THE SYNTHESIS OF SOME ALKYL AND ALKOXYALKYL AMINOTETRAZOLES AND THEIR ALKYLATION

By

JOSEPH W. HORTON

A THESIS

Submitted to the School of 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

1960

G 24559
3/13/63

ACKNOWLEGEMENT

The writer wishes to express his appreciation for the most helpful counsel and guidance extended to him by Dr. Robert M. Herbst during the course of this work and to Parke, Davis and Company for financial assistance in the form of a fellowship.

THE SYNTHESIS OF SOME ALKYL AND ALKOXYALKYL AMINOTETRAZOLES AND THEIR ALKYLATION

By

JOSEPH W. HORTON

AN ABSTRACT

Submitted to the School of 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

1960

Approved Robert M. Herbst

ABSTRACT

The alkylation of 1-substituted-5-aminotetrazoles by the method of Herbst, Roberts and Harvill (1) has been shown to yield 1,4-disubstituted-5-iminotetrazolines (2), with the original substituent remaining in the 1-position and the alkylating agent attacking the 4-position to form the appropriate disubstituted iminotetrazoline. However, in the alkylation of 1-(1',1',3',3'-tetramethylbutyl)-5-aminotetrazole with p-chlorobenzyl chloride, the product was not the expected 1-(1',1',3',3'-tetramethylbutyl)-4-(p-chlorobenzyl)-5-iminotetrazoline. The tertiary alkyl group was displaced during the course of the reaction with the formation of 1,4-di-(p-chlorobenzyl)-5-iminotetrazoline.

To show the fate of the tertiary alkyl group and also to determine if the reaction is characteristic of 1-tertiary alkyl-5-aminotetrazoles, 1-tertiary butyl-5-aminotetrazole was prepared and alkylated with benzyl chloride; two products were isolated. The solid product of the reaction was 1,4-dibenzyl-5-iminotetrazoline; the displaced tertiary butyl group appeared as isobutylene.

1-(1',1',3',3'-Tetramethylbutyl)-5-aminotetrazole was alkylated with benzyl chloride and the products of the reaction shown to be 1,4-dibenzyl-5-iminotetrazoline and a mixture of 2,4,4-trimethyl-1-pentene and 2,4,4-trimethyl-2-pentene closely corresponding to the commercial mixture of

the two isomeric trimethylpentenes known as "diisobutylene".

To demonstrate that the displacement reaction is a function of tertiary alkyl groups only, and not merely one of size, 1-(3'-heptyl)-5-aminotetrazole was synthesized and alkylated with benzyl chloride. Normal alkylation occurred with the formation of 1-(3'-heptyl)-4-benzyl-5-iminotetrazoline.

The displacement of tertiary alkyl groups on alkylation was shown to be a general reaction by the use of ethyl p-toluenesulfonate as an alkylating agent for 1-tertiary butyl-5-aminotetrazole. Isobutylene and 1,4-diethyl-5-iminotetrazoline were the products of the alkylation.

5-Hydroxytetrazoles have hitherto been prepared from tetrazoles containing a sulfur atom attached to the 5-position of the tetrazole ring. An attempt to prepare 1-substituted-5-hydroxytetrazoles by proceeding through the 1-alkyl-4-benzyl-5-ketotetrazolines was made. Also investigated at the same time were the preparation and properties of a group of 1-alkoxyalkyl and 1-aryloxyalkyl-5-aminotetrazoles.

The following tetrazoles were prepared using a procedure adapted from Garbrecht and Herbst (3): 1-(3'-isopropoxypropyl)-5-aminotetrazole, 1-(3'-methoxypropyl)-5-aminotetrazole, 1-(2'-methoxyethyl)-5-aminotetrazole, 1-(2'-phenoxyethyl)-5-aminotetrazole and 1-(3'-phenoxypropyl)-5-aminotetrazole. The tetrazoles were prepared from the corresponding alkoxyalkyl or aryloxyalkylamines by interaction

with cyanogen bromide in aqueous ethanolic solution, followed by treatment with hydrazoic acid.

All of the above compounds, except 1-(3'-methoxypropyl)-5-aminotetrazole were benzylated to form the corresponding 1-alkoxyalkyl-4-benzyl-5-iminotetrazolines. 1-(3'-Methoxypropyl)-5-aminotetrazole was alkylated with 2-phenoxyethyl bromide to form 1-(3'-methoxypropyl)-4-(2'-phenoxyethyl)-5-iminotetrazoline.

Conversion of the iminotetrazolines to the corresponding ketotetrazolines was done by acetolysis in a manner similar to the method of Percival (4). Attempted hydrogenolysis of 1-(2'-phenoxyethyl)-4-benzyl-5-ketotetrazoline failed to cleave the benzyl group from the ketotetrazoline and produce the desired 5-hydroxytetrazole.

LITERATURE CITED

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

2. R. Herbst and D. Percival, J. Org. Chem., 19, 439 (1954).

3. W. Garbrecht and R. Herbst, J. Org. Chem., 18, 1014 (1953).

4. D. Percival and R. Herbst, J. Org. Chem., 22, 925 (1957).

To my wife Jo An

TABLE OF CONTENTS

TABLE OF CONTENTS

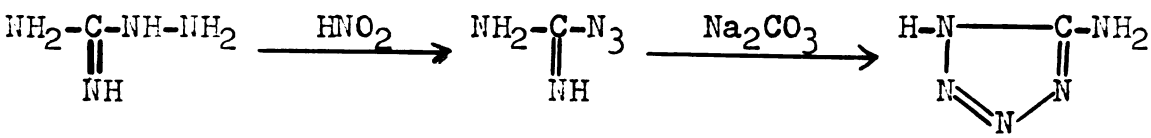
LIST OF TABLES

LIST OF FIGURES

HISTORICAL INTRODUCTION

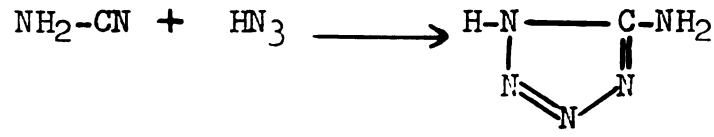
Historical Introduction

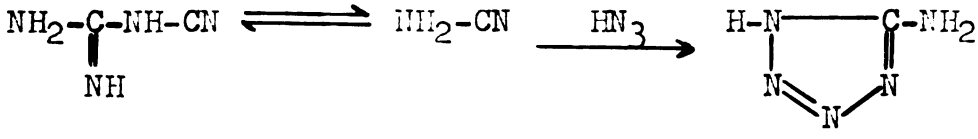
The first report of the synthesis of 5-aminotetrazole was made by Thiele (1) who prepared guanyl azide by interaction of aminoguanidine and nitrous acid. The guanyl azide was then heated with an aqueous solution of sodium carbonate or sodium acetate to bring about the desired ring closure to 5-aminotetrazole.



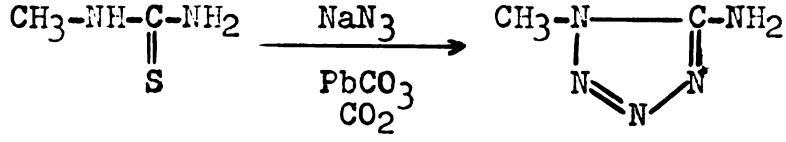
Thiele, in collaboration with Ingle (2), reported on the products obtained from the direct alkylation of 5-aminotetrazole. Methylation, ethylation and benzylation gave mixtures of products containing both mono and disubstituted aminotetrazoles. Some of these compounds were again prepared by Herbst and Percival (3) and it was found that the compounds reported by Thiele and Ingle as the "dimethyl", "diethyl" and "'alpha' dibenzyl 5-aminotetrazoles" were actually 1,4-disubstituted-5-iminotetrazolines.

Sodium azide and hydrazoic acid have been used in the preparation of substituted 5-aminotetrazoles. Cyanamide (4) or dicyandiamide (5), which is known to dissociate to cyanamide, will react with hydrazoic acid to form 5-aminotetrazole.



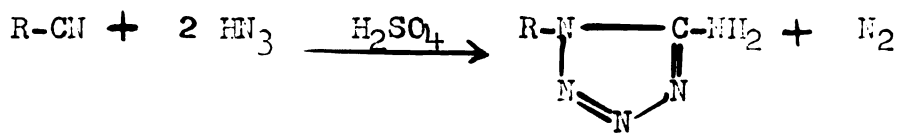


Stolle, in 1932 (6), reported the preparation of 1-methyl-5-aminotetrazole by interaction of N-methylthiourea with sodium azide and lead carbonate in a carbon dioxide atmosphere.

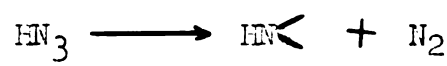


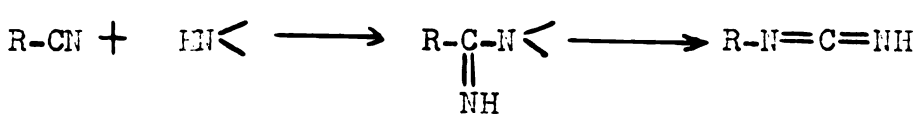
In the same manner he also prepared a number of 1-aryl-5-aminotetrazoles from the corresponding N-arylthioureas.

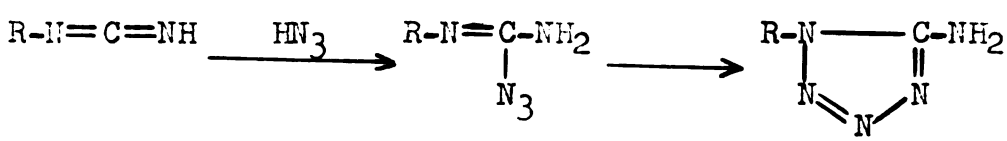
A procedure, developed by von Braun and Keller (7), eliminates the use of lead carbonate in the preparation of 1-substituted-5-aminotetrazoles. Nitriles and hydrazoic acid react in the presence of concentrated sulfuric acid as follows:



The mechanism which was proposed by von Braun and Keller involved a decomposition of hydrazoic acid to the free imine radical, followed by addition of the imine radical to the nitrile to form a substituted carbodiimide. The carbodiimide was then attacked by another molecule of hydrazoic acid to form a substituted guanyl azide which cyclized to the 1-substituted-5-aminotetrazole.

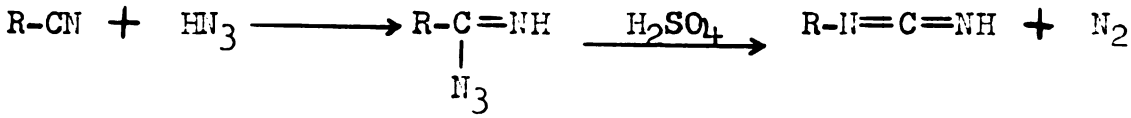


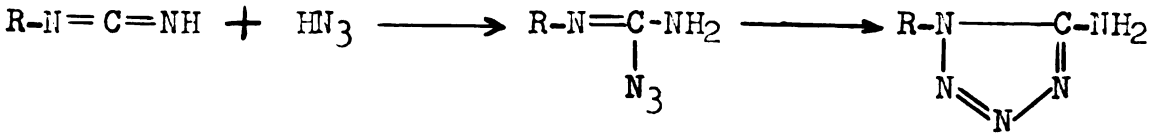




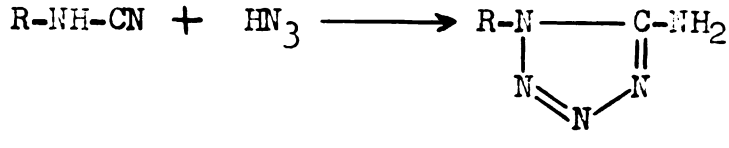
Herbst, Roberts and Harvill (8), proposed a mechanism which did not involve the use of the free imine radical first postulated by Schmidt (9) and used in the mechanism of von Braun and Keller. The mechanism suggested by Herbst, et al., involved the addition of hydrazoic acid to the

nitrile, followed by an acid catalyzed rearrangement similar to a Curtius rearrangement of acid azides. The rearrangement, accompanied by the loss of nitrogen, resulted in the same carbodiimide postulated as an intermediate by von Braun and Keller. Upon the addition of another molecule of hydrazoic acid, the substituted carbodiimide was converted to a substituted guanyl azide which cyclized to form the 1-substituted-5-aminotetrazole.



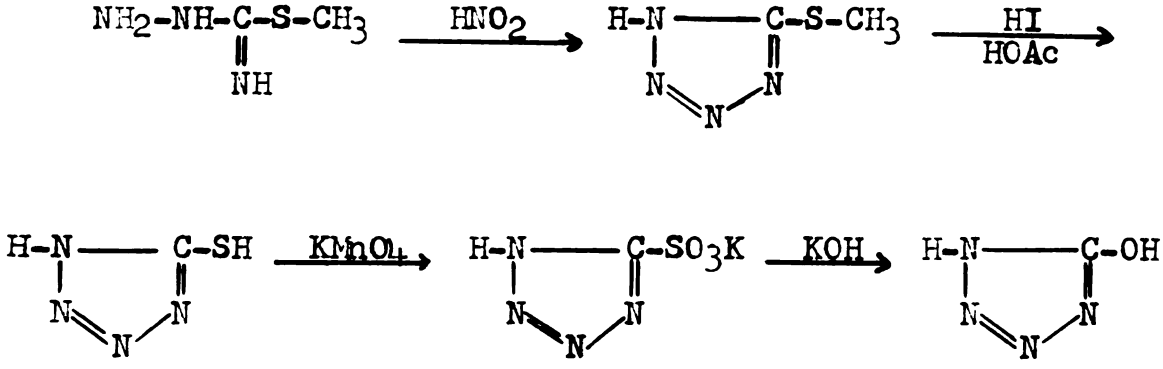


The work of Hantzsch and Vagt (4) has been expanded by Garbrecht and Herbst (10), who found that the reaction of monosubstituted cyanamides with hydrazoic acid in ethereal or aqueous alcoholic solution resulted in the formation of 1-substituted-5-aminotetrazoles.



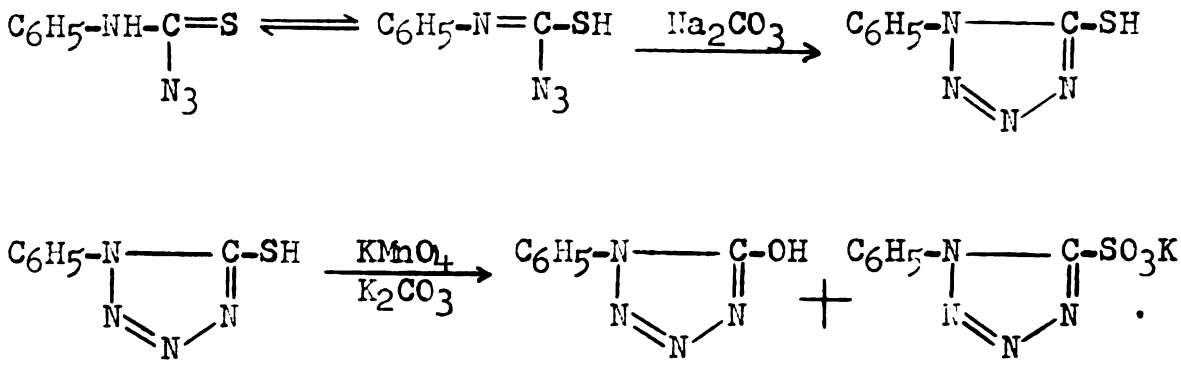
Herbst, Roberts and Harvill (5, 11) have developed several methods for alkylation of 1-substituted-5-aminotetrazoles. Alkyl or aralkyl halides, alkyl sulfates or alkyl sulfonates are used as alkylating agents to produce 1,4-disubstituted-5-iminotetrazolines.

The first preparation of 5-hydroxytetrazole was reported by Freund and Paradies (12) in 1901, who prepared the compound by fusion of 5-tetrazolesulfonic acid with potassium hydroxide. The 5-tetrazolesulfonic acid was prepared through a series of reactions from S-methylthiosemicarbazide. The complete reaction sequence is as follows:

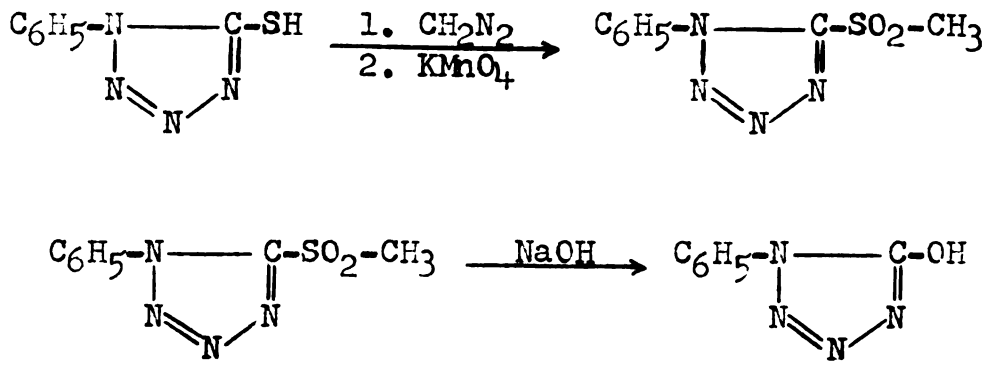


Stolle (5) also prepared 5-hydroxytetrazole, but used 5-aminotetrazole as his starting material. The diazonium sulfate formed by diazotization of 5-aminotetrazole was treated successively with cupric hydroxide, hydrogen sulfide and barium chloride. Stolle also prepared 5-hydroxytetrazole by the hydrolysis of 5-iodotetrazole with 60% sodium hydroxide.

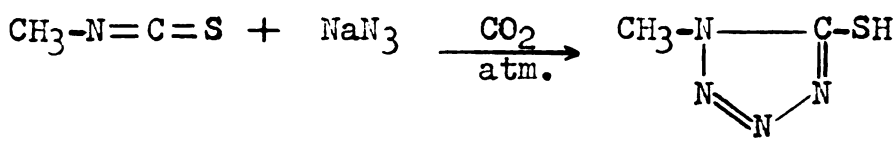
Freund and Hempel (13) prepared 1-phenyl-5-mercaptotetrazole from thiocarbanilic acid azide and partially converted it to 1-phenyl-5-hydroxytetrazole by oxidation with basic permanganate.

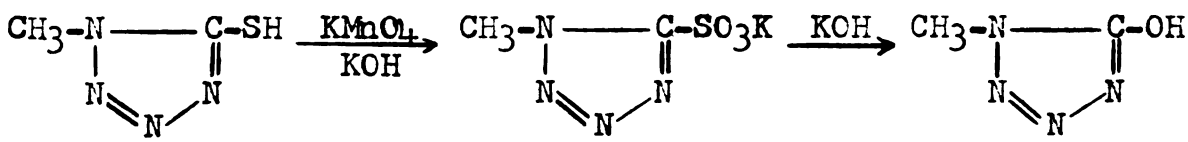


In an analogous manner, Stolle and Henke-Stark (14) prepared 1-phenyl-5-mercaptotetrazole and converted it to 1-phenyl-5-hydroxytetrazole by preparing the S-methyl ether with diazomethane; oxidizing the thioether with acid permanganate to the sulfone and hydrolyzing the sulfone with 10% sodium hydroxide.

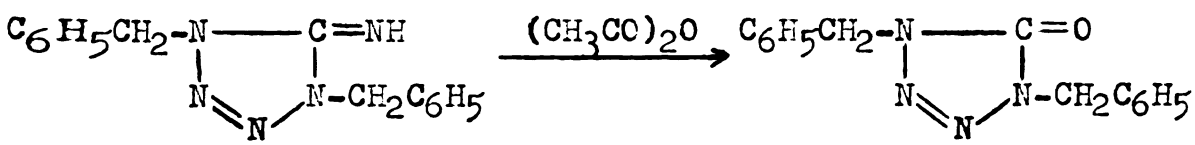


Stolle and Henke-Stark (14) also prepared 1-methyl-5-hydroxytetrazole from 1-methyl-5-mercaptotetrazole by oxidation to 1-methyl-5-tetrazolesulfonic acid with basic permanganate and cleaving the sulfonate with concentrated potassium hydroxide. 1-Methyl-5-mercaptotetrazole was obtained by interaction of methyl isothiocyanate and sodium azide.





Percival (15) treated 1,4-dibenzyl-5-iminotetrazoline with acetic anhydride and obtained, instead of the expected acetylimino compound, 1,4-dibenzyl-5-ketotetrazoline.



The acetolysis technique of Percival and the hydrogenolysis techniques of Herbst and Percival (3, 16) were used as a basis for the experimental work of this thesis.

DISCUSSION

PART ONE

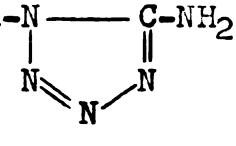
Discussion

It was found that the benzylation of 1-(1',1',3',3'-tetramethylbutyl)-5-aminotetrazole caused displacement of the tertiary alkyl group; the product of the reaction was not the expected 1-(1',1',3',3'-tetramethylbutyl)-4-benzyl-5-iminotetrazoline, but was instead 1,4-dibenzyl-5-imino-tetrazoline. Accordingly, the first part of this investigation was to determine if the displacement of the "tertiary octyl" group was unique or if this type of displacement was characteristic of any 1-tertiary alkyl-5-aminotetrazole.

The simplest of the 1-tertiary alkyl-5-aminotetrazoles, 1-tertiary butyl-5-aminotetrazole, was prepared by interaction of tertiary butylamine with cyanogen bromide in aqueous alcoholic solution followed by treatment with sodium azide and hydrochloric acid. The procedure was analogous to the one perfected by Garbrecht and Herbst (10).

$$R\text{-}NH_2 + Br\text{-}CN \longrightarrow R\text{-}NH\text{-}CN + HBr$$

$$R\text{-}NH\text{-}CN + HN_3 \longrightarrow$$



R = tertiary butyl

The alkylation of 1-tertiary butyl-5-aminotetrazole was carried out by the procedure of Herbst, Roberts and Harvill (8, 11). The 5-aminotetrazole was treated with enough benzyl chloride not only to alkylate the compound to a 1,4-disubstituted-5-iminotetrazoline, but also to replace the tertiary butyl group, if it could be replaced. The apparatus in which the alkylation was carried out was modified in such a way that any effluent gases would be condensed in a trap which was cooled in a dry ice-acetone bath. The reaction mixture was maintained at a temperature of 140-145° C. for five and one half hours, during which time the mixture became homogeneous. A gas was evolved and condensed in the cold trap as a clear colorless liquid. The volatile material absorbed bromine with the formation of a product identical with an authentic sample of isobutylene dibromide. The solid product of the reaction proved to be 1,4-dibenzyl-5-iminotetrazoline, which was isolated and identified as the hydrochloride. A mixture melting point with an authentic sample of 1,4-dibenzyl-5-iminotetrazoline hydrochloride showed no depression of melting point. The elemental analysis of the benzylation product was in conformity with the dibenzyl derivative.

The results of this sequence of reactions led to the hypothesis that a tertiary alkyl group would be displaced during the course of the benzylation and would appear as the corresponding olefin. Accordingly, the benzylation of

1-(1',1',3',3'-tetramethylbutyl)-5-aminotetrazole was carried out under similar circumstances; the dry ice-acetone bath was replaced with a salt-ice bath; the temperature held between 145-150° C. The reaction mixture turned to a clear melt and the volatile product evolved was caught in the cold trap. The solid product of the benzylation proved to be 1,4-dibenzyl-5-iminotetrazoline hydrochloride. The melting point of the pure compound isolated from the alkylation mixture and a mixture melting point with an authentic sample of 1,4-dibenzyl-5-iminotetrazoline hydrochloride were identical. Thus benzyl chloride was also capable of displacing the tertiary octyl group from the 5-aminotetrazole.

The volatile product from the alkylation decolorized a solution of bromine in carbon tetrachloride; the rapid decolorization of the solution suggested an unsaturated product, possibly a hydrocarbon. Therefore, the material was oxidized with permanganate to determine, if possible, the position of the double bond. After refluxing the olefin-permanganate mixture for thirty minutes (17), the reaction mixture was slowly distilled into a solution of 2,4-dinitrophenylhydrazine in perchloric acid. A precipitate formed, which on recrystallization from 95% ethanol melted at 125-126° C. The melting point corresponded to that of acetone 2,4-dinitrophenylhydrazone, demonstrating that the end of the olefin consisted of an isopropylidene unit.

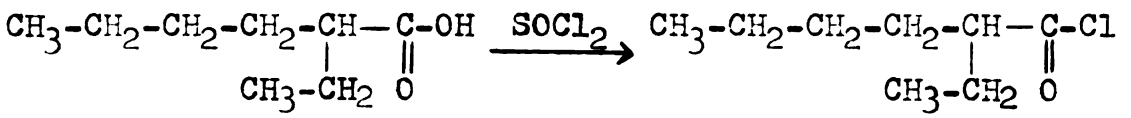
Since the olefin was produced by the displacement of the 1,1,3,3-tetramethylbutyl group from the 5-aminotetrazole, it was assumed to have the molecular formula of C_8H_{16}, and the molecular structure corresponding to either 2,4,4-trimethyl-1-pentene or 2,4,4-trimethyl-2-pentene. Accordingly, a determination of the degree of unsaturation and bromine number was performed. A modification of McIlhiney's technique (18) was used. A bromine number of 144 was obtained as the average of four determinations, compared to the theoretical bromine number of 143 for a C_8H_{16} hydrocarbon. The average molecular weight of the hydrocarbon calculated from the bromine number, assuming one double bond, was 111 compared to a molecular weight of 112 for an octene.

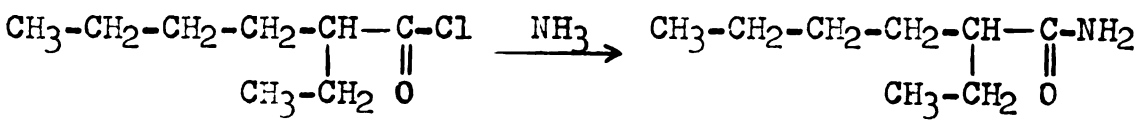
Infrared spectra of 2,4,4-trimethyl-1-pentene and 2,4,4-trimethyl-2-pentene were compared with the spectrum of the unknown hydrocarbon. Similar bands in the spectra of all three hydrocarbons led to the conclusion that the displaced 1,1,3,3-tetramethylbutyl group from 1-(1',1',3',3'-tetramethylbutyl)-5-aminotetrazole was a mixture of the two isomeric hydrocarbons. A comparison with the spectrum of diisobutylene, a commercially available mixture of the two isomeric octenes, also showed the same bands.

To demonstrate that the displacement of the alkyl group was a function of the tertiary character of the group and not merely one of size, a primary amine with a large second-

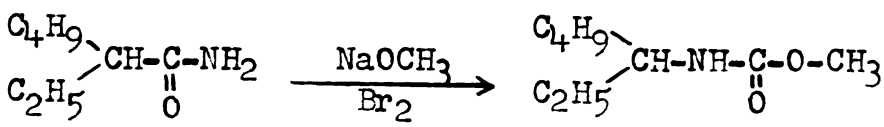
ary alkyl group was prepared and the corresponding 1-secondary alkyl-5-aminotetrazole was synthesized.

The primary amine chosen was 3-aminoheptane and was synthesized from 2-ethylhexanoic acid by the following sequence of reactions. The amide of 2-ethylhexanoic acid was prepared from the acid by first making the acid chloride by interaction with thionyl chloride and treating the acid chloride with concentrated aqueous ammonia.

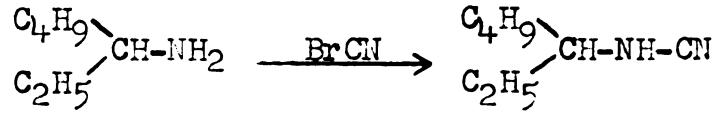


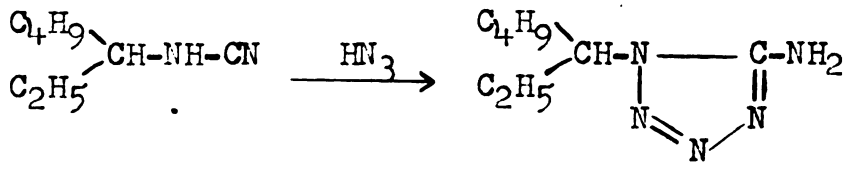


The amide was then caused to undergo a Hofmann rearrangement using bromine and sodium methoxide to form the methyl carbamate; the carbamate was hydrolyzed by refluxing for 14 hours with constant boiling hydrochloric acid.



The 1-(3'-heptyl)-5-aminotetrazole was prepared from the 3-aminoheptane by interaction with cyanogen bromide in aqueous ethanol, followed by treatment with sodium azide and hydrochloric acid.





When the benzylation of 1-(3'-heptyl)-5-aminotetrazole was carried out in a fashion similar to the previous cases, taking similar precautions to trap volatile products, the normal benzylation product, 1-(3'-heptyl)-4-benzyl-5-imino-tetrazoline, was obtained and characterized as the hydrochloride. No volatile material was evolved. This indicates that the displacement reaction observed in the cases of 1-tertiary butyl-5-aminotetrazole and 1-(1',1',3',3'-tetramethylbutyl)-5-aminotetrazole is due to the presence of the tertiary alkyl group on the 1-position of the tetrazole ring, and not merely due to the size of the alkyl group.

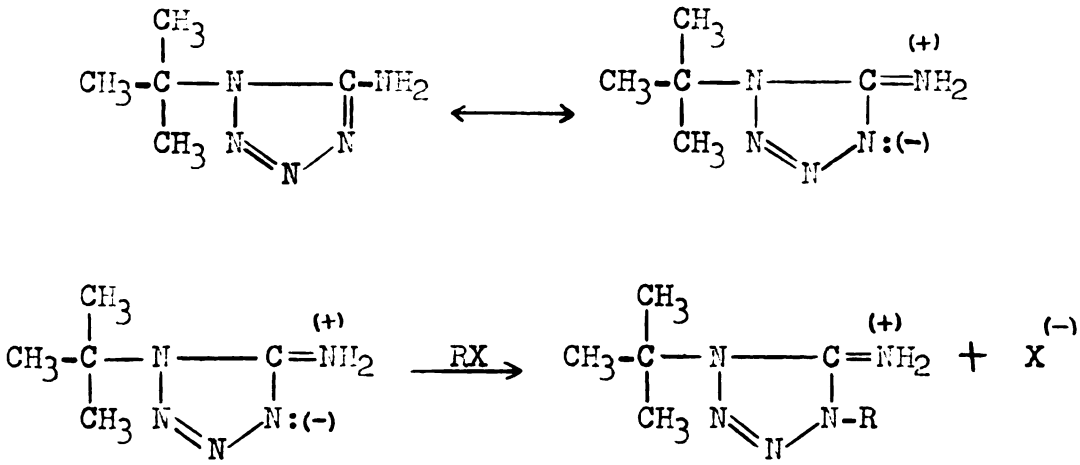
To further demonstrate that the displacement of the tertiary alkyl groups is a characteristic of the alkyl groups only, and not dependent in part upon the benzyl

group, the following experiment was performed. Ethyl p-toluenesulfonate was used in the alkylation of 1-tertiary butyl-5-aminotetrazole. When the alkylation mixture was heated to a temperature of 140-145° C., the evolution of a gaseous material was observed, and on subsequent analysis, the gas was shown to be isobutylene. The 1,4-dialkyl-5-iminotetrazoline proved to be 1,4-diethyl-5-iminotetrazoline. A mixture melting point with an authentic sample of 1,4-diethyl-5-iminotetrazoline hydrochloride showed no depression.

The above alkylations of 1-tertiary alkyl-5-aminotetrazoles with various alkylating agents indicate that the displacement of the tertiary alkyl group is a function of the tertiary character of the group alone, and not a function of the alkylating agent or the size of the alkyl group of either reactant. This conclusion is borne out by the findings that both tertiary butyl and "tertiary octyl" (1,1,3,3-tetramethylbutyl) groups are displaced with equal facility by alkylating agents such as benzyl chloride, p-chlorobenzyl chloride and ethyl p-toluenesulfonate.

A possible mechanism which could be postulated for the elimination of the tertiary alkyl group with the formation of an olefin and a symmetrically dialkylated iminotetrazoline can be illustrated using 1-tertiary butyl-5-aminotetrazole as an example. The 1-tertiary butyl-5-aminotetrazole could be alkylated according to the mechanism proposed by Percival (15). This mechanism involves the 1-substituted-5-amino-

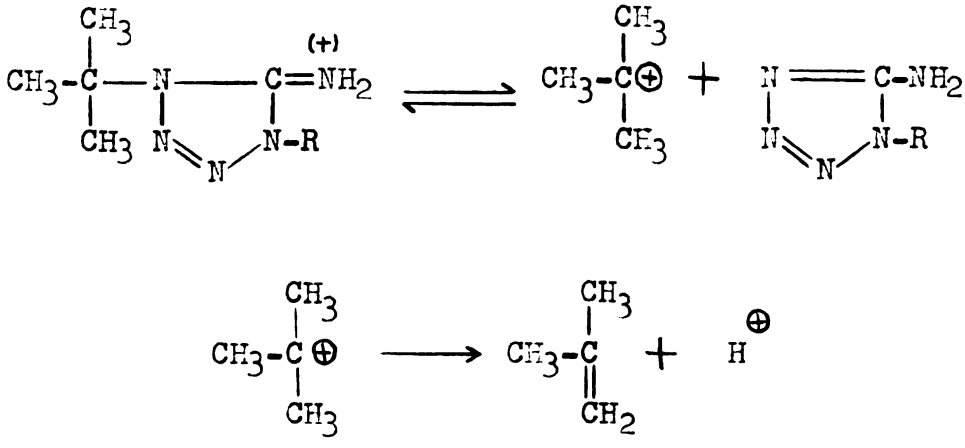
tetrazole in its polar resonance form, which is converted to the 1,4-disubstituted-5-iminotetrazoline salt.



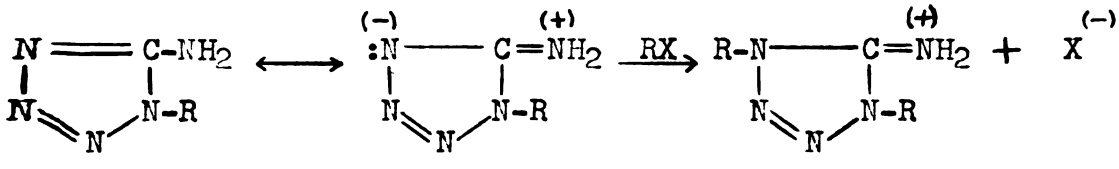
R = $C_6H_5CH_2$-, C_2H_5-

X = Cl, p-CH_3-$C_6H_4SO_3$

The cation of the 1-tertiary alkyl-4-alkyl-5-iminotetrazoline salt dissociates into a tertiary alkyl carbonium ion and a molecule of 1-alkyl-5-aminotetrazole. This step may be explained by an electronic shift brought about by the influence of the positively charged imino group and aided by the known tendency of tertiary alkyl compounds to undergo ionic dissociation to form the relatively stable tertiary carbonium ion and associated anion. The tertiary butyl carbonium ion can stabilize itself by the ejection of a proton and the formation of the corresponding olefin.



After a resonance shift into the dipolar ionic form, the 1-alkyl-5-aminotetrazole could undergo a second alkylation in the manner suggested by Percival to form a symmetrically substituted 1,4-dialkyl-5-iminotetrazoline salt.



The above mechanism can be used to explain the fact that the elimination of tertiary alkyl groups is independent of the size of the alkyl group in the 1-tertiary alkyl-5-aminotetrazole or the nature of the alkylating agent.

EXPERIMENTAL

PART ONE

Experimental[1,2]

SYNTHESIS OF 1-ALKYL-5-AMINOTETRAZOLES

These compounds were prepared by methods only slightly different than those used by Garbrecht and Herbst (10).

Preparation of 1-(1',1',3',3'-tetramethylbutyl)-5-aminotetrazole.

A solution of 129 g. (1 mole) of 1,1,3,3-tetramethylbutylamine in 800 ml. of 95% ethanol was cooled to about 5° C. in a three liter three necked flask equipped with a stirrer, dropping funnel, alcohol thermometer and an exit tube. With continued stirring and cooling, a solution of 106 g. (1 mole) of cyanogen bromide in 200 ml. of 95% ethanol and 200 ml. of distilled water was added at such a rate that the temperature of the reaction mixture did not rise above 10° C. Subsequently a solution of 40 g. (1 mole) of sodium hydroxide in 100 ml. of water was added with cooling and stirring again at such a rate that the tempera-

---

1. Microanalyses were done by Micro-Tech Laboratories, Skokie, Illinois.
2. Melting points were taken in open capillary tubes and were uncorrected.

ture did not rise above 10° C. The resulting solution was stirred in the ice bath for two and one half hours, after which a solution of 81 g. (1.25 moles) of sodium azide in 250 ml. of water was added, followed by 103 ml. of concentrated hydrochloric acid diluted with 100 ml. of water, both at such a rate that the temperature of the reaction mixture remained below 10° C. The reaction flask was then transferred to a steam bath, equipped with an efficient reflux condenser and boiled under reflux for six hours.

On cooling the mixture, the product separated as a mass of needles, which were separated on a Buchner funnel. Concentration of the mother liquor gave a further quantity of crude product. The combined crude fractions (140 g.) were recrystallized from one liter of 75% isopropyl alcohol, from which the product separated first as long, glistening needles that changed to heavy, glistening rods on further cooling. A total of 117 g. (60% of theory) of product, m.p. 201-202° C. was recovered.

The analytical sample was recrystallized again from 99% isopropyl alcohol and melted at 202-202.5° C. The product is moderately soluble in hot alcohols and aqueous alcohol, only very slightly soluble in water, benzene, ether or petroleum ether.

Analysis. Calculated for $C_9H_{19}N_5$: C, 54.8; H, 9.7; N, 35.5. Found: C, 54.9; H, 9.6; N, 35.8.

Preparation of 1-tertiary butyl-5-aminotetrazole.

A solution of 73.1 g. (1 mole) of tertiary butylamine in 800 ml. of 95% ethanol was treated dropwise, while stirring and cooling, with a solution of 106 g. (1 mole) of cyanogen bromide in 200 ml. of 95% ethanol and 200 ml. of distilled water. The cyanogen bromide solution was added at such a rate that the temperature did not exceed 10° C. After the cyanogen bromide had been added, a solution of 40 g. (1 mole) of sodium hydroxide in 100 ml. of distilled water was added, keeping the temperature below 10° C.

Following the addition of the sodium hydroxide, the reaction mixture was stirred for one and one half hours, maintaining the low temperature. Next, a solution of 78 g. (1.2 moles) of sodium azide in 240 ml. of distilled water was added over a period of five minutes, followed by 100 ml. (1.2 moles) of concentrated hydrochloric acid diluted with 100 ml. of distilled water. Addition was done at such a rate that the temperature did not exceed 10° C., and the reaction mixture was stirred for one hour after the addition of the hydrochloric acid, keeping the temperature below 10° C.

The reaction mixture was boiled under reflux for six hours and allowed to stir at room temperature for an additional eight hours, at which time approximately one liter of solvent was removed by distillation. After cooling, the crude product separated and was collected by filtration.

The crude 1-tertiary butyl-5-aminotetrazole was washed with 500ml. of distilled water and was recrystallized from distilled water. The yield was 104 g., 73% of the theoretical, and the purified compound melted at 185-186° C.

Analysis. Calculated for $C_5H_{11}N_5$: C, 42.5; H, 7.9; N, 49.6. Found: C, 42.7; H, 7.8; N, 49.8.

The acetyl derivative of 1-tertiary butyl-5-aminotetrazole was prepared by heating one gram of the tetrazole with 10 ml. of acetic anhydride for two hours. The compound, 1-tertiary butyl-5-acetylaminotetrazole, was recrystallized from a mixture of ethyl acetate and petroleum ether and melted at 98.5-99.5° C.

Analysis. Calculated for $C_7H_{13}N_5O$: C, 45.9; H, 7.2; N, 38.2. Found: C, 46.0; H, 7.2; N, 38.0.

Synthesis of 1-(3'-heptyl)-5-aminotetrazole.

A. Preparation of 2-ethylhexanoyl chloride.

A one liter three necked flask was fitted with a condenser, mechanical stirrer and dropping funnel and placed in a water bath. Two hundred sixty-eight grams, (2.25 moles) of thionyl chloride was placed in the flask and 288 g. (2 moles) of 2-ethylhexanoic acid was added dropwise with stirring, using the cold water bath as a means of absorbing the initial heat of the reaction. After all of the acid was added, the cold water bath was replaced by a heating mantle and the reaction mixture was heated at 85° C. for

30 minutes. At the end of the heating period, no more fumes of hydrogen chloride and sulfur dioxide were evolved; therefore the reaction mixture was cooled to room temperature.

The apparatus was modified for distillation under reduced pressure and the 2-ethylhexanoyl chloride distilled at 74-76° C. at 16 mm. pressure (19). The yield of acid chloride was 278.5 g., 85.8% of the theoretical amount.

B. Preparation of 2-ethylhexanamide.

A three liter three necked flask was fitted with a mechanical stirrer, dropping funnel and thermometer. In the flask was placed 800 ml. of concentrated aqueous ammonia, and the flask was cooled in an ice bath to 10° C. Then 278.5 g. (1.71 moles) of 2-ethylhexanoyl chloride was added dropwise while stirring, keeping the temperature below 15° C. After all the acid chloride was added, the reaction mixture was stirred for one hour at 10° C. The contents of the flask were filtered with suction and washed with three 500 ml. portions of ice cold distilled water to remove ammonium chloride; the 2-ethylhexanamide was recrystallized from distilled water and dried overnight in the oven at a temperature of approximately 70° C. The yield of 2-ethylhexanamide was 210 g. (86% of theory) of material melting at 101-102° C. (20).

C. Preparation of methyl N-3'-heptyl carbamate.

A modified Hofmann reaction (21) was used to prepare methyl N-3'-heptyl carbamate. A three liter three necked flask was fitted with a reflux condenser, dropping funnel and a mechanical stirrer. Anhydrous methanol (1500 ml.) was placed in the flask and 67.4 g. (2.93 moles) of metallic sodium was dissolved in the methanol. After the sodium had dissolved, 210 g. (1.47 moles) of 2-ethylhexanamide dissolved in 1000 ml. of anhydrous methanol was added. At this point, 234 g. (1.47 moles) of bromine was added dropwise with constant stirring, and the reaction mixture was boiled under reflux for 30 minutes on the steam bath after the addition of the bromine. The reaction mixture was acidified with acetic acid and the methanol was removed by distillation under diminished pressure. The residue in the flask was a pasty mixture of methyl N-3'-heptyl carbamate, sodium bromide and sodium acetate. The mixture was washed with two 500 ml. portions of distilled water to remove the inorganic salts. The crude urethane was a light yellow oil.

D. Preparation of 3-aminoheptane hydrochloride.

The crude methyl N-3'-heptyl carbamate was boiled under reflux for approximately 14 hours with 20% hydrochloric acid. At the end of the reflux period, almost all of the crude urethane had gone into solution. The aqueous layer was separated and evaporated almost to dryness under diminished pres-

sure. The remaining water was removed by azeotropic distillation with anhydrous ethanol. The crude 3-aminoheptane hydrochloride was dissolved in absolute ethanol and precipitated by the addition of anhydrous ether. Yield was 109 g. (72% of theory).

E. Preparation of 1-(3'-heptyl)-5-aminotetrazole.

A two liter three necked flask was fitted with an alcohol thermometer, mechanical stirrer, dropping funnel and reflux condenser. In the flask was placed a solution of 75.8 g. (0.5 mole) of 3-aminoheptane hydrochloride in 400 ml. of 95% ethanol and the resulting solution was cooled to 0° C. in an ice-salt bath. A solution of 53 g. (0.5 mole) of cyanogen bromide in 100 ml. of 95% ethanol and 100 ml. of distilled water was added while stirring, keeping the temperature of the reaction below 10° C. Stirring was continued during the whole sequence of the reaction. After the addition of the cyanogen bromide solution, 40 g. (1 mole) of sodium hydroxide, dissolved in 100 ml. of distilled water, was added while the temperature of the reaction mixture was held below 10° C. Following the addition of the sodium hydroxide solution, the reaction mixture was stirred for one and one half hours, keeping the temperature below 10° C.

A solution of 39 g. (0.6 mole) of sodium azide in 120 ml. of distilled water was then added over a five minute period, followed by the addition of 50 ml. (0.6 mole) of

concentrated hydrochloric acid diluted with 50 ml. of distilled water. During the addition of the sodium azide solution and the hydrochloric acid, the temperature of the reaction mixture was not allowed to rise above 10° C. The ice bath was removed and the reaction mixture was stirred at room temperature for three hours, followed by boiling under reflux on the steam bath for three hours, after which the reaction mixture was allowed to stand for eight hours.

The ethanol was removed by distillation and the reaction mixture was stirred in an ice-salt bath until crystallization occurred. The crude 1-(3'-heptyl)-5-aminotetrazole was recrystallized from heptane. The yield was 45.2 g. (49.5% of theory) of material which melted at 145-146° C. (8). No depression in melting point was observed on admixture with an authentic sample of 1-(3'-heptyl)-5-aminotetrazole.

ALKYLATION OF 1-ALKYL-5-AMINOTETRAZOLES

The 1-substituted-5-aminotetrazoles were alkylated by procedures only slightly modified from those of Herbst, Roberts and Harvill (8).

Alkylation of 1-(1',1',3',3'-tetramethylbutyl)-5-aminotetrazole with p-chlorobenzyl chloride.

A mixture of 9.9 g. (0.05 mole) of 1-(1',1',3',3'-

tetramethylbutyl)-5-aminotetrazole and 8.9 g. (0.055 mole) of p-chlorobenzyl chloride was heated in an oil bath at 135-140° C. for 18 hours. The reactants liquified completely to form a two phase system in which there was ebullition and apparently gas evolution. After cooling, the crude solid product was taken up in about 100 ml. of hot 95% ethanol, the solution diluted with 500 ml. of water and distilled to remove ethanol and excess p-chlorobenzyl chloride. The aqueous solution was made alkaline with 15 g. of sodium hydroxide to liberate the iminotetrazoline base.

The latter was extracted with two 100 ml. and two 50 ml. portions of warm benzene. Warm extraction was necessary to prevent crystallization of the base. Evaporation of the combined benzene extracts left the base as a solid residue.

One gram of the crude base was recrystallized first from toluene-cyclohexane mixture, then from 99% isopropyl alcohol and then from toluene-cyclohexane mixture again. The pure base was obtained as coarse, glistening prisms, m.p. 148-149° C.

Analysis. Calculated for $C_{15}H_{13}Cl_2N_5$: Cl, 21.2; N, 21.0. Found: Cl, 21.1, 20.9; N, 21.2, 21.2.

The composition of the base indicated, in addition to the expected ring benzylation, that the 1,1,3,3-tetramethylbutyl group had been displaced by a p-chlorobenzyl group.

The remainder of the crude base was taken up in 50 ml. of 99% isopropyl alcohol and converted into the hydrochloride by the addition of 15 ml. of concentrated hydrochloric acid. The crude hydrochloride, 12.5 g, of tan crystals. was suspended in 50 ml. of boiling toluene. After cooling, the solid was filtered off by suction; 9 g. of hydrochloride, m.p. 214-215° C. remained. The material was recrystallized from 80% isopropyl alcohol from which it separated as glistening needles of a dihydrate, m.p. 214-215° C.

Analysis. Calculated for $C_{15}H_{14}Cl_3N_5 \cdot 2\ H_2O$: Cl, 26.2; N, 17.2; H_2O, 7.9. Found: Cl, 26.6, 26.5; N, 17.5, 17.5; H_2O, 7.9.

A sample of the dihydrate was dried at 80° C. in a vacuum; the melting point was not changed.

Analysis. Calculated for $C_{15}H_{14}Cl_3N_5$: Cl, 28.7; N, 18.9. Found: Cl, 28.6; N, 18.9.

Alkylation of 1-(1',1',3',3'-tetramethylbutyl)-5-aminotetrazole with benzyl chloride.

A mixture of 9.85 g. (0.05 mole) of 1-(1',1',3',3'-tetramethylbutyl)-5-aminotetrazole and 15 g. (0.12 mole) of benzyl chloride was placed in a side-arm test tube fitted with a mechanical stirrer and connected to a trap which was cooled by a crushed ice-water bath. The reaction mixture was heated to a temperature of 145-155° C. in an oil bath for two hours. The reaction mixture first turned to a clear

melt and a volatile product distilled into the cold trap. After slightly more than an hour, the melt began to solidify and at the end of two hours, the reaction mixture was solid and no more material could be distilled into the cold trap. The cold trap was disconnected, sealed and stored in the refrigerator for further work-up.

The solid material was dissolved in hot 95% ethanol and placed in a one liter three necked flask fitted with a mechanical stirrer, a distillation head and a dropping funnel. Five hundred milliliters of distilled water was added to the approximately 300 ml. of 95% ethanol and the ethanol was removed by distillation; after which roughly 400 ml. of water was steam distilled to remove the excess benzyl chloride. When the distillate was no longer cloudy, the reaction mixture was cooled in an ice bath, 25 g. of solid potassium hydroxide was added and the mixture stirred for two hours. The cold suspension was stirred for one half hour with 150 ml. of ether and the ether layer was separated. The aqueous portion was extracted with three 50 ml. portions of ether and the ethereal extracts were combined and dried over anhydrous potassium carbonate.

The ether solution was decanted from the potassium carbonate and evaporated to dryness on the steam bath with the aid of an air jet. The oil which remained was taken up in 100 ml. of benzene and was treated with hydrogen chloride

gas to precipitate the 1,4-dialkyl-5-iminotetrazoline as the hydrochloride.

The crude tetrazoline hydrochloride was a light tan solid and was recrystallized from 50% ethanol. The material had the same melting point as 1,4-dibenzyl-5-iminotetrazoline hydrochloride and the melting point was not depressed on admixture with an authentic sample of 1,4-dibenzyl-5-imino-tetrazoline hydrochloride (15).

Alkylation of 1-tertiary butyl-5-aminotetrazole with benzyl chloride.

A mixture of 7 g. (0.05 mole) of 1-tertiary butyl-5-aminotetrazole and 15 g. (0.12 mole) of benzyl chloride was placed in a urea tube which was connected to a cold trap immersed in a dry ice-acetone bath. The urea tube was heated in an oil bath to a temperature of 140-145° C. for five and one half hours. During the heating period, the reaction mixture liquified to a clear melt and a gas was evolved, which condensed in the cold trap to a clear, colorless liquid. The melt solidified in the later stages of the heating period.

The solid material was dissolved in 250 ml. of hot 95% ethanol and the resulting solution was placed in a flask fitted for steam distillation. Three hundred milliliters of distilled water was added; the alcohol distilled, and approximately 500 ml. of water was distilled to remove any

excess benzyl chloride. After cooling, 25 g. of solid potassium hydroxide was added and the reaction mixture was stirred for one and one half hours, followed by extraction of the free base with three 100 ml. portions of ether. The ether extracts were combined and dried over anhydrous potassium carbonate.

The ether extract was decanted from the potassium carbonate and evaporated to dryness. The dark brown residue was taken up in benzene and the benzene solution was partially decolorized with Norite. Gaseous hydrogen chloride was passed into the benzene solution until precipitation was complete. The crude 1,4-dibenzyl-5-iminotetrazoline hydrochloride was recrystallized from 70% ethanol.

The purified compound melted at 212-213° C. with decomposition and showed no depression in melting point when mixed with an authentic sample of 1,4-dibenzyl-5-iminotetrazoline hydrochloride (15).

Alkylation of 1-tertiary butyl-5-aminotetrazole with ethyl p-toluenesulfonate.

A mixture of 7 g. (0.05 mole) of 1-tertiary butyl-5-aminotetrazole and 25 g. (0.125 mole) of ethyl p-toluenesulfonate was placed in a urea tube which was connected to a cold trap immersed in a dry ice-acetone bath. The urea tube was placed in an oil bath and heated for six hours at a temperature of 140-145° C. During the course of the

heating period, the reaction mixture turned to a clear melt and after a few minutes at 140° C., evolution of gas commenced. The volatile material was condensed in the cold trap and preserved for further study.

At the end of the heating period, the reaction mixture was poured into 200 ml. of distilled water. A brown oil separated, which was found to be excess ethyl p-toluenesulfonate. Fifteen grams of sodium hydroxide was added to the reaction mixture in order to free the 1,4-dialkyl-5-iminotetrazoline from its p-toluenesulfonic acid salt, followed by the addition of 100 g. of potassium carbonate which was added in one portion to salt out the free base. The free base was extracted from the water by two 100 ml. portions and two 50 ml. portions of ether. The ethereal extracts were dried over anhydrous potassium carbonate. After evaporation of the solvent, the 1,4-dialkyl-5-iminotetrazoline remained as an oily residue.

The material was dissolved in isopropyl alcohol, decolorized with carbon, treated with 10 ml. of concentrated hydrochloric acid, and the solution evaporated to dryness. The resulting solid was recrystallized from an isopropyl alcohol-ether mixture. The melting point of the material was 227.5-228° C., and showed no depression of melting point when mixed with an authentic sample of 1,4-diethyl-5-iminotetrazoline hydrochloride (C).

Alkylation of 1-(3'-heptyl)-5-aminotetrazole with benzyl chloride.

A side-arm test tube was placed in an oil bath and connected to a trap which was cooled by an ice-salt mixture. The side-arm test tube was charged with 9.2 g. (0.05 mole) of 1-(3'-heptyl)-5-aminotetrazole and 15 g. (0.12 mole) of benzyl chloride. A mechanical stirrer sealed the top of the test tube and the reaction mixture was heated, while stirring, for five hours. No gaseous product evolved, even though the temperature of the oil bath was held at 145° C. The reaction mixture formed a clear melt which later partially solidified.

The partially solidified reaction mixture was dissolved in hot 95% ethanol and placed in a one liter three necked flask which was fitted with a distillation apparatus, dropping funnel and mechanical stirrer. Enough alcohol was added to make a volume of 300 ml. Five hundred milliliters of distilled water was added and the solution was slowly distilled to remove the alcohol and the excess benzyl chloride. Another 500 ml. of distilled water was added through the dropping funnel at the same rate at which it was being removed by distillation. This procedure was necessary to remove unchanged benzyl chloride and benzyl alcohol.

When the steam distillation was completed, the aqueous solution of 1-(3'-heptyl)-4-benzyl-5-iminotetrazoline hydrochloride was cooled in an ice bath, 20 g. (0.5 mole) of

sodium hydroxide was added and the reaction mixture stirred for two hours. At the end of this time, 150 ml. of ether was added to dissolve the brown, gummy free 1-(3'-heptyl)-4-benzyl-5-iminotetrazoline which had separated from the aqueous reaction mixture. The mixture was stirred for one half hour and the ether layer was separated. The aqueous layer was extracted with three 50 ml. portions of ether; the ethereal layers combined and dried over anhydrous potassium carbonate.

The ethereal solution was decanted from the potassium carbonate and evaporated to dryness on the steam bath with the aid of an air jet. The oily, crude tetrazoline was taken up in 100 ml. of 95% ethanol and its hydrochloride precipitated with the addition of 20 ml. of concentrated hydrochloric acid. The impure 1-(3'-heptyl)-4-benzyl-5-iminotetrazoline hydrochloride was redissolved in hot 70% ethanol and decolorized with charcoal, after which crystallization was allowed to occur. The reaction gave 12 g. (71.4% of theory) of material melting at 150-151° C.

Analysis. Calculated for $C_{15}H_{24}ClN_5$: C, 58.1; H, 7.8; Cl, 11.4; N, 22.6. Found: C, 58.1; H, 7.9; Cl, 11.3; N, 22.5.

Identification of the gaseous product of the benzylation of 1-tertiary butyl-5-aminotetrazole.

The cold trap containing the clear, colorless product

from the benzylation of 1-tertiary butyl-5-aminotetrazole was removed from the dry ice-acetone bath and connected to a nitrogen cylinder. A stream of nitrogen was used to sweep the volatile material into a solution of bromine in ether, which was partially decolorized. The excess bromine was removed with a solution of sodium bisulfite and the organic layer was separated, washed with three 20 ml. portions of water and dried over anhydrous sodium sulfate. The ether was evaporated and the boiling point, density, index of refraction and infrared spectrum of the residual material were determined.

An authentic sample of isobutylene dibromide was prepared by dehydrating tertiary butyl alcohol with sulfuric acid and passing the isobutylene into a bromine-ether solution. The isobutylene dibromide was purified as in the above case, and the same physical properties were determined.

Table I

Isobutylene dibromide (22)		Unknown material	
b.p.	149-151° C.	b.p.	149-150° C.
D_4^{20}	1.7287	D_4^{20}	1.7284
n_D^{20}	1.51186	n_D^{20}	1.5118

The infrared spectra of isobutylene dibromide and the unknown material showed the same bands at approximately equal intensities.

Identification of the gaseous product from the alkylation of 1-tertiary butyl-5-aminotetrazole with ethyl p-toluenesulfonate.

The volatile material from the above alkylation was passed into a solution of bromine in ether, and after purification, the brominated product was shown to be isobutylene dibromide.

Identification of the volatile product from the alkylation of 1-(1',1',3',3'-tetramethylbutyl)-5-aminotetrazole with benzyl chloride.

A. Oxidative degradation.

The oxidation was done according to procedure B. as recommended by Shriner and Fuson (17).

One gram of the volatile material was added to 30 ml. of water which contained four grams of potassium permanganate. One milliliter of 10% sodium hydroxide was added and the reaction mixture was refluxed for 30 minutes. At the end of the heating period, the apparatus was modified for distillation and the reaction mixture was distilled very slowly into a test tube which contained a 5% solution

of 2,4-dinitrophenylhydrazine in 20% perchloric acid. A precipitate formed, which after recrystallization from 95% ethanol, melted at 125-126° C. This melting point corresponded to the melting point of acetone 2,4-dinitrophenylhydrazone and indicated the volatile material contained a grouping which could be converted to acetone on oxidation.

B. Degree of unsaturation and Bromine Number.

The volatile material decolorized a solution of bromine in carbon tetrachloride, so this technique was used to determine the molecular weight of the compound. A modification of McIlhiney's technique (18) was used. The results are as follows:

Table II

Determination	% Bromine Uptake	Bromine Number	Molecular Weight
I	102.9	146.7	108.9
II	100.3	143.1	111.7
III	99.3	141.9	112.6
IV	101.4	144.5	110.6
Average	101.0	144.1	111.0
Theoretical*	100.0	142.6	112.1

* Based on the assumption of molecular formula of C_8H_{16}

C. Infrared spectra comparison.

The infrared spectrum of the olefin was compared with the known spectra of 2,4,4-trimethyl-1-pentene and 2,4,4-trimethyl-2-pentene (23). In addition, the spectrum of diisobutylene, a commercially available mixture of the two isomeric hydrocarbons, was determined and compared with the infrared spectrum of the olefin. Similar bands, both in intensity and position, were found in all spectra.

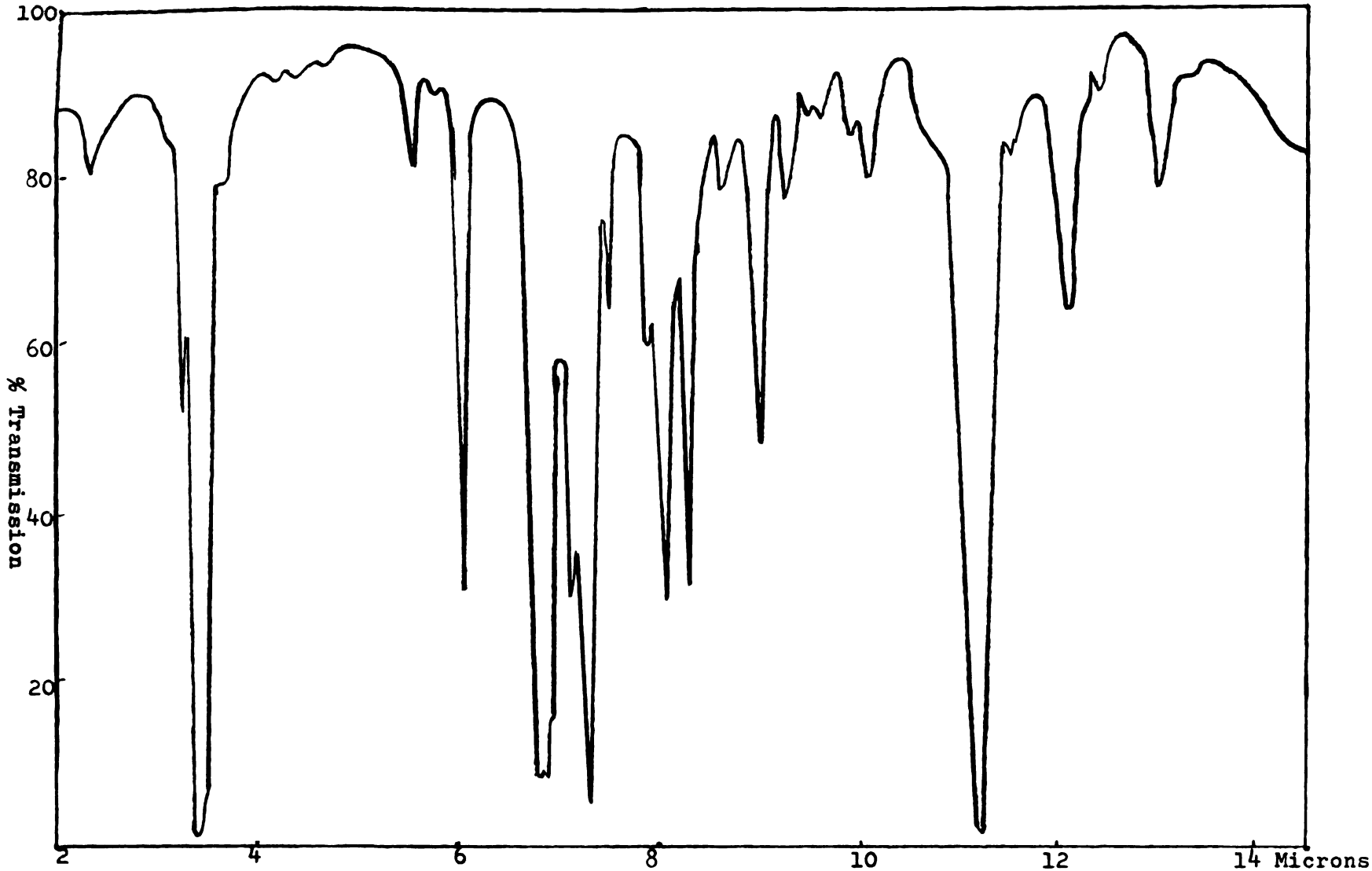


Figure I. Infrared Spectrum of Olefin Displaced From 1-(1',1',3',3'-tetramethylbutyl)-5-aminotetrazole.

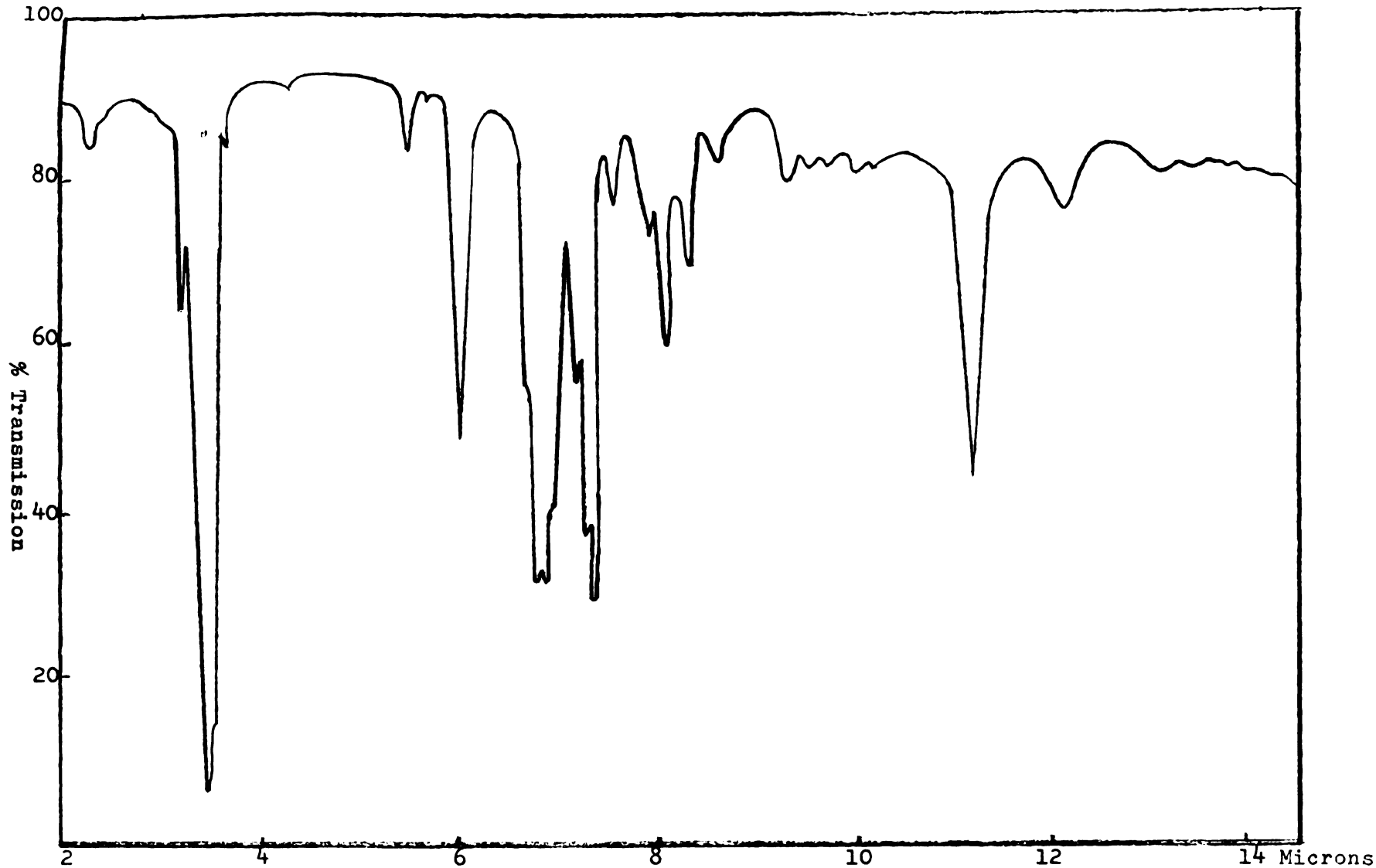


Figure II. Infrared Spectrum of Commercial Diisobutylene.

DISCUSSION

PART TWO

Discussion

Many different methods have been employed in the preparation of 5-hydroxytetrazoles (24). These methods, however, almost without exception, have used a tetrazole which has been substituted by a sulfur containing group in the 5-position with the sulfur atom attached directly to the tetrazole ring. The purpose of this part of the investigation was twofold: to explore the possibility of preparing a group of 1-substituted-5-hydroxytetrazoles and to determine the effect of an alkoxyalkyl or aryloxyalkyl group on the reactions of a 1-substituted-5-aminotetrazole.

A group of 1-alkoxyalkyl-5-aminotetrazoles and 1-aryloxyalkyl-5-aminotetrazoles was prepared from the corresponding alkoxyalkylamines or aryloxyalkylamines by interaction with cyanogen bromide and hydrazoic acid in aqueous ethanolic solution (10). The compounds chosen for study were: 1-(3'-isopropoxypropyl)-5-aminotetrazole, 1-(3'-methoxypropyl)-5-aminotetrazole, 1-(2'-methoxyethyl)-5-aminotetrazole, 1-(2'-phenoxyethyl)-5-aminotetrazole and 1-(3'-phenoxypropyl)-5-aminotetrazole.

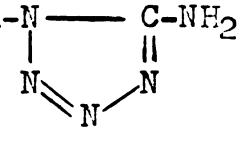
The proposed route of synthesis of the various 1-substituted-5-hydroxytetrazoles was: (1) Preparation of the appropriate 1-substituted-5-aminotetrazole, (2) Alkylation of the 5-aminotetrazole with benzyl chloride to form the

1-alkyl-4-benzyl-5-iminotetrazoline, (3) Acetolysis of the 5-iminotetrazoline to the corresponding 5-ketotetrazoline and finally, (4) Hydrogenolysis to the 1-substituted-5-hydroxytetrazole.

The 1-alkoxyalkyl-5-aminotetrazoles were prepared by a modification of the procedure of Garbrecht and Herbst (10).

$$R\text{-}NH_2 + BrCN \longrightarrow R\text{-}NH\text{-}CN + HBr$$

$$R\text{-}NH\text{-}CN + HN_3 \longrightarrow$$



$$R = \begin{cases} CH_3\text{-}O\text{-}CH_2\text{-}CH_2\text{-},\ CH_3\text{-}O\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-} \\ C_6H_5\text{-}O\text{-}CH_2\text{-}CH_2\text{-},\ C_6H_5\text{-}O\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-} \\ (CH_3)_2CH\text{-}O\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-} \end{cases}$$

Due to the nature of the compounds, some changes had to be made in the separation techniques.

1-(3'-Isopropoxypropyl)-5-aminotetrazole was prepared from 3-isopropoxypropylamine by interaction with cyanogen bromide in aqueous ethanolic solution. The reaction was conducted at temperatures between 0-10° C. to minimize side reactions due to the reactivity of the monoalkylcyanamide. The hydrazoic acid was generated <u>in situ</u> from sodium azide

and hydrochloric acid. At the end of the reaction the tetrazole was sufficiently insoluble in water to crystallize from the cold reaction mixture after removal of the ethanol by distillation.

The second member of the group, 1-(3'-methoxypropyl)-5-aminotetrazole was prepared in much the same fashion as 1-(3'-isopropoxypropyl)-5-aminotetrazole. Interaction of cyanogen bromide and 3-methoxypropylamine produced the corresponding monosubstituted cyanamide which was not isolated. The cyanamide was treated with sodium azide and hydrochloric acid as before and the reaction mixture was subjected to distillation to remove the ethanol portion of the solvent. On cooling, however, the 1-(3'-methoxypropyl)-5-aminotetrazole could not be induced to crystallize from the aqueous mixture. The solution was taken to dryness and the mixture of crude tetrazole and inorganic salts was extracted repeatedly with hot anhydrous methanol in order to separate the tetrazole from the inorganic residue. As isolated, the crude 1-(3'-methoxypropyl)-5-aminotetrazole was a thick, viscous oil which would not crystallize spontaneously. Various solvents and combinations of solvents were used in attempts to crystallize the tetrazole. The most successful method was treatment of the viscous oil with hot benzene. The hot benzene solution was decanted from the residual oil and chilled. 1-(3'-Methoxypropyl)-5-aminotetrazole crystallized from the hot benzene extract on cooling.

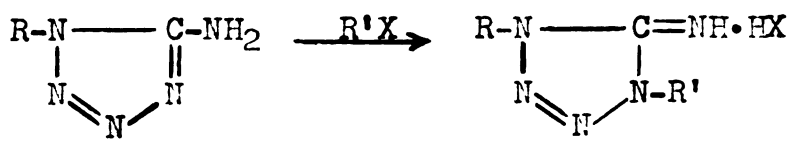
1-(2'-Methoxyethyl)-5-aminotetrazole was prepared from 2-methoxyethylamine by the same sequence of reactions. It too did not precipitate from aqueous solution on removal of the ethanol portion of the solvent. The product was obtained by evaporating the reaction mixture to dryness and extracting the 1-(2'-methoxyethyl)-5-aminotetrazole from the residue of inorganic salts with anhydrous ether in a Soxhlet extraction apparatus.

Both 1-(2'-phenoxyethyl)-5-aminotetrazole and 1-(3'-phenoxypropyl)-5-aminotetrazole were sufficiently insoluble in water so that they precipitated on removal of ethanol from the reaction mixture.

2-Methoxyethylamine, 3-methoxypropylamine and 3-isopropoxypropylamine were available from commercial sources. 2-Phenoxyethylamine and 3-phenoxypropylamine were prepared by an adaptation of the general method of Sheehan and Bolhofer (25). Potassium phthalimide was alkylated with the appropriate phenoxyalkyl bromide; hydrazinolysis of the resulting phthalimidoalkyl phenyl ether gave the desired phenoxyalkylamine. Conversion of the amine to the corresponding tetrazole was done by interaction with cyanogen bromide in aqueous ethanolic solution followed by treatment with sodium azide and hydrochloric acid in the manner previously described.

The 1,4-disubstituted-5-iminotetrazolines were prepared by application of the general procedure outlined by Herbst,

Roberts and Harvill (8, 11). The 1-alkoxyalkyl-5-aminotetrazole or 1-aryloxyalkyl-5-aminotetrazole was heated with a slight excess of the alkylating agent at a temperature of 140-145° C. for several hours during which time a mildly exothermic reaction usually took place.



R = alkoxyalkyl or aryloxyalkyl (see p. 40)

R' = $C_6H_5CH_2$-, C_6H_5-O-CH_2-CH_2-

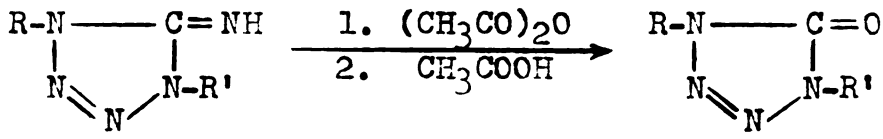
X = Cl, Br

When benzyl chloride was used as the alkylating agent, the reaction mixture was dissolved in ethanol at the end of the heating period and steam distilled to remove any unreacted benzyl chloride. In the case of 1-(3'-methoxypropyl)-4-(2"-phenoxyethyl)-5-iminotetrazoline, the excess alkylating agent, 2-phenoxyethyl bromide, was removed by extracting an aqueous solution of the tetrazoline hydrobromide with ether.

All alkylation products were treated with base to free the 1,4-disubstituted-5-iminotetrazolines from their salts with the hydrogen halides; the free tetrazoline bases were extracted from their water suspensions with ether and the ether solutions were dried over anhydrous potassium carbon-

ate. The 1,4-disubstituted-5-iminotetrazoline hydrochlorides were prepared from the free bases in one of three ways: precipitation from an ethereal solution with gaseous hydrogen chloride, precipitation from a benzene solution in the same manner or precipitation from an ethanolic solution by the addition of concentrated hydrochloric acid. All of the 1,4-disubstituted-5-iminotetrazoline hydrochlorides were colorless crystalline solids.

The next phase of the investigation was the conversion of the various 1,4-disubstituted-5-iminotetrazolines to the corresponding 5-ketotetrazolines. Acetolysis techniques, similar to those of Percival (15) were used in the conversion of the iminotetrazolines to the desired keto compounds.



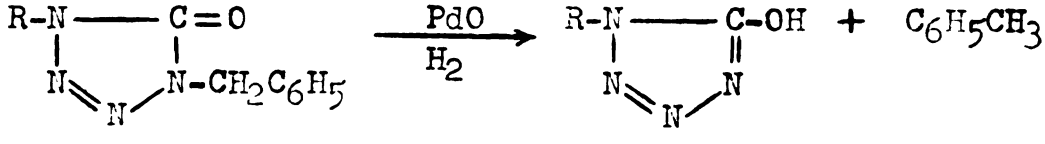
R = alkoxyalkyl or aryloxyalkyl (see p. 40)

R' = $C_6H_5CH_2$-, C_6H_5-O-CH_2-CH_2-

Of the five ketotetrazolines which were prepared, only one was isolable as a solid. 1-(2'-Phenoxyethyl)-4-benzyl-5-ketotetrazoline was prepared from the similarly substituted 5-iminotetrazoline by boiling with acetic anhydride for one hour followed by treatment with glacial acetic acid.

The acetic acid solution was evaporated to dryness. The oily residue was extracted with water to remove acetamide. The residual ketotetrazolines were taken up in warm cyclohexane in which they were only moderately soluble. The 1-(2'-phenoxyethyl)-4-benzyl-5-ketotetrazoline separated from solution as an oil which solidified slowly on long standing. The four other 5-ketotetrazolines, prepared in analogous fashion, could not be induced to crystallize and were purified by molecular distillation under diminished pressure. The ketotetrazolines solidified on the dry ice-isopropyl alcohol cooled condensing surface but melted on warming to room temperature.

The final phase of the investigation was the attempted hydrogenolysis of 1-(2'-phenoxyethyl)-4-benzyl-5-ketotetrazoline in order to prepare the 1-(2'-phenoxyethyl)-5-hydroxytetrazole.



R = alkoxyalkyl or aryloxyalkyl (see p. 40)

A Burgess-Parr low pressure hydrogenation apparatus was used, with absolute ethanol as solvent and palladium oxide as catalyst. Reaction time was extended for as long as twelve hours

without effecting the desired hydrogenolysis. The hydrogenolysis was also attempted using platinum oxide or palladium black as catalysts. Results were negative in all three cases. 1-(2'-Phenoxyethyl)-4-benzyl-5-ketotetrazoline was recovered unchanged from the reaction mixture.

It has been observed by Birkofer (16) that N-benzylurea and N-benzylurethane structures failed to undergo catalytic hydrogenolysis of the N-benzyl group. The 1-substituted-4-benzyl-5-ketotetrazolines show a similar linkage.

EXPERIMENTAL

PART TWO

Experimental

SYNTHESIS OF PHTHALIMIDOALKYL PHENYL ETHERS

These compounds were prepared in a manner which corresponded very closely to the method of Sheehan and Bolhofer (25).

Preparation of 2-phthalimidoalkyl phenyl ether.

A solution of 40.2 g. (0.2 mole) of 2-phenoxyethyl bromide in 150 ml. of N,N-dimethylformamide was placed in a 500 ml. three necked flask fitted with a mechanical stirrer and thermometer. The flask was placed in an oil bath and 37 g. (0.2 mole) of potassium phthalimide was added. The reaction mixture was heated, with stirring, at 80° C. for one hour and then allowed to cool to room temperature, still with constant stirring.

After the reaction mixture had cooled, 150 ml. of chloroform was added and the solution was stirred for ten minutes. The reaction mixture was poured into 300 ml. of distilled water; the chloroform layer was separated and the aqueous layer was extracted with three 50 ml. portions of chloroform. The chloroform extracts were combined and washed with three 50 ml. portions of 0.2 N sodium hydroxide to remove any unreacted potassium phthalimide, then washed with three 50 ml. portions of distilled water to remove the

residual sodium hydroxide. The chloroform solution was dried over anhydrous sodium sulfate. The chloroform was evaporated on the steam bath with the aid of an air jet and the remaining solid was ground with 100 ml. of ether to remove any occluded chloroform. The ether was evaporated on the steam bath and the 2-phthalimidoethyl phenyl ether was dried at 90° C.

The yield was 52.6 g. (98.4% of theory) of material melting at 127-128° C. (26).

Preparation of 3-phthalimidopropyl phenyl ether.

A 500 ml. three necked flask was fitted with a mechanical stirrer and thermometer and charged with a mixture of 46.2 g. (0.25 mole) of potassium phthalimide, 53.8 g. (0.25 mole) of 3-bromopropyl phenyl ether and 200 ml. of N,N-dimethylformamide. The reaction mixture was heated with stirring at 80° C. in an oil bath for two hours, then allowed to cool to room temperature, still with constant stirring. Two hundred milliliters of chloroform was added and the mixture was stirred for ten minutes, after which it was poured into 200 ml. of distilled water. The chloroform layer was separated and the aqueous layer was extracted with three 50 ml. portions of chloroform. The chloroform layers were combined and extracted with three 50 ml. portions of 0.2 N sodium hydroxide to remove any unreacted potassium phthalimide and then washed with three 50 ml. portions of distilled water

to remove traces of sodium hydroxide. The wet chloroform solution was dried over anhydrous sodium sulfate, then evaporated to dryness on the steam bath with the aid of a jet of air. The crude 3-phthalimidopropyl phenyl ether was recrystallized from ethanol to yield 63 g. (89.6% of theory) of material melting at 88-89° C. (27).

SYNTHESIS OF PHENOXYALKYLAMINE HYDROCHLORIDES

The hydrazinolyses of the phthalimidoalkyl phenyl ethers were accomplished in a fashion similar to the method of Sheehan and Bolhofer (25).

Preparation of 2-phenoxyethylamine hydrochloride.

A solution of 107 g. (0.4 mole) of 2-phthalimidoethyl phenyl ether in 1000 ml. of methanol was placed in a two liter flask and treated with 24 ml. (0.4 mole) of 85% aqueous hydrazine hydrate. The reaction mixture was boiled under reflux for two hours. After cooling, 500 ml. of distilled water was added and the methanol was removed by distillation under reduced pressure. The residual aqueous suspension was treated with 100 ml. of concentrated hydrochloric acid, at which time a very voluminous precipitate of phthalhydrazide formed. The reaction mixture was heated on the steam bath to a temperature of 50° C. for one half hour, cooled to 0° C., and filtered with suction. The

precipitate of phthalhydrazide was washed with distilled water until the washings were no longer acidic to litmus, and the filtrate and washings were combined and evaporated almost to dryness under diminished pressure. The white slurry of 2-phenoxyethylamine hydrochloride was washed from the flask with absolute ethanol and the alcohol-water mixture was removed by heating on the steam bath with the aid of a jet of air. The colorless amine hydrochloride was washed with ether and dried to yield 60.4 g. (87% of theory) of material melting at 213-214° C. (26).

Preparation of 3-phenoxypropylamine hydrochloride.

A solution of 63 g. (0.22 mole) of 3-phthalimidopropyl phenyl ether in 350 ml. of methanol was placed in a one liter flask fitted with a reflux condenser. To this solution was added 13.7 ml. (0.22 mole) of 85% hydrazine hydrate and the resulting mixture was boiled under reflux for two hours on the steam bath. The reaction mixture was cooled to room temperature and 100 ml. of distilled water was added. The methanol was then removed by distillation under reduced pressure. After the methanol was removed, 25 ml. of concentrated hydrochloric acid was added to the residual suspension, causing a voluminous precipitate of phthalhydrazide to form. The reaction mixture was heated on the steam bath at a temperature of 50° C. for one hour, cooled to 0° C., and filtered with suction. The precipitate of phthalhydrazide

was washed with distilled water until the washings were no longer acidic to litmus and the washings were combined with the original filtrate. The combined washings and filtrate were then evaporated to dryness, first by means of a reduced pressure distillation and then on a steam bath by means of an air jet. The colorless amine hydrochloride was washed with anhydrous ether and dried. The yield of 3-phenoxypropylamine hydrochloride was 37.5 g. (89% of theory) of material melting at 165-166° C. (27).

SYNTHESIS OF 1-ALKOXYALKYL-5-AMINOTETRAZOLES

These compounds were prepared by methods only slightly different than those used by Garbrecht and Herbst (10).

Preparation of 1-(3'-isopropoxypropyl)-5-aminotetrazole.

A one liter three necked flask fitted with a mechanical stirrer, dropping funnel, reflux condenser and alcohol thermometer was charged with a solution of 23.4 g. (0.2 mole) of 3-isopropoxypropylamine in 160 ml. of 95% ethanol and the solution was cooled to 0° C. A solution of 21.2 g. (0.2 mole) of cyanogen bromide in 40 ml. of distilled water and 40 ml. of 95% ethanol was added with stirring at such a rate that the temperature did not exceed 10° C. After all the cyanogen bromide solution had been added, a solution of 8 g. (0.2 mole) of sodium hydroxide in 20 ml. of distilled water

was added dropwise with stirring, keeping the temperature below 10° C. After the complete addition of the sodium hydroxide solution, the reaction mixture was stirred for one and one half hours with the temperature held below 10° C.

A solution of 15.6 g. (0.24 mole) of sodium azide in 50 ml. of distilled water was added with stirring over a period of five minutes, followed by 20 ml. (0.24 mole) of concentrated hydrochloric acid diluted with 20 ml. of distilled water. The diluted acid was added at such a rate that the temperature did not exceed 10° C. After the addition of the hydrochloric acid, the reaction mixture was stirred for three hours, during which time it was allowed to warm to room temperature. At the end of that time, the reaction mixture was heated under reflux on the steam bath for an additional three hours, still with constant stirring, and then allowed to stand overnight.

The ethanol and part of the water were removed by distillation. The tetrazole precipitated on cooling the solution. The solid product was separated by filtration and the filtrate was further concentrated to obtain a second crop of the crude tetrazole. The crude 1-(3'-isopropoxypropyl)-5-aminotetrazole was recrystallized from distilled water. The yield was 24 g. (65% of theory) of material melting at 128-129° C.

Analysis. Calculated for $C_7H_{15}N_5O$: C, 45.4; H, 8.2; N, 37.8. Found: C, 45.1; H, 7.9; N, 37.8.

Preparation of 1-(3'-methoxypropyl)-5-aminotetrazole.

A solution of 89 g. (1 mole) of 3-methoxypropylamine in 800 ml. of 95% ethanol was placed in a three liter three necked flask which was fitted with a dropping funnel, reflux condenser, mechanical stirrer and alcohol thermometer. The solution was cooled to 0° C. and a solution of 106 g. (1 mole) of cyanogen bromide in 200 ml. of distilled water and 200 ml. of 95% ethanol was added dropwise, with stirring, at such a rate that the temperature of the reaction mixture did not exceed 10° C. A solution of 40 g. (1 mole) of sodium hydroxide in 100 ml. of distilled water was then added dropwise, with stirring, while holding the temperature below 10° C. After the addition of the sodium hydroxide, the solution was stirred for one and one half hours while holding the temperature below 10° C.

A solution of 78 g. (1.2 moles) of sodium azide in 240 ml. of distilled water was added over a period of approximately five minutes and then a mixture of 100 ml. (1.2 moles) of concentrated hydrochloric acid and 100 ml. of distilled water was added to the reaction mixture at such a rate that the temperature did not exceed 10° C. After the hydrochloric acid solution had been added, the reaction mixture was boiled under reflux on the steam bath, with stirring, for six hours and then allowed to stand overnight.

The solution was evaporated to dryness and the residue, a paste of mineral salts suspended in the oily, crude tetra-

zole, was treated with three 100 ml. portions of ice-cold anhydrous methanol to remove the tetrazole from the inorganic salts. The methanol solution was decolorized with charcoal and the methanol was removed under diminished pressure. The tetrazole remained as an oil, and was induced to crystallize by treating with hot benzene and cooling the benzene solution. The yield was 64 g. (63.4% of theory) of material melting at a temperature of 92-93° C.

Analysis. Calculated for $C_5H_{11}N_5O$: C, 38.2; H, 7.1; N, 44.6. Found: C, 38.2; H, 7.0; N, 44.6.

Preparation of 1-(2'-methoxyethyl)-5-aminotetrazole.

A two liter three necked flask was fitted with a mechanical stirrer, dropping funnel, alcohol thermometer and reflux condenser. In the flask was placed a solution of 58 g. (approximately 0.5 mole) of an aqueous solution of 2-methoxyethylamine (65-70%) in 500 ml. of 95% ethanol and the resulting mixture was cooled to 0° C. in an ice bath. A solution if 53 g. (0.5 mole) of cyanogen bromide in 100 ml. of 95% ethanol and 100 ml. of distilled water was added dropwise with stirring, keeping the temperature below 10° C. during the course of the addition. Following the addition of the cyanogen bromide solution, 20 g. (0.5 mole) of sodium hydroxide dissolved in 50 ml. of distilled water was added with stirring, keeping the temperature of the reaction below 10° C. After complete addition of the sodium hydroxide

solution, the reaction mixture was stirred for one and one half hours, maintaining the low temperature.

A solution of 39 g. (0.6 mole) of sodium azide in 150 ml. of distilled water was added over a period of five minutes, followed by the addition of 50 ml. (0.6 mole) of concentrated hydrochloric acid diluted with an equal volume of distilled water. The hydrochloric acid solution was added at such a rate that the temperature of the reaction mixture did not exceed 10° C. Following the addition of the hydrochloric acid, the reaction mixture was stirred for three hours, during which time it was allowed to warm to room temperature, after which it was boiled under reflux for four hours.

The apparatus was modified for distillation and the ethanol was removed by distillation under diminished pressure. The reaction mixture was cooled in an ice bath, but no product precipitated. The remainder of the solvent was removed by distillation under reduced pressure; the residue was transferred to a Soxhlet apparatus and continuously extracted with anhydrous ether for twelve hours.

The crude 1-(2'-methoxyethyl)-5-aminotetrazole which was only very sparingly soluble in ether was recrystallized from an absolute ethanol-ether mixture to yield 22.5 g. (31.5% of theory) of product melting at 112-113° C.

Analysis. Calculated for $C_4H_9N_5O$: C, 33.6; H, 6.3; N, 48.9. Found: C, 33.5; H, 6.3; N, 48.9.

Preparation of 1-(2'-phenoxyethyl)-5-aminotetrazole.

A one liter three necked flask fitted with a dropping funnel, mechanical stirrer, low temperature alcohol thermometer and reflux condenser was charged with a solution of 43.5 g. (0.25 mole) of 2-phenoxyethylamine hydrochloride in 200 ml. of 95% ethanol. The solution was cooled to 0° C. and a solution of 26.5 g. (0.25 mole) of cyanogen bromide in 50 ml. of 95% ethanol and 50 ml. of distilled water was added at such a rate that the temperature did not exceed 10° C. After the cyanogen bromide had been added, a solution of 20 g. (0.5 mole) of sodium hydroxide in 50 ml. of distilled water was added at such a rate that the reaction temperature did not exceed 10° C. Following the addition of the sodium hydroxide solution, the reaction mixture was stirred for an additional one and one half hours, keeping the temperature below 10° C.

A solution of 19.5 g. (0.3 mole) of sodium azide in 60 ml. of distilled water was added, followed by 25 ml. (0.3 mole) of concentrated hydrochloric acid diluted with an equal volume of distilled water. The two solutions were added at such a rate that the temperature of the mixture did not exceed 10° C. The reaction mixture was then stirred overnight at room temperature. In the morning, a crude yellow product had crystallized from the solution. The solid was removed by filtration and the mother liquor was concentrated to obtain a second crop of crude product.

The crude 1-(2'-phenoxyethyl)-5-aminotetrazole was recrystallized from absolute ethanol to give 28 g. (57% of theory) of material melting at 174-175° C.

Analysis. Calculated for $C_9H_{11}N_5O$: C, 52.7; H, 5.4; N, 34.1. Found: C, 52.8; H, 5.5; N, 34.2.

Preparation of 1-(3'-phenoxypropyl)-5-aminotetrazole.

A solution of 47 g. (0.25 mole) of 3-phenoxypropylamine hydrochloride in 200 ml. of 95% ethanol was placed in a one liter three necked flask fitted with an alcohol thermometer, reflux condenser, mechanical stirrer, and dropping funnel. The contents of the flask were cooled to 0° C. and a solution of 26.5 g. (0.25 mole) of cyanogen bromide in 50 ml. of 95% ethanol and 50 ml. of distilled water was added at such a rate that the temperature did not exceed 10° C. A solution of 20 g. (0.5 mole) of sodium hydroxide in 50 ml. of distilled water was then added, keeping the temperature below 10° C., and the reaction mixture was stirred for one and one half hours at the low temperature.

Next, a solution of 19.5 g. (0.3 mole) of sodium azide in 50 ml. of distilled water was added, keeping the temperature below 10° C. Twenty-five milliliters (0.3 mole) of concentrated hydrochloric acid diluted with 25 ml. of distilled water was then added, maintaining the lowered temperature, and the reaction mixture was stirred for three hours, during which time it was allowed to reach room temperature.

After the warm-up period, the reaction mixture was heated to reflux temperature and this temperature was maintained for twelve hours.

At the end of the reflux period, the ethanol was removed by distillation and the solution was cooled until the crude 1-(3'-phenoxypropyl)-5-aminotetrazole precipitated. The precipitate was removed by filtration and the aqueous mother liquor was concentrated and a second crop of material was obtained. The crude tetrazole was recrystallized from absolute ethanol to yield 29 g. (53% of theory) of material which melted at 168-169° C.

Analysis. Calculated for $C_{10}H_{13}N_5O$: C, 54.8; H, 6.0; N, 32.0. Found: C, 54.9; H, 6.2; N, 31.7.

SYNTHESIS OF 1,4-DISUBSTITUTED-5-IMINOTETRAZOLINES

The 1,4-disubstituted-5-iminotetrazolines were prepared by procedures only slightly modified from those of Herbst, Roberts and Harvill (8).

Preparation of 1-(3'-isopropoxypropyl)-4-benzyl-5-iminotetrazoline.

A mixture of 18.5 g. (0.1 mole) of 1-(3'-isopropoxypropyl)-5-aminotetrazole and 15.2 g. (0.12 mole) of benzyl chloride was placed in a urea tube and heated in an oil bath to a temperature of 140-145° C. for a period of four hours.

The material first turned to a clear melt which solidified during the later stages of heating. At the end of the heating period, the crude reaction mixture was washed out of the reaction tube with hot 95% ethanol and transferred to a one liter three necked flask fitted with a mechanical stirrer, dropping funnel and distillation apparatus. The ethanol solution was diluted with 500 ml. of distilled water and the ethanol was removed by distillation. Following the removal of the ethanol, approximately 500 ml. of water was steam distilled to remove any excess benzyl chloride. The reaction mixture was cooled and 10 g. (0.25 mole) of sodium hydroxide was added to convert the crude 1-(3'-isopropoxypropyl)-4-benzyl-5-iminotetrazoline hydrochloride to the free tetrazoline base. The reaction mixture was stirred for one half hour following the addition of the sodium hydroxide. One hundred milliliters of ether was added to the flask and the mixture was stirred for one half hour, after which the ethereal layer was separated and the aqueous layer was extracted further with two 50 ml. portions of ether. The ethereal extracts were combined and dried over anhydrous potassium carbonate. The dry ether solution was decanted from the potassium carbonate and evaporated to dryness on the steam bath with the aid of an air jet.

The oily, residual 1-(3'-isopropoxypropyl)-4-benzyl-5-iminotetrazoline was taken up in 50 ml. of 95% ethanol and precipitated as the hydrochloride by the addition of 20 ml.

of concentrated hydrochloric acid. The light tan solid was redissolved in hot ethanol and the resulting solution was decolorized with charcoal. After recrystallization from ethanol, the yield of 1-(3'-isopropoxypropyl)-4-benzyl-5-iminotetrazoline hydrochloride was 21.3 g. (68.4% of theory) of material melting at 163-164° C.

Analysis. Calculated for $C_{14}H_{22}ClN_5O$: C, 53.9; H, 7.1; Cl, 11.4; N, 22.5. Found: C, 53.9, 53.9; H, 7.1, 7.0; Cl, 11.6, 11.6; N, 22.4, 22.6.

Preparation of 1-(2'-methoxyethyl)-4-benzyl-5-iminotetrazoline.

A urea tube was charged with 14.3 g. (0.1 mole) of 1-(2'-methoxyethyl)-5-aminotetrazole and 15.2 g. (0.12 mole) of benzyl chloride. A mechanical stirrer was introduced and the reaction mixture was heated to a temperature of 140-145° C. for a period of four hours. The mixture first turned to a clear melt and later partially solidified. At the end of the heating period, the partially solidified reaction mixture was washed from the tube with hot 95% ethanol and transferred to a one liter three necked flask fitted with a distillation apparatus, mechanical stirrer and dropping funnel. Five hundred milliliters of distilled water was added and the alcohol was removed by distillation. Following the removal of the alcohol, 500 ml. of water was steam distilled to remove any unreacted benzyl chloride; the reaction mix-

ture was cooled and treated with 10 g. (0.25 mole) of sodium hydroxide to liberate the free tetrazoline base. After stirring for one half hour, 100 ml. of ether was added and stirring was continued for an additional one half hour. The ethereal layer was separated and the aqueous layer was extracted with three 50 ml. portions of ether. The ethereal extracts were combined and dried over anhydrous potassium carbonate. The ether was removed by evaporation on the steam bath with the aid of a jet of air; the residual 1-(2'-methoxyethyl)-4-benzyl-5-iminotetrazoline was dissolved in 20 ml. of 95% ethanol and decolorized with charcoal.

The alcoholic solution was treated with 10 ml. of concentrated hydrochloric acid and the precipitated 1-(2'-methoxyethyl)-4-benzyl-5-iminotetrazoline hydrochloride was recrystallized from ethanol to yield 17.2 g. (64% of theory) of material melting at 161-162° C.

Analysis. Calculated for $C_{11}H_{16}ClN_5O$: C, 48.9; H, 6.0; Cl, 13.1; N, 26.0. Found: C, 48.8; H, 6.1; Cl, 13.4; N, 25.8.

Preparation of 1-(2'-phenoxyethyl)-4-benzyl-5-iminotetrazoline.

A mixture of 10.4 g. (0.05 mole) of 1-(2'-phenoxyethyl)-5-aminotetrazole and 7.6 g. (0.06 mole) of benzyl chloride was placed in a urea tube and heated in an oil bath at 140-145° C. for five hours. The reaction mixture was cooled,

and the crude benzylation product was washed from the tube with 100 ml. of hot alcohol. The crude material was placed in a one liter three necked flask fitted with a mechanical stirrer, dropping funnel and distillation apparatus. Two hundred milliliters of distilled water was added and the ethanol was removed by distillation. After the removal of the ethanol, 300 ml. of water was steam distilled to remove unreacted benzyl chloride. The reaction mixture was cooled and 10 g. (0.25 mole) of sodium hydroxide was added to liberate the 1-(2'-phenoxyethyl)-4-benzyl-5-iminotetrazoline from its hydrochloride. The mixture was stirred for one half hour, followed by extraction of the free base with three 50 ml. portions of ether. The ethereal extracts were combined and dried over anhydrous potassium carbonate. The dry ether solution was decanted from the potassium carbonate and saturated with dry hydrogen chloride. The desired compound, 1-(2'-phenoxyethyl)-4-benzyl-5-iminotetrazoline hydrochloride, precipitated from solution and was recrystallized from ethanol. The yield was 15 g. (88.2% of theory) of material melting at 174-175° C.

Analysis. Calculated for $C_{16}H_{18}ClN_5O$: C, 57.9; H, 5.5; Cl, 10.7; N, 21.1. Found: C, 57.7; H, 5.3; Cl, 10.6; N, 21.1.

Preparation of 1-(3'-phenoxypropyl)-4-benzyl-5-iminotetrazoline.

A mixture of 7.2 g. (0.033 mole) of 1-(3'-phenoxypropyl)-5-aminotetrazole and 4.5 g. (0.035 mole) of benzyl chlroide was placed in a urea tube and heated to a temperature of 140-145° C. in an oil bath for five hours. The mixture first liquified to a clear melt which solidified during the later stages of heating. At the end of the heating period, the reaction mixture was washed out of the urea tube with 100 ml. of hot 95% ethanol and placed in a one liter three necked flask fitted with a dropping funnel, mechanical stirrer and distillation apparatus. Two hundred milliliters of distilled water was added and the ethanol was removed by distillation. Approximately 400 ml. of water was added dropwise at the same rate it was removed by distillation. Any unreacted benzyl chloride was removed by this procedure. The reaction mixture was then cooled and 10 g. of potassium hydroxide was added to liberate the free 1-(3'-phenoxypropyl)-4-benzyl-5-iminotetrazoline. One hundred milliliters of ether was added and the basic reaction mixture was stirred for one hour, while cooling in an ice bath to minimize the evaporation of ether. The ethereal layer was separated and the aqueous layer was extracted three times with 50 ml. portions of ether. The ethereal extracts were combined and dried over anhydrous potassium carbonate.

The dried ether solution of 1-(3'-phenoxypropyl)-4-benzyl-5-iminotetrazolene was decanted from the potassium carbonate and anhydrous hydrogen chloride was passed into the ethereal solution until precipitation was complete. The crude 1-(3'-phenoxypropyl)-4-benzyl-5-iminotetrazoline hydrochloride was recrystallized from ethanol to yield 9.8 g. (85.9% of theory) of material melting at 175-176° C.

Analysis. Calculated for $C_{17}H_{20}ClN_5O$: C, 59.0, H, 5.8; Cl, 10.3; N, 20.3. Found: C, 58.9; H, 5.8; Cl, 10.3; N, 20.5.

Preparation of 1-(3'-methoxypropyl)-4-(2"-phenoxyethyl)-5-iminotetrazoline.

A urea tube was charged with 15.7 g. (0.1 mole) of 1-(3'-methoxypropyl)-5-aminotetrazole and 24.1 g. (0.12 mole) of 2-phenoxyethyl bromide. The tube was placed in an oil bath and heated to a temperature of 140-145° C. for five hours. The reaction mixture turned to a clear melt which darkened slowly during the course of the heating period. At the end of the heating period, the reaction mixture was washed from the urea tube by means of 100 ml. of hot 95% ethanol and the ethanol solution was transferred to a 500 ml. flask and diluted with 200 ml. of distilled water. The ethanol was removed by distillation; the contents of the flask were cooled and extracted with two 50 ml. portions of ether to remove any unreacted 2-phenoxyethyl

bromide. The ethereal extracts were discarded and the aqueous portion was treated with 10 g. (0.25 mole) of sodium hydroxide in order to free 1-(3'-methoxypropyl)-4-(2"-phenoxyethyl)-5-iminotetrazoline from its hydrobromide. The free tetrazoline base was extracted from its aqueous suspension with three 50 ml. portions of ether and the ethereal layers were combined and dried over anhydrous potassium carbonate. The dry ether solution was decanted from the potassium carbonate and saturated with gaseous hydrogen chloride. The precipitate of 1-(3'-methoxypropyl)-4-(2"-phenoxyethyl)-5-iminotetrazoline hydrochloride was recrystallized from ethanol to yield 17.6 g. (56% of theory) of material melting at 145-146° C.

Analysis. Calculated for $C_{13}H_{20}ClN_5O_2$: C, 49.8; H, 6.4; Cl, 11.3; N, 22.3. Found: C, 49.8; H, 6.4; Cl, 11.2; N, 22.2.

PHENYLTHIOUREA DERIVATIVES OF 1,4-DISUBSTITUTED-5-IMINOTETRAZOLINES

Phenylthiourea derivative of 1-(3'-isopropoxypropyl)-4-benzyl-5-iminotetrazoline.

One gram of 1-(3'-isopropoxypropyl)-4-benzyl-5-iminotetrazoline hydrochloride was dissolved in 10 ml. of distilled water and treated with approximately two grams of potassium hydroxide. The aqueous suspension of the oily

iminotetrazoline base was extracted with three 10 ml. portions of ether and the ethereal extracts were combined and dried over potassium carbonate. The ethereal solution of the free base was evaporated to dryness on the steam bath with the aid of a stream of air and the residual oil was treated with 0.5 ml. of phenyl isothiocyanate and warmed on the steam bath for ten minutes. The crude product was cooled and washed successively with two 5 ml. portions of petroleum ether and two 5 ml. portions of 50% isopropyl alcohol. The crude product, a viscous oil, was chilled in a dry ice-isopropyl alcohol bath and stirred until crystallization took place. The crude phenylthiourea derivative was recrystallized from isopropyl alcohol and melted at 121-122° C.

Analysis. Calculated for $C_{21}H_{26}N_6OS$: C, 61.4; H, 6.4; N, 20.5; S, 7.8. Found: C, 61.4; H, 6.2; N, 20.7; S, 7.8.

Phenylthiourea derivative of 1-(2'-methoxyethyl)-4-benzyl-5-iminotetrazoline.

A solution of one gram of 1-(2'-methoxyethyl)-4-benzyl-5-iminotetrazoline hydrochloride in 10 ml. of distilled water was treated with two grams of potassium hydroxide and the resulting suspension of the free iminotetrazoline base was extracted with three 10 ml. portions of ether. The ethereal extracts were combined, dried over anhydrous potassium carbonate and the ether removed on a steam bath with

the aid of a current of air. The residual 1-(2'-methoxyethyl)-4-benzyl-5-iminotetrazoline was treated with 0.5 ml. of phenyl isothiocyanate and the resulting reaction mixture was warmed on the steam bath for ten minutes. The material was allowed to cool and then was washed with two 5 ml. portions of petroleum ether and two 5 ml. portions of 50% isopropyl alcohol. The crude phenylthiourea derivative was chilled in a dry ice-isopropyl alcohol bath to induce crystallization. Recrystallization from 75% isopropyl alcohol gave a material melting at 99.5-100.5° C.

Analysis. Calculated for $C_{18}H_{20}N_6OS$: C, 58.7; H, 5.5; N, 22.8; S, 8.7. Found: C, 58.9; H, 5.6; N, 22.9; S, 8.5.

Phenylthiourea derivative of 1-(2'-phenoxyethyl)-4-benzyl-5-iminotetrazoline.

Two grams of potassium hydroxide was used to liberate the free base from a solution of one gram of 1-(2'-phenoxyethyl)-4-benzyl-5-iminotetrazoline hydrochloride in 10 ml. of distilled water. The free base was extracted with three 10 ml. portions of ether and the combined ethereal extracts were dried over anhydrous potassium carbonate. The ether was removed on a steam bath with the aid of a current of air and the residual free tetrazoline base was treated with 0.5 ml. of phenyl isothiocyanate. The reaction mixture was warmed for ten minutes on the steam bath, cooled and washed with two 5 ml. portions of petroleum ether and two 5 ml.

portions of 50% isopropyl alcohol. The crude phenylthiourea derivative was chilled in a dry ice-isopropyl alcohol bath to promote crystallization and the solid was recrystallized from 75% isopropyl alcohol to give a substance melting at 118-119° C.

Analysis. Calculated for $C_{23}H_{22}N_6OS$: C, 64.2; H, 5.2; N, 19.5; S, 7.5. Found: C, 64.1; H, 5.5; N, 18.9; S, 7.3.

Phenylthiourea derivative of 1-(3'-phenoxypropyl)-4-benzyl-5-iminotetrazoline.

A solution of one gram of 1-(3'-phenoxypropyl)-4-benzyl-5-iminotetrazoline hydrochloride in 10 ml. of distilled water was treated with two grams of potassium hydroxide and the resulting aqueous suspension of the tetrazoline base was extracted with three 10 ml. portions of ether. The ethereal extracts were combined, dried over anhydrous potassium carbonate and the ether removed by heating on a steam bath with the aid of an air jet. The residual 1-(3'-phenoxypropyl)-4-benzyl-5-iminotetrazoline was treated with 0.5 ml. of phenyl isothiocyanate and warmed on the steam bath for ten minutes. The reaction mixture was cooled, washed with two 5 ml. portions of petroleum ether and two 5 ml. portions of 50% isopropyl alcohol and then chilled in a dry ice-isopropyl alcohol bath to induce crystallization. The crude phenylthiourea derivative was recrystallized from 75% isopropyl alcohol to give a material melting at 89-90° C.

Analysis. Calculated for $C_{24}H_{25}N_6OS$: C, 64.8; H, 5.4; N, 18.9; S, 7.2. Found: C, 64.9; H, 5.5; N, 18.9; S, 7.2.

Phenylthiourea derivative of 1-(3'-methoxypropyl)-4-(2"-phenoxyethyl)-5-iminotetrazoline.

One gram of 1-(3'-methoxypropyl)-4-(2"-phenoxyethyl)-5-iminotetrazoline hydrochloride was dissolved in 10 ml. of distilled water and treated with two grams of potassium hydroxide. The aqueous suspension of the free tetrazoline base was extracted with three 10 ml. portions of ether and the ethereal extracts were combined and dried over anhydrous potassium carbonate. The ether was removed with the aid of an air jet by warming on the steam bath and the residual free base was treated with 0.5 ml. of phenyl isothiocyanate. The reaction mixture was heated on the steam bath for ten minutes, cooled and then washed with two 5 ml. portions of petroleum ether and two 5 ml. portions of 50% isopropyl alcohol. The crude phenylthiourea was chilled in a dry ice-isopropyl alcohol bath to aid crystallization and the solid was recrystallized from 75% isopropyl alcohol to yield a material melting at 92.5-93.5° C.

Analysis. Calculated for $C_{20}H_{24}N_6O_2S$: C, 58.2; H, 5.9; N, 20.4; S, 7.8. Found: C, 58.4; H, 5.9; N, 20.2; S, 7.6.

SYNTHESIS OF 1,4-DISUBSTITUTED-5-KETOTETRAZOLINES

These compounds were prepared by a slight modification of the procedure of Percival (15).

Preparation of 1-(3'-isopropoxypropyl)-4-benzyl-5-keto-tetrazoline.

One gram of 1-(3'-isopropoxypropyl)-4-benzyl-5-imino-tetrazoline was obtained from its hydrochloride by dissolution of the hydrochloride in 10 ml. of distilled water and treatment of the water solution with two grams of potassium hydroxide. The aqueous suspension of the free iminotetrazoline base was extracted with three 10 ml. portions of ether and the ethereal solution was dried over anhydrous potassium carbonate. The ethereal solution of the free base was evaporated to dryness on the steam bath with the aid of a current of air and the residual oil was boiled under reflux for one half hour with 10 ml. of acetic anhydride, after which the acetic anhydride was removed by evaporation on the steam bath. The oily residue was treated with 10 ml. of glacial acetic acid and the mixture was boiled under reflux for thirty minutes, at which time the acetic acid was removed by evaporation on the steam bath with the aid of an air jet. The process was repeated with another 10 ml. portion of glacial acetic acid and, after evaporation of the acid, the residue was washed with two

5 ml. portions of distilled water to remove acetamide.

The 1-(3'-isopropoxypropyl)-4-benzyl-5-ketotetrazoline was subjected to molecular distillation at a temperature of 130-135° C./ 1 mm. pressure. The compound solidified on the cold finger, which was chilled with dry ice-isopropyl alcohol, but liquified on warming to room temperature.

Analysis. Calculated for $C_{14}H_{20}N_4O_2$: C, 60.8; H, 7.3; N, 20.4. Found: C, 60.8; H, 7.1; N, 20.5.

Preparation of 1-(2'-methoxyethyl)-4-benzyl-5-ketotetrazoline.

An amount of 1-(2'-methoxyethyl)-4-benzyl-5-iminotetrazoline hydrochloride sufficient to prepare one gram of the free iminotetrazoline base was dissolved in 10 ml. of distilled water and treated with two grams of potassium hydroxide. The aqueous suspension of the free base was extracted with three 10 ml. portions of ether; the ethereal extracts were combined and dried over anhydrous potassium carbonate. The dried solution was warmed on the steam bath in a current of air to remove the ether and the residual iminotetrazoline was boiled under reflux for thirty minutes with 10 ml. of acetic anhydride. The reaction mixture was evaporated to dryness on the steam bath with the aid of an air jet and the residual oil was heated under reflux with 10 ml. of glacial acetic acid for one half hour, after which the solution was taken to dryness on the steam bath. The process was

repeated with another 10 ml. portion of glacial acetic acid and taken to dryness as before. The crude 1-(2'-methoxyethyl)-4-benzyl-5-ketotetrazoline was washed with two 5 ml. portions of cold distilled water tc remove acetamide and subjected to molecular distillation at a temperature of 130-135° C. The ketotetrazoline solidified on the cold finger, which was cooled with dry ice-isopropyl alcohol, but melted on warming to room temperature.

Analysis. Calculated for $C_{11}H_{14}N_4O_2$: C, 56.4; H, 6.0; N, 23.9. Found: C, 56.2; H, 6.1; N, 23.8.

Preparation of 1-(2'-phenoxyethyl)-4-benzyl-5-ketotetrazoline.

A water solution of 11 g. (0.033 mole) of 1-(2'-phenoxyethyl)-4-benzyl-5-iminotetrazoline hydrochloride was treated with potassium hydroxide to liberate the free iminotetrazoline base and the aqueous suspension was extracted with three 50 ml. portions of ether. The ethereal solution was dried over anhydrous potassium carbonate, decanted from the potassium carbonate and the ether removed by warming on the steam bath. Fifteen milliliters of acetic anhydride was added and the mixture was boiled under reflux for one hour, at which time 25 ml. of isopropyl alcohol was added and the mixture was distilled until approximately one half of the volume was removed. The reaction mixture was transferred to a steam bath and the remainder of the liquid

was removed with the aid of an air jet. The residual oil was treated with glacial acetic acid and warmed on the steam bath for one hour, after which the acetic acid was removed with the aid of an air jet.

The residual oil was washed with cold distilled water to remove acetamide, and the non-aqueous portion was taken up in cyclohexane and chilled. The crude 1-(2'-phenoxyethyl)-4-benzyl-5-ketotetrazoline was recrystallized from cyclohexane to yield 7 g. (71% of theory) of material melting at 84-85° C.

Analysis. Calculated for $C_{16}H_{16}N_4O_2$: C, 64.8; H, 5.4; N, 18.9. Found: C, 65.0; H, 5.5; N, 18.9.

Preparation of 1-(3'-phenoxypropyl)-4-benzyl-5-ketotetrazoline.

Enough 1-(3'-phenoxypropyl)-4-benzyl-5-iminotetrazoline hydrochloride to prepare one gram of the free tetrazoline base was dissolved in 10 ml. of distilled water and treated with two grams of potassium hydroxide. The aqueous suspension of the free base was extracted with three 10 ml. portions of ether; the ethereal extracts were combined and dried over anhydrous potassium carbonate. The ethereal solution of 1-(3'-phenoxypropyl)-4-benzyl-5-iminotetrazoline was evaporated to dryness and the residue was boiled with 20 ml. of acetic anhydride for one hour, then the reaction mixture was evaporated to dryness on the steam bath. The

residual oil was mixed with 10 ml. of glacial acetic acid and evaporated to dryness on the steam bath. The procedure was repeated with an additional 10 ml. of glacial acetic acid; the residual oil was washed with 10 ml. of ice-cold distilled water to remove acetamide and the oil was finally subjected to molecular distillation at a temperature of 130-135° C./ 1 mm. pressure. The 1-(3'-phenoxypropyl)-4-benzyl-5-ketotetrazoline solidified on the cold finger, but liquified on coming to room temperature.

Analysis. Calculated for $C_{17}H_{18}N_4O_2$: C, 65.8; H, 5.8; N, 18.5. Found: C, 63.5, 63.8; H, 6.0, 6.0; N, 18.3.

The anomalous values for the percentage of carbon in this determination may be accounted for by the presence of acetamide in the amount of 5-10%. This quantity of acetamide could lower the value of carbon without raising the value of hydrogen and nitrogen percentages out of the bounds indicated by the above values.

Preparation of 1-(3'-methoxypropyl)-4-(2"-phenoxyethyl)-5-ketotetrazoline.

An amount of 1-(3'-methoxypropyl)-4-(2"-phenoxyethyl)-5-iminotetrazoline hydrochloride sufficient to prepare one gram of the free tetrazoline base was dissolved in 10 ml. of distilled water and treated with two grams of potassium hydroxide to liberate the free base. The aqueous suspension of the iminotetrazoline was extracted with three 10 ml. por-

tions of ether; the ethereal extracts were combined and dried over anhydrous potassium carbonate. The dried ethereal solution was heated on the steam bath in a current of air to remove the ether and the residual 1-(3'-methoxypropyl)-4-(2"-phenoxyethyl)-5-iminotetrazoline was boiled under reflux for thirty minutes with 10 ml. of acetic anhydride. The reaction mixture was evaporated to dryness on the steam bath with the aid of an air jet; the residual oil was warmed with 10 ml. of glacial acetic acid for thirty minutes and the acetic acid was removed by evaporation on the steam bath with the aid of a current of air. The process was repeated with another 10 ml. portion of glacial acetic acid and the 1-(3'-methoxypropyl)-4-(2"-phenoxyethyl)-5-ketotetrazoline was washed with two 5 ml. portions of distilled water to remove acetamide.

The ketotetrazoline was subjected to molecular distillation at a temperature of 130-135° C./ 1 mm. pressure. The compound solidified on the cold finger, which was chilled with dry ice-isopropyl alcohol, but liquified on warming to room temperature.

Analysis. Calculated for $C_{13}H_{18}N_4O_3$: C, 56.1; H, 6.5; N, 20.1. Found: C, 56.0; H, 6.6; N, 20.0.

ATTEMPTED SYNTHESIS OF 1-(2'-PHENOXYETHYL)-5-HYDROXYTETRAZOLE

The procedure used was only slightly modified from that of Herbst and Percival (3).

A solution of 2.96 g. (0.01 mole) of 1-(2'-phenoxyethyl)-4-benzyl-5-ketotetrazoline in 100 ml. of absolute ethanol was shaken with 0.1 g. of palladium oxide at a hydrogen pressure of 50 p.s.i. in a Burgess-Parr low pressure hydrogenation apparatus. After shaking for twelve hours, the catalyst was filtered off, washed with hot ethanol and the ethanol solution was evaporated to dryness. The residue was recrystallized from cyclohexane to give a material which melted at 84-85° C. No depression of the melting point was observed on admixture with an authentic sample of 1-(2'-phenoxyethyl)-4-benzyl-5-ketotetrazoline.

The hydrogenolysis was attempted under the same experimental conditions with platinum oxide and palladium black as catalysts. No hydrogenolysis was observed.

SUMMARY

Summary

1. The alkylation of 1-(1',1',3',3'-tetramethylbutyl)-5-aminotetrazole with p-chlorobenzyl chloride resulted in the displacement of the 1,1,3,3-tetramethylbutyl group and the formation of 1,4-di-(p-chlorobenzyl)-5-iminotetrazoline.

2. 1-Tertiary butyl-5-aminotetrazole was prepared and alkylated with benzyl chloride. Products of the reaction were 1,4-dibenzyl-5-iminotetrazoline and isobutylene.

3. Alkylation of 1-tertiary butyl-5-aminotetrazole with ethyl p-toluenesulfonate also displaced the tertiary alkyl group to give 1,4-diethyl-5-iminotetrazoline and isobutylene as products.

4. Alkylation of 1-(1',1',3',3'-tetramethylbutyl)-5-aminotetrazole with benzyl chloride gave 1,4-dibenzyl-5-iminotetrazoline and an olefin which was shown to be a mixture of 2,4,4-trimethyl-1-pentene and 2,4,4-trimethyl-2-pentene.

5. Preparation and alkylation of 1-(3'-heptyl)-5-aminotetrazole with benzyl chloride gave no displacement of the secondary alkyl group. The normal alkylation product, 1-(3'-heptyl)-4-benzyl-5-iminotetrazoline was formed.

6. A group of 1-alkoxyalkyl-5-aminotetrazoles and 1-aryloxyalkyl-5-aminotetrazoles were prepared by interaction of the corresponding alkoxy- or aryloxyalkylamines with cyanogen bromide and treatment of the resulting cyanamide with hydrazoic acid.

7. Alkylation of the 1-alkoxyalkyl-5-aminotetrazoles with either benzyl chloride or 2-phenoxyethyl bromide produced the desired 1,4-disubstituted-5-iminotetrazolines. The iminotetrazolines were characterized as their hydrochlorides and phenylthiourea derivatives.

8. Acetolysis of the iminotetrazolines produced the corresponding ketotetrazolines. Attempted hydrogenolysis of 1-(2'-phenoxyethyl)-4-benzyl-5-ketotetrazoline failed to remove the benzyl group and produce the desired 5-hydroxytetrazole.

LITERATURE CITED

Literature Cited

1. J. Thiele, Ann., 270, 54 (1892).
2. J. Thiele and H. Ingle, Ann., 287, 232 (1895).
3. R. Herbst and D. Percival, J. Org. Chem., 19, 439 (1954).
4. A. Hantzsch and A. Vagt, Ann., 314, 339 (1901).
5. R. Stolle, Ber., 62, 1118 (1929).
6. R. Stolle, J. prakt. Chem., 134, 282 (1932).
7. J. von Braun and W. Keller, Ber., 65, 1677 (1932).
8. R. Herbst, C. Roberts, and E. Harvill, J. Org. Chem., 16, 139 (1951).
9. K. Schmidt, Ber., 57, 704 (1924).
10. W. Garbrecht and R. Herbst, J. Org. Chem. 18, 1014 (1953).
11. R. Herbst and C. Froberger, J. Org. Chem., 22, 1050 (1957).
12. M. Freund and T. Paradies, Ber., 34, 3115 (1901).
13. M. Freund and H. Hempel, Ber., 28, 78 (1895).
14. R. Stolle and Fr. Henke-Stark, J. prakt. Chem., 124, 261 (1930).
15. D. Percival and R. Herbst, J. Org. Chem., 22, 925 (1957).
16. L. Birkofer, Ber., 75, 429 (1942).
17. R. Shriner and R. Fuson, The Systemic Identification of Organic Compounds, Third Edition, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 198.
18. Organic Analysis, Vol. III, Interscience Publishers Inc., New York, N. Y., 1956, p. 237.
19. M. Tiffeneau, Bull. Soc. Chim., (4) 33, 186 (1923).

20. H. Raper, J. Chem. Soc., 91, 1837 (1907).

21. Organic Reactions, Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 283.

22. W. Keretinsky, Ber., 55, 2757 (1922).

23. Catalog of Infrared Spectral Data of the American Petroleum Institute Research Project 44, Spectrum Serial Numbers 40 and 449.

24. F. Benson, Chem. Rev., 41, 1 (1947).

25. J. Sheehan and W. Bolhofer, J. Am. Chem. Soc., 72, 2786 (1950).

26. C. Schmidt, Ber., 22, 3255 (1889).

27. J. Lohman, Ber., 24, 2634 (1891).