CYANOETHYLATION OF THE 5-AMINOTETRAZOLES

By

Donald Walter Renn

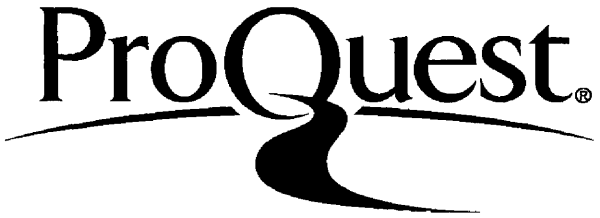
A THESIS

Submitted to the School for 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

1957



ACKNOWLEDGMENT

Sincere appreciation is expressed to Doctor Robert M. Herbst, under whose direction this investigation was accomplished, for his inspiration, guidance, patience, and understanding which made this thesis possible.

- - - -

Appreciation is also extended to the American Viscose Corporation for their financial assistance in the form of a fellowship during the academic year 1955-1956, to the Monsanto Chemical Company for their fellowship during the academic year 1956-1957, and to Michigan State University for summer scholarships during 1956 and 1957.

To my wife Pat

CYANOETHYLATION OF THE 5-AMINOTETRAZOLES

By

Donald Walter Renn

AN ABSTRACT

Submitted to the School for 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

Year 1957

Approved Robert M. Herbst

ABSTRACT

The original purpose of this investigation was to study the cyanoethylation, chloromethylation, and Mannich reactions as applied to the 5-aminotetrazoles. After preliminary experimentation, research was directed exclusively toward a study of the reaction of acrylonitrile with 1-benzyl-5-aminotetrazole and 5-aminotetrazole.

Since there is no evidence in the literature of the application of the cyanoethylation reaction to the 5-aminotetrazoles, it was necessary not only to study the reaction of acrylonitrile with the 5-aminotetrazoles but also to establish the structures of the products.

The reaction of 1-benzyl-5-aminotetrazole and acrylonitrile in the presence of benzyltrimethylammonium hydroxide yielded two products. Elemental analysis indicated that one of these was a mono-cyanoethylated and the other a di-cyanoethylated 1-benzyl-5-aminotetrazole. The mono-cyanoethylated derivative was shown to be 1-benzyl-5-β-cyanoethylaminotetrazole. The isomeric 1-benzyl-4-β-cyanoethyl-5-iminotetrazoline was prepared both by alkylation of 1-benzyl-5-aminotetrazole with β-haloproprionitriles and by benzylation of 1-β-cyanoethyl-5-aminotetrazole.

Debenzylation of the di-cyanoethylated 1-benzyl-5-aminotetrazole produced a compound that was identical with 5-N,N-di-β-cyanoethylaminotetrazole prepared from β,β'-iminodipropionitrile by reaction with cyanogen bromide and hydrazoic acid. These results indicated that the di-cyanoethylated 1-benzyl-5-aminotetrazole was 1-benzyl-5-N,N-di-β-cyanoethylaminotetrazole. Attempts to synthesize the latter

compound from N-benzyl-N',N'-di-β-cyanoethylthiourea and from 4-benzylthiosemicarbazide were unsuccessful.

Cyanoethylation of 5-aminotetrazole, again using a benzyltrimethylammonium hydroxide catalyst, resulted in the formation of two mono-cyanoethylated derivatives, as indicated by the elemental analyses. One of these was identical with 1-β-cyanoethyl-5-aminotetrazole prepared by the reaction of β-aminopropionitrile with cyanogen bromide and hydrazoic acid successively. The other mono-cyanoethylated 5-aminotetrazole was postulated to be 2-β-cyanoethyl-5-aminotetrazole by a process of elimination and by isolation of an identical compound from the reaction of β-bromopropionitrile and 5-aminotetrazole in a basic medium. Also produced in this reaction was 1-β-cyanoethyl-5-aminotetrazole. Henry and Finnegan (1) have demonstrated that 1- and 2-alkyl-5-aminotetrazoles are the chief products obtained from the alkylation of 5-aminotetrazole in a basic solution.

In an unsuccessful attempt to prepare 5-β-cyanoethylaminotetrazole, 1,4-dibenzyl-5-iminotetrazoline was caused to react with acrylonitrile in the presence of benzyltrimethylammonium hydroxide. The product obtained exhibited peculiar properties and the proposed debenzylation to yield 5-β-cyanoethylaminotetrazole was not effected.

Decyanoethylation occurred during the hydrolysis of 1-β-cyanoethyl-5-aminotetrazole with barium hydroxide. Hydrolysis with concentrated hydrochloric acid gave an acidic compound which was not characterized.

Possible mechanisms for the reaction of acrylonitrile with 5-aminotetrazole and 1-benzyl-5-aminotetrazole have been postulated which employ an apparent analogy between the base-catalyzed cyanoethylation reaction and the alkylation of 5-aminotetrazole in a basic medium.

Reference Cited

1. R. A. Henry and W. G. Finnegan, J. Am. Chem. Soc., 76, 923 (1954).

TABLE OF CONTENTS

TABLE OF CONTENTS - continued

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

The original purpose of this study was to investigate the cyanoethylation, chloromethylation, and the Mannich reactions applied to the 5-aminotetrazole system with the possibility of obtaining some interesting synthetic intermediates. It was hoped that these compounds could be interrelated by relatively straight-forward chemical reactions. However, after preliminary experimentation, attention was directed exclusively toward an investigation of the cyanoethylation reaction with the 5-aminotetrazoles.

Although the results of the cyanoethylation of various amines and nitrogen heterocyclics have been recorded and discussed in the literature (1,2), there is no record of application of the reaction to the 5-aminotetrazoles. Because of this, it has been necessary not only to study the reaction of acrylonitrile with the 5-aminotetrazoles, but also to establish the structure of the products.

The general method of attack followed in this investigation has been that of isolating the products resulting from the cyanoethylation reactions and then postulating structures using the results of the elemental analyses in conjunction with physical and chemical properties. Final proof of structure was accomplished by synthetic and degradative procedures whenever possible. The preparation of derivatives of some of these compounds has been attempted.

HISTORICAL

An extensive review of the cyanoethylation reaction has been prepared by Bruson (1) and general descriptions of this reaction may be found in most treatises on organic chemistry. Therefore, only those specific phases of cyanoethylation which are pertinent to the application to the 5-aminotetrazoles are contained in this section.

The base-catalyzed cyanoethylation reaction has been referred to as a specific type of Michael condensation (3,4) where a compound containing a labile hydrogen adds to the acrylonitrile molecule. The overall result is the replacement of a labile hydrogen with a β-cyanoethyl residue, e.g.

$$=N-H + CH_2=CH-C\equiv N \rightleftharpoons =N-CH_2CH_2C\equiv N$$

Addition always takes place in such a manner that the more anionic portion of the addend goes to the β end of the α,β double bond (3).

The cyanoethylation reaction has been observed to be an equilibrium reaction. When equimolar portions of secondary amines and acrylonitrile react, some unreacted starting materials are always recovered and the yield of product is never as high as when an excess of one of the reactants is used (5). Frequently, heating a cyanoethylated derivative near its boiling point will cause gradual decomposition to the original compound and acrylonitrile or some polymer thereof (1). Reversibility has been observed extensively with the cyanoethylation of alcohols. The cyanoethylated products have been observed to undergo thermal dissociation in the presence of alkaline

materials into the original alcohol and a polymer of acrylonitrile (6).

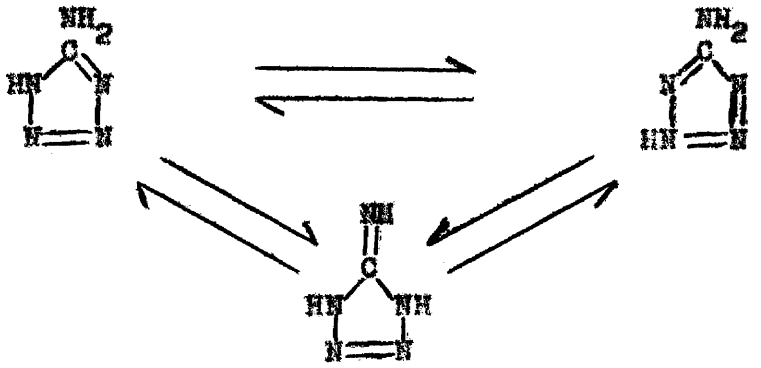
With compounds containing more than one replaceable hydrogen, the products obtained are dependent upon the conditions of the reaction. Mono-cyanoethylated compounds predominate at lower temperatures (1).

While reaction of acrylonitrile with some compounds containing labile hydrogens is spontaneous and highly exothermic, in most instances the assistance of a catalyst to hasten attainment of equilibrium is required. Benzyltrimethylammonium hydroxide is apparently a quite versatile cyanoethylation catalyst (1).

Previous applications of the cyanoethylation reaction to various amines and nitrogen heterocyclics have been tabulated by Bruson (1). The only more recent reference directly applicable to the present investigation concerns the cyanoethylation of benzimidazole and its 2-methyl analog. Efros and Porai-Koshit (2) found that both of these compounds gave N-cyanoethylated derivatives. Hydrolysis of these products in hot 10 percent sodium hydroxide resulted in decyanoethylation with the recovery of the corresponding benzimidazole. Hydrolysis with barium hydroxide gave a 95 percent yield of 1-benzimidazolepropionic acid as the barium salt. Decyanoethylation was not encountered using a hydrochloric acid hydrolysis medium.

DISCUSSION

5-Aminotetrazole may be represented by a number of tautomeric structures with the hydrogens arranged in various positions about the tetrazole nucleus and the exocyclic amino nitrogen. Derivatives of the three tautomeric forms represented below were encountered in the study of the cyanoethylation of the 5-aminotetrazole system.

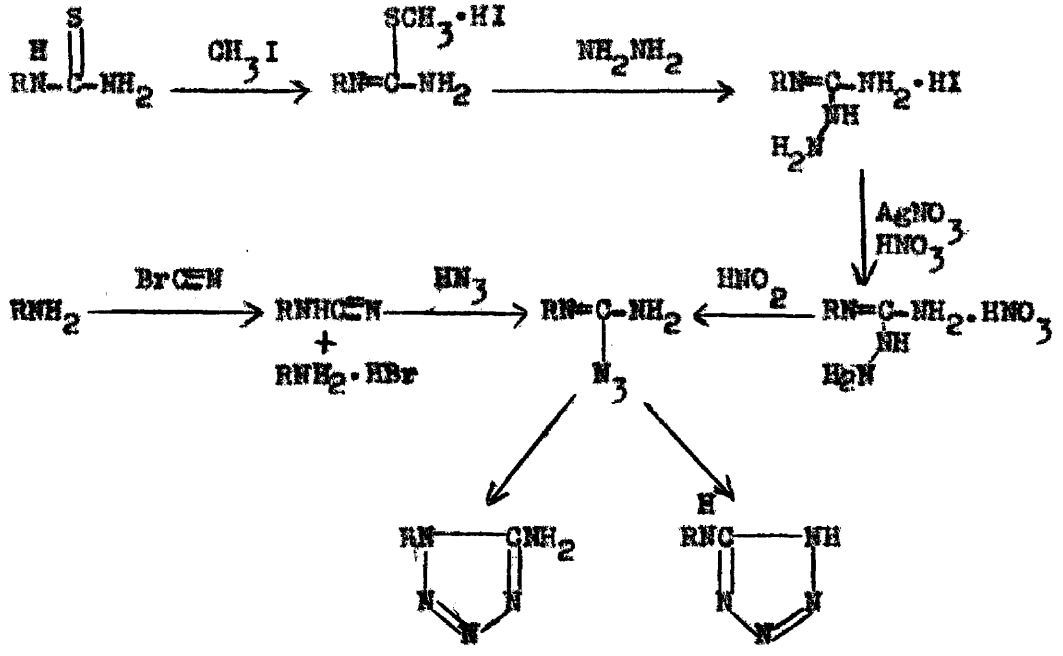


An inspection of these tautomeric structures reveals that three mono-cyanoethylated products could arise from the reaction of 5-aminotetrazole with acrylonitrile. The β-cyanoethyl residue could be attached to the 1 or 2 nuclear positions or the 5-amino nitrogen. An even greater number of isomers of di- and tri-cyanoethylated 5-aminotetrazole is possible. In view of the total number of products that could conceivably result from the reaction of 5-aminotetrazole with acrylonitrile, separation difficulties appeared to be inevitable.

In order to limit the number of possible isomers, several 1-substituted 5-aminotetrazoles were initially chosen for the study. With an alkyl or an aryl substituent in the 1 position, a maximum of two hydrogens could be replaced by β-cyanoethyl groups. Although the

possibility of obtaining quite a number of products still existed, it was hoped that just one or two different cyanoethylated 5-aminotetrazoles would be produced in the reaction of a 1-substituted 5-aminotetrazole with acrylonitrile. Therefore, several 1-substituted 5-aminotetrazoles were synthesized.

1-Phenyl-5-aminotetrazole was prepared from phenyl thiourea using the method of Finnegan et al (7), modified to permit successive steps without isolating the intermediates. The 1-cyclohexyl and 1-benzyl-5-aminotetrazoles were prepared from the corresponding amines using Wilson's modification (8) of the method devised by Garbrecht and Herbst (9). In both of these methods, the 5-aminotetrazole is presumably formed by the cyclization of a guanyl azide intermediate.



R = alkyl or aryl

It is conceivable that the guanyl azide could cyclize in either of two ways to yield a 1-substituted 5-aminotetrazole or a 5-substituted aminotetrazole. However, a previous study (9) has shown that in all instances, even with substituents of varying electronegativities, the only product obtained was the 1-substituted 5-aminotetrazole.

1-Benzyl-5-aminotetrazole was also prepared by benzylation of 5-aminotetrazole following the procedure of Herbst and Garbrecht (10). Also isolated from this reaction were 5-benzylaminotetrazole and 1-benzyl-5-benzylaminotetrazole.

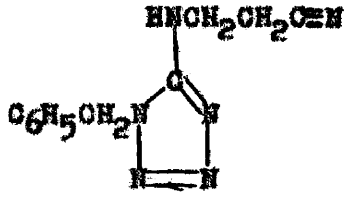
Although the 1-phenyl, 1-cyclohexyl, and 1-benzyl-5-aminotetrazoles were prepared with the intention of investigating the products from the reaction of each with acrylonitrile, only the 1-benzyl-5-aminotetrazole was actually used. The reason for this was the apparent ease with which the benzyl group can be removed by catalytic hydrogenolysis according to the method of Birkofer (11). By the use of this degradative procedure, the products from the reaction of acrylonitrile with 1-benzyl-5-aminotetrazole could be related to 5-aminotetrazoles containing only β-cyanoethyl substituents.

In the cyanoethylation studies, it was found that intimate mixing of the reactants and the catalyst and the use of freshly distilled acrylonitrile were necessary conditions for reaction to occur. A survey of previous applications of the cyanoethylation reaction indicated that benzyltrimethylammonium hydroxide was an extremely versatile catalyst. Therefore, a 40 percent aqueous solution of this compound was utilized in all experiments. No attempt was made

to determine whether some other catalyst would have been more satisfactory. Ethylene dichloride was used as the initial solvent for the products since this solvent has been found to dissolve cyanoethylated products selectively. Any polymers of acrylonitrile formed during the reaction remained undissolved (1).

When a mole-to-mole ratio of 1-benzyl-5-aminotetrazole and freshly distilled acrylonitrile was caused to react in the presence of a 40 percent aqueous solution of benzyltrimethylammonium hydroxide catalyst, a crystalline compound resulted. Elemental analysis showed that monocyanoethylation had occurred. The two most reasonable positions for the introduction of the β-cyanoethyl residue appeared to be in the 4 position (I) or attachment to the amino nitrogen (II).

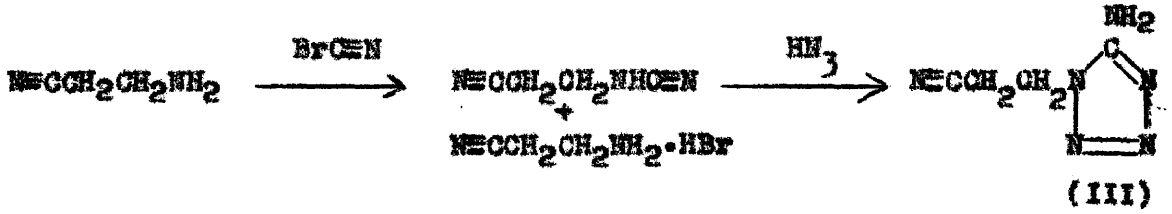
(I)



(II)

1,4-Disubstituted 5-iminotetrazolines (I) exhibit quite basic properties and readily form hydrochlorides of definite composition (12). The mono-cyanoethylated 1-benzyl-5-aminotetrazole was only slightly basic and failed to form a hydrochloride of definite composition. Since this behavior is characteristic of the 1-alkyl-5-alkylaminotetrazoles (13), tentative assignment of structure as 1-benzyl-5-β-cyanoethylaminotetrazole (II) to the mono-cyanoethylated 1-benzyl-5-aminotetrazole was made.

For comparative purposes, the synthesis of 1-benzyl-4-β-cyanoethyl-5-iminotetrazoline (I) was undertaken. It was felt that the most desirable approach was the benzylation of 1-β-cyanoethyl-5-aminotetrazole if this compound could be prepared. Using this method and barring rearrangements, the attachment of the β-cyanoethyl group at position 1 of the tetrazole ring would be established. Preparation of 1-β-cyanoethyl-5-aminotetrazole (III) was accomplished in the following manner. β-Aminopropionitrile, synthesized from ammonia and acrylonitrile (14), was used as the starting material. Interaction of β-aminopropionitrile with cyanogen bromide in diethyl ether gave a cyanamide which reacted with hydrazoic acid in boiling xylene, according to the method of Garbrecht and Herbst(9), to give the desired tetrazole as a colorless crystalline product, m.p. 115-116°C. This series of reactions is represented below.

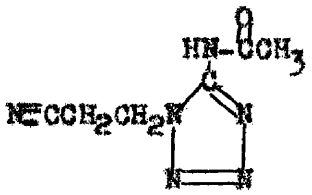


(III)

Elemental analysis supported the postulation that this product was 1-β-cyanoethyl-5-aminotetrazole (III), but could not exclude the possibility that 5-β-cyanoethylaminotetrazole had formed. The neutral character of the product indicated that the ring closure had not produced a 5-alkylaminotetrazole; all known 5-alkylaminotetrazoles exhibit definite acidic properties. In addition, previous investigations using the synthetic route employed in the preparation of (III)

have shown that ring closure of the guanyl azide intermediate occurs only in the direction yielding a 1-substituted 5-aminotetrazole (9).

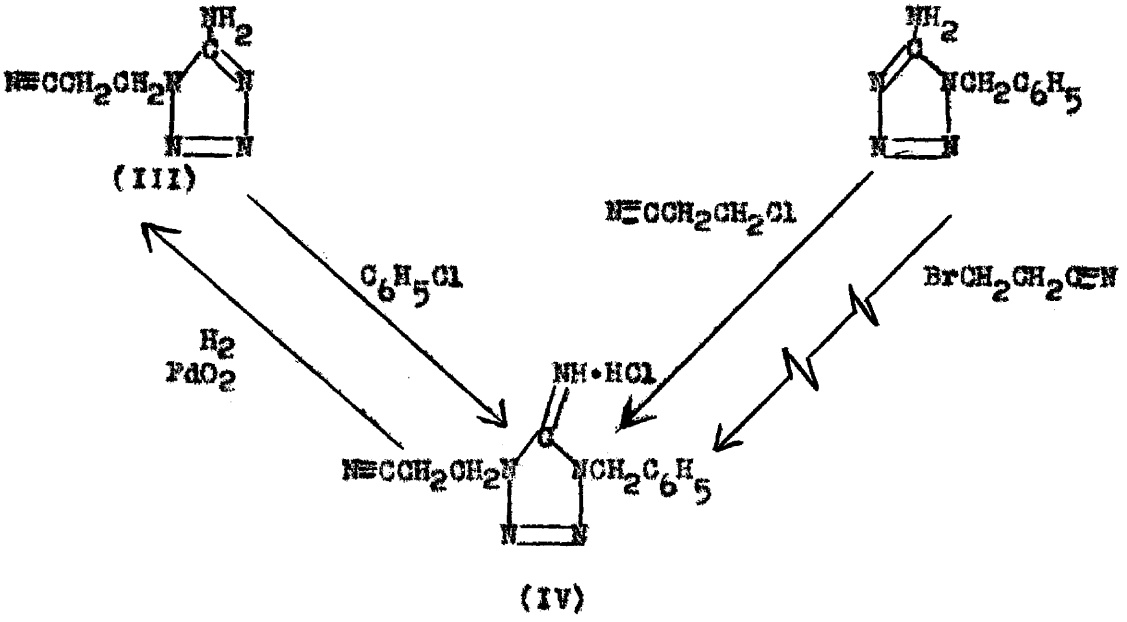
An acetyl derivative (IIIa) of 1-β-cyanoethyl-5-aminotetrazole was prepared by refluxing it with acetic anhydride (10).



(IIIa)

When a mixture of 1-β-cyanoethyl-5-aminotetrazole (III) and an equimolar quantity of benzyl chloride was heated in an oil bath (15), an exothermic reaction ensued and the mixture solidified. Recrystallization of the crude product gave a colorless crystalline solid whose elemental analysis was correct for 1-benzyl-4-β-cyanoethyl-5-iminotetrazoline hydrochloride (IV). A compound of identical infra-red spectrum, melting point, and mixture melting point was prepared by the alkylation of 1-benzyl-5-aminotetrazole with β-chloropropionitrile, using the same technique (15). Preparation of the 1-benzyl-4-β-cyanoethyl-5-iminotetrazoline hydrochloride was also accomplished from 1-benzyl-5-aminotetrazole using β-bromopropionitrile as the alkylating reagent. In the latter case, the crude tetrazoline hydrobromide was treated with aqueous sodium hydroxide to yield an extremely basic pale yellow oil. When this oil was caused to react with gaseous hydrogen chloride, 1-benzyl-4-β-cyanoethyl-5-iminotetrazoline hydrochloride (IV) was formed instantaneously.

After several attempts, catalytic debenzylation of 1-benzyl-4-β-cyanoethyl-5-iminotetrazoline hydrochloride (IV) using the method of Birkofer (11) yielded a product whose melting point was not depressed by admixture with 1-β-cyanoethyl-5-aminotetrazole (III). The preceding transformations may be summarized schematically:

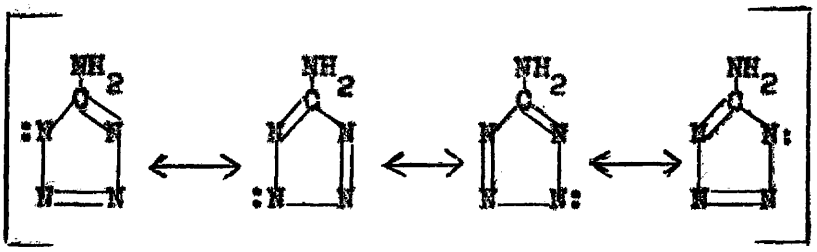


(IV)

From this phase of the investigation, the following interpretations may be drawn. Since 1-benzyl-4-β-cyanoethyl-5-iminotetrazoline hydrochloride (IV) was formed regardless of the order of introduction of the benzyl and the -cyanoethyl groups and since 1-β-cyanoethyl-5-aminotetrazole (III) resulted from the catalytic debenzylation of this compound, it may be concluded that compound (IV) is 1-benzyl-4-β-cyanoethyl-5-iminotetrazoline hydrochloride. This conclusion is supported by Percival's investigation establishing the site of mono-alkylation of the 1-substituted 5-aminotetrazoles (12).

Furthermore, this series of reactions substantiates the assumption that the 5-aminotetrazole prepared from β-aminopropionitrile contained the β-cyanoethyl residue in the 1 position as previously postulated. Most important, however, is the basic nature of the oil liberated by aqueous sodium hydroxide from the product of the reaction of 1-benzyl-5-aminotetrazole and β-bromopropionitrile and from 1-benzyl-4-β-cyanoethyl-5-iminotetrazoline hydrochloride (IV). Although no elemental analysis was obtained for the pale yellow oil, the fact that 1-benzyl-4-β-cyanoethyl-5-iminotetrazoline hydrochloride (IV) was formed immediately upon contact of this oil with hydrogen chloride indicates that this substance was the free base, 1-benzyl-4-β-cyanoethyl-5-iminotetrazoline (I). From a comparison of the behavior of this compound with that of the mono-cyanoethylated 1-benzyl-5-aminotetrazole, (II), it was apparent that these compounds were not identical.

An examination of the structural formula of 1-β-cyanoethyl-5-aminotetrazole (III) reveals that this compound could conceivably result from the cyanoethylation of 5-aminotetrazole. Alkylation studies involving the sodium salt of 5-aminotetrazole (16) have demonstrated that the formation of salts of 5-aminotetrazole involves chiefly the 1 and 2 nuclear positions. This may be interpreted as meaning that the anion resulting from the removal of a proton is stabilized by resonance and reacts as though the free electrons are localized in the nuclear positions.



Since the 1 and 4 positions and the 2 and 3 positions are equivalent in the 5-aminotetrazole nucleus which contains no substituents, only two nuclear substituted products can be formed.

The Michael condensation, of which base-catalyzed cyanoethylation is a specific type, involves the addition of a compound containing a labile hydrogen to an activated carbon to carbon double bond. A mechanism advanced for this reaction (3) involves the abstraction of the labile hydrogen by the basic catalyst followed by the addition of the resulting anion to the more positive end of the polarized double bond.

$$\rangle N\text{-}H + B^-(\text{base}) \rightleftharpoons \rangle N:^- + HB$$

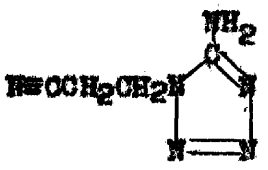
$$\rangle N:^- + \overset{\delta^+}{C}H_2{=}CH\text{-}\overset{\delta^-}{C}{\equiv}N \rightleftharpoons \rangle N\text{-}CH_2\dot{C}H\text{-}C{\equiv}N$$

$$\rangle N\text{-}CH_2\dot{C}H\text{-}C{\equiv}N + HB \rightleftharpoons \rangle N\text{-}CH_2\text{-}CH_2\text{-}C{\equiv}N + B^-$$

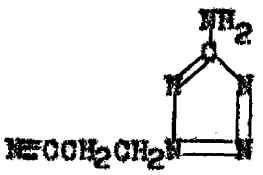
In view of the predominance of the 1 and 2-substituted 5-aminotetrazoles arising from a reaction which involves anion formation and the mechanism for the base-catalyzed cyanoethylation reaction which also involves anion formation, it was hoped that the number of products resulting from the cynnoethylation of 5-aminotetrazole would be limited. With this in mind, cyanoethylation of 5-aminotetrazole was attempted.

When a mole-to-mole ratio of acrylonitrile was added to 5-aminotetrazole containing a few drops of a 40 percent aqueous solution of benzyltrimethylammonium hydroxide catalyst and the mixture was well blended, an exothermic reaction occurred giving a yellow solution. After heating this solution for twelve hours at reflux temperature followed by chilling, a yellow crystalline solid resulted, m.p. 97-106°C., whose melting point range was not appreciably narrowed by repeated recrystallizations from absolute ethanol. Separation into two components was accomplished, however, by extraction of the solid with hot ethylene dichloride. When the ethylene dichloride extract was chilled, colorless platelets, (A), precipitated. After recrystallization, this material melted at 117.0-117.5°C. Characterization of this compound, (A), will be discussed later. The residue from the ethylene dichloride extraction upon recrystallization from 95 percent ethanol gave a colorless crystalline solid, (B), m.p. 115-116°C., which was found to be identical with 1-β-cyanoethyl-5-aminotetrazole (III). Mixtures of (A) and (B) melted below 100°C.

Elemental analysis indicated that product (A) was also a monocyanoethylated derivative of 5-aminotetrazole. A survey of the possible positions to which the β-cyanoethyl group could be attached showed that three isomers were possible: 1-β-cyanoethyl-5-aminotetrazole (III), 2-β-cyanoethyl-5-aminotetrazole (V), and 5-β-cyanoethylaminotetrazole (VI).



(III)



(V)

(VI)

Since a mixture melting point of this compound and an authentic sample of 1-β-cyanoethyl-5-aminotetrazole (III) was depressed by 27°C, and because the infra-red spectrum of the solid was unlike that of the spectrum of 1-β-cyanoethyl-5-aminotetrazole (III), the possibility of the presence of the β-cyanoethyl residue in the 1 position was eliminated. Thus, the compound could not be a polymorphic modification of (III). In addition, the acetyl derivative of this substance, (A), exhibited a melting point of 136-137°C. compared to that of 104-105°C. for the acetyl derivative, (IIIa), of 1-β-cyanoethyl-5-aminotetrazole (III).

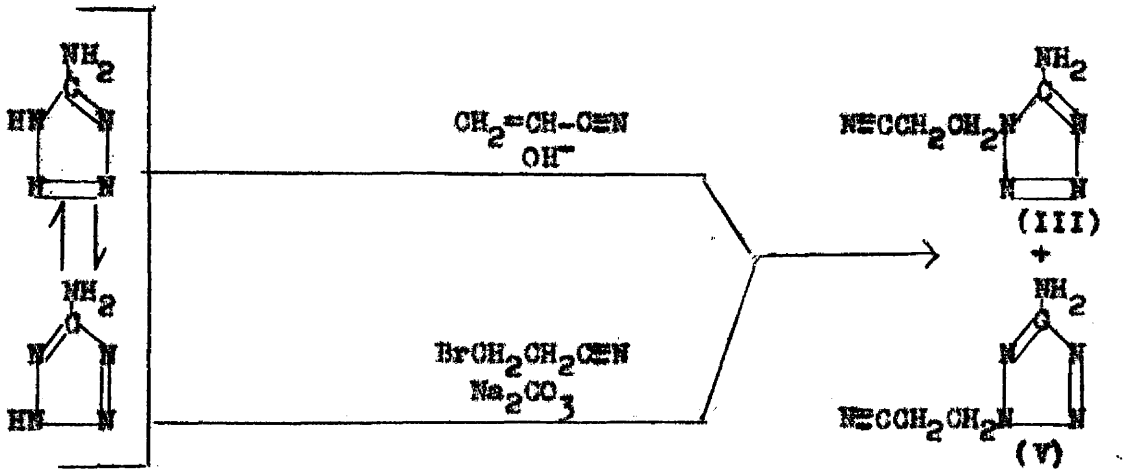
The fact that different acetyl derivatives were obtained is also evidence that the material, (A), could not be 5-β-cyanoethylaminotetrazole (VI). It has been demonstrated that under the conditions employed, 1-alkyl-5-aminotetrazoles and 5-alkylaminotetrazoles containing the same alkyl group form the same acetyl derivative (10). Also, all known 5-alkylaminotetrazoles are acidic and the results of an attempted potentiometric titration of the second mono-cyanoethylated derivative of 5-aminotetrazole indicated that its aqueous solution was slightly basic. Upon examining the infra-red spectrum of the solid obtained from an attempted thermal rearrangement (17) of

compound (A), it was found that the minor differences in the spectrum compared with an infra-red spectrum of the starting material could probably be attributed to some decomposition which was observed. Unless the substituents are relatively electronegative, it has been shown (17) that 5-substituted aminotetrazoles will undergo thermal rearrangement to the corresponding 1-substituted 5-aminotetrazoles.

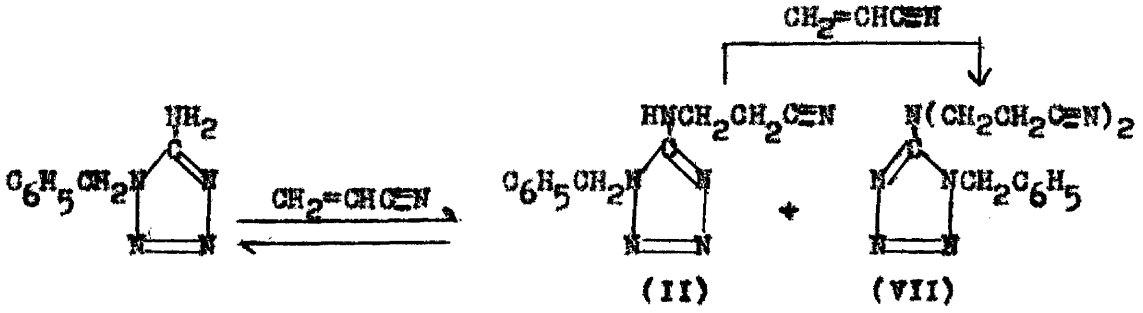
On the basis of the above facts, (III) and (IV) have been eliminated as possible structures for the ethylene dichloride soluble product, (A), from the cyanoethylation of 5-aminotetrazole. The possibility that the compound is 2-β-cyanoethyl-5-aminotetrazole (V) still remained.

Independent synthesis was not attempted since all known procedures for the synthesis of 2-substituted 5-aminotetrazoles require hydrolytic or reductive procedures too drastic for the nitrile group to withstand. Instead, an alkylation of 5-aminotetrazole with β-bromopropionitrile in a basic aqueous-ethanolic medium was effected. Henry and Finnegan have reported (16) that such an alkylation yields chiefly 1 and 2 substituted 5-aminotetrazoles with only trace amounts of other products. Two products were isolated from this reaction, one a compound, m.p. 115-116°C., that was identical in all respects to 1-β-cyanoethyl-5-aminotetrazole (III), and the other, a solid exhibiting a melting point of 116-117°C. A mixture melting point of the latter with product (A) from the cyanoethylation of 5-aminotetrazole showed no depression. In addition, their infra-red spectra were identical. It is felt that on the basis of the evidence presented, it is reasonable to assume that compound (A) is 2-β-cyanoethyl-5-amino-tetrazole (V).

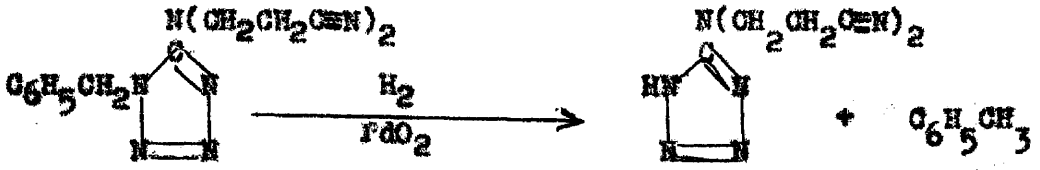
The cyanoethylation and the alkylation of 5-amino-tetrazole which have been discussed may be represented diagrammatically as follows:



Further experimentation with the cyanoethylation of 1-benzyl-5-aminotetrazole revealed that by the use of an excess of acrylonitrile, varying amounts of another product could be obtained in addition to 1-benzyl-5-β-cyanoethylaminotetrazole (II). Elemental analysis indicated the presence of two cyanoethyl residues. This compound could also be prepared by further reaction of 1-benzyl-5-β-cyanoethylaminotetrazole (II) with acrylonitrile in the presence of benzyltrimethylammonium hydroxide as a catalyst. For this compound, structure (VII) representing 1-benzyl-5-N,N-di-β-cyanoethylaminotetrazole was postulated.

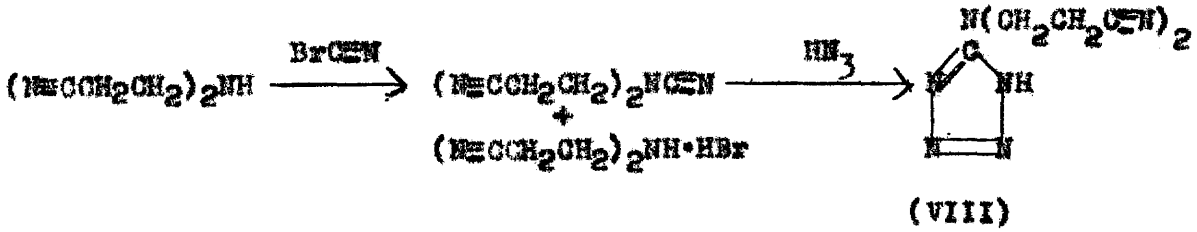


Hydrogenolysis of 1-benzyl-5-N,N-di-β-cyanoethylaminotetrazole (VII) should lead to 5-N,N-di-β-cyanoethylaminotetrazole (VIII).



(VII) (VIII)

However, before hydrogenolysis was attempted, the anticipated product was prepared by an independent synthetic route. When a solution of β,β'-iminodipropionitrile in ethyl acetate was treated with cyanogen bromide and the resulting cyanamide refluxed with a benzene solution of hydrazoic acid according to the procedure of Garbrecht and Herbst (18), a colorless crystalline product was obtained whose aqueous solution was definitely acidic. This indicated a 5-substituted aminotetrazole. An elemental analysis was correct for 5-N,N-di-β-cyanoethylaminotetrazole (VIII), the desired compound. The series of reactions leading to the formation of this compound are represented below:



(VIII)

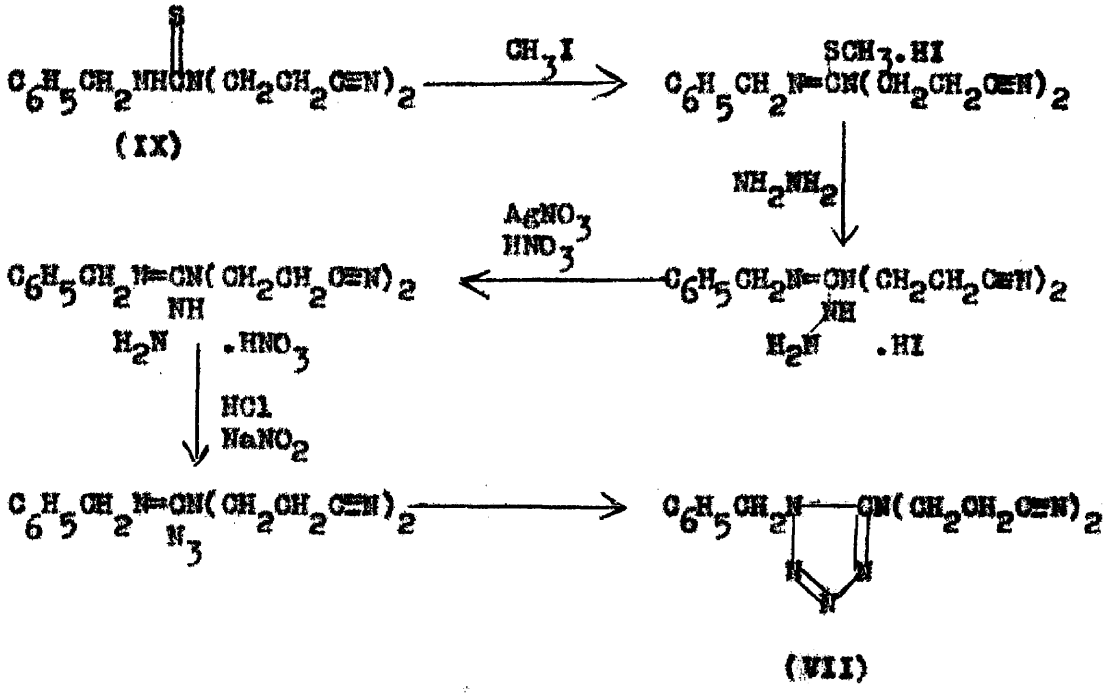
It was found that the behavior of 5-N,N-di-β-cyanoethylaminotetrazole (VIII) in a potentiometric titration with sodium hydroxide was analogous to that of a carboxylic acid. From the titration curve

an equivalent weight of 191.6 was obtained which agreed well with the value of 191.2 calculated from the molecular formula. Calculation of the pK by the 50 percent neutralization method (19) gave an approximate value of 4.85.

After several unsuccessful attempts, debenzylation of the dicyanoethylated 1-benzyl-5-aminotetrazole (VII), using the method of Birkofer (11), yielded a crystalline solid, m.p. 127-129°C. Although the melting point could not be raised by repeated recrystallizations, a mixture melting point determination of this compound and an authentic sample of 5-N,N-di-β-cyanoethylaminotetrazole (VIII) showed no depression. Identity of the compounds was also established by a comparison of infra-red spectra. This information supported the assignment of structure (VII) for the compound.

In order to further substantiate this assignment of structure, two different routes were explored for an unequivocal synthesis of 1-benzyl-5-N,N-di-β-cyanoethylaminotetrazole (VII). Although numerous attempts at both of these methods failed, a brief summary of each of the two approaches is included.

The first method, that of Finnegan et al. (7), utilized N-benzyl-N',N'-di-β-cyanoethylthiourea (IX) as the starting material. This compound was prepared from benzylisothiocyanate and β,β'-iminodipropionitrile using a modification of the method of Dyson and Hunter (20). The following diagram illustrates this synthetic approach:



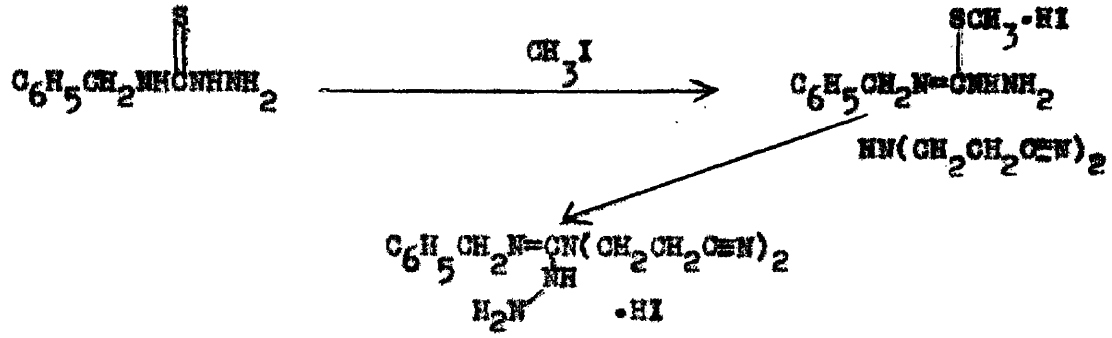
(IX)

(VII)

In each of the unsuccessful attempts, the reactions appeared to be proceeding satisfactorily to the point where silver nitrate solution was added to metathetically replace the iodide with a nitrate ion. Upon the addition of the silver nitrate, an insoluble plastic material precipitated along with the silver iodide. After the precipitate was removed by filtration, dissolution of the filtrate gave a red oil whose infra-red spectrum was unlike that of 1-benzyl-5-N,N-di-β-cyanoethylaminotetrazole (VII).

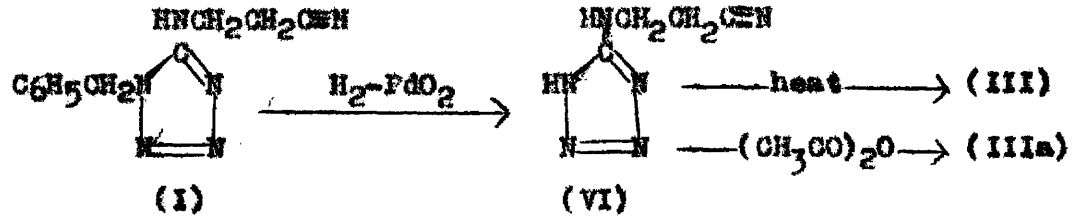
The other approach to the synthesis of (VII) involved a different procedure for the preparation of the aminoguanidine hydriodide intermediate. Although there is no record of this approach in the literature, the method seemed to be a reasonable one. 4-Benzylthiosemicarbazide was used as the starting material. The procedure leading to the formation of the guanidine hydriodide intermediate may

be represented as follows:



Evidence that S-methylation occurred was the evolution of methyl mercaptan upon the addition of β,β'-iminodipropionitrile. After the preparation of a solution of the compound assumed to be the aminoguanidine hydriodide, the same succession of steps was followed as with the other method. Again, the same difficulties were encountered and no 1-benzyl-5-N,N-di-β-cyanoethylaminotetrazole (VII) was obtained.

Although the postulation that the structure of the mono-cyanoethylated 1-benzyl-5-aminotetrazole is represented by (I) was strengthened by the fact that further cyanoethylation of this compound yielded 1-benzyl-5-N,N-di-β-cyanoethylaminotetrazole (VII), additional proof of structure seemed to be desirable. Debenzylation of this compound should result in the formation of 5-β-cyanoethylaminotetrazole (VI). This compound, (VI), should be acidic in nature, undergo thermal rearrangement to the 1-β-cyanoethyl-5-aminotetrazole (III), and form the same acetyl derivative, (IIIa). Therefore, catalytic debenzylation

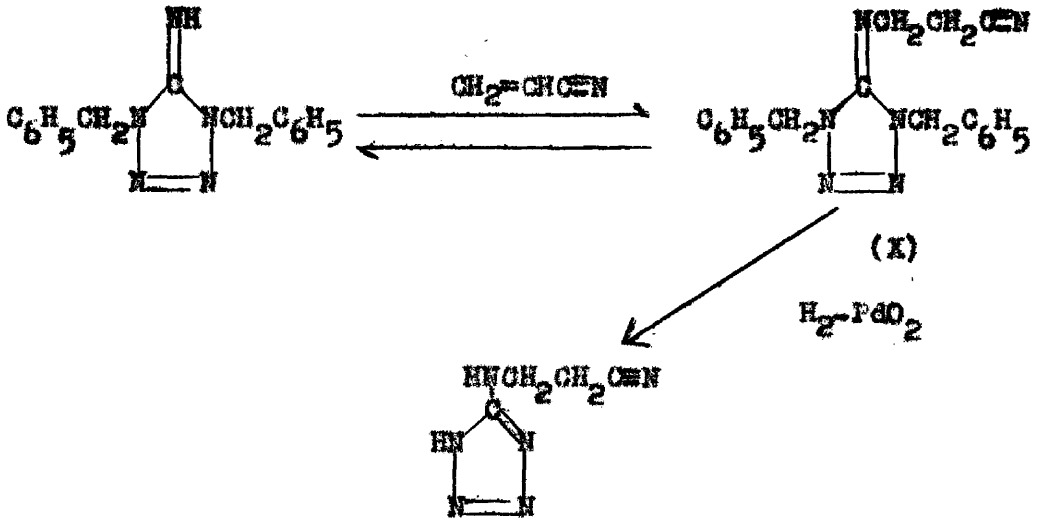


of (I) was attempted, again using the method of Birkofer (11).

Many attempts were unsuccessful and resulted in the recovery of starting material or a substance exhibiting the characteristic odor of an amine which was not identified. One attempted hydrogenolysis using glacial acetic acid as the solvent and palladium oxide as the catalyst gave evidence of debenzylation having occurred. The orange oil isolated from this reaction was acidic, formed a salt when neutralized with aqueous sodium hydroxide, and reacted with acetic anhydride at reflux temperature to yield an acetyl derivative which was identical with that formed from 1-β-cyanoethyl-5-aminotetrazole(III) and acetic anhydride. The infra-red spectrum of the oil was different from that of the starting material, 1-benzyl-5-β-cyanoethylaminotetrazole (I). When thermal rearrangement of the oil was attempted, no rearrangement occurred when the oil was heated at 120°C. for two hours. Upon heating the oil at 165°C. for four hours, some darkening occurred and a glassy solid was obtained. The infra-red spectrum of this material was unlike that of the original oil. Attempts to isolate 1-β-cyanoethyl-5-aminotetrazole from the glassy solid were unsuccessful. Although a sample of the oil from the hydrogenolysis of 1-benzyl-5-β-cyanoethylaminotetrazole (I) could not be purified sufficiently for elemental analysis, it appears that debenzylation of (I) yielded a substance some of whose properties were those predicted for 5-β-cyanoethylaminotetrazole (VI).

In order to obtain a cyanoethylated 5-aminotetrazole with the β-cyanoethyl residue in the 5 position, cyanoethlation of 1,4-dibenzyl-5-iminotetrazoline was attempted. Debenzylation of the

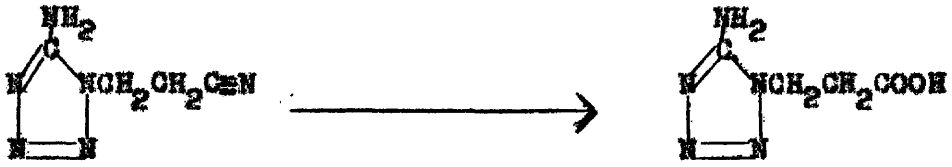
expected product from this reaction, 1,4-dibenzyl-5-β-cyanoethyliminotetrazoline (X), should produce 5-β-cyanoethylaminotetrazole (VI). The proposed scheme may be represented as follows:



A red viscous oil which eventually solidified to an orange solid, m.p. 83-140°C. was obtained on cyanoethylation of 1,4-dibenzyl-5-iminotetrazoline. Purification was attempted by solution of this material in acetone, decolorization with Norite, and reprecipitation with n-hexane. A creamy white solid resulted which darkened and was transformed into an oil upon exposure to the air. After several days the oil solidified to an orange mass, m.p. ca. 123 with some decomposition. Because of this behavior, debenzylation of the product was not attempted.

Several attempts were made to obtain the carboxylic acid derived from 1-β-cyanoethyl-5-aminotetrazole (III). Basic and acidic conditions were employed to hydrolyze the nitrile group of (III) to

form the corresponding acid (XI).



(III) (XI)

Decyanoethylation occurred when barium hydroxide was used as the hydrolytic reagent and 5-aminotetrazole was isolated from the reaction mixture. Because of the equilibrium nature of the cyanoethylation reaction, elimination of the cyanoethyl group in alkaline media is not without precedent. Alkali catalyzed decyanoethylation has been observed in other instances (1,2,6). An acidic product which underwent decomposition with gas evolution at its melting point was obtained from one hydrolysis using concentrated hydrochloric acid. However, a titration of this substance with aqueous sodium hydroxide revealed an equivalent weight of 141 compared to the calculated value of 157 and no elemental analysis was obtained for this substance.

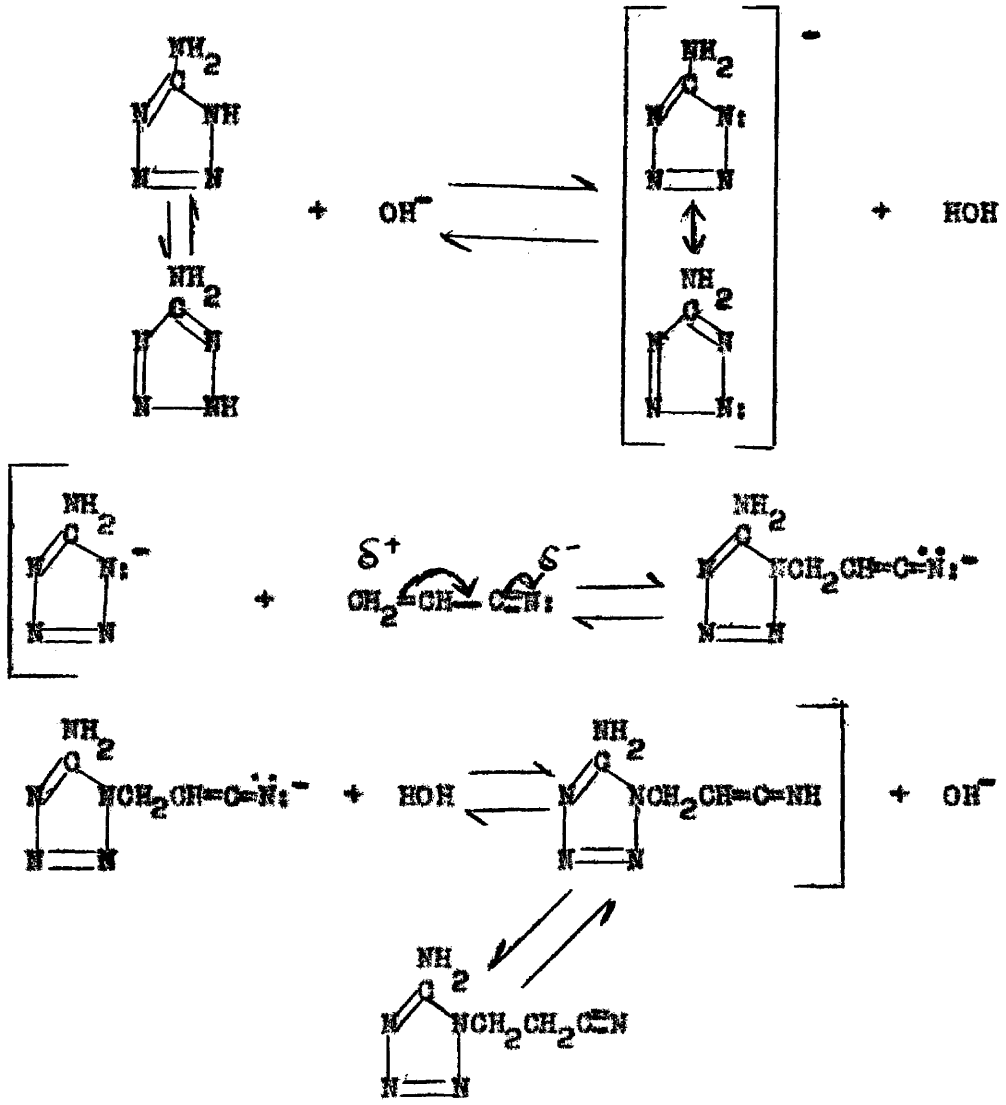
In an attempt to synthesize the carboxylic acid (XI), or some derivative thereof, preparation of the 5-aminotetrazoles from β-alanine and the ethyl ester of β-alanine was undertaken using the method of Garbrecht and Herbst (9). The desired products could not be isolated from these reactions.

On the basis of the results of the investigations concerning the cyanoethylation of the 5-aminotetrazoles, the reaction of acrylonitrile with 5-aminotetrazole in the presence of benzyltrimethylammonium

hydroxide was found to produce mono-cyanoethylation on the nitrogens contained within the tetrazole nucleus, yielding 2-β-cyanoethyl-5-aminotetrazole (III) and 2-β-cyanoethylaminotetrazole (V). The reaction of acrylonitrile with 1-benzyl-5-aminotetrazole using the same catalyst caused cyanoethylation of the exocyclic amino nitrogen with formation of 1-benzyl-5-β-cyanoethylaminotetrazole (I) and 1-benzyl-5-N,N-di-β-cyanoethylaminotetrazole (VII).

In view of the positions of attachment of the β-cyanoethyl residue in the reaction of acrylonitrile with 5-aminotetrazole and with 1-benzyl-5-aminotetrazole, some speculations can be made concerning the mechanisms involved. 5-Aminotetrazole is an acidic compound and readily forms salts. As previously discussed, investigations concerning the alkylation reactions of the 5-aminotetrazole molecule which proceed through anion formation yield chiefly 1- and 2-alkyl-5-aminotetrazoles as the mono-alkylation products (16). Since the base-catalyzed cyanoethylation of 5-aminotetrazole also produced 1- and 2-substituted 5-aminotetrazoles, the possibility exists that this reaction occurred via formation of the anion of 5-aminotetrazole.

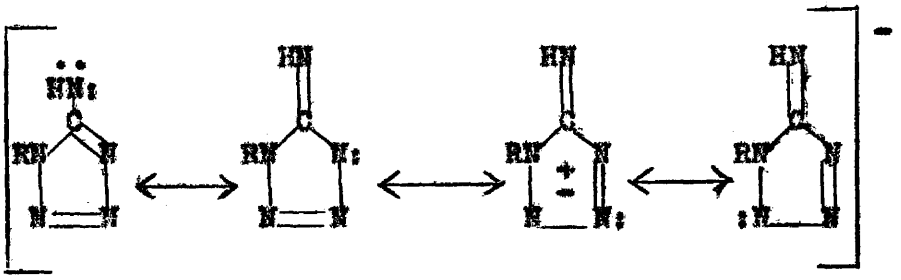
It is conceivable that benzyltrimethylammonium hydroxide could abstract the labile hydrogen as a proton from 5-aminotetrazole to form the anion. This anion could induce polarization of the acrylonitrile molecule followed by attack of the anion at the more positive end of the dipolar species. The resulting anion could then react with a water molecule to give the cyanoethylated 5-aminotetrazole and regenerate the catalyst. This mechanism may be represented as follows:



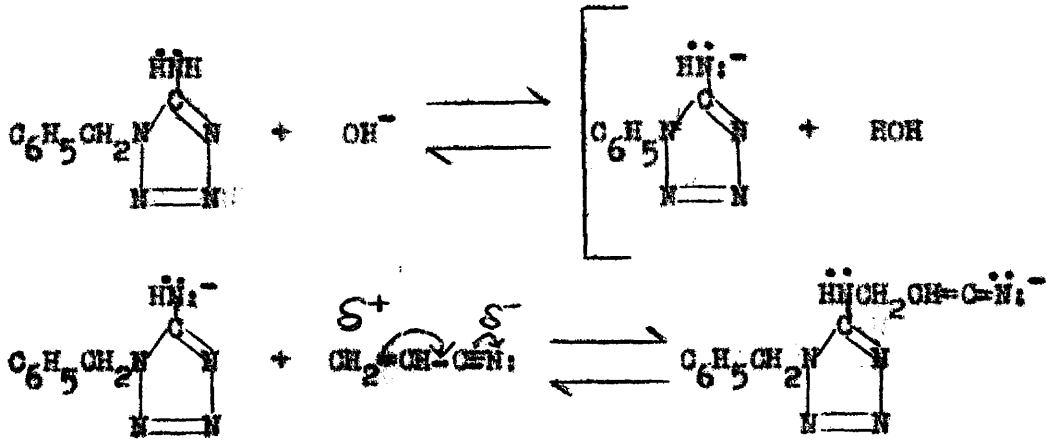
Since dialkylation of 5-aminotetrazole in basic media results in the introduction of the second alkyl group chiefly on the amino group in the 5 position, Henry and Finnegan (16) have suggested that 1- and 2- alkyl-5-aminotetrazoles are formed initially and further alkylation proceeds through these compounds to yield 1- and 2-alkyl-5-alkylaminotetrazoles.

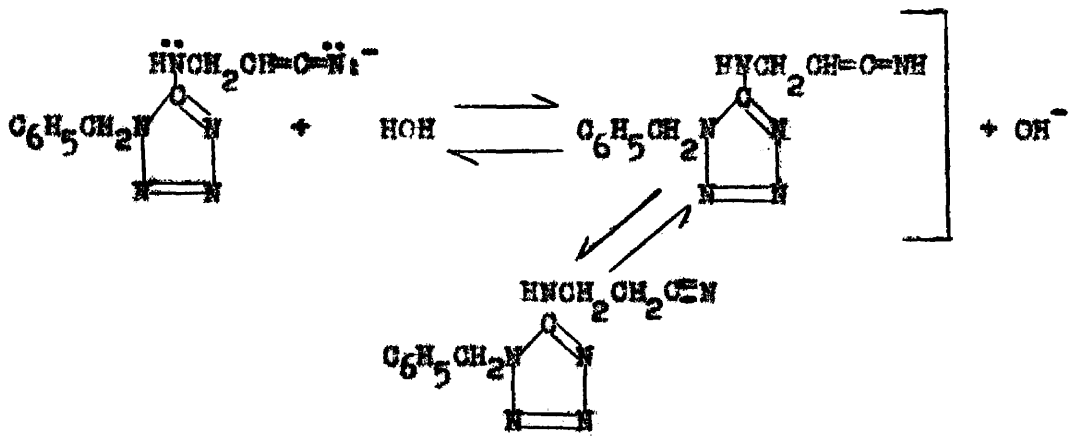
Although 1-alkyl-5-aminotetrazoles are slightly basic, it is possible that in the presence of a stronger base, one of the amino

hydrogens can be removed to form an anionic species. Conceivably, contributing structures to the resonance hybrid of the anion could have the free pair of electrons localized at the 2, 3, or 4 nuclear nitrogens or the 5-amino nitrogen. In view of the products formed, the anion behaves as though the negative charge was localized at the 5-amino position.

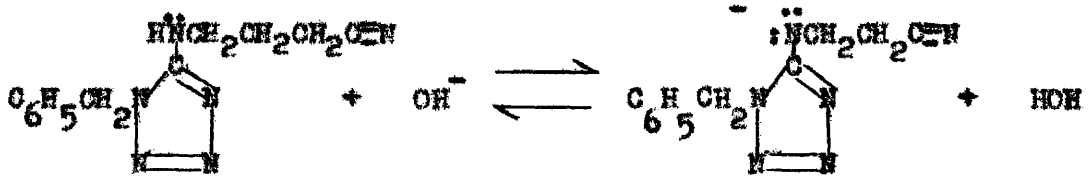


Using this analogy with the base-catalyzed cyanoethylation reaction, a mechanism similar to the one advanced for the cyanoethylation of 5-aminotetrazole can be postulated for the reaction of 1-benzyl-5-aminotetrazole with acrylonitrile. This may be represented by the following series of equations:



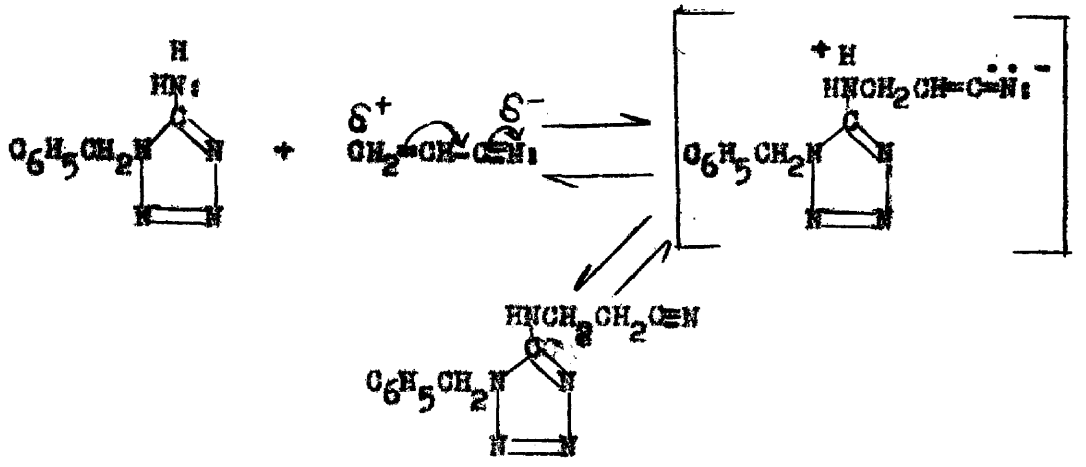


To explain the formation of 1-benzyl-5-N,N-di-β-cyanoethylamino-tetrazole the remaining hydrogen could be abstracted as a proton from the mono-cyanoethylated 1-benzyl-5-aminotetrazole. Further reaction of 1-benzyl-5-β-cyanoethylaminotetrazole with acrylonitrile produced the di-cyanoethylated compound and lends support to this supposition. The formation of the anion is represented below. This anion could react with the acrylonitrile molecule as previously indicated to yield



1-benzyl-5-N,N-di-β-cyanoethylaminotetrazole.

Although the preceding mechanism for the cyanoethylation of 1-benzyl-5-aminotetrazole seems to be a reasonable one, the possibility of at least one other mechanism remains. In this mechanism, the 1-benzyl-5-aminotetrazole molecule could react with an acrylonitrile molecule whose dipolar character has been enhanced by the presence of the basic catalyst. This species could then undergo an intra-molecular proton shift to produce the desired product, i.e.



Further reaction of this molecule with acrylonitrile could produce the di-cyanoethylated product by an analogous path.

EXPERIMENTAL *,**

Preparation of 1-phenyl-5-aminotetrazole

1-Phenyl-5-aminotetrazole was prepared in a 75 percent yield from phenylthiourea using the procedure of Finnegan et al. (7) modified to allow successive steps without isolation of the intermediates.

A suspension of 152 g. (1 mole) of N-phenylthiourea in 300 ml. of absolute ethanol was cooled to 5°C. and treated with 150 g. (1.06 moles) of methyl iodide over a period of one-half hour with constant stirring. Stirring was continued for an additional hour and a half as the ice melted and the temperature gradually rose. During this time the slurry was transformed to a clear yellow solution from which a solid precipitated. The reaction mixture was heated to reflux temperature and held there for one hour during which time the solid dissolved to form an orange solution. One hundred milliliters of distillate were removed. The residual solution was diluted to the original volume with absolute ethanol, chilled, and 50 g. (1 mole) of 64 percent hydrazine were added slowly with stirring. (The methyl mercaptan evolved was trapped in aqueous potassium hydroxide.) Following this addition, the solution was heated to reflux and

---

*All analyses were done by Micro-Tech Laboratories, Skokie, Ill.

**The acrylonitrile used in this research was donated by Monsanto Chemical Co. and the β,β'-iminodipropionitrile by American Cyanamid Co.

maintained there for an hour. Upon slight cooling, water-vacuum was applied and the ethanol was removed. Three hundred milliliters of water were added and 200 ml. of distillate were collected to remove any residual ethanol. The solution was diluted with 500 ml. of distilled water and acidified to litmus with 15 ml. of concentrated nitric acid. To this was added dropwise, with stirring, a solution of 170 g. (1 mole) of silver nitrate in 250 ml. of water over a period of half an hour. Fifteen milliliters of concentrated hydrochloric acid was added to remove excess silver ion and stirring was continued for an hour. The insoluble silver salts were filtered from the solution and washed with hot water. Immediately the combined filtrates were chilled to 5°C. in an ice - salt mixture and 69 g. (1 mole) of sodium nitrite in 200 ml. of water were added with stirring at a rate such that the temperature did not exceed 8°C. When an excess of nitrous acid was indicated by starch - potassium iodide paper, the mixture was stirred for an additional 15 minutes, neutralized with aqueous potassium hydroxide and stirred for 30 minutes, reacidified with 150 ml. concentrated hydrochloric acid, warmed to 35°C. and allowed to cool slowly. After room temperature was attained, the mixture was chilled and filtered and the solid was washed with cold water. Recrystallization was effected from isopropyl alcohol using Darco as the decolorizing agent. Seventy-eight grams of 1-phenyl-5-aminotetrazole resulted as colorless platelets, m.p. 159 - 160°C. (7).

Preparation of 1-cyclohexyl-5-aminotetrazole:

One mole (99 g.) of cyclohexylamine dissolved in 500 ml. of 95 percent ethanol was cooled to 4°C. To this solution was added with stirring a solution of 106 g. (1 mole) of cyanogen bromide in 200 ml. of 95 percent ethanol and 200 ml. of distilled water at such a rate that the temperature did not rise above 10°C. This addition required about one and a half hours.

Forty grams (1 mole) of sodium hydroxide dissolved in 100 ml. of distilled water were added slowly with continued stirring keeping the temperature ca.10°C. Following this addition the mixture was stirred for two hours in an ice-water bath. A solution of 81 g. (1.25 moles) of sodium azide in 250 ml. of distilled water was then added in one portion. One hundred milliliters of concentrated hydrochloric acid diluted with 100 ml. of distilled water were added slowly maintaining a temperature of 10°C. After this addition was completed, the solution was heated at reflux for six hours, and then was allowed to stand overnight during which time crystallization occurred. The colorless platelets were filtered from the solution and dried. The yield of product, m.p. 217 - 219°C., was 118 g. An additional 15 g. of material of the same melting point range was obtained by concentrating the filtrate. Recrystallization of the combined fractions from 30 percent aqueous isopropyl alcohol resulted in the recovery of 115 g. of 1-cyclohexyl-5-aminotetrazole, m.p. 218 - 219°C. (15).

Preparation of 1-benzyl-5-aminotetrazole:

Preparation of 1-benzyl-5-aminotetrazole from one mole of benzylamine by a procedure analogous to that used for the preparation of 1-cyclohexyl-5-aminotetrazole resulted in an 80 percent yield of a white crystalline product, m.p. 189 - 190°C. (15).

Benzylation of 5-aminotetrazole:

One mole (85 g.) of anhydrous 5-aminotetrazole was benzylated following the procedure of Herbst and Garbrecht (10) resulting in the recovery of 17.1 g. (10%) of 1-benzyl-5-aminotetrazole, m.p. 185 - 189°C., 51.1 g. (30%) of 5-benzylaminotetrazole, m.p. 186 - 188°C., and 14.9 g. (7%) of 1-benzyl-5-benzylaminotetrazole, m.p. 168 - 170°C.

Cyanoethylation of 1-benzyl-5-aminotetrazole:

The conditions for the reaction of acrylonitrile with 1-benzyl-5-aminotetrazole were varied somewhat with each reaction. It was found that equimolar quantities of 1-benzyl-5-aminotetrazole and acrylonitrile produced a mono-cyanoethylated product. When an excess of acrylonitrile was used, varying amounts of dicyanoethylated product accompanied the mono-cyanoethylated material. Three representative reactions are described: One, a general method for obtaining the mono-cyanoethylated 1-benzyl-5-aminotetrazole; another, a reaction in which a small amount of dicyanoethylated product was obtained; and a third which resulted in a reasonable yield of dicyanoethylated 1-benzyl-5-aminotetrazole.

- - -

Seven grams (0.04 mole) of 1-benzyl-5-aminotetrazole were intimately mixed with four drops of a 40 percent aqueous solution of benzyltrimethylammonium hydroxide and the mixture chilled in an ice-bath. Two and twelve-hundredths grams (0.04 mole) of redistilled acrylonitrile were added dropwise with stirring. The mixture liquefied and then solidified to a yellow mass. The latter liquefied again upon heating on a steam bath for one hour and then almost immediately solidified. The solid was dissolved in hot ethylene dichloride and the solution was allowed to cool gradually to room temperature during which time snowball-like clusters of crystals began to precipitate from the orange solution. Chilling and filtration were effected and the resulting product was recrystallized from 95 percent ethanol to yield 5.4 g. (59 % of theory) of colorless clusters of 1-benzyl-5-β-cyanoethylaminotetrazole, m.p. 132.5-133.0°C.

Analysis: Calculated for $C_{11}H_{12}N_6$: C, 57.9%; H, 5.3%; N, 36.8%.

Found: C, 58.1%; H, 5.5%; N, 36.6%.

A slight modification of the above procedure resulted in the recovery of some dicyanoethylated 1-benzyl-5-aminotetrazole. A small excess of acrylonitrile was used with 14 g. (0.08 mole) of 1-benzyl-5-aminotetrazole and eight drops of the catalyst. This reaction mixture was heated in a water bath at 75°C. for five minutes after which the pale yellow solid was allowed to stand at room temperature for one hour. Crystallization from ethylene dichloride gave a crude product, m.p. 79-121°C. When recrystallization from

95 percent ethanol was attempted, shimmering platelets separated while the solution was still warm. Collection by filtration yielded 3.2 g. (14% of theory) of 1-benzyl-5-N,N-di-β-cyanoethylaminotetrazole, m.p. 80 - 81.5°C.

Analysis: Calculated for $C_{14}H_{15}N_7$: C, 59.7%; H, 5.34% N, 34.9%

Found: C, 59.6%; H, 5.35%; N, 35.1%

On chilling the filtrate, 12.0 g. (66% of theory) of crude 1-benzyl-5-β-cyanoethylaminotetrazole separated. The melting point of the product recrystallized from 95 percent ethanol was 115-116°C.

Further experimentation regarding conditions for the reaction revealed that when 1-benzyl-5-aminotetrazole was heated at reflux for 16 hours with a five-fold excess of acrylonitrile using benzyltrimethylammonium hydroxide as the catalyst, a 46 percent yield of the dicyanoethylated product was obtained.

Preparation of 1-β-cyanoethyl-5-aminotetrazole:

To a well-stirred solution of seven grams (0.1 mole) of β-aminopropionitrile (14) and 100 ml. of anhydrous diethyl ether immersed in an ice-bath was added dropwise a solution of 10.6 g. (0.1 mole) of cyanogen bromide in 50 ml. of anhydrous ether keeping the temperature about 10°C. (During this addition a white precipitate formed which presumably was the amine hydrobromide.) Upon completion of the addition, the reaction mixture was allowed to stand at room temperature for two hours. The solid was filtered by suction

and the resulting filtrate was heated under reflux with 40 ml. of xylene containing 4.5 g. (0.1 mole) of hydrazoic acid for twenty hours. The straw-colored solution was chilled and the tan precipitate collected by filtration. Recrystallization was effected from absolute ethanol using Darco as the decolorizing agent. Four and two-tenths grams (15% of theory) of colorless crystals of 1-β-cyanoethyl-5-aminotetrazole, m.p. 115-116°C., were obtained.

Analysis: Calculated for $C_4H_6N_6$: C, 34.8%; H, 4.4%; N, 60.8%.
Found: C, 35.0%; H, 4.4%; N, 60.7%.

Preparation of the acetyl derivative of 1-β-cyanoethyl-5-aminotetrazole:

A mixture of 2.76 g. (0.02 mole) of 1-β-cyanoethyl-5-aminotetrazole and 15 ml. of acetic anhydride was heated at reflux for two hours. Twenty-five milliliters of 95 percent ethanol were added and the solution was evaporated to dryness. The resulting yellow oil was placed under dry benzene and chilled while stirring vigorously. Crystallization occurred, resulting in a crude yellow product. Recrystallization was effected from 95 percent ethanol using Darco as the decolorizing agent. Two and one-half grams of 1-β-cyanoethyl-5-acetylaminotetrazole were obtained as colorless crystals, m.p. 104-105°C.

Analysis: Calculated for $C_6H_8ON_6$: C, 40.0%; H, 4.5%; N, 46.8%.
Found: C, 40.1%; H, 4.5%; N, 46.8%.

Preparation of 1-benzyl-4-β-cyanoethyl-5-iminotetrazoline hydrochloride:

A. Benzylation of 1-β-cyanoethyl-5-aminotetrazole:

A mixture of 0.138 g. (0.001 mole) of 1-β-cyanoethyl-5-aminotetrazole and 0.126 g (0.001 mole) of benzyl chloride was heated in an oil bath to 125°C. At this temperature, two liquid layers were discernible. The mixing of these layers by stirring resulted in an exothermic reaction followed by immediate solidification. A minimum amount of hot 95 percent ethanol was used to dissolve the crude product. Chilling this solution followed by filtration produced a white powdery solid. Subsequent recrystallization from 95 percent ethanol yielded 0.24 g. (93% of theory) of 1-benzyl-4-β-cyanoethyl-5-iminotetrazoline hydrochloride as colorless needles, m.p. 215-216°C. with some decomposition.

Analysis: Calculated for $C_{11}H_{13}N_6Cl$: N, 31.8%; Cl, 13.4%.
Found: N, 31.8%; Cl, 13.4%.

Repetitions of the above procedure with quantities up to 0.05 mole were carried out, however, with these quantities the reaction became quite violent and some charring of the product occurred.

B. Reaction of 1-benzyl-5-aminotetrazole with β-chloropropionitrile:

A mixture of 1.75 g. (0.01 mole) of 1-benzyl-5-aminotetrazole and 0.875 g. (0.01 mole) of β-chloropropionitrile was heated in an oil bath at 150°C. for one half hour. During this time, no apparent reaction occurred so the mixture was heated at 150°C. for an additional

hour and a half. The resulting melt solidified upon cooling. Recrystallization of this crude solid from 95 percent ethanol gave a white product, m.p. 213 - 215°C. The product obtained was identical with that prepared by benzylation of 1-β-cyanoethyl-5-aminotetrazole as shown by a mixture melting point determination and correspondence of the infra-red spectra.

C. Reaction of 1-benzyl-5-aminotetrazole with β-bromopropionitrile:

A mixture of 1.75 g. (0.01 mole) of 1-benzyl-5-aminotetrazole and 1.34 g. (0.01 mole) of β-bromopropionitrile was heated at 145°C. for one-half hour. An exothermic reaction occurred and the melt solidified. The crude hydrobromide was treated with an aqueous solution of sodium hydroxide. Isolation of the resulting yellow oil, the reaction of this free base with hydrogen chloride gas, followed by recrystallization from 95 percent ethanol gave 1.97 g. (64% of theory) of 1-benzyl-4-β-cyanoethyl-5-iminotetrazoline hydrochloride, m.p. 214-215°C.

Debenzylation of 1-benzyl-4-β-cyanoethyl-5-iminotetrazoline hydrochloride:

A solution of one gram of 1-benzyl-4-β-cyanoethyl-5-iminotetrazoline in 75 ml. of 80 percent aqueous ethanol was placed in a Burgess-Parr hydrogenation flask. Two-tenths of a gram of palladium oxide catalyst was added and the mixture was shaken under an initial hydrogen pressure of 49.0 p.s.i. for 2.25 hours. A temperature slightly above room temperature was maintained by means of a heating jacket controlled

by a Powerstat set at 10 volts. The catalyst was filtered from the solution and washed with hot 95 percent ethanol. Solid sodium carbonate was added to the combined filtrate, which emitted a detectable odor of toluene, to neutralize the hydrogen chloride released during the reaction. The ethanolic solution was freed from solid material by filtration and then concentrated. Chilling the concentrate resulted in the formation of colorless crystalline material. Recrystallization of this material from 95 percent ethanol yielded a small amount of product, m.p. 112-114°C. A mixture melting point of this substance with 1-β-cyanoethyl-5-aminotetrazole showed no depression. In addition, a comparison of the infra-red spectra of these products indicated their identity.

Reaction of 5-aminotetrazole with acrylonitrile:

To a cooled, intimate mixture of 8.5 g. (0.1 mole) of 5-aminotetrazole and four drops of a 40 percent aqueous solution of benzyltrimethylammonium hydroxide were added with stirring 5.3 g. (0.1 mole) of freshly distilled acrylonitrile. After the initial exothermic reaction had ceased, the mixture was heated to reflux and maintained there for twelve hours during which time the pasty mixture was transformed into a yellowish-orange solution which solidified to yellow crystals, m.p. 97-106°C., when cooled. Recrystallization of this material from absolute ethanol did not appear to narrow the melting point range. Upon attempted solution of the crude product in hot ethylene dichloride, it was found that only about half of the material

dissolved. Advantage was taken of this fact in obtaining two distinct products. The hot ethylene dichloride extract was cooled to room temperature and then chilled, followed by filtration to remove the colorless plates which had precipitated. Recrystallization of this material from 95 percent ethanol resulted in the recovery of 3.7 g. (27% of theory) of product, m.p. 117-117.5°C., which is apparently 2-β-cyanoethyl-5-aminotetrazole.

Analysis: Calculated for $C_4H_6N_6$: C, 34.8%; H, 4.4%; N, 60.8%.
2-β-cyanoethyl-5-aminotetrazole. [illegible]%; H, 4.4%; N, 60.7%.

Following two recrystallizations from 95 percent ethanol, the ethylene dichloride insoluble portion of the crude product yielded 4.6 g. (33% of theory) of colorless clusters, m.p. 115-116°C. Correspondence of the infra-red spectra of this compound and 1-β-cyanoethyl-5-aminotetrazole prepared from β-aminopropionitrile established its identity. A mixture melting point of the two products was not depressed.

Repetition of this reaction under essentially identical conditions did not appear to result in a fixed ratio of the 1- and 2-substituted products.

Preparation of an acetyl derivative of 2-β-cyanoethyl-5-aminotetrazole:

To a suspension of 1.5 g. of 2-β-cyanoethyl-5-aminotetrazole in 15 ml. of chloroform were added five milliliters of reagent grade acetic anhydride. This suspension which gradually became a clear solution was heated to reflux and maintained there for four and one-half hours. After cooling to room temperature, the solution was

placed in a refrigerator for 24 hours during which time a colorless crystalline precipitate formed. The precipitate was removed by filtration, washed well with cold chloroform and then dried in an oven at 50°C. One and seven-tenths grams (87% of theory) of 2-β-cyanoethyl-5-acetylaminotetrazole, m.p. 136-137°C. (shrinking at 133°C.), were obtained.

Analysis: Calculated for $C_6H_8ON_6$: C, 40.0%; H, 4.5%; N, 46.6%.
Found: C, 40.2%; H, 4.6%; N, 46.6%.

Alkylation of 5-aminotetrazole with β-bromopropionitrile:

To a well-stirred solution of 8.5 g. (0.1 mole) of 5-aminotetrazole in 150 ml. 95 percent ethanol maintained at reflux temperature was added dropwise 6.2 g. (0.05 mole) of sodium carbonate monhydrate dissolved in 35 ml. of water. (Too rapid addition caused violent evolution of carbon dioxide.) Upon completion of this addition, the solution was stirred on a steam-bath for one hour, followed by the dropwise addition of 13.4 g. (0.1 mole) of β-bromopropionitrile dissolved in 15 ml. of 95 percent ethanol. Stirring and refluxing were continued for an additional two hours. The solution was then concentrated under a vacuum while gradually adding absolute ethanol to replace the ethanol-water solvent. A small amount of a white crystalline precipitate, presumably sodium bromide, which had formed during this process was removed by filtration. The filtrate was evaporated to dryness and the resulting crude product was extracted with hot ethylene dichloride. After concentrating and chilling the ethylene dichloride

extract, a mass of colorless platelets was obtained. Recrystallization of this material from 95 percent ethanol yielded 4.2 g. (32% of theory) of the compound assumed to be 2-β-cyano-ethyl-5-aminotetrazole, m.p. 116-117°C.

The remaining portion of the crude product was extracted with acetone. Evaporation of this extract, washing the remaining solid material with dilute aqueous sodium hydroxide solution to remove any unreacted 5-aminotetrazole, followed by several recrystallizations from 95 percent ethanol, yielded 3.7 g. (27% of theory) of a crystalline product, m.p. 115-116°C. Correlation of infra-red spectra and mixture melting point data showed this material to be 1-β-cyanoethyl-5-aminotetrazole.

Formation of 1-benzyl-5-N,N-di-β-cyanoethylaminotetrazole from 1-benzyl-5-β-cyanoethylaminotetrazole:

An intimate mixture of 2.25 g. (0.01 mole) of 1-benzyl-5-β-cyanoethylaminotetrazole, five milliliters of redistilled acrylonitrile, and four drops of the 40 percent aqueous benzyltrimethylammonium hydroxide catalyst was heated at reflux on a steam-bath for two hours. The red oil which resulted was dissolved in hot ethylene dichloride and the solution was allowed to cool gradually, then chilled. Yellow platelets formed which were collected and recrystallized from 95 percent ethanol using Darco as the decolorizing agent. After drying, the colorless platelets of 1-benzyl-5-N, N-di-β-cyanoethylaminotetrazole exhibited a melting point of 79-81°C. A comparison of the infra-red spectra and the melting point

of this compound and that of the di-cyanoethylated compound isolated from the cyanoethylation of 1-benzyl-5-aminotetrazole established these compounds as identical.

Preparation of 5-N,N-di-β-cyanoethylaminotetrazole:

To a well-stirred solution of 24.6 g. (0.2 mole) of β,β'-iminodipropionitrile dissolved in 50 ml. of ethyl acetate and chilled to about 5°C. was added dropwise a solution of 10.6 g. (0.1 mole) of cyanogen bromide and 50 ml. of ethyl acetate at such a rate to maintain a temperature below 10°C. Upon completion of the addition, stirring was continued for one hour in an ice-bath and then at room temperature for eight hours. During this time a white precipitate, presumably the amine hydrobromide, became evident. This precipitate was removed by filtration and washed with hot ethyl acetate. The filtrate was then concentrated under a vacuum to about 50 ml. to this solution were added 100 ml. of benzene containing 15 g. of hydrazoic acid and the resulting solution was maintained at reflux temperature for eight hours. One hundred more milliliters of the benzene solution of hydrazoic acid were added and the reaction solution was refluxed for an additional 16 hours. Masses of colorless crystals became discernible in the pink solution. Chilling of the solution followed by filtration to remove the precipitate yielded 11.8 g. (62% of theory) of pink tinted crystals, m.p. 129-132°C. After one recrystallization from 95 percent ethanol, 9.0 g. of 5-N,N-di-β-cyanoethylaminotetrazole were obtained as colorless crystals, m.p. 133.5-134.0°C.

Analysis: Calculated for $C_7H_9N_7$: C, 44.0%; H, 4.8%; N, 51.2%.
Found: C, 43.9%; H, 4.8%; N, 51.2%.

On occasion when reaction was incomplete, attempted isolation of the tetrazole resulted in the recovery of a low-melting solid, m.p. 48-50°C. Elemental analysis of this substance indicated that this compound was probably the N,N-di-β-cyanoethyl cyanamide.

Analysis: Calculated for $C_7H_8N_4$: C, 56.7%; H, 5.5%; N, 37.8%.
Found: C, 56.3%; H, 5.6%; N, 36.8%.

Determination of the equivalent weight and apparent pK of 5-N,N-di-β-cyanoethylaminotetrazole:

A weighed sample, 0.5508 g., of 5-N,N-di-β-cyanoethylaminotetrazole was dissolved in 200 ml. of distilled water. This solution was titrated with 0.1032 N aqueous sodium hydroxide at 27°C. By using a Beckman pH Meter, Model G, the pH was recorded after each addition of base. From a plot of the pH versus the volume of base added (See Table 1 in the Appendix), the equivalence point was determined. It was found that 27.75 ml. of 0.1032 N aqueous sodium hydroxide were required. From this value, an equivalent weight of 191.6 was calculated compared with 191.2 calculated from the molecular formula. The apparent pK determined from the pH at 50 percent neutralization (19) was 4.85.

Debenzylation of 1-benzyl-5-N,N-di-β-cyanoethylaminotetrazole:

One gram of 1-benzyl-5-N,N-di-β-cyanoethylaminotetrazole dissolved in 50 ml. of 95 percent ethanol and one milliliter of concentrated

hydrochloric acid were placed in a 500 ml. Burgess-Parr pressure bottle. To this was added 0.1 g. of 5 percent palladium on charcoal catalyst and the mixture was shaken under an initial hydrogen pressure of 49.5 p.s.i. for five hours. The catalyst was filtered from the solution and washed with hot 95 percent ethanol. A strong odor of toluene was noticeable in the filtrate. Evaporation of the solvent resulted in the formation of an orange pasty mass. Attempted recrystallization of this material from 95 percent ethanol using Darco as the decolorizing agent yielded a clear viscous oil. By stirring this oil with several portions of ether while chilling, crystallization was induced. Recrystallization of the white semi-solid material yielded a small amount of a colorless crystalline solid, m.p. 127-129°C. The infrared spectrum of this product was identical with that of an independently synthesized sample of 5-N,N-di-β-cyanoethylaminotetrazole. A mixture melting point of these compounds showed no depression. In an attempt to isolate more of the hydrogenolysis product, the ethanolic solution was evaporated almost to dryness. Chilling of this solution yielded a solid material which liquefied on the filter paper.

Preparation of N-benzyl-N',N'-di-β-cyanoethylthiourea:

The benzyl isothiocyanate used in this synthesis was prepared in a 74 percent yield from benzylamine and carbon disulphide following the procedure of Percival (21).

A well-stirred solution of 74.5 g. (0.5 mole) of benzyl isothiocyanate and 25 ml. of absolute ethanol was chilled to approximately 10°C. in an ice-water bath. To this solution was added dropwise a

solution of 61.5 g (0.5 mole) of β,β'-iminodipropionitrile in 25 ml. of absolute ethanol while maintaining a temperature of less than 20°C. Upon completion of the addition, stirring was continued while the temperature of the solution was gradually raised to the reflux point and maintained there for one hour. When this solution was cooled to room temperature and then chilled, only a few crystals were evident in a syrupy solution. Crystallization was induced by the addition of 500 ml. of hot absolute ethanol, allowing the solution to cool gradually with periodic chilling. The crude product was collected by filtration and then recrystallized twice from absolute ethanol. One hundred twenty-one and three-tenths grams (89% of theory) of N-benzyl-N',N'-di-β-cyanoethylthiourea were obtained as colorless, flat crystals, m.p. 145-145.5°C.

Analysis: Calculated for $C_{14}H_{16}N_4S$: C, 61.7%; H, 5.92%; N, 20.6%; S, 11.8%.

Found: C, 61.8%; H, 5.99%; N, 20.4%; S, 11.6%.

Attempted syntheses of 1-benzyl-5-N,N-di-β-cyanoethylaminotetrazole:

Although all of the many attempts leading to the synthesis of this compound were unsuccessful, two independent routes were investigated - a typical example of each is described below. Essentially, the procedure is that utilized in the preparation of the 1-phenyl-5-aminotetrazole.

A. Using N-benzyl-N',N'-di-β-cyanoethylthiourea:

To a well-stirred solution of 10.9 g. (0.04 mole) of N-benzyl-N',N'-di-β-cyanoethylthiourea and 150 ml. of absolute ethanol

immersed in an ice bath 10 g. of methyl iodide was added in one portion. Stirring at ice-bath temperature was continued for two hours after which the solution was stirred at room temperature for two additional hours, and then under reflux conditions for one hour. One hundred milliliters of distillate were collected under a vacuum to remove any excess methyl iodide. Absolute ethanol was then added to restore the original volume, followed by the dropwise addition of 1.28 g. (0.04 mole) of anhydrous hydrazine dissolved in 50 ml. of absolute ethanol. Stirring was continued for 15 minutes at room temperature after which the methyl mercaptan that had formed was expelled by heating the solution at reflux for half an hour. The ethanol was removed under reduced pressure, adding water during the final stages of the distillation to flush any remaining ethanol from the system and to effect a complete transference to an aqueous solution without allowing a solventless condition to intervene. This solution was acidified to litmus with concentrated nitric acid. To this was added dropwise with stirring a solution of 6.8 g. (0.04 mole) of silver nitrate in 50 ml. of distilled water. (At this point, along with the coagulated silver iodide, a red plastic precipitate was formed which solidified to an extremely hard substance for which only one solvent, glacial acetic acid, was found. The original material could not be recovered from its solution in glacial acetic acid.) After the addition of concentrated hydrochloric acid to precipitate the excess silver, the insoluble material was filtered from the solution and the residue was washed with hot water. Diazotization of this solution was

effected with sodium nitrite, but only a foul-smelling, red oil could be isolated which showed no tendency toward crystal formation. The infra-red spectrum of the red oil was quite unlike the spectrum of 1-benzyl-5-N,N-di-β-cyanoethylaminotetrazole.

B. Using 4-benzylthiosemicarbazide:

The 4-benzylthiosemicarbazide used in this reaction was prepared using a modification of the method employed by Pulvermacher (22). A mixture of 29.8 g. (0.2 mole) of benzyl isothiocyanate and 50 ml. of 95 percent ethanol was chilled in an ice-bath. To this was added slowly with stirring a solution of 6.6 g. of 95 percent hydrazine in 50 ml. of 95 percent ethanol. During this addition, a white precipitate formed. After the addition was completed, the solution was allowed to stand in an ice-bath for one hour. The crystals were removed by filtration, washed with cold ethanol, and air-dried. Twenty-eight and eight-tenths grams (80% of theory) of 4-benzylthiosemicarbazide, m.p. 124-126°C., were obtained.

In the attempted synthesis of 1-benzyl-5-N,N-di-β-cyanoethylaminotetrazole, 9.05 g. (0.05 mole) of 4-benzyl-thiosemicarbazide dissolved in 50 ml. of absolute ethanol were chilled to 4°C. To this solution was added dropwise with stirring a solution of 7.5 g. (0.052 mole) of methyl iodide in 25 ml. of ethanol. Upon completion of this addition, stirring was continued for one and one-half hours at ice-bath temperature and two and one-half hours at room temperature. This solution was concentrated under a vacuum to remove the unreacted

methyl iodide. Absolute ethanol was used to restore the original volume and the solution was chilled. A solution of 6.15 g. (0.05 mole) of β,β'-iminodipropionitrile in 25 ml. of absolute ethanol was added dropwise with stirring. Stirring was continued for two hours after the removal of the ice-bath. (The distinct odor of methyl mercaptan was observed.) Using reduced pressure, the ethanol was removed while gradually replacing the ethanol with distilled water. The aqueous solution was cooled and 3.3 ml. (ca. 0.05 eq.) of concentrated nitric acid were added, followed by the dropwise addition while stirring, of 8.5 g. (0.05 mole) of silver nitrate dissolved in 75 ml. of distilled water. Again, a plastic material precipitated along with the coagulated silver iodide. When the precipitated material was removed and the filtrate diazotized, the only product isolated was a reddish-brown oil which was readily soluble in benzene. The 1-benzyl-5-N,N-di-β-cyanoethylaminotetrazole prepared from the cyanoethylation of 1-benzyl-5-aminotetrazole exhibited very limited solubility in benzene.

Debenzylation of 1-benzyl-5-β-cyanoethylaminotetrazole:

After numerous attempts to debenzylate 1-benzyl-5-β-cyanoethylaminotetrazole using a variety of solvents and catalysts, the following procedure gave the best evidence that reaction had occurred. In some of the attempts, no hydrogenolysis resulted and the starting material was recovered. In others, material exhibiting a definite amine-like odor was recovered, but not identified.

One gram of 1-benzyl-5-β-cyanoethylaminotetrazole dissolved in 35 ml. of warm glacial acetic acid and 0.7 g. of palladium oxide

catalyst were shaken together in a Burgess-Parr hydrogenation flask for five hours under an initial hydrogen pressure of 50 p.s.i. The catalyst was removed by filtration and washed with hot glacial acetic acid. Evaporation of the solvent from the combined filtrates under reduced pressure yielded an orange oil which increased in viscosity when stirred with successive portions of n-hexane. When this material was placed under anhydrous benzene and allowed to stand for a few days, needle-like crystals dispersed throughout the oil were observed. Complete crystallization could not be induced by chilling and vigorous stirring.

Some of the crude product was refluxed with an excess of acetic anhydride for three hours. Twenty milliliters of 95 percent ethanol were added and the solution was concentrated to remove the unreacted acetic anhydride. Solution of the resulting red oil in 95 percent ethanol was effected followed by decolorization with Norite. Evaporation of the ethanol produced a clear viscous oil which eventually crystallized when stirred with successive portions of anhydrous benzene. After recrystallization of this material from absolute ethanol, a small amount of a colorless crystalline solid, m.p. 102-104°C., was obtained. A mixture melting point determination revealed that this compound was identical to that obtained from the acetylation of 1-β-cyanoethyl-5-aminotetrazole.

Since this indicated the possible presence of the desired compound (10), 5-β-cyanoethylaminotetrazole, further attempts were made to obtain a pure product. The oil containing dispersed crystalline material

was dissolved in absolute ethanol and decolorized with Norite. Evaporation of the ethanol under reduced pressure yielded a pale yellow oil. An aqueous-ethanolic solution of a small amount of this oil was acidic and upon neutralization with aqueous sodium hydroxide, a white precipitate formed which gave a residue when ignited. Another portion of the oil was dissolved in absolute ethanol and petroleum ether (b.p. 30-60°C.) was added until the solution became cloudy. Chilling produced a white flocculent precipitate which was transformed into a red oil a few seconds after removal by filtration. Further attempts to isolate a pure sample of this material were unsuccessful.

In an attempt to determine whether the oil would undergo thermal rearrangement to form 1-β-cyanoethyl-5-aminotetrazole, a small amount (ca. one millilliter) of this oil was heated for two hours in an oil-bath at 120°C. No change in the infra-red spectrum of the oil was noted after this treatment. When another sample was heated at 165°C. in an oil-bath for four hours, some darkening occurred. Upon cooling to room temperature, a glassy solid was obtained from which no 1-β-cyanoethyl-5-aminotetrazole could be isolated. Although the infra-red spectrum of this solid was different from the infra-red spectrum of the original oil and contained some peaks similar to those present in an infra-red spectrum of 1-β-cyanoethyl-5-aminotetrazole, the results of the thermal rearrangement were inconclusive.

Attempted cyanoethylation of 1,4-dibenzyl-5-iminotetrazoline:

1,4-Dibenzyl-5-iminotetrazoline hydrochloride was prepared by alkylation of 1-benzyl-5-aminotetrazole with benzyl chloride (13).

A benzene solution of the free base was prepared by dissolving 12.2 g. (0.04 mole) of the hydrochloride in warm water to which a small amount of ethanol had been added, treating this solution with an excess of aqueous sodium hydroxide, and then extracting the iminotetrazoline base with several portions of benzene.

The benzene solution containing 10.7 g. (0.04 mole) of 1,4-dibenzyl-5-iminotetrazoline (assuming quantitative recovery of the free base) was concentrated to the point where solid material just began to separate. To this solution was added 25 ml. of freshly distilled acrylonitrile and a few drops of 40 percent aqueous benzyltrimethylammonium hydroxide catalyst. After the reaction mixture had refluxed for 16 hours, a dark red oil, which solidified when the solution was chilled, became evident. The solid was collected by filtration and washed with cold benzene to remove any unreacted iminotetrazoline. In an attempt to purify the crude product, m.p. 83-140°C., it was dissolved in acetone heated to its boiling point, decolorized with Norite, and then precipitated by the addition of n-pentane. When the creamy white precipitate was filtered and exposed to the air, immediate darkening and softening to an oil occurred. Upon standing for several days, the oil deposited an orange solid, m.p. ca. 123°C. with some decomposition.

Attempted hydrolysis of 1-β-cyanoethyl-5-aminotetrazole:

A. Basic hydrolysis: (23)

Nine and six-tenths grams (0.032 mole) of barium hydroxide octahydrate were heated on a steam bath until self-solution had occurred.

This solution was stirred mechanically and a solution of 4.14 g. of 1-β-cyanoethyl-5-aminotetrazole in 50 ml. of hot water was added dropwise while maintaining a temperature of 85-90°C. Upon completion of the addition, the reaction mixture was heated on a steam bath for two hours. The odor of ammonia could be detected over the reaction mixture. Two grams of powdered asbestos and 250 ml. of hot water were added. The mixture was then saturated with carbon dioxide by gradual addition of dry ice. This mixture was filtered through fluted filter paper and the filter cake was washed with several portions of hot water. The combined filtrates were evaporated under reduced pressure. Crystallization of the resulting oil was induced by treatment with successive portions of benzene. Ignition of a portion of this material on the end of a spatula indicated the presence of inorganic matter. Therefore, the crude product was dissolved in water and successive portions of dilute aqueous sulfuric acid were added followed each time by centrifugation to remove the precipitated barium sulfate. When the centrifugate remained clear following the addition of the sulfuric acid, it was concentrated on a steam bath, then allowed to cool. Chilling produced a colorless crystalline precipitate which was removed by filtration. Recrystallization was effected from distilled water and after drying, the product exhibited a melting point of 200-201°C. with some decomposition. Detonation of the material occurred upon heating in a free flame. This behavior and the melting point range indicated that this material was 5-aminotetrazole. A mixture melting point and equivalent weight determination confirmed this assumption.

B. Acid hydrolysis:

A mixture of 5.52 g. (0.04 mole) of 1-β-cyanoethyl-5-aminotetrazole and 30 ml. of concentrated hydrochloric acid was heated on a steam bath for four hours and then allowed to stand at room temperature overnight. The colorless needle-like crystals were removed by filtration and air dried, m.p. 147-150°C. In order to determine whether this material was free from ammonium chloride, solution in absolute ethanol was attempted. A small amount of residue remained insoluble. Some of the material was then recrystallized from absolute ethanol, filtering off the insoluble ammonium chloride while the solution was hot. After two recrystallizations, a colorless crystalline material was obtained, m.p. 146-147°C. with much evolution of gas. An equivalent weight determination by titration of this substance with aqueous sodium hydroxide gave a value of 141 compared to the calculated value of 157. Because of this discrepancy, no elemental analysis was obtained.

Infra-red absorption spectra:

The infra-red absorption spectra (See Appendix) were obtained using a Perkin-Elmer Recording Spectrophotometer, Model 21. All compounds were run as Nujol mulls.

SUMMARY

1. Cyanoethylation of 1-benzyl-5-aminotetrazole in the presence of a benzyltrimethylammonium hydroxide catalyst produced 1-benzyl-5-β-cyanoethylaminotetrazole and 1-benzyl-5-N,N-di-β-cyanoethylaminotetrazole.

2. The reaction of 5-aminotetrazole with acrylonitrile using benzyltrimethylammonium hydroxide as a catalyst yielded 1-β-cyanoethyl-5-aminotetrazole and 2-β-cyanoethyl-5-aminotetrazole.

3. Other new compounds containing the β-cyanoethyl residue have been prepared during the process of establishing the structures of the cyanoethylated derivatives of 5-aminotetrazole and 1-benzyl-5-aminotetrazole by synthetic and degradative procedures. These are 1-benzyl-4-β-cyanoethyl-5-iminotetrazoline hydrochloride, 5-N,N-di-β-cyanoethylaminotetrazole, N-benzyl-N',N'-di-β-cyanoethylthiourea, 1-β-cyanoethyl-5-acetylaminotetrazole, and 2-β-cyanoethyl-5-acetyl-

1-β-cyanoethyl-5-acetylaminotetrazole, and 2-β-cyanoethyl-5-acetyl-

4. Possible mechanisms for the cyanoethylation of 5-aminotetrazole and 1-benzyl-5-aminotetrazole have been proposed.

LITERATURE CITED

1. H. A. Bruson, "Organic Reactions", John Wiley and Sons, Inc., New York, 1949, Vol. V, pp. 79-135.

2. L. S. Efros and B. A. Porai-Koshit, Zhur. Obshei Khim., 23, 697; C.A. 48, 7603H (1954).

3. E. R. Alexander, "Principles of Ionic Organic Reactions", John Wiley and Sons, Inc., New York, 1953, p. 152.

4. C. K. Ingold, "Structure and Mechanism in Organic Chemistry", Cornell University Press, Ithaca, N. Y., 1953, p. 691.

5. F. C. Whitmore, H. S. Mosher, R. R. Adams, R. B. Taylor, E. C. Chapin, C. Weisel, and W. Yanko, J. Am. Chem. Soc., 66, 725 (1944).

6. J. H. MacGregor and C. Pugh, J. Chem. Soc., 1945, 535.

7. W. G. Finnegan, R. A. Henry, and E. Lieber, J. Org. Chem., 18, 779 (1953).

8. K. R. Wilson, Alkylation Studies with Aminotriazoles and Aminotetrazoles, Ph.D. Thesis, Michigan State University, 1957.

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

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

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

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

13. D. F. Percival, Alkylated 5-Aminotetrazoles, Their Preparation and Properties, Ph.D. Thesis, Michigan State College, 1955.

14. S. R. Buc, "Organic Syntheses", Col. Vol. III, John Wiley and Sons, Inc., New York, 1955, p. 93.

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

16. R. A. Henry and W. G. Finnegan, J. Am. Chem. Soc., 76, 923 (1954).

17. W. L. Garbrecht and R. M. Herbst, J. Org. Chem., 18, 1269 (1953).

18. W. L. Garbrecht and R. M. Herbst, J. Org. Chem., 18, 1003 (1953).

19. A. Weissberger, ed., "Physical Methods of Organic Chemistry", 2nd. ed., Interscience Publishers Inc., New York, 1949, Vol. I, pt. 2, p. 1[illegible]4.

20. G. M. Dyson and R. F. Hunter, Rec. Trav. Chim., 45, 421 (1926).

21. D. F. Percival, Alkylated Guanidines, Their Preparation and Properties, M. S. Thesis, Michigan State College, 1952.

22. G. Pulvermacher, Ber., 27, 613 (1894).

23. J. H. Ford, "Organic Syntheses", Col. Vol. III, John Wiley and Sons, Inc., New York, 1955, p. 34.

APPENDIX

TABLE I

Data for the Titration of 0.5508 g. of 5-N,N-di-β-cyanoethylamino-tetrazole with 0.1032 N Aqueous Sodium Hydroxide:

Volume of NaOH (ml.)	pH	Volume of NaOH (ml.)	pH
0.00	3.44	26.00	6.14
2.00	3.88	26.50	6.30
4.00	4.14	27.09	6.65
6.00	4.34	27.50	7.68
8.00	4.50	27.70	8.01
10.00	4.65	28.00	9.77
12.00	4.78	28.20	10.06
13.00	4.84	28.54	10.35
14.00	4.89	29.01	10.55
14.50	4.91	30.00	10.82
15.00	4.97	32.00	11.07
15.50	4.99	34.00	11.19
16.00	5.01	36.00	11.35
18.00	5.14	38.00	11.41
20.00	5.29	40.00	11.51
22.01	5.48	50.00	11.71
24.00	5.72		

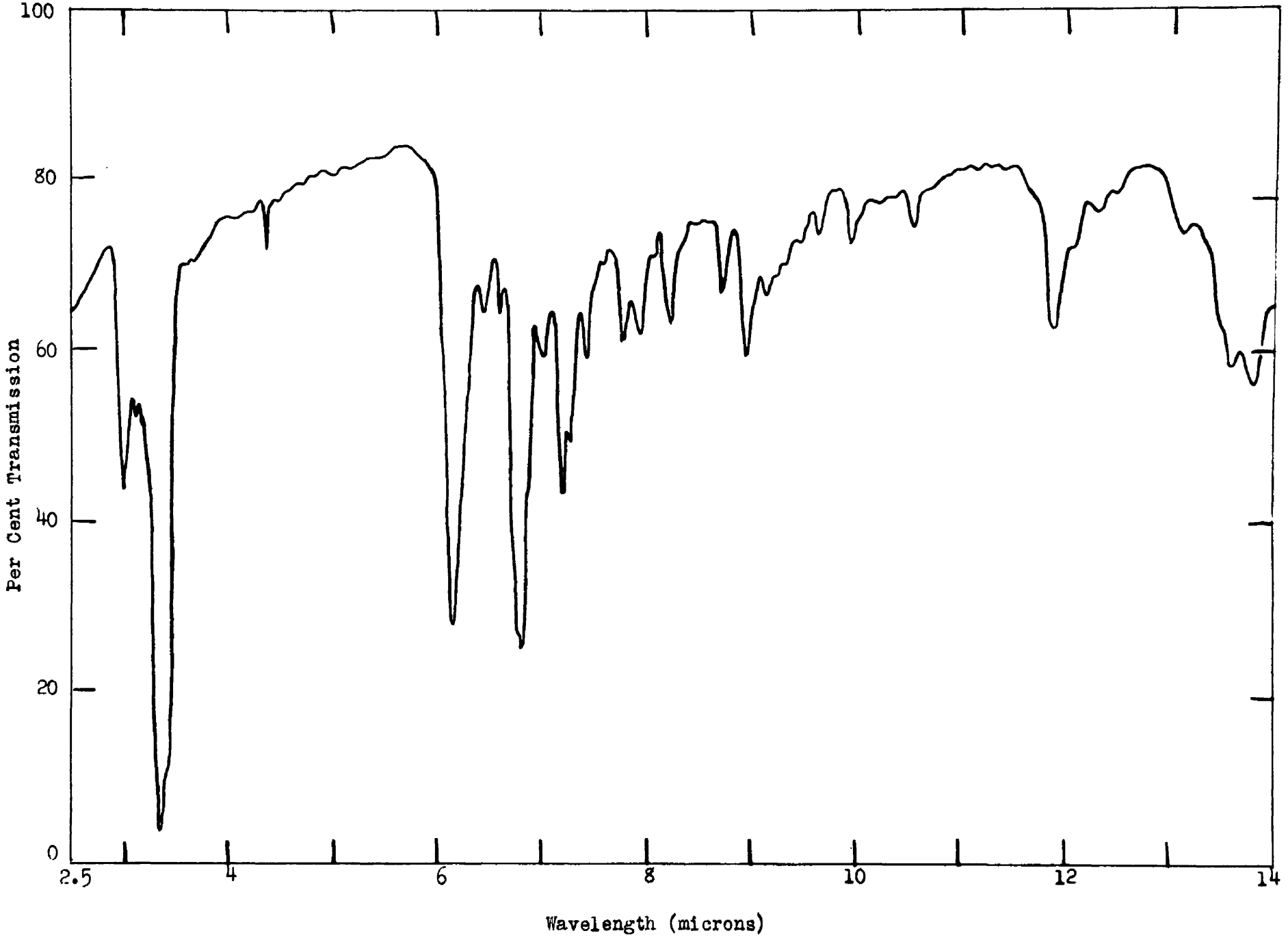


Figure 1. Infra-red Spectrum of 1-Benzyl-5-β-cyanoethylaminotetrazole

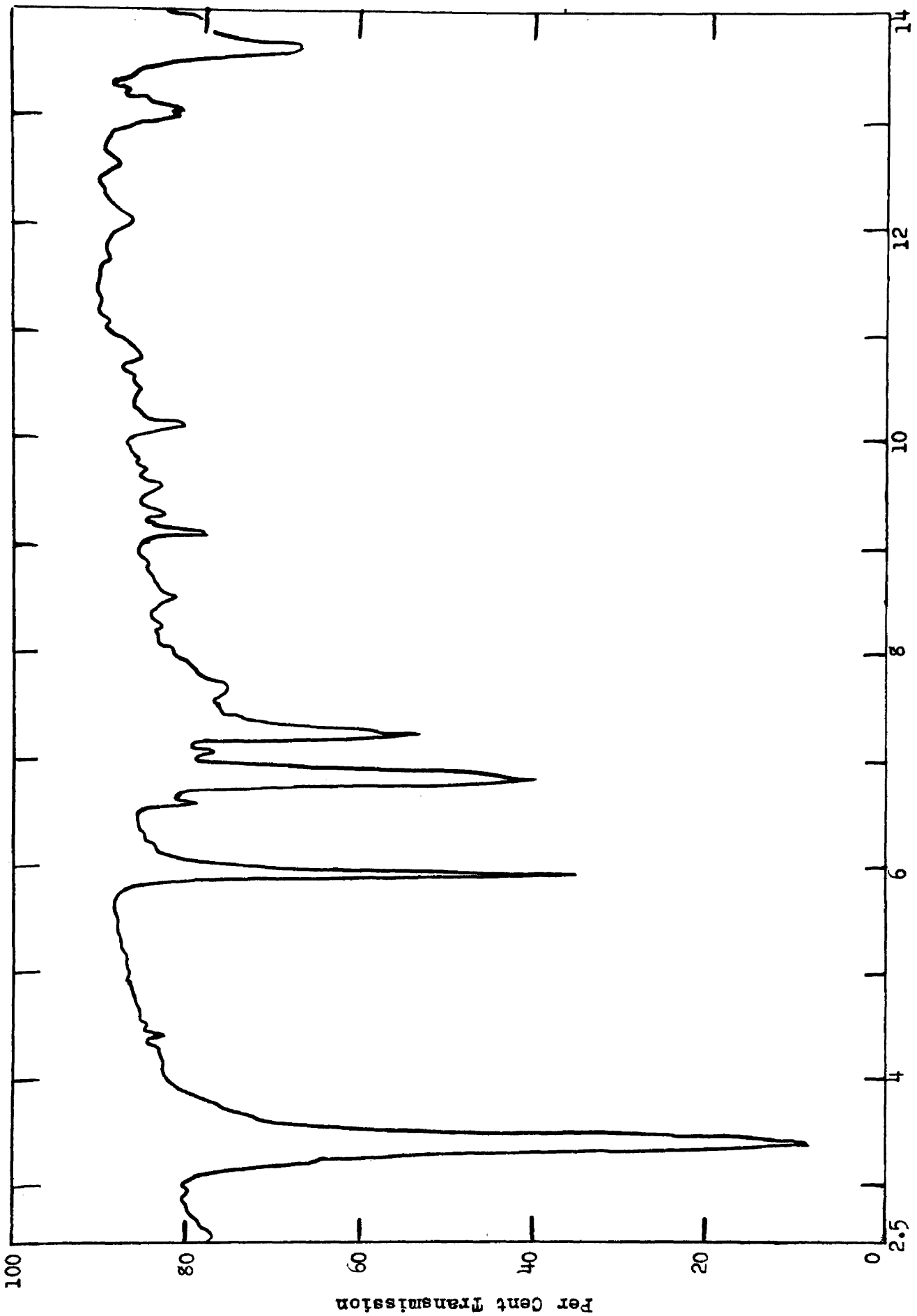


Figure 2. Infra-red Spectrum of 1-Benzyl-4-β-cyanoethyl-5-iminotetrazoline.HCl

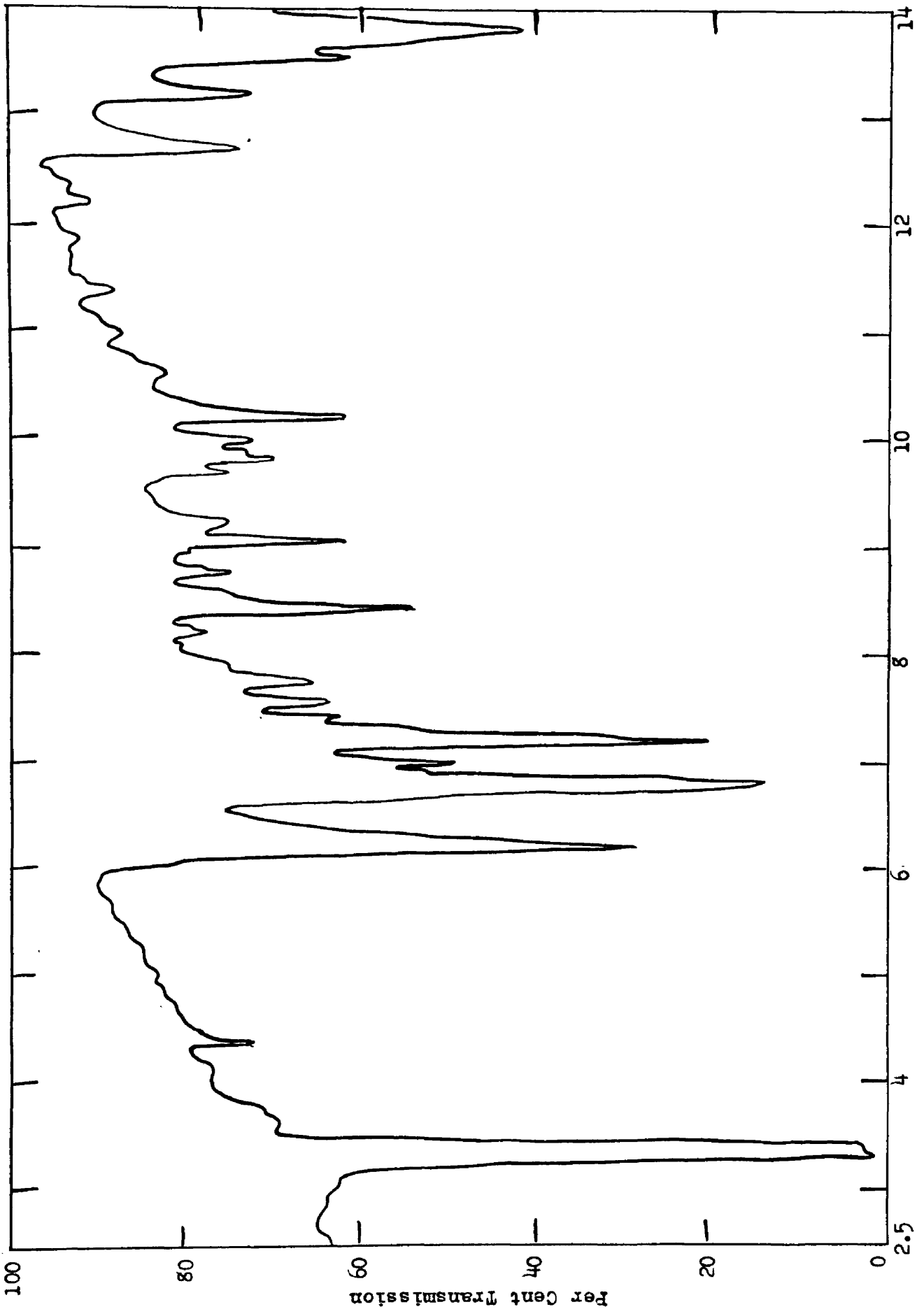


Figure 3. Infra-red Spectrum of 1-Benzyl-5-N,N-di-β-cyanoethylaminotetrazole

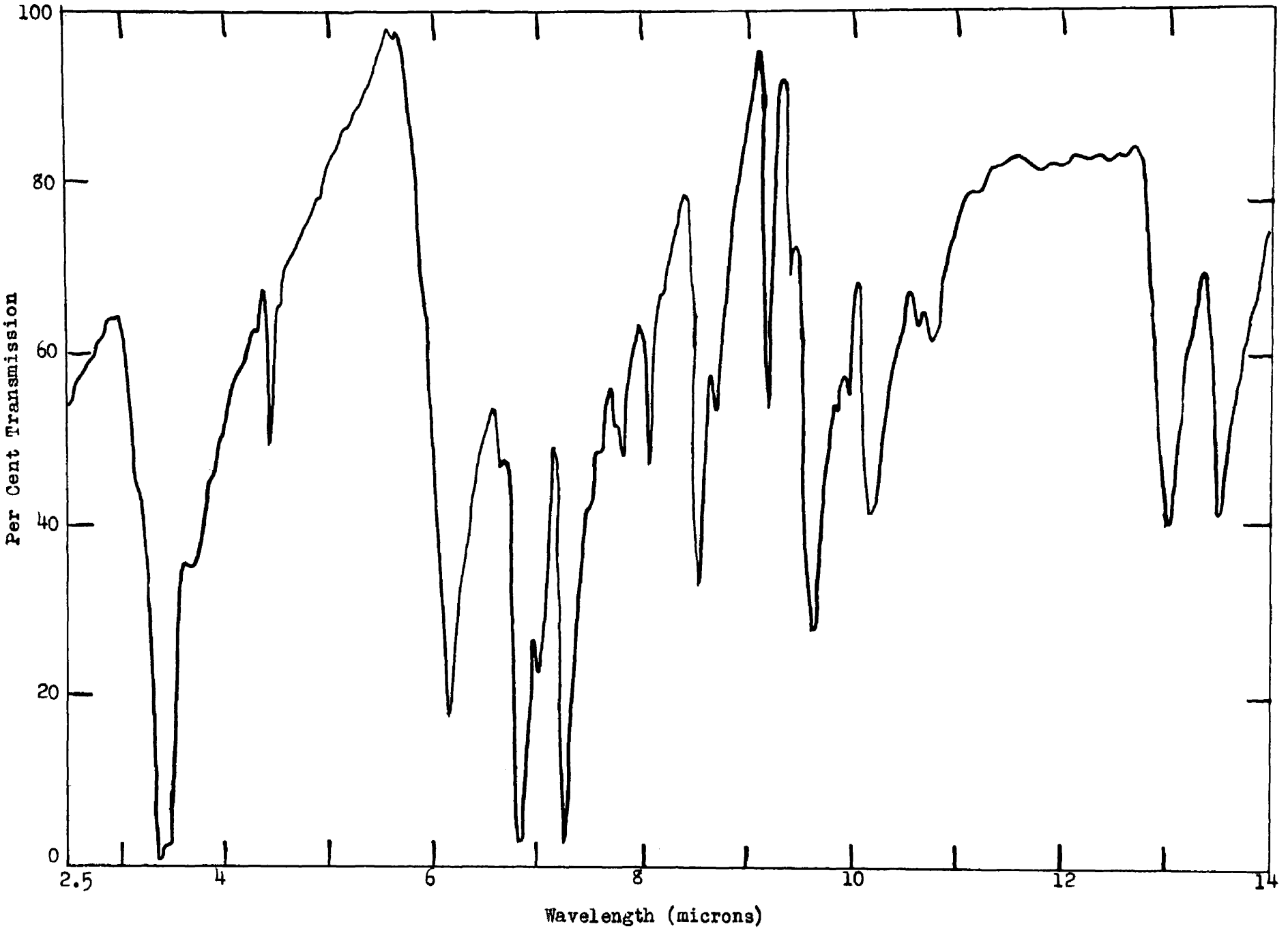


Figure 4. Infra-red Spectrum of 5-N,N-di-β-cyanoethylaminotetrazole

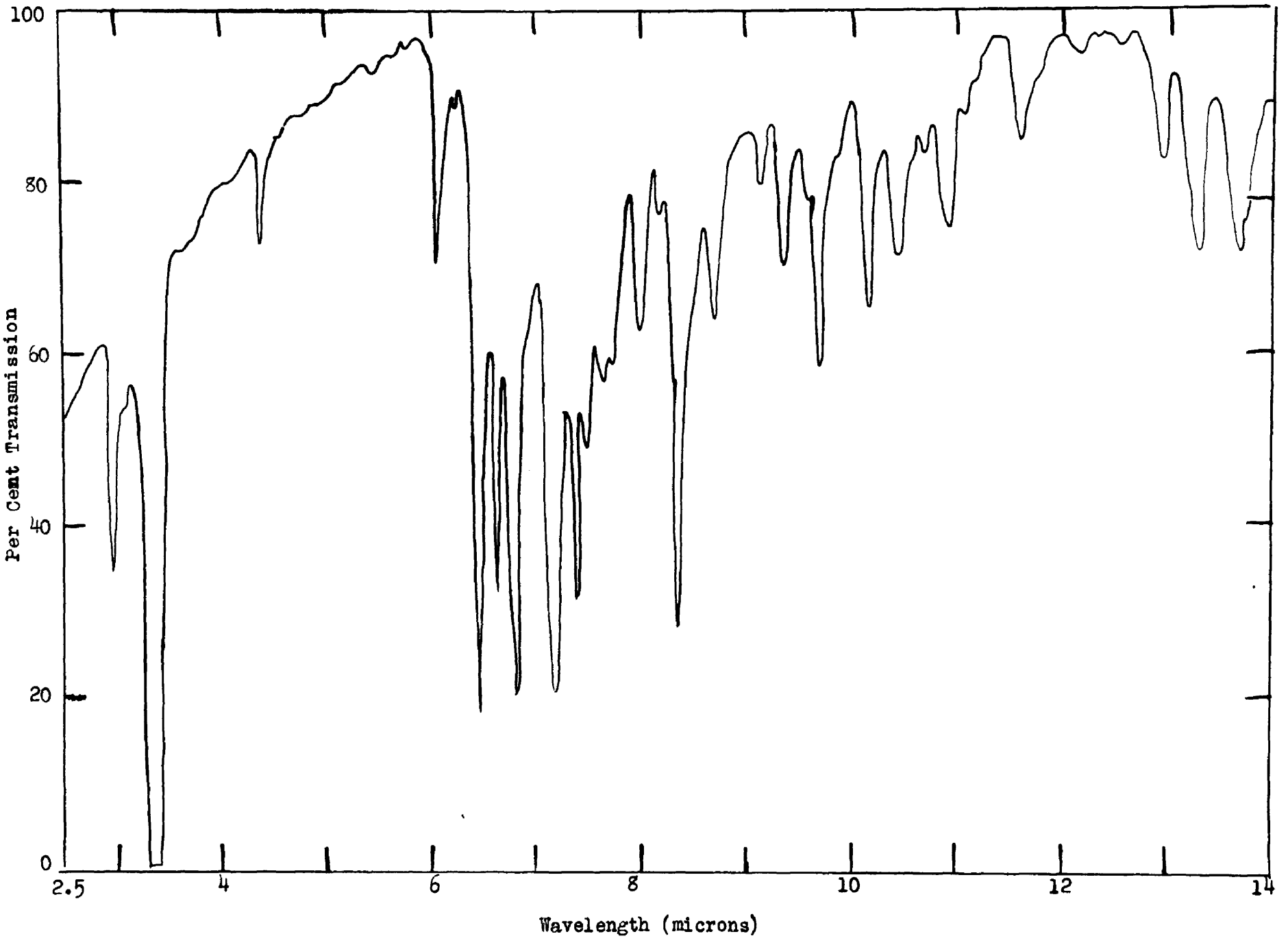


Figure 5. Infra-red Spectrum of N-Benzyl-N',N'-di-β-cyanoethylthiourea

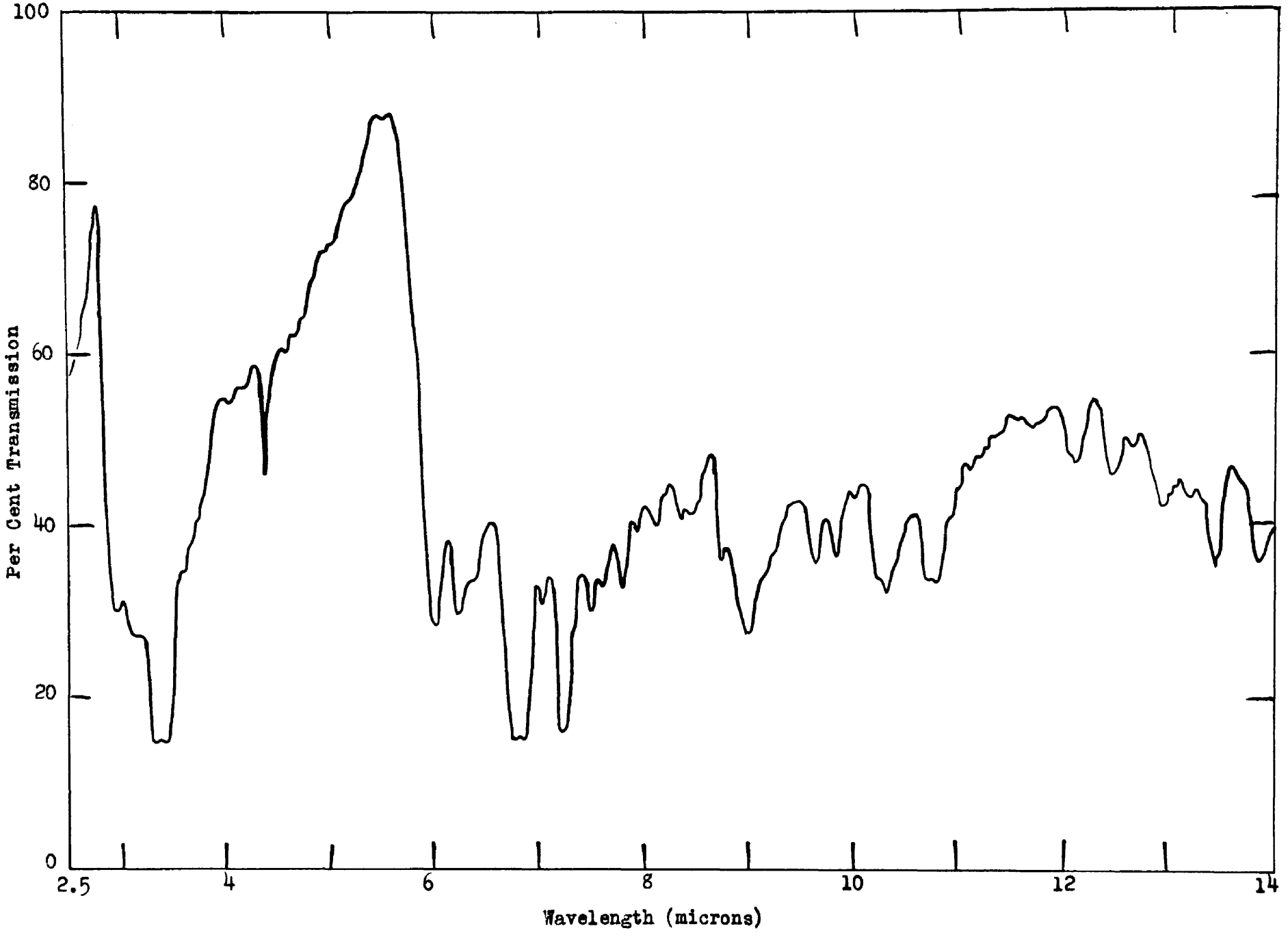


Figure 6. Infra-red Spectrum of 1-β-Cyanoethyl-5-aminotetrazole

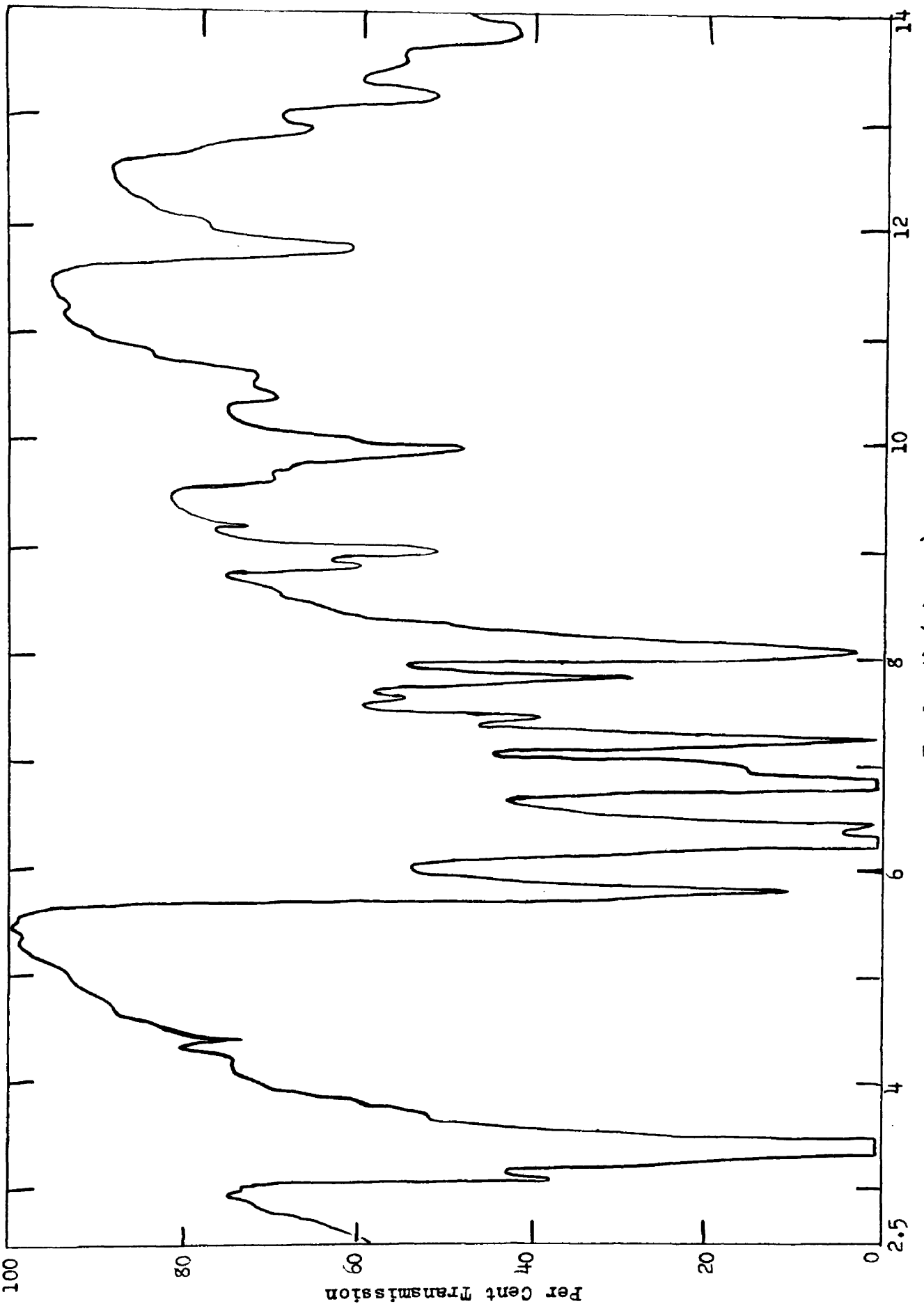


Figure 7. Infra-red Spectrum of 1-β-cyanoethyl-5-acetylaminotetrazole

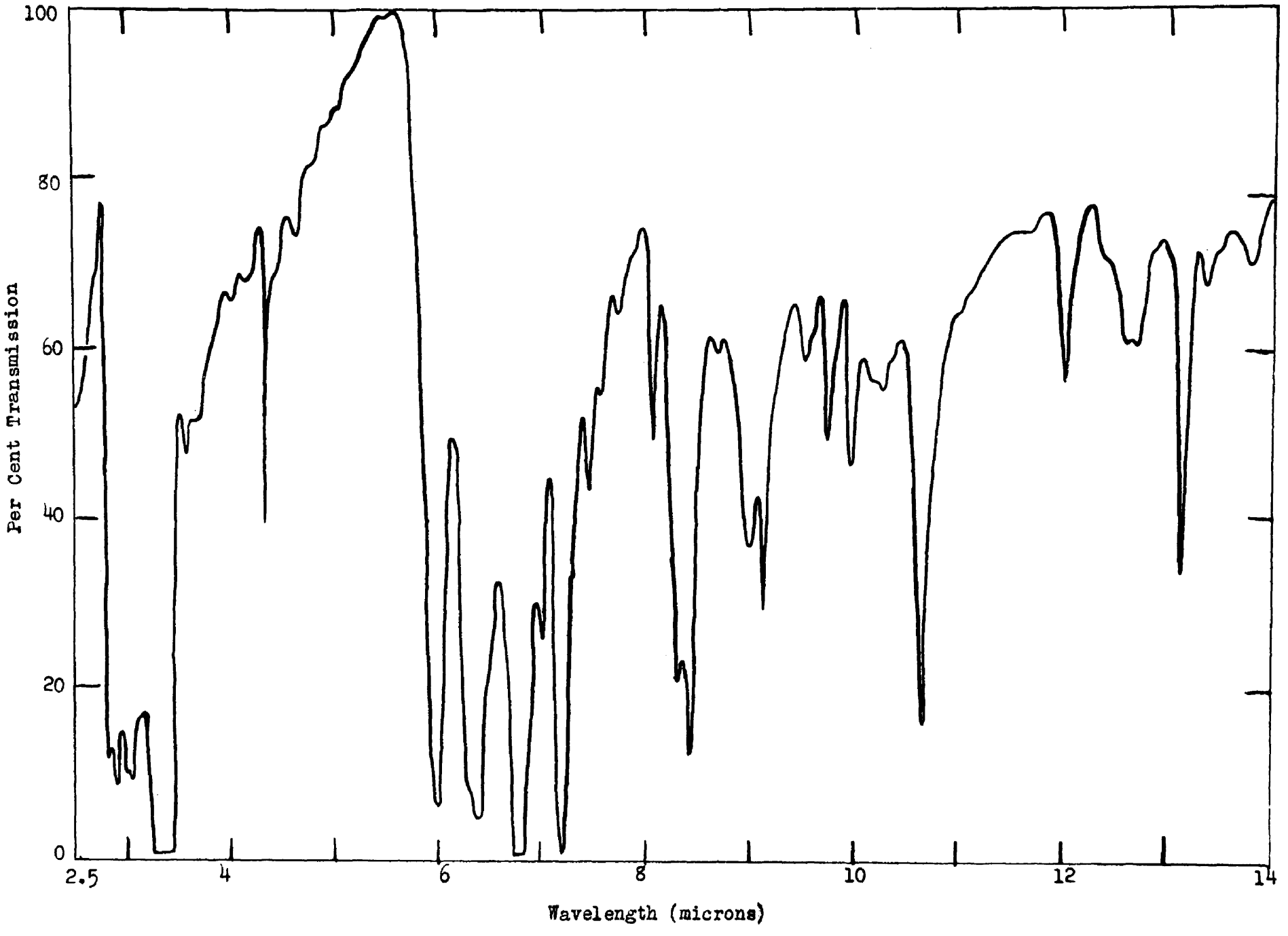


Figure 8. Infra-red Spectrum of 2-β-cyanoethyl-5-aminotetrazole

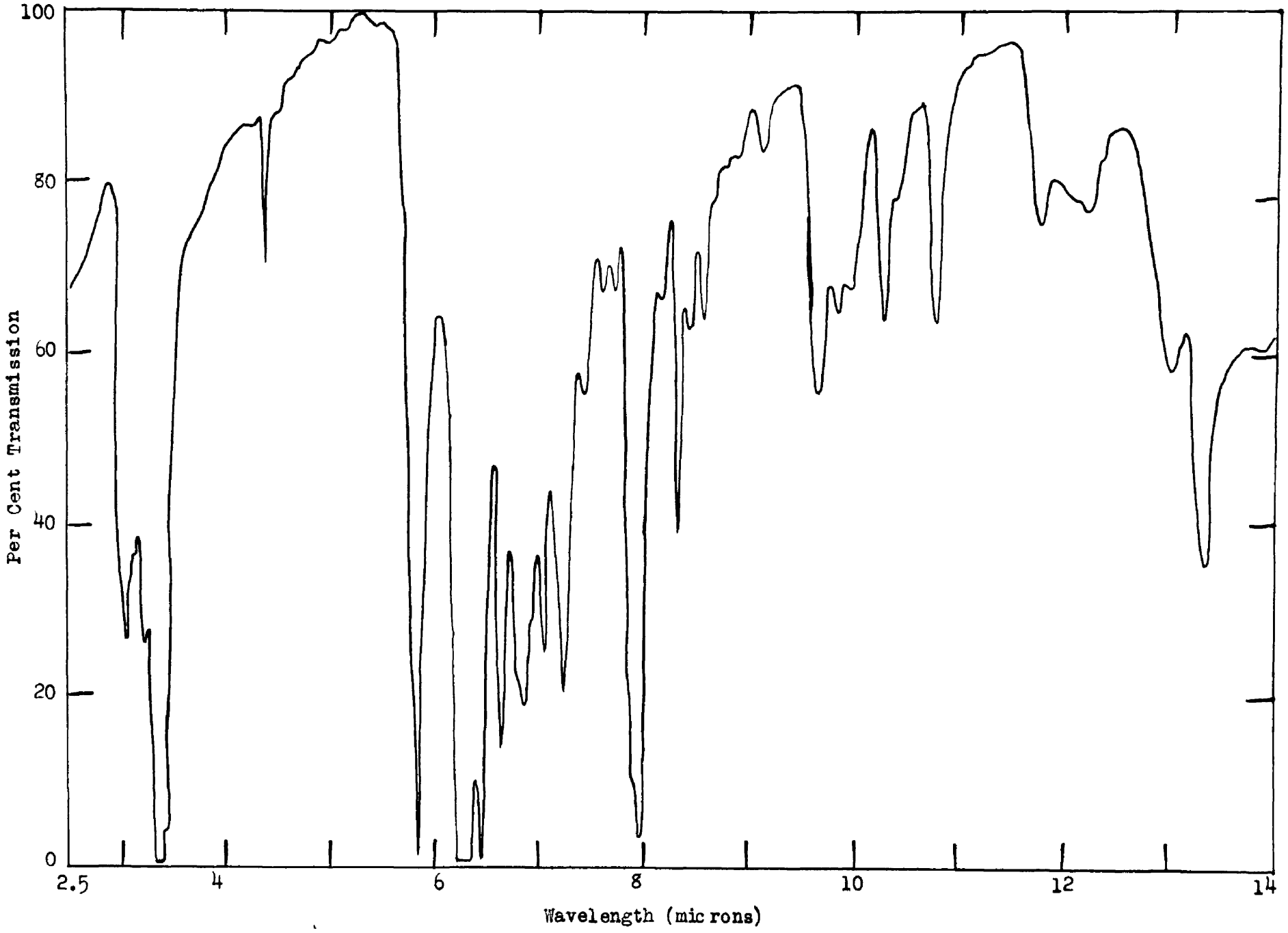


Figure 9. Infra-red Spectrum of 2-β-cyanoethyl-5-acetylaminotetrazole