ALKYLATION STUDIES WITH AMINOTRIAZOLES AND AMINOTETRAZOLES

Thesis for the Degree of Ph. D.

MICHIGAN STATE UNIVERSITY

Kenneth Ralph Wilson

1957

THESIS

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By

Kenneth Ralph Wilson

A THESIS

Submitted to the College of Advanced Graduate Studies of Michigan State University of Agriculture and Applied Science in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Department of Chemistry

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AN ABSTRACT

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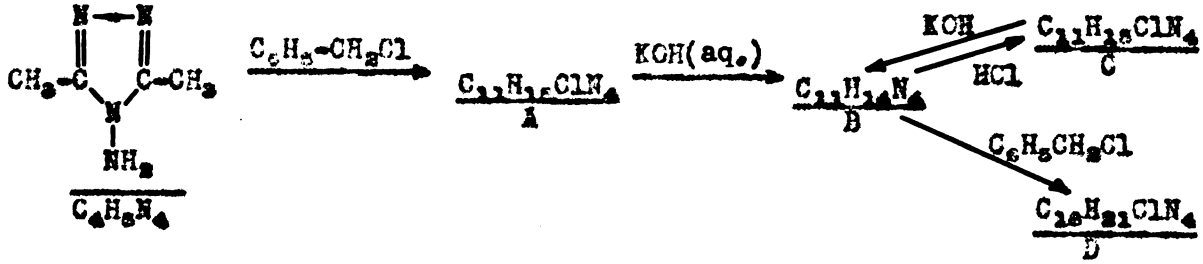
Approved Robert M. Herbst

ABSTRACT

Since the reaction of 1-alkyl-5-aminotetrazoles with alkyl halides and alkyl benzenesulfonates had been shown to lead to 1,4-dialkyl-5-iminotetrazolines (1,2) a study of the alkylation of 4-amino-1,2,4-triazoles was undertaken.

When 3,5-dimethyl-4-amino-1,2,4-triazole was treated with benzyl-chloride a product resulted which appeared to be a quaternary chloride. This quaternary chloride when treated with potassium hydroxide gave an amine base which would form a hydrochloride isomeric with the quaternary chloride. Treatment of the base obtained from the quaternary chloride leads to a second quaternary chloride. The reactions described above may be summarized by the following scheme:



When 3,5-diphenyl-4-amino-1,2,4-triazole was treated with benzyl chloride a quaternary chloride was obtained that appeared to be similar in nature to the chloride obtained from 3,5-dimethyl-4-amino-1,2,4-triazole and benzyl chloride. Treatment of the diphenyl quaternary chloride with base gave an oil from which a pure product could not be isolated.

Methylation of 3,5-dimethyl-4-amino-1,2,4-triazole and 3,5-diphenyl-4-amino-1,2,4-triazole with methyl benzenesulfonate was attempted; however, the products which were obtained were not characterized.

During the course of this investigation a sensitivity to one or more of the compounds being handled forced a cessation of further work with 4-amino-1,2,4-triazoles.

Because of this sensitivity, the direction of the problem was altered to include the aralkylation of 1-cycloalkyl-5-aminotetrazoles with the intention of preparing potentially microbiologically active, 1-cycloalkyl-4-aralkyl-5-iminotetrazoline hydrochlorides.

A series of 1-cycloalkyl-4-aralkyl-5-iminotetrazoline hydrochlorides was prepared by treatment of 1-cyclohexyl- and 1-cyclohexylmethyl-5-aminotetrazole with benzyl chloride, p-chlorobenzyl chloride, o-chlorobenzyl chloride, 2,4-dichlorobenzyl chloride, 3,4-dichlorobenzyl chloride, p-nitrobenzyl chloride, m-nitrobenzyl chloride, beta-phenylethyl bromide and gamma-phenylpropyl bromide. These compounds were characterized by formation of phenylthioureas by reaction of the free base with phenyl isothiocyanate and, in some instances, by the isolation of the free iminotetrazoline as a crystalline solid. The structure of the compounds was established by the analogy of the method of preparation with that described for the preparation of compounds of known structure and by comparison of their infra-red spectra with spectra of similar compounds of known structure (2).

References Cited

(1) R. A. Henry, W. G. Finnegan and E. Lieber, J. Am. Chem. Soc., 76, 2894 (1954).

(2) D. F. Percival, "Alkylated 5-aminotetrazoles, Their Preparation and Properties," Ph. D. Thesis, Michigan State College, 1955.

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FOREWORD

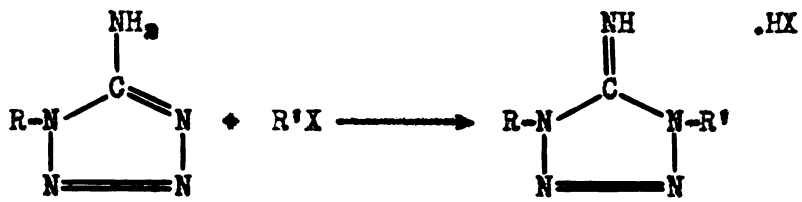
The original intent of this work was to study the alkylation of 4-amino-1,2,4-triazoles, however, during the course of this investigation the author developed a sensitivity to one or more of the compounds being used. This sensitivity manifested itself in the form of skin eruptions and made further work on this problem impossible. Part I of this thesis is concerned with the results of the investigation obtained up to the time of the development of the sensitivity.

Since work on 4-amino-1,2,4-triazoles was impossible, the object of the problem was changed to include a study of the alkylation of 1-cycloalkyl-5-aminotetrazoles with benzyl chloride, ring substituted benzyl chlorides, beta-phenylethyl bromide and gamma-phenylpropyl bromide. The results of this investigation are contained in Part II of this thesis.

PART I

INTRODUCTION

Recent studies of the structure of the products resulting from the alkylation of 1-alkyl-5-aminotetrazoles with alkyl halides and alkyl benzenesulfonates (1,2) have shown that alkylation of a nitrogen atom of the tetrazole ring occurs in preference to the expected alkylation of the amino nitrogen.



A report on the methylation of 2-methyl-5-aminotetrazole has been made (3) in which the authors showed that the product was not 2-methyl-5-methylaminotetrazole and proposed that the product was a meso-ionic compound 1,3-dimethyl-5-iminotetrazole. In view of these findings a study of the alkylation of other amino substituted heterocyclic systems in which the heterocyclic ring contains nitrogen would be of interest.

The preparation of 4-amino-1,2,4-triazoles which have a substituent on the amino group, has been accomplished only in the case of 3,5-diphenyl-4-phenylamino-1,2,4-triazole and compounds of this type with a substituent in the benzene ring of the phenyl group (4,5,6). The synthesis was accomplished by heating a mixture of dibenzhydrazidyl dichloride ($C_6H_5CCl{=}N{-}N{=}CClC_6H_5$) with phenylhydrazine. This method of synthesis does not appear to be readily applicable to the

preparation of 4-alkylamino-1,2,4-triazoles with alkyl groups in the three and five positions. Thus an investigation into the possibility of the introduction of an alkyl substituent onto the amino group of 4-amino-1,2,4-triazoles also appears to be attractive.

Studies of the alkylation of 4-amino-1,2,4-triazoles have been reported in only two instances. Ruhemann et al. (7,8) had treated 4-amino-1,2,4-triazole and 3,5-dimethyl-4-amino-1,2,4-triazole with methyl iodide and obtained products which they described as methiodides but did not further characterize. At the time of their studies, 4-amino-1,2,4-triazoles were thought to be dihydro-1,2,4,5-tetrazines so that most of their conclusions were of little value.

The purpose of this work is to investigate the alkylation of 4-amino-1,2,4-triazoles. In addition to those reasons already stated, 4-amino-1,2,4-triazoles were selected for study because they are relatively easy to prepare (9) and are usually quite stable compounds. Both the methylation and benzylation of 3,5-dimethyl- and 3,5-diphenyl-4-aminotriazole are described in this work. Development of a sensitivity to the compounds handled during the course of this work halted the investigation before the objective had been reached; however, some conclusions as to the nature of this alkylation could be realized from the work that had been done.

DISCUSSION

When a mixture of 3,5-dimethyl-4-amino-1,2,4-triazole and benzyl chloride was heated at about 125°C. an exothermic reaction began which first caused the formation of a homogeneous melt then solidification of the melt. Purification of this benzylation product by recrystallization gave a somewhat hygroscopic white crystalline compound. This product was very soluble in water and in hot alcohol but insoluble in other common organic solvents. Elemental analysis indicated that monobenzylation had occurred to give a product with an empirical formula of $C_{11}H_{15}ClN_4$ which, for discussion purposes, has been designated compound A.

The dissolution of compound A in 2N aqueous potassium hydroxide gave a yellow solution which upon heating on a steam bath for about one hour gave a yellow oil. Upon cooling the oil solidified to a mass of yellow crystals that, after purification by recrystallization, gave a colorless crystalline product melting at 153-154°C. The same product was obtained if the basic solution was allowed to stand for one day at room temperature. This product was soluble in chloroform, hot water and hot alcohol. Elemental analysis showed that the product had an empirical formula of $C_{11}H_{14}N_4$ and that it differed from compound A by loss of the elements of hydrogen chloride. This product has been designated compound B.

Treatment of an alcoholic solution of compound B with hydrochloric acid caused the formation of a solid material which melted at 228-229°C.

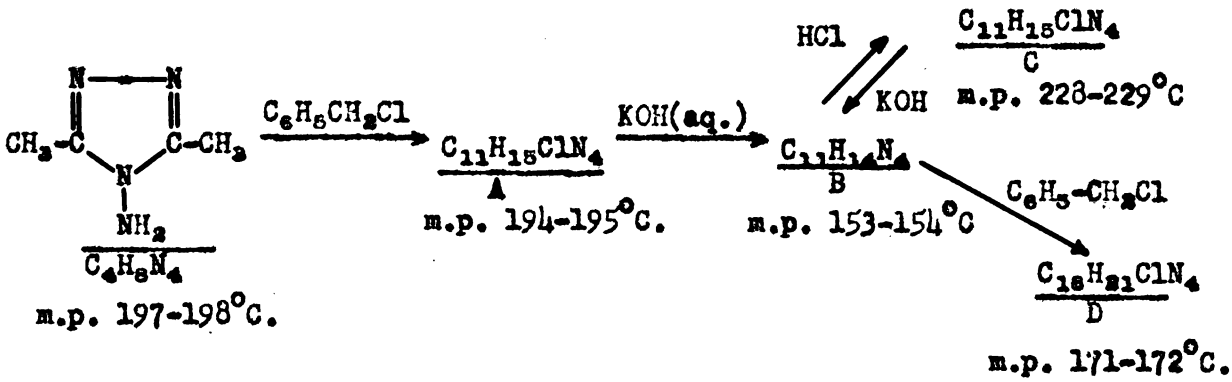
This product was soluble in water and hot alcohol but insoluble in other common organic solvents. The product, designated compound C, has an empirical formula $C_{11}H_{15}ClN_4$ as shown from elemental analysis. Thus the formula corresponds to the addition of hydrogen chloride to compound B and shows that compound C is isomeric with compound A.

Addition of base to a solution of compound C in water caused the immediate formation of a powdery precipitate of compound B. This behavior indicated that compound C is actually the hydrochloride of compound B.

When compound B was mixed with benzyl chloride and heated to about 125°C. an exothermic reaction took place. At the beginning of the reaction a homogeneous melt developed but as the reaction proceeded the melt slowly solidified. After purification by recrystallization a very hygroscopic colorless solid was obtained which melted at 171-172°C. The material was very soluble in water and alcohol but quite insoluble in other organic solvents. From the results of an elemental analysis it was deduced that the compound resulted from the introduction of a second benzyl group into compound B and that the compound had an empirical formula of $C_{18}H_{21}ClN_4$. This compound has been designated compound D.

Treatment of compound D with aqueous potassium hydroxide gave a yellow solution. After heating the solution on a steam bath for one hour an orange oil separated. The oil did not crystallize and did not appear to be soluble in aqueous hydrochloric acid. Development of a sensitivity forced a halt to further attempts to purify and characterize this product.

The benzylation of 3,5-dimethyl-4-amino-1,2,4-triazole and the subsequent reactions of this product may be illustrated by the following scheme:



Heating a mixture of 3,5-diphenyl-4-amino-1,2,4-triazole and benzyl chloride to about 125°C. initiated an exothermic reaction. From this reaction a colorless solid material was isolated that decomposed when heated to 202-204°C. Analysis of this product indicated that monobenzylation had occurred.

Treatment of the diphenyl monobenzylation product with aqueous potassium hydroxide gave a yellow solution. After heating the solution on a steam bath for about one hour a red oil had separated. When attempts were made to purify this product only tarry material was obtained.

The benzylation of 3,5-diphenyl-4-amino-1,2,4-triazole appears to produce a compound analogous to compound A. In the treatment of the benzylation product with base the reaction appears to be similar to the reaction of the monobenzylated 3,5-dimethyl compound with base, at least in the first stages, in that a yellow solution, which produces

an oily product upon heating or after a long period at room temperature, forms in both cases. The difficulty encountered in isolating a pure product could then occur either because of the instability of the diphenyl product or because the reaction took a different course during a later stage.

Methylation of 3,5-dimethyl- and 3,5-diphenyl-4-amino-1,2,4-triazole by heating with methyl benzenesulfonate led to an exothermic reaction as in the benzylation. With 3,5-dimethyl-4-amino-1,2,4-triazole a crystalline product was isolated which exhibited the correct analysis for a benzenesulfonic acid salt of a methylated 3,5-dimethyl-4-amino-1,2,4-triazole. With 3,5-diphenyl-4-amino-1,2,4-triazole, however, only a glassy material that would not crystallize could be isolated.

Heating methylated 3,5-dimethyl-4-amino-1,2,4-triazole with 2N potassium hydroxide did not appear to cause any reaction but when the base strength was increased to 4N a yellow color developed and a small amount of precipitate formed. The behavior of the precipitate upon heating indicated that it might be an organic salt.

With the hope of synthesizing an authentic sample of 3,5-dimethyl-4-dimethylamino-1,2,4-triazole, 3,5-dimethyl-4-amino-1,2,4-triazole was treated with a mixture of formic acid and formaldehyde according to the Eschweiler-Clarke procedure (10). The product obtained from this treatment could not be crystallized either as a free base or as a hydrochloride. Although this method of reductive alkylation is generally applicable to the preparation of dimethylated amines, it has been reported to be unsuccessful in instances where the amino group is

influenced by a strongly electronegative group (10) or where the amine reacts with formaldehyde to give an unreactive condensation product (11).

The infra-red absorption spectra of 3,5-dimethyl-4-amino-1,2,4-triazole, compound A, compound B, compound C and compound D were obtained in order to aid in the characterization of these compounds. Inspection of these spectra, shown in Figure 1, reveals appreciable differences in the location of the bands exhibited by these compounds. Although these differences may be indicative of profound structural differences, it must be recalled that three of the compounds probably involve ionic structures which could cause spectral differences while still retaining considerable structural similarity. Examination of the individual spectra, however, allows some conclusions to be drawn as to the nature of the structures of the compounds.

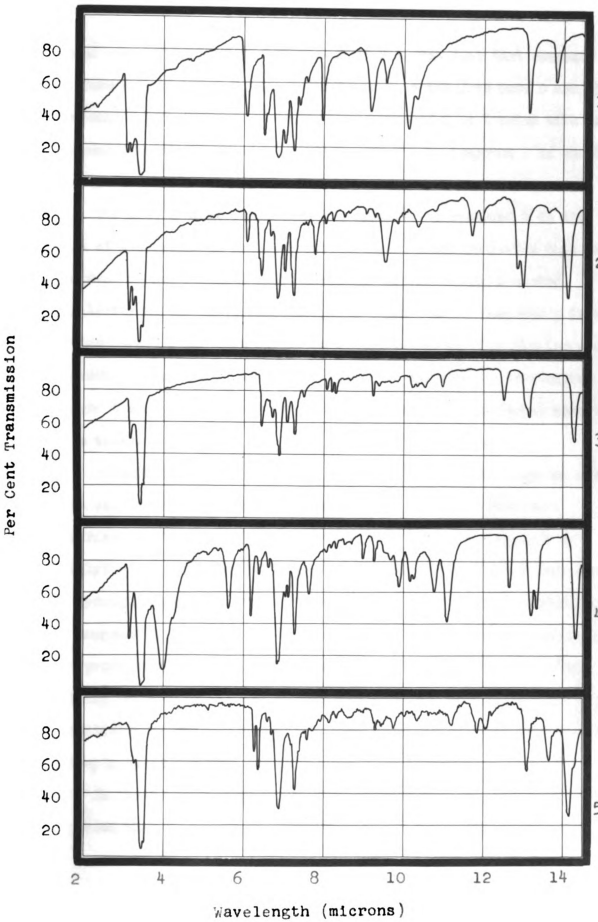
The spectrum of compound A shows two notable features which give some insight as to the structure of this compound. Absorption bands at 3.16, 3.26 and 6.08 μ may be attributed to the presence of a primary amine function (12) while the absence of any absorption at 3.75-4.0 μ indicates the absence of an amine hydrochloride structure (13). Thus, one may conclude that compound A is probably a quaternary chloride and not a hydrochloride.

Compound B shows a single absorption band at 3.16 μ and no absorption near 6.1 μ, indicating that it has a secondary amine function and not a primary amino group.

The strong absorption bands at 4.0 μ and at 5.61 μ exhibited in the spectrum of compound C clearly demonstrate that compound C is an

Figure 1. Infra-red Spectra

1. 3,5-Dimethyl-4-amino-1,2,4-triazole
2. Compound A
3. Compound B
4. Compound C
5. Compound D


Per Cent Transmission
80
60
40
20
1
2
3
4
5
2
4
6
8
10
12
14
Wavelength (microns)

amine hydrochloride (13). This coupled with the fact that compound C is formed by addition of hydrochloric acid to the free base B and that compound B is rapidly regenerated when compound C is treated with cold aqueous potassium hydroxide solution, shows that compound C is simply the hydrochloride of compound B.

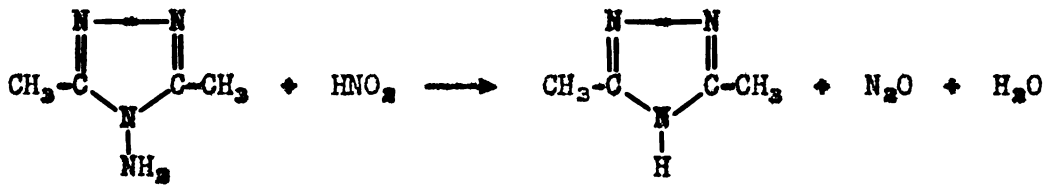
The most notable feature of the spectrum of compound D is its lack of absorption in the four micron region which indicates that this compound is not an amine hydrochloride. There is also a marked similarity in the spectrum of compound D and that of compound A in the region beyond 8 μ. This may be taken as indicative of a similar ring structure since the region of the infra-red spectrum at wavelengths longer than 8 μ is associated with vibrations of the skeletal structure as a whole.

Attempts were made to remove the benzyl group from compound A and from compound B by catalytic hydrogenolysis using the procedure described by Birkhofer (14). Compound B resisted all attempts at catalytic debenzylation while compound A took up the theoretical amount of hydrogen in six hours under the same conditions. The debenzylation of compound A gave a strong odor of toluene in the reaction bottle but the product isolated from the reaction mixture did not give a sharp melting point after several recrystallizations. The development of a sensitivity to the compounds handled in this work halted further attempts to purify this material.

In the 5-aminotetrazole series Garbrecht and Herbst (15,16) have reported that a benzyl group attached to the one position of the

tetrazole ring can be removed in a few hours by catalytic hydrogenolysis according to the procedure given by Birkhofer while a benzyl group attached to the amino group can be removed only after long treatment, if at all. This behavior may be analogous to the situation with compound A and compound B in that the benzyl group may be attached to a heterocyclic ring nitrogen atom in compound A and attached to an amino group nitrogen atom in compound B, thus accounting for the relatively easy removal of the benzyl group from compound A and the lack of reactivity of compound B.

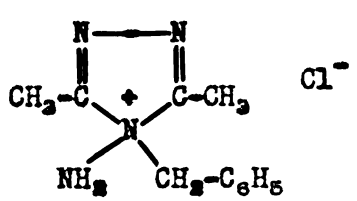
Treatment of 4-amino-1,2,4-triazoles with nitrous acid has been reported to remove the amino group with the resulting formation of a 1,2,4-triazole and nitrous oxide according to the following reaction scheme (17,18,19,20):



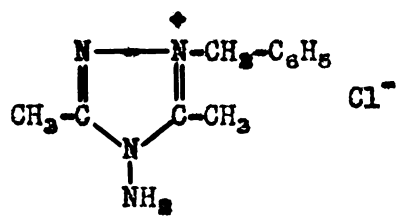
In the hope of obtaining a similar reaction at the primary amino group, compound A was treated with nitrous acid. A vigorous evolution of a colorless gas occurred but in an attempt to isolate the organic product only an oil that darkened upon heating was obtained. Attempts to purify the product were halted because of the development of a sensitivity to some of these compounds. Treatment of compound B with nitrous acid in a like manner resulted in the formation of a blue color but no gas evolution was observed.

It was thought that the reaction of compound A with nitrous acid might establish the structure of compound A, since if the benzyl group of compound A were located on a nitrogen atom of a 1,2,4-triazole ring the product of this reaction should be 3,5-dimethyl-1,2,4-triazole with a benzyl substituent in either the one or four position. The reaction does serve as a qualitative test for a primary, secondary, or tertiary amino group since a primary amino group would evolve nitrous oxide, a secondary amino group should form a N-nitroso derivative that would be colored, while a tertiary amino group would not react with nitrous acid. As a qualitative test the reaction shows that compound A has a primary amino group and that compound B has a secondary amino group.

From the reactions and infra-spectrum of compound A one may conclude that the material is a quaternary chloride with a primary amino group and probably contains a benzyl group attached to a nitrogen atom of a heterocyclic ring. These facts may be explained by structures of the type I and II.



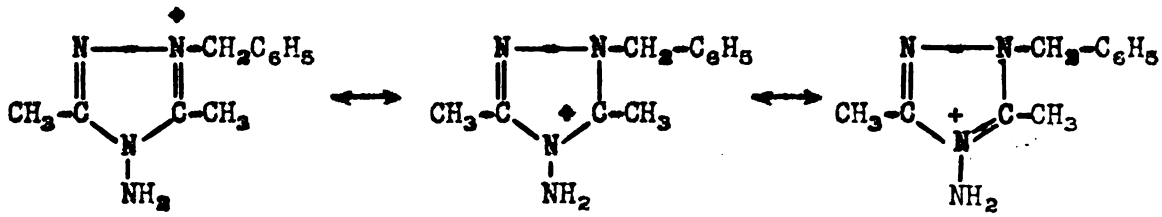
I



II

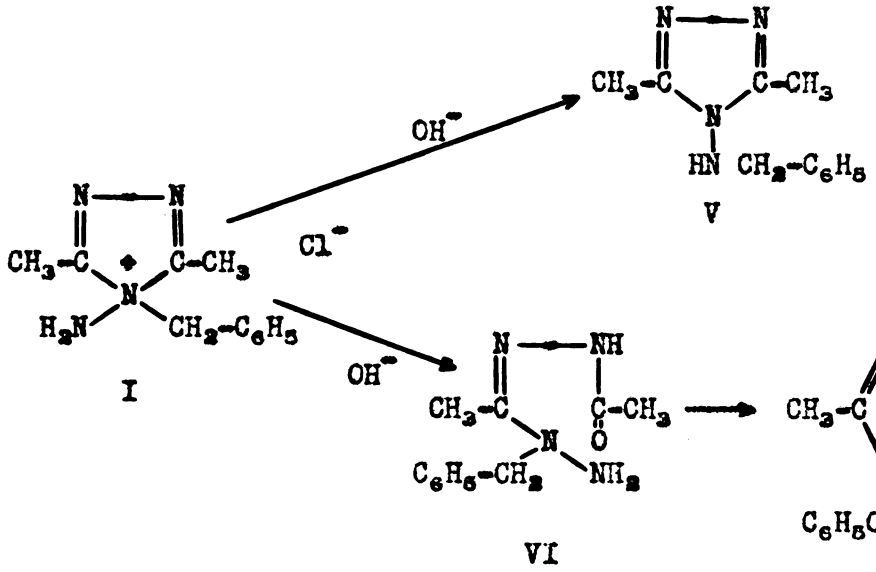
A compound of the type shown in I, arising from benzylation of the 4-position of the triazole ring, presents a situation similar to that arising when unsym. disubstituted hydrazines are treated with an alkylating agent to give a hydrazinium salt. In the benzylation of

N-benzyl-N-phenylhydrazine with benzyl chloride N,N-dibenzyl-N-phenylhydrazinium chloride has been shown to arise (21). A structure of the type shown in II, arising from benzylation of the 1-position of the triazole ring, would be expected to be stabilized by virture of the hybrid arising from resonance contributions of forms, II, III and IV, of the cations.



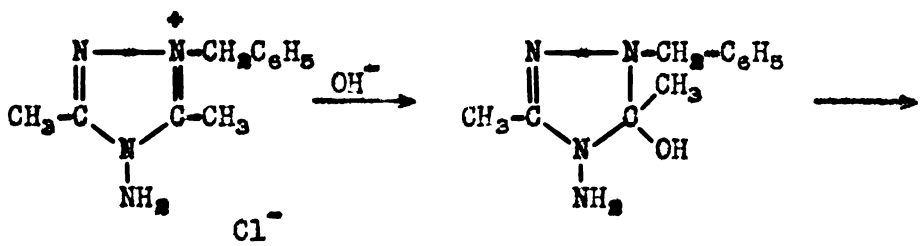
II III IV

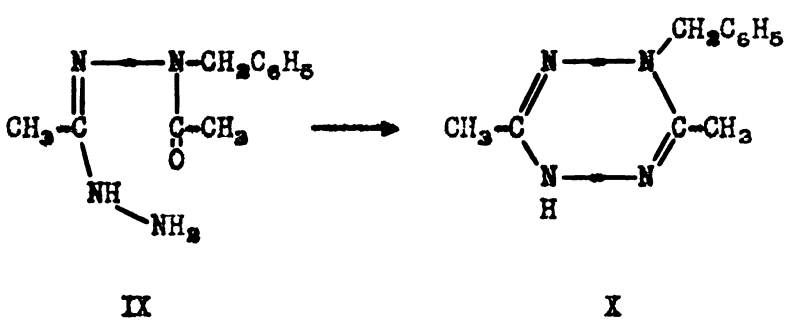
The infra-red spectrum and properties of compound B indicate that this material is a heterocyclic compound with a secondary amine function. From a consideration of the reactions which structures of the type I and II are likely to undergo upon treatment with base, two structures for compound B can be visualized as arising from the reactions illustrated in the following schemes:



1a

1b



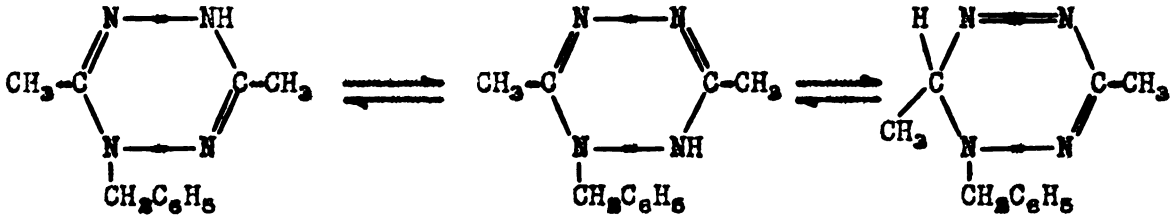


2

In scheme 1a the product would be 3,5-dimethyl-4-benzylamino-1,2,4-triazole and could result from the migration of the benzyl group in a manner somewhat similar to that of a Stevens rearrangement or from elimination of the benzyl group as a benzyl carbonium ion followed by

attack of the amino nitrogen by the benzyl carbonium ion. This product would also serve to explain the difficulty encountered in attempts to remove the benzyl group by hydrogenolysis.

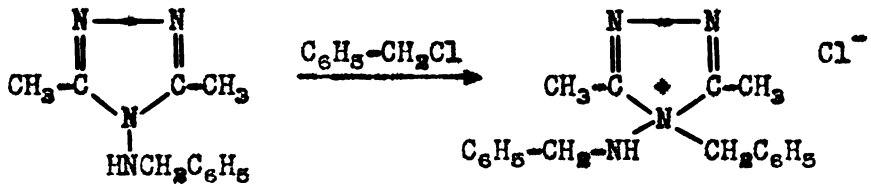
Either scheme 1b or scheme 2 would lead to the same product 1-benzyl-3,6-dimethyl-1,4-dihydro-1,2,4,5-tetrazine which could be in tautomeric equilibrium with other dihydro-1,2,4,5-tetrazine structures



X XI XII

In scheme 1b compound A is converted by base into the hydrazidine VI which could then cyclize as shown, while in scheme 2 the hydrazidine IX, which could arise from a pseudo base such as VIII, is cyclized to give the same product as that resulting from scheme 1b.

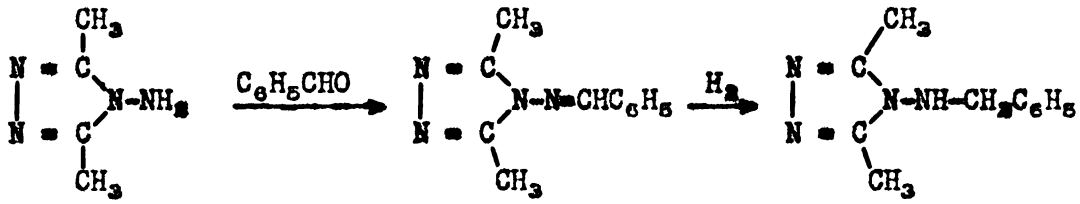
Of the two products which would result from the above schemes 3,5-dimethyl-4-benzylamino-1,2,4-triazole seems more probable since compound B is a colorless solid that is stable towards heat while the dihydro-1,2,4,5-tetrazines are reported to be yellow solids that rearrange to 4-amino-1,2,4-triazoles upon heating (22). The behavior of compound D could also be explained since the benzylation of 3,5-dimethyl-4-benzylamino-1,2,4-triazole might be expected to give a product similar to compound A.



V XIII

This would lead to a quaternary chloride and would account for the similarities in the spectra of compound A and compound D.

Since 4-amino-1,2,4-triazoles have been reported to condense with aldehydes and ketones to give a hydrazone-like product (23,24), it was felt that this might offer an opportunity to synthesize 3,5-dimethyl-4-benzylamino-1,2,4-triazole through catalytic hydrogenation of the condensation product of benzaldehyde and 3,5-dimethyl-4-amino-1,2,4-triazole.



When benzaldehyde and 3,5-dimethyl-4-amino-1,2,4-triazole were heated together a yellow oil was the only product isolated. Condensation of anisaldehyde with 3,5-dimethyl-4-amino-1,2,4-triazole also gave a yellow oil, but salicylaldehyde and 3,5-dimethyl-4-amino-1,2,4-triazole condensed to produce a small amount of a crystalline product. Hydrogenation of the benzaldehyde condensation product resulted in a rapid initial uptake of hydrogen which quickly slowed but did not stop after 1 mole of hydrogen had been taken up. Stopping the reaction

after absorption of various percentages of the calculated hydrogen uptake gave only an unstable oil and some 3,5-dimethyl-4-amino-1,2,4-triazole.

The condensation of benzaldehyde with 3,5-diphenyl-4-amino-1,2,4-triazole gave an oily product; however, 4-amino-1,2,4-triazole and benzaldehyde condensed rapidly to give a solid product. When the condensation product of benzaldehyde and 4-amino-1,2,4-triazole was subjected to the same hydrogenation conditions as the condensation product of benzaldehyde and 3,5-dimethyl-4-amino-1,2,4-triazole no reaction occurred. Increasing the temperature and amount of catalyst also failed to induce a reaction.

EXPERIMENTAL

Preparation of 3,5-Disubstituted 4-Amino-1,2,4-Triazoles

The preparation of 3,5-dimethyl-4-amino-1,2,4-triazole and 3,5-diphenyl-4-amino-1,2,4-triazole was accomplished by the method reported by Garrison and Herbst (9). Interaction of dibenzoyl hydrazine and hydrazine gave the diphenyl compound while the dimethyl compound was synthesized from acetic acid and hydrazine.

3,5-Diphenyl-4-amino-1,2,4-triazole

A mixture of 24 g. (0.10 mole) of dibenzoyl hydrazine, prepared according to Hatt (25), and 11.8 g. (0.20 mole) of an 85% hydrazine hydrate solution was sealed in a Pyrex combustion tube. The tube was heated to 185°C. and maintained at that temperature for two days. After opening the tube a white solid material was obtained that gradually darkened upon standing. The contents of the tube were dissolved in boiling ethanol and digested with Norite. Filtration and cooling produced 12.7 g. (54% based on the dibenzoyl hydrazine) of lusterous white platelets of 3,5-diphenyl-4-amino-1,2,4-triazole melting at 261-262°C.

Two preparations were carried out as described above with the substitution of anhydrous hydrazine for the 85% hydrazine hydrate solution. In both instances excessive pressures were developed in the sealed tubes as noted upon opening the tubes. A very strong odor of

ammonia was also noted upon opening the tubes. The yields of 3,5-diphenyl-4-amino-1,2,4-triazole from these runs were 43% and 48%.

3,5-Dimethyl-4-amino-1,2,4-triazole

A round-bottomed flask was charged with 240 g. (4 moles) of glacial acetic acid and cooled in an ice bath. With continued cooling, 355 g. (6 moles) of an 85% hydrazine hydrate solution was added dropwise at a rate which kept the temperature of the reaction mixture below 50°C. After complete addition of the hydrazine solution the flask was fitted for distillation and slowly heated on an oil bath to 225°C. The temperature was then maintained at this level for six hours. During the heating period the course of the reaction was followed by measuring the water and hydrazine which was distilled from the reaction vessel. At the end of the heating period the flask contained a colorless liquid which crystallized upon cooling. Recrystallization of the product from isopropyl alcohol gave a crop of thick prisms. Concentration of the mother liquor to about half its former volume gave a second crop of thick prisms. The total yield of 3,5-dimethyl-4-amino-1,2,4-triazole melting at 197-198°C. was 159 g. (71% based on the acetic acid).

A small amount of 3,5-dimethyl-4-amino-1,2,4-triazole was dissolved in 25 ml. of ethanol and acidified with concentrated hydrochloric acid solution. Addition of 25 ml. of ether caused the slow formation of fine needle-like crystals. Recrystallization from 50% isopropyl ether-ethanol gave needles of 3,5-dimethyl-4-amino-1,2,4-triazole hydrochloride melting at 228-229°C. (19).

Alkylation of 3,5-Disubstituted 4-Amino-1,2,4-Triazoles

Both 3,5-diphenyl- and 3,5-dimethyl-4-amino-1,2,4-triazole were methylated and benzylated by simply heating a mixture of the 4-amino-1,2,4-triazole with benzyl chloride or methyl benzenesulfonate. An exothermic reaction occurred after which the product was purified by recrystallization.

Methylation of 3,5-diphenyl-4-amino-1,2,4-triazole

A mixture consisting of 9.44 g. (0.04 mole) of 3,5-diphenyl-4-amino-1,2,4-triazole and 7.25 g. (0.042 mole) of methyl benzenesulfonate was heated on an oil bath. When the temperature of the mixture reached about 70°C., an exothermic reaction began which raised the temperature to 120°C. and caused the formation of a homogeneous liquid. After the reaction had subsided somewhat, the mixture was maintained at 110°C. for 15 minutes. The reaction mixture was dissolved in boiling isopropyl alcohol and upon cooling a yellow viscous oil separated. Several attempts to crystallize the oily material by dissolving in hot isopropyl alcohol and subsequent cooling gave only the same viscous oil. The oil was then allowed to stand in a vacuum desiccator over phosphorus pentoxide for three weeks but at the end of that period the product had only thickened slightly. It was not examined further.

Methylation of 3,5-dimethyl-4-amino-1,2,4-triazole

A mixture of 5.60 g. (0.05 mole) of 3,5-dimethyl-4-amino-1,2,4-triazole and 8.94 g. (0.052 mole) of methyl benzenesulfonate was slowly

heated on an oil bath. As the temperature of the mixture reached 50°C. a vigorous exothermic reaction began which caused the temperature of the mixture to reach 125°C. During the course of the reaction the mixture became a homogeneous yellow liquid. After the exothermic reaction had subsided the contents of the reaction vessel were maintained at 90°C. for 15 minutes. Digestion of the material with a small amount of boiling isopropyl alcohol produced a white powdery precipitate. Recrystallization from 90% isopropyl alcohol produced a fine white precipitate. Drying the precipitate for five days in a vacuum desiccator over phosphorous pentoxide followed by eight hours drying in an oven at 130°C. gave 11.2 g. (79% yield based on 3,5-dimethyl-4-amino-1,2,4-triazole and assuming a 1:1 reaction ratio) of a product melting at 189-190°C.

Analysis: Calculated for $C_{11}H_{16}N_4O_3S$: C, 46.5%; H, 5.7%; N, 19.7%; S, 11.0%.

Found: C, 46.5%; H, 5.8%; N, 19.7%; S, 11.0%.

Benzylation of 3,5-dimethyl-4-amino-1,2,4-triazole

A mixture of 11.2 g. (0.10 mole) of 3,5-dimethyl-4-amino-1,2,4-triazole and 14.0 g. (0.11 mole) of benzyl chloride was slowly heated on an oil bath. As the temperature reached 105°C. a homogeneous melt formed and at 125°C. an exothermic reaction began which carried the temperature to 180°C. During the course of the exothermic reaction the melt gradually solidified. The product was kept at 140°C. for half an hour after the reaction mixture began to cool. The solid product was dissolved in hot isopropyl alcohol and upon cooling a fine

white precipitate formed. From a second recrystallization from isopropyl alcohol small platelets were obtained that were dried in a vacuum desiccator and in an oven at 110°C. The yield of compound A was 19.5 g. (82% based upon 3,5-dimethyl-4-amino-1,2,4-triazole and a 1:1 reaction ratio), melting at 194-195°C.

Analysis: Calculated for $C_{11}H_{18}ClN_4$: C, 55.3%; H, 6.3%; Cl, 14.9%; N, 23.5%.

Found: C, 55.9%; H, 6.3%; Cl, 14.7%; N. 23.0%.

In four repetitions of the above procedure the yield of compound A was found to range from 80% to 90%.

Reaction of Monoalkylated Products with Base

Treatment of methylated 3,5-dimethyl-4-amino-1,2,4-triazole with base

A solution containing 5.7 g. (0.02 mole) of the product of the reaction of 3,5-dimethyl-4-amino-1,2,4-triazole with methyl benzenesulfonate in 50 ml. of 2N potassium hydroxide solution was heated on a steam bath for one hour. No evidence of reaction was observed after the solution was cooled, so 5.6 g. (0.10 mole) of potassium hydroxide was dissolved in the solution and the solution again heated on a steam bath. After about 15 minutes a bright yellow color developed which gradually faded. The color had almost completely disappeared after one hour of heating, when the solution was removed and cooled. A small amount of powdery precipitate which had formed upon cooling was removed and recrystallized from isopropyl alcohol containing about 35% isopropyl ether. This product did not melt when heated to 275°C. and charred slightly when heated in a direct flame.

Treatment of benzylated 3,5-diphenyl-4-amino-1,2,4-triazole with base

A solution consisting of 7.24 g. (0.020 mole) of the product resulting from treatment of 3,5-diphenyl-4-amino-1,2,4-triazole with benzyl chloride, 1.7 g. (0.03 mole) of potassium hydroxide and 50 ml. of water was gently warmed on a steam bath. After a few minutes the solution turned bright yellow and after one hour a dark red oil had separated. The solution was then cooled and the oil extracted with chloroform. Gradual addition of isopropyl ether to the hot chloroform extracts until a faint turbidity was observed followed by slow cooling of the solution again caused separation of a red oil. The oil was separated from the solvent and heated with benzene. This treatment resulted in the formation of a black tar.

In a second reaction using the above procedure the chloroform solution of the red oil was treated with dry hydrogen chloride. A yellow-orange semi-solid material precipitated and was separated. The resulting product was extracted with dilute hydrochloric acid but neutralization of the acid extracts failed to give an unsoluble product.

Treatment of benzylated 3,5-dimethyl-4-amino-1,2,4-triazole with base

Dissolving 19.0 g. (0.08 mole) of compound A, the product of the reaction of 3,5-dimethyl-4-amino-1,2,4-triazole with benzyl chloride, in 100 ml. of 2 N potassium hydroxide solution gave a colorless solution which slowly turned yellow upon standing. Gentle heating of the solution on a steam bath for about one hour caused the formation of a white precipitate and a yellow-orange oil. Upon cooling, the oil crystallized to a mass of pale yellow crystals. If the alkaline solution was not

heated on a steam bath, but allowed to stand at room temperature for one day the same pale yellow precipitate was formed. The solid material was removed by filtration and thoroughly washed with water. Purification of the crude product by recrystallization first from water, then from isopropyl alcohol containing 20% isopropyl ether gave 13.0 g. (80% based on the assumption that the elements of hydrogen chloride were eliminated by this treatment) of fine, colorless needles melting at 153-154°C. This compound was designated compound B.

Analysis: Calculated for $C_{11}H_{14}N_4$: C, 65.3%; H, 7.0%; N, 27.7%.

Found: C, 65.6%; H, 7.1%; N, 27.8%.

A small portion of the base, compound B, was dissolved in ethanol then acidified with concentrated hydrochloric acid. Addition of a small amount of ether initiated the formation of fine needle-like crystals. Recrystallization of this product from isopropyl alcohol containing 20% isopropyl ether gave a compound, designated compound C, melting at 227-228°C.

Analysis: Calculated for $C_{11}H_{15}ClN_4$: C, 55.3%; H, 6.3%; Cl, 14.9%; N, 23.5%.

Found: C, 55.0%; H, 6.3%; Cl, 15.0%; N, 23.4%.

When a small portion of compound C was dissolved in water and made alkaline with potassium hydroxide solution, a powdery solid was obtained. Recrystallization of the solid material from water gave fine needles of the base, compound B, melting at 153-154°C. No depression in the melting point was observed when this product was mixed with an authentic sample of compound B.

Benzylation of Compound B

A mixture of 7.14 g. (0.030 mole) of the base, compound B, obtained by benzylation of 3,5-dimethyl-4-amino-1,2,4-triazole, and 5.06 g. (0.040 mole) of benzyl chloride was slowly heated on an oil bath. A homogeneous melt formed when the temperature of the reaction mixture reached 115°C. and when the temperature reached 125°C. an exothermic reaction began that raised the temperature to 145°C. The temperature of the melt was then slowly raised to 170°C. and held there for one hour. Upon cooling the melt crystallized and was dissolved in boiling isopropyl alcohol. The pale orange solution was digested with Norite and filtered thus giving an almost colorless solution. Addition of isopropyl ether until the solution contained about 50% ether initiated the growth of fine crystals. The product was removed and recrystallized from a 50% isopropyl alcohol-isopropyl ether solution giving 8.4 g. (77% based upon compound B and the assumption that the reaction ratio was 1:1) of very fine, colorless needles melting at 171-172°C. This product was designated as compound D.

Analysis: Calculated for $C_{18}H_{21}ClN_4$: C, 65.8%; H, 6.4%; Cl, 10.8%; N, 17.0%.

Found: C, 65.6%; H, 6.7%; Cl, 10.9%; N, 16.8%.

Reaction of Compound D with Base

The addition of 6.6 g. (0.020 mole) of compound D to 50 ml. of 2 N potassium hydroxide solution gave a yellow solution which slowly became turbid. Heating on a steam bath for one hour resulted in the separation

of a yellow oil. The mixture was diluted with 150 ml. of water, cooled and extracted with chloroform. Evaporation of the chloroform left an oily residue which was dissolved in isopropyl alcohol and acidified with concentrated hydrochloric acid solution. The addition of ether to the alcoholic solution did not cause the formation of any precipitate. Removal of the solvents left a dark red oil which was digested with benzene for one hour then allowed to stand, with occasional stirring, for three days. At the end of this treatment some color was observed in the benzene but the oil did not appear to have changed.

Hydrogenolysis of Benzylated Products

Attempts to remove the benzyl group from the benzylated products were carried out in the manner recommended by Birkofer (14) for catalytic debenzylation. The reaction was carried out in a low pressure apparatus using palladium as a catalyst and either alcohol or acetic acid as the solvent.

Attempted debenzylation of compound B

A Parr bottle was charged with 4.3 g. (0.02 mole) of the base obtained from the product of the reaction of 3,5-dimethyl-4-amino-1,2,4-triazole and benzyl chloride, compound B, 2.5 ml. of 12 N hydrochloric acid solution, 5 g. of 5% palladium on charcoal and 160 ml. of 90% ethanol. The contents of the flask were put under a hydrogen pressure of 45 p.s.i. and shaken for 25 hours. During the last ten hours of shaking the bottle was heated to 65°C. and held at that temperature. At the end of this period no pressure drop had been

observed (the theoretical pressure drop was 2 lbs.), so the hydrogen was released. No odor of toluene could be detected in the bottle. After removal of the catalyst and addition of 100 ml. of ether to the alcoholic solution a precipitate of the hydrochloride of compound B, compound C, was obtained. Treatment of this hydrochloride with aqueous potassium hydroxide gave the starting material, compound B.

Other attempts to debenzylate compound B were made using the procedure described above but with either ommission of the hydrochloric acid or with the use of glacial acetic acid as the solvent. In no instance was any pressure drop observed or any toluene odor detected. The only product isolated was the starting material or its hydrochloride.

A check of the activity of the 5% palladium on charcoal catalyst was made by hydrogenolysis of a 0.020 mole sample of 1-benzyl-5-acetylaminotetrazole. This compound gave the calculated pressure drop in 20 minutes and upon opening the bottle a very strong odor of toluene was detected.

Debenzylation of compound A

A Parr bottle was charged with 11.9 g. (0.050 mole) of the product of the reaction of 3,5-dimethyl-4-amino-1,2,4-triazole and benzyl chloride, compound A; 5 g. of 5% palladium on charcoal and 100 ml. of 95% ethanol. Shaking under an initial hydrogen pressure of 47.0 p.s.i. at 66°C. for six hours resulted in a pressure drop of 3.8 lbs. (calculated drop: 4.0 lbs.). Upon opening of the bottle a strong odor of toluene was detected. The solution was concentrated to about 50 ml. then acidified with concentrated hydrochloric acid. Addition of a small

amount of ether induced the formation of a powdery white precipitate. The precipitate melted over a range of 25° beginning at 190°C. and after four recrystallizations from 50% isopropyl alcohol-isopropyl ether a melting range of 216-225°C. was observed.

Condensation of 4-amino-1,2,4-triazoles with Aldehydes

The condensation of aromatic aldehydes with 4-amino-1,2,4-triazoles was conducted according to the procedures described by Ruhemann and Merriman (23) and by Bulow and Weber (24). Condensation was effected by heating equimolar amounts of the aldehyde and the 4-amino-1,2,4-triazole in an ethanolic solution containing a catalytic amount of piperidine or acetic acid.

Methylation was attempted by the reaction of 3,5-dimethyl-4-amino-1,2,4-triazole with formic acid and formaldehyde according to the Eschweiler-Clarke method (10). The reaction appeared to proceed somewhat slower than is normal and no crystalline product could be isolated.

Condensation of aromatic aldehydes with 3,5-dimethyl-4-amino-1,2,4-triazole

A mixture of about 0.2 g. of 3,5-dimethyl-4-amino-1,2,4-triazole and about 0.2 ml. of salicylaldehyde was dissolved in ethanol and 2 drops of piperidine added. The solution turned pale yellow upon gentle warming on a steam bath. After adding enough water to dilute to 50% ethanol the solution was allowed to stand for one day. At the end of this time a feathery white precipitate had formed. The precipitate was recrystallized 50% aqueous ethanol and gave a product melting at

189-190°C. (23). Using the procedure just described with the substitution of 2 drops of acetic acid for the piperidine the same product was obtained.

Attempts were made to condense benzaldehyde and anisaldehyde with 3,5-dimethyl-4-amino-1,2,4-triazole using the above procedure, with both acetic acid and piperidine catalyst. In all instances a yellow color was observed but no crystalline product was obtained.

The use of this procedure with 3,5-diphenyl-4-amino-1,2,4-triazole and benzaldehyde also failed to give any solid product.

Condensation of benzaldehyde with 4-amino-1,2,4-triazole

A mixture of 16.8 g. (0.20 mole) of 4-amino-1,2,4-triazole and 21.2 g. (0.20 mole) of benzaldehyde was dissolved in 75 ml. of ethanol and five drops of piperidine added to the solution. The solution was heated gently on a steam bath for one hour and then cooled. A mass of fluffy white crystals had formed and this product was recrystallized from ethanol. The yield of product, previously described as N-benzylidene-4-amino-1,2,4-triazole (23), melting at 171-172°C. was 26.7 g. (78%).

Reaction of 3,5-dimethyl-4-amino-1,2,4-triazole with formic acid-formaldehyde

To 22.4 g. (0.2 mole) of 3,5-dimethyl-4-amino-1,2,4-triazole, 51.0 g. (1 mole) of 90% formic acid was slowly added with cooling. After addition of 37.6 g. (0.44 mole) of a 35% aqueous formaldehyde solution the mixture was heated on a steam bath for 30 hours. During the early part of the heating period evolution of a gas was observed but as heating was continued the evolution became unnoticeable. At the

end of the heating period 100 ml. of 3 N hydrochloric acid was added to the reaction mixture and heating continued for five hours. Evaporation of the excess liquids under reduced pressure gave a yellow viscous oil. The oil was readily taken up in isopropyl alcohol but addition of ether caused the separation of the oil. After standing under benzene for several days the oil appeared to be unchanged.

Hydrogenation of Benzaldehyde-4-Amino-1,2,4-Triazole Mixtures

A mixture of benzaldehyde and 3,5-dimethyl-4-amino-1,2,4-triazole, which had been heated together, was subjected to hydrogenation using platinum oxide catalyst. The mixture took up hydrogen but the reaction did not appear to involve a one mole addition. The only products isolated were starting material and unstable oils.

Hydrogenation of benzaldehyde-3,5-dimethyl-4-amino-1,2,4-triazole

A mixture of 5.6 g. (0.05 mole) of 3,5-dimethyl-4-amino-1,2,4-triazole and 5.3 g. (0.050 mole) of benzaldehyde was heated together on a steam bath until a thick oil had been produced. This product was transferred to a Parr bottle along with 100 ml. of 95% ethanol and 0.2 g. of platinum oxide. The bottle was put under a hydrogen pressure of 47.5 p.s.i. and shaking begun. After 30 minutes a drop of 2.0 lbs. had occurred (4.0 lbs. theoretical), after seven hours a 4.0 lb. drop was observed and after eleven hours a five lb. drop was noted. The bottle was opened at this time and no odor of ammonia or toluene noted. Removal of the catalyst and evaporation of most of the ethanol under

reduced pressure gave a yellow oil. The oil was taken up in chloroform and was regenerated by evaporation of the chloroform. During these steps the oil darkened considerably until a very dark red tar was left.

In other runs using the same technique as above the reaction was stopped after various percentages of the theoretical hydrogen drop had occurred. When the reaction was stopped before 125% of the theoretical drop had been observed a red oil similar to that described above was obtained along with various amounts of starting material. The per cent of starting material isolated after various percentages of the theoretical pressure drop may be summarized as follows: 60% drop--95% of the starting material, 75% drop--50% of the starting material, 100% drop--15% of the starting material.

Attempted hydrogenation of the benzaldehyde 4-amino-1,2,4-triazole condensation product

A Parr bottle was charged with 17.2 g. (0.10 mole) of the condensation product of benzaldehyde with 4-amino-1,2,4-triazole, 150 ml. of ethanol and 0.2 g. of platinum oxide. The bottle was put under an initial hydrogen pressure of 47.2 p.s.i. and shaken for 15 hours. During this time the temperature was held at 66°C. and after five hours, shaking was stopped and an additional 0.2 g. of platinum oxide added to the mixture. No pressure drop was observed during this 15 hour treatment. The bottle was opened and the contents filtered while hot. Cooling the filtrate gave a crop of fluffy white crystals of the starting material melting at 170-171°C. Concentration of the filtrate

to about 50 ml. gave a second crop of starting material. The total amount of starting material isolated was 15.9 g. (96% of the original starting material).

Reaction of Nitrous Acid with 3,5-Dimethyl-4-amino-1,2,4-triazole and Its Benzylation Products

Reaction of 3,5-dimethyl-4-amino-1,2,4-triazole with nitrous acid

A solution of 7.4 g. (0.050 mole) of 3,5-dimethyl-4-amino-1,2,4-triazole hydrochloride dissolved in 50 ml. of water was cooled in an ice bath. A solution of 3.8 g. (0.055 mole) of sodium nitrite in about 15 ml. of water was then slowly added to the cold triazole solution. A vigorous evolution of a colorless gas occurred upon mixing the two solutions. After complete addition of the sodium nitrite the resulting mixture was allowed to come to room temperature, then slowly warmed on a steam bath. Evaporation of the liquid under reduced pressure left a residue of white crystals. By heating on a steam bath under reduced pressure 3.9 g. of 3,5-dimethyl-1,2,4-triazole melting at 140-141°C. (19) was collected by sublimation (81% yield based on 3,5-dimethyl-4-amino-1,2,4-triazole).

Reaction of Compound A with nitrous acid

A solution of 5.95 g. (0.025 mole) of the product of the reaction of 3,5-dimethyl-4-amino-1,2,4-triazole with benzyl chloride, compound A, and 2.5 ml. of 12 N hydrochloric acid (0.03 moles) in 2.5 ml. of water was cooled in an ice bath. Addition, in small portions, of a solution containing 1.9 g. (0.0275 mole) of sodium nitrite dissolved in 10 ml. of

water produced a vigorous evolution of a colorless gas. The reaction mixture was allowed to come to room temperature then gently warmed on a steam bath for half an hour. At this point the solution had taken on a pale yellow color. The solution was cooled and 1.9 g. (0.034 mole) of potassium hydroxide was added. A yellow oil separated and was extracted with chloroform. Bubbling hydrogen chloride through the chloroform extracts resulted in the formation of a brown-orange precipitate. The solid was removed by filtration and dissolved in ethanol. Addition of ether gave only a dark yellow oil.

Reaction of compound C with nitrous acid

A small sample of compound C dissolved in water and cooled in an ice bath was treated with a sodium nitrite solution. No evolution of gas was detected and the solution turned blue. Standing for several hours at room temperature caused the precipitation of a dark blue solid material.

Infra-red Absorption Spectra

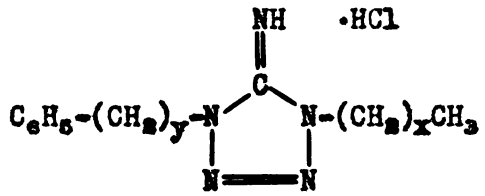
The infra-red absorption spectra of 3,5-dimethyl-4-amino-1,2,4-triazole, compound A, compound B, compound C and compound D were obtained using a Perkin-Elmer Doublebeam Recording Spectrophotometer, Model 21. All samples were run as oil mulls. The spectra are reproduced in Figure 1 on page 8.

PART II

INTRODUCTION

Recently interest in ring substituted iminotetrazolines has developed due to their microbiological activity. A study by Reutner, Peters and Elslager (26) has revealed that many iminotetrazoline hydrochlorides were active against a rather wide range of bacteria as well as several cultures of fungi and protozoa. A detailed report of the effect of structure on the antitrichomonal activity was also presented in this paper.

A series of 1-alkyl-4-aralkyl-5-iminotetrazoline hydrochlorides of the type shown in I were tested *in vitro* against *Trichomonas foetus* by Reutner *et al.*



I

It was found that trichomonacidal activity reached a maximum when y = 1 and x = 7, that is, when one substituent was benzyl and the other substituent n-octyl. Further tests revealed that substituents in the phenyl ring of the benzyl group had an effect on the activity, with a maximum being reached when a *para* chloro substituent was present in the phenyl ring. Thus the greatest activity of all the compounds tested was found in 1-n-octyl-4-p-chlorobenzyl-5-iminotetrazoline hydrochloride. Since these results show that the activity of

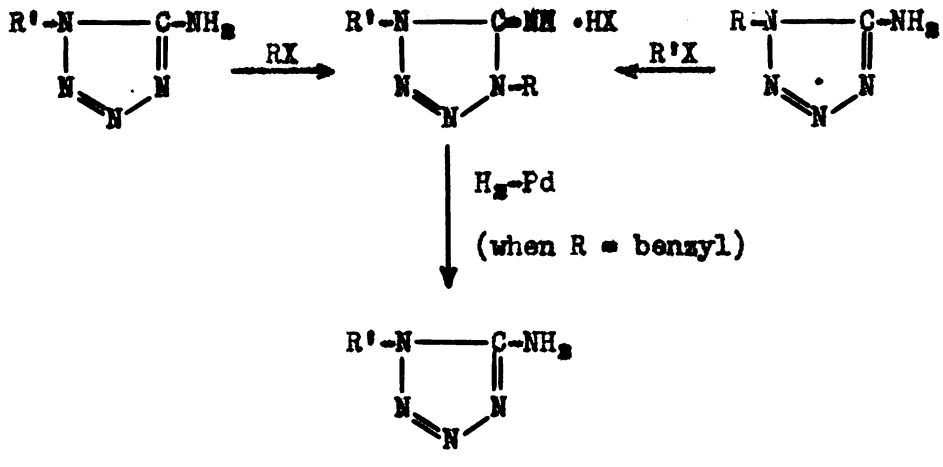
5-iminotetrazoline hydrochlorides is greatly dependent upon the nature of an alkyl substituent and upon a substituted benzyl group further changes in the alkyl substituent would be of interest.

The purpose of this study is to prepare a series of 5-iminotetrazoline hydrochlorides containing a cycloalkyl group and an aralkyl substituent. In this work the cycloalkyl group is the cyclohexyl and cyclohexylmethyl group while the aralkyl substituents are the benzyl, substituted benzyl, beta-phenylethyl and gamma-phenylpropyl groups. The structure of the compounds is based on the analogy of the methods of synthesis employed with those described for the preparation of compounds of known structure and is further established by comparison of their infra-red absorption spectra with spectra of similar structures reported by Percival (27).

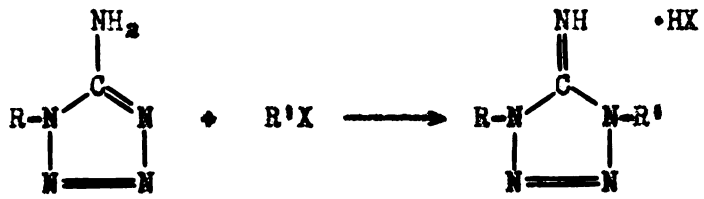
DISCUSSION

The preparation of 1,4-disubstituted 5-iminotetrazolines may be accomplished by alkylation of 1-substituted 5-aminotetrazoles with either alkyl halides or alkyl benzenesulfonates (1,2,28,29). In earlier work (28,29) the product of this reaction was thought to be 1-alkyl-5-alkylaminotetrazole. Recent investigations (1,2) have shown that the product resulting from the alkylation of a 1-alkyl-5-aminotetrazole is a 1,4-dialkyl-5-iminotetrazoline.

Percival and Herbst (1) have elucidated the structure of the alkylation products of 1-alkyl-5-aminotetrazoles in the following manner. By introduction of the group R by alkylation of 1-R'-5-aminotetrazole a product was obtained which was identical with the product obtained when the group R' was introduced by alkylation of 1-R-5-aminotetrazole.



These results could be realized only if the product of alkylation contained substituents situated in equivalent positions, that is, the 1 and 4 position of the tetrazole nucleus. Additional evidence was offered by the catalytic hydrogenolysis to remove the benzyl group from a number of 1-alkyl-4-benzyl-5-iminotetrazolines prepared either by alkylation of 1-benzyl-5-aminotetrazole or by benzylation of a 1-alkyl-5-aminotetrazole. In every instance 1-alkyl-5-aminotetrazoles were obtained from the debenzylation reaction, a result which could arise only if the substituents are located in the one and four positions of the tetrazole ring. Thus the reaction of an alkyl halide with a 1-alkyl-5-aminotetrazole may be represented by the following equation:



The 5-iminotetrazoline hydrochlorides described in this work were prepared by alkylation of 1-cyclohexyl- and 1-cyclohexylmethyl-5-aminotetrazole by the method described by Herbst (30). The groups introduced by alkylation were the benzyl, p-chlorobenzyl,o-chlorobenzyl,2,4-dichlorobenzyl, 3,4-dichlorobenzyl, p-nitrobenzyl, m-nitrobenzyl, beta-phenylethyl and gamma-phenylpropyl. Of the group of iminotetrazoline hydrochlorides prepared only 1-cyclohexyl-4-benzyl-5-iminotetrazoline hydrochloride had been described before (29). In the same paper is a

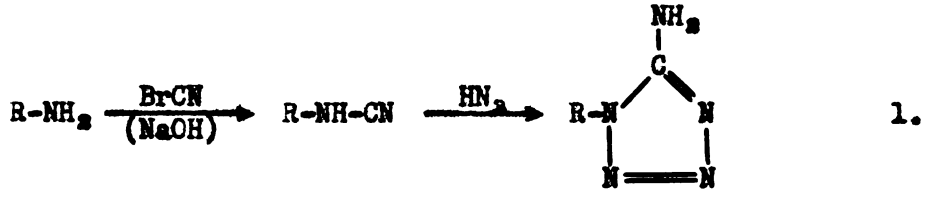
report of the preparation of 1-cyclohexyl-4-beta-phenylethyl-5-imino-tetrazoline hydrobromide.

In the preparation of the iminotetrazoline hydrochlorides the 1-alkyl-5-aminotetrazole was mixed with the appropriate alkyl halide and heated on an oil bath at 130-145°C. for three to eight hours. The use of about a 50% excess of the alkyl halide facilitated the formation of a homogeneous melt during the early part of the heating period and probably increased the yields. After the heating period excess alkyl halide was removed by steam distillation and the residual product separated from any unreacted 1-alkyl-5-aminotetrazole by conversion of the iminotetrazoline hydrochloride to the free base and removal of the free base by extraction with ether. Finally the imino-tetrazoline was again converted into the hydrochloride and further purified by recrystallization.

During the extraction of the free base with ether it was found that good separation of the iminotetrazoline was somewhat difficult to accomplish. Apparently the iminotetrazoline hydrochlorides, which are not very soluble in water, do not react very rapidly with the aqueous base to liberate the free iminotetrazoline. Besides this the free iminotetrazoline forms a very viscous oil that coats the unreacted hydrochloride thus making liberation of free base even more difficult. In order to extract the iminotetrazoline with ether the mixture must be shaken for a long period of time. Addition of a few milliliters of alcohol to the extraction mixture will make separation more rapid but this appears to increase the water content of the ether extracts.

The free bases which were liberated from the hydrochlorides were pale yellow, viscous oils in most instances. In the case of five iminotetrazolines which had cyclohexylmethyl substituents the oils could be crystallized to give low melting, colorless solids. The free bases formed hydrochlorides in either aqueous or alcoholic solutions and were readily condensed with phenyl isothiocyanate to give phenylthioureas. This behavior is in direct contrast with the properties of 1-alkyl-5-alkylaminotetrazoles (1) which do not condense with phenyl isothiocyanate.

The 1-cyclohexyl- and 1-cyclohexylmethyl-5-aminotetrazole used in this work were prepared by a method similar to that used by Garbrecht and Herbst (31) and may be represented by the following scheme:



1.

All of the steps were carried out successively in the same flask without isolation of any of the intermediate products. In carrying out the reaction, amine hydrobromide is formed in the first step along with the cyanamide but addition of an equimolar amount of sodium hydroxide allows all of the amine to be converted into the desired cyanamide. The final step in the reaction as shown in scheme 1 was carried out by addition of a sodium azide solution to the reaction mixture followed by hydrochloric acid in order to dispense with the necessity of preparing and handling separately solutions of hydrazoic acid. Presumably the reaction of hydrazoic acid with a cyanamide leads to an intermediate guanyl azide

which cyclises upon heating. This intermediate could conceivably cyclise in either of two ways to give a 1-alkyl-5-aminotetrazole or a 5-alkylaminotetrazole, however, in all instances reported the only product obtained was a 1-alkyl-5-aminotetrazole; even when the substituent groups, R, were of quite different electronegativity, such as methyl and para-nitrophenyl (31).

1-Cyclohexyl-5-aminotetrazole had been described before (29) but in order to further characterize the hitherto unknown 1-cyclohexylmethyl-5-aminotetrazole a small amount was converted into 1-cyclohexylmethyl-5-acetylaminotetrazole by heating with acetic anhydride.

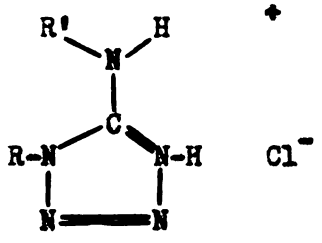
The cyclohexylmethylamine used to synthesize 1-cyclohexylmethyl-5-aminotetrazole was prepared by means of a Schmidt reaction from cyclohexylacetic acid. A solution of one mole of carboxylic acid in nine moles of sulfuric acid was employed and the hydrazoic acid was added in the form of a 17% benzene solution. Although the scale of the reaction was somewhat larger than is usually encountered (32) no serious difficulties were met with. The reaction was strongly exothermic but the temperature could easily be held below 50°C. by control of the rate of addition of the hydrazoic acid or by use of a cooling bath. In more recent applications of the Schmidt reaction on a small scale (32) solid sodium azide was added to the reaction mixture but, in the present case, the use of a benzene solution of hydrazoic acid made possible easier control of the reaction temperature. Isolation of the amine was facilitated by the formation of an insoluble amine salt, probably the acid sulfate, upon dilution of the sulfuric acid with water. Removal of

this insoluble material made the neutralisation of the large amount of sulfuric acid unnecessary in order to isolate the free amine. This procedure appears to offer a good method for the preparation of aliphatic amines in those instances where the corresponding carboxylic acid is available.

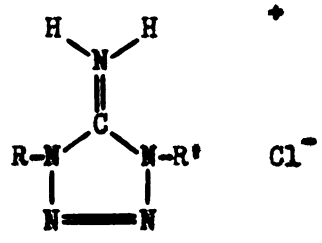
The infra-red absorption spectra of a number of the iminotetrazolines and their hydrochlorides were obtained in order to distinguish these compounds from other alkylation products which could arise. Examination of these spectra revealed several notable features. The iminotetrazoline hydrochlorides show very strong absorption at about 5.95 μ and a notable lack of absorption at 2.9 - 3.2 μ and at 3.7 - 4.4 μ; the regions usually associated with N-H vibrations and amine hydrochlorides, respectively. In the spectra of the free bases the dominant features are the absorption band at 3.0 μ and the strong band at 6.5 μ.

A study of the infra-red spectra of a series of tetrazoles consisting of 5-alkylaminotetrazoles, 5-dialkylaminotetrazoles, 1-alkyl-5-aminotetrazoles, 1-alkyl-5-alkylaminotetrazoles, 1-alkyl-5-alkylaminotetrazole hydrochlorides and 1,4-dialkyl-5-iminotetrazoline hydrochlorides by Percival (27) revealed several absorption bands which can serve to distinguish one from the others. For instance, 1-alkyl-5-alkylamino-tetrazole hydrochlorides can easily be distinguished from 1,4-dialkyl-5-iminotetrazoline hydrochlorides by the strong and rather broad absorption band at 4.0 - 4.4 μ which appears in the spectra of 1-alkyl-5-alkylaminotetrazole hydrochlorides.

The 1-cycloalkyl-4-aralkyl-5-iminotetrazoline hydrochlorides prepared in this work show spectra very similar to those of the 1,4-dialkyl-5-iminotetrazoline hydrochlorides reported by Percival (27). Their lack of absorption at 3.7 - 4.4 μ indicates that they are not 1-cycloalkyl-5-aralkylaminotetrazole hydrochlorides, even though there are many similarities to the spectra of 1-alkyl-5-alkylaminotetrazole hydrochlorides reproduced by Percival. From an inspection of possible structures of the hydrochlorides such as those shown in I and II one might expect some similarity in the infra-red absorption spectra.

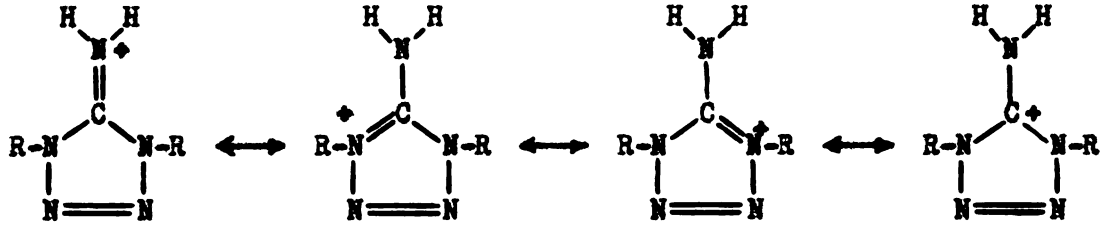


I



II

Both of these compounds would exist as resonance hybrids as a result of guanidinium ion type resonance as shown in III, IV, V and VI.

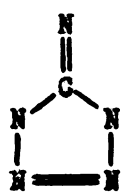


III IV V VI

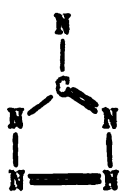
The infra-red spectra of the free 1,4-disubstituted-5-iminotetrazolines have several characteristic features which serve to distinguish

them from the 1-alkyl-5-alkylaminotetrazoles. The most prominent of these features is a strong band at 6.03 μ in the iminotetrazolines while the 1-alkyl-5-alkylaminotetrazoles exhibit no absorption at 6.03 μ but have a strong band at 6.28 μ.

Some work on the infra-red absorption spectra of a number of tetrazoles has been reported (27,33,34) and attempts made to associate certain structures with specific absorption bands. When one examines these assignments some uncertainty becomes apparent. In the studies reported by Lieber et al. (33) absorption in the six micron region shown by 5-aminotetrazole was attributed to the amino group but in the same paper absorption at 5.95 to 6.02 μ present in the spectra of guanidines was attributed to the imino group. Murphy and Picard (34) have examined the spectra of 1,4-dimethyl-5-iminotetrazole and have assigned the band at 6.0 μ to the exo-imino group. A suggestion has been made by Percival that the absorption band at 6.0 μ may be due to structures such as VII while the band often found in tetrazoles at 6.3 μ could arise from structures like VIII.



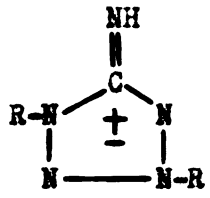
VII



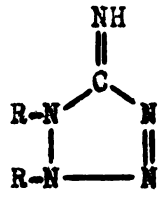
VIII

In some aminotetrazoles often written as VIII, resonance forms involving structures such as VII may be written with charge separation and thus impart imino character to the molecule. The bands at 6.0 μ and 6.3 μ may then give a measure of the relative contribution of each resonance form.

Henry, Finnegan and Lieber (2) have alkylated a series of 1-alkyl-5-aminotetrazoles and reported that the major products were 1,4-dialkyl-5-iminotetrazoline hydrochlorides, however, they reported the isolation of a small amount of a second product which they describe as a mesoionic compound, 1,3-dialkyl-5-iminotetrazole IX.



IX



X

This type of compound has been reported to result from the alkylation of 2-alkyl-5-aminotetrazoles (3). The structure assigned to the compound was based on data obtained from X-ray diffraction studies and its chemical properties; however, the chemical evidence offered could also be explained on the basis of a 1,2-dialkyl-5-iminotetrazoline X. In the alkylations conducted in this work no by-product was found in either the tetrazolines or their condensation products with phenyl isothiocyanate.

EXPERIMENTAL

Preparation of Cyclohexylmethylamine

Cyclohexylmethylamine was prepared from cyclohexylacetic acid by means of a Schmidt reaction. The procedure was devised from the data reported in studies by Oesterlein (35) and by Schuerch and Huntress (36).

A 5 l. flask was fitted with a reflux condenser, alcohol thermometer, stirrer and 500 ml. dropping funnel and set up over a cold water bath which could be elevated in order to control the temperature of the contents of the flask. The flask was charged with 213 g. (1.5 moles) of cyclohexylacetic acid (b.p. 139-140°C./17 mm.), 2500 ml. of benzene and 715 ml. (13.5 moles) of concentrated sulfuric acid. From the dropping funnel, 475 ml. of a benzene solution of hydrazoic acid containing 17.0 g. of hydrazoic acid per 100 ml. of solution (1.8 moles of hydrazoic acid) was added to the reaction mixture with vigorous stirring at a rate of about 3 ml. per minute. An exothermic reaction took place but the temperature of the reaction mixture was kept between 42° and 48°C. by adjustment of the water bath. After complete addition of the hydrazoic acid solution the reaction mixture was held between 42° and 48°C. for one hour by gentle warming on a steam bath.

The contents of the flask were cooled in an ice bath and the sulfuric acid layer separated from the benzene layer. Dropping the sulfuric acid solution into a 4 l. beaker filled with crushed ice resulted in the formation of a dense white precipitate. The precipitated amine salt was

filtered rapidly with suction, pressed as dry as possible and immediately transferred to a 4 l. beaker. After mixing the solid with 1 l. of water the mixture was made alkaline by the addition of about 600 g. of potassium hydroxide in the form of a 50% solution. This treatment caused the separation of a pale yellow amine layer which was separated from the aqueous residues by steam distillation. The amine was separated from the water of the distillate by extraction with ether and the etherial solution dried over potassium carbonate. From the ether extracts there was obtained, by distillation, 131 g. of cyclohexylmethylamine, b.p. 162-163°C. at atmospheric pressure, n_D^{25} 1.4632 (37). The yield based on cyclohexylacetic acid was 68%.

A small portion of the sulfuric acid filtrate, from which the amine salt separated, was made alkaline by the addition of 50% potassium hydroxide. Steam distillation followed by extraction of the distillate with ether failed to reveal any appreciable amount of amine.

1-Alkyl-5-Aminotetrazoles

Preparation of 1-cyclohexyl- and 1-cyclohexylmethyl-5-aminotetrazoles was accomplished by a method similar to that reported by Garbrecht and Herbst (31).

1-Cyclohexylmethyl-5-aminotetrazole

A solution of 113 g. (1 mole) of cyclohexylmethylamine in 800 ml. of ethanol was cooled to about 4°C. in an ice bath. A solution of 106 g. (1 mole) of cyanogen bromide dissolved in 400 ml. of 50% ethanol was added dropwise, with stirring, at such a rate that the temperature of

the reaction mixture remained between 8° and 10°C. With the temperature of the reaction mixture still maintained at 8° to 10°C., 40 g. (1 mole) of sodium hydroxide dissolved in 200 ml. of water was slowly added. The reaction mixture was then treated with 81 g. (1.25 moles) of sodium azide dissolved in 250 ml. of water followed by dropwise addition of 210 ml. of 6 N hydrochloric acid (1.25 moles). Addition of the hydrochloric acid was adjusted so that the temperature of the reaction did not rise above 12°C. After addition of the hydrochloric acid solution the reaction mixture was refluxed gently for three hours. At the beginning of the reflux period a white precipitate began to form and after half an hour of heating precipitation appeared to stop. The flask was cooled after refluxing and the product removed by filtration. This gave 145 g. of fluffy white needles of 1-cyclohexylmethyl-5-aminotetrazole (80% yield based on cyclohexylmethylamine) melting at 250-251°C.

Analysis.* Calculated for $C_8H_{15}N_5$: C, 53.0%; H, 8.3%; N, 38.6%.
Found: C, 52.9%; H, 8.3%; N, 38.8%.

An acetyl derivative was prepared by gently refluxing 1 g. of 1-cyclohexylmethyl-5-aminotetrazole with 2 ml. of acetic anhydride for about 15 minutes. The resulting 1-cyclohexylmethyl-5-acetylaminotetrazole was recrystallized from 50% ethanol giving a product melting at 129-130°C.

Analysis.* Calculated for $C_{10}H_{17}N_5O$: C, 53.8%; H, 7.7%; N, 31.4%.
Found: C, 53.7%; H, 7.6%; N, 31.4%.

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* Analyses were done by Micro-Tech. Laboratories, Skokie, Illinois.

Preparation of 1-cyclohexyl-5-aminotetrazole in the same manner as that used for the preparation of 1-cyclohexylmethyl-5-aminotetrazole gave a 62% yield of a product melting at 217-218°C. (29).

1,4-Disubstituted 5-Iminotetrazoline Hydrochlorides

These compounds were prepared according to the method given by Herbst (30). The appropriate 1-alkyl-5-aminotetrazole was mixed with an alkyl halide and heated on an oil bath at 130-145°C. After a short period of heating a viscous solution was formed which slowly solidified. Heating was then continued for from two to six hours after the melt had completely solidified. The crude material was dissolved in a hot alcohol-water mixture and subjected to steam distillation in order to remove unreacted alkyl halide. The residual product was made alkaline and the free iminotetrazoline extracted from the basic solution with ether. Evaporation of the ether extracts left the crude iminotetrazoline which was dissolved in aqueous alcohol and converted to the hydrochloride by the addition of hydrochloric acid. This product was then recrystallized from aqueous ethanol. Alkylating agents used were substituted benzyl chlorides, beta-phenylethyl bromide and gamma-phenylpropyl bromide. Examples of the method of preparation are given in the following preparations of 1-cyclohexyl-4-p-chlorobenzyl-5-iminotetrazoline hydrochloride and 1-cyclohexylmethyl-4-beta-phenylethyl-5-iminotetrazoline hydrochloride.

1-Cyclohexyl-4-p-chlorobenzyl-5-iminotetrazoline hydrochloride

A mixture of 8.4 g. (0.050 mole) of 1-cyclohexyl-5-aminotetrazole and 12.1 g. (0.075 mole) of p-chlorobenzyl chloride was heated on an oil bath at 140°C. After heating for about half an hour a homogeneous melt formed which slowly solidified over a period of about half an hour. Heating was continued for two hours after the melt had become completely solid. The solid material was removed by dissolving in about 200 ml. of boiling 50% aqueous ethanol. The alcoholic solution was diluted with water and subjected to steam distillation. After the distillate came over clear, the residue was made alkaline by addition of 4.0 g. (0.10 mole) of sodium hydroxide. The alkaline solution was shaken vigorously for approximately half an hour then extracted with ether. In order to remove all of the free iminotetrazoline three portions of ether were used and in each case the mixture was shaken for about 20 minutes. Evaporation of the ether extracts left a yellow oil which was taken up in 50 ml. of ethanol. A pale yellow precipitate was produced upon acidification of the solution with concentrated hydrochloric acid. An additional 50 ml. of ethanol and 100 ml. of water was added to the mixture and the precipitate dissolved by heating. Digestion with Norite, filtration and subsequent cooling produced a crop of colorless needle-like crystals. Recrystallization of this product from 50% aqueous isopropyl alcohol gave 11.6 g. (70% yield based on the aminotetrazole) of pure colorless crystals of 1-cyclohexyl-4-p-chlorobenzyl-5-iminotetrazoline hydrochloride melting at 229-230°C. with accompanying decomposition.

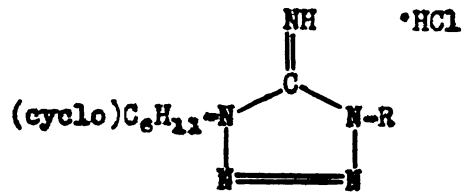
1-Cyclohexylmethyl-4-beta-phenylethyl-5-iminotetrazoline hydrochloride

A mixture of 9.1 g. (0.050 mole) of 1-cyclohexylmethyl-5-aminotetrazole and 13.9 g. (0.075 mole) of beta-phenylethyl bromide was heated in an oil bath at 145°C. The mixture gradually formed a homogeneous melt that slowly solidified over a period of about one hour. Heating was continued for six hours after the melt had completely solidified. The product was dissolved in hot 50% ethanol then diluted with water and subjected to steam distillation. When the distillate began to come over clear the residue was made basic by addition of 4.0 g. (0.10 mole) of sodium hydroxide. The alkaline solution was shaken vigorously for half an hour then extracted with three portions of ether which were also shaken for about half an hour. Upon evaporation of the ether extracts a brownish oil remained which was dissolved in 50 ml. of ethanol and converted into the hydrochloride by addition of concentrated hydrochloric acid along with 50 ml. of water. The crude hydrochloride was dissolved by heating with an additional 100 ml. of water and then digested with Norite. After filtration and cooling a fine colorless precipitate formed. A second recrystallization from 20% aqueous isopropyl alcohol gave 10.3 g. (67% based on the aminotetrazole) of 1-cyclohexylmethyl-4-beta-phenylethyl-5-iminotetrazoline hydrochloride melting at 234-235°C. with decomposition.

All of the iminotetrazoline hydrochlorides were prepared in the same manner and are listed in Tables I and II along with descriptive data. Analytical data are listed in Tables III and IV.

TABLE I

1-CYCLOHEXYL-4-ARALKYL-5-IMINOTETRAZOLINE HYDROCHLORIDES

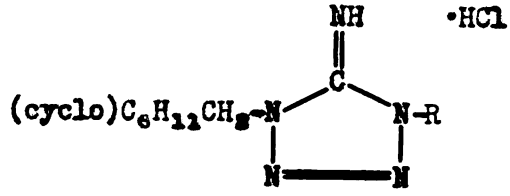


R	M.P. °C.*	Yield Percent	Recrystallised From
Benzyl	230	72	50% isopropyl alcohol
p-Chlorobenzyl	229-230	70	50% isopropyl alcohol
o-Chlorobenzyl	222-223	54	50% isopropyl alcohol
2,4-Dichlorobenzyl	235-236	49	60% isopropyl alcohol
3,4-Dichlorobenzyl	219-220	58	60% isopropyl alcohol
p-Nitrobenzyl	241-242	54	70% isopropyl alcohol
m-Nitrobenzyl	217-218	64	70% isopropyl alcohol
beta-Phenyl	220-221	53	25% isopropyl alcohol
gamma-Phenylpropyl	222-223	54	25% isopropyl alcohol

* All compounds melted with accompanying decomposition.

TABLE II

1-CYCLOHEXYLMETHYL-4-ARALKYL-5-IMINOTETRAZOLINE HYDROCHLORIDES

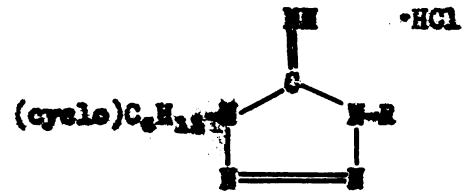


R	M.P. °C.[a]	Yield Percent	Recrystallized From
Benzyl	217-218	61	50% isopropyl alcohol
p-Chlorobenzyl	210-211	70	50% isopropyl alcohol
o-Chlorobenzyl	234-235	58	50% isopropyl alcohol
2,4-Dichlorobenzyl	220	66	60% isopropyl alcohol
3,4-Dichlorobenzyl	216	73	70% isopropyl alcohol
p-Nitrobenzyl	232	71	80% isopropyl alcohol
m-Nitrobenzyl	218-219	65	60% isopropyl alcohol
beta-Phenylethyl	234-235	67	20% isopropyl alcohol
gamma-Phenylpropyl	240-241	69	20% isopropyl alcohol

[a] All compounds melted with accompanying decomposition.

TABLE III

ANALYSIS OF 1-CYCLOHEXYL-4-ARALKYL-5-IMINOTETRAZOLINE HYDROCHLORIDES[a]

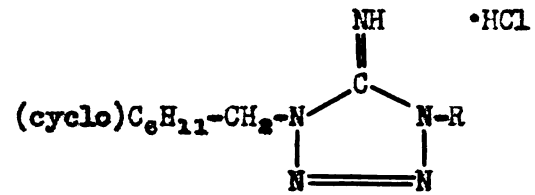


R	Formula	Percent C		Percent H		Percent Cl		Percent N	
		Calc'd	Found	Calc'd	Found	Calc'd	Found	Calc'd	Found
Benzyl	$C_{14}H_{20}ClN_5$	57.2	56.9	6.8	6.8	12.1	12.2	23.8	23.6
p-Chlorobenzyl	$C_{14}H_{19}Cl_2N_5$	51.2	51.2	5.8	6.0	21.6	21.6	21.3	21.4
o-Chlorobenzyl	$C_{14}H_{19}Cl_2N_5$	51.2	51.2	5.8	5.7	21.6	21.4	21.3	21.2
2,4-Dichlorobenzyl	$C_{14}H_{18}Cl_3N_5$	46.4	46.4	5.0	5.1	29.3	29.4	19.3	19.3
3,4-Dichlorobenzyl	$C_{14}H_{18}Cl_3N_5$	46.4	46.3	5.0	5.0	29.3	29.3	19.3	19.3
p-Nitrobenzyl	$C_{14}H_{19}ClN_6O_2$	49.6	49.8	5.6	5.7	10.5	10.3	24.8	24.8
m-Nitrobenzyl	$C_{14}H_{19}ClN_6O_2$	49.6	49.5	5.6	5.9	10.5	10.7	24.8	24.8
beta-Phenylethyl	$C_{15}H_{22}ClN_5$	58.5	58.6	7.2	7.2	11.5	11.5	22.8	23.0
gamma-Phenylpropyl	$C_{16}H_{24}ClN_5$	59.5	59.6	7.5	7.6	11.0	11.3	21.7	21.3

[a] Analyses were done by Micro-Tech Laboratories, Skokie, Illinois.

TABLE IV

ANALYSIS OF 1-CYCLOHEXYLMETHYL-4-ARALKYL-5-IMINOTETRAZOLINE HYDROCHLORIDES[a]



R	Formula	Percent C		Percent H		Percent Cl		Percent N	
		Calc'd	Found	Calc'd	Found	Calc'd	Found	Calc'd	Found
Benzyl	$C_{15}H_{22}ClN_5$	58.5	58.7	7.2	7.2	11.5	11.5	22.8	22.6
p-Chlorobenzyl	$C_{15}H_{21}Cl_2N_5$	52.6	52.8	6.2	6.2	20.7	20.7	20.5	20.6
o-Chlorobenzyl	$C_{15}H_{21}Cl_2N_5$	52.6	52.6	6.2	6.3	20.7	21.0	20.5	20.6
2,4-Dichlorobenzyl	$C_{15}H_{20}Cl_3N_5$	47.8	48.1	5.4	5.6	28.2	28.3	18.6	18.9
3,4-Dichlorobenzyl	$C_{15}H_{20}Cl_3N_5$	47.8	48.1	5.4	5.4	28.2	28.2	18.6	18.7
p-Nitrobenzyl	$C_{15}H_{21}ClN_6O_2$	51.1	51.2	6.0	5.9	10.0	10.1	23.8	23.9
m-Nirrobenzyl	$C_{15}H_{21}ClN_6O_2$	51.1	51.2	6.0	6.1	10.0	10.0	23.8	23.8
beta-Phenylethyl	$C_{16}H_{24}ClN_5$	59.7	59.5	7.5	7.3	11.0	11.2	21.8	22.0
gamma-Phenylpropyl	$C_{17}H_{26}ClN_5$	60.8	60.6	7.8	7.9	10.6	10.7	20.8	21.1

[a] Analyses were done by Micro-Tech Laboratories, Skokie, Illinois.

Derivatives With Phenyl Isothiocyanate

All of the iminotetrazolines were characterized as phenylthioureas by treatment of the free base with phenyl isothiocyanate. The preparation of the phenylthiourea derived from 1-cyclohexyl-4-p-chlorobenzyl-5-iminotetrazoline is typical of the method used.

Phenylthiourea derived from 1-cyclohexyl-4-p-chlorobenzyl-5-iminotetrazoline

About 1 g. of 1-cyclohexyl-4-p-chlorobenzyl-5-iminotetrazoline hydrochloride was shaken vigorously with 5 ml. of 2 N sodium hydroxide solution. The resulting iminotetrazoline was extracted with ether and the ether extracts dried over sodium sulfate. After removal of the drying agent the ether was evaporated on a warm water bath. A viscous oil remained which was treated with approximately 0.5 g. of phenyl isothiocyanate and heated on a steam bath for from 5 to 10 minutes. The yellow oil so obtained was crystallized by stirring with 5 ml. of hexane. Recrystallization from isopropyl alcohol gave a colorless product melting at 153.5 to 154°C.

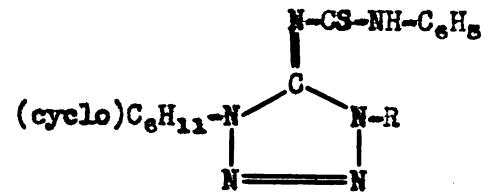
All phenylthioureas were prepared in the same manner and could be recrystallized from either isopropyl alcohol or heptane. Melting points and analytical results are given in Tables V and VI.

1-Cyclohexylmethyl-4-aralkyl-5-iminotetrazolines

The free bases were prepared by neutralization of their hydrochlorides. The procedure used may be illustrated by the preparation of 1-cyclohexylmethyl-4-p-chlorobenzyl-5-iminotetrazoline. About 1 g. of

TABLE V

PHENYLTHIOUREAS DERIVED FROM 1-CYCLOHEXYL-4-ARALKYL-5-IMINOTETRAZOLINES[a]

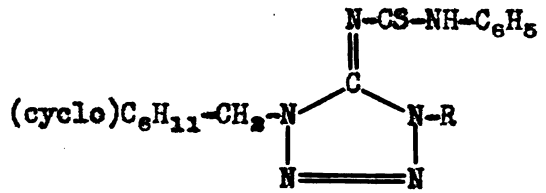


R	M.P. °C.	Formula	Percent Cl Calc'd	Percent Cl Found	Percent N Calc'd	Percent N Found	Percent S Calc'd	Percent S Found
Benzyl	147-148	$C_{21}H_{24}N_6S$	—	—	21.4	21.2	8.2	8.0
p-Chlorobenzyl	153.5-154.5	$C_{21}H_{23}ClN_6S$	8.3	8.1	19.7	19.5	7.5	7.4
o-Chlorobenzyl	134.5-135.5	$C_{21}H_{23}ClN_6S$	8.3	8.0	19.7	19.7	7.5	7.6
2,4-Dichlorobenzyl	121-122	$C_{21}H_{22}Cl_2N_6S$	15.4	15.2	18.2	18.5	7.0	7.0
3,4-Dichlorobenzyl	188-189	$C_{21}H_{22}Cl_2N_6S$	15.4	15.4	18.2	18.5	7.0	6.9
p-Nitrobenzyl	160.5-161.5	$C_{21}H_{23}N_7O_2S$	—	—	22.4	22.7	7.3	7.3
m-Nirrobenzyl	174-175	$C_{21}H_{23}N_7O_2S$	—	—	22.4	22.7	7.3	7.2
beta-Phenylethyl	106-107	$C_{22}H_{26}N_6S$	—	—	20.7	20.7	7.9	7.7
gamma-Phenylpropyl	98.5-99.5	$C_{23}H_{28}N_6S$	—	—	20.0	20.0	7.6	7.8

[a] Analyses were done by Micro-Tech Laboratories, Skokie, Illinois

TABLE VI

PHENYLTHIOUREAS DERIVED FROM 1-CYCLOHEXYLMETHYL-4-ARALKYL-5-IMINOTETRAZOLINES[a]

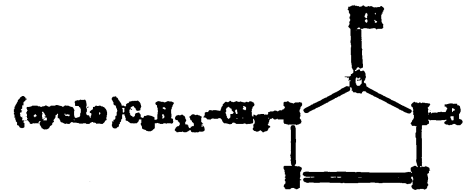


R	M.P. °C.	Formula	Percent Cl		Percent N		Percent S	
			Calc'd	Found	Calc'd	Found	Calc'd	Found
Benzyl	173.5-174.5	$C_{22}H_{26}N_6S$	—	—	20.7	21.0	7.9	7.9
p-Chlorobenzyl	155.5-156.5	$C_{22}H_{25}ClN_6S$	8.0	7.8	19.1	19.0	7.3	7.2
o-Chlorobenzyl	131-132	$C_{22}H_{25}ClN_6S$	8.0	8.0	19.1	19.3	7.3	7.0
2,4-Dichlorobenzyl	129.5-130	$C_{22}H_{24}Cl_2N_6S$	14.9	14.8	17.7	17.8	6.7	6.5
3,4-Dichlorobenzyl	179-180	$C_{22}H_{24}Cl_2N_6S$	14.9	15.0	17.7	17.8	6.7	6.5
p-Nitrobenzyl	158-159	$C_{22}H_{25}N_7O_2S$	—	—	21.7	21.8	7.1	7.0
m-Nirrobenzyl	160-161	$C_{22}H_{25}N_7O_2S$	—	—	21.7	21.6	7.1	7.0
beta-Phenylethyl	87.5-88.5	$C_{23}H_{28}N_6S$	—	—	20.0	20.2	7.6	7.5
gamma-Phenylpropyl	117-118	$C_{24}H_{30}N_6S$	—	—	19.3	19.5	7.4	7.3

* Analyses were done by Micro-Tech Laboratories, Skokie, Illinois.

TABLE VII

1-CYCLOHEXYLMETHYL-4-ARALKYL-5-IMINOTETRAZOLINES[a]



R	M.P. °C.	Formula	Percent C		Percent H		Percent Cl		Percent N	
			Calc'd	Found	Calc'd	Found	Calc'd	Found	Calc'd	Found
Benzyl	93-93.5	$C_{15}H_{21}N_5$	66.4	66.4	7.8	7.8	—	—	25.8	25.7
p-Chlorobenzyl	82-83	$C_{15}H_{20}ClN_5$	58.9	58.3	6.6	6.7	—	—	22.9	23.1
2,4-Dichlorobenzyl	103-104	$C_{15}H_{19}Cl_2N_5$	53.0	52.9	5.6	5.9	20.8	21.0	20.6	20.7
3,4-Dichlorobenzyl	75-76	$C_{15}H_{19}Cl_2N_5$	53.0	53.0	5.6	5.7	20.8	20.7	20.6	20.7
m-Nitrobenzyl	90-91	$C_{15}H_{20}N_6O_2$	56.9	57.0	6.4	6.6	—	—	26.6	26.7

[a] Analyses were done by Micro-Tech Laboratories, Skokie, Illinois.

1-cyclohexylmethyl-4-p-chlorobenzyl-5-iminotetrazoline hydrochloride was shaken vigorously with 5 ml. of 2 N sodium hydroxide solution then extracted with ether. The ether extracts were dried over sodium sulfate and then the ether evaporated by means of a warm water bath. A viscous pale yellow oil resulted which solidified upon cooling in an ice bath. Dissolving the crude solid in hot cyclohexane followed by very slow cooling gave colorless needles of 1-cyclohexylmethyl-4-p-chlorobenzyl-5-iminotetrazoline melting at 82-83°C.

Attempts were made to prepare the free bases from all of the hydrochlorides, however, only five of the compounds gave solid products. The solid compounds isolated are listed in Table VII along with their melting points and analytical results.

Infra-red Absorption Spectra

Infra-red absorption spectra were obtained for a series of iminotetrazoline hydrochlorides and the corresponding free bases using a Perkin-Elmer Doublebeam Recording Spectrophotometer, Model 21. All compounds were run in oil mulls with the concentration of solid great enough to give strong adsorption in the six micron region. The spectra are reproduced in Figures 2 to 16 of the Appendix.

SUMMARY

1. The reaction of 3,5-dimethyl-4-amino-1,2,4-triazole with benzyl chloride was shown to lead to a quaternary chloride which contains a primary amino group.

2. The quaternary chloride has been shown to react with aqueous potassium hydroxide to give an organic base that forms a hydrochloride isomeric with the quaternary chloride. Treatment of the base with benzyl chloride results in the formation of a second quaternary chloride.

3. A series of 1-cycloalkyl-4-aralkyl-5-iminotetrazoline hydrochlorides has been prepared by the aralkylation of 1-cycloalkyl-5-aminotetrazoles. The compounds were characterized by formation of phenylthioureas by reaction with phenyl isothiocyanate. The structure of these compounds was established by comparison of their infra-red spectra with the spectra of known structures and by analogy of the method of synthesis with that described for the preparation of compounds of known structure.

LITERATURE CITED

(1) R. M. Herbst and D. F. Percival, J. Org. Chem., 19, 439 (1954).

(2) R. A. Henry, W. G. Finnegan and E. Lieber, J. Am. Chem. Soc., 76, 2894 (1954).

(3) J. Bryden, R. A. Henry, W. G. Finnegan, R. Boschan, W. S. McEwan and R. Z. Van Dolah, J. Am. Chem. Soc., 75, 4863 (1953).

(4) R. Stollé, J. prakt. Chem., [2], 68, 468 (1903), Chem. Zentr., 74, 793 II (1903).

(5) R. Stollé and K. Thoma, J. prakt. Chem., 73, 288 (1906), Chem. Zentr., 1906, 1783 I.

(6) R. Stollé, J. prakt. Chem., 75, 416 (1907), Chem. Zentr. 1907, 250 II.

(7) S. Ruhemann and H. Stapleton, J. Chem. Soc., 81, 261 (1902).

(8) S. Ruhemann, J. Chem. Soc., 89, 1268 (1906).

(9) R. M. Herbst and J. A. Garrison, J. Org. Chem., 18, 872 (1953).

(10) H. Clarke, H. Gillespie and S. Weisshaus, J. Am. Chem. Soc., 55, 4571 (1933).

(11) E. Wagner, J. Am. Chem. Soc., 55, 724 (1933).

(12) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," Menthuen & Co. Ltd., London; John Wiley & Sons, Inc., New York, 1954.

(13) N. B. Colthup, J. Optical Soc. Am., 40, 397 (1950).

(14) L. Birkofer, Ber., 75B, 429 (1942).

(15) W. L. Garbrecht and R. M. Herbst, J. Org. Chem., 18, 1022 (1953).

(16) R. M. Herbst and W. L. Garbrecht, J. Org. Chem., 18, 1283 (1953).

(17) A. Pinner, Ber., 27, 984 (1894).

(18) A. Pinner, Ann., 297, 221 (1897).

(19) O. Silberrad, J. Chem. Soc., 77, 1185 (1900).

(20) T. Curtius, A. Darapsky and E. Muller, Ber., 40, 1194 (1907).

(21) B. Phillips and A. Michaelis, Ann., 252, 292 (1889).

(22) A. Pinner, Ber., 30, 1871 (1897).

(23) S. Ruhemann and R. Merriman, J. Chem. Soc., 87, 1768 (1905).

(24) C. Bulow and F. Weber, Ber., 42, 2715 (1909).

(25) H. H. Hatt, "Organic Synthesis" Col. Vol. II, John Wiley & Sons, Inc., New York, 1943, p. 208.

(26) T. F. Reutner, J. C. Peters and E. F. Elslager, "Abstracts of Papers Presented at the 129th National American Chemical Society Meeting," Dallas, April, 1956, p. 7M.

(27) D. F. Percival, "Alkylated 5-Aminotetrazoles, Their Preparation and Properties," Ph. D. Thesis, Michigan State College, 1955.

(28) J. Thiele and H. Ingle, Ann., 287, 233 (1895).

(29) R. M. Herbst, C. W. Roberts, E. J. Harvill, J. Org. Chem., 16, 139 (1951).

(30) R. M. Herbst, U. S. Patent 2,735,852.

(31) W. L. Garbrecht and R. M. Herbst, J. Org. Chem., 18, 1014 (1953).

(32) H. Wolf, "Organic Reactions," John Wiley & Sons, New York, 1949, pp. 307-335.

(33) E. Lieber, D. Levering and L. Patterson, Anal. Chem., 23, 1594 (1951).

(34) D. R. Murphy and J. P. Picard, J. Org. Chem., 19, 1807 (1954).

(35) M. Oesterlin, Z. angew. Chemie, 45, 536 (1932).

(36) C. Schmerch and E. Huntress, J. Am. Chem. Soc., 71, 2233 (1949).

(37) J. Gut, Ber., 40, 2065 (1907).

APPENDIX

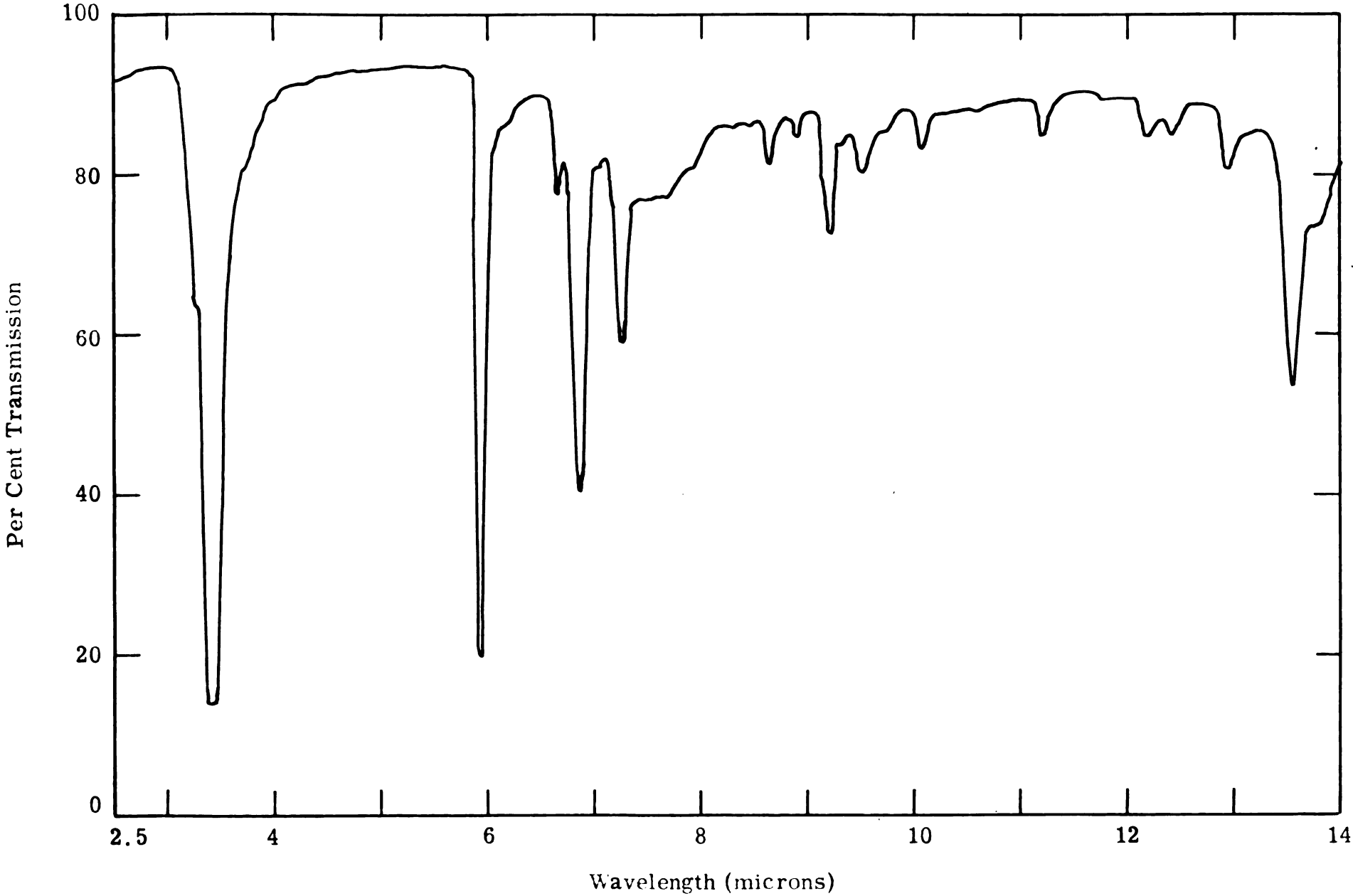


Figure 2. Infra-red Spectrum of 1-Cyclohexyl-4-benzyl-5-iminotetrazoline Hydrochloride

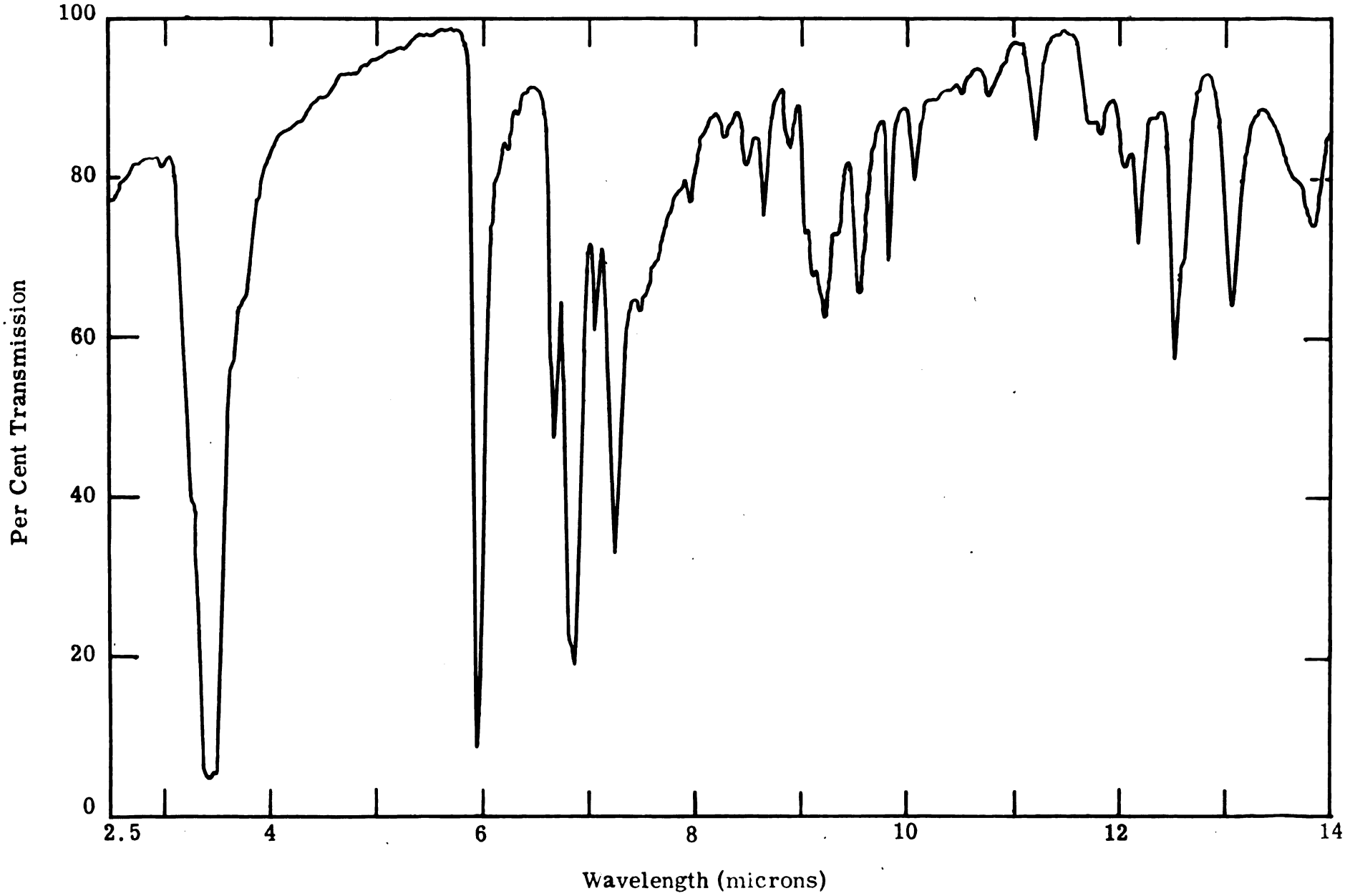


Figure 3. Infra-red Spectrum of 1-Cyclohexyl-4-p-Chlorobenzyl-5-iminotetrazoline Hydrochloride

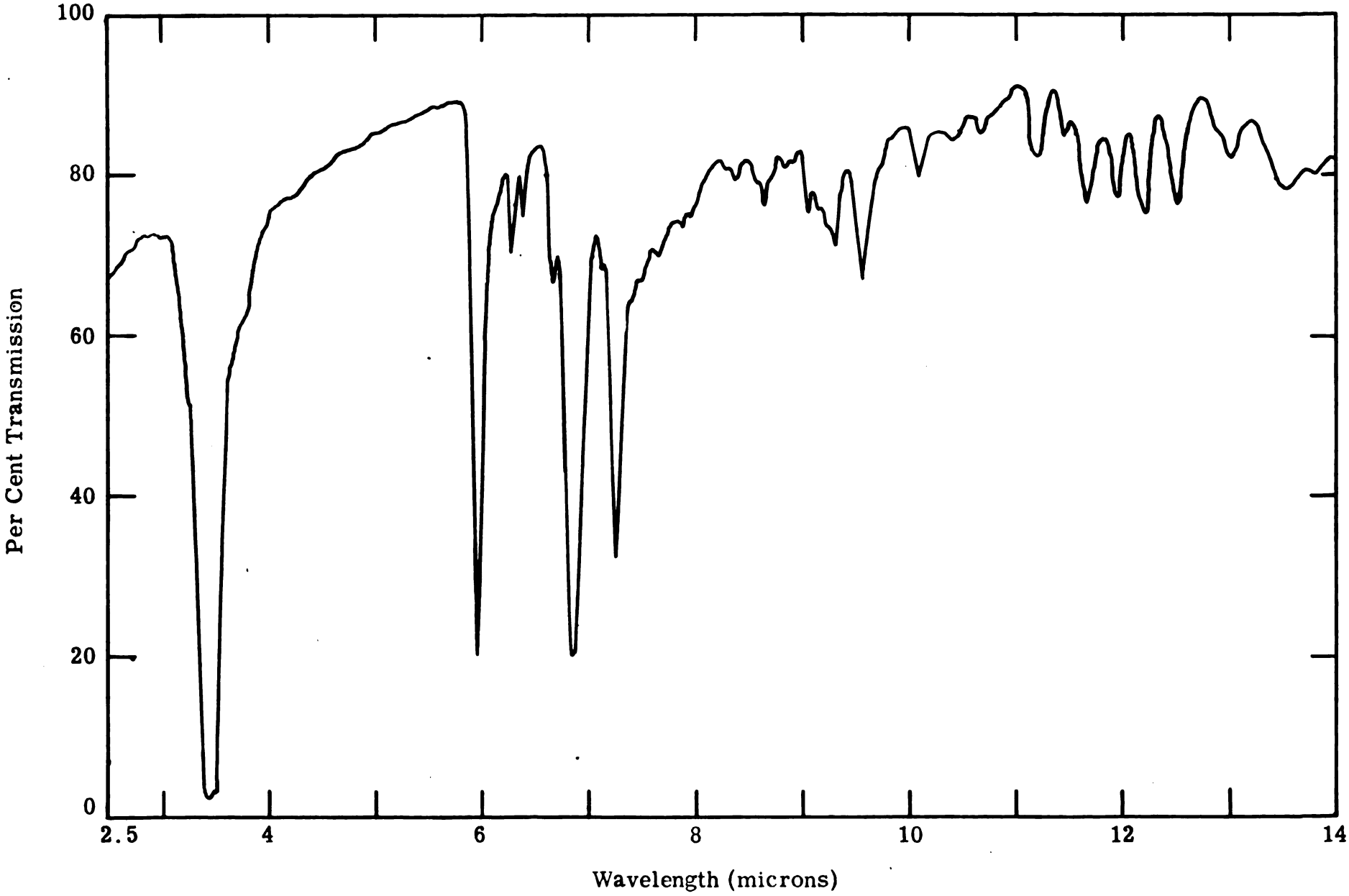


Figure 4. Infra-red Spectrum of 1-Cyclohexyl-4-(2, 4-dichlorobenzyl)-5-iminotetrazoline Hydrochloride

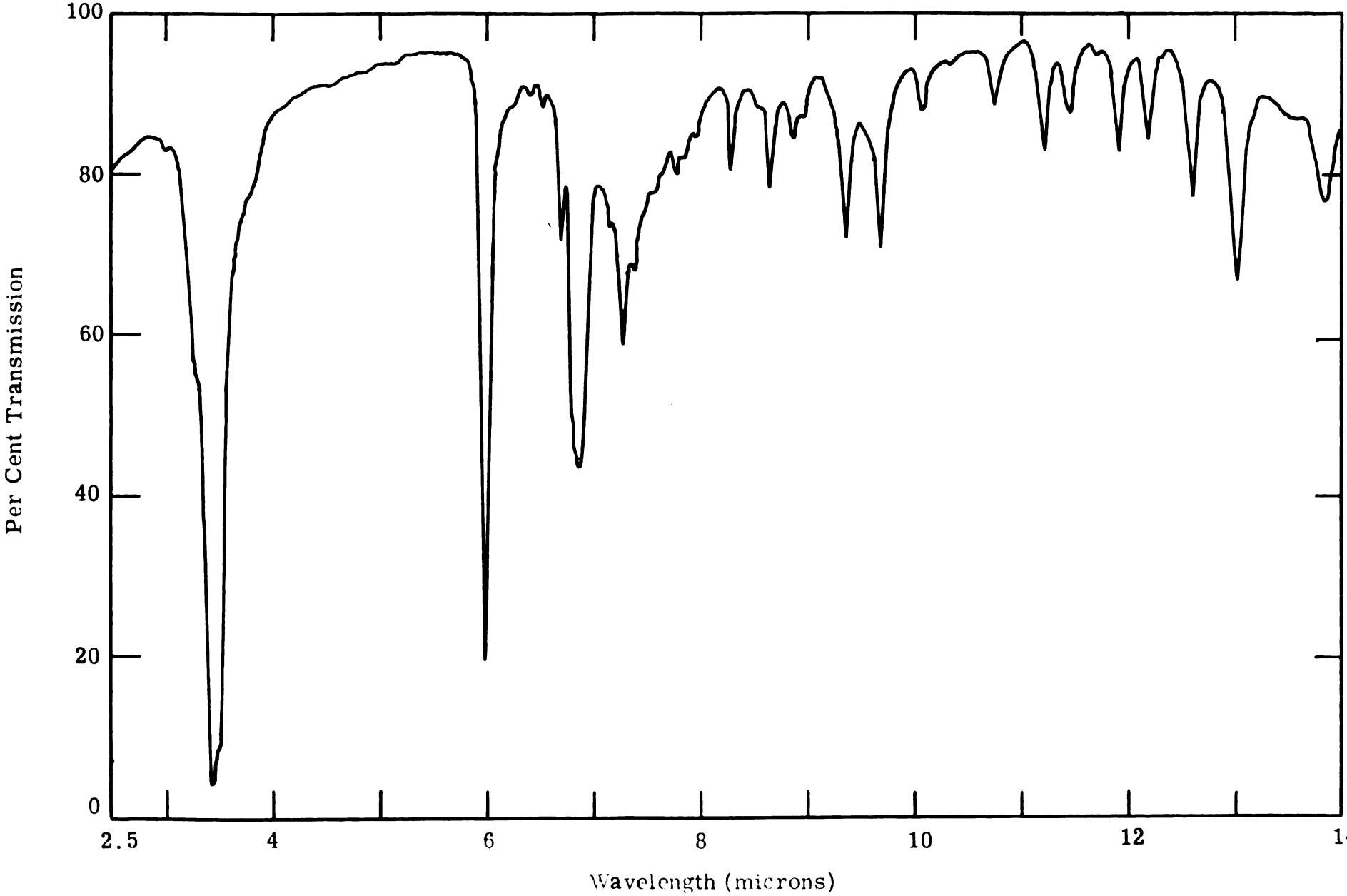


Figure 5. Infra-red Spectrum of 1-Cyclohexyl-4-(3,4-dichlorobenzyl)-5-iminotetrazoline Hydrochloride

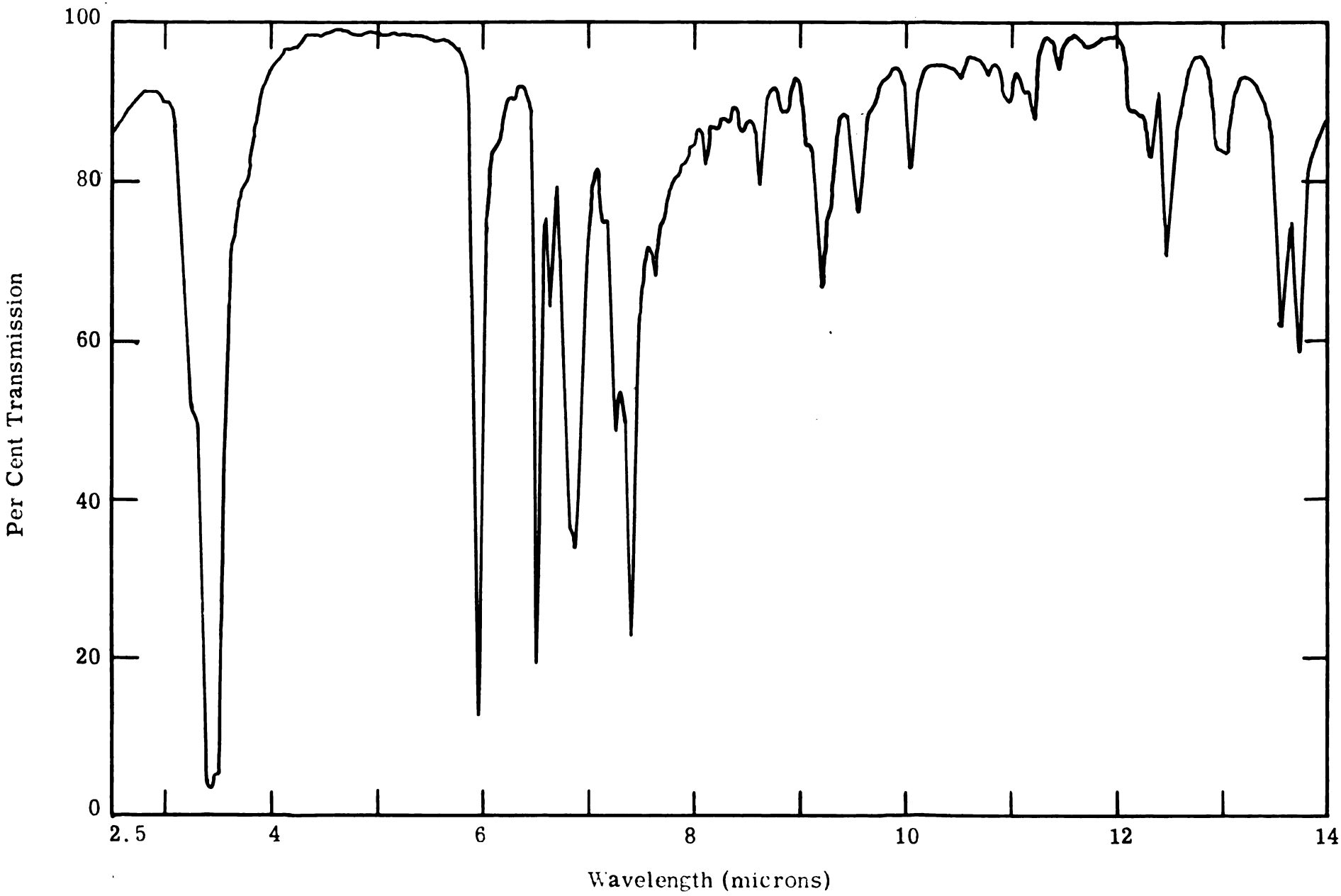


Figure 6. Infra-red Spectrum of 1-Cyclohexyl-4-(p-nitrobenzyl-5-iminotetrazoline Hydrochloride

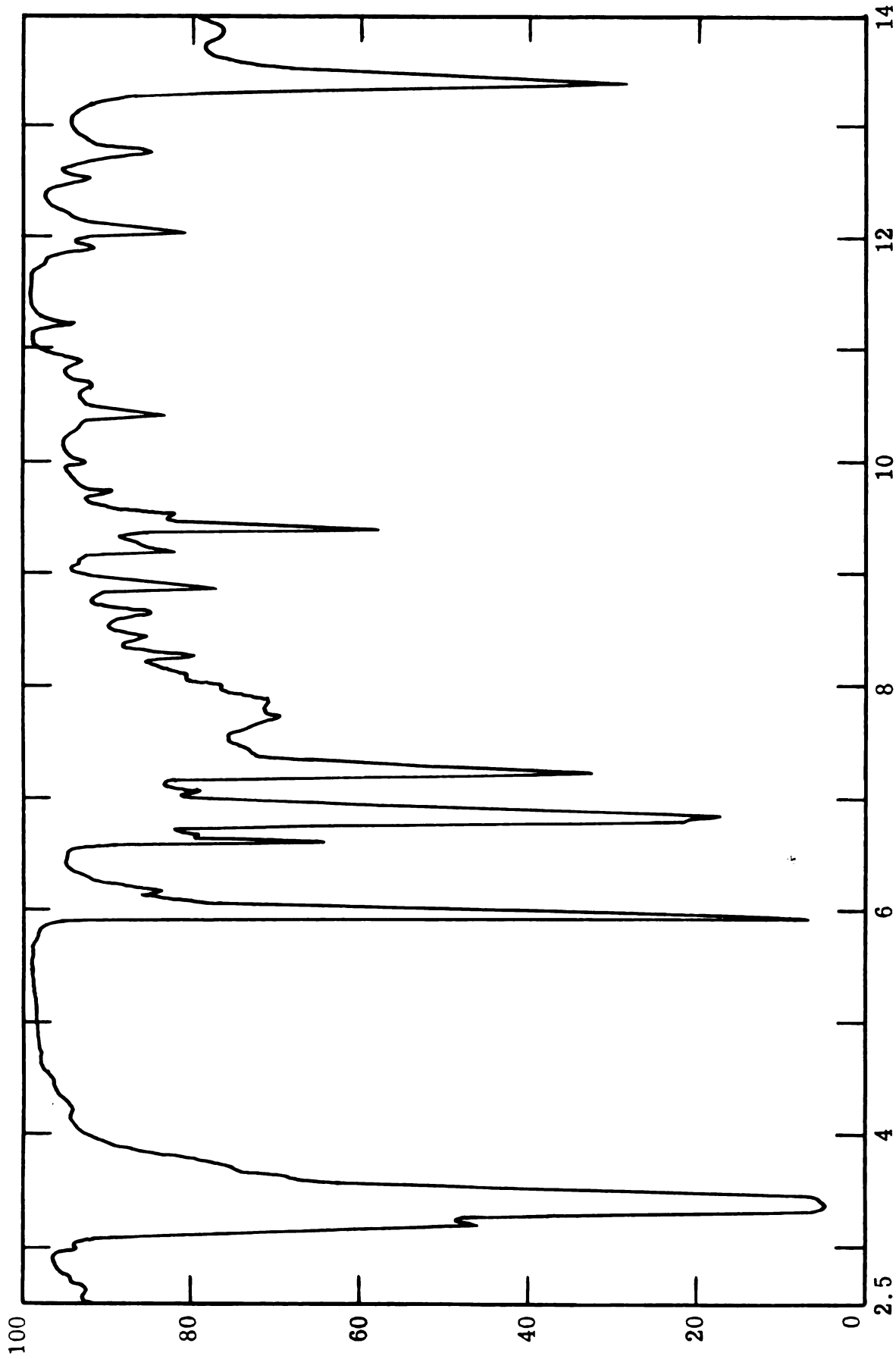


Figure 7. Infra-red Spectrum of 1-Cyclohexylmethyl-4-benzyl-5-iminotetrazoline Hydrochloride

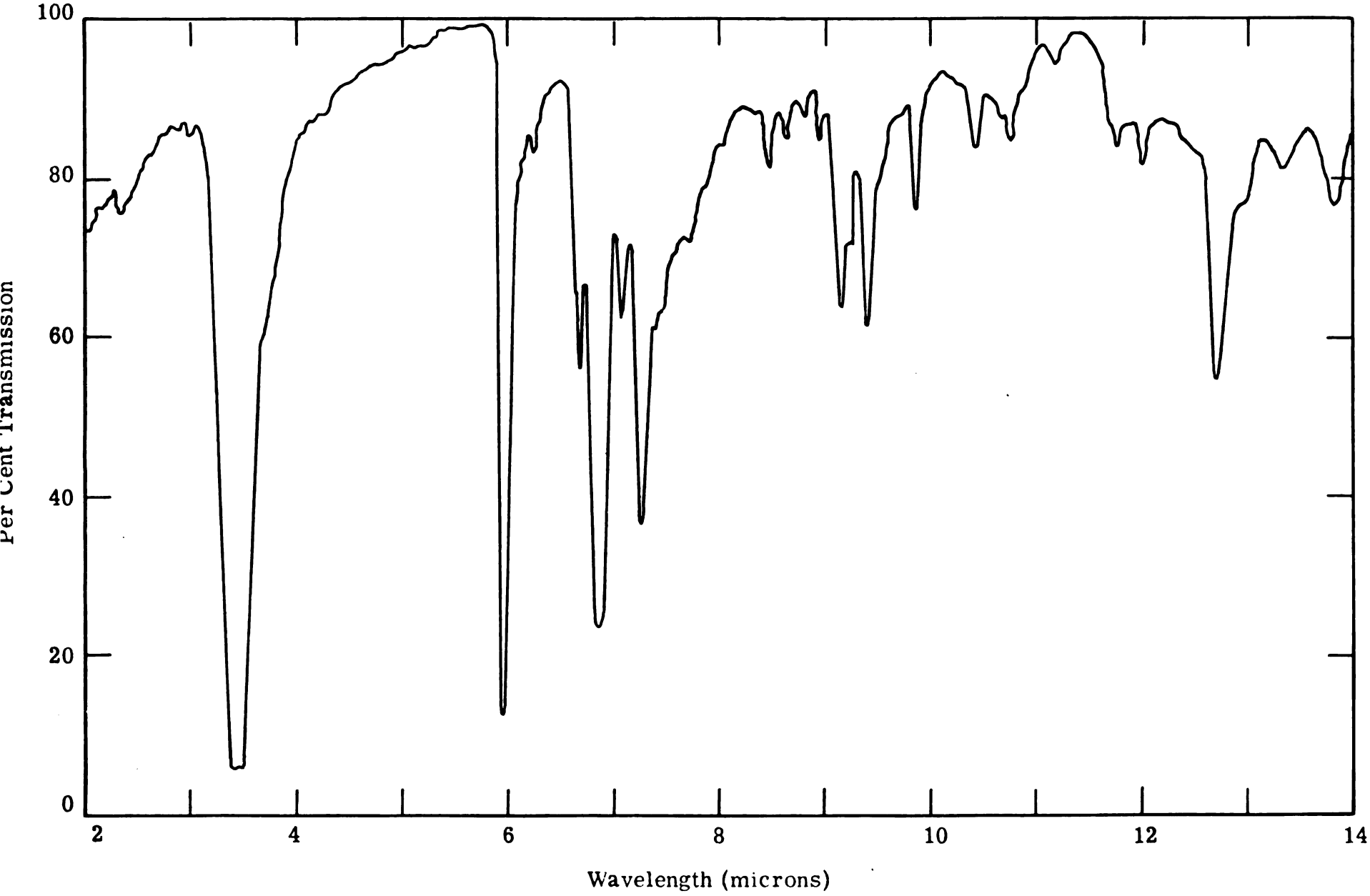


Figure 8. Infra-red Spectrum of 1-Cyclohexylmethyl-4-p-chlorobenzyl-5-iminotetrazoline Hydrochloride

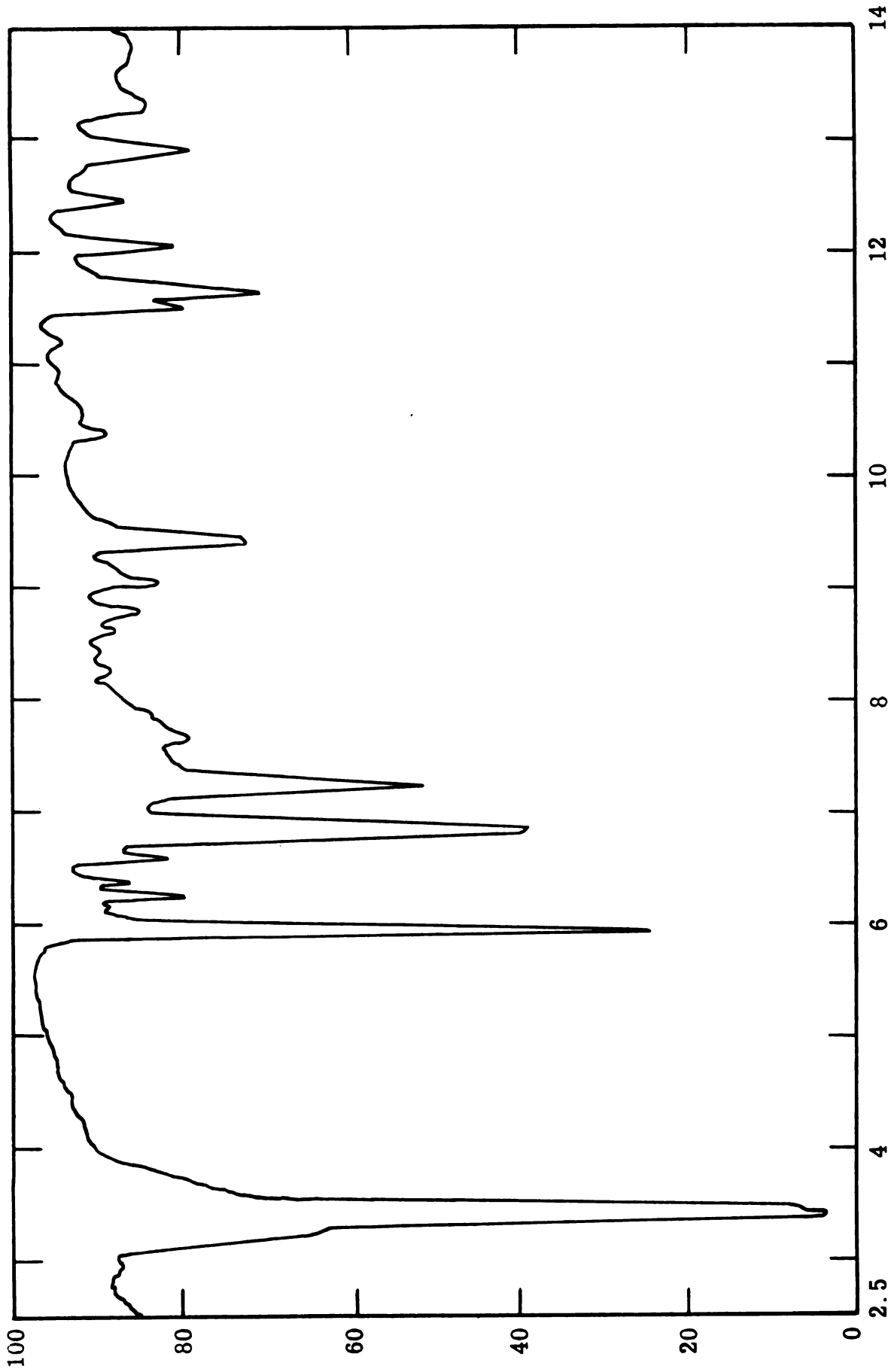


Figure 9. Infra-red Spectrum of 1-Cyclohexylmethyl-4-(2,4-dichlorobenzyl)-5-iminotetrazoline Hydrochloride

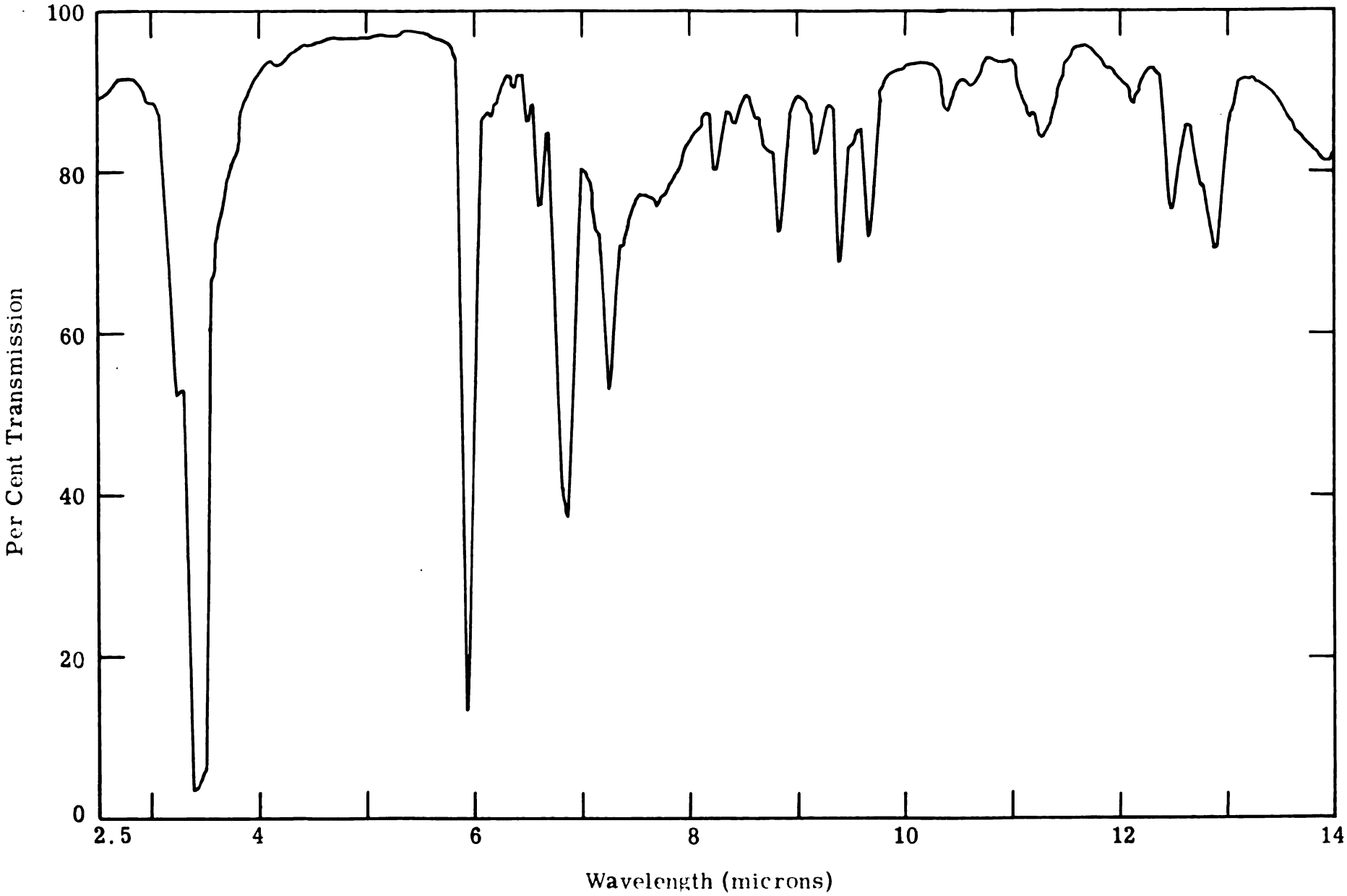


Figure 10. Infra-red Spectrum of 1-Cyclohexylmethyl-4-(3, 4-dichlorobenzyl)-5-iminotetrazoline Hydrochloride

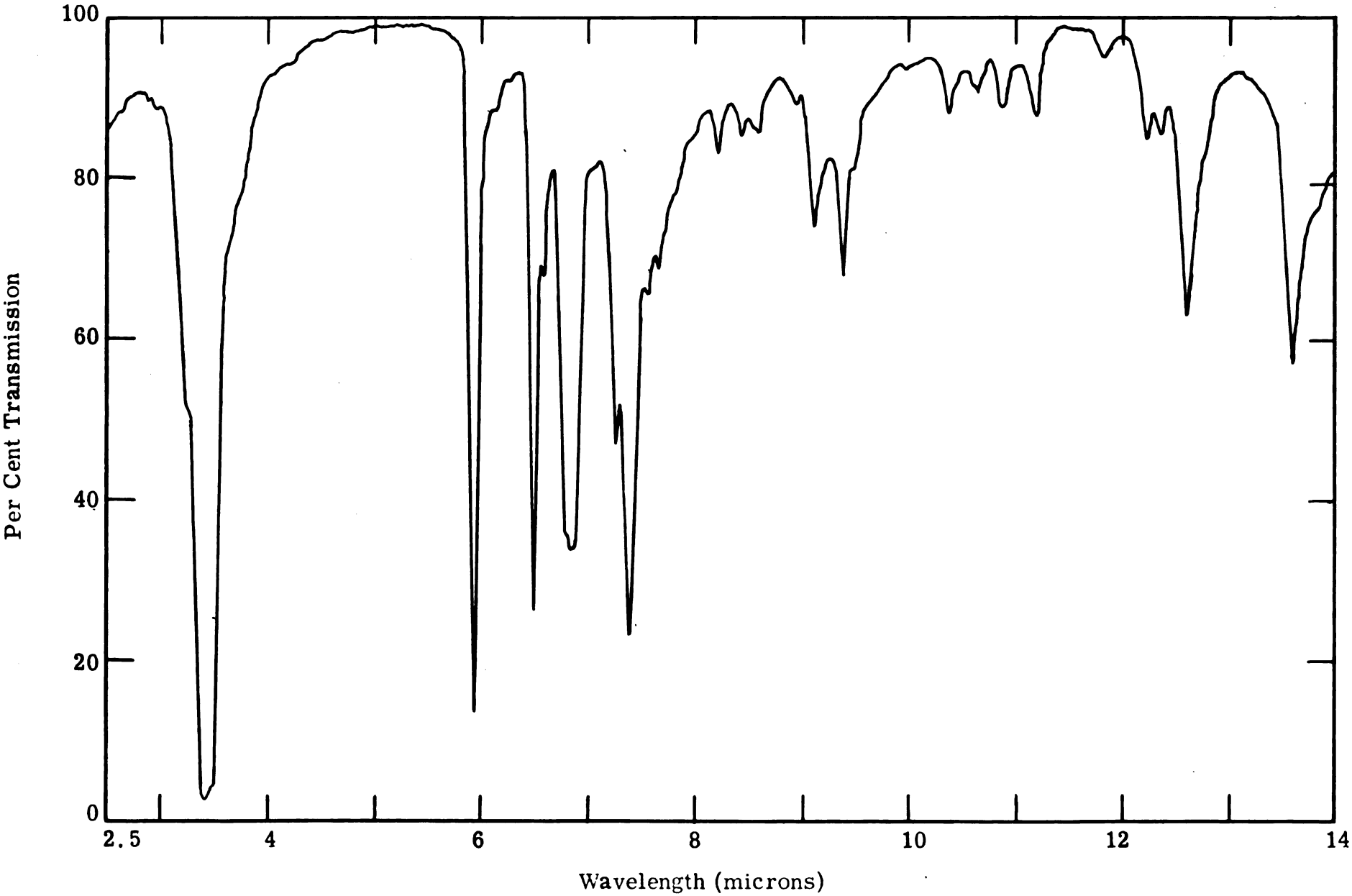


Figure 11. Infra-red Spectrum of 1-Cyclohexylmethyl-4-p-nitrobenzyl-5-iminotetrazoline Hydrochloride

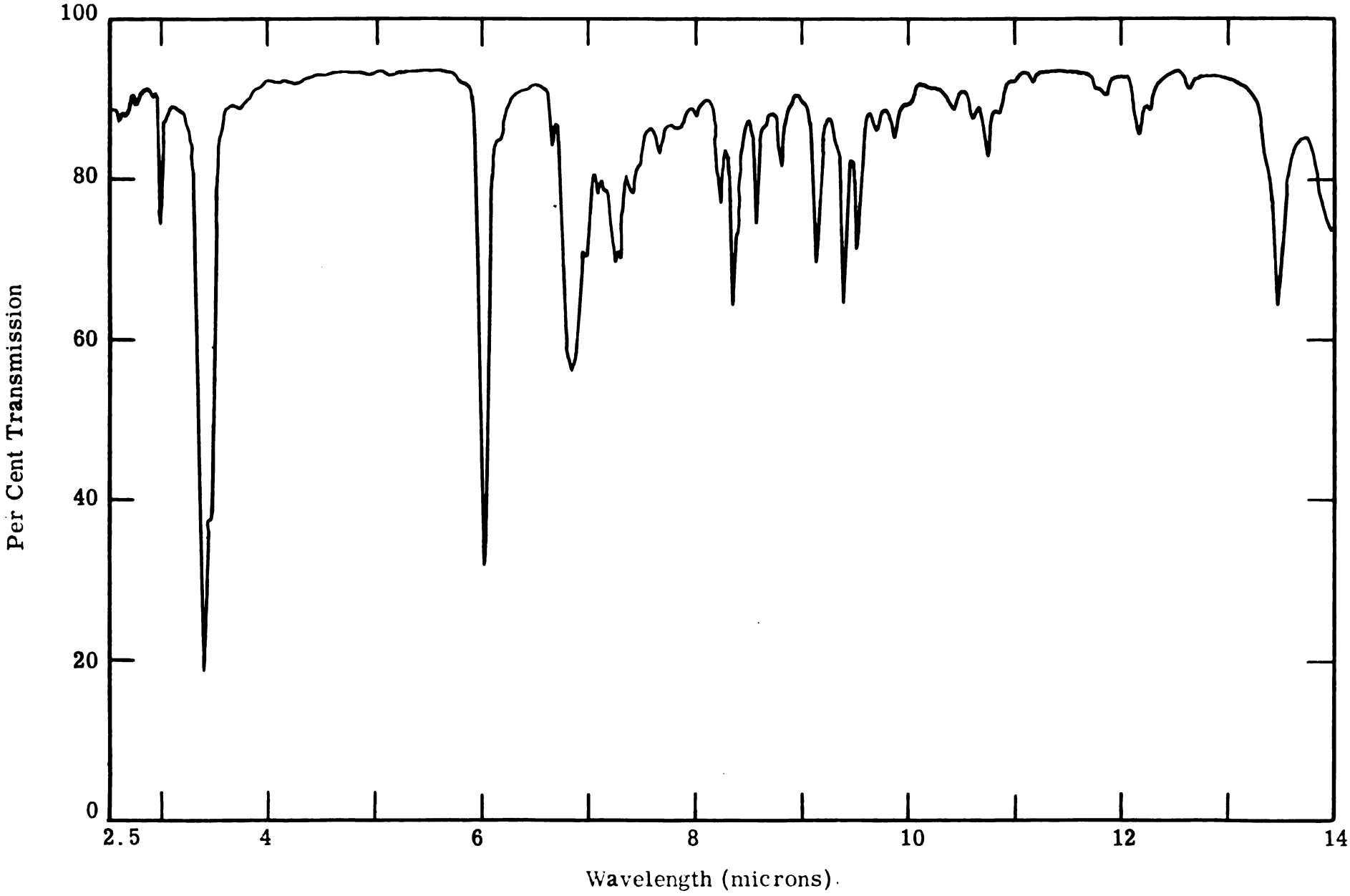


Figure 12. Infra-red Spectrum of 1-Cyclohexylmethyl-4-benzyl-5-iminotetrazoline

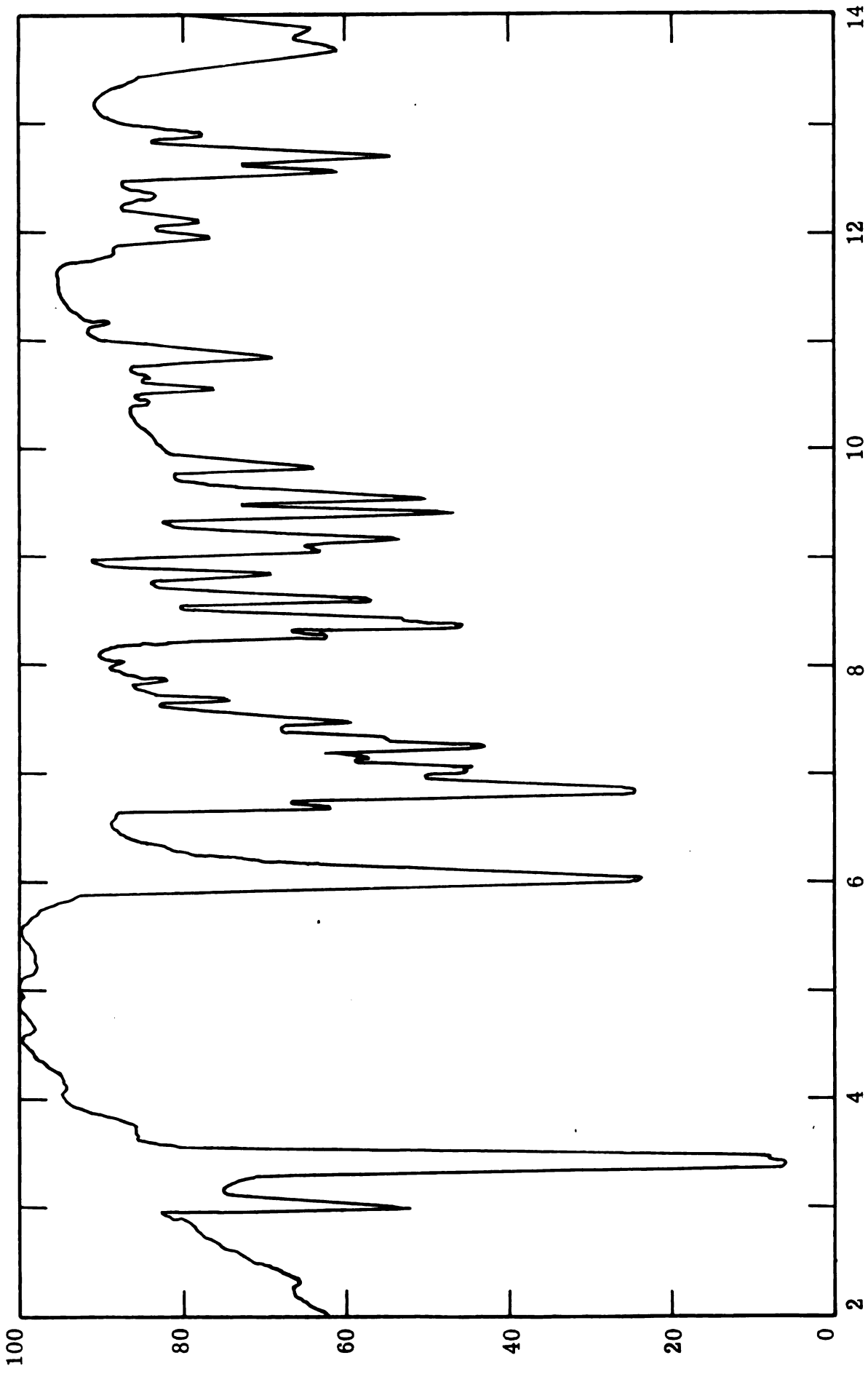


Figure 13. Infra-red Spectrum of 1-Cyclohexylmethyl-4-p-chlorobenzyl-5-iminotetrazoline

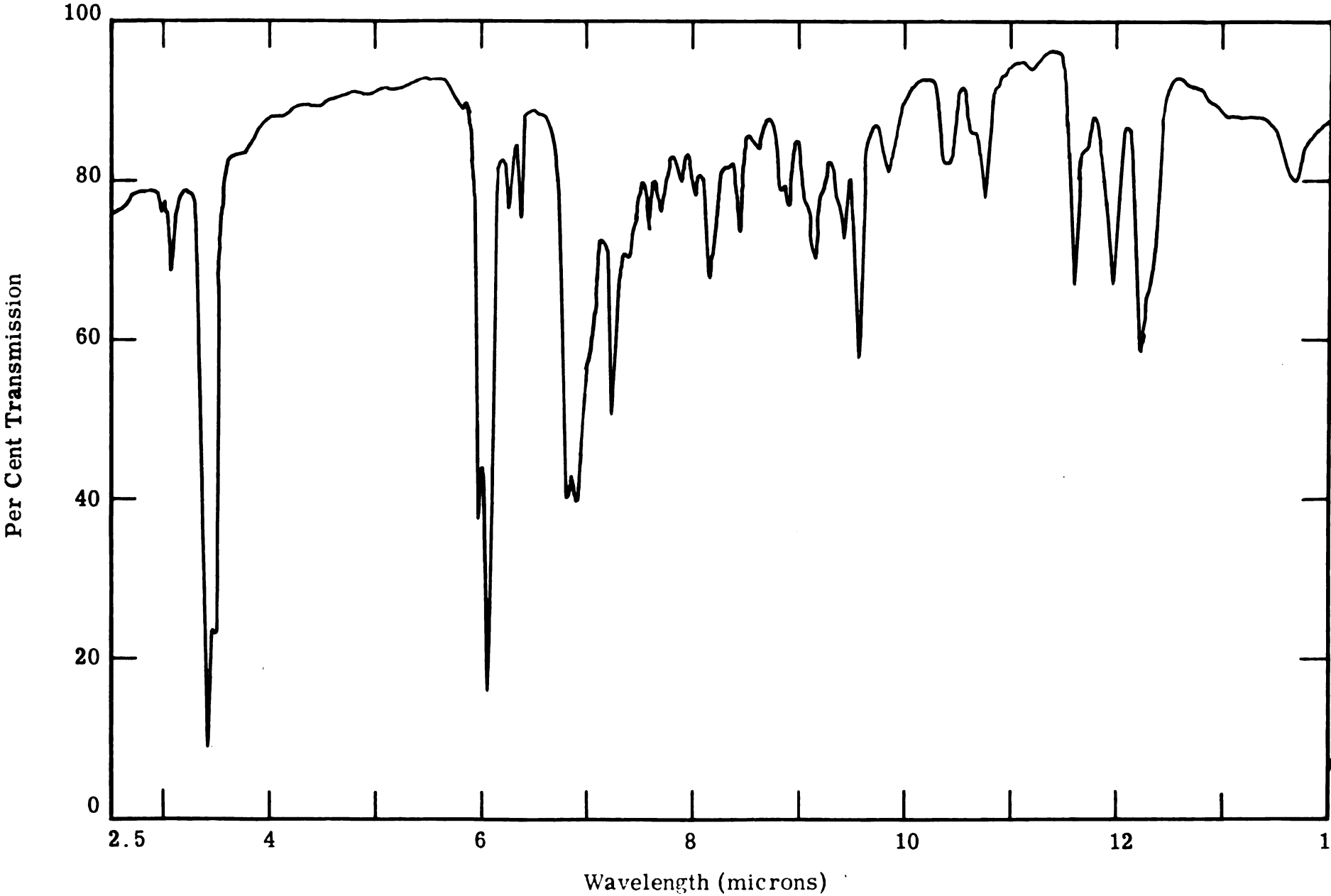


Figure 14. Infra-red Spectrum of 1-Cyclohexylmethyl-4-(2, 4-dichlorobenzyl)-5-iminotetrazoline

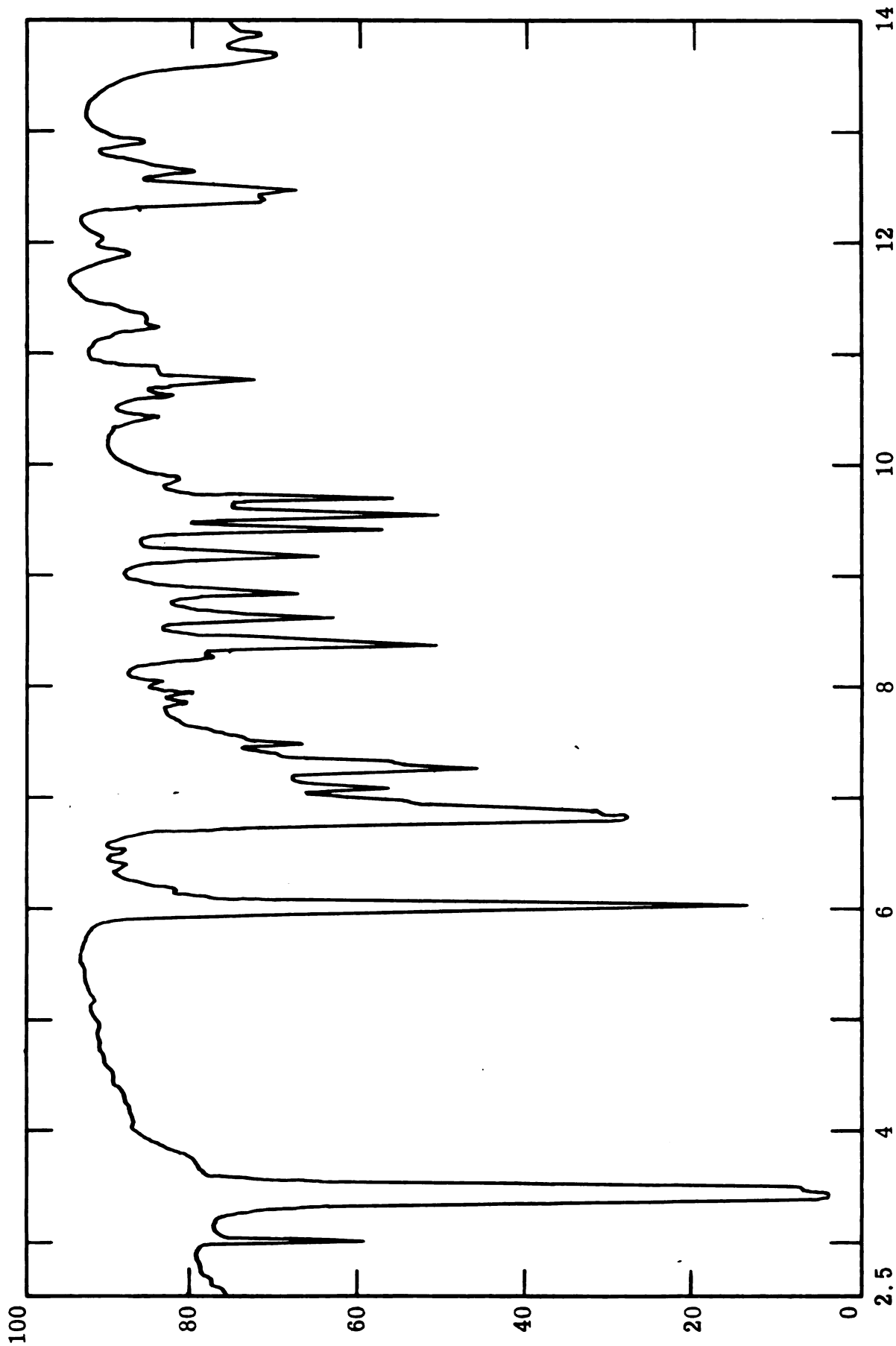


Figure 15. Infra-red Spectrum of 1-Cyclohexylmethyl-4-(3, 4-dichlorobenzyl)-5-iminotetrazoline

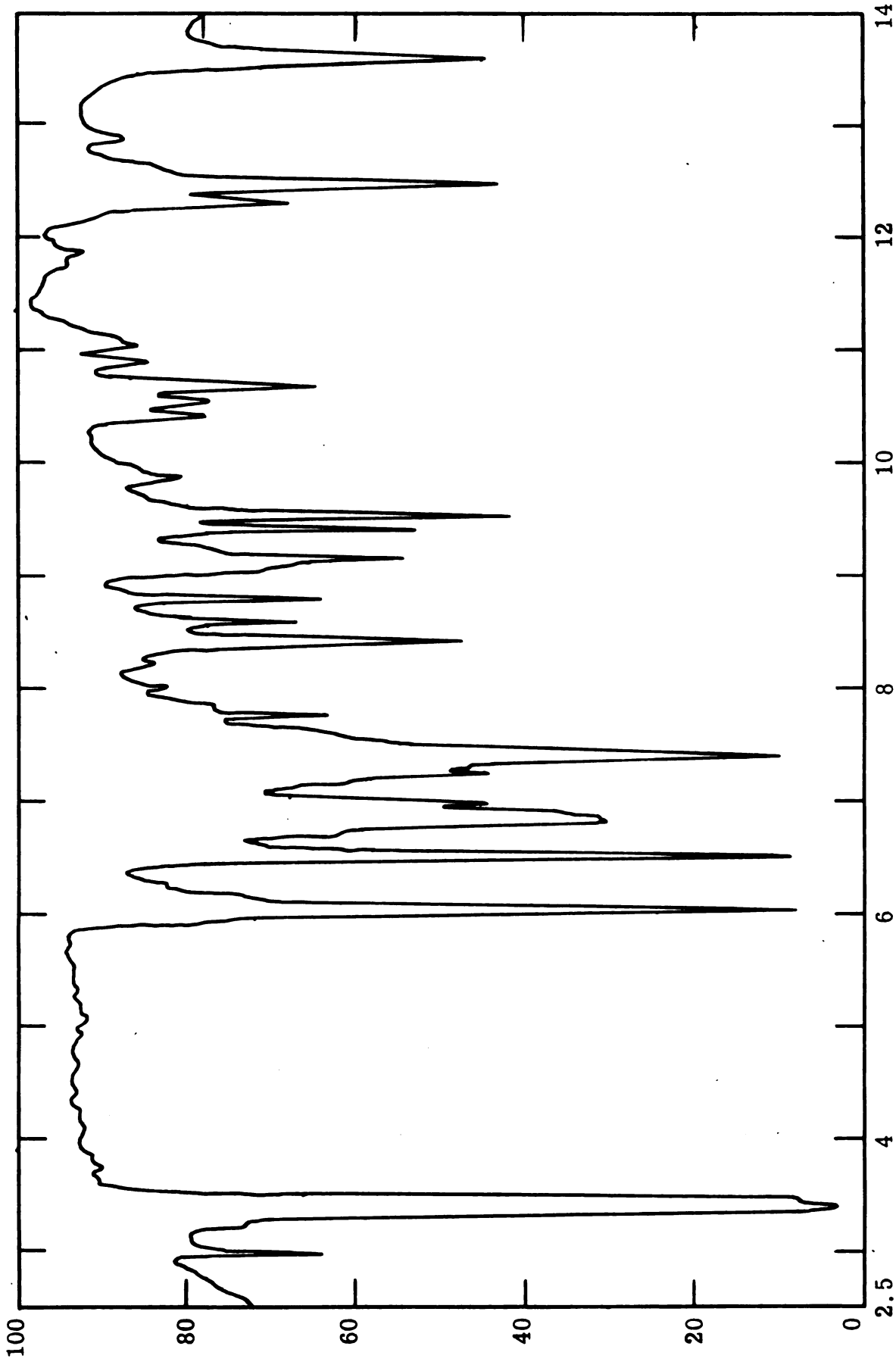


Figure 16. Infra-red Spectrum of 1-Cyclohexylmethyl-4-p-nitrobenzyl-5-iminotetrazoline

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