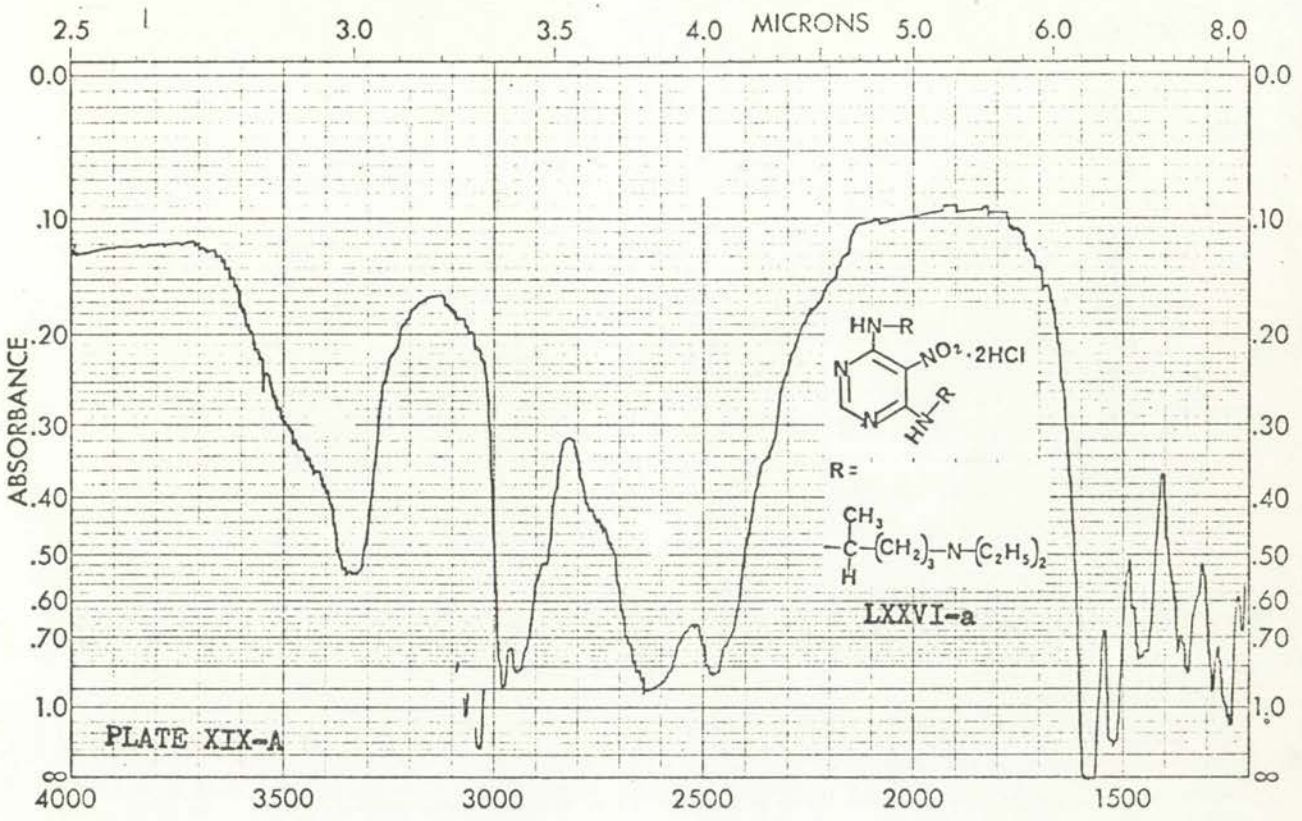


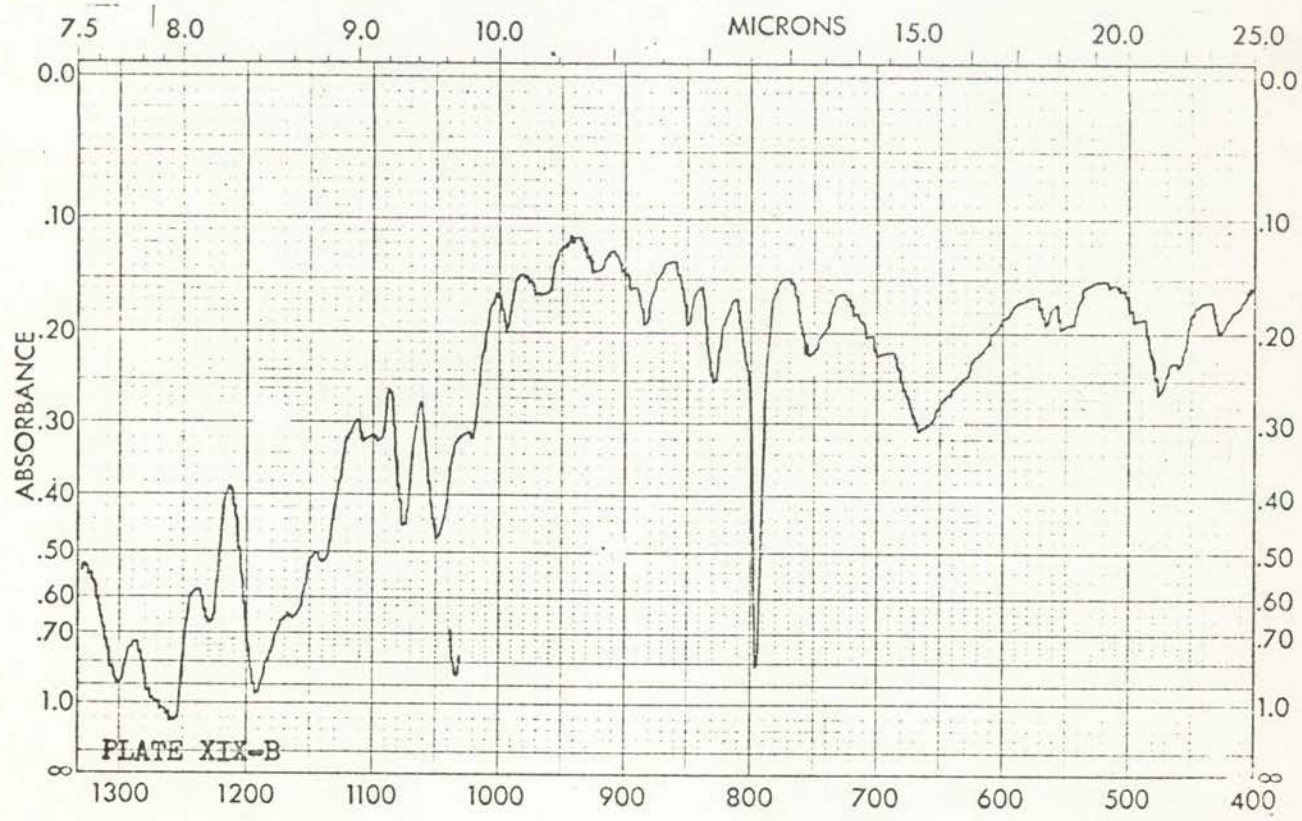

2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
ABSORBANCE
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
4000
3500
3000
2500
2000
1500
SH
N
N
N
N
H
CH3
LXXII
PLATE XVII-A

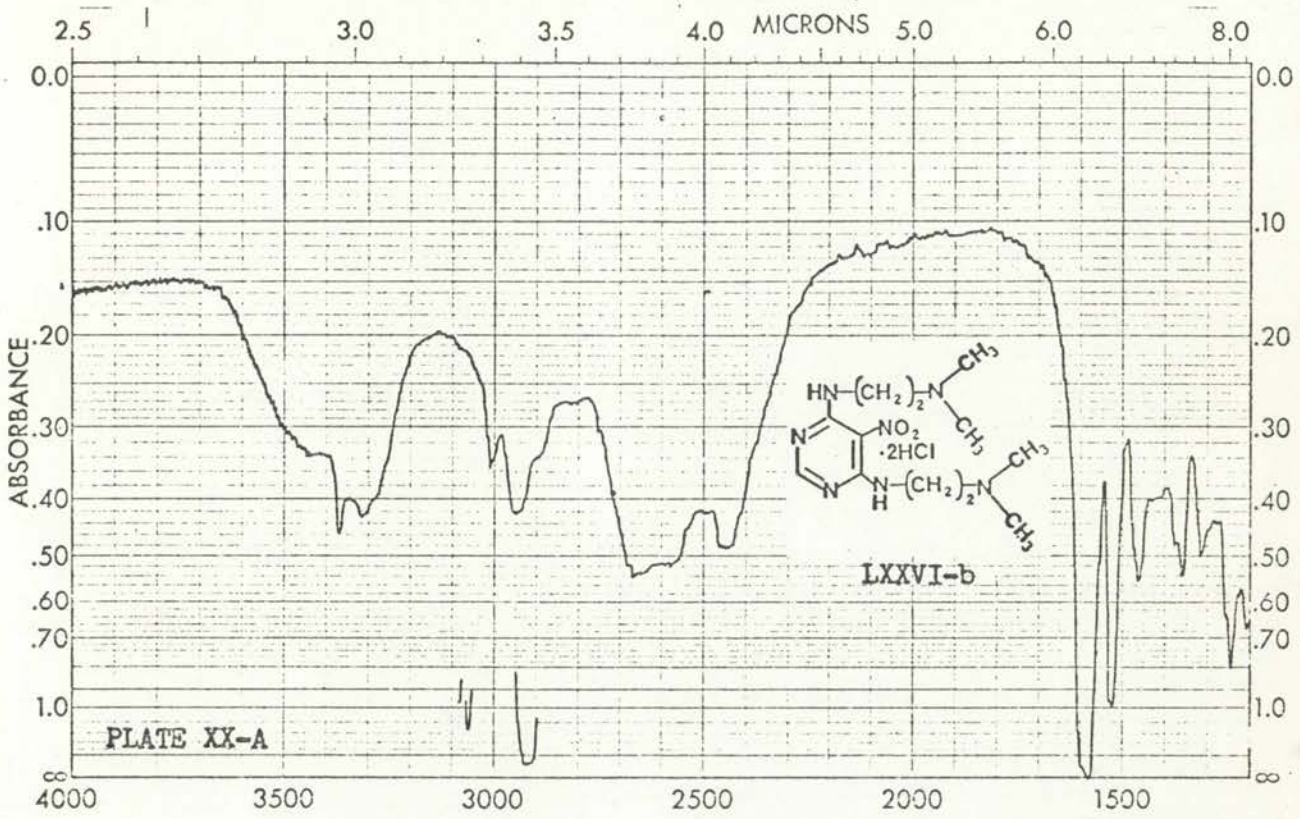

7.5
8.0
9.0
10.0
MICRONS
15.0
20.0
25.0
ABSORBANCE
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
1300
1200
1100
1000
900
800
700
600
500
400
PLATE XVII-B

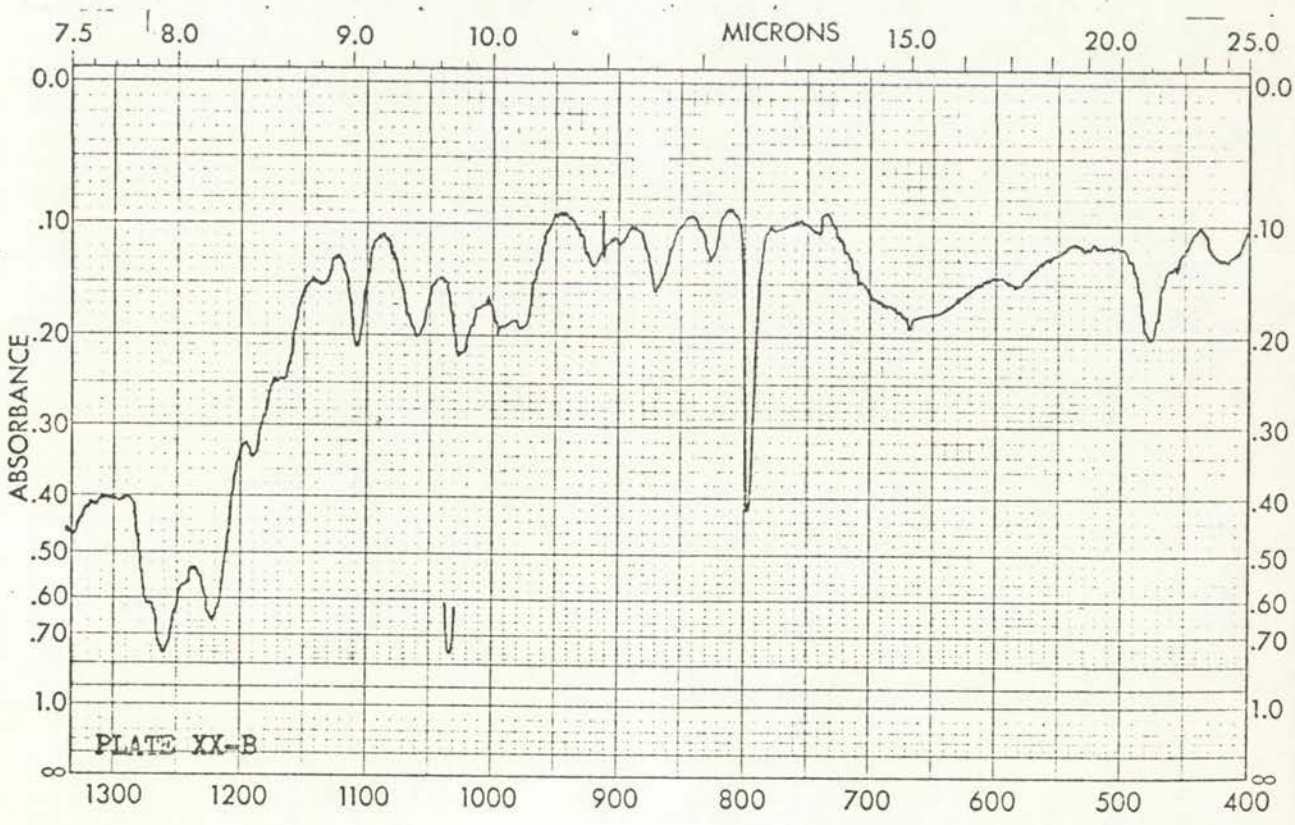

2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
ABSORBANCE
SCH3
CH3
N
H
LXXIII
PLATE XVIII-A
4000
3500
3000
2500
2000
1500

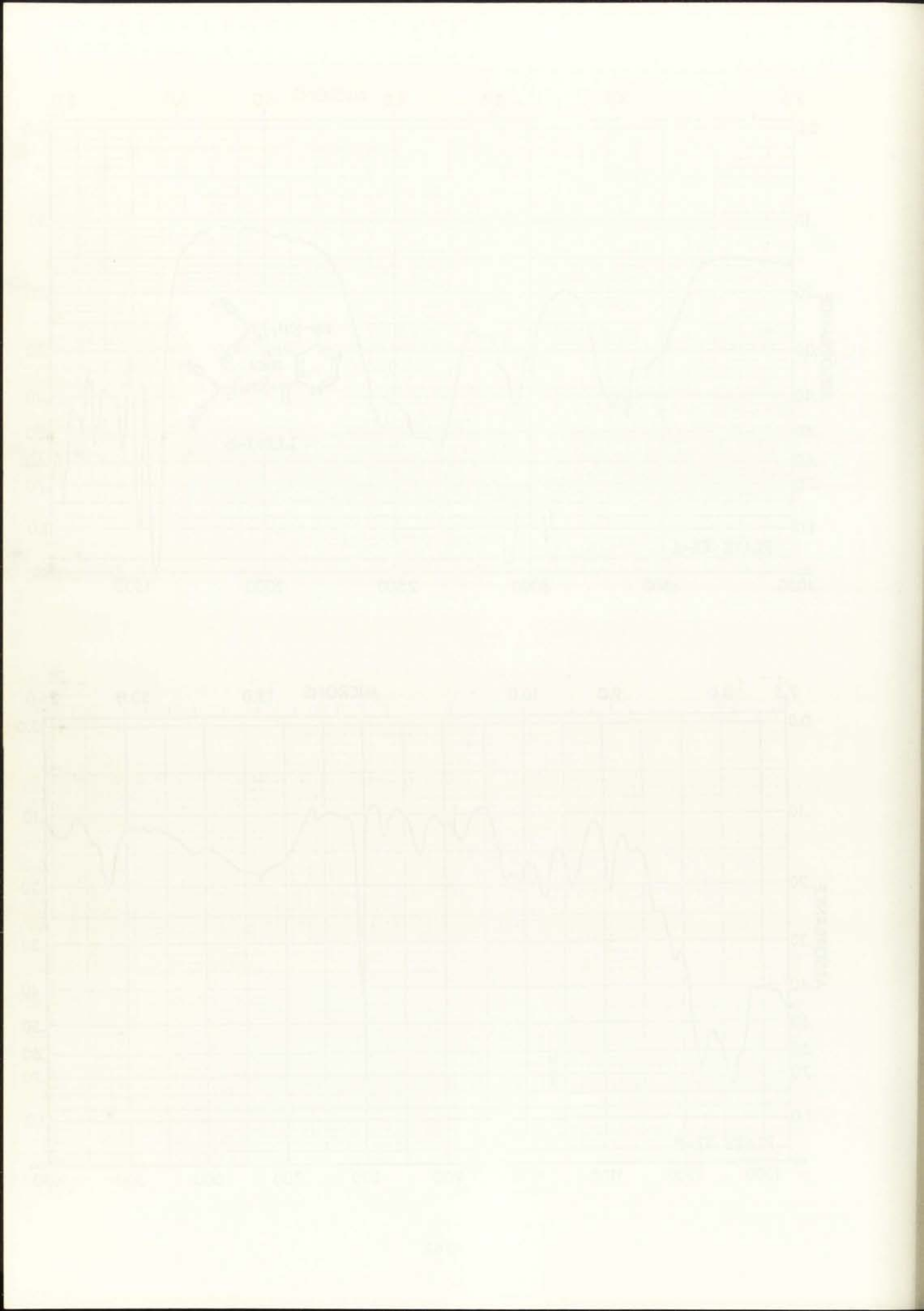

7.5
8.0
9.0
10.0
MICRONS
15.0
20.0
25.0
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
ABSORBANCE
PLATE XVIII-B
1300
1200
1100
1000
900
800
700
600
500
400

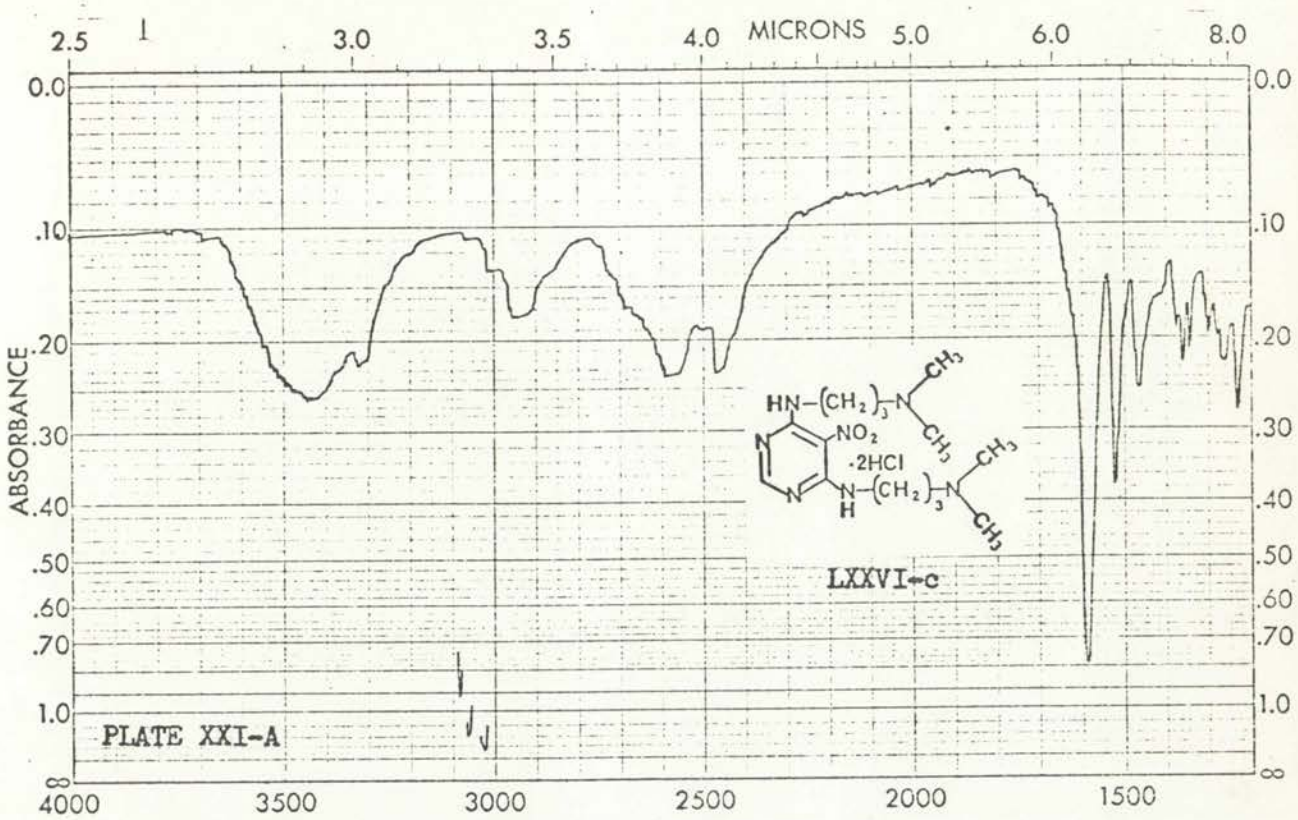

2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
ABSORBANCE
HN—R
NO₂·2HCl
HN—R
R=
CH₃
—C—(CH₂)₃—N—(C₂H₅)₂
H
LXXVI-a
PLATE XIX-A
4000
3500
3000
2500
2000
1500

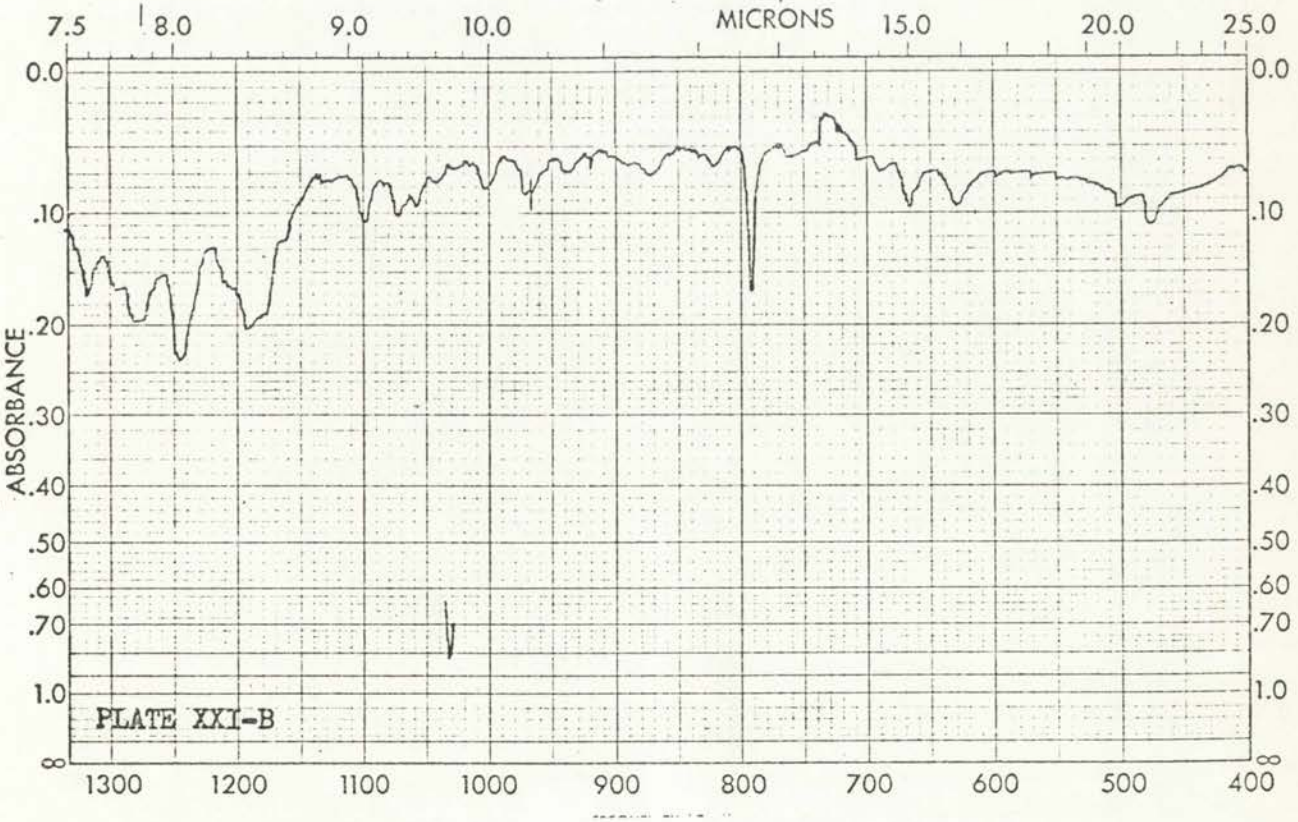

7.5
8.0
9.0
10.0
MICRONS
15.0
20.0
25.0
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
ABSORBANCE
PLATE XIX-B
1300
1200
1100
1000
900
800
700
600
500
400

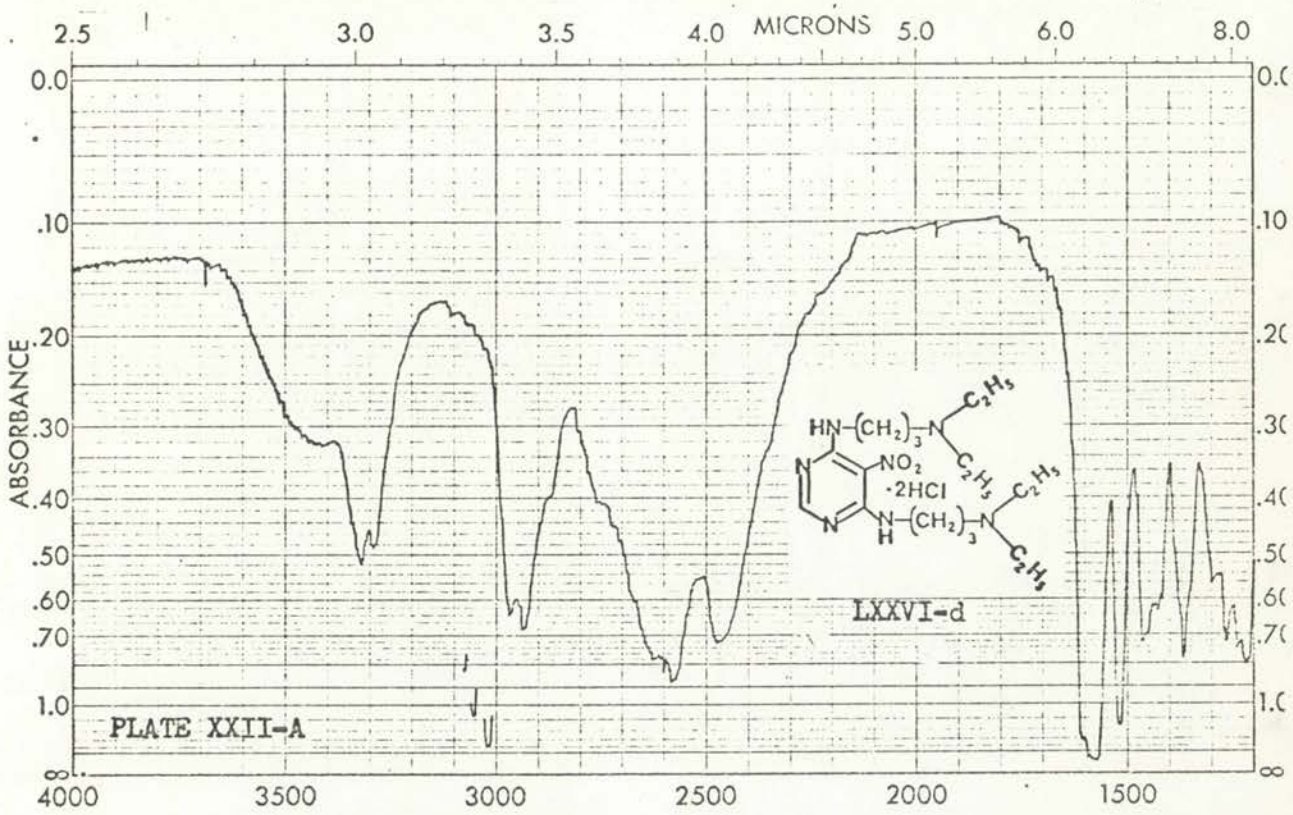

2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
ABSORBANCE
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
4000
3500
3000
2500
2000
1500
LXXVI-b
PLATE XX-A

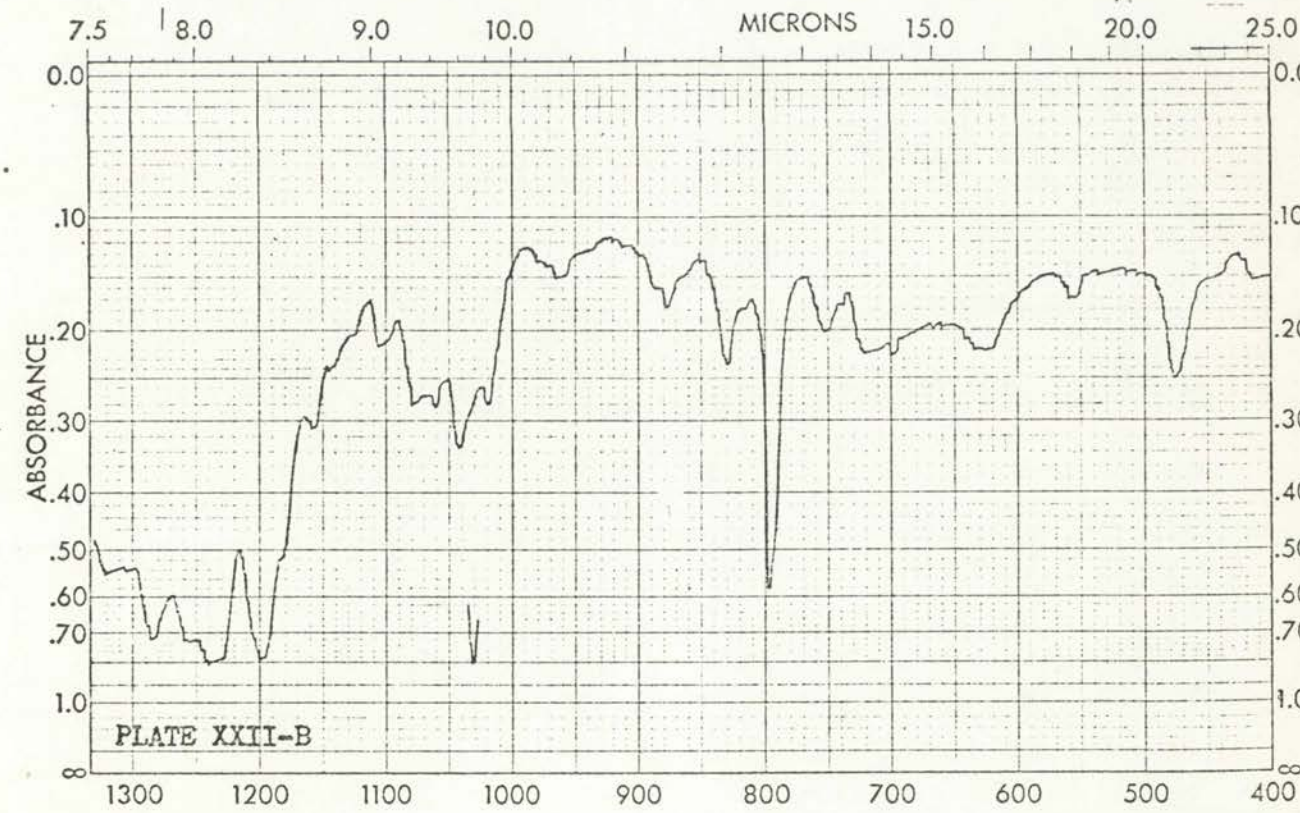

7.5
8.0
9.0
10.0
MICRONS
15.0
20.0
25.0
ABSORBANCE
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
1300
1200
1100
1000
900
800
700
600
500
400
PLATE XX-B

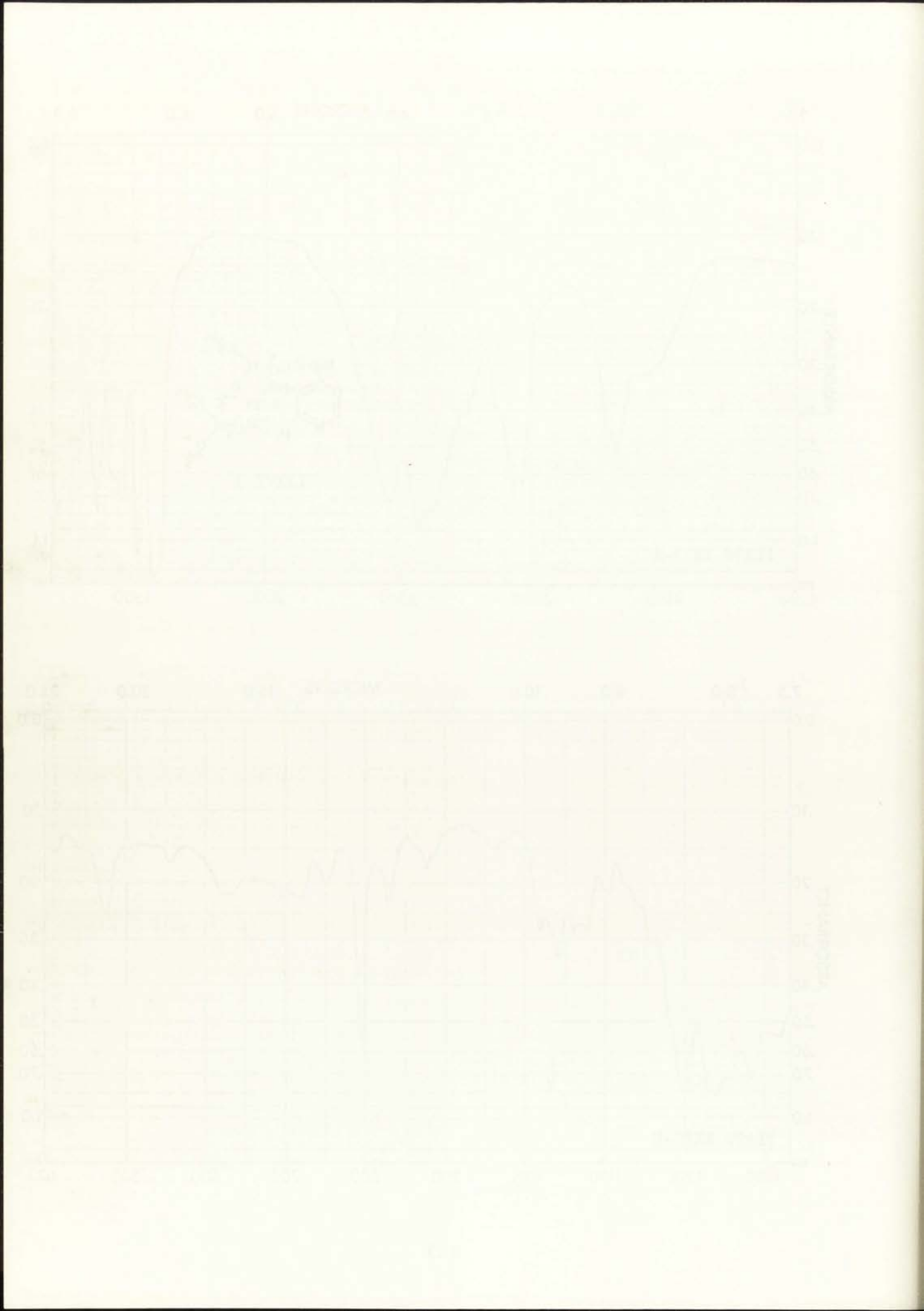


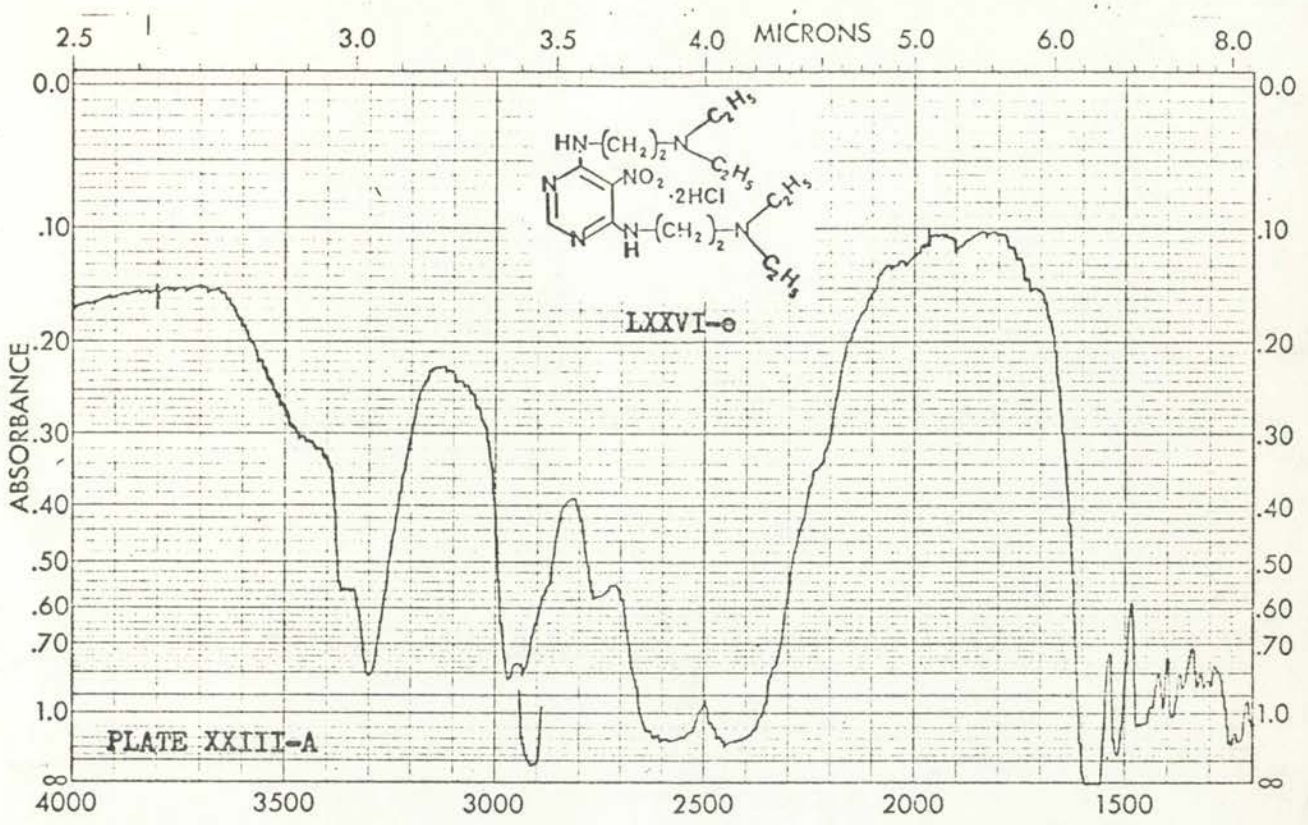

2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
ABSORBANCE
4000
3500
3000
2500
2000
1500
PLATE XXI-A
LXXVI-c

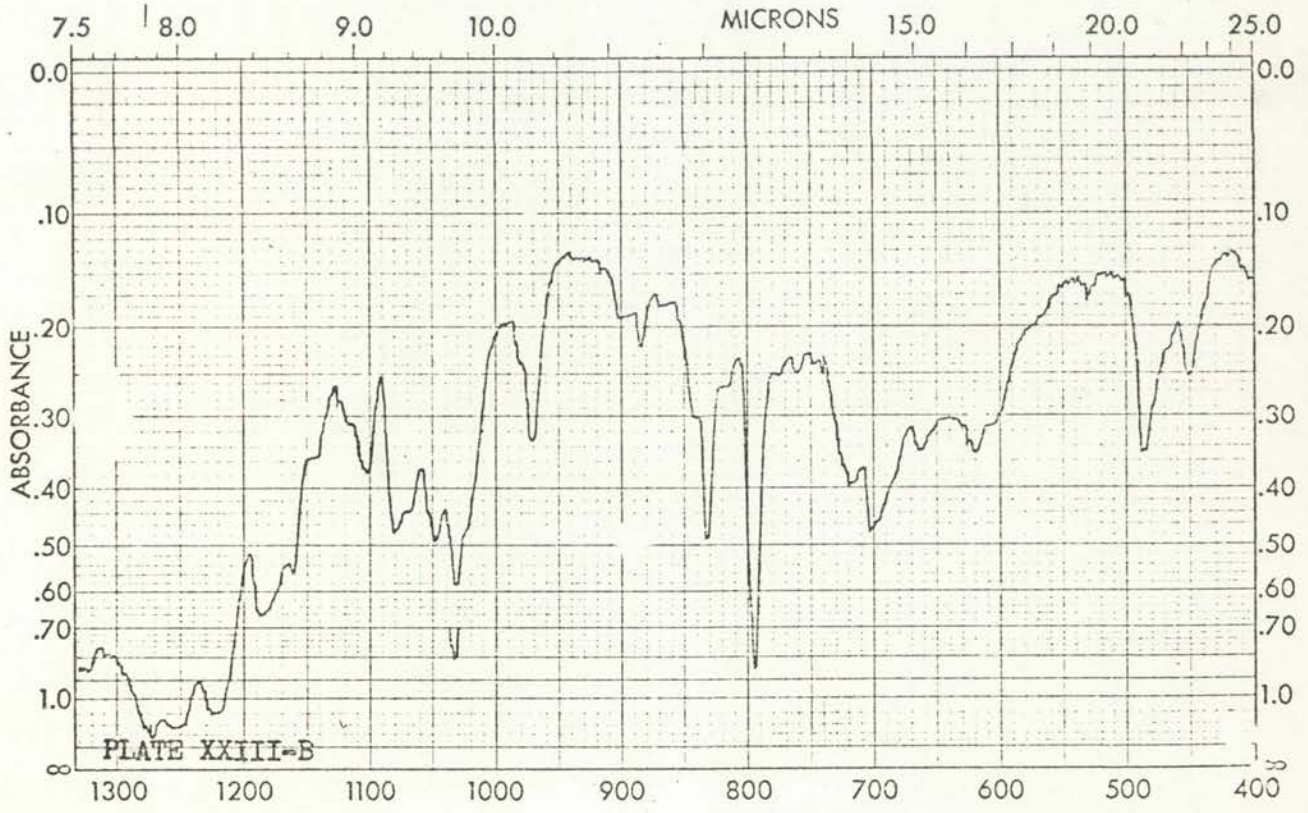

7.5
8.0
9.0
10.0
MICRONS
15.0
20.0
25.0
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
ABSORBANCE
1300
1200
1100
1000
900
800
700
600
500
400
PLATE XXI-B

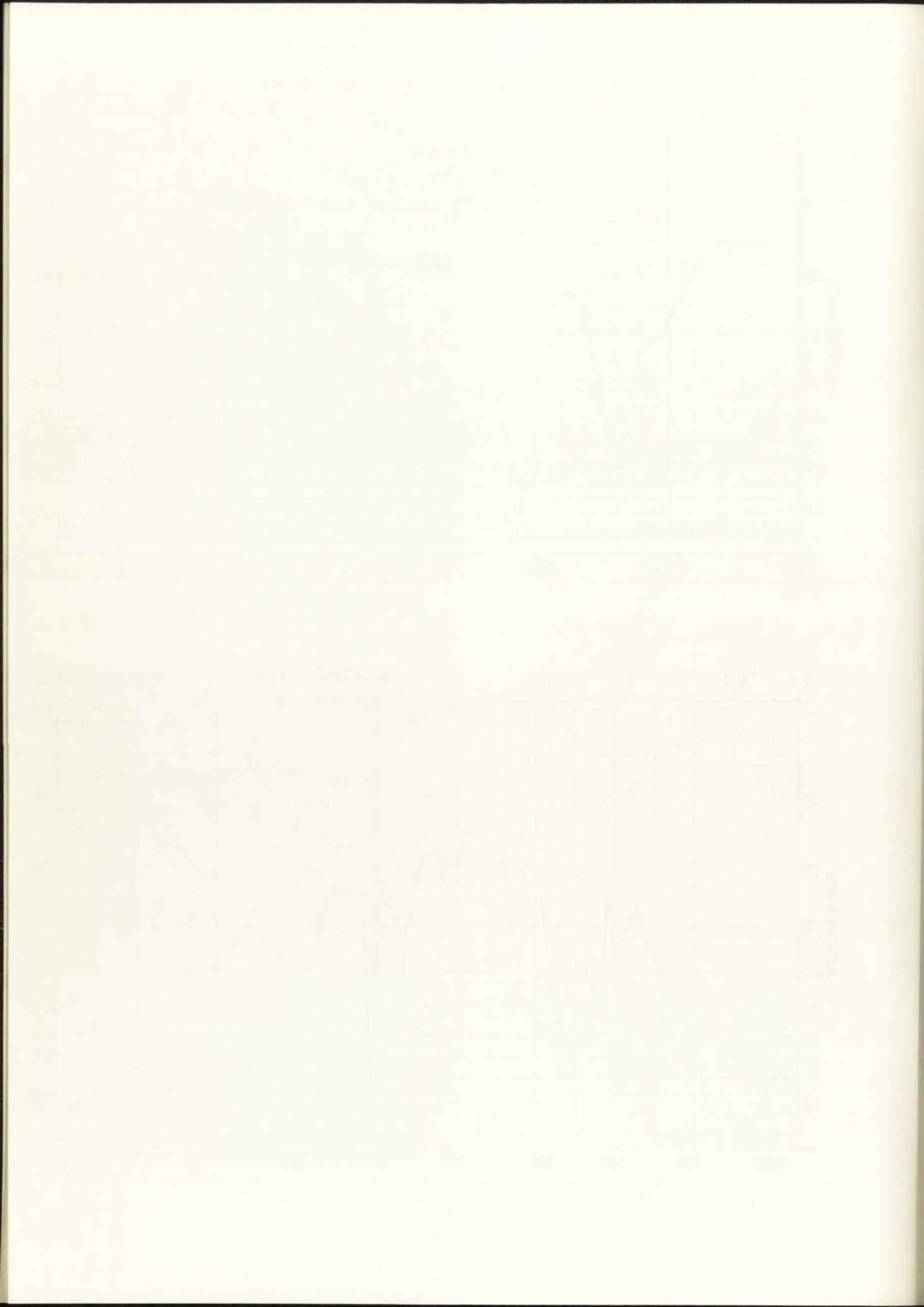

2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
ABSORBANCE
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
4000
3500
3000
2500
2000
1500
PLATE XXII-A
LXXVI-d

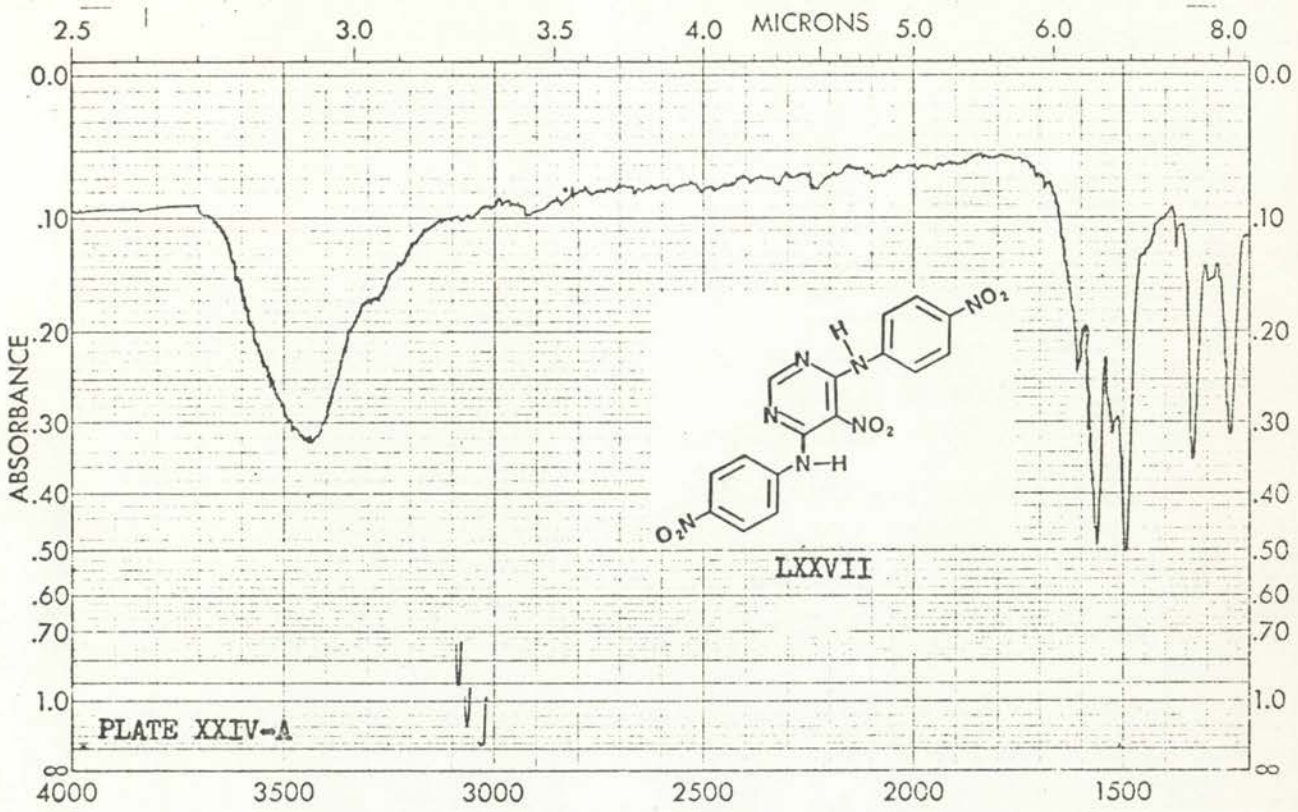

7.5
8.0
9.0
10.0
MICRONS
15.0
20.0
25.0
ABSORBANCE
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
1300
1200
1100
1000
900
800
700
600
500
400
PLATE XXII-B



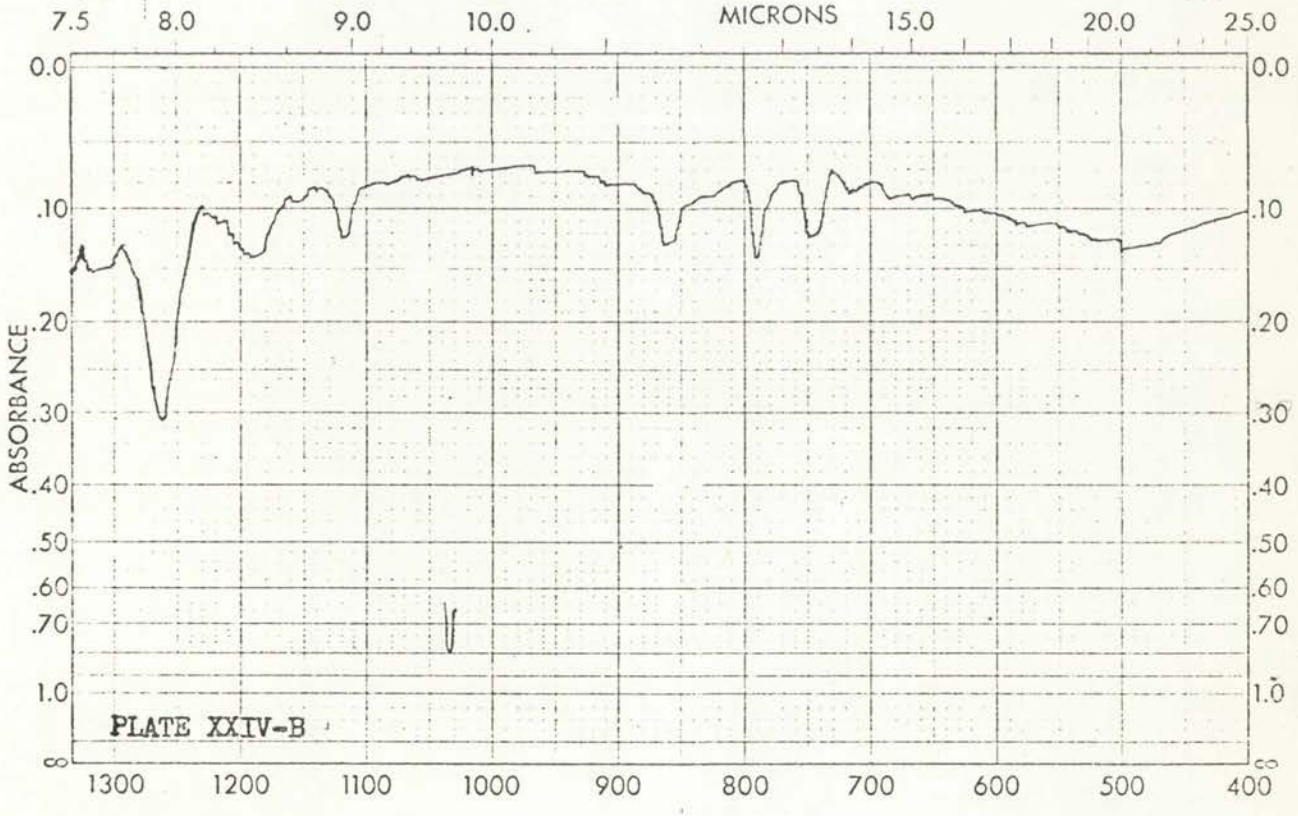

2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
ABSORBANCE
LXXVI-e
PLATE XXIII-A
4000
3500
3000
2500
2000
1500

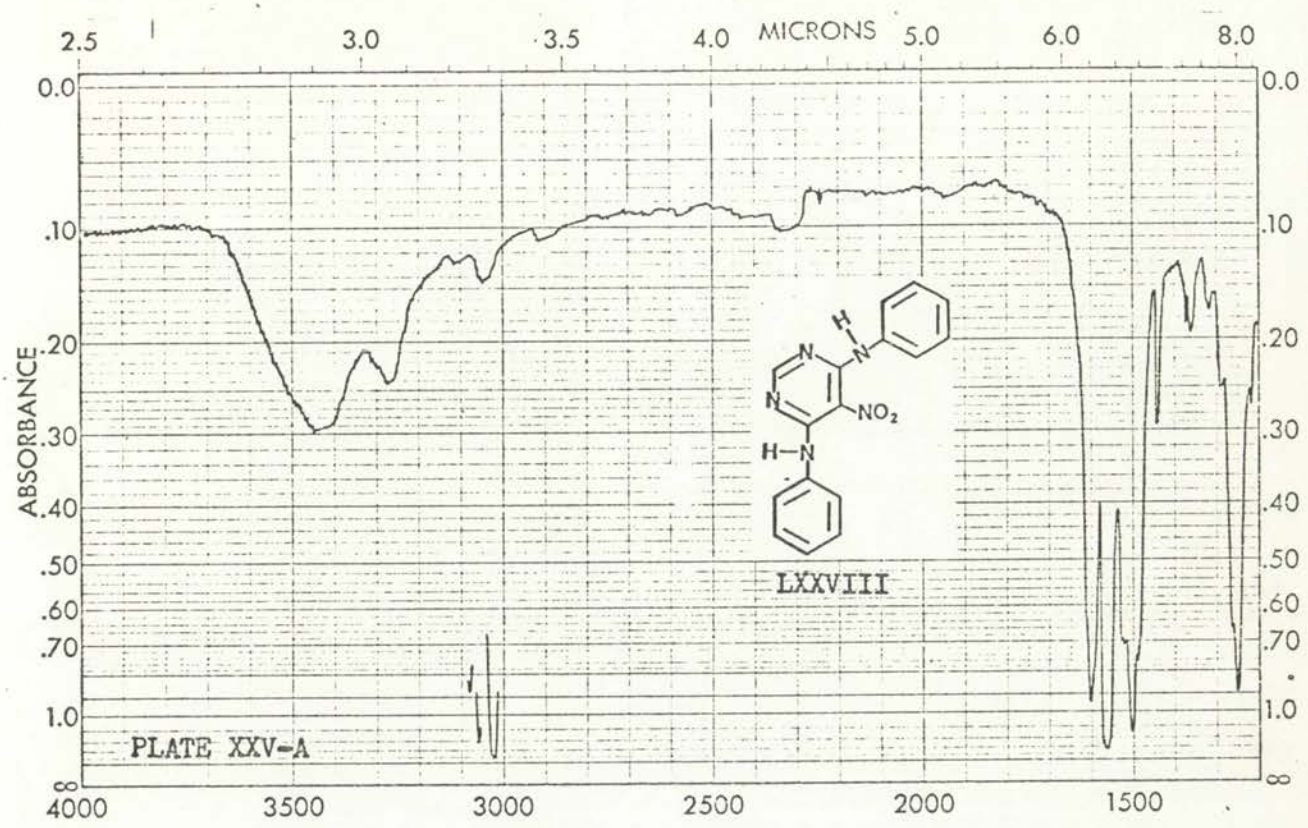

7.5
8.0
9.0
10.0
MICRONS
15.0
20.0
25.0
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
ABSORBANCE
PLATE XXIII-B
1300
1200
1100
1000
900
800
700
600
500
400

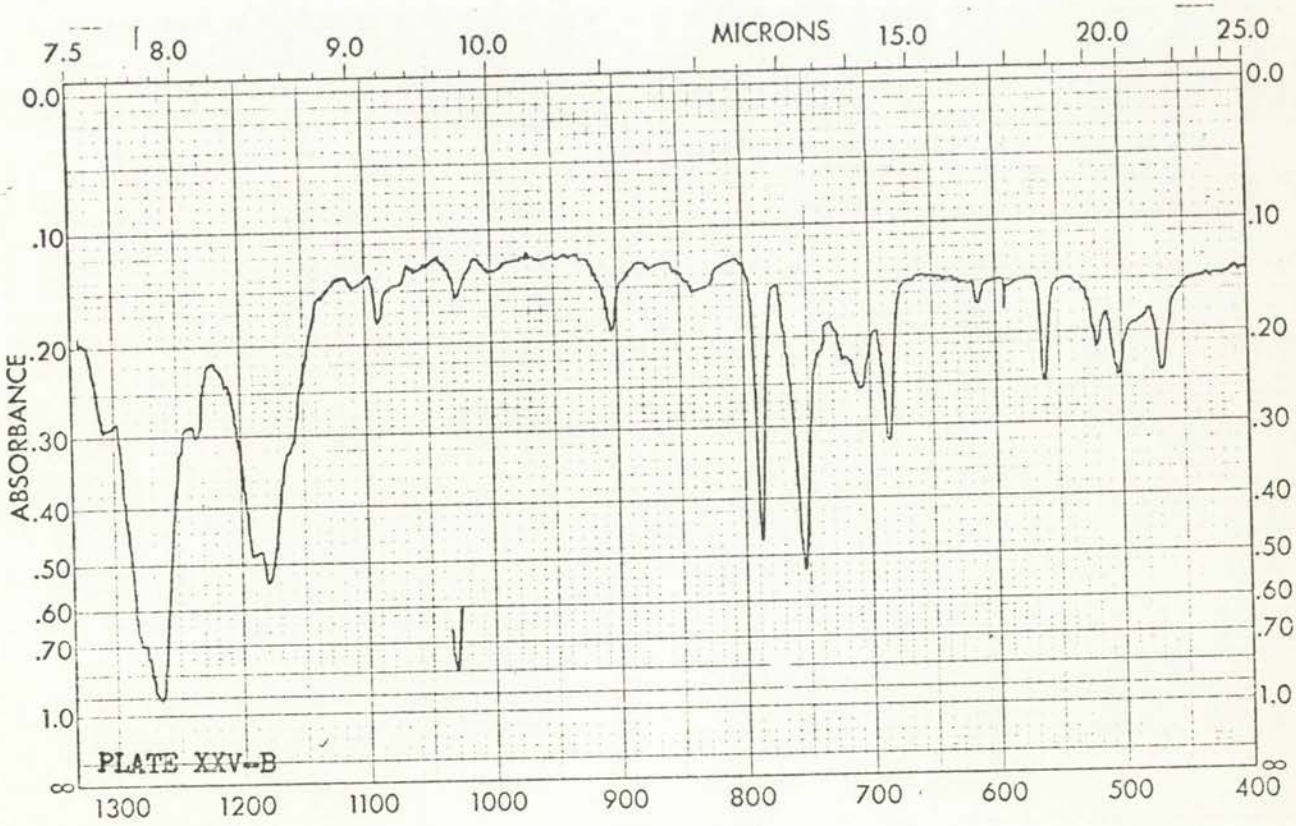


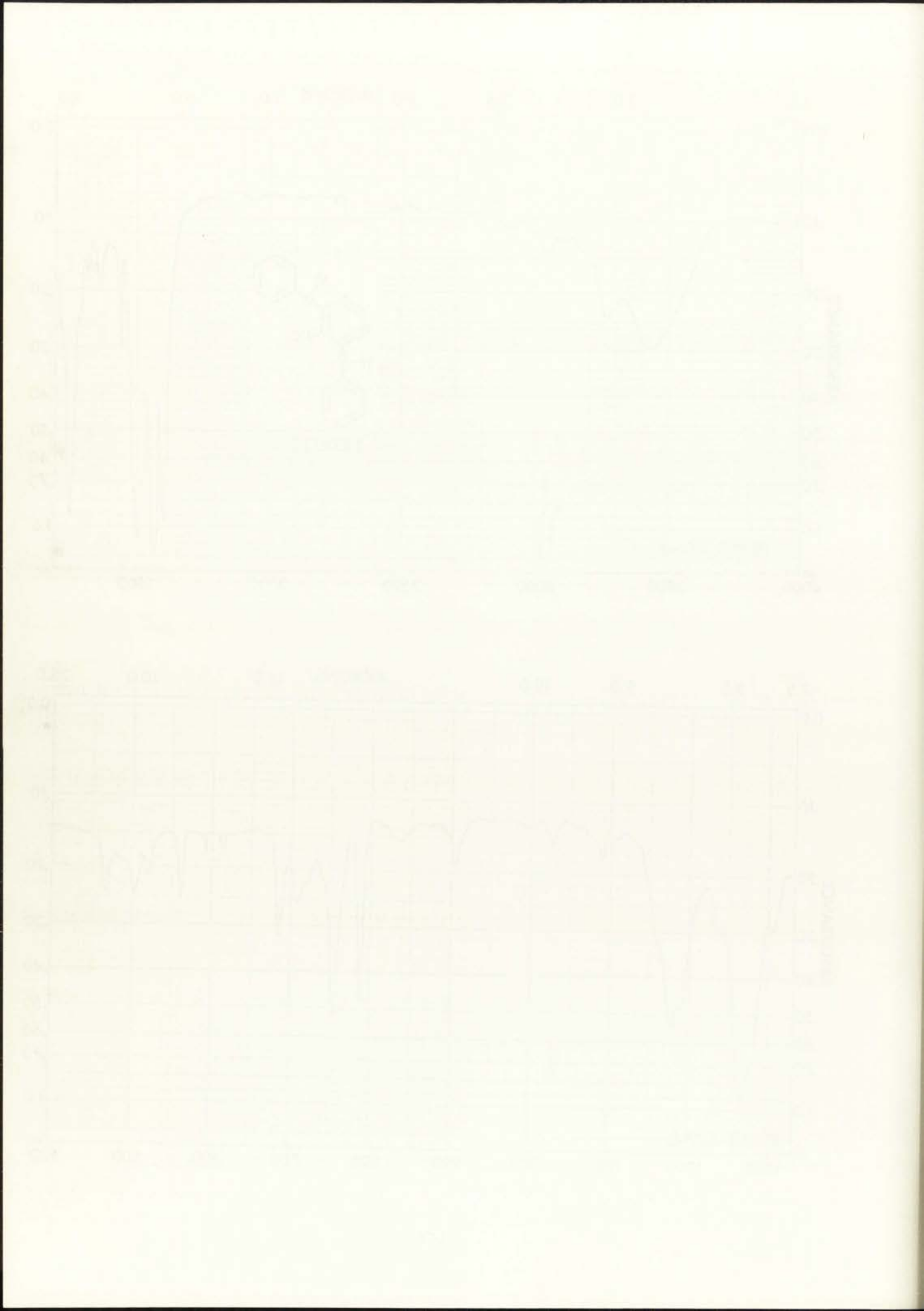

2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
ABSORBANCE
4000
3500
3000
2500
2000
1500
PLATE XXIV-A

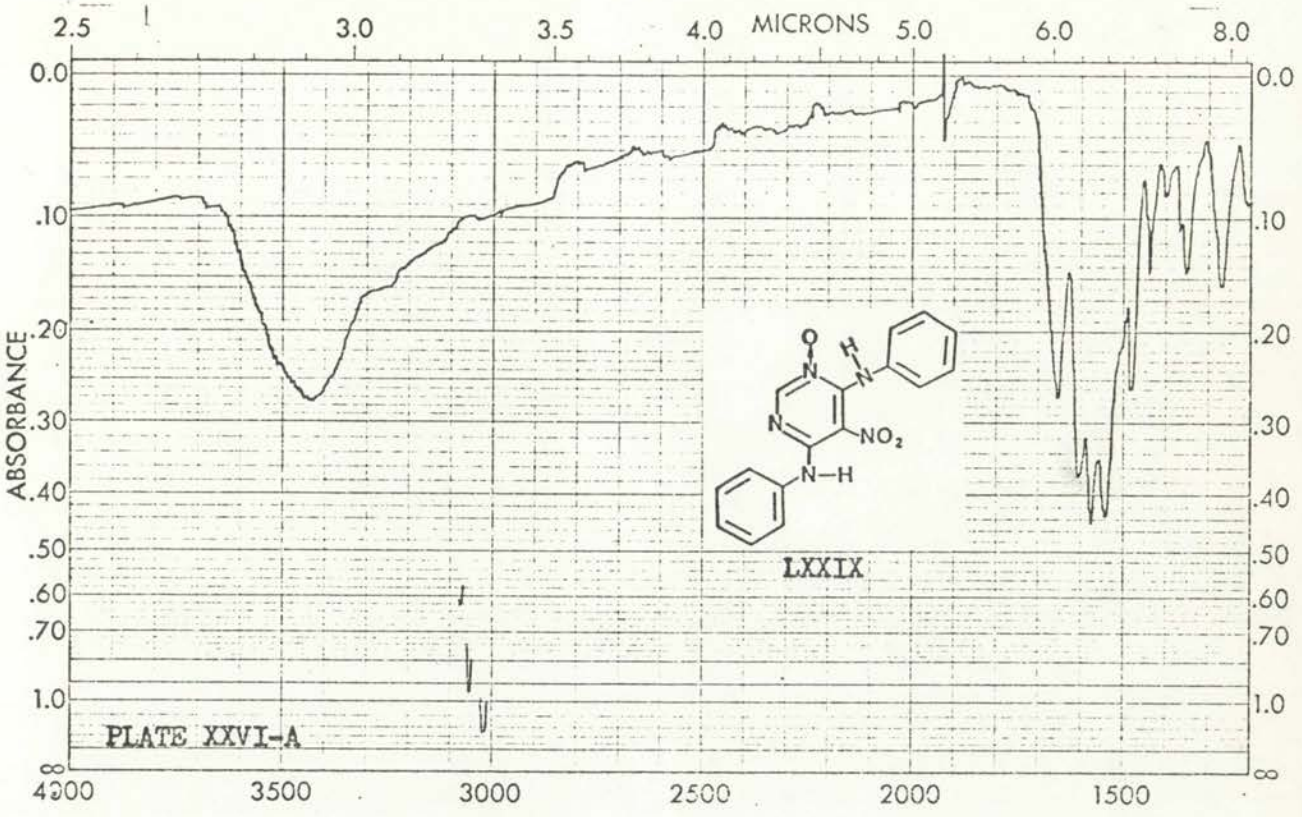
LXXVII


7.5
8.0
9.0
10.0
MICRONS
15.0
20.0
25.0
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
ABSORBANCE
1300
1200
1100
1000
900
800
700
600
500
400
PLATE XXIV-B

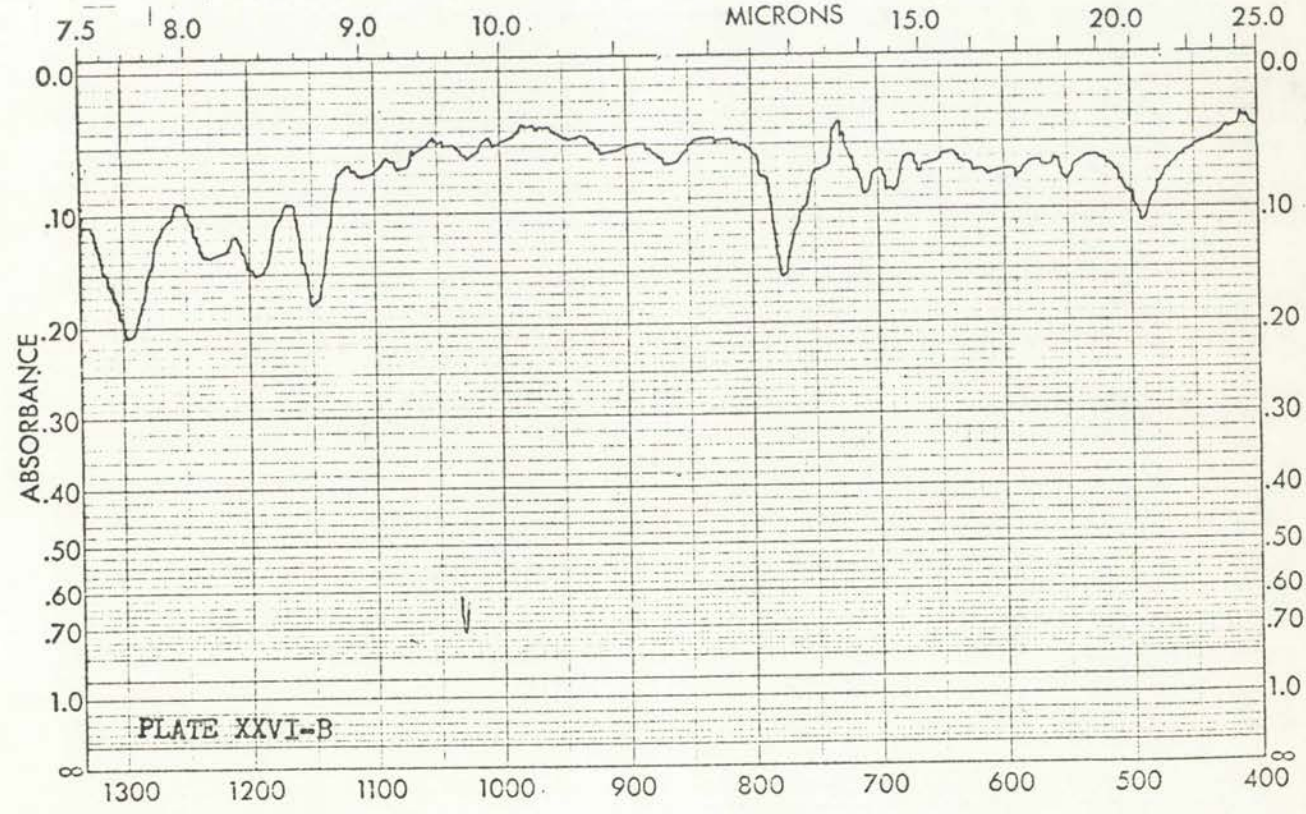

2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
ABSORBANCE
PLATE XXV-A
4000
3500
3000
2500
2000
1500
LXXVIII

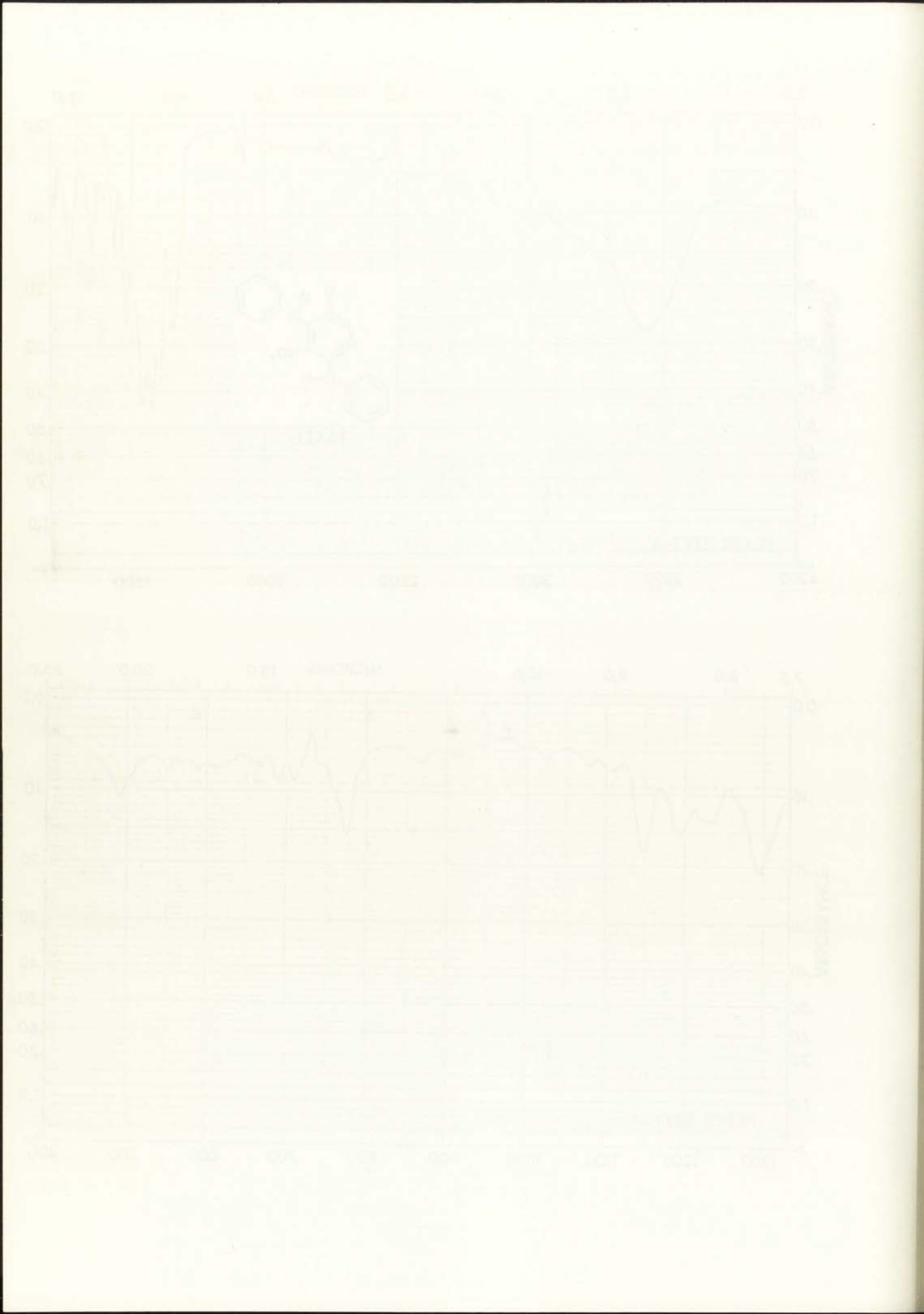

7.5
8.0
9.0
10.0
MICRONS
15.0
20.0
25.0
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
ABSORBANCE
PLATE XXV-B
1300
1200
1100
1000
900
800
700
600
500
400

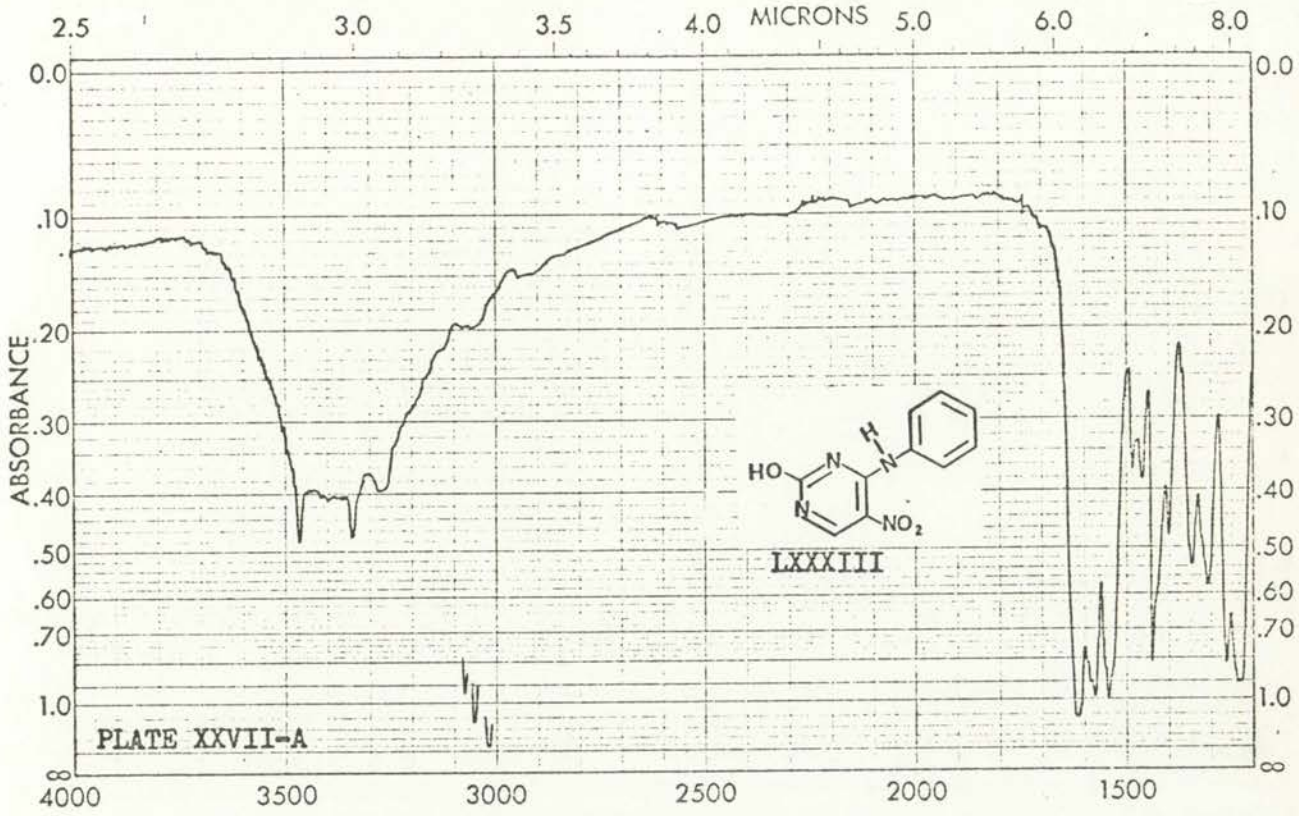



2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
ABSORBANCE
4000
3500
3000
2500
2000
1500
PLATE XXVI-A

LXXIX


7.5
8.0
9.0
10.0
MICRONS
15.0
20.0
25.0
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
ABSORBANCE
1300
1200
1100
1000
900
800
700
600
500
400
PLATE XXVI-B





LXXXIII

PLATE XXVII-A

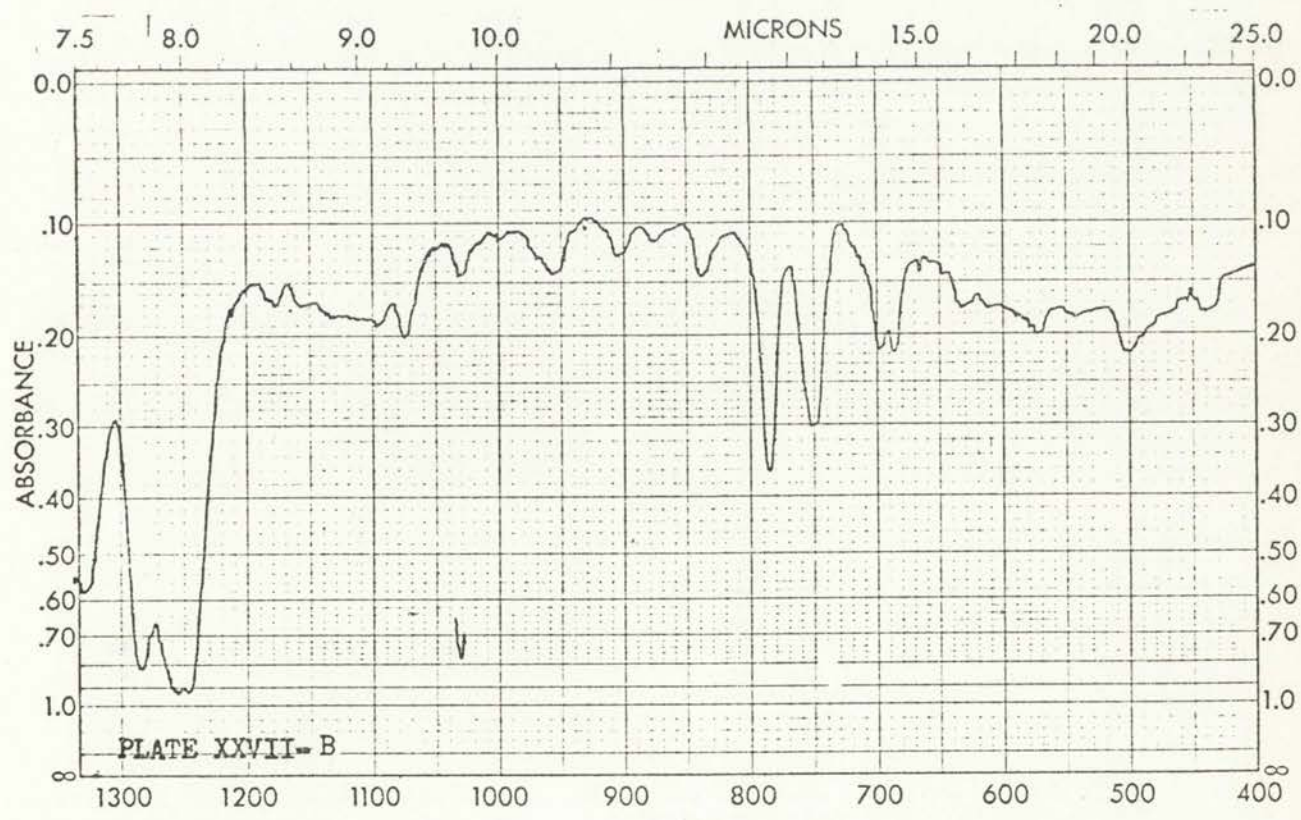
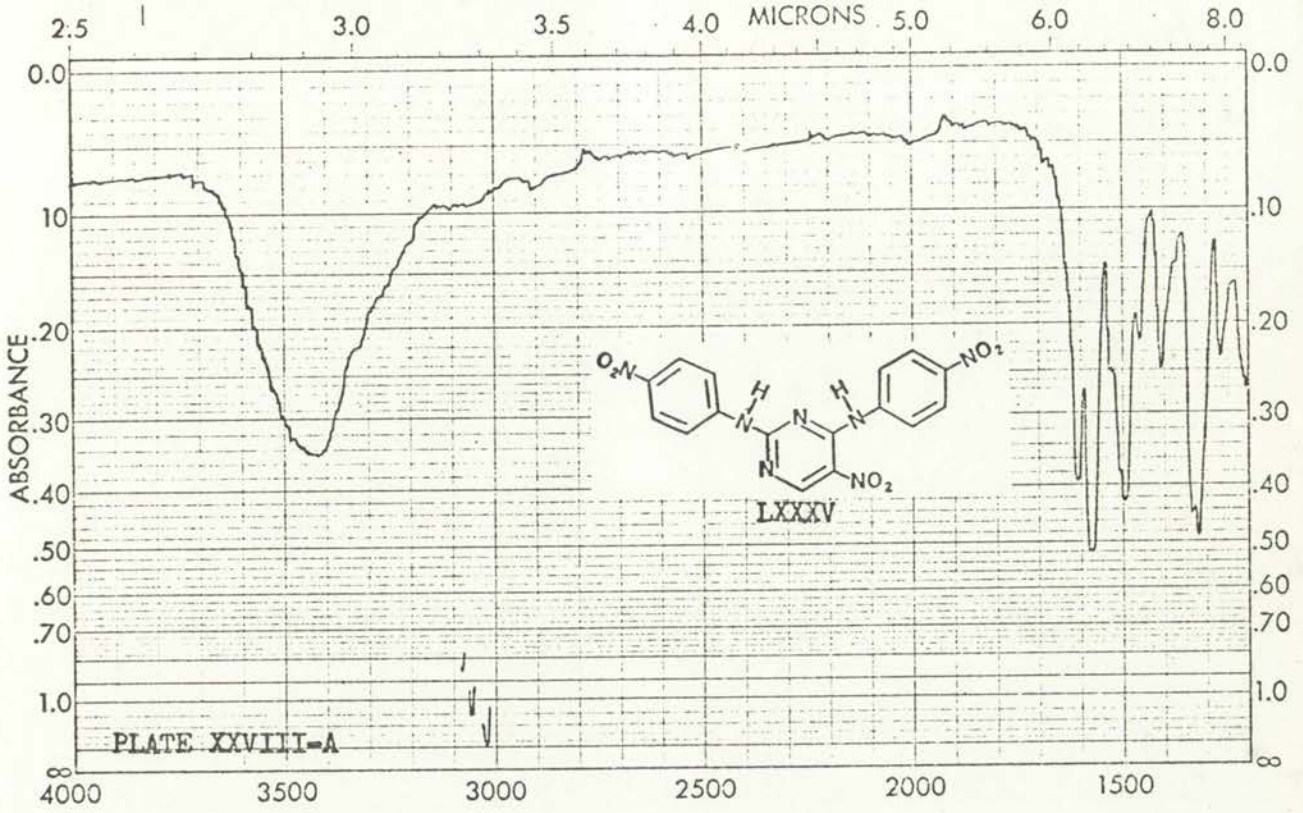
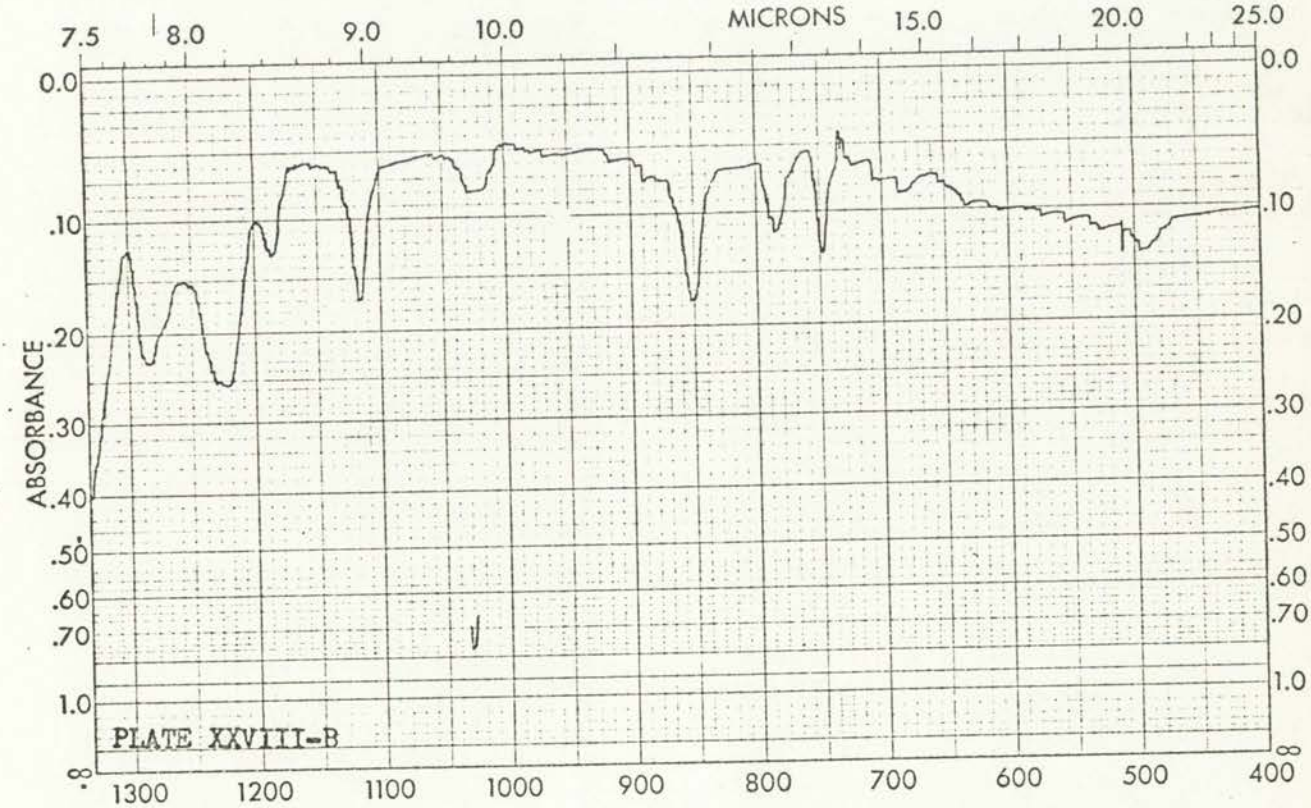
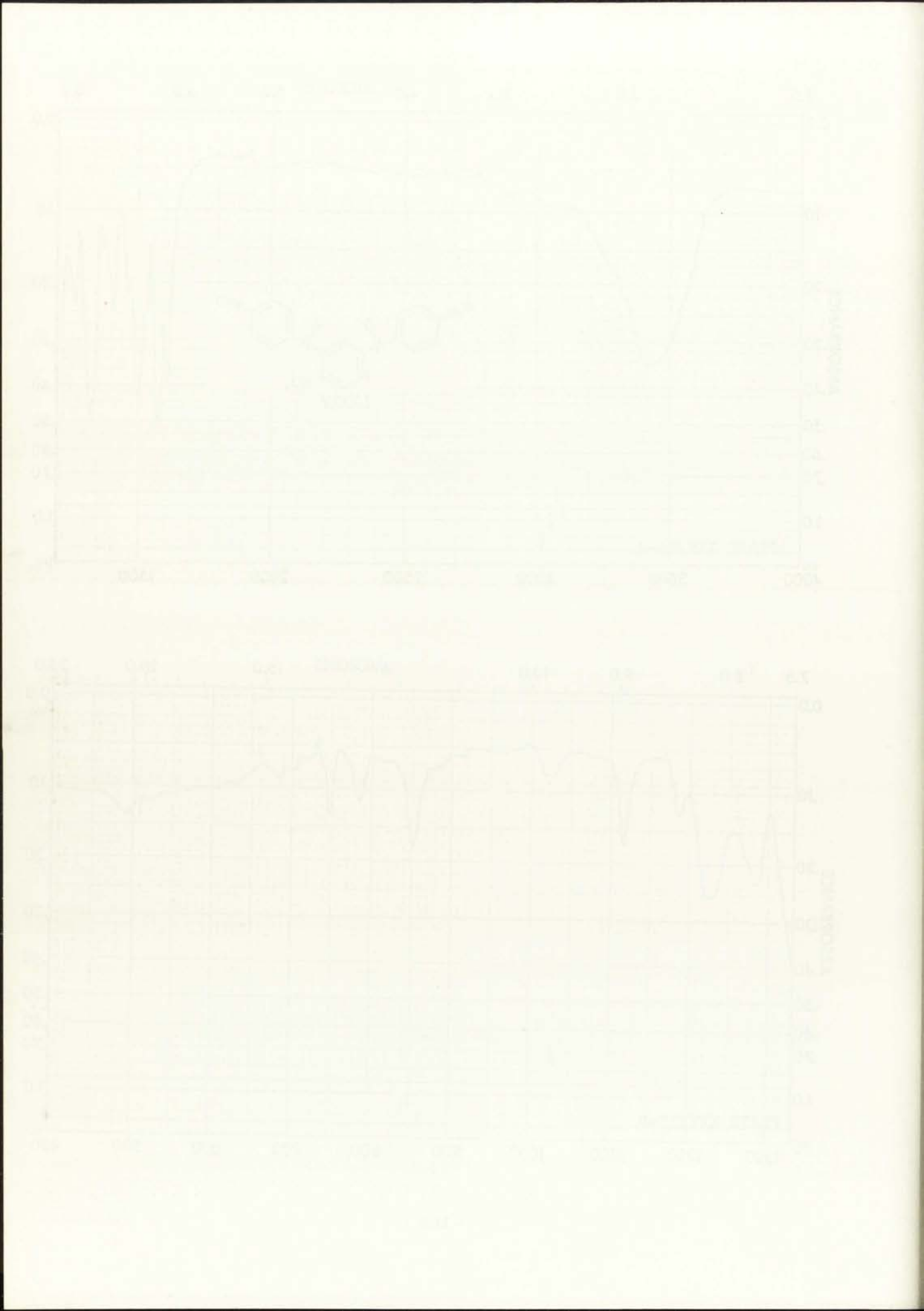


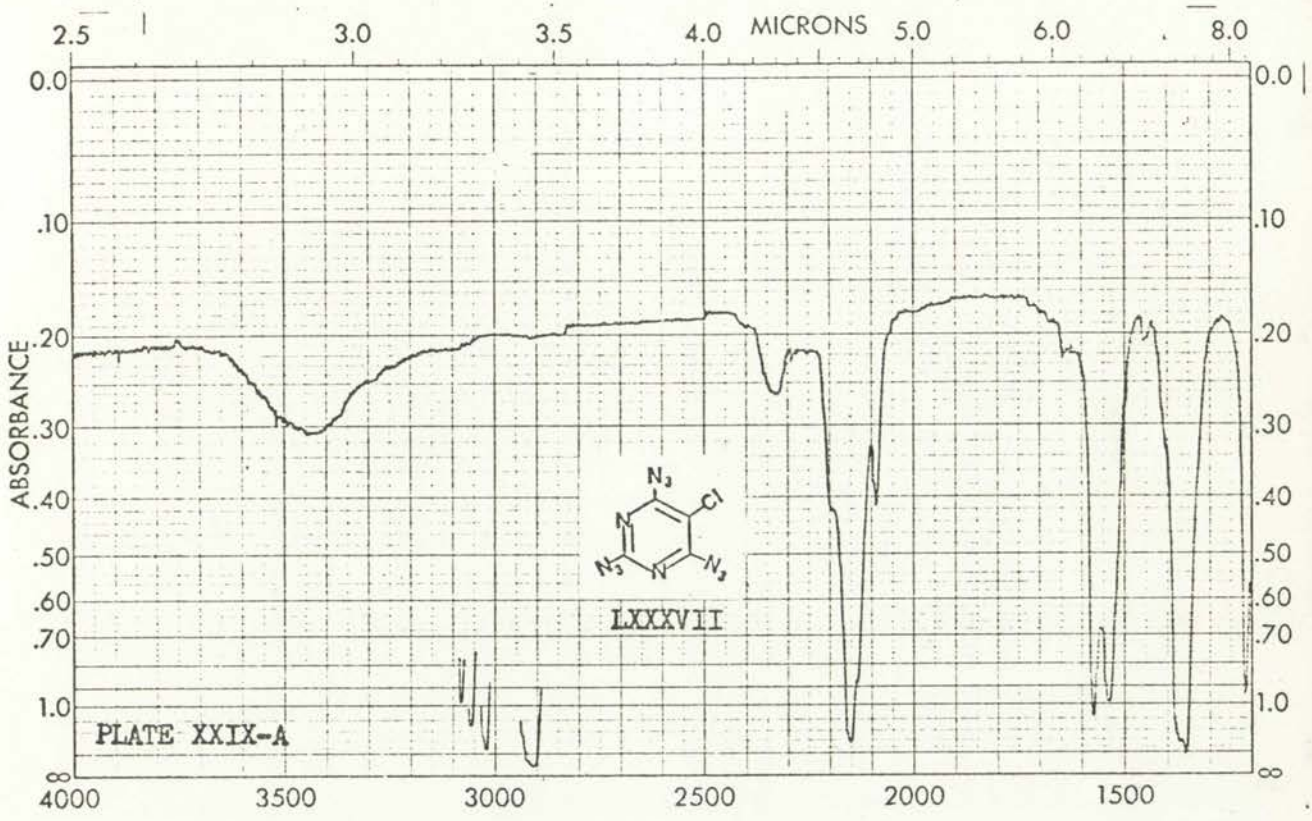
PLATE XXVII-B


2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
ABSORBANCE
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
4000
3500
3000
2500
2000
1500
PLATE XXVIII-A

LXXXV

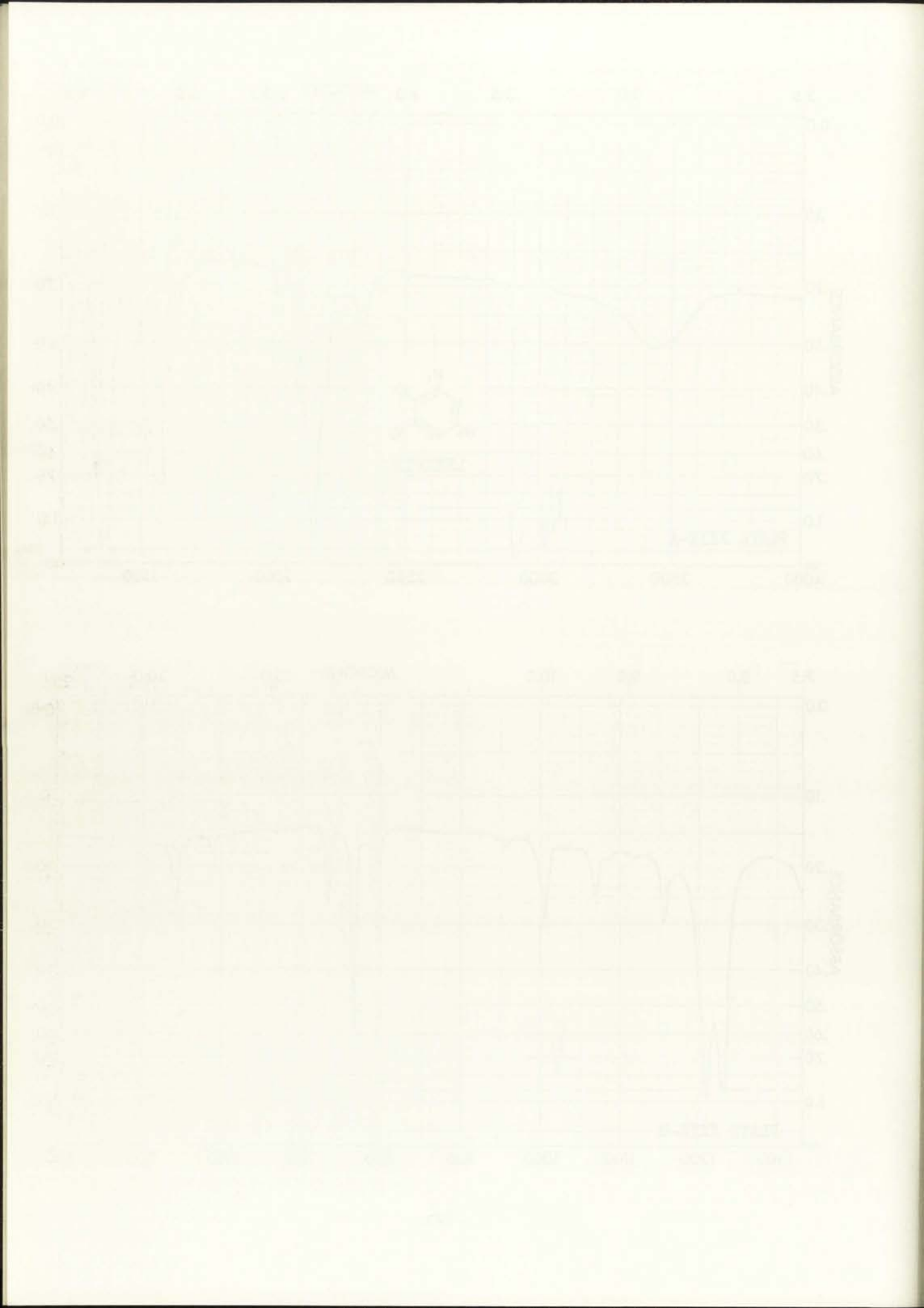

7.5
8.0
9.0
10.0
MICRONS
15.0
20.0
25.0
ABSORBANCE
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
1300
1200
1100
1000
900
800
700
600
500
400
PLATE XXVIII-B

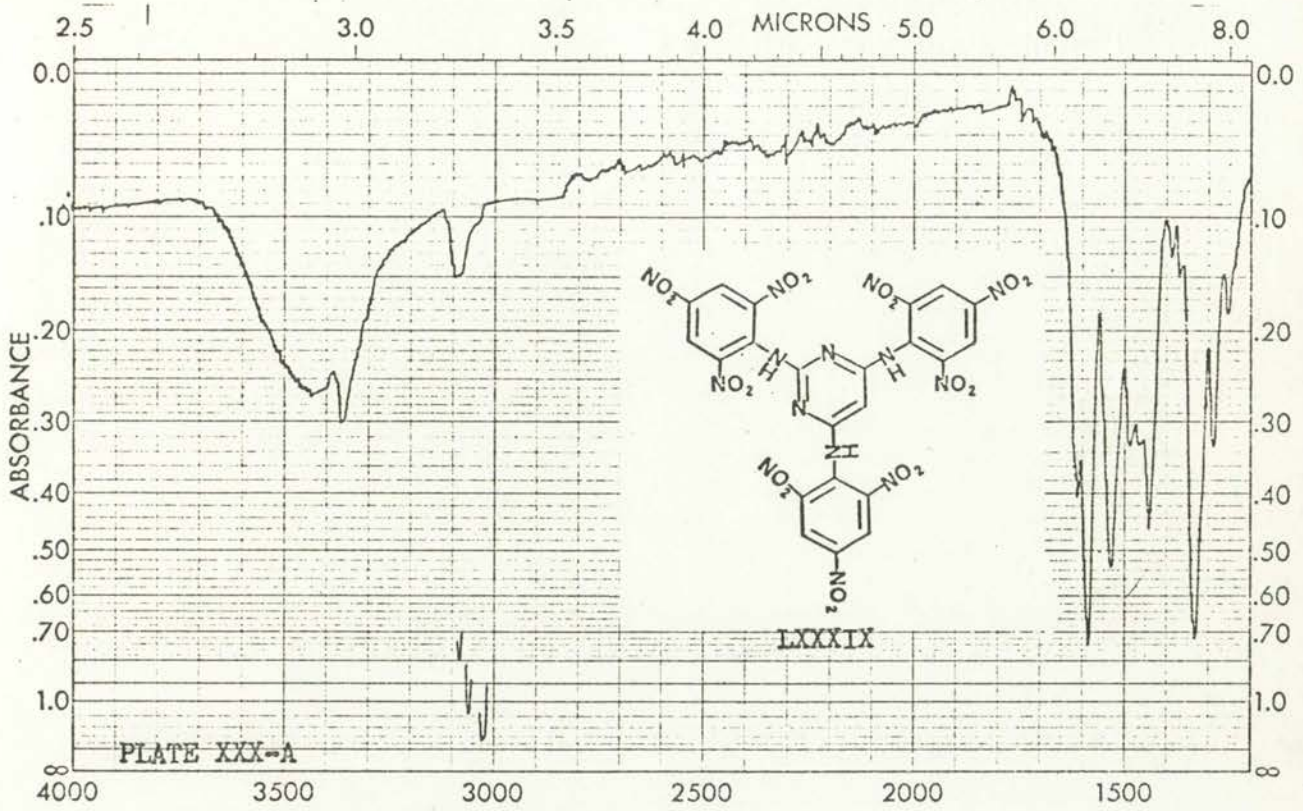



2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
ABSORBANCE
4000
3500
3000
2500
2000
1500
PLATE XXIX-A

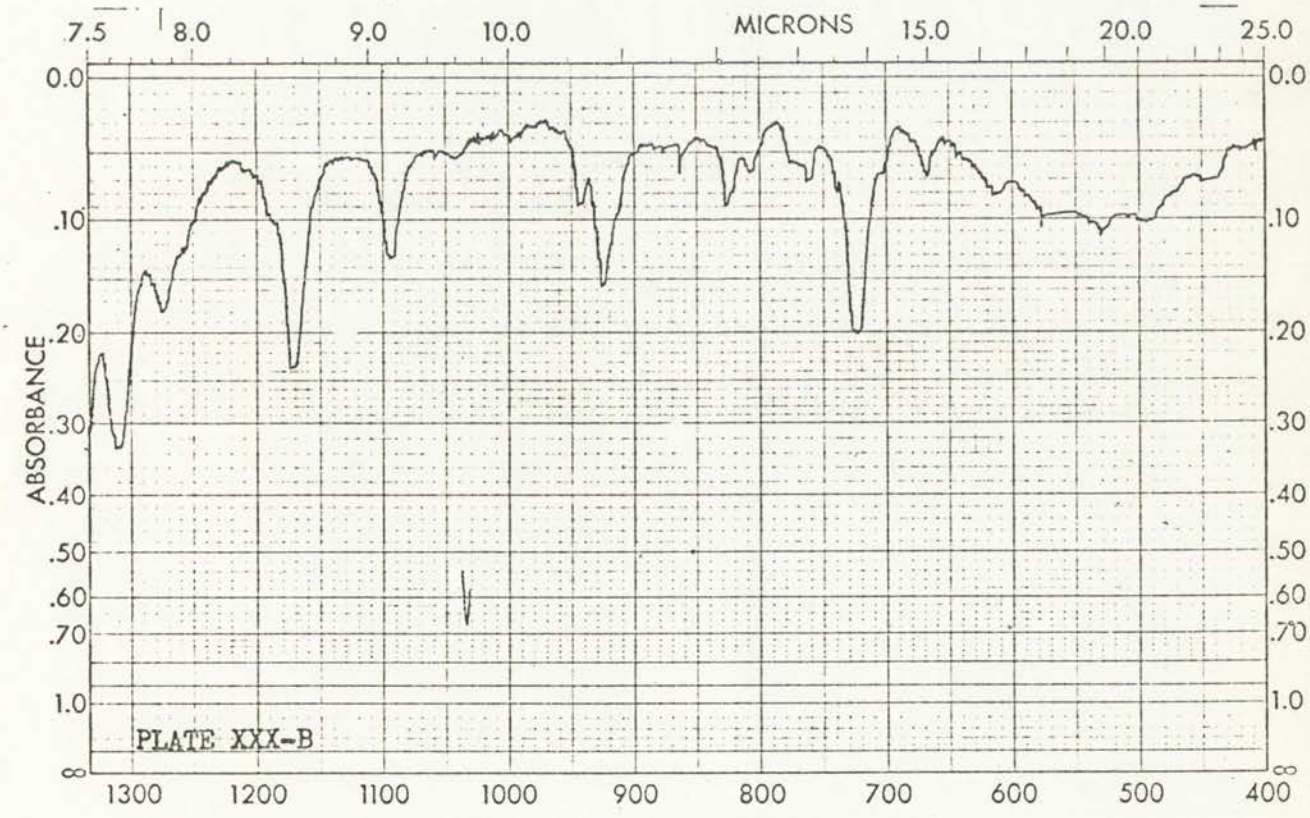
LXXXVII

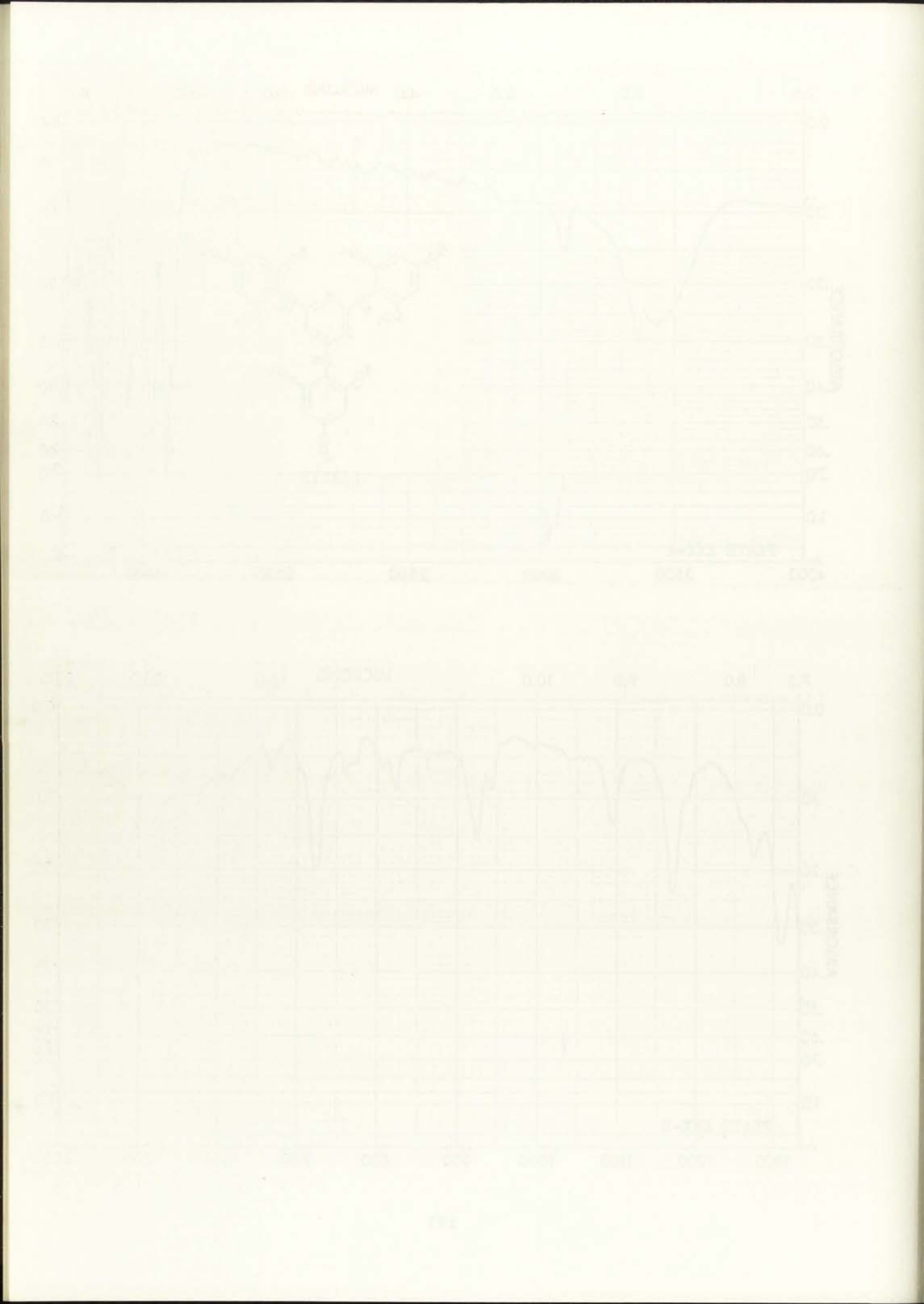

7.5
8.0
9.0
10.0
MICRONS
15.0
20.0
25.0
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
ABSORBANCE
1300
1200
1100
1000
900
800
700
600
500
400
PLATE XXIX-B

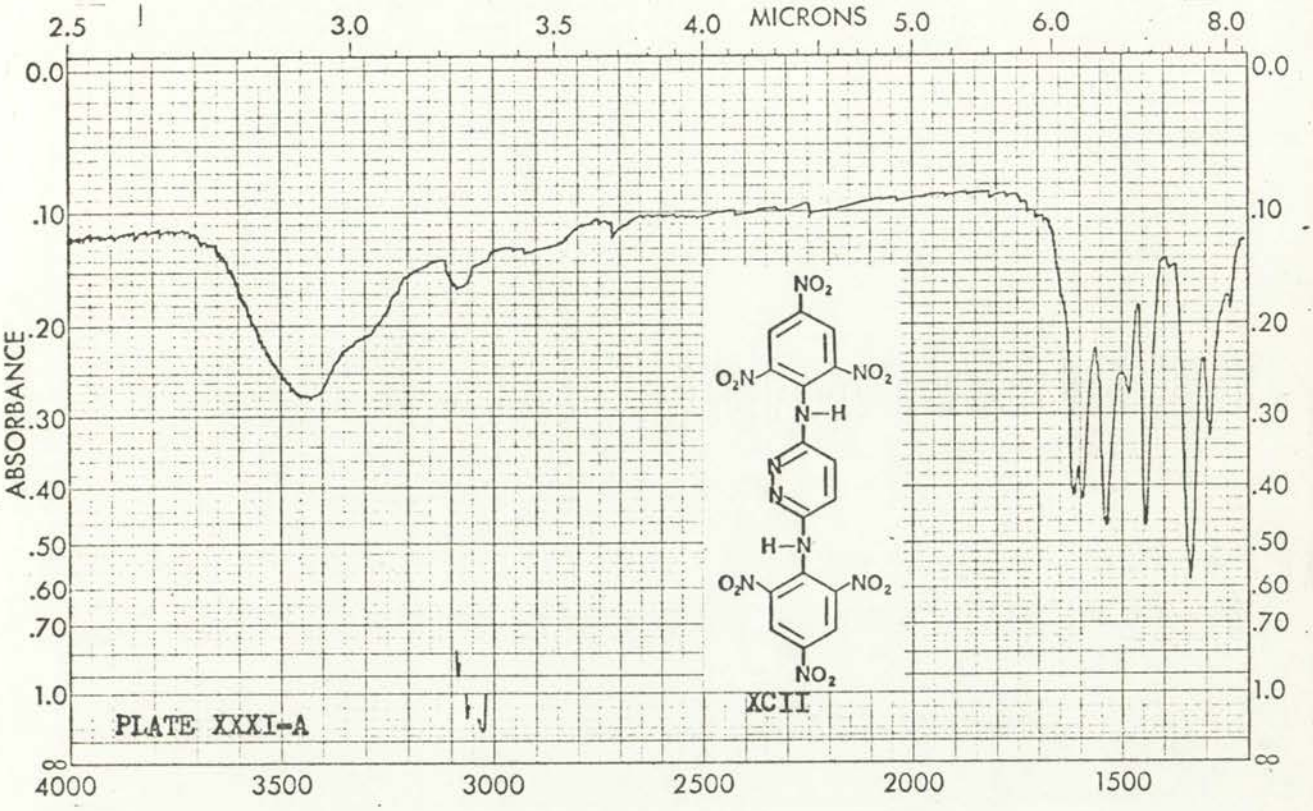


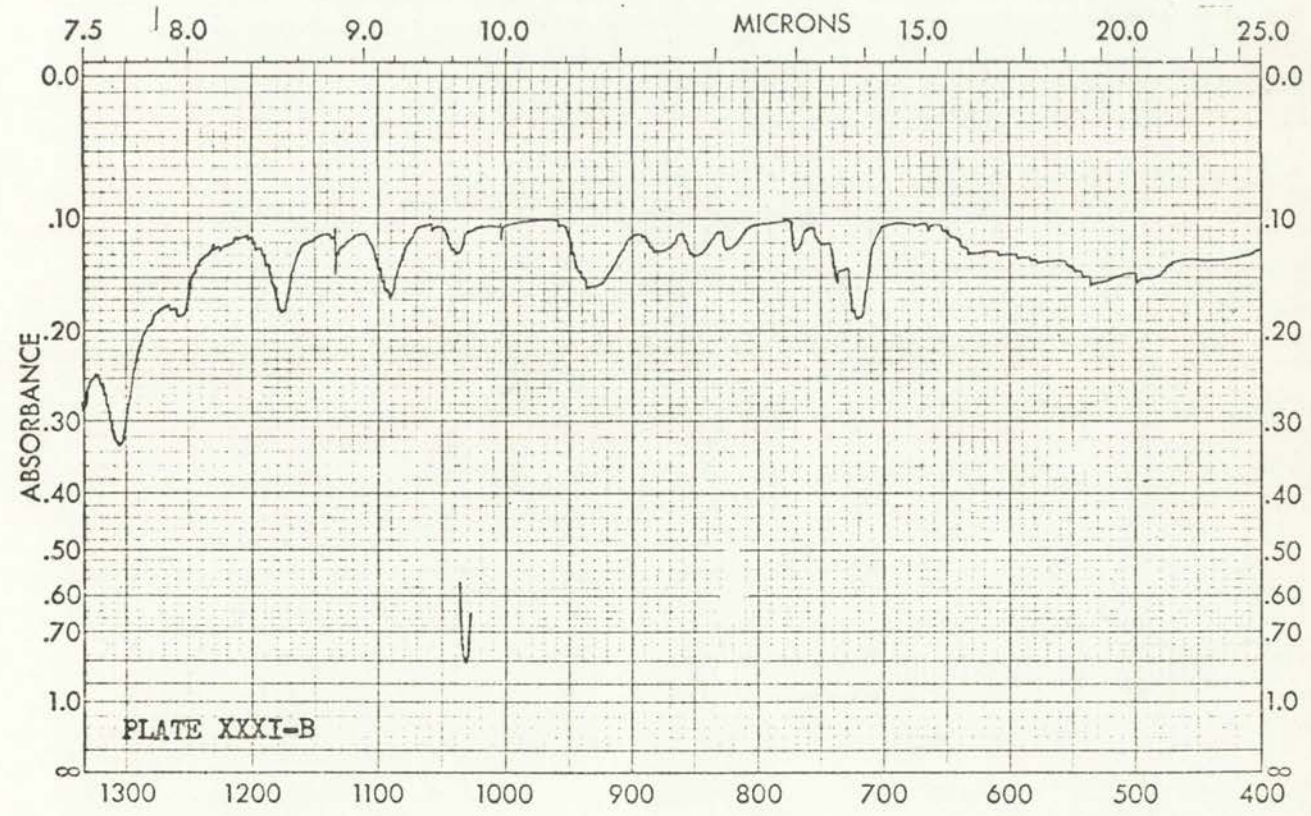

2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
ABSORBANCE
4000
3500
3000
2500
2000
1500
PLATE XXX-A

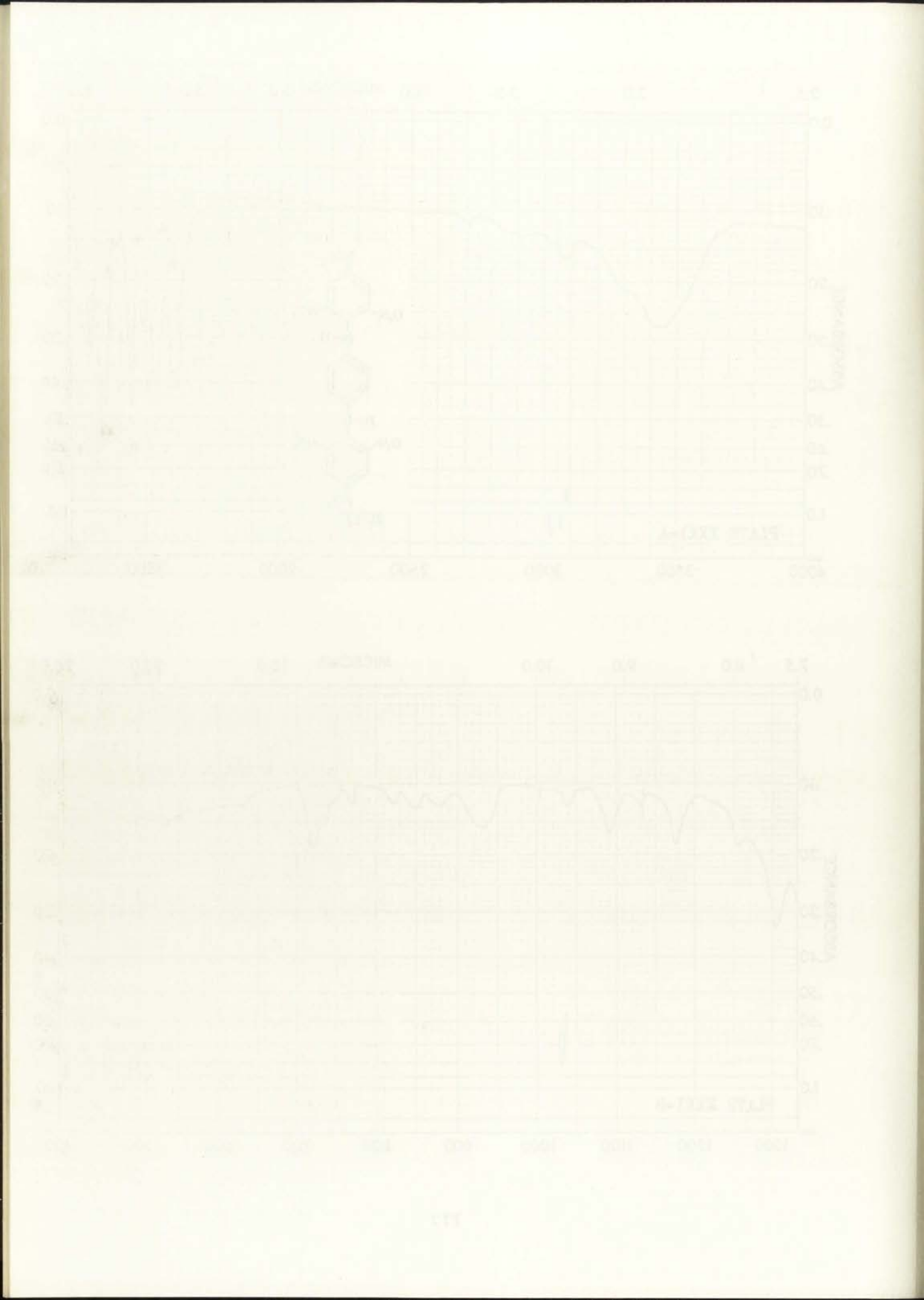
LXXXIX

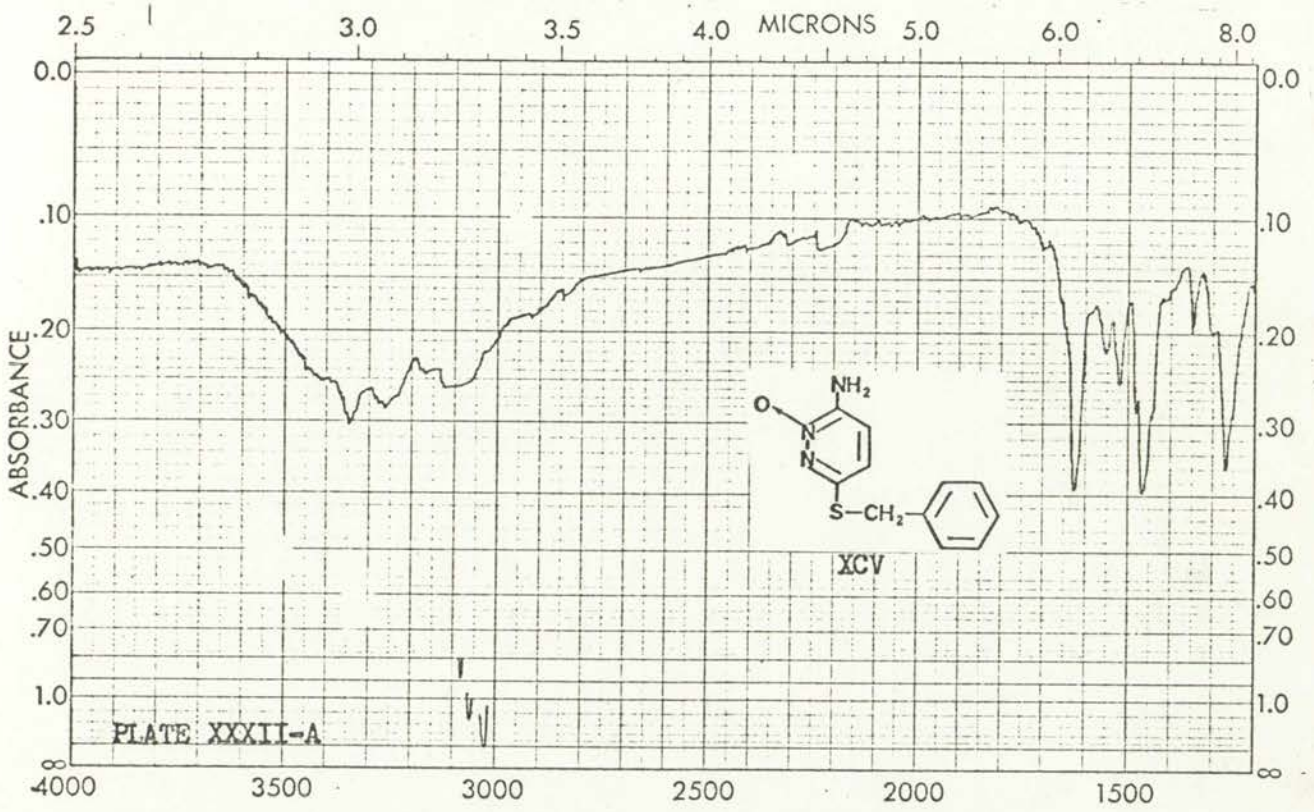

7.5
8.0
9.0
10.0
MICRONS
15.0
20.0
25.0
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
ABSORBANCE
1300
1200
1100
1000
900
800
700
600
500
400
PLATE XXX-B

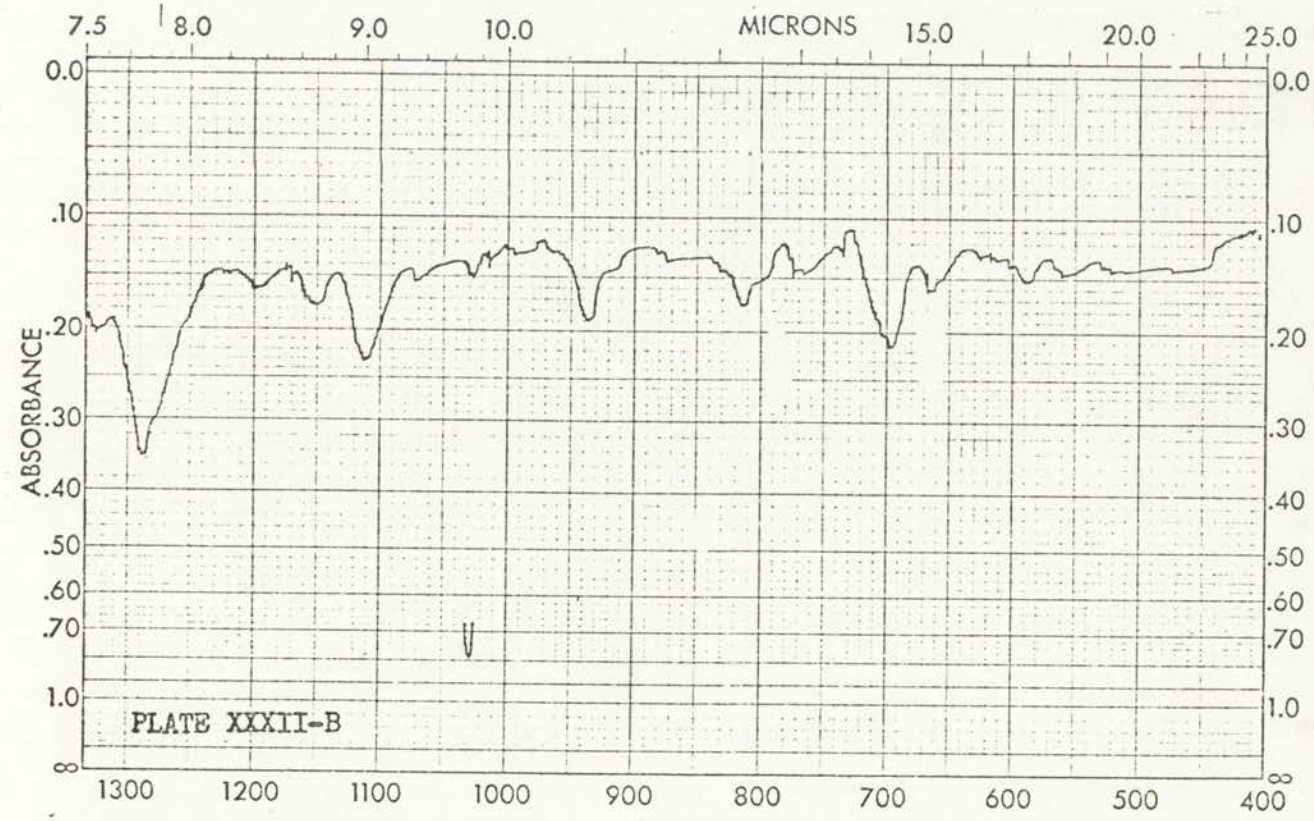


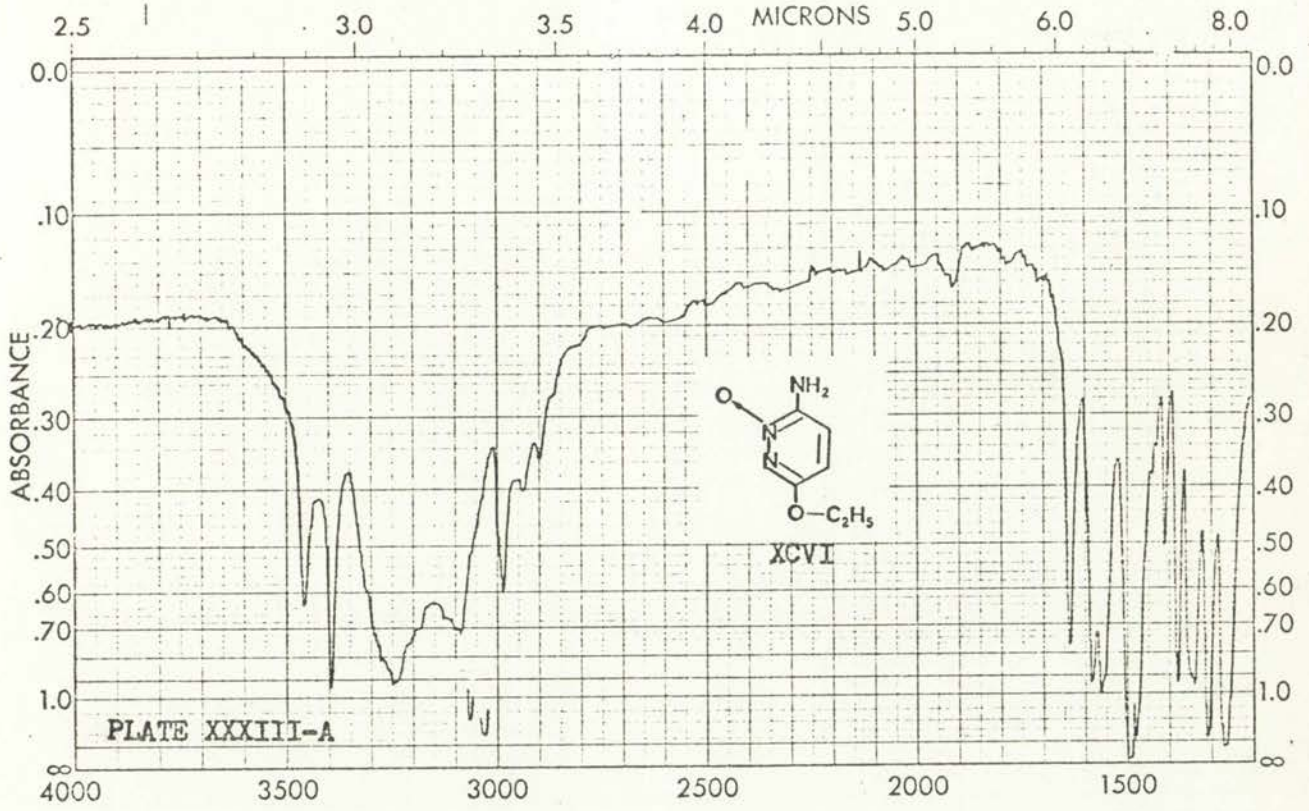

2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
ABSORBANCE
4000
3500
3000
2500
2000
1500
PLATE XXXI-A
XCII

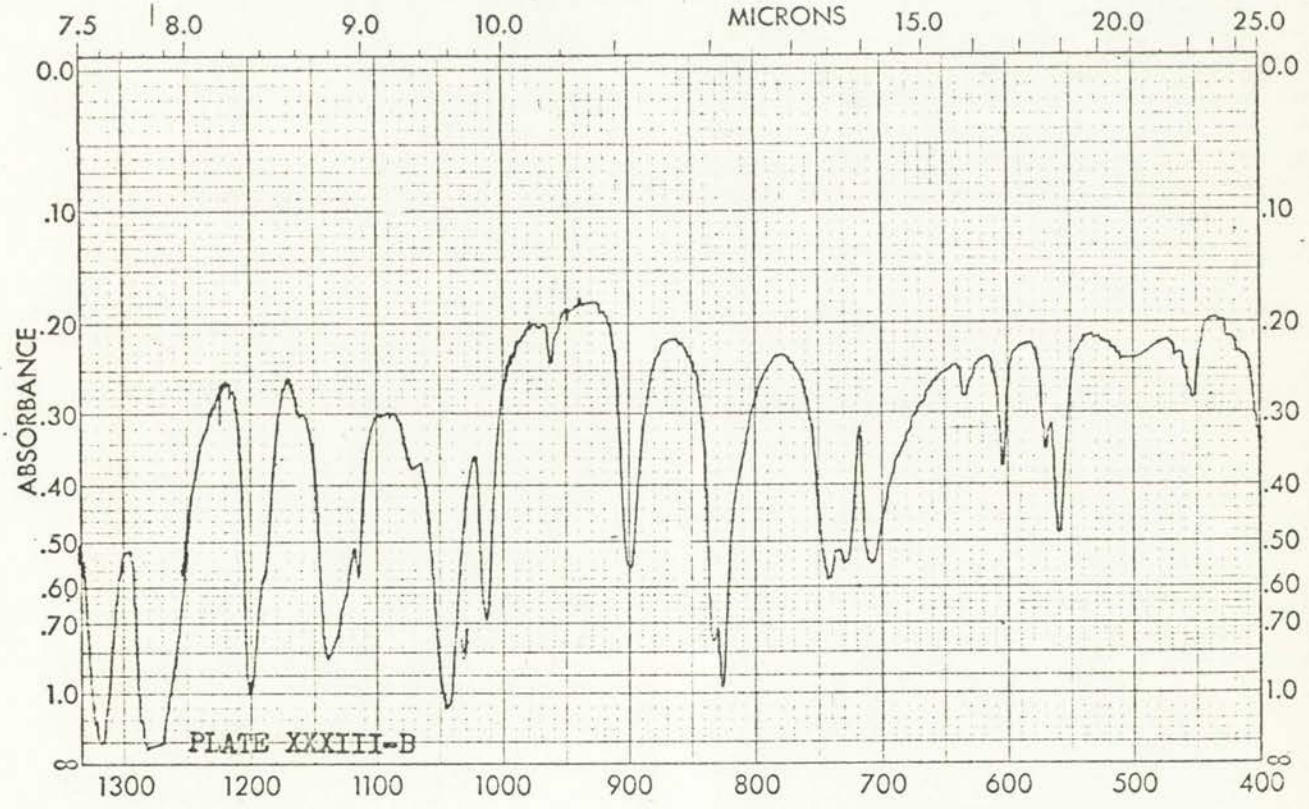

7.5
8.0
9.0
10.0
MICRONS
15.0
20.0
25.0
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
ABSORBANCE
1300
1200
1100
1000
900
800
700
600
500
400
PLATE XXXI-B

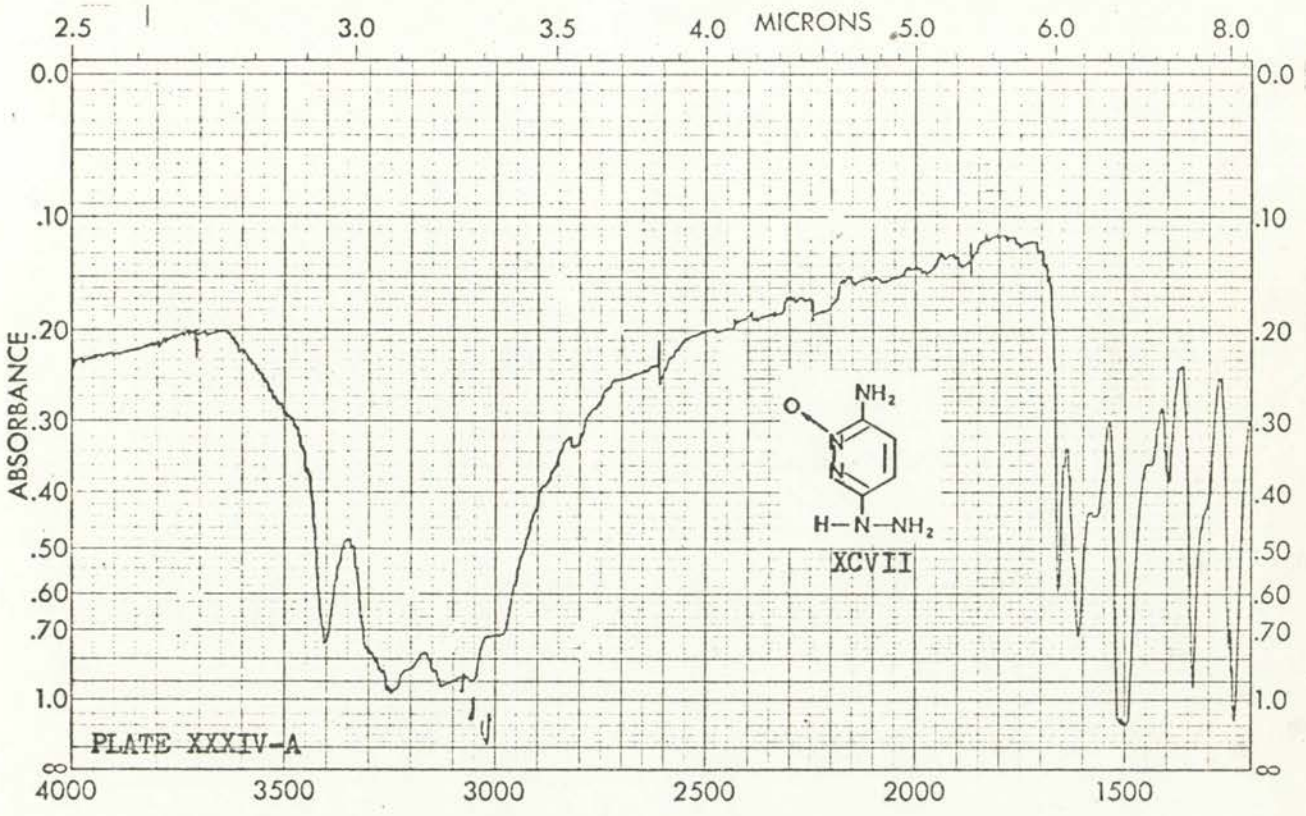


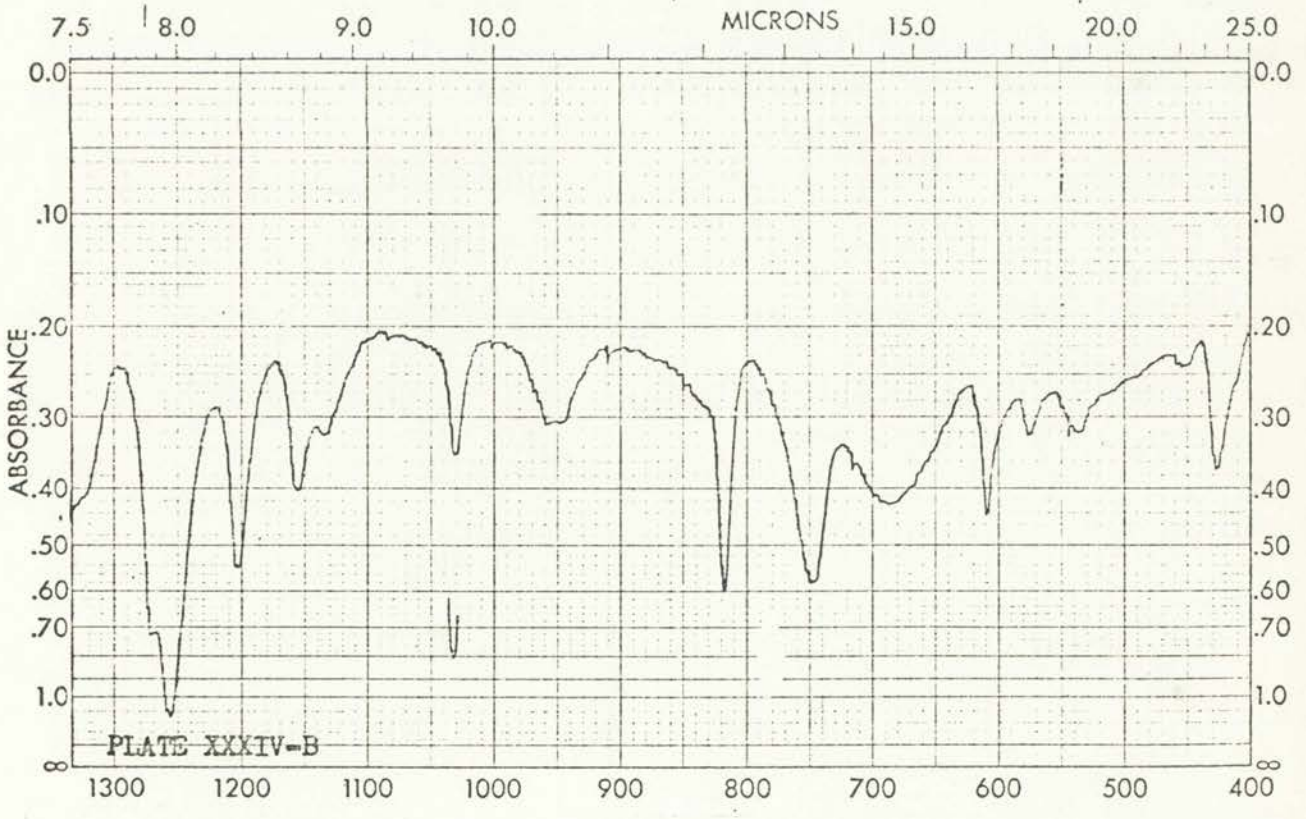

2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
ABSORBANCE
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
4000
3500
3000
2500
2000
1500
NH2
O
N
N
S—CH2
XCV
PLATE XXXII-A

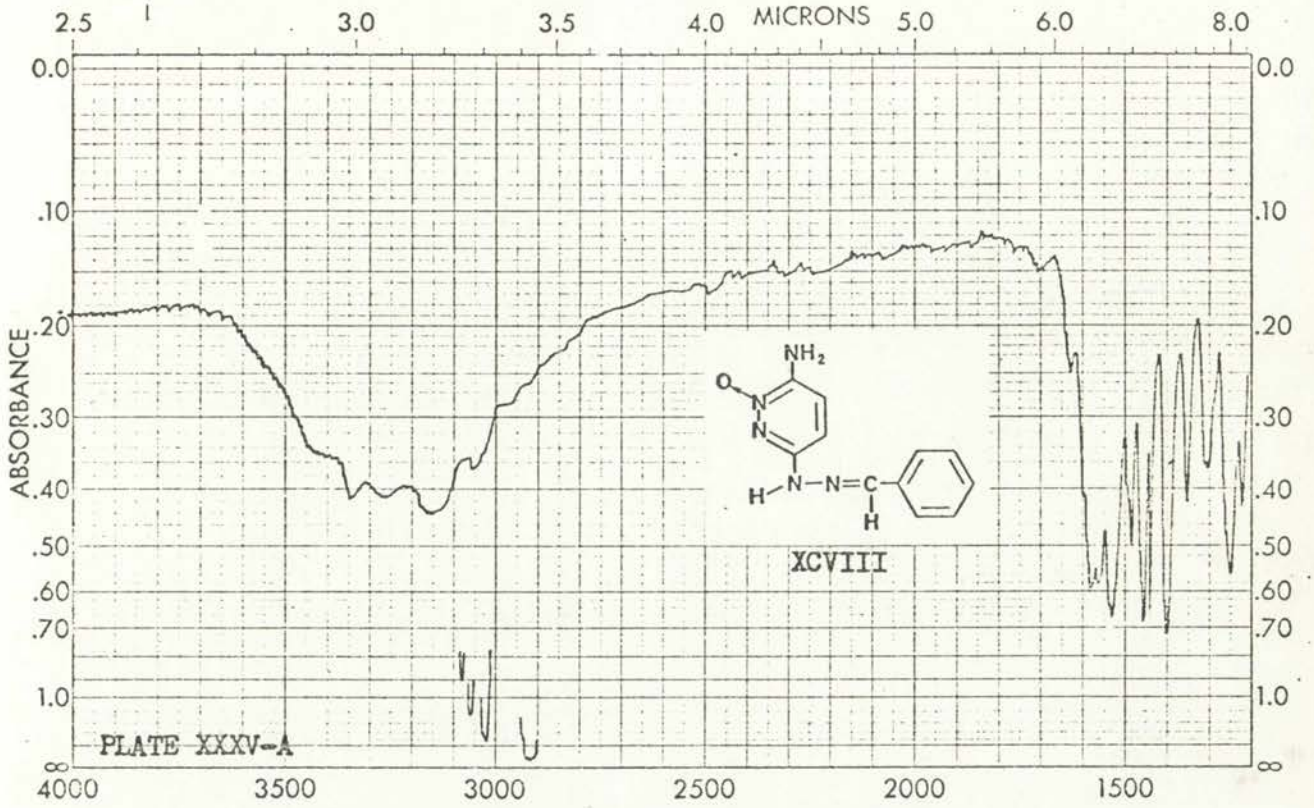

7.5
8.0
9.0
10.0
MICRONS
15.0
20.0
25.0
ABSORBANCE
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
1300
1200
1100
1000
900
800
700
600
500
400
PLATE XXXII-B


2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
ABSORBANCE
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
4000
3500
3000
2500
2000
1500
NH2
O
N
N
O—C2H5
XCVI
PLATE XXXIII-A

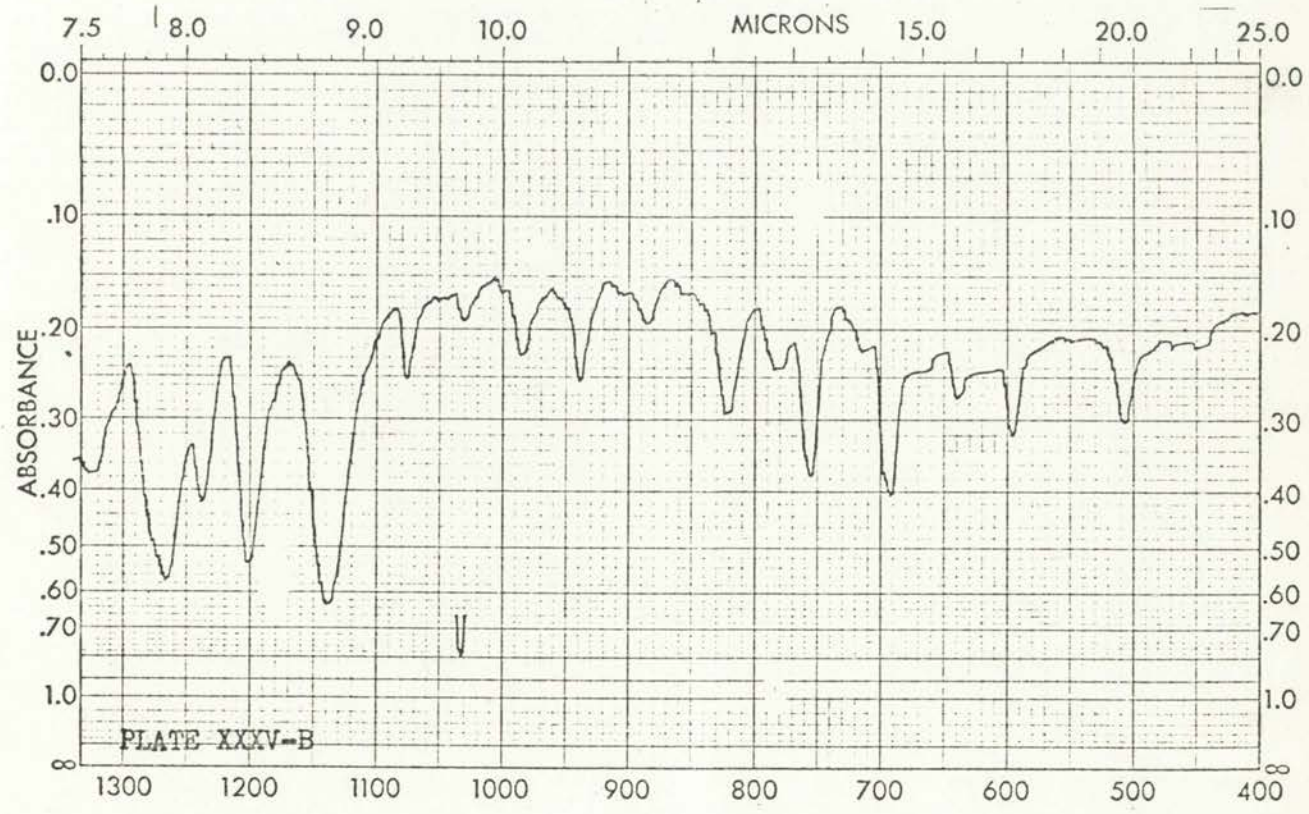

7.5
8.0
9.0
10.0
MICRONS
15.0
20.0
25.0
ABSORBANCE
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
1300
1200
1100
1000
900
800
700
600
500
400
PLATE XXXIII-B

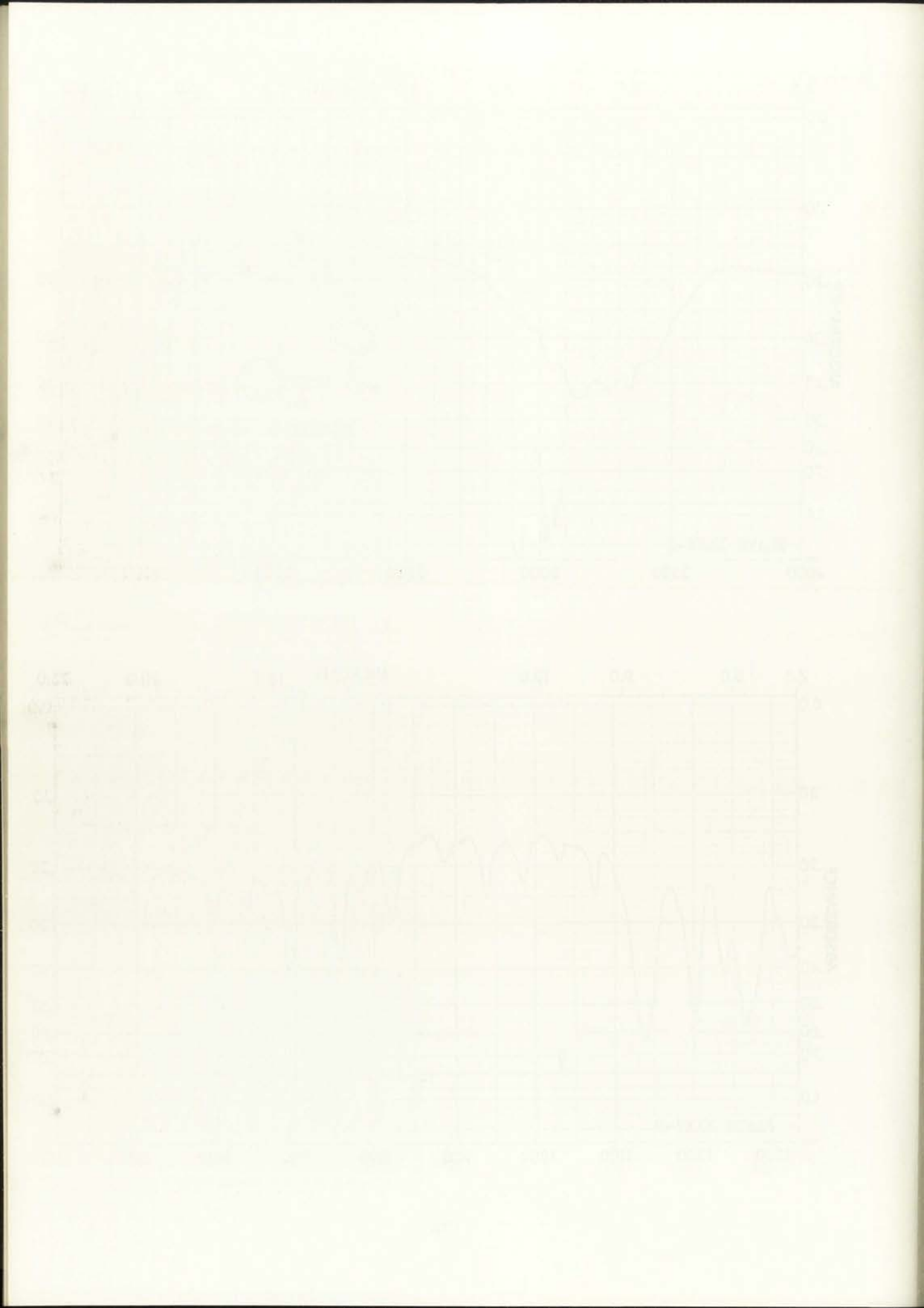

2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
ABSORBANCE
NH2
O
N
N
H—N—NH2
XCVII
PLATE XXXIV-A
4000
3500
3000
2500
2000
1500

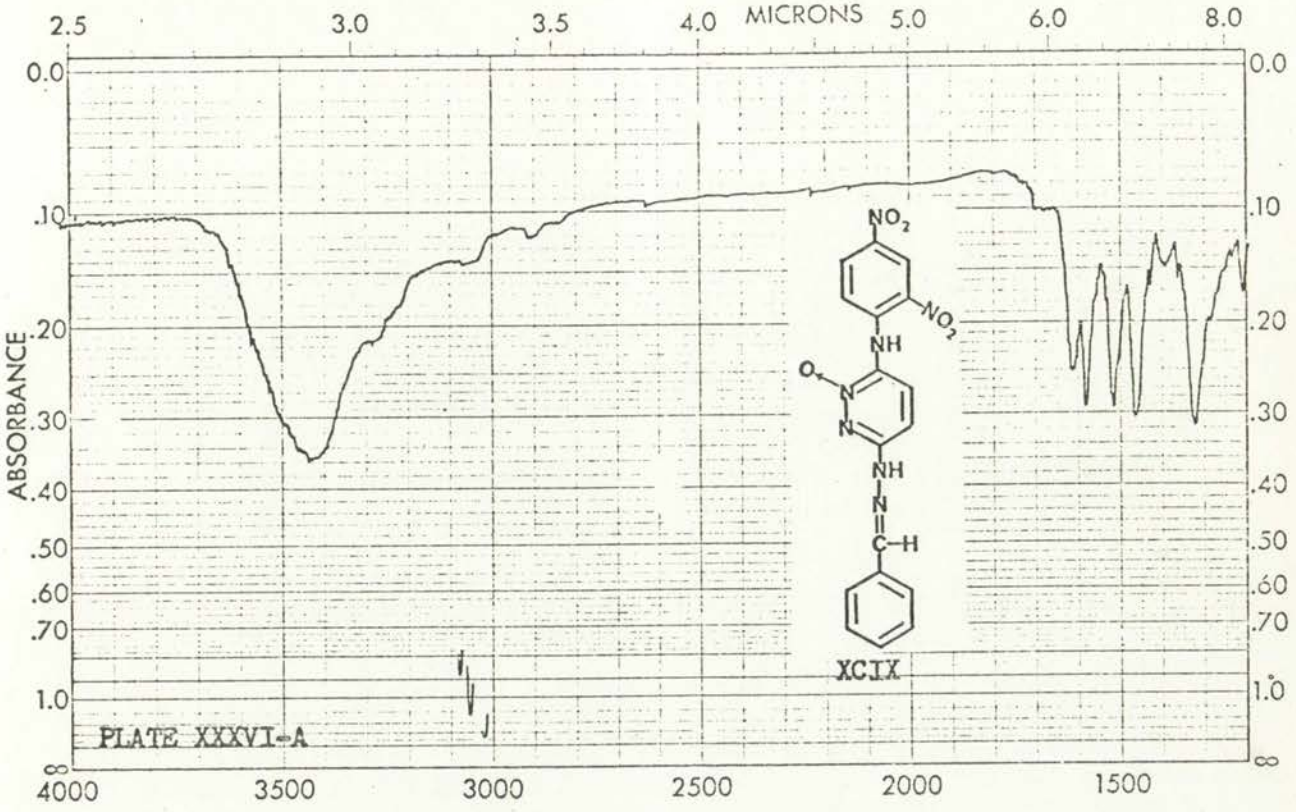

7.5
8.0
9.0
10.0
MICRONS
15.0
20.0
25.0
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
ABSORBANCE
PLATE XXXIV-B
1300
1200
1100
1000
900
800
700
600
500
400

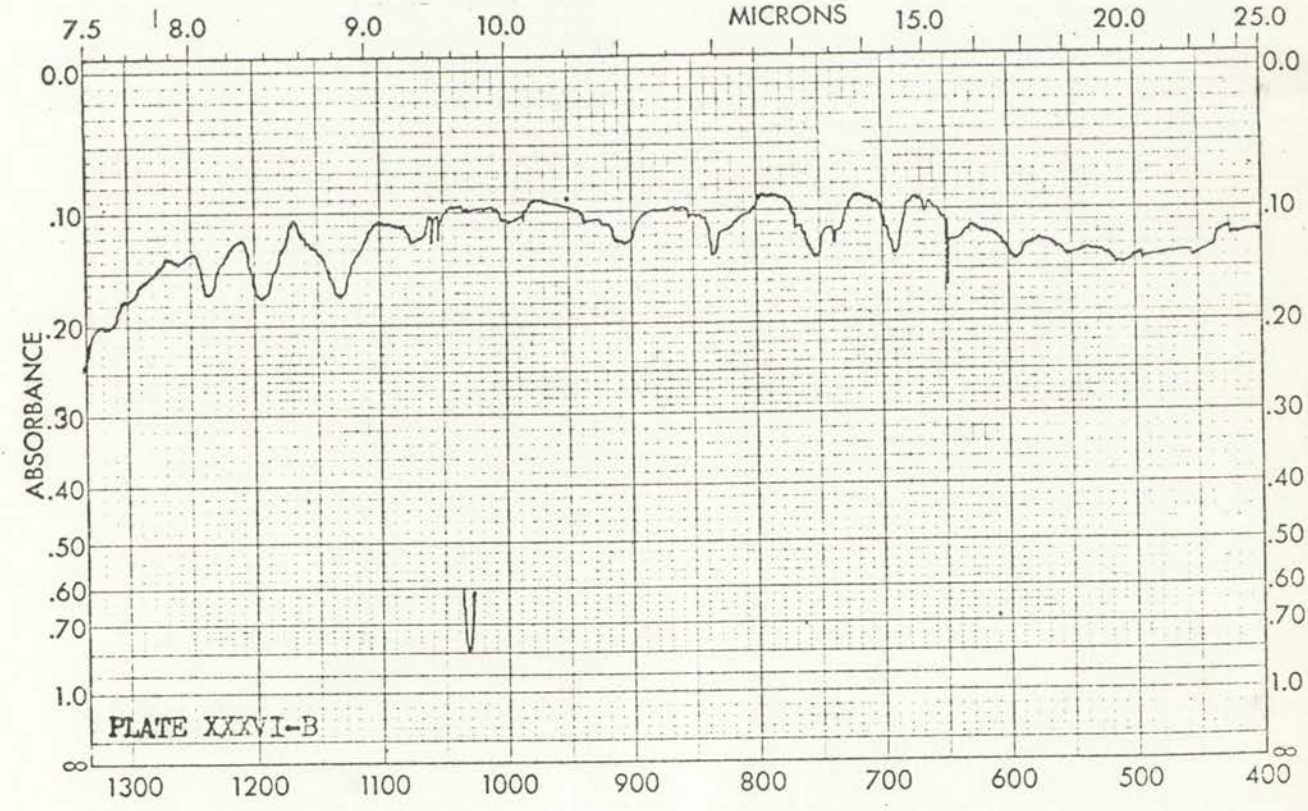

2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
ABSORBANCE
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
4000
3500
3000
2500
2000
1500
PLATE XXXV-A

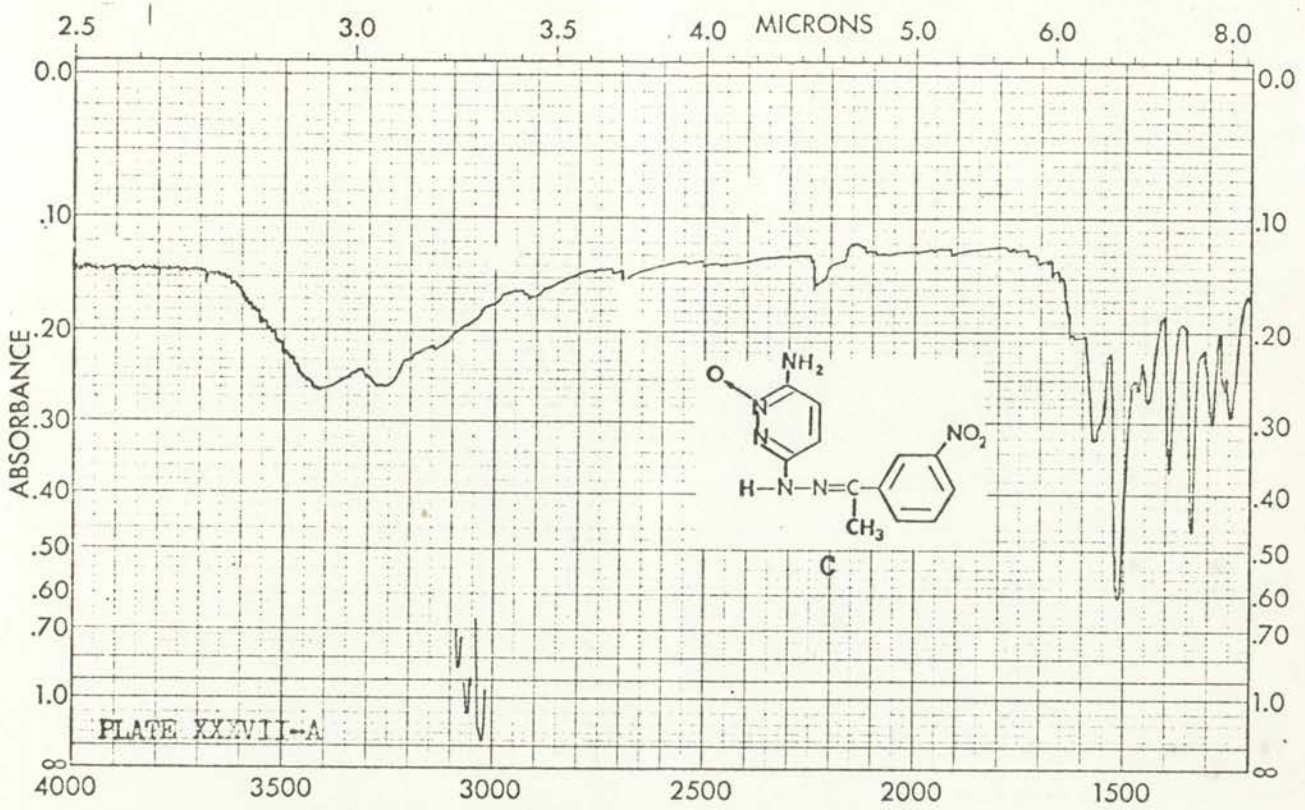
XCVIII

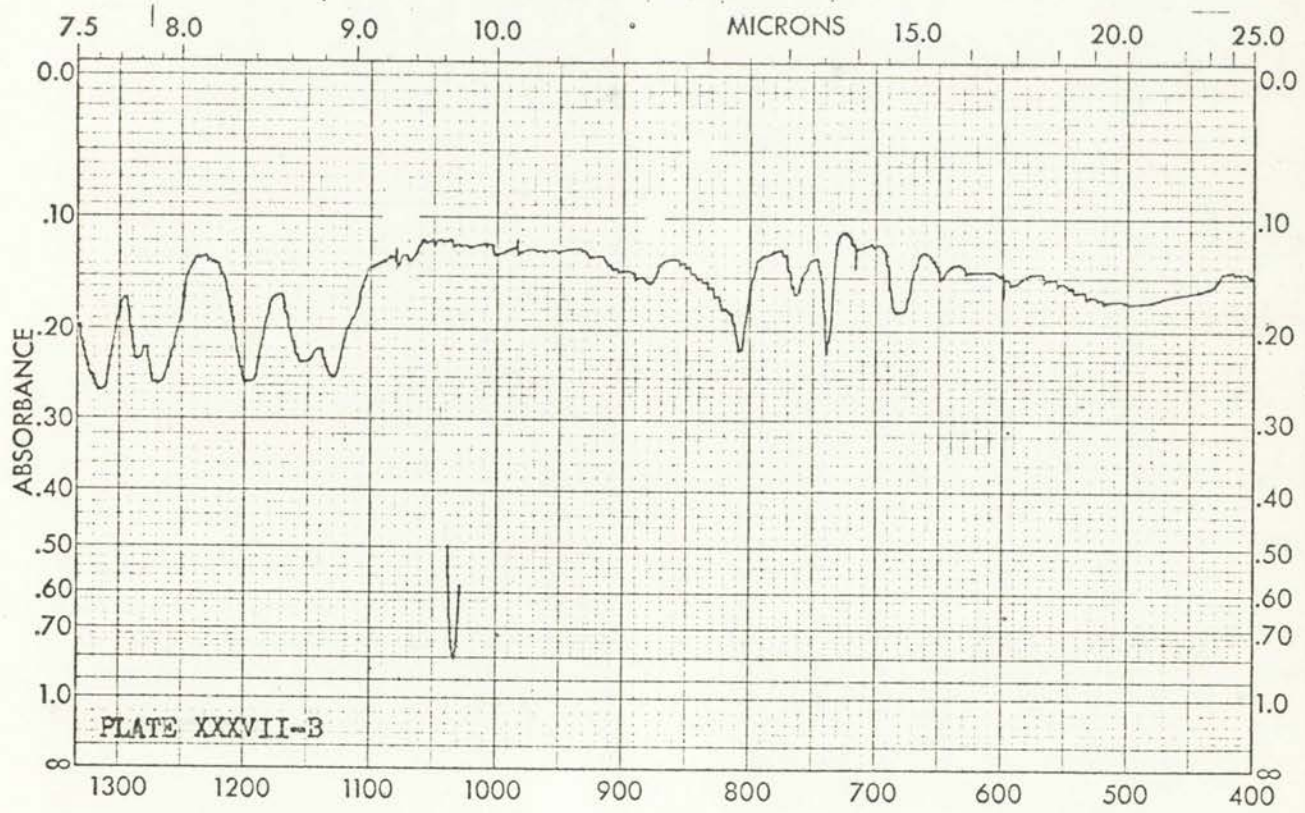

7.5
8.0
9.0
10.0
MICRONS
15.0
20.0
25.0
ABSORBANCE
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
1300
1200
1100
1000
900
800
700
600
500
400
PLATE XXXV-B

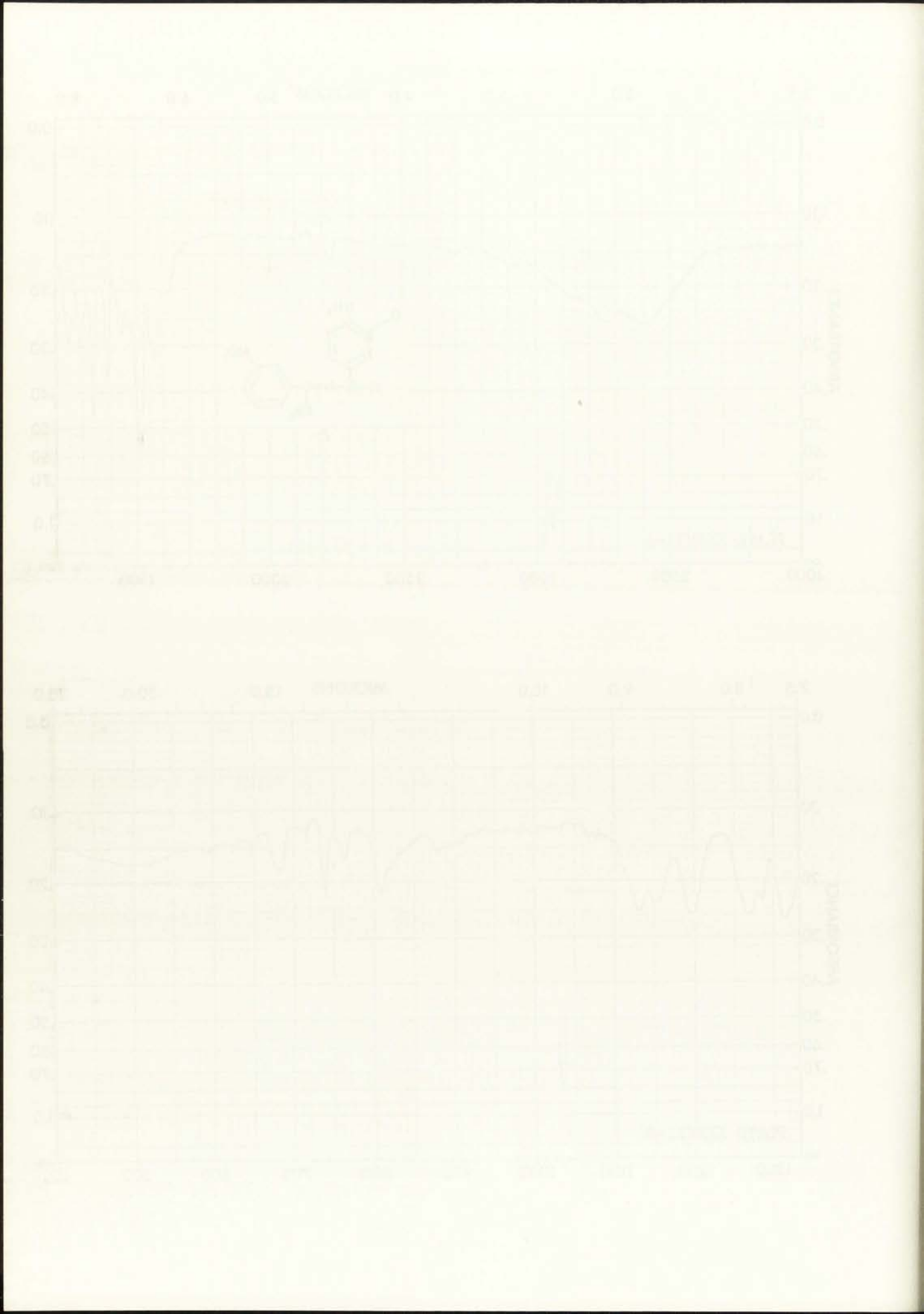


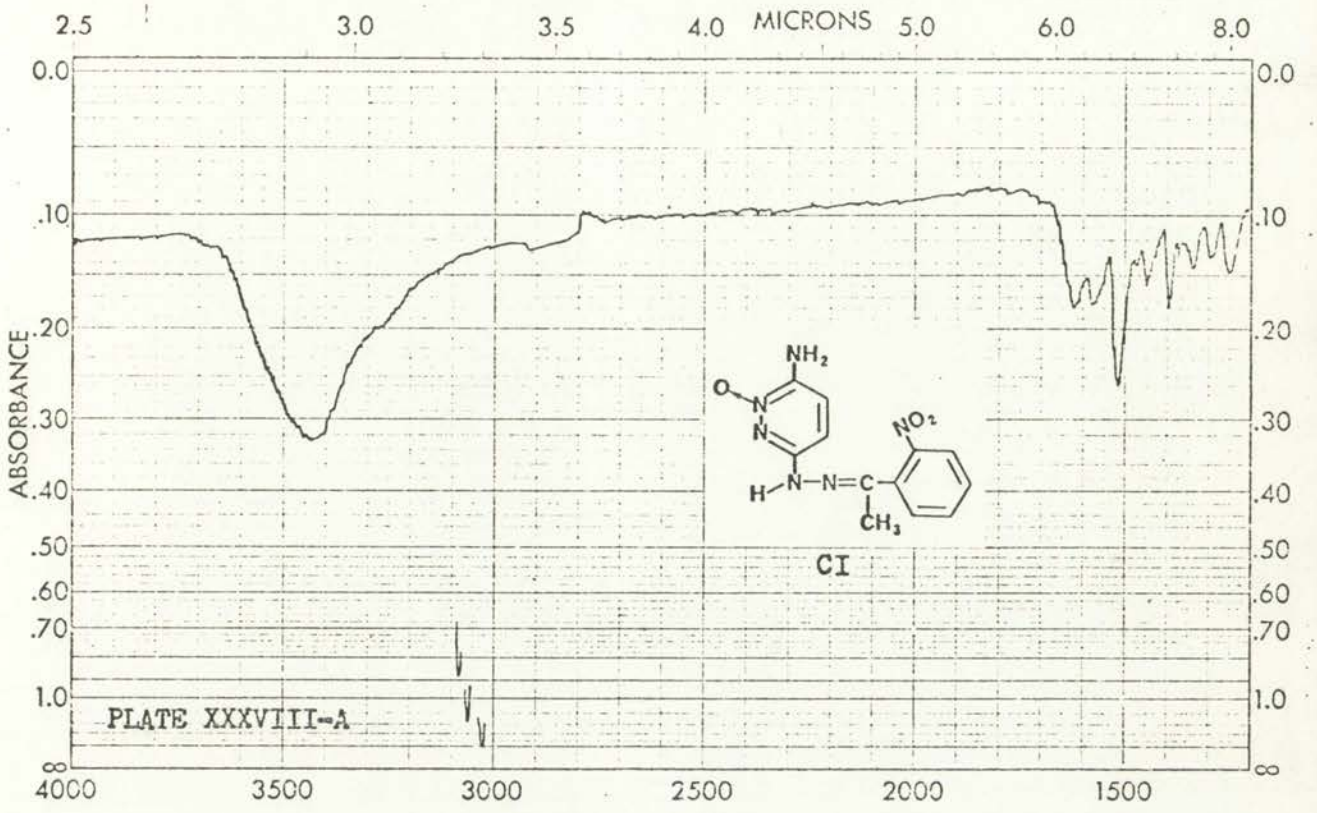

2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
ABSORBANCE
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
4000
3500
3000
2500
2000
1500
PLATE XXXVI-A
XCIX


7.5
8.0
9.0
10.0
MICRONS
15.0
20.0
25.0
ABSORBANCE
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
1300
1200
1100
1000
900
800
700
600
500
400
PLATE XXXVI-B

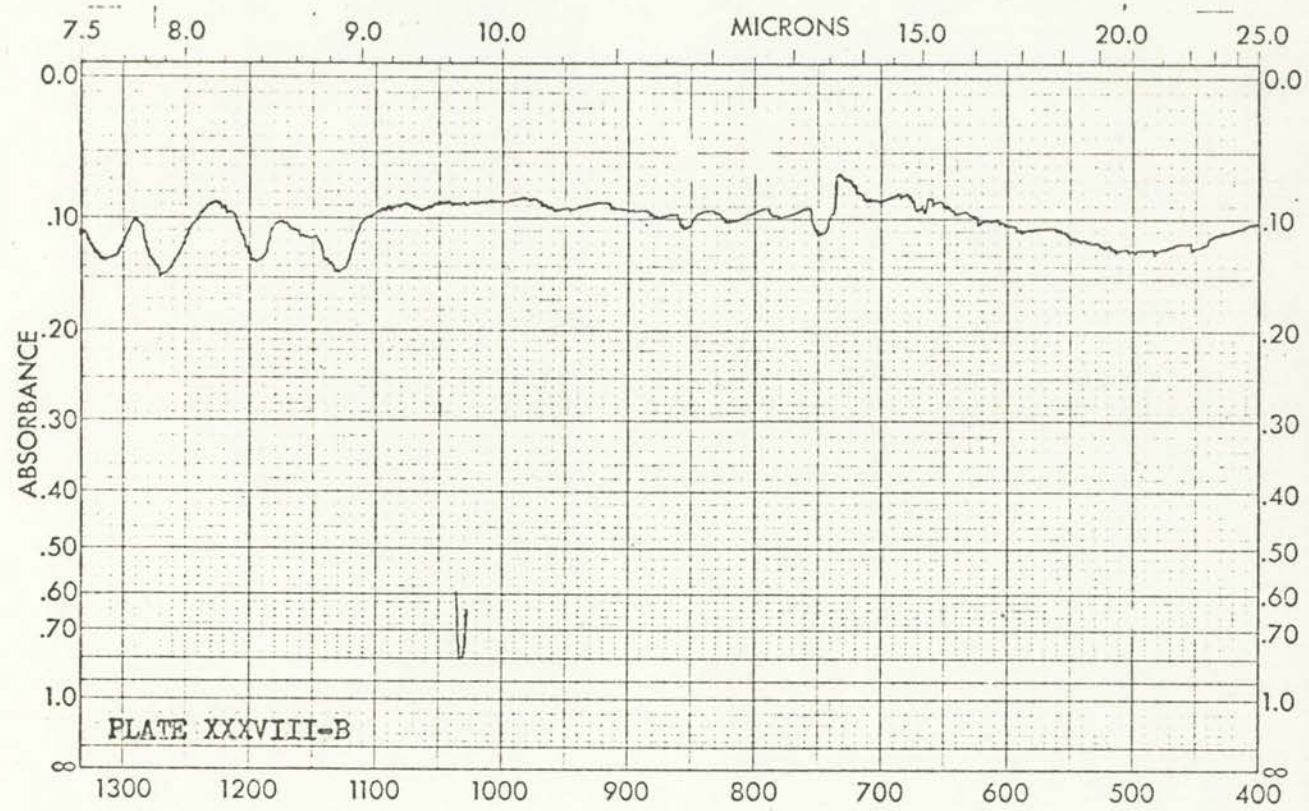

2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
ABSORBANCE
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
4000
3500
3000
2500
2000
1500
NH2
O
N
N
H–N–N=C
CH3
NO2
C
PLATE XXXVII-A

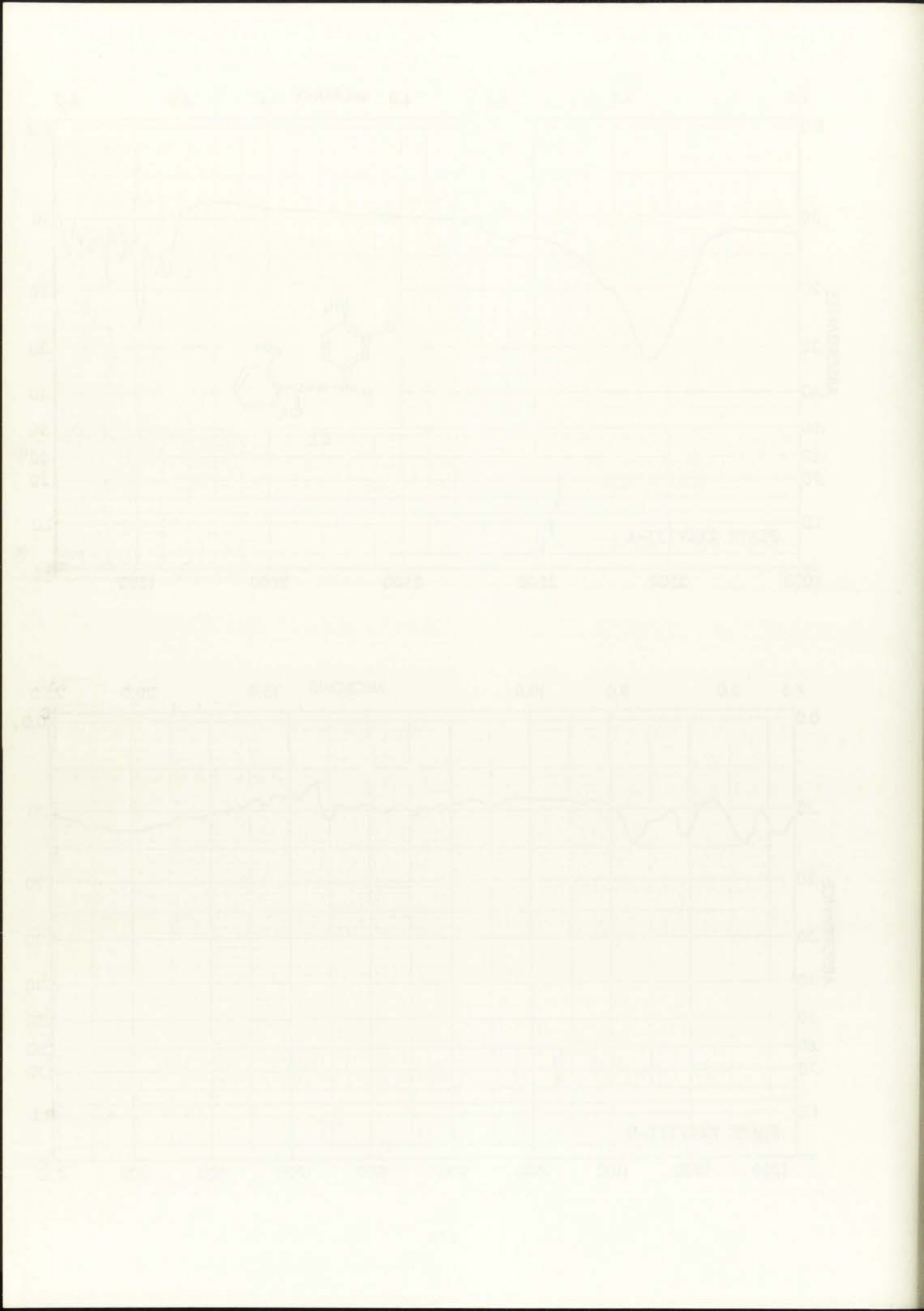

7.5
8.0
9.0
10.0
MICRONS
15.0
20.0
25.0
ABSORBANCE
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
1300
1200
1100
1000
900
800
700
600
500
400
PLATE XXXVII-B

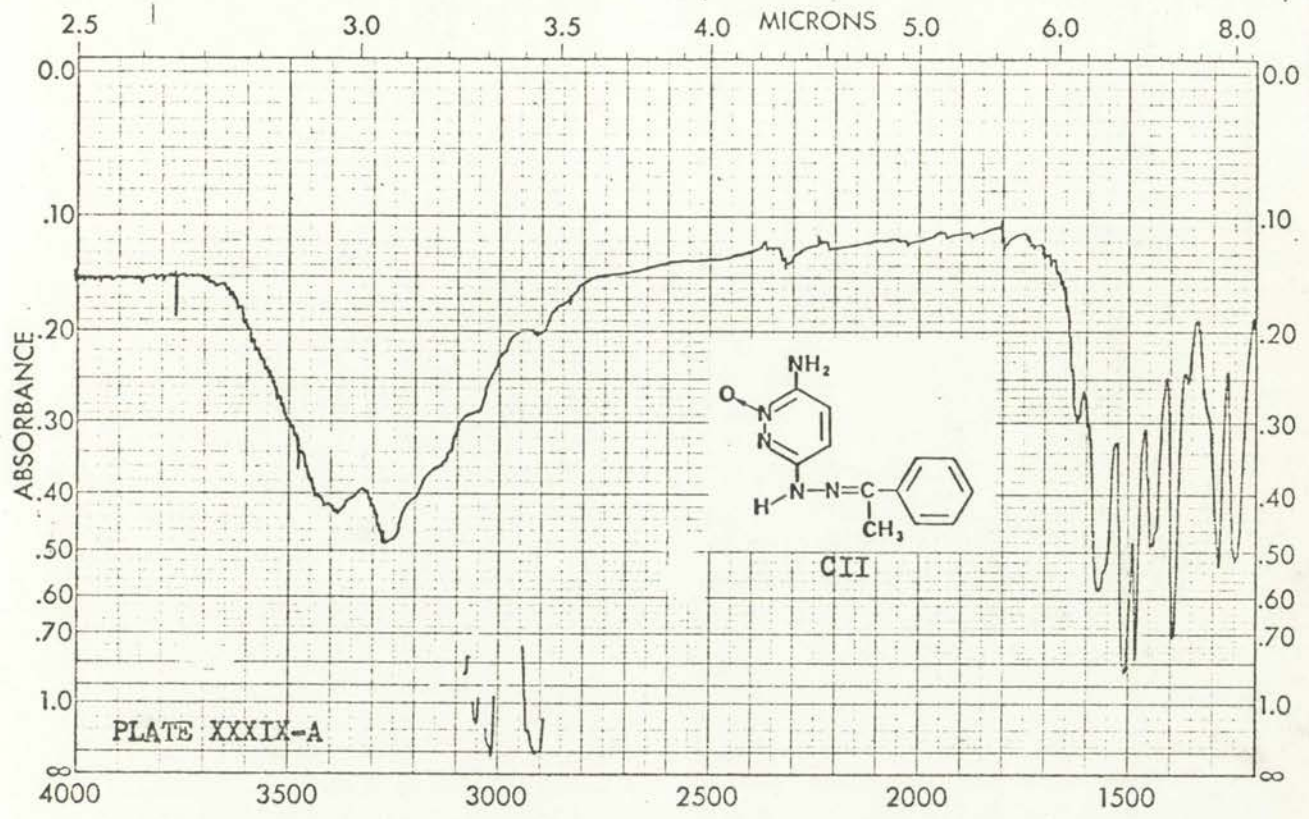


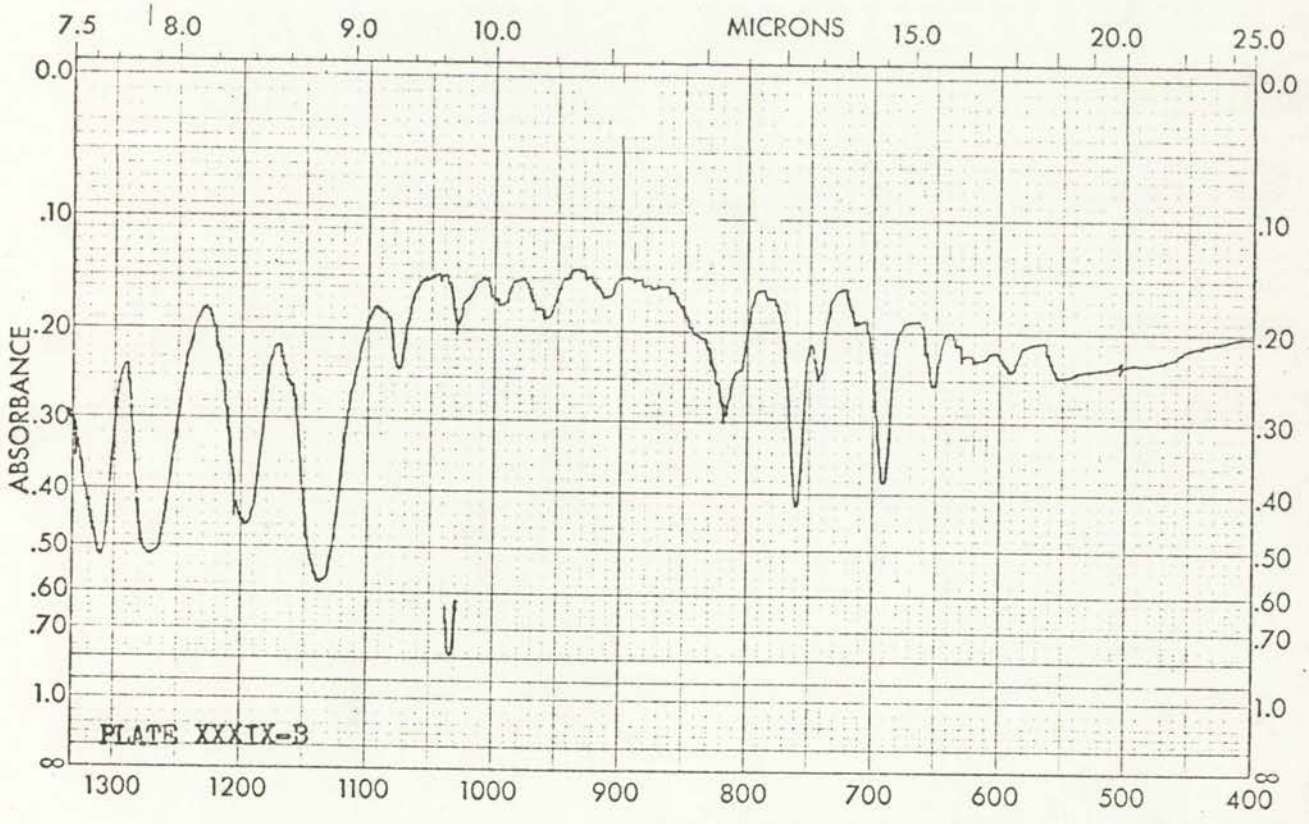

2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
ABSORBANCE
4000
3500
3000
2500
2000
1500
PLATE XXXVIII-A

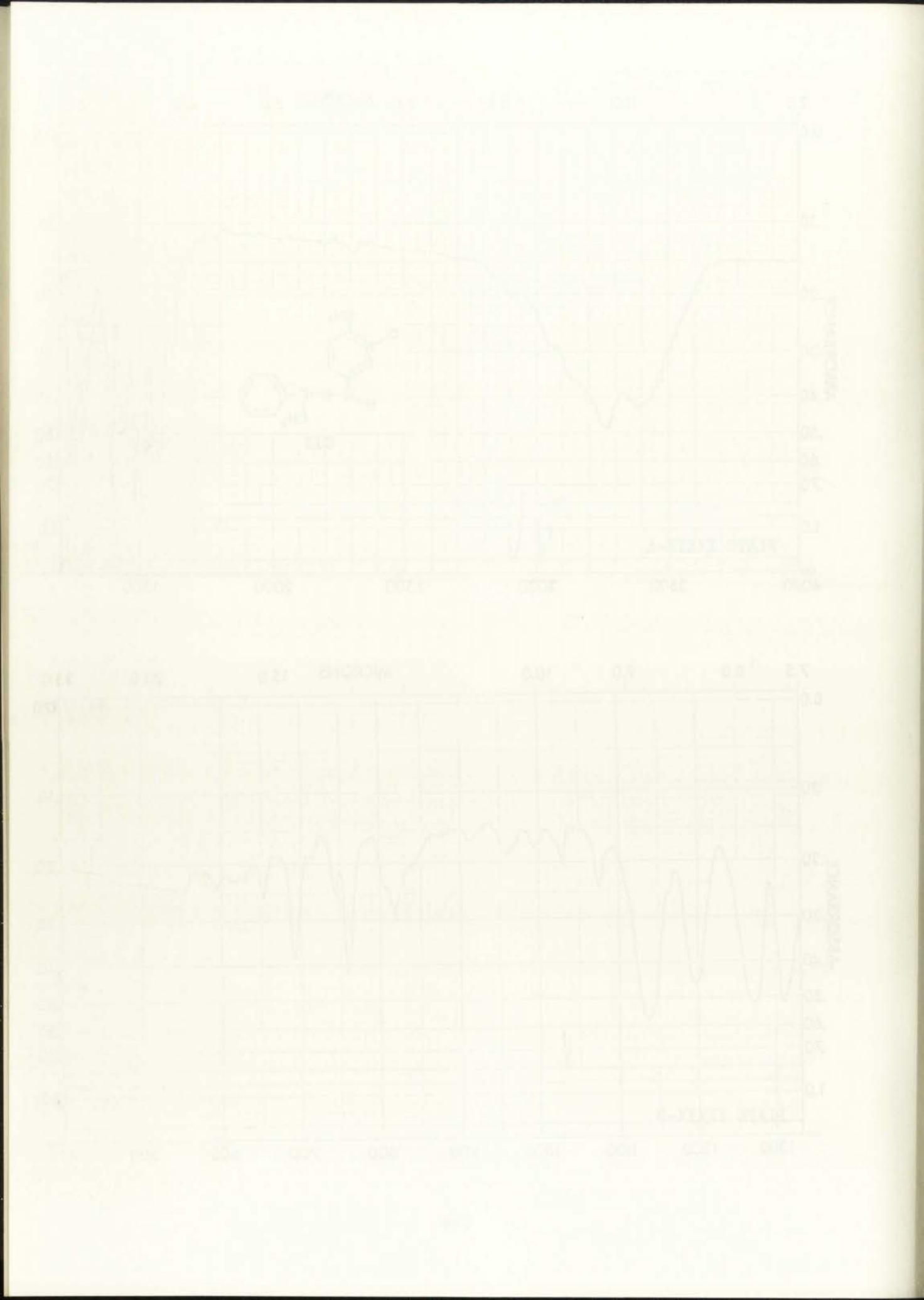
CI

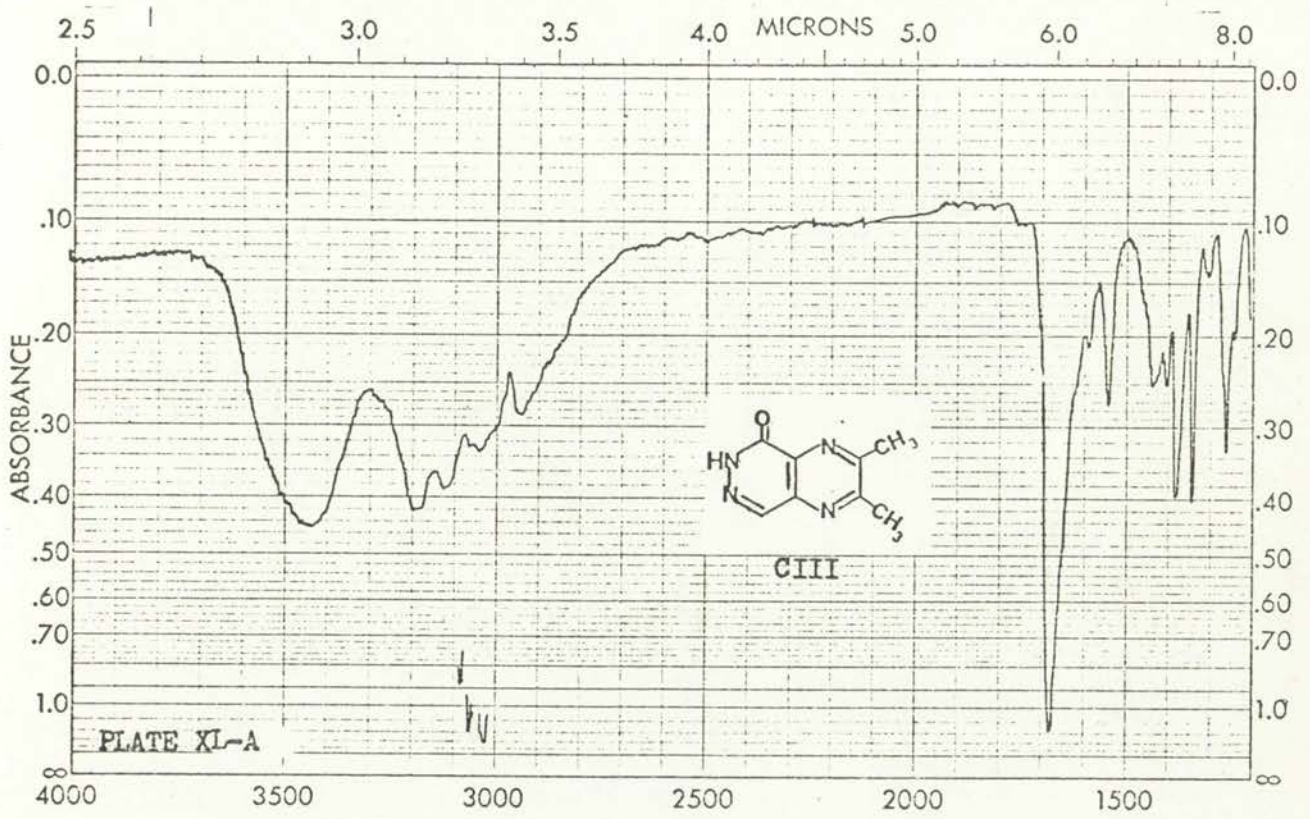

7.5
8.0
9.0
10.0
MICRONS
15.0
20.0
25.0
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
ABSORBANCE
1300
1200
1100
1000
900
800
700
600
500
400
PLATE XXXVIII-B

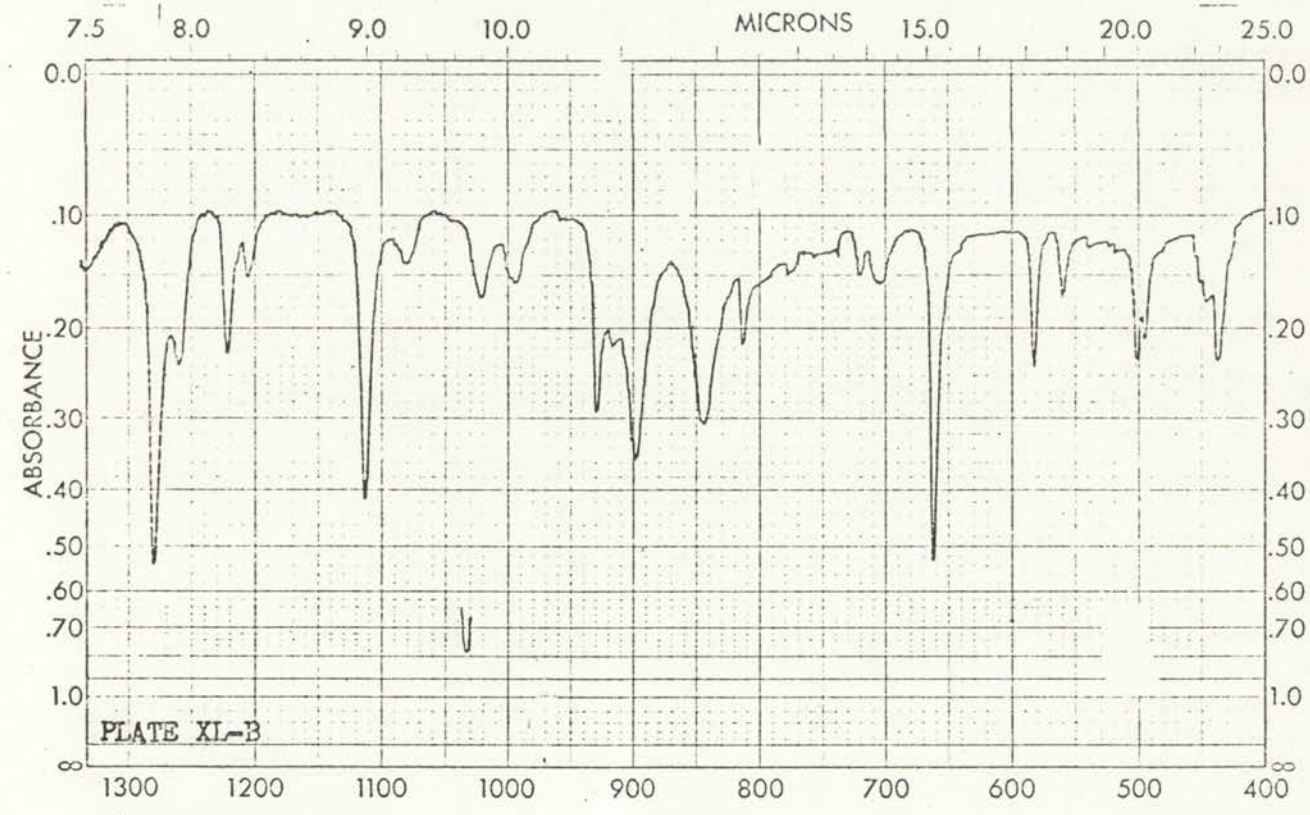


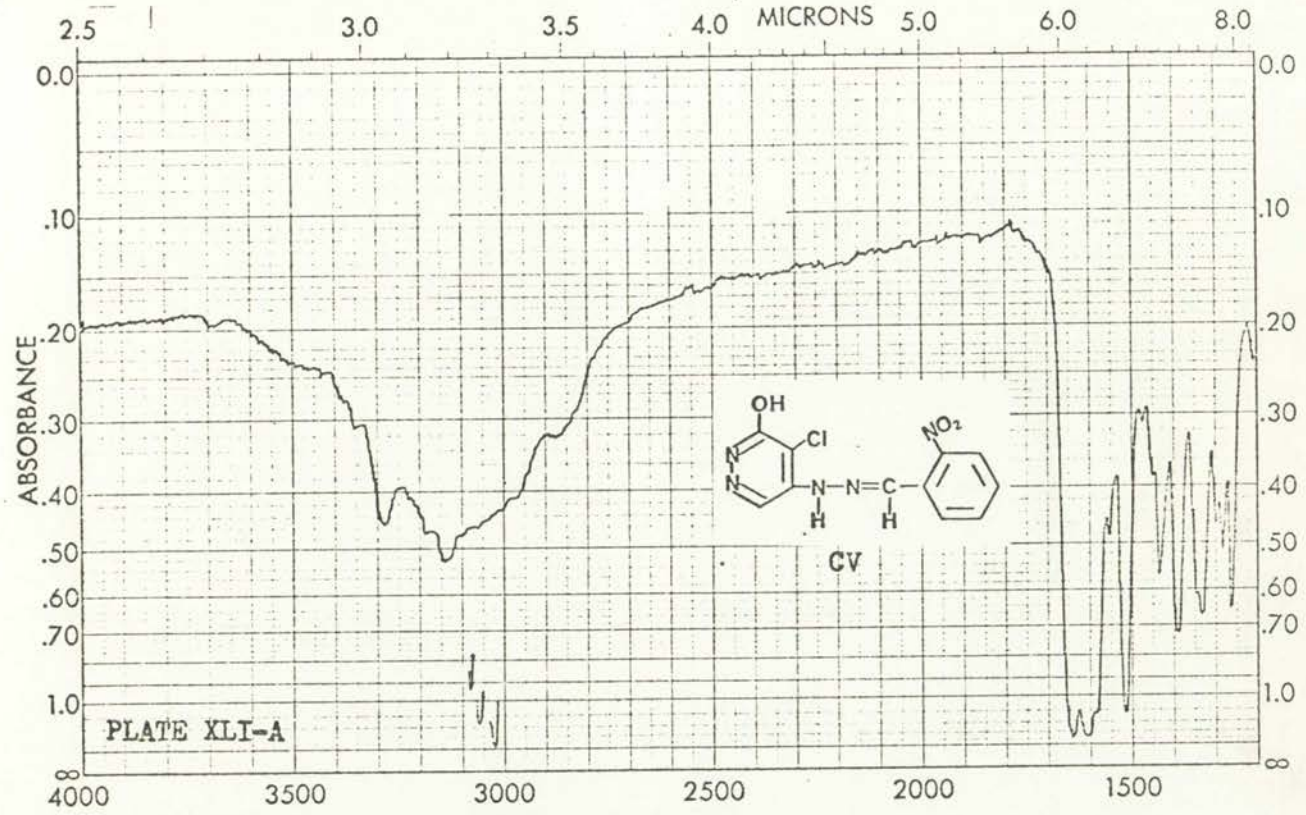

2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
ABSORBANCE
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
4000
3500
3000
2500
2000
1500
NH2
O
N
N
H
N–N=C
CH3
CII
PLATE XXXIX-A

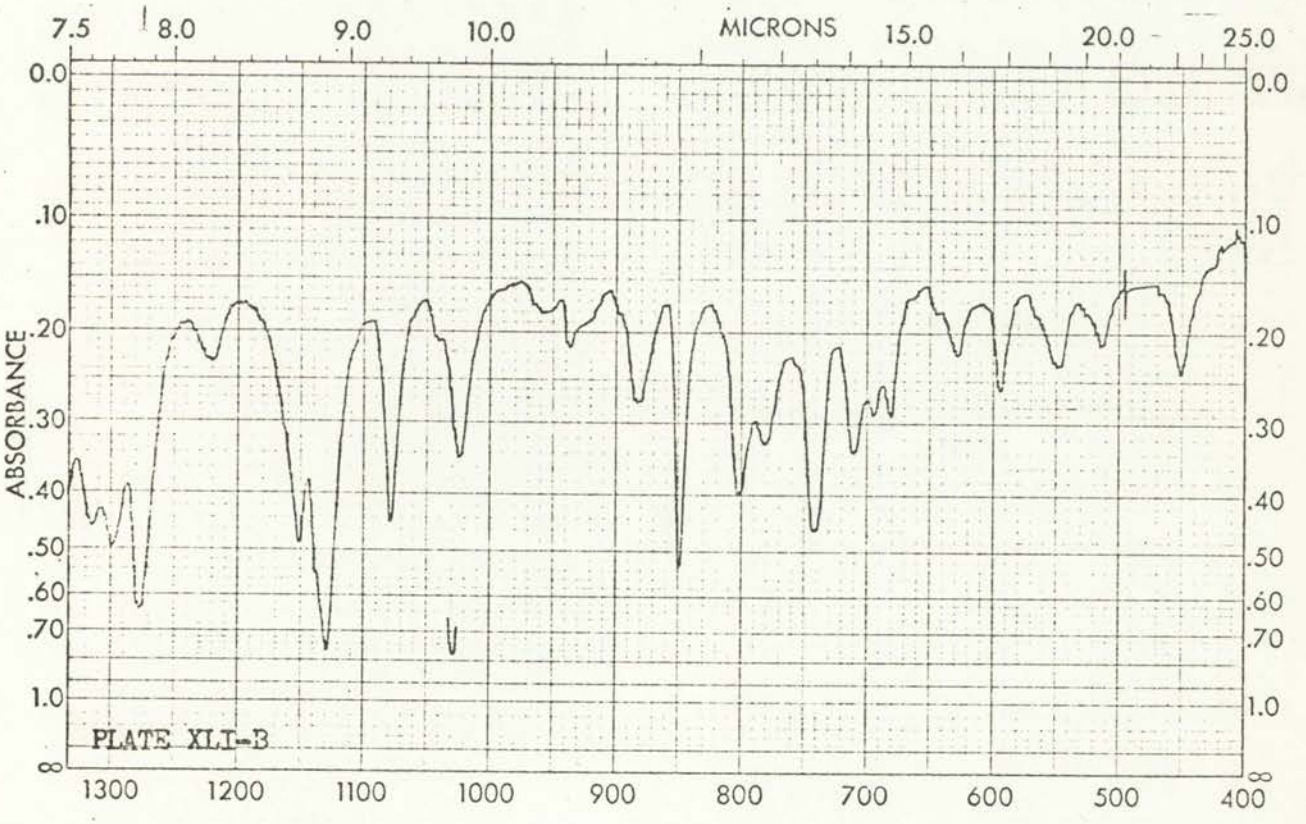

7.5
8.0
9.0
10.0
MICRONS
15.0
20.0
25.0
ABSORBANCE
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
1300
1200
1100
1000
900
800
700
600
500
400
PLATE XXXIX-B

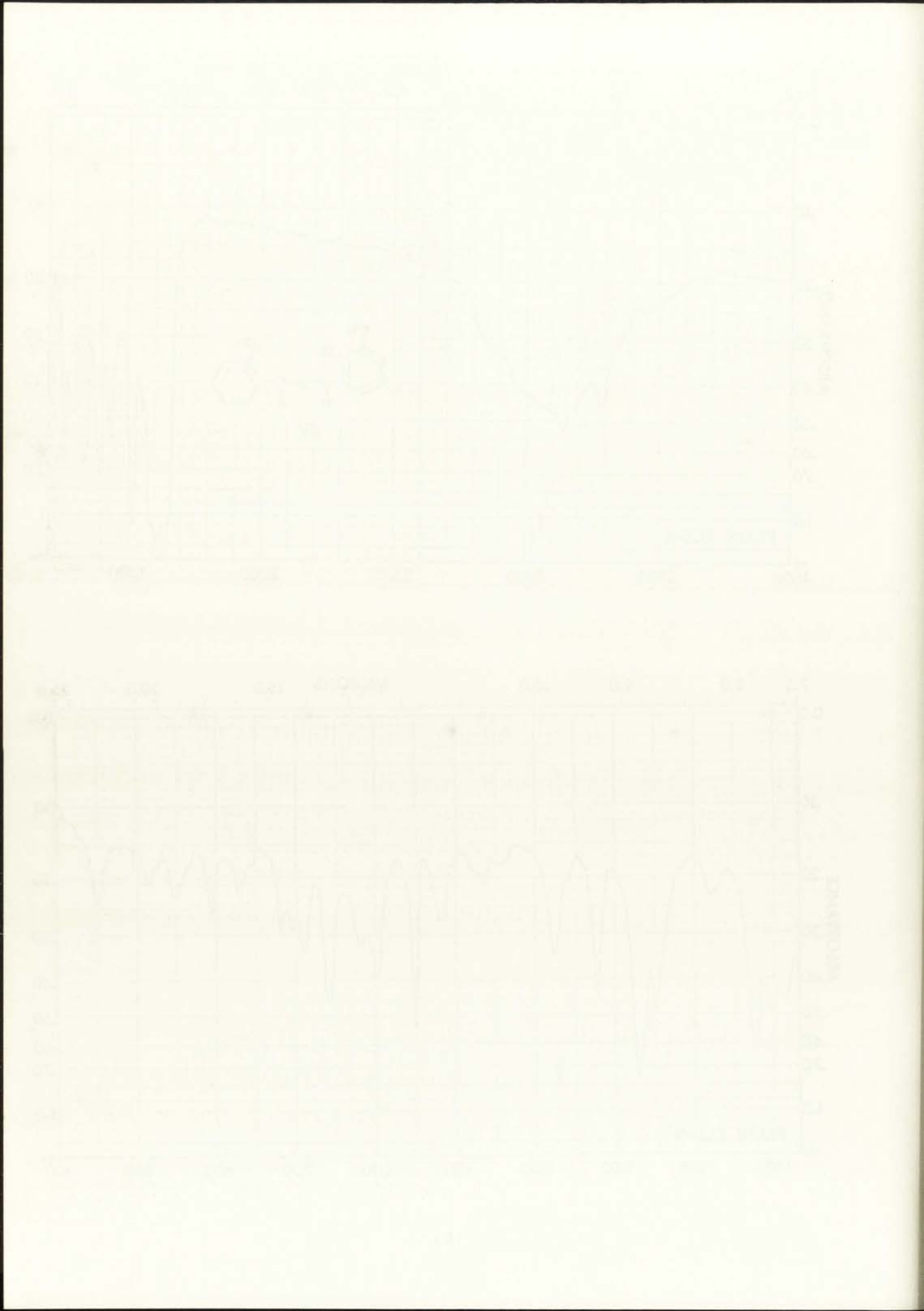


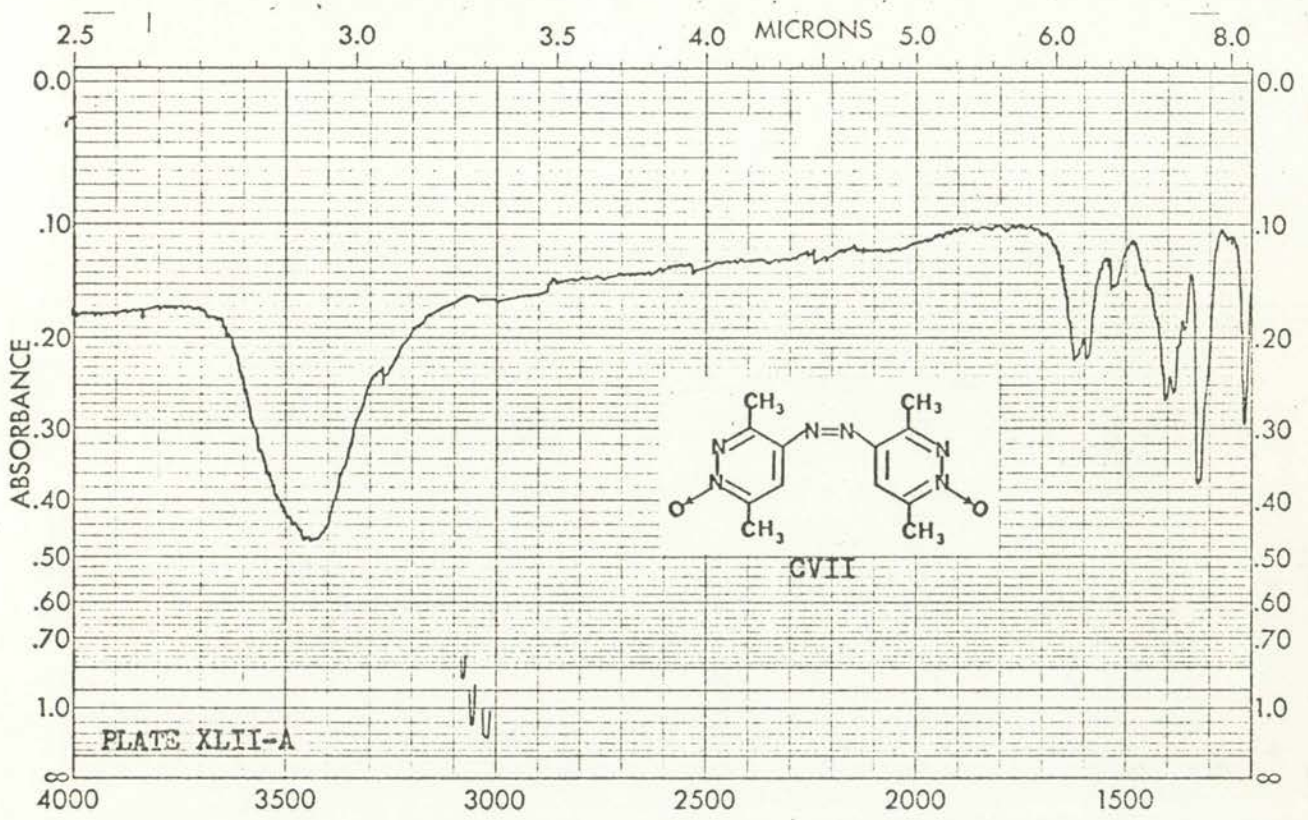

2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
ABSORBANCE
PLATE XL-A
4000
3500
3000
2500
2000
1500
CIII


7.5
8.0
9.0
10.0
MICRONS
15.0
20.0
25.0
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
ABSORBANCE
PLATE XL-B
1300
1200
1100
1000
900
800
700
600
500
400


2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
ABSORBANCE
OH
Cl
NO2
N
N
N–N=C
H
H
CV
PLATE XLI-A
4000
3500
3000
2500
2000
1500

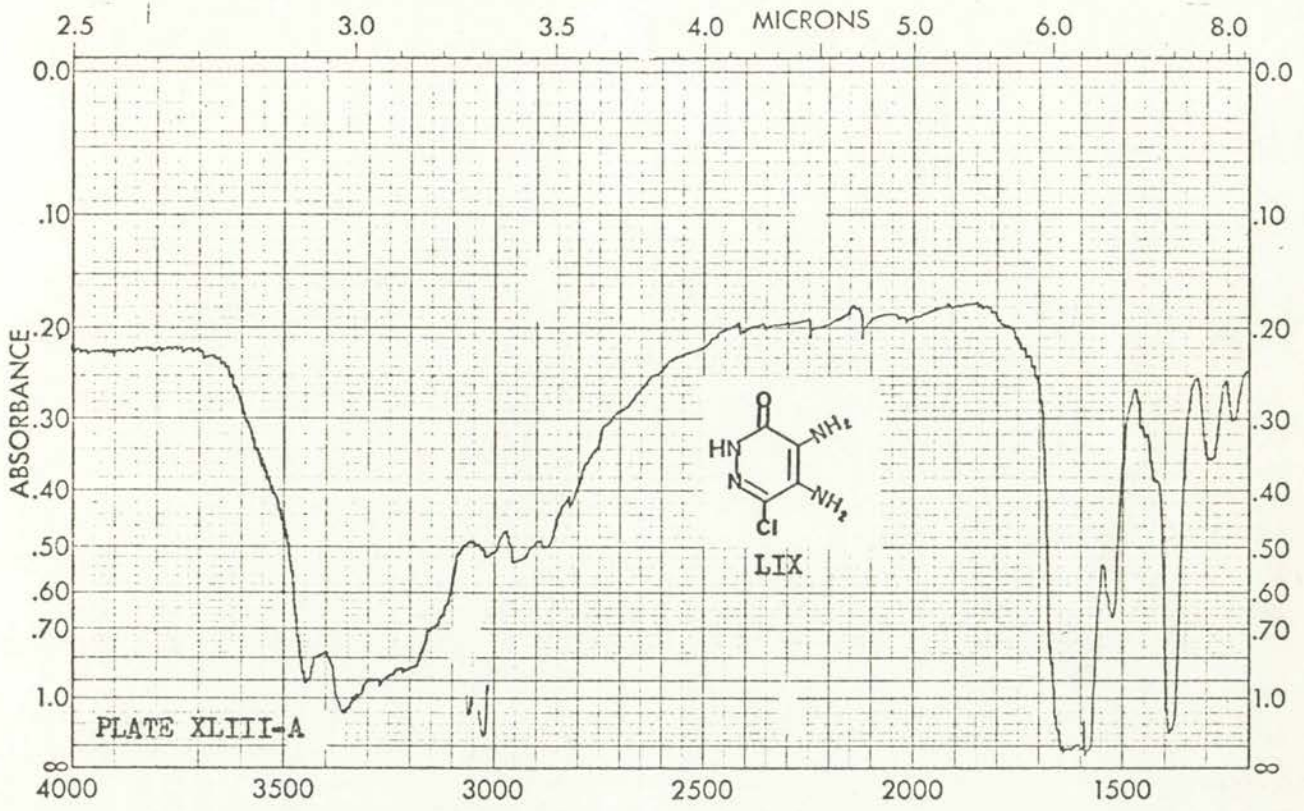

7.5
8.0
9.0
10.0
MICRONS
15.0
20.0
25.0
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
ABSORBANCE
PLATE XLI-B
1300
1200
1100
1000
900
800
700
600
500
400

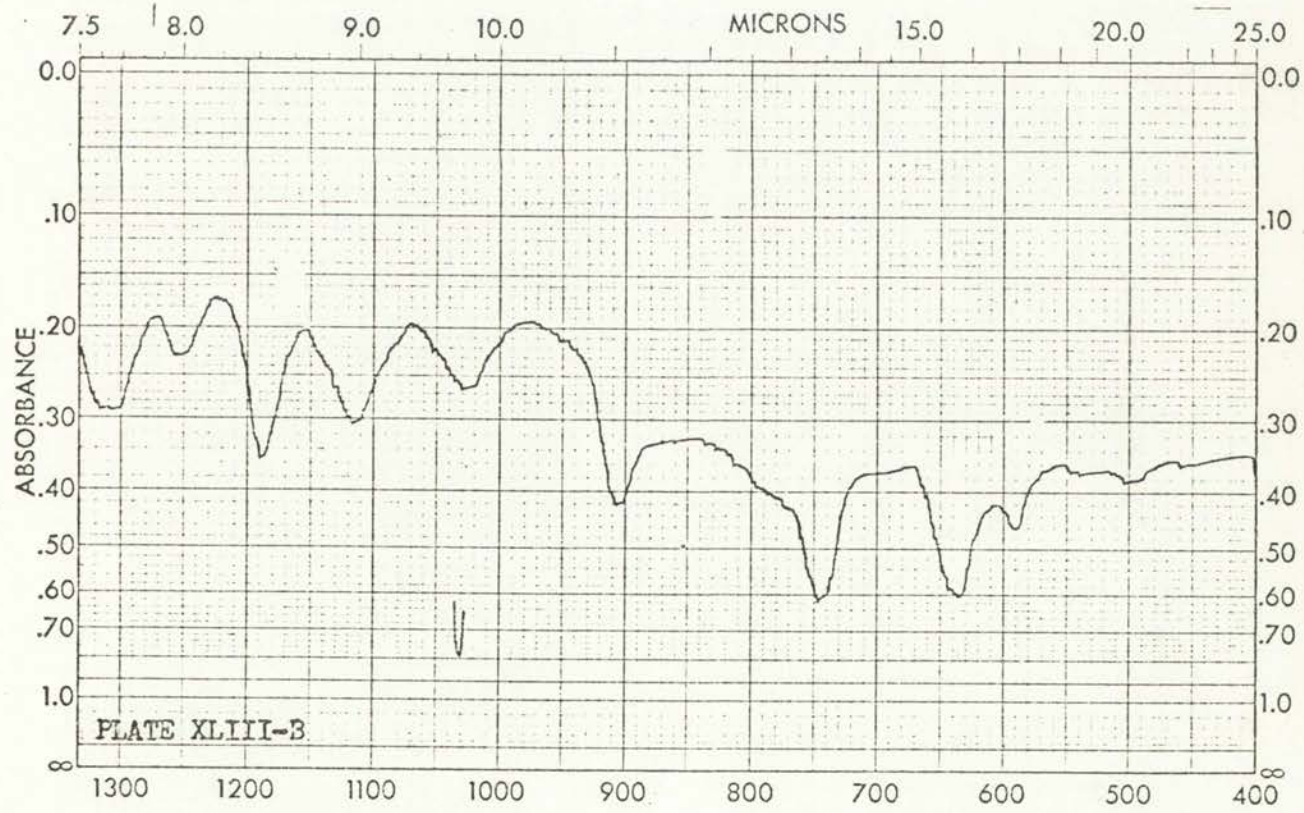



2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
ABSORBANCE
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
4000
3500
3000
2500
2000
1500
PLATE XLII-A

CVII


7.5
8.0
9.0
10.0
MICRONS
15.0
20.0
25.0
ABSORBANCE
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
1300
1200
1100
1000
900
800
700
600
500
400
PLATE XLII-B


2.5
3.0
3.5
4.0
MICRONS
5.0
6.0
8.0
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
ABSORBANCE
HN
N
NH₂
NH₂
Cl
O
LIX
PLATE XLIII-A
4000
3500
3000
2500
2000
1500


7.5
8.0
9.0
10.0
MICRONS
15.0
20.0
25.0
0.0
.10
.20
.30
.40
.50
.60
.70
1.0
∞
ABSORBANCE
PLATE XLIII-B
1300
1200
1100
1000
900
800
700
600
500
400

VIII. References

VIII. References

1. A. D. Ainley and H. King, Proc. Roy. Soc., B125, 60 (1938).

2. D. L. Aldous and R. N. Castle, Arzneim.-Forsch., 13, 878 (1963).

3. P. W. Allan and L. L. Bennett, Jr., Proc. Am. Assoc. Cancer Res., 9, 2 (1968).

4. P. W. Allan, H. P. Schneble and L. L. Bennett, Jr., Biochem. Biophys. Acta, 114, 647 (1966).

5. F. Ansfield, J. Am. Med. Assoc., 190, 234 (1964).

6. F. Ansfield, G. Ramirez and S. Mackman, Cancer Res., 29, 1062 (1969).

7. M. E. Balis, H. C. Nathan and G. H. Hitchings, Arch. Biochem., 71, 358 (1957).

8. L. L. Bennett, Jr. and P. W. Allan, Cancer Res., 31, 152 (1971).

9. S. J. Berman, J. Am. Med. Assoc., 207, 128 (1969).

10. A. Bertho and F. Holder, J. Prakt. Chem., 227, 189 (1928).

11. J. Bertino, Cancer Res., 23, 1286 (1963).

12. W. R. Boon, N. G. Jones and G. R. Ramage, J. Chem. Soc., 96 (1951).

13. L. Bosch, E. Harbers, C. Heidelberger, Cancer Res., 18, 335 (1958).

14. R. W. Brockman, Advan. Cancer Res., 7, 129 (1963).

15. M. H. Brooks, J. P. Malloy, P. J. Bartilloni, W. Sheey and K. G. Barry, Clin. Pharacol. Theraput., 10, 85 (1969).

16. J. Brown, J. Appl. Chem., (London), 2, 239 (1952).

17. J. J. Buchall and G. H. Hitchings, Mol. Pharmacol., 1, 126(1965).

18. J. Burchenal and R. Ellison, Clin. Pharmacol. Ther., 2, 53 (1961).

19. J. H. Burkhalter, F. H. Tendick, E. M. Jones, P. A. Jones, W. F. Halcomb and A. L. Rawlins, J. Am. Chem. Soc., 70, 1363 (1948).

20. C. J. Canfield, Bull. N. Y. Acad. Med., 45, 1043 (1969).

21. H. C. Carrington, A. F. Crowther and G. J. Stacy, J. Chem. Soc., 1017 (1954).

22. N. K. Chaudhuri, K. L. Mukherjee and C. Heidelberger, Biochem. Pharmacol. 1,328 (1959).

23. C. C. Cheng and R. K. Robins, J. Org. Chem., 23, 852 (1958).

24. L. Cheough, M. A. Rich and M. L. Eidenoff, Cancer Res., 20, 1602 (1960).

25. S. J. Childress and R. L. McKee, J. Am. Chem. Soc., 72, 4271 (1950).

26. T. Q. Chou, F. Y. Fu and Y. S. Kao, J. Am. Chem. Soc., 70, 1765 (1948).

27. G. R. Clemo and H. McIlwain, J. Chem. Soc., 79 (1938).

28. D. F. Clyde, Trans. Roy. Soc. Trop. Med. Hyg., 64, 834 (1970).

29. E. J. Colwell, J. D. Brown, P. K. Russell, S. C. Boone and L. J. Legters, Mil. Med., 134, 1409 (1969).

30. L. H. Conover, A. R. English and C. E. Larrabee, (Chas. Pfizer Co.) U. S. Patent 2,921,073 Jan. 12, 1960 [Chem. Abstr., 54, 8860 (1960)].

31. W. C. Cooper, Public Health Reports (US), 64, 717 (1949).

32. G. Covell, G. R. Coatney, J. W. Field, and J. Singh, "Chemotherapy of Malaria," World Health Organization, Geneva (1951), p. 32.

33. F. Curd, D. Davey, and F. Rose, Ann. Trop. Med. Parasitol., 39, 157 (1945).

34. J. W. Daly and B. E. Christensen, J. Org. Chem., 21, 177 (1956).

35. R. L. Degowin, Am. J. Trop. Med., 14, 519 (1965).

36. K. L. Dille, M. L. Sutherland and B. E. Christensen, J. Org. Chem., 20, 171 (1955).

37. M. D. Dowling, Jr., I. H. Krakoff and D. A. Karnofsky, "Chemotherapy of Cancer," W. H. Cole, ed., Lea & Febiger (1970), p. 1.

38. J. Druey, K. Meier and K. Eichenberger, Helv. Chim. Acta, 37, 121 (1954).

39. J. D. Dutcher and O. Wintersteiner, J. Biol. Chem., 155, 359 (1944).

40. J. F. B. Edeson, Ann. Trop. Med. Parasitol., 48, 160 (1954).

41. R. C. Elderfield, E. Chafflin, H. Mertel, O. McCurdy, R. Mitch, C. VerNooy, B. Wark and I. Wempen, J. Am. Chem. Soc., 77, 4819 (1955).

42. R. C. Elderfield, C. B. Kremer, S. M. Kupchan, O. Birstein and G. Cortes, J. Am. Chem. Soc., 69, 1258 (1947).

43. G. B. Elion, Biochem. Pharmacol., 12, 85 (1963).

44. G. B. Elion and G. H. Hitchings, Advan. Chemother., 2, 91 (1965).

45. R. Ellison and B. Hoogstraten, Proc. Am. Assoc. Cancer Res., 6, 17 (1955).

46. L. Erichomovitch and F. L. Chubb, Can. J. Chem., 44, 2095 (1966).

47. R. D. Estensen, A. K. Krey and F. E. Hahn, Mol. Pharmacol., 5, 532 (1969).

48. N. H. Fairly, Trans. Roy. Soc. Trop. Med. Hyg., 40, 105 (1946).

49. S. Farber, L. K. Diamond, R. D. Mercer, R. F. Sylvester, Jr., and J. A. Wolff, New Eng. J. Med., 283, 787 (1948).

50. G. M. Findley, "Recent Advances in Chemotherapy," Vol. II, Blakiston, Philadelphia (1951), p. 83.

51. C. D. Fitch, Proc. Natl. Acad. Sci., 64, 1181 (1969).

52. C. D. Fitch, Science, 169, 289 (1970).

53. G. R. Greenberg, Fed. Proc., 13, 745 (1954).

54. P. Guttman and P. Ehrlich, Berlin Klin. Wochschr., 28, 953 (1891).

55. M. Hakala, Biochim. Biophys. Acta, 102, 198 (1965).

56. J. Hartman, M. Origenes and M. Murphy, Cancer Chemother. Rep., 34, 51 (1964).

57. S. C. Hartman, B. Levenberg and J. M. Buchanan, J. Am. Chem. Soc., 77, 501 (1955).

58. C. Heidelberger, N. Chadhuri, P. Danneberg, D. Mooren and L. Griesbach, Nature, 179, 663 (1957).

59. G. H. Hitchings, "Drugs Parasites and Hosts," (London) Churchill, (1962) pp. 196-210.

60. A. G. Hogan and E. M. Parrot, J. Biol. Chem., 128, 46 (1939).

61. R. G. Houel and W. T. VanGoor, Bull. Soc. Pathol. Exotique, 47, 254 (1954).

62. B. L. Hutchings, S. Gordon, F. Ablondi, C. F. Wolf and J. H. Williams, J. Org. Chem., 17, 19 (1952).

63. T. Itai and S. Kamiya, Chem. Pharm. Bull. (Tokyo), 9, 87 (1961).

64. T. Itai and S. Kamiya, Chem. Pharm. Bull. (Tokyo), 2, 348 (1963).

65. T. Itai and T. Nakashima, Chem. Pharm. Bull. (Tokyo), 10, 347 (1962).

66. T. Itai and T. Nakashima, Chem.Pharm. Bull. (Tokyo), 16, 934 (1962).

67. T. Itai and S. Natsume, Chem. Pharm. Bull. (Tokyo), 11, 342 (1963).

68. T. Itai and S. Suzuki, Chem. Pharm. Bull. (Tokyo), 8, 999 (1960).

69. R. L. Jacobs, J. Parisitol., 51, 481 (1965).

70. D. A. Karnofsky and B. D. Clarkson, Ann. Rev. Pharmacol., 3, 361 (1963).

71. D. A. Karnofsky, M. L. Murphy and C. R. Lacon, Proc. Am. Assoc. Cancer Res., 2, 312 (1958).

72. D. Kessel, T. Hall and D. Roberts, Science, 150, 752 (1965).

73. J. B. Koepfli, J. F. Mead and J. A. Brockman, Jr., J. Am. Chem. Soc., 69, 1837 (1947).

74. J. B. Koepfli, J. F. Mead and J. A. Brockman, Jr., J. Am. Chem. Soc., 71, 1048 (1949).

75. W. Krivit, C. Brubaker, J. Hartman, M. Murphy, M. Pierce and G. Thatcher, J. Pediat., 68, 965 (1966).

76. M. Kumagai, Nippon Kogaku Zasshi, 82, 227 (1966); [Chem. Abstr., 56, 10139i (1962)].

77. F. Leonard and A. Wanjgurt, J. Org. Chem., 21, 1077 (1956).

78. A. S. Levine, L. Sharp, J. Mitchell, W. Krivit and M. E. Nesbit, Cancer Chemother. Rep., 53, 1 (1969).

79. R. B. Livingston and S. K. Carter, "Single Agents in Cancer Chemotherapy," Plenum, (1970) p. 131.

80. R. F. Loeb, J. Am. Med. Assoc., 130, 1069 (1946).

81. D. C. Martin and J. D. Arnold, J. Clin. Pharmacol., 9, 155 (1969).

82. S. J. Martin and R. N. Castle, J. Heterocyclic Chem., 6, 93 (1969).

83. R. J. McCollister, W. A. Gilber, D. M. Ashton and H. G. Palmer, Am. J. Med., 40, 548 (1966).

84. C. Moertel, R. Reitemeier and R. Hahn, Cancer Chemother. Rep., 53, 283 (1959).

85. C. Moertel, R. Reitemeier and R. Hahn, Surg. Gyn. Obstet., 130, 292 (1970).

86. G. Moore, I. Bross and R. Ausman, Cancer Chemother. Rep., 52, 655 (1968).

87. T. Nakagome, Yakugaku Zasshi, 82, 253 (1962).

88. G. T. Newbold and F. S. Spring, J. Chem. Soc., 2052 (1956).

89. H. Nishimura, H. Kano, K. Tawara, M. Ogata and Y. Tonaka, Shinogi Kenkyusho Nempo, 14, 86 (1964).

90. R. L. O'Brien and J. E. Hahn, Antibiotic Agents and Chemotherapy, 315 (1965).

91. Olin Matheson Chem. Corp., British Patent 761,171 Nov. 14, 1956; Chem. Abstr., 51, 13327 (1957).

92. H. T. Openshaw, "The Alkaloids," 3, 112 (1953).

93. F. S. Parker and J. L. Irvin, J. Biol. Chem., 199, 889 (1952).

94. L. Pauling and R. B. Corey, Arch. Biochem. Biophys., 54, 164 (1956).

95. V. G. Pesin, Izv. Akad. Nauk SSSR, Ser Khim., 106, 31 (1956).

96. V. G. Pesin, A. M. Khalelskii and C. Chzi-chzhun, Zh. Obshch. Khim., 27, 1643 (1957).

97. W. Peters, Trans. Roy. Soc. Trop. Med. Hyg., 63, 25 (1969).

98. R. D. Powell, Bull. World Health Organ., 31, 379 (1964).

99. R. D. Powell and W. D. Tigertt, Annual Rev. Med., 19, 81 (1968).

100. W. P. Purcell, Ann. Prog. Rep., (US Government) Contract DA-49-193, MD-2779, (1970).

101. W. Regelson, J. Holland and E. Frei, Cancer Chemother. Rep., 36, 41 (1964).

102. F. Reicheneder and K. Dury, Belgian Patent, 660,637; [Chem. Abstr., 64, 5108 (1966)].

103. D. Roberts and I. Wodinsky, Cancer Res., 28, 1955 (1968).

104. R. K. Robins, J. Am. Chem. Soc., 78, 784 (1956).

105. R. K. Robins, F. W. Furcht, A. D. Grauer and J. W. Jones, J. Am. Chem. Soc., 78, 784 (1956).

106. R. O. Roblin, Jr., J. O. Lampen, J. P. English, Q. P. Cole and J. R. Vaughn, Jr., J. Am. Chem. Soc., 67, 290 (1945).

107. I. M. Rollo, "Proceedings of the Third International Pharmacological Meeting," Sao Paulo, Brazil, 1, 45 (1966).

108. I. M. Rollo, "Proceedings of the Third International Pharmacological Meeting," Sao Paulo, Brazil, 1, 47 (1966).

109. I. M. Rollo, "Proceedings of the Third International Pharmacological Meeting," Sao Paulo, Brazil, 1, 49 (1966).

110. R. Rosso, M. G. Dorelli, G. Franchi and S. Garattini, Cancer Chemother. Rep., 54, 79 (1970).

111. P. F. Russel, "Practical Malariology," Oxford University Press, London, (1963) p. 47.

112. S. R. Safir and J. H. Williams, J. Org. Chem., 17, 1298 (1952).

113. K. A. Schellenberg and G. R. Coatney, Biochem. Pharmacol., 6, 143 (1961).

114. F. Schonhofer, Z. Physiol. Chem., 274, 1 (1942).

115. W. Schulemann, F. Schonhofer and A. Wingler, Berlin Klin. Wochschr., 11, 381 (1932).

116. D. R. Seeger, D. B. Comlich, J. M. Smith, Jr. and M. E. Hultquist, J. Am. Chem. Soc., 71, 1753 (1949).

117. R. Seka and H. Preissecker, Monatsh. Chem., 57, 71 (1931); [Chem. Abstr., 25, 1826 (1931)].

118. I. Sekikawa, Bull. Chem. Soc. Japan, 31, 252 (1958).

119. I. Sekikawa, Bull. Chem. Soc. Japan, 32, 1229 (1960).

120. I. Sekikawa, J. Heterocyclic Chem., 6, 129 (1969).

121. O. Selawry, J. Am. Med. Assoc., 194, 75 (1965).

122. O. Selawry, Proc. Am. Assoc. Cancer Res., 11, 283 (1970).

123. H. E. Skipper, Proc. Am. Assoc. Cancer Res., 1, 51 (1953).

124. H. E. Skipper, R. K. Robins, J. R. Thompson, C. C. Cheng, R. W. Brockman and F. M. Schabel, Jr., Cancer Res., 17, 579 (1957).

125. M. Sullivan, M. Haggard, M. Donaldson, Proc. Am. Assoc. Cancer Res., 11, 306 (1970).

126. A. R. Surrey and H. F. Hammer, J. Am. Chem. Soc., 70, 1363 (1948).

127. G. M. Timmis, J. Pharm. Pharmacol., 9, 81 (1957).

128. S. Tindel, J. Am. Med. Assoc., 200, 913 (1967).

129. C. W. Walker, B. L. Hutchings, J. H. Mowat, E. L. R. Stokstad, J. H. Boothe, R. B. Angier, J. Semb, Y. SubbaRow, D. B. Comlich, M. J. Fahrenbach, M. E. Hultquist, E. Kuh, E. H. Northey, D. R. Seegar, J. P. Sichels and J. M. Smith, Jr., J. Am. Chem. Soc., 70, 19 (1948).

130. W. Weihheiser, Cancer Res., 23, 1277 (1963).

131. S. Weiss and R. Raskind, Int. Surg., 51, 149 (1969).

132. W. Wells and R. Winzler, Cancer Res., 19, 1086 (1959).

133. R. Y. Wen, Diss. Abstr., 23, 4121 (1963).

134. E. C. White and J. H. Hill, J. Bacteriol., 45, 433 (1943).

135. N. Whittaker, J. Chem. Soc., 1565 (1951).

136. J. Wyatt and L. McAninch, Can. J. Surg., 10, 421 (1967).

137. M. D. Young, Am. J. Trop. Med., 12, 305 (1963).

IX. Curriculum Vitae

CURRICULUM VITAE

Donald E. Pichler was born on February 8, 1940, in New York City, New York. He attended Manhattan College and Villanova University. In 1961, he was awarded the B.S. degree from Manhattan College with a major in Chemistry and a minor in Mathematics and in 1964 the M.S. degree in Chemistry was conferred by Villanova University. He served on active duty with the United States Air Force at Kirtland Air Force Base from 1963 to 1966 as a nuclear research officer. He was honorably discharged in May of 1966 and enrolled in the University of New Mexico as a graduate student in the Department of Chemistry. He was a graduate assistant in the Department of Chemistry from September 1966 to June 1969. He is an associate member of Sigma XI, and the American Association of University Professors. He has received an appointment to the faculty of the Department of Chemistry at the University of Albuquerque. His publications are:

1. Walter W. Zajac, Jr. and D. E. Pichler, "1,4-Diarylphthalazines and 1,3-Diarylisobenzofurans," Can. J. Chem. 44, 833 (1966).
2. R. D. Sherwood and D. E. Pichler, "Roller Coaster Project Officers' Report, Electron Microprobe Particulate Analysis," Isotopes, Inc. -POR-2507-(1966).