THE SYNTHESIS OF SOME 1, 4-DISUBSTITUTED-5-IMINOTETRAZOLINES

Thesis for the Degree of M. S.

MICHIGAN STATE UNIVERSITY

Willard Jason Haak

1957

THE SYNTHESIS OF SOME 1,4-DISUBSTITUTED-5-IMINOTETRAZOLINES

By

Willard Jason Haak

A THESIS

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

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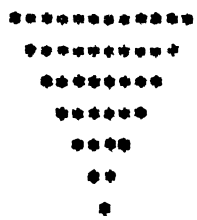

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AN ABSTRACT

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

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Year 1957

Approved Robert M. Keefer

Approved

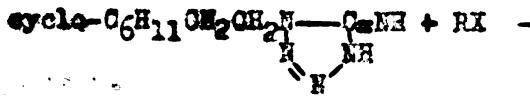
WILLARD JASON HLAK

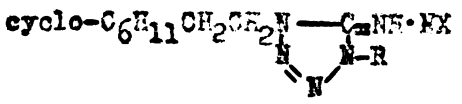
ABSTRACT

Recent work (1) has shown that 1-p-chlorobenzyl-4-n-octyl-5-iminotetrazoline has cidal action against *Trichomonas foetus in vitro*. It was also highly active against certain fungi, *Candida albicans* and *Trichophyton mentagrophytes* v. *interdigitale*.

A series of new 1,4-disubstituted-5-iminotetrazolines were prepared for testing using the cyclohexylethyl group in place of the n-octyl group. The series has the following groups in the 4-position: benzyl, o-chlorobenzyl, p-chlorobenzyl, 2,4-dichlorobenzyl, 3,4-dichlorobenzyl, m-nitrobenzyl, p-nitrobenzyl, 3-phenylpropyl and 2-phenylethyl.

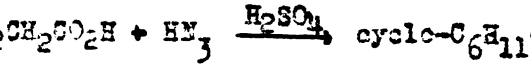
The 5-iminotetrazolines were prepared by alkylation of 1-(2-cyclohexylethyl)-5-aminotetrazole with the aralkyl halide using the method of Herbst, Roberts and Harvill (2) with some modifications.





R = aralkyl

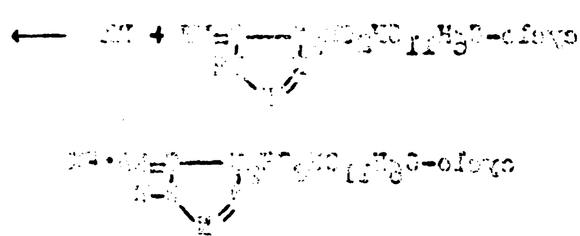
1-(2-Cyclohexylethyl)-5-aminotetrazole is a new compound prepared by the following series of reactions: 2-Cyclohexylethylamine, an intermediate, was prepared from 3-cyclohexylproprionic acid by the Schmidt reaction using hydrazoic acid (3).



Recent work (1) has shown that 1-p-chlorophenyl-3-n-octyl-5-iminotetrazoline has good in vitro activity against Trichomonas foetus in vitro. It was also highly active against certain fungi, Candida albicans and Trichophyton mentagrophytes, in vitro.

A series of new 1,4-disubstituted-5-iminotetrazolines were prepared for testing using the cycloalkyl group in place of the n-octyl group. The series has the following groups in the 4- position: phenyl, o-chlorophenyl, p-nitrophenyl, 2,4-dichlorophenyl, 3,4-dichlorophenyl, m-nitrophenyl, p-methoxyphenyl, 2-pyridyl and 2-phenylethyl.

The 5-iminotetrazolines were prepared by alkylation of 1-(2-cyclohexylethyl)-5-aminotetrazole with the aryl halide using the method of Herbst, Roberts and Harvill (2) with some modifications.



R = aryl

1-(2-Cyclohexylethyl)-5-aminotetrazole is a new compound prepared by the following series of reactions: 2-Cyclohexylethylamine, an intermediate, was prepared from 3-cyclohexylpropionic acid by the Schmidt reaction using Wolff's method (3).

$$\text{cyclo-}C_6H_{11}CH_2CH_2COOH + HN_3 \xrightarrow{H_2SO_4} \text{cyclo-}C_6H_{11}CH_2CH_2NH_2 + N_2 + CO_2$$

The amine was then allowed to react with cyanogen bromide to form the monosubstituted cyanamide.

$$R^1NH_2 + CNBr \longrightarrow R^1NH\text{-}C{\equiv}N \Longleftrightarrow R^1N{=}C{=}NH$$

$$R^1 = \text{cyclo-}C_6H_{11}CH_2CH_2\text{-}$$

The 2-cyclohexylethylcyanamide was treated with hydrazoic acid and the resulting product cyclized to 1-(2-cyclohexylethyl)-5-aminotetrazole (4).

$$R^1N{=}C{=}NH + HN_3 \longrightarrow R^1N{=}C(N_3)\text{-}NH_2 \longrightarrow \text{1-(2-cyclohexylethyl)-5-aminotetrazole} \Longleftrightarrow \text{1-(2-cyclohexylethyl)-5-iminotetrazoline}$$

$$R^1 = \text{cyclo-}C_6H_{11}CH_2CH_2\text{-}$$

1-(2-Cyclohexylethyl)-5-aminotetrazole was characterized as the pure solid, acetyl derivative, and infrared spectra.

Characterization of the 1-(2-cyclohexylethyl)-4-aralkyl-5-iminotetrazolines was as the hydrochloride, phenylthiourea and the solid free base when it could be obtained.

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2. R. M. Herbst, C. Roberts, E. Marvill, J. Org. Chem., 16, 139 (1951) with modifications.

3. K. Wilson, unpublished work.

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

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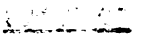

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INTRODUCTION

Recently a series of 1-4,disubstituted-5-iminotetrazoline hydrochlorides have been tested in the Parke, Davis Laboratories (1) for their cidal effects against Trichomonas foetus in vitro. The testing showed that, of the compounds tested, 1-(p-chlorobenzyl)-4-octyl-5-iminotetrazoline proved to be the most effective and is presently being prepared for clinical testing. These compounds were also tested and were active against Trichomonas vaginalis and as fungicides against Candida Albicans and Trichophyton mentagraphytes v. interdigitale.

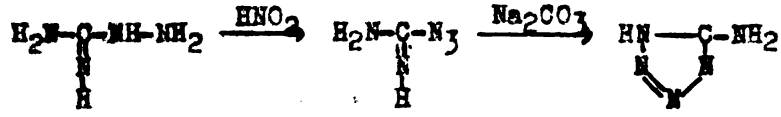
It was decided to prepare a series of similarly substituted 5-iminotetrazolines as their hydrochlorides with the n-octyl group replaced by a 2-cyclohexylethyl group. These salts are presently being tested for antitrichomonal and other chemotherapeutic effects.

A new monosubstituted 5-aminotetrazole, 1-(2-cyclohexylethyl)-5-aminotetrazole was prepared as an intermediate for the synthesis of the tetrazolines.

The tetrazole was characterized by infrared spectra, melting point, and as the acetyl derivative. The tetrazolines were characterized as the free bases, hydrochlorides and phenylthioureas.

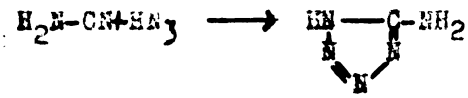
HISTORICAL

The synthesis of 5-aminotetrazole was first reported by Thiele (2) who prepared guanyl azide by interaction of aminoguanidine and nitrous acid. The guanyl azide was heated with aqueous sodium carbonate or sodium acetate to bring about ring closure to 5-aminotetrazole.

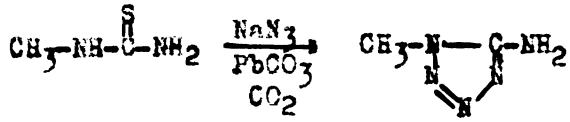


Thiele and Ingle (3) reported a number of products obtained from the direct alkylation of 5-aminotetrazole. Methylation, ethylation, and benzylation led to mixtures of products, both mono and disubstituted aminotetrazoles. The preparation of some of these compounds was repeated by Herbst and Percival (4) and it was found that the dimethyl, diethyl and "alpha" dibenzyl 5-aminotetrazoles obtained by Thiele and Ingle were 1,4-disubstituted-5-iminotetrazolines.

Sodium azide and hydrazoic acid have frequently been used in the synthesis of substituted 5-aminotetrazoles. Cyanamide (5) or dicyandiamide (6), which dissociates to cyanamide, react with hydrazoic acid to give 5-aminotetrazole.

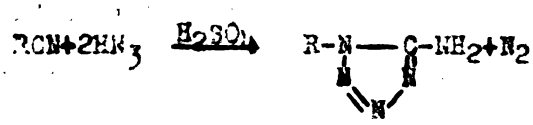


Stolle (7) prepared 1-methyl-5-aminotetrazole by interaction of N-methylthiourea with sodium azide in an atmosphere of carbon dioxide in the presence of lead carbonate.

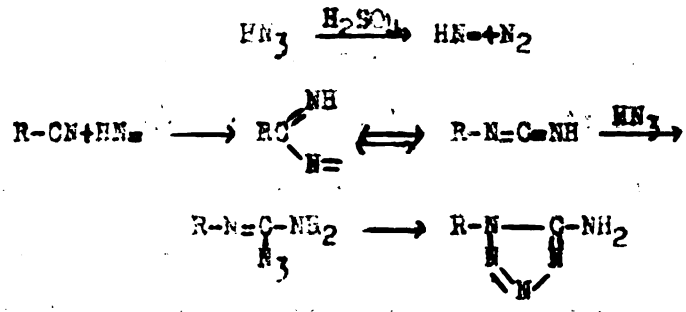


By this reaction he also prepared a number of 1-aryl-5-aminotetrazoles from the corresponding N-arylthioureas (8,9).

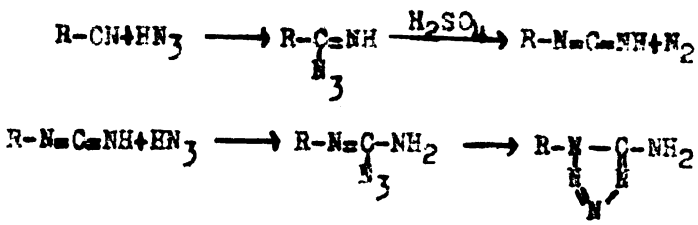
A procedure that eliminates the use of lead carbonate in the presence of sodium azide or hydrazoic acid was developed by von Braun and Keller (10). The procedure involves the interaction of nitriles and hydrazoic acid in the presence of concentrated sulfuric acid according to the following equation.



The intermediate was assumed to be a substituted carbodiimide to which the second mole of hydrazoic acid added, followed by cyclization.



A more logical explanation of this sequence of reactions was offered by Herbst, Roberts and Harvill (11) which did not use the free imine radical (HN_3), first postulated by Schmidt (12) and used by von Braun and Keller. Herbst, et al. (11) suggested the addition of hydrazoic acid directly to the cyanide linkage, followed by an acid catalyzed rearrangement accompanied by the elimination of nitrogen, similar to the Curtius rearrangement for acid azides. The same intermediate is assumed to result. After the addition of another molecule of hydrazoic acid to the rearrangement product, the resulting guanyl azide cyclizes to the 1-alkyl-5-aminotetrazole.



Garbrecht and Herbst (13) have extended the work of Hantzsch and Vagt (5) and found that the action of hydrazoic acid on monosubstituted cyanamides led to the production of only 1-substituted-5-aminotetrazoles. In this method the alkylcyanamide is allowed to react with hydrazoic acid in ether or aqueous alcohol solution.

Recently several methods for the alkylation of monosubstituted 5-aminotetrazoles have been developed by Herbst, Roberts and Harvill (11). The products are 1,4-disubstituted-5-iminotetrazolines (as mentioned before on p. 3). These methods use alkyl sulfonates, alkyl sulfates, aralkyl and alkyl halides as alkylating agents. With some modifications of technique (14) these methods were employed for the syntheses of the iminotetrazolines in this thesis.

DISCUSSION

The Schmidt reaction (15) in which primary amines are prepared from the carboxylic acid containing one more carbon by the action of hydrazoic acid was used in the preparation of

$$RCO_2H + HN_3 \xrightarrow{H_2SO_4} RNH_2 + CO_2 + N_2$$

2-cyclohexylethylamine (18). One requirement of the Schmidt reaction is that the organic acid used be stable to sulfuric acid. 3-Cyclohexylpropionic acid, which was used here, satisfied this requirement.

When compared with other methods for the preparation of primary amines from carboxylic acids such as the Hofmann and Curtius reactions several advantages of the Schmidt reaction are apparent: (1) the yields from longer chain acids are usually better and (2) only a single step is involved. Initiation and control of the reaction, which is exothermic, often are difficult since best results are obtained if the temperature is kept between 40-60°C. These problems were solved in the present case by raising the temperature of the reaction mixture to 30-35°C. before beginning addition of the hydrazoic acid solution. Subsequently, the temperature rose to 55-60°C. where it could be maintained easily by adjusting the rate of addition of hydrazoic acid and the degree of immersion in the cooling bath.

In the preparation of the benzene solution of hydrazoic acid by addition of concentrated sulfuric acid to a water slurry of sodium azide (19) covered with benzene, it was found that by using half again as much water as suggested by Garbrecht and Herbst (16) a benzene solution of hydrazoic acid of comparable concentration was obtained. The additional water permitted better stirring and the temperature could be more easily controlled.

Benson (17) in his survey of the chemistry of tetrazoles has included several methods for the preparation of 1-substituted 5-aminotetrazoles. Some of these have been described in the historical part. It was decided that the method of Garbrecht and Herbst (13) in which a monosubstituted cyanamide is treated with hydrazoic acid would be used. The cyanamide is prepared by interaction of cyanogen bromide and a primary amine.

$$RNH_2 + CNBr \longrightarrow RNH\text{-}C{\equiv}N \longleftrightarrow RN{=}C{=}NH$$

The cyanamide is then allowed to react with hydrazoic acid to form a substituted guanyl azide which then cyclizes to the 5-aminotetrazole.

$$RN{=}C{=}NH + HN_3 \longrightarrow RN{=}C(N_3)\text{-}NH_2 \longrightarrow \text{(1-substituted 5-aminotetrazole)}$$

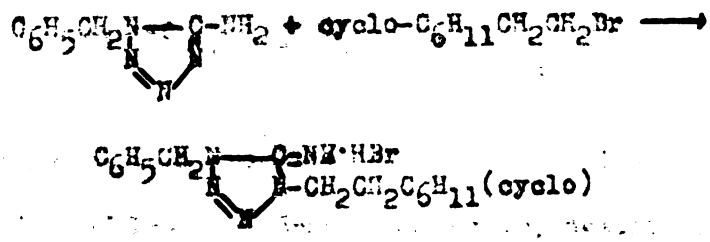
With recent improvements of technique from this laboratory there is no need for separating the cyanamide, and the hydrazoic acid is generated in the reaction vessel.

These improvements in the method of preparation of the tetrazole and the preparation of the amine by the Schmidt reaction have reduced the overall time required for the preparation of the tetrazole starting with the carboxylic acid when compared with the method of von Braun and Keller (10), where preparation of the nitrile may be necessary. The methods give reasonable yields of a product which is quite easily purified.

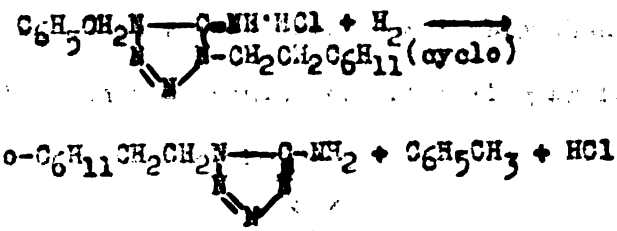
Since 1-(2-cyclohexylethyl)-5-aminotetrazole had not been prepared before it was also prepared by another method. Alkylation of 1-benzyl-5-aminotetrazole[a] with 2-cyclohexylethyl bromide (20) gave 1-benzyl-

[a] The 1-benzyl-5-aminotetrazole was prepared in this laboratory by the method of Garbrecht and Herbst (13).

4-(2-cyclohexylethyl)-5-iminotetrazoline hydrobromide. The hydrobromide was converted to the hydrochloride

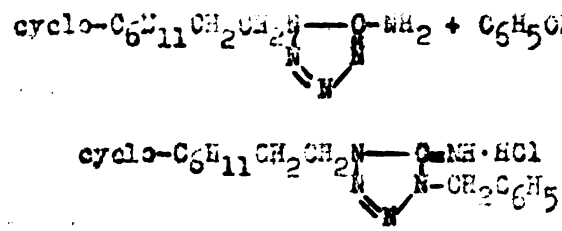


by liberating the base with potassium hydroxide and treating the free base with concentrated hydrochloric acid. The hydrochloride was then debenzylated by hydrogenolysis using the general techniques of Birkhofer(21).



In the first method the tetrazole ring was formed from 2-cyclohexylethylamine in such a way that the amino-N became the 1-nitrogen of the tetrazole ring; in the second method the 2-cyclohexylethyl group was added as a ring substituent on a preformed tetrazole structure. The formation of the same compound by both procedures supports the assignment of the structure of the product as 2-cyclohexylethyl-5-amino-tetrazole.

Infrared spectra, figures I and II, and mixture melting points which gave no depression were used to show that the products of the two methods were identical. Benzylation of the 1-(2-cyclohexylethyl)-5-aminotetrazole



gave a product whose hydrochloride was identical with that obtained from the alkylation of 1-benzyl-5-aminotetrazole, described above, as shown by infrared spectra, figures III and IV, and mixture melting points, which showed no depression. Since the same compound is formed regardless of the order in which the two substituents are introduced, the 2-cyclohexylethyl and benzyl groups must occupy equivalent positions on the tetrazole ring. This requirement is met only when R and R^1 occupy 1- and 4- positions on the 5-aminotetrazole ring as in structure I.

I

R or R^1 = 2-cyclohexylethyl or benzyl.

Structure I was further substantiated by the debenzylation of the tetrazoline formed from the alkylation of 1-benzyl-5-aminotetrazole with 2-cyclohexylethyl bromide, to give 1-(2-cyclohexylethyl)-5-aminotetrazole in 71% yield, indicating that the 2-cyclohexylethyl group occupied the 1- (or 4-) position on the ring. Since only the 4- position is equivalent to the 1- position, substitution in any other position in the ring would lead to different products. Rearrangement during the debenzylation is rather unlikely since rather mild conditions were used.

The 1-(2-cyclohexylethyl)-4-aralkyl-5-iminotetrazoline hydrochlorides were prepared by the method of Herbst, Roberts and Harvill (11) with more recent improvements in technique from this laboratory (14). The method

involved the heating of the aralkyl halide with the 1-alkyl-5-amino-tetrazole at temperatures of 120-150°C. for a period of time. Usually a homogeneous melt formed, followed by a mildly exothermic reaction. The salt of the 1-4,disubstituted-5-iminotetrazoline crystallized from the hot mixture and was purified by steam distilling the excess benzyl halide from the mixture. The free base was formed and then extracted either with ether or benzene. The hydrochloride was formed by evaporating the dried ether solution, dissolving the residual oil in aqueous alcohol and adding concentrated hydrochloric acid, or by treating the dried benzene solution with anhydrous hydrochloride.

It was found in the preparation of this series of tetrazoline hydrochlorides that the use of a larger excess (50%) of benzyl halide made it easier to handle and dissolve the crude tetrazoline salts.

No dialkylation was apparent even with the large excess of halide.

In the purification complete solution of the crude tetrazoline salt in alcohol before steam distillation was necessary to insure the complete removal of the alkylating agent.

All of the 1-(2-cyclohexylethyl)-4-aralkyl-5-iminotetrazoline hydrochlorides prepared are listed in Tables I and II.

The lower yield of the p-nitrobenzyl substituted tetrazoline hydrochloride was due to the dark colored impurities in the crude product which caused greater losses during purification.

Longer reaction times were used for the alkylations with 3-phenylpropyl and 2-phenylethyl halides because of the lower reactivity of these reagents compared with that of the benzyl halides.

During the preparation of the tetrazoline hydrochlorides it was found that the free tetrazoline base of the 2,4-dichlorobenzyl

substituted tetrazoline was a solid. Attempts to prepare the free bases of the other tetrazolines were made by treating the pure hydrochloride with potassium hydroxide and extracting with ether. After drying the ether solution, the ether was evaporated and the residual oil crystallized. The free bases were recrystallized from either cyclohexane or petroleum ether.

Solid bases were obtained for all but the 1-(3-phenylpropyl)-4-(2-cyclohexylethyl)-5-iminotetrazoline. Formulae, melting points and analyses are found in Table IV.

EXPERIMENTAL

Benzene Solution of Hydrazoic Acid

The method of Garbrecht and Herbst (16) was used with slight modifications of technique to permit easier handling.

The benzene solutions of hydrazoic acid were prepared as follows: 300 ml. of water are added to 208 g. of sodium azide in a 3 l. flask fitted with an alcohol thermometer, efficient stirrer and a 200 ml. dropping-funnel with outlet below the liquid level. The flask should be vented. Six hundred milliliters of benzene are added. While keeping the temperature below 30°C. with an ice-water bath, 100 ml. of concentrated sulfuric are added dropwise over a period of one and a half hours. The solution turns a deep red until the last 5-10 ml. of acid are added. Stirring is continued for two hours and the mixture is allowed to stand for one hour after which the benzene layer is decanted and dried over sodium sulfate.

The concentration of the hydrazoic acid was determined by titration of an aliquot with standard aqueous alkali using phenolphthalein indicator. The above procedure gives solutions containing initial concentrations of 15-17 g. of hydrazoic acid per 100 ml. of solution.

2-Cyclohexylethylamine

The technique developed by Wilson (22) for the preparation of a primary amine by the Schmidt reaction from the corresponding acid was employed with slight modification as follows: 203 g. (1.3 moles) of 3-cyclohexylproprionic acid are dissolved in 2.2 l. of benzene in a 5 l. flask fitted with an alcohol thermometer, efficient stirrer, 500 ml. dropping-funnel and a reflux condenser. Six hundred and twenty milliliters of concentrated sulfuric acid are added with stirring. Four hundred and eighty milliliters of a benzene solution of hydrazoic acid (14.6 g. of hydrazoic acid per 100 ml., 1.625

Preparation of 3-(2-Chloroethyl)-4-methyl-5-(2-hydroxyethyl)thiazolium Chloride

The mixture of thiazolium chloride (10) was used with slight modifications of procedure in preparing other 3-substituted thiazolium salts.

The benzene solution of 3-(2-chloroethyl)-4-methyl-5-(2-hydroxyethyl)thiazolium chloride was washed with 2 x 100 ml. of water, the aqueous layer was extracted with 100 ml. of benzene, and the benzene layer was discarded. The aqueous layer was diluted with an alcohol-acetone mixture, 1:1 by vol., to a total volume of 500 ml. and decolorized with charcoal below the boiling point. The charcoal should be removed. Six hundred milliliters of benzene was added. Crude product was precipitated by the addition of petroleum ether, bp 30-60°, with cooling in an ice-water bath. 200 ml. of petroleum ether was added dropwise over a period of two and a half hours. The solution became a deep red until the last 50-60 ml. of ether was added. Scratching the container with a glass rod caused the product to solidify in about ten minutes after addition of petroleum ether was completed and then allowed to stand for one hour at room temperature before it was cooled and dried over sodium sulfate.

The concentration of the hydrazide used was determined by titration of an aliquot with standard aqueous nitrous acid using Thymol Blue as indicator. The above procedure gives satisfactory isolated yields of 17-17 g. of hydrazide acid per 100 ml. of a 1 M solution.

3-Carbethoxymethylene-2-keto-1,2,3,4-tetrahydropyrimidine

The reduction involved by Wilson (13) for the preparation of a pyrimidine ring by the catalytic reduction of the corresponding acid was modified with slight modification as follows: 0.5 g. (1.5 moles) of 3-carbethoxymethyl-6-methyluracil are dissolved in 5-6 ml. of benzene in a 5 l. flask fitted with an efficient thermometer, sufficient ethanol, 500 ml. dry tetrahydrofuran and a reflux condenser. Six hundred and twenty milliliters of concentrated and anhydrous acid are reduced with platinum oxide catalyst. Some hydrogen pressure of hydrazoic acid (1.6 g. of hydrazoic acid per 100 ml., 1.65

moles) are then added dropwise with stirring at such a rate as to maintain a reaction temperature of 60°C. The addition of the hydrazoic acid solution required about one hour. After complete addition of the hydrazoic acid stirring is continued for an hour while the reaction vessel is in a water bath at 65°C.

After separating the benzene layer the sulfuric acid layer is poured in a very thin stream into 3,000-4,000 g. of ice in a 4 l. beaker. A voluminous precipitate presumably of the amine acid sulfate results. The mixture is poured onto a large filter and suction applied until the surface of the precipitate begins to liquify. Retain the last 100 ml. of filtrate. The precipitate and the last 100 ml. of the filtrate are returned to the 5 l. flask, dissolved in 1 l. of water and the solution made basic to litmus with 50% potassium hydroxide solution. The amine is steam distilled until about 1 l. of distillate is obtained. One hundred milliliters of ether are added to the distillate and the ether layer separated. The water layer is extracted three times with 50 ml. portions of ether, the ether layers are combined and dried over potassium carbonate. The ether is removed by distillation using a Vigreux column. The amine may be further dried after the ether is removed by adding 20 ml. of benzene and distilling the azeotropic mixture through the column. The column is removed for the final distillation and the amine collected, BP 154°-155°C. (uncorrected) n_D^{25} 1.4637 (IS) yield 134 g. (82%) based on 3-cyclohexylethylproprionic acid.

1-(2-Cyclohexylethyl)-5-Aminotetrazole

The methods described by Garbrecht and Herbst (16) for the synthesis of 1-alkyl-5-aminotetrazoles were used in a modified form evolved in this laboratory.

The methods described by Gerhardt and Lambert (12) for the synthesis of 1-alkyl-3-aminobenzotriazoles were used in a modified form evolved in this laboratory.

1-(2-Hydroxyethyl)-3-aminobenzotriazole

1-(2-Hydroxyethyl)-3-nitrobenzotriazole. (Unrecrystd.) M_D^{25} 1.6317 (12) yield 17 g. (3:1) bread on 2-hydroxyethylhydrazinoacetanilide.

1-(2-Hydroxyethyl)-3-aminobenzotriazole. A mixture of 17 g. of the nitro base, 200 ml. of 95% ethanol and 1 g. of 5% palladium-on-charcoal catalyst was shaken in a Parr hydrogenation apparatus at room temperature under 50 p.s.i. of hydrogen. The reduction was complete in 1 hr. The catalyst was removed by filtration and the filtrate was evaporated to dryness in vacuo. The residue was recrystallized from 100 ml. of ethanol. Two crops of white needles were collected, M. 127-128°. (Uncorrected) M_D^{25} 1.6317 (12) yield 12 g. (85%).

The procedure of Gerhardt and Lambert (12) was followed in the preparation of 1-(2-hydroxyethyl)-3-aminobenzotriazole. A 5% palladium-on-charcoal catalyst was used in the reduction of the nitro base. After removal of the catalyst by filtration, the solvent was evaporated in vacuo. The residue was recrystallized from 95% ethanol to give white needles, m.p. 127-128°. (Uncorrected) M_D^{25} 1.6317 (12) yield 12 g. (85%).

The tetrazole was prepared as follows: 127 g. (1 mole) of 2-cyclohexylethylamine are dissolved in 800 ml. of 95% ethanol in a 3 l. flask fitted with an alcohol thermometer, efficient stirrer, and a 500 ml. dropping-funnel. The flask must be vented. After cooling below 10°C.(a) in an ice-water bath 106 g. (1 mole) of cyanogen bromide, dissolved in 200 ml. of water and 200 ml. of 95% ethanol, are added dropwise. Forty grams (1 mole) of sodium hydroxide, dissolved in 100 ml. of water, are added and the solution stirred for an hour and a half. Seventy-eight grams (1.2 moles) of sodium azide, dissolved in 240 ml. of water, are added followed by 200 ml. (1.2 moles) of 1:1 hydrochloric acid added dropwise. After stirring for a half hour after the hydrochloric acid is added, the solution is boiled under reflux on a steam bath for six hours. The reaction mixture is allowed to cool slowly to room temperature and then is chilled in an ice-water bath. The precipitate is filtered(b) and dried over calcium chloride and potassium hydroxide in a vacuum dessicator. The dried product is refluxed with 500 ml. of 99% isopropyl alcohol, the suspension cooled, filtered and dried. The yield was 89.1 g., 47% (based on amine), MP 212.5°-213.5°C. (uncorrected).

Analysis. Calc'd. for $C_9H_{17}N_5$: C, 55.36; H, 8.78; N, 35.87. Found: C, 55.35; H, 8.53; N, 35.80.

Acetyl Derivative of 1-(2-Cyclohexylethyl)-5-Aminotetrazole

Two grams of the tetrazole are refluxed with 10 ml. of acetic anhydride for half an hour. Ten milliliters of isopropyl alcohol and 10 ml. of water

(a) The temperature should be kept below 10°C. until refluxing is begun. Vigorous stirring should be continuous throughout the process.

(b) This is done in the hood because of the excess hydrazoic acid present.

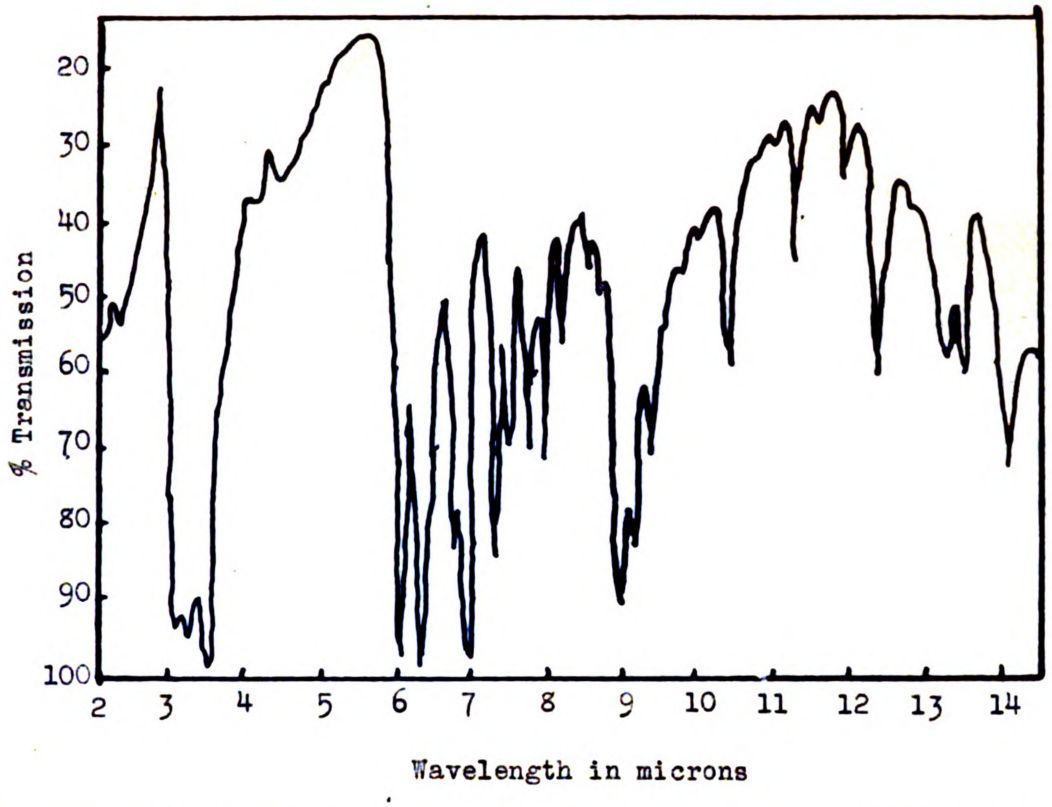


Figure I. Infrared spectrum of 1-(2-cyclohexylethyl)-5-amino-tetrazole from amine. (Nujol mull)

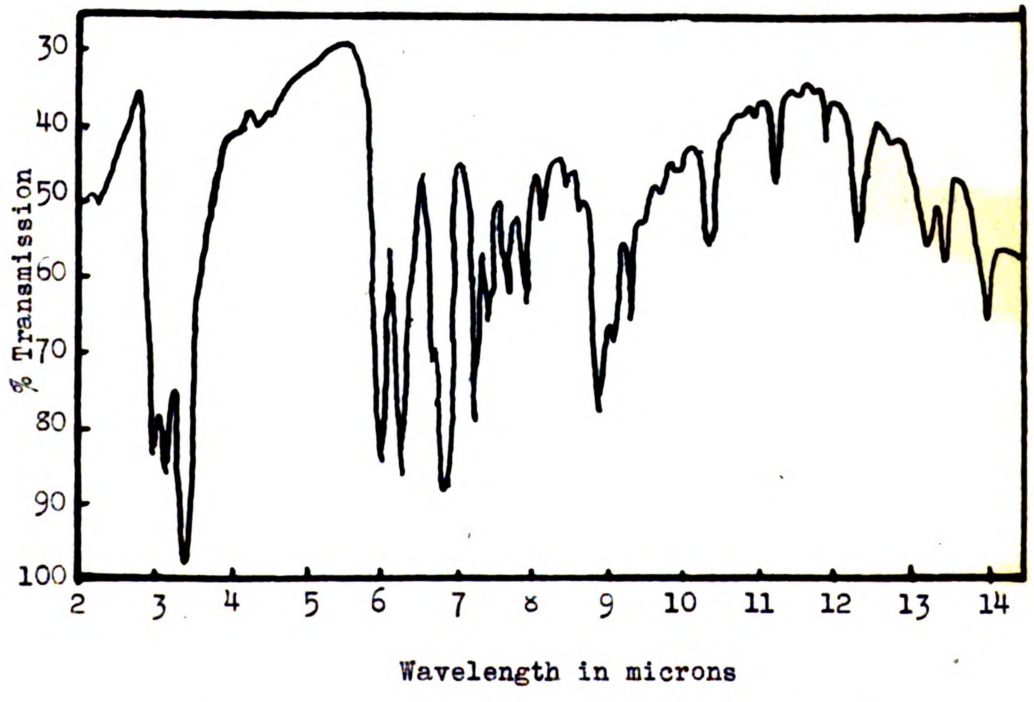


Figure II. Infrared spectrum of 1-(2-cyclohexylethyl)-5-amino-tetrazole from debenzylation. (Nujol mull)

are added and the solution is heated on a steam bath to remove the excess anhydride. The oily product is crystallized from cyclohexane, MP 95.5°-96.5°C. (uncorrected).

Analysis. Calc'd. for $C_{11}H_{19}N_5O$: C, 55.67; H, 8.07; N, 29.72. Found: C, 55.59; H, 7.98; N, 29.72.

1-(2-Cyclohexylethyl)-4-Aralkyl-5-Iminotetrazoline Hydrochlorides

The methods of Herbst, Roberts and Harvill (11) and Herbst (14) were used. Two procedures were used for the extraction of the amine and precipitation of the hydrochloride. Examples of both procedures are given below.

The formation of 1-(2-cyclohexylethyl)-4-m-nitrobenzyl-5-imino-tetrazoline hydrochloride will illustrate method A. The tetrazoline hydrochloride is prepared as follows: 11.8 g. (.06 moles) of 1-(2-cyclohexylethyl)-5-aminotetrazole are heated with 15.4 g. (.09 moles) of m-nitrobenzyl chloride at 140°C. in an oil bath. Formation of a homogeneous melt is followed by a rapid exothermic reaction after which the mixture solidifies. The bath is kept at 140°C. for an hour and a half after the exothermic reaction subsides. The crude product is dissolved in 300 ml. of boiling ethanol. Five hundred milliliters of water are added and the mixture steam distilled until the distillate is clear. More water is added slowly during the distillation to maintain a volume of about 300 ml. of water in the flask. Thirty grams of potassium hydroxide are slowly added to the warm residue and the solution stirred for two hours. One hundred and fifty milliliters of ether are added after cooling with ice. Stirring is continued for half an hour. The ether layer is separated and the water layer extracted three times with 50 ml. portions of ether. The combined ether solutions are dried over potassium

carbonate. After evaporating the ether, the residual oil is dissolved in 300 ml. of 95% aqueous ethanol and 20 ml. of concentrated hydrochloric acid are added. The precipitate of the hydrochloride is redissolved by heating the suspension. The hot solution is filtered, cooled and the solid so obtained is filtered and dried.

Method B is as follows: the procedure is the same as method A through the addition of the potassium hydroxide and stirring. Benzene is used in similar quantities to extract the iminotetrazolines. The hydrochloride is formed by passing anhydrous hydrogen chloride through the dried benzene solution. The product is filtered and washed with 50 ml. of fresh benzene.

The addition of one gram of Norite was necessary to remove colored impurities in the purification of the p-nitrobenzyl- and 3-phenylpropyl-substituted tetrazolines.

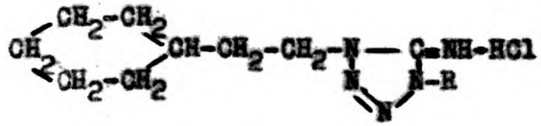
Formulae, melting points, method, reaction times and analyses are given in Tables I and II.

Benzylation of 1-(2-Cyclohexylethyl)-5-aminotetrazole

1-(2-Cyclohexylethyl)-5-aminotetrazole (11.8 g., .06 moles) is heated at 150°C. in an oil bath with 11.4 g. (.09 moles) of benzyl chloride. Formation of a homogeneous melt is followed by a rapid exothermic reaction after which the mixture solidifies. The bath is kept at 150°-160°C. for two hours after the exothermic reaction subsides. The crude product is dissolved in 250 ml. of 95% ethanol and 600 ml. of water are added. The mixture is steam distilled until the distillate is clear. The warm residue is made basic with 15 g. of potassium hydroxide. After cooling, 150 ml. of ether are added and the mixture shaken vigorously for five

TABLE I

1-(2-Cyclohexylethyl)-4-Aralkyl-5-Iminotetrazoline Hydrochlorides



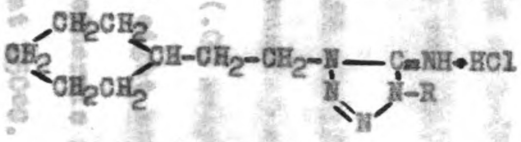
R	Method of Preparation	Reaction(a) Time (hours)	Yield(b) Based on Tetrazole	M.P. °C.(c)	
Benzyl	A	3	81%	209	210
o-Chlorobenzyl	A	1.5	75%	223.5	224.5
p-Chlorobenzyl	B	3	81%	208	209
2,4-Dichlorobenzyl	A	1.5	74%	210.5	211.0
3,4-Dichlorobenzyl	B	1.5	71%	208.5	209.0
p-Nitrobenzyl	B	2.5	58%	209.5	210.5
m-Nitrobenzyl	A	1.5	73%	205.0	206.0
3-Phenylpropyl	B	16	55%	214.0	215.0
2-Phenylethyl	A	10	52%	250.5	251.0

Analyses by Micro-Tech. Laboratories, Skokie, Illinois.

(a) Reaction times indicate the heating period after the exothermic reaction subsides.
(b) Pure products.
(c) Uncorrected. All of the hydrochlorides melt with decomposition.

TABLE II

Analysis of 1-(2-Cyclohexylethyl)-4-Aralkyl-5-Iminotetrazoline Hydrochlorides

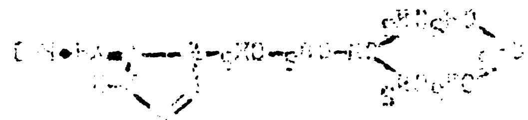


R	Formula	%C Calc.	%C Found	%H Calc.	%H Found	%N Calc.	%N Found	%Cl Calc.	%Cl Found
Benzyl	$C_{16}H_{24}ClN_5$	59.71	59.77	7.52	7.52	21.76	21.76	11.01	11.00
o-Chlorobenzyl	$C_{16}H_{23}Cl_2N_5$	53.93	54.00	6.51	6.35	19.66	19.74	19.90	19.70
p-Chlorobenzyl	$C_{16}H_{23}Cl_2N_5$	53.93	54.05	6.51	6.46	19.66	19.77	19.90	19.81
2,4-Dichlorobenzyl	$C_{16}H_{22}Cl_3N_5$	49.18	49.33	5.66	5.78	17.92	18.01	27.22	27.04
3,4-Dichlorobenzyl	$C_{16}H_{22}Cl_2N_5$	49.18	48.98	5.66	5.49	17.92	17.92	27.22	27.23
p-Nitrobenzyl	$C_{16}H_{23}ClN_6O_2$	52.38	52.70	6.32	6.47	22.91	23.06	9.67	9.37
m-Nitrobenzyl	$C_{16}H_{23}ClN_6O_2$	52.38	52.49	6.32	6.40	22.91	22.86	9.67	9.83
3-Phenylpropyl	$C_{18}H_{28}ClN_5$	61.78	62.03	8.07	8.07	20.02	20.28	10.13	10.21
2-Phenylethyl	$C_{17}H_{26}ClN_5$	60.78	60.84	7.80	7.77	20.85	20.87	10.56	10.67

Analyses by Micro-Tech. Laboratories, Skokie, Illinois.

TABLE II

Analysis of N-(2-Cyclohexylethyl)-1-Aralkyl-2-imidazoline Hydrochlorides



R	Formula	% C Calcd.	% C Found	% H Calcd.	% H Found	% N Calcd.	% N Found	% Cl Calcd.	% Cl Found
Phenyl	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
o-Chlorophenyl	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
p-Nitrophenyl	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
2,4-Dichlorophenyl	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
3,4-Dichlorophenyl	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Analyses by Micro-Tech Laboratories, Skokie, Illinois.

minutes. After separation of the ether layer 30 ml. of ethanol are added to the water layer to dissolve the remaining solids. The water solution is extracted with four 50 ml. portions of ether. The ether solutions are combined and dried over potassium carbonate. The ether is evaporated on a steam bath and 100 ml. of ethanol and 50 ml. of water are added to the oily residue. Concentrated hydrochloric acid is then added until Congo red indicator paper changed to blue (20 ml.). The hydrochloride is redissolved by heating the suspension. The hot solution is filtered, cooled and the solvent removed by suction on a filter. The solid is washed with 50 ml. of ethanol two times and dried. The yield of 1-(2-cyclohexylethyl)-4-benzyl-5-iminotetrazoline hydrochloride was 15.7 g. (81%), MP 209°-210°C. (uncorrected).

Alkylation of 1-Benzyl-5-Aminotetrazole with 2-cyclohexylethyl Bromide

1-Benzyl-5-aminotetrazole (10.5 g., .06 moles) (13) was heated with 17.5 g. (.09 moles) of 2-cyclohexylethyl bromide at 150°C. in an oil bath for eight hours. Formation of a homogeneous melt is followed by a rapid exothermic reaction after which the mixture solidifies. The bath is kept at 150°C. for eight hours after the exothermic reaction subsides. The mixture is dissolved in 200 ml. of boiling ethanol and 600 ml. of water is added. After steam distilling until about 500 ml. of distillate is obtained, the hot water layer of the residue is decanted from an oily brown liquid. Thirty grams of potassium hydroxide are added to the water solution and the solution stirred for half an hour. The water layer is cooled and 150 ml. of ether are added with shaking. The ether layer is separated and the water layer extracted with 100 ml. of ether and 50 ml. of benzene. The ether and benzene solutions are combined and the solvents

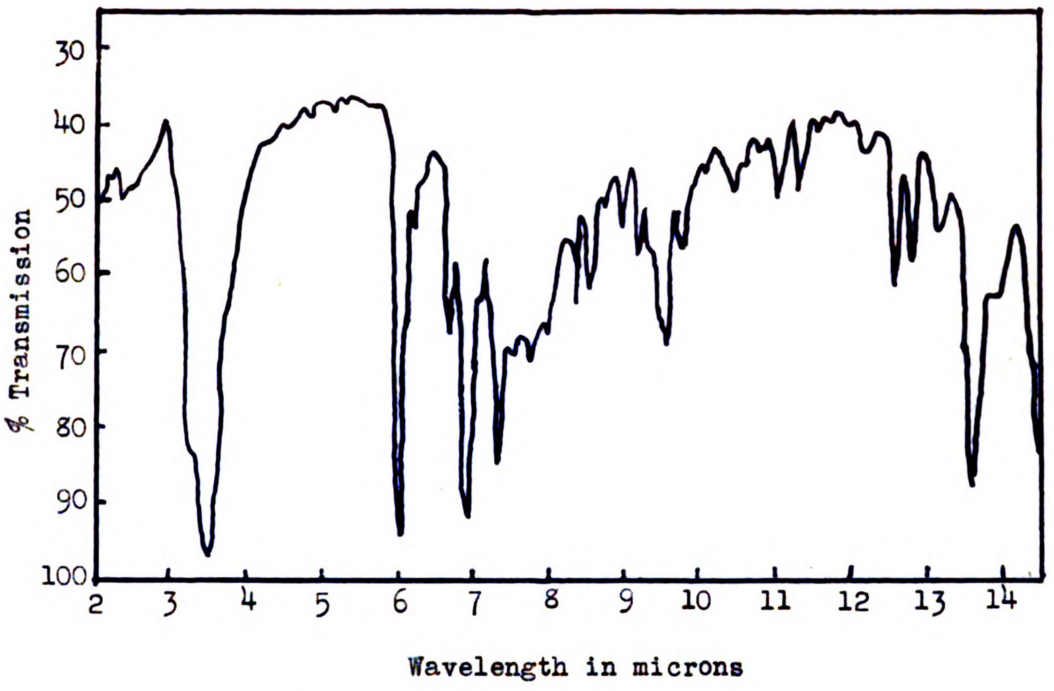


Figure III. Infrared spectrum of 1-(2-cyclohexylethyl)-4-benzyl-5-iminotetrazoline hydrochloride from 1-(2-cyclohexylethyl)-5-aminotetrazole. (Nujol mull)

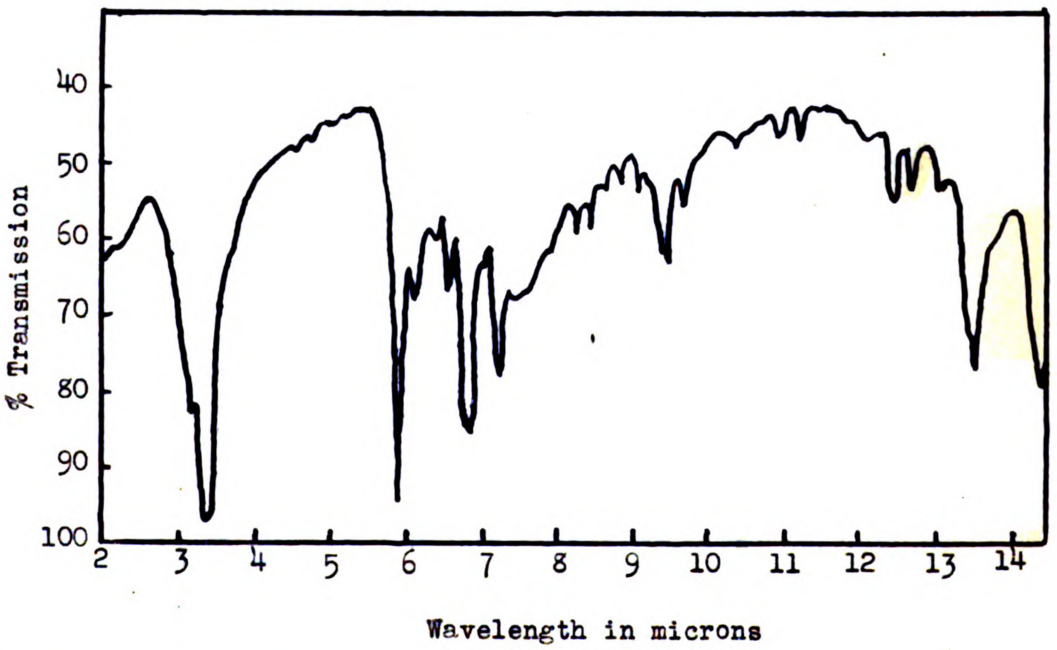


Figure IV. Infrared spectrum of 1-(2-cyclohexylethyl)-4-benzyl-5-iminotetrazoline hydrochloride from 1-benzyl-5-aminotetrazole. (Nujol mull)

evaporated. The residue is dissolved in 100 ml. of 95% ethanol and 50 ml. of water. A small amount of an insoluble product is formed when 30 ml. of concentrated hydrochloric acid have been added and is filtered off before the hydrochloride precipitates. The crude hydrochloride is redissolved by heating the suspension. The hot solution is filtered and chilled with an ice-water bath. The solid so obtained is filtered and dried. The yield of 1-(2-cyclohexylethyl)-4-benzyl-5-iminotetrazoline hydrochloride was 4.4 g. (23%). After two recrystallizations of this product from aqueous alcohol the product melted at 209°-210°C. Mixture melting points of this product and that made by the benzylation of 2-cyclohexylethyl-5-aminotetrazole showed no depression.

Debenzylation of 1-(2-Cyclohexylethyl)-4-Benzyl-5-Iminotetrazoline Hydrochloride

The method of Birkhofer (21) and Percival (4) was used. The hydrogenolysis or debenzylation is done as follows: 1-(2-cyclohexylethyl)-4-benzyl-5-iminotetrazoline hydrochloride (3.22 g., .01 mole) is dissolved in 50 ml. of ethanol. One gram of 5% palladium on charcoal is added and 50 p.s.i. of hydrogen is applied to the system for two hours with shaking in a Burgess-Parr low pressure hydrogenation apparatus. The theoretical amount of hydrogen is absorbed in half an hour. The catalyst is filtered and washed with hot ethanol. Sodium carbonate (0.5 g.) is added and the solution is concentrated. Yield of 1-(2-cyclohexylethyl)-5-aminotetrazole was 1.4 g. (71%) MP 212.5°-213.5°C. (uncorrected).

A mixture melting point of this product and that produced by the reaction of 2-cyclohexylethylamine, cyanogen bromide and hydrazoic acid gave no depression.

Phenylthioureas Derived from 1,4-Disubstituted-5-Iminotetrazolines

One gram of the iminotetrazoline hydrochloride is mixed with 1.4 g. of potassium hydroxide in 5 ml. of water and 1 ml. of ethanol. The solution is extracted successively with 10 ml. and 5 ml. of ether. The combined ether layers are dried over sodium carbonate. After evaporating the ether the residual, liquid base is treated with half its volume of phenylisothiocyanate and the mixture is heated for 1-5 minutes on a steam bath. The crude product is washed with 5 ml. of petroleum ether and 5 ml. of 50% isopropyl alcohol. The phenylthioureas are recrystallized from 75% isopropyl alcohol.

It was necessary to cool the washed product with dry ice to cause crystallization in the preparation of the phenylthioureas derivatived from the 3-phenylpropyl and 2-phenylethyl substituted tetrazolines.

The addition of half a gram of Norite was necessary in purifying the derivatives of the p-nitrobenzyl, m-nitrobenzyl and 3-phenylpropyl substituted tetrazolines.

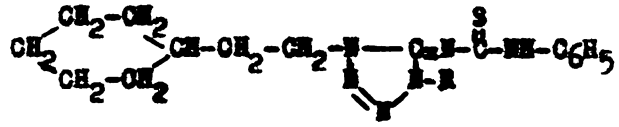
Formulae, melting points and analyses are given in Table III.

1-(2-Orthophenylethyl)-4-Aralkyl-5-Iminotetrazolines

The iminotetrazoline bases were prepared as follows: 2 g. of the hydrochloride are treated with 1 g. of potassium hydroxide, 5 ml. of water and 20 ml. of ether. The mixture is refluxed on a steam bath until both layers are clear. After cooling, the ether layer is separated and the water layer extracted with 10 ml. of ether. The combined ether layers are dried over sodium carbonate and the ether evaporated under reduced pressure on a steam bath. The residual oils were cooled with ice or dry ice to cause crystallization when necessary. No

TABLE III

Phenylthioureas Derived from 1-(2-Cyclohexylethyl)-4-Aralkyl-5-Iminotetrazolines



R	Formula	MP* °C		%N Calc.	%N Found	%S Calc.	%S Found	%Cl Calc.	%Cl Found
Benzyl	$C_{23}H_{28}N_6S$	139.0	139.5	19.98	20.04	7.62	7.34	-	-
o-Chlorobenzyl	$C_{23}H_{27}ClN_6S$	117.5	118.5	18.47	18.69	7.05	7.04	7.79	7.50
p-Chlorobenzyl	$C_{23}H_{27}ClN_6S$	128.0	128.5	18.47	18.64	7.05	7.06	7.79	7.67
2,4-Dichlorobenzyl	$C_{23}H_{26}Cl_2N_6S$	115.0	115.5	17.17	17.34	6.55	6.63	14.49	14.26
3,4-Dichlorobenzyl	$C_{23}H_{26}Cl_2N_6S$	144.0	145.0	17.17	17.25	6.55	6.58	14.49	14.27
p-Nitrobenzyl	$C_{23}H_{27}N_7O_2S$	133.5	134.5	21.06	21.02	6.89	6.88	-	-
m-Nitrobenzyl	$C_{23}H_{27}N_7O_2S$	129.0	129.5	21.06	21.24	6.89	7.01	-	-
3-Phenylpropyl	$C_{25}H_{32}N_6S$	112.5	113.5	18.73	18.67	7.15	7.08	-	-
2-Phenylethyl	$C_{24}H_{30}N_6S$	86.5	87.0	19.34	19.49	7.38	7.17	-	-

Analyses by Micro-Tech. Laboratories, Skokie, Illinois.

*Uncorrected

Benzene, melting point, and boiling point is 80°C.

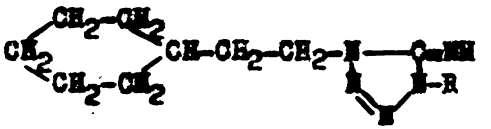
p-dichlorobenzene is solid at room temperature.

Petroleum ether was used to provide the energy, therefore, we did
not have to provide energy to boil off the solvent.

Hexane was used to provide the energy, therefore, we did not have to provide energy to boil off the solvent.

TABLE IV

1-(2-Cyclohexylethyl)-4-Aralkyl-5-Iminotetrazolines



R	Formula	MP(a) °C		%C Calc.	%C Found	%H Calc.	%H Found	%N Calc.	%N Found	%Cl Calc.	%Cl Found
Benzyl	$C_{16}H_{23}N_5$	120.0	121.0	67.33	-	8.12	-	24.54	-	-	-
o-Chlorobenzyl	$C_{16}H_{22}ClN_5$	58.0	59.0	60.08	60.21	6.93	7.05	21.90	21.72	11.09	11.28
p-Chlorobenzyl	$C_{16}H_{22}ClN_5$	52.5	53.5	60.08	59.89	6.93	6.78	21.90	21.73	11.09	11.32
2,4-Dichlorobenzyl	$C_{16}H_{21}Cl_2N_5$	69.5	70.5	54.24	54.13	5.98	5.92	19.77	19.90	20.02	20.11
3,4-Dichlorobenzyl	$C_{16}H_{21}Cl_2N_5$	94.5	95.0	54.24	54.33	5.98	6.05	19.77	19.76	20.02	20.02
p-Nitrobenzyl	$C_{16}H_{22}N_6O_2$	108.0	109.0	58.16	58.13	6.71	6.91	25.44	25.59	-	-
m-Nitrobenzyl	$C_{16}H_{22}N_6O_2$	83.5	84.5	58.16	58.43	6.71	6.68	25.44	25.30	-	-
3-Phenylpropyl	$C_{18}H_{27}N_5$	(b)		68.97	-	8.68	-	22.35	-	-	-
2-Phenylethyl	$C_{17}H_{25}N_5$	50.0	50.5	68.19	68.18	8.42	8.23	23.39	23.23	-	-

Analyses by Micro-Tech. Laboratories, Skokie, Illinois.

(a) Uncorrected.
(b) Could not be obtained as a solid.

SUMMARY

1. The preparation and properties of a new monosubstituted 5-aminotetrazole have been described.
2. The preparation and properties of a series of 1-(2-cyclohexylethyl)-4-aralkyl-5-iminotetrazolines and their hydrochlorides have been described.
3. The monoalkylation of a 1-substituted-5-aminotetrazole to give a 1,4-disubstituted-5-iminotetrazoline has been discussed.
4. A proof of structure for the 1-(2-cyclohexylethyl)-5-aminotetrazole has been described.

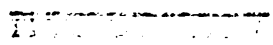
1. The preparation and [illegible] of a [illegible] -
[illegible] have been [illegible].

2. The preparation and [illegible] of a series of 1-[illegible] -
[illegible] have
been described.

3. The monoalkylation of a [illegible] to give a
1-[illegible]-substituted [illegible] [illegible].

4. A proof of structure for [illegible] 1-[illegible]
has been described.

LITERATURE CITED



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