THE STEREOCHEMISTRY OF THE FORMATION OF AMINOTETRAZOLES FROM NITRILES

Thesis for the Degree of M. S.

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Frances Fallon

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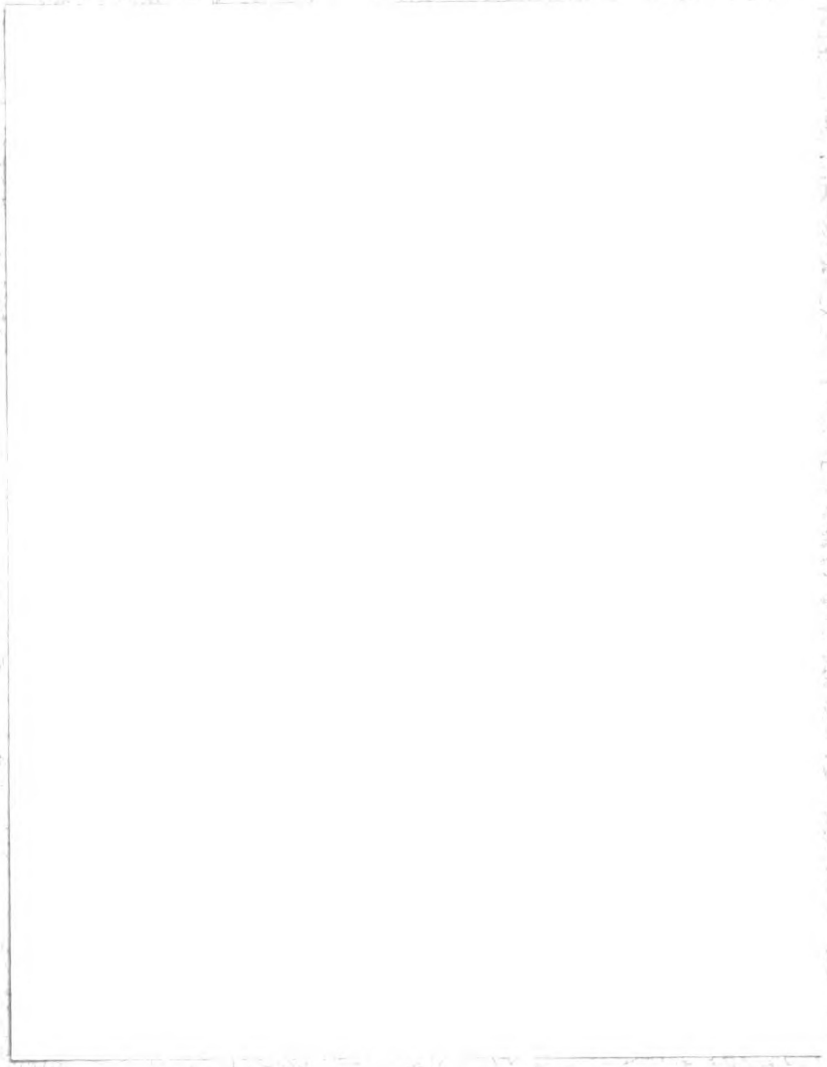

THE STEREOCHEMISTRY OF THE FORMATION OF AMINOTETRAZOLES FROM NITRILES

By

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A THESIS

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INTRODUCTION

INTRODUCTION

Alkyl cyanides are known to react with two moles of hydrazoic acid, in the presence of sulfuric acid, to give 1-alkyl-5-aminotetrazoles (1). It is apparent that the alkyl group has shifted from carbon to nitrogen in the course of this reaction.

A mechanism has been suggested by Herbst, Roberts, and Harvill (2) relating this rearrangement to the so-called "1-2 shifts," most of which also proceed in the presence of sulfuric acid. In the case of the Hofmann, Beckmann, Curtius, Lossen, and Schmidt rearrangements optically active starting materials have been shown to form optically active products.

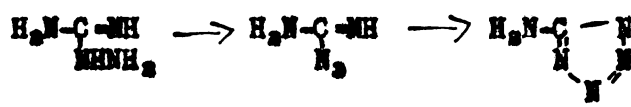
It was the purpose of this work to study the rearrangement of optically active nitriles in the presence of hydrazoic acid and sulfuric acid. The formation of an optically active 1-alkyl-5-aminotetrazole under these conditions would be predicted on the basis of the mechanism proposed for this reaction.

Preliminary studies were made using benzyl cyanide to determine the effect of variations in reaction temperature and order of addition of reagents on the yield of 1-benzyl-5-aminotetrazole. The nitrile chosen for the main part of the study was α-ethylcapronitrile, since the corresponding inactive tetrazole had already been prepared by this method (2), and procedures for the resolution of α-ethylcaproic acid and preparation of the active nitrile were known (3,4,5).

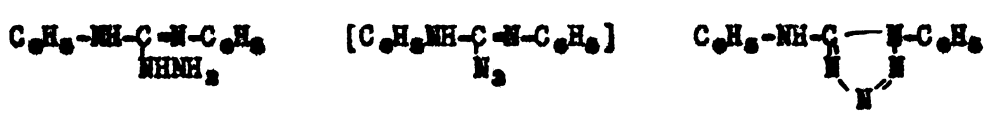
DISCUSSION

DISCUSSION

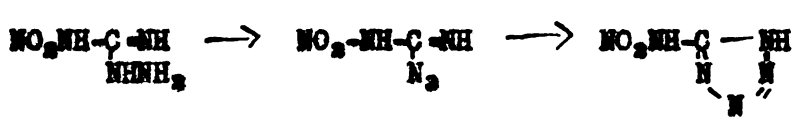
The formation of 5-aminotetrazole and some of its substitution products has been observed in a number of reactions. Thiele (6) was the first to describe compounds of this type when he noted the formation of the parent compound, 5-aminotetrazole, when aminoguanidine was treated with nitrous acid. A rather unstable guanylazide was formed as an intermediate in this reaction.



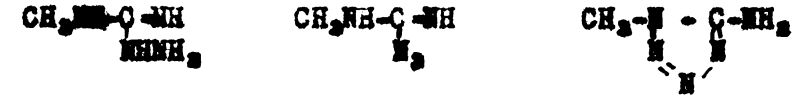
Although this reaction has not been applied to the preparation of other 5-aminotetrazoles in which the amino group is unsubstituted, it has been used with some success in the preparation of a number of substituted derivatives. For instance, Busch and Bauer (7) have described the preparation of 1-aryl-5-arylaminotetrazoles from N-N'-diaryl-N''-aminoguanidines on interaction with nitrous acid.



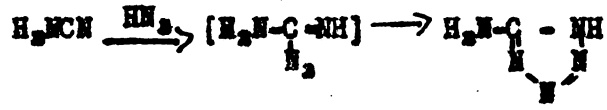
Similarly the interaction of N-nitro-N'-aminoguanidine and nitrous acid has been reported to lead to the formation of 5-nitroaminotetrazole (8).



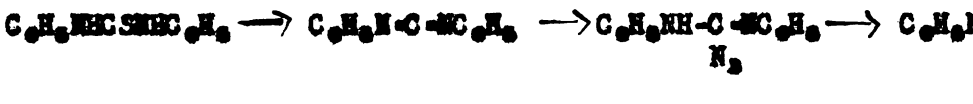
In this laboratory, N-methyl-N'-aminoguanidine has been observed to give 1-methyl-5-aminotetrazole on treatment with nitrous acid (9).

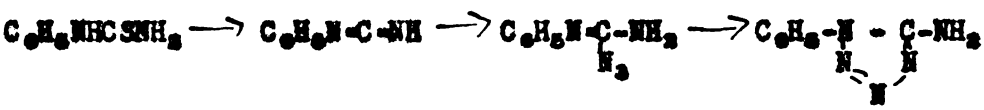


The formation of 5-aminotetrazole by addition of hydrazoic acid to cyanamide was described by Hantzsch and Vagt (10). The application of a similar reaction to monoalkylcyanamides and to dialkylcyanamides has been observed to lead to 1-alkyl-5-aminotetrazoles and 5-dialkylaminotetrazoles, respectively (9).



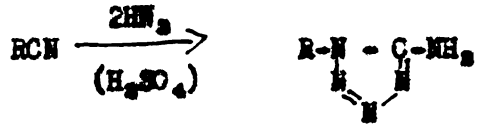
A procedure of somewhat different character has been described by Stollé (11,12). It involved treatment of N-substituted thioureas derivatives with sodium azide in the presence of lead oxide or lead carbonate in a carbon dioxide atmosphere. Under these conditions phenylthiourea was observed to give 1-phenyl-5-aminotetrazole and N,N'-diphenylthiourea gave 1-phenyl-5-phenylaminotetrazole. The sequence of reactions has been represented as involving the initial conversion of the thiourea into a substituted carbodiimide followed by addition of hydrazoic acid to the carbon-nitrogen unsaturation.



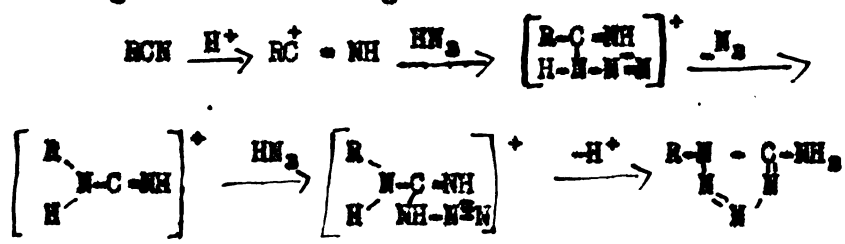


More recently, von Braun and Keller (1) have studied the reaction between alkyl and arylcyanides and hydrazoic acid in the presence of

sulfuric acid. It was the hope of these investigators to prepare 5-alkyl and 5-aryltetrazoles in this way. Hydrazoic acid had been observed to add to the carbon nitrogen unsaturation of hydrocyanic acid (13), cyanogen (14), cyanogen bromide and ethyl cyanoformate (15) with the formation, respectively, of tetrazole, 5-bromotetrazole and ethyl tetrazole-5-carboxylate. In the presence of sulfuric acid, however, the reaction followed quite a different course with the result that 1-alkyl and 1-aryl-5-aminotetrazoles were formed from the alkyl and aryl cyanides.



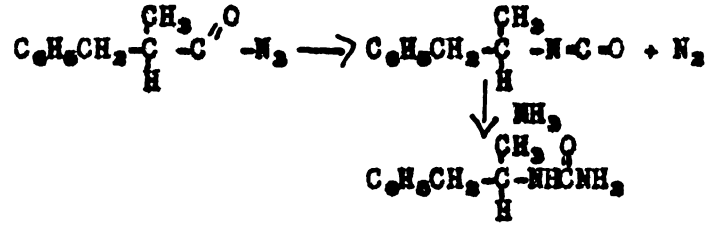
Of the several methods for the synthesis of 5-aminotetrazole derivatives it will be observed that the von Braun and Keller method is the only one that involves a rearrangement and a change of the position of attachment of a substituent group. This reaction has been used by Herbst, Roberts and Harvill to prepare and study a series of 1-alkyl-5-aminotetrazoles (2). These authors have suggested that the migration of the substituent group involves a typical 1,2 shift similar to that postulated for other common rearrangements involving adjacent carbon and nitrogen atoms such as the Beckmann, Curtius, Hofmann, Lossen and Schmidt reactions. On this basis they have postulated tetrazole formation according to the following mechanism:



If the above picture is the correct one, it should be possible to obtain an optically active tetrazole by starting with an optically active nitrile.

In the study of the mechanisms of such rearrangements the use of optically active compounds has been particularly rewarding. It is essential that the asymmetry of the migrating group should involve the point of attachment. Under this condition it has been assumed that complete detachment of the migrating group during the course of rearrangement would lead to racemization of the group, and formation of an optically active product has been assumed to indicate that the migrating group has never been completely detached from the molecule. In all cases that have been carefully studied, optical activity has always been observed in the products.

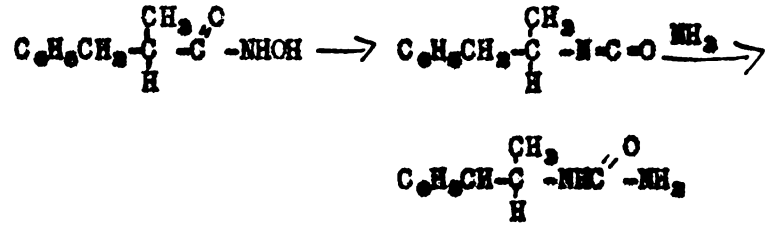
Jones and Wallis (16) showed that the Curtius rearrangement of (+)-benzylmethylacetazide gave (+)-phenylisopropyl-isocyanate. With ammonia the isocyanate was converted into the corresponding (+)-N-phenyl-isopropyl urea.



Similar studies on the Curtius rearrangement were done with the azides of (+)-hydratropic acid (17) and of both (+)- and (-)-6-nitro-2-methyl-diphenyl-2'-carboxylic acid (18). Optical activity in the former instance is due to the presence of an asymmetric carbon atom while

in the latter case restricted rotation about a carbon-carbon bond gives rise to molecular asymmetry. There was no evidence of racemization in any case.

Wallis and Dripps (19) prepared (+)-N-phenylisopropyl urea through the Lossen rearrangement of (+)-benzylmethylacethydroxamic acid:

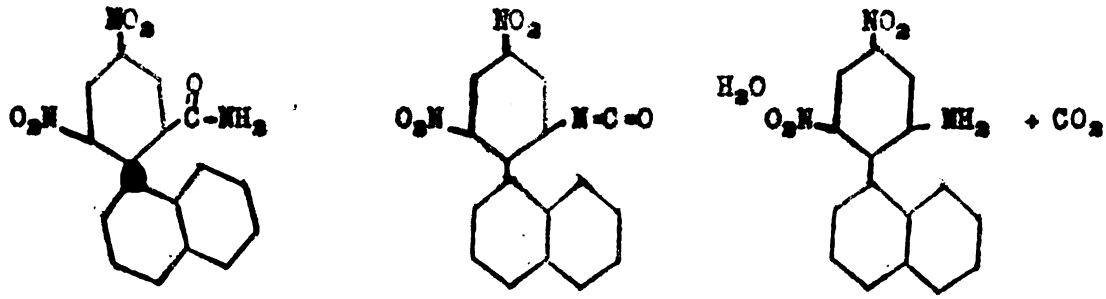


The substituted urea from the Lossen rearrangement of (+)-benzylmethylacethydroxamic acid (19) was identical with the product obtained after the Curtius rearrangement of (+)-benzylmethylacetazide (16). Solutions of equal concentration of both products gave the same rotation values within the limits of experimental error.

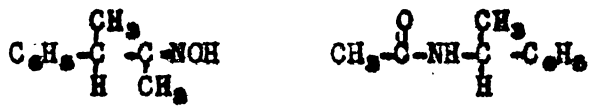
The Lossen rearrangement has also been studied using (+)-phenylmethylacethydroxamic acid (20). The product retained its optical activity in this case too.

A number of studies on the Hofmann rearrangement have been made employing (+)-benzylmethylacetamide (21), (+)-hydratropamide (22), and the amide of (+)-2,5-dinitro-6-(α-naphthyl)-benzoic acid (23). This last example is an especially interesting case, since the optical activity is due to restriction of rotation about the bond between the phenyl and naphthalene groups. If the group involved were ever completely free during the shift from carbon to nitrogen, at least partial racemization should take place. Since the product had a very large specific

rotation which did not change upon recrystallization, it was concluded that no racemization had occurred, and that the migrating group had never been completely free.



The Beckmann rearrangement of several optically active oximes has been studied by Kenyon and his co-workers (17,20). Both (+)-methyl-γ-heptylketoxime (17) and (+)-α-phenylethyl methyl ketoxime (20) were rearranged to the corresponding amines with over 99% retention of optical activity. Using the latter as an example:



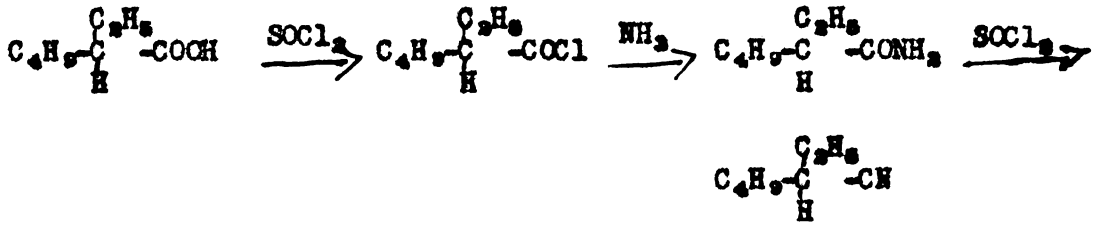
Since the formation of 5-aminotetrazole derivatives from nitriles has been assumed to involve a typical 1,2 shift similar to that observed in the reactions just discussed, a study of tetrazole formation from an optically active nitrile was undertaken to establish this relationship more firmly. The example chosen was the conversion of optically active α-ethylcapronitrile to 1-(3'-heptyl)-5-aminotetrazole. The inactive form of the product was known, since it had been prepared by Herbst, Roberts, and Harvill (2). Furthermore, α-ethylcaproic acid was commercially available, its resolution into the optically active forms had been described (3,5), and the transformation of these latter to the optically active nitriles had been reported (4).

The resolution of α-ethylcaproic acid was accomplished by repeated crystallization of its quinine salt from 50% acetone. The yield of (-)-α-ethylcaproic acid obtained in this way was lower than expected from the report of Kenyon and Platt (5). Since the quinine salt is readily soluble in acetone, this low yield is probably due to the use of excess solvent in the later recrystallizations. Some difficulty was experienced in obtaining slow development of crystals. If the warm saturated solution was allowed to cool undisturbed, the quinine salt separated as an oily layer, which solidified to a hard cake on stirring or seeding. On the other hand, seeding of the solution while it was still very warm was not feasible, since the added crystal merely dissolved. The material used for seeding was prepared in a preliminary small-scale run and recrystallized six times.

Kenyon and Platt (5) had reported the melting point of the quinine salt of (-)-α-ethylcaproic acid as 64-65°C. We have observed that the melting point was subject to considerable variation depending on the extent to which the salt was dried. An air-dried sample that melted at 67-71°C. was found to melt at 107-108°C. after drying in a vacuum desiccator. The salt appeared to be hygroscopic since the melting point of the vacuum-dried material was lowered after exposure to the atmosphere for a day.

It was found necessary to dry the recrystallized salt completely before regenerating the acid, since a sticky mass was formed when acetone was present at the time of addition of sodium hydroxide solution.

The (-)-α-ethylcaproic acid was converted to its chloride by treatment with thionyl chloride. The crude chloride was distilled only once and used immediately to prepare the amide. The crude amide in turn was dehydrated to the nitrile by means of thionyl chloride without isolation or purification. The scheme outlined above follows the procedure of Levene and Kuna (4) and leads to a satisfactory yield of the (-)-nitrile. In preliminary runs, an attempted variation in the preparation of the acid chloride resulted in partially or completely racemized nitrile. The revised procedure involved refluxing of the reaction mixture with heat supplied by a micro-burner, whereas the original, and successful, procedure allowed the reactants to stand together overnight before heating under reflux on a steambath for one hour.



Herbst, Roberts and Harvill (2) prepared 1-alkyl-5-aminotetrazoles by adding sulfuric acid to a benzene solution of the nitrile and hydrazoic acid. Since the principal by-product of the reaction was the amide corresponding to the nitrile, it seemed possible that amide-formation might be minimized by changing the order of addition of the reagents. Preliminary experiments with benzyl cyanide showed that the order of addition of the reagents did not markedly affect the yield of 1-alkyl-5-aminotetrazole. However, in practice, it was found convenient for the

final small-scale reaction with α-ethylcapronitrile to add the nitrile to a mixture of hydrazoic acid dissolved in benzene and sulfuric acid.

Although the yields of tetrazole derivatives are low due to the formation of the corresponding amides, in this case difficulties in separation and purification of the product lowered the yield still more. The organic materials can be separated from inorganic salts satisfactorily by extraction with isopropyl alcohol. However, evaporation of the extract leaves a dark red, waxy mass which does not crystallize from either acetic acid or isopropyl alcohol. Use of n-heptane as a crystallizing solvent, as suggested by Herbst, Roberts and Harvill, did not give a good separation from the amide, since the latter dissolved more readily in hot solvent than the desired product. However, cold n-heptane proved successful in causing the formation of crystalline material from the original wax-like residue. The slurry of crystals so formed was then decanted and filtered. Repetition of this process reduced the residue to a very small amount of highly colored material. The crude crystalline product recrystallized readily from acetic acid, but here again, no satisfactory substitute was found for mechanical separation of the colored impurity from the surface of the cooling mixture. This purification procedure leads to mechanical loss, but attempts to improve or simplify it have so far been unsuccessful.

The levorotatory α-ethylcaproic acid gave a levorotatory nitrile, which furnished a dextrorotatory tetrazole derivative, with a melting point significantly higher than that of the inactive product. This tetrazole derivative has not previously been prepared in optically active

form, and no method for resolution of the inactive compound is available. Consequently, it is not possible at present to show conclusively that no racemisation took place during this rearrangement. However, the optical activity of the product obtained supports the mechanism suggested by Herbst, Roberts and Harvill.

Throughout the studies on the related rearrangements mentioned above, the suggestion has repeatedly been made that configuration, as well as asymmetry, is retained in the migrating radical. The evidence in favor of this view is reviewed by Kenyon and Young (17) and also by Lane and Wallis (24,25). The conclusion is drawn that configuration is retained in all intramolecular rearrangements. To this evidence might be added the summary given by Campbell and Kenyon (20), in which they show that (+)-hydratropic acid has been converted, by means of suitable intermediates, to the same (-)-α-phenyl ethylamine through the Curtius, Hofmann, Lossen and Beckman rearrangements, with better than 99% retention of asymmetry in all cases except the Hofmann, where the drop to 95.8% retention of optical activity is explained by enolization. The most conclusive evidence is reported by Lane and Wallis (24), who carried out a Wolff rearrangement of an optically active diazoketone, and degraded the product to the same acid used to prepare the starting diazoketone. In this cycle the only step involving the asymmetric center was the rearrangement itself. Since no inversion was observed in the cycle, the rearrangement proceeded without inversion.

On the basis of this evidence, it seems quite probable that both asymmetry and configuration are also retained in the formation of

optically active 1-alkyl-5-aminotetrazoles, though rigid proof is impossible in the absence of an independent synthesis of the optically active product.

EXPERIMENTAL

EXPERIMENTAL[1]

Reagents

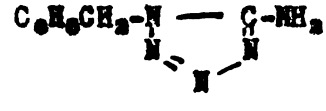
Sodium Azide was obtained from E. I. Dupont deNemours and Company, Explosives Division.

Hydrazoic acid solutions in benzene were prepared by treating a vigorously stirred sludge of equal weights of sodium azide and water under benzene with concentrated sulfuric acid, added slowly, while the temperature was kept below 25°C. The benzene solution was separated from the aqueous sludge and dried over sodium sulfate. The concentration of the hydrazoic acid depended on the volume of benzene employed and was determined by titration of an aliquot of the benzene solution with a standard aqueous sodium hydroxide solution using phenolphthalein as indicator.

Benzyl cyanide was obtained from Eastman Kodak Company.

α-Ethylcaproic acid was obtained from the Distillation Products Industries, Division of Eastman Kodak Company.

1-Benzyl-5-aminotetrazole



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1 All melting points are uncorrected, unless otherwise stated.

Method A

Benzylcyanide (29 g.) and 250 ml. of a 13.1% solution of hydrazoic acid in benzene were placed in a one-liter three-necked flask equipped with thermometer, mechanical stirrer, and dropping funnel. The thermometer was held in a glass tube with a side-arm open to the atmosphere, and the dropping funnel was extended by means of a thick-walled capillary tube which dipped below the surface of the hydrazoic acid solution. Concentrated sulfuric acid (75 ml.) was added slowly with stirring, and reaction temperature was controlled when necessary with a cold water bath. Stirring was continued about eight hours after addition of the sulfuric acid was complete. The acid layer was separated and diluted by pouring over ice. The reaction flask and funnel were rinsed with a small amount of sulfuric acid, which was added to the diluted mixture. This solution was neutralized to litmus with 50% potassium hydroxide, cooled, and filtered. The filter cake, which consisted of the product mixed with much potassium sulfate, was extracted with hot isopropyl alcohol. The alcohol extract was evaporated to a smaller volume, cooled, and the crude product filtered off. The filtrate was then evaporated further to give a second crop. Apparently the corresponding amide is more soluble in isopropyl alcohol than the tetrazole, since the first crop consistently shows a higher melting point than later ones. A typical preparation gave the following crude yields: 12.3 g., m.p. 187-190°C. and 2.0 g., m.p. 163-183°C.

The crude product was recrystallized from isopropyl alcohol. In some runs, the hot alcohol solutions were decolorized with charcoal

before filtering. Yields by this method were 21-27% of theory. Two runs were made at 30-35°C., one at 20-25°C., but no significant effect on the yield was noticed. Melting points after one recrystallization of the first crop varied from 187-189°C. to 189-191°C. (Herbst, Roberts, and Harvill (2) give 186.5-187.5°C.) However, percentage yields include all once-recrystallized products melting at 180°C. and above.

Method B

Apparatus and quantities used were the same as in the above method. The solution of hydrazoic acid in benzene was placed in the flask and stirred rapidly while first the sulfuric acid, then the benzyl cyanide were added, with the temperature controlled at 20-25°C. Total addition required 15 minutes and temperature control was much easier than in Method A. Stirring was continued nine hours longer, with temperature controlled below 25°C. From this point on, the reaction mixture was treated as described above. The crude yield was obtained in two crops: 7.5 g. melting at 170-186°C., and 4.3 g. melting at 167-170°C. Accidental loss of one of the fractions prevented comparison of yields on the purified material, but the crude yield is clearly no better than in Method A, and may be somewhat lower.

Resolution of α-ethylcaproic acid (3,5)

A five-liter flask equipped with a reflux condenser was charged with 450 g. of quinine, 173 g. of α-ethylcaproic acid, 900 ml. of acetone and 900 ml. of water. The mixture was heated on the steambath until the

quinine dissolved, the solution was clarified with a small additional amount of acetone, and allowed to cool. While the solution was still slightly warm, it was seeded with the quinine salt of the (-) acid, obtained from a preliminary small-scale run, and allowed to stand overnight.

The salt which crystallised was filtered and recrystallised six times from 50% acetone, with a decrease in the amount of solvent each time. The yield (50.7 g.) was lower than expected, probably due to excess solvent in the later recrystallisations.

The quinine salt has a strong tendency to separate as an oil. If the mixture is swirled or scratched after it has cooled and separated into two layers, the oily layer may form a hard solid cake, difficult to remove from the flask.

The melting point of this salt depends largely on the degree of drying. Some material, recrystallised six times and dried in a vacuum desiccator melted 107-108°C., while material allowed to dry in air melted 67-71°C. If the crystals are dried in a vacuum desicator and then exposed to the air, the melting point again drops.

The dry quinine salt (94 g.) was stirred in an open beaker with a solution of 20 g. of solid sodium hydroxide in 500 ml. of water. After standing a while, the mixture was filtered by suction and the filter cake again treated with a solution of sodium hydroxide as before. After the second filtration, the filter cake should consist of recovered quinine. The combined filtrates were acidified to Congo Red and extracted with ether. The ether extracts were dried over anhydrous sodium sulfate,

the ether removed at reduced pressure, and the acid distilled, b.p. 108-114°C. at 24 mm. Heating was done through an oil bath maintained 160-165°C. The yield was 14.8 g.; $[\alpha]_D$ -7.94° at room temperature.

Inactive α-ethylcaproyl chloride

A two-liter flask equipped with dropping funnel and reflux condenser was charged with 240 g. (148 ml.) of thionyl chloride. The thionyl chloride was heated to reflux temperature; the flame was removed, and 216 g. of inactive α-ethylcaproic acid was added slowly over a period of 20 minutes. The mixture was refluxed with a free flame for two hours, then distilled at reduced pressure. The main distillate was colorless, b.p. 77-78°C. at 28 mm. The yield was 188.7 g. (77.6% of theory).

Inactive α-ethylcaprenitrile

The inactive α-ethylcaproyl chloride (188.7 g.) was added dropwise with stirring over a period of four hours to 600 ml. of alcohol saturated with ammonia, with the temperature kept below 5°C. by means of an ice-alcohol bath. The precipitate of ammonium chloride was filtered off, and the alcohol removed from the filtrate under reduced pressure with slight warming on a steam bath. The ammonium chloride filter cake was washed with benzene, and the washings added to the residue left after evaporation of the alcohol. The benzene was then removed under reduced pressure. The crude amide thus obtained was dissolved in 260 ml. of thionyl chloride and refluxed one hour on the steambath. Thionyl chloride

was removed at reduced pressure and the residue was dissolved in ether, washed with three 100-ml. portions of water, and dried over anhydrous sodium sulfate. After filtration, the ether was removed at reduced pressure and the residue distilled. The main fraction boiled 100-102°C. at 27 mm. The yield was 106.9 g. (73.7% of theory based on acid chloride).

(-)-α-Ethylcaproyl chloride (4)

(-)-α-Ethylcaproic acid (14.4 g.) was added with swirling to 135 ml. of thionyl chloride and allowed to stand overnight, then refluxed two hours on the steambath. Excess thionyl chloride was removed at reduced pressure and the acid chloride distilled, b.p. 77-78°C. at 28 mm. (Oil bath temperature 127-140°C.) The yield was 14.9 g. (91.4% of theory).

(-)-α-Ethylcapronitrile (4)

(-)-α-Ethylcaproyl chloride (14.9 g.) was added slowly, over 20 minutes, to 50 ml. of 95% ethyl alcohol saturated with ammonia, while mixture was maintained below 10°C. in an ice-salt bath. Ammonium chloride was filtered off, and the alcohol filtrate evaporated to dryness under reduced pressure. The ammonium chloride was washed with benzene and the solution added to the solid residue from the alcohol filtrate. The resulting mixture was again evaporated to dryness. The crude amide thus obtained was refluxed one hour on the steambath with 25 ml. of thionyl chloride. After filtration, excess thionyl chloride was removed at reduced pressure. The residue was dissolved in 25 ml. of ether, washed with three 10 ml.

portions of water, and dried over anhydrous sodium sulfate. The ether was removed at reduced pressure and the nitrile distilled, b.p. 77-78°C. at 18 mm. The yield was 5.8 g. (50.4% of theory from acid chloride); $[\alpha]_D$-9.85° at room temperature.

(+)-1 (3'-heptyl)-5-aminotetrazole

In a preliminary preparation of the tetrazole, a 36 g. sample of partially resolved acid, $[\alpha]$+1.2°, was converted to the acid chloride by the method used with the inactive acid. The yield was 37 g. (91.4% of theory); b.p. 105-109°C. at 75 mm. The acid chloride was converted, by the above procedure to the corresponding nitrile, b.p. 74-78°C. at 16 mm. The yield was 21.5 g., $[\alpha]_D$+0.2°. The nitrile was converted to 1-(3'-heptyl)-5-aminotetrazole by the method described below for preparation of the dextrorotatory compound. The yield was 3.7 g., m.p. 147-148°C. A one-gram sample in ethanol exhibited no optical activity. The melting point of this material was the same as that of the inactive tetrazole derivative. The melting point reported for the inactive tetrazole derivative is 146-146.5°C. (2).

A 14.2% solution of hydrazoic acid in benzene (45 ml.) was placed in a 300 ml. two-necked flask equipped with a dropping funnel and thermometer, arranged as described for the preparation of 1-benzyl-5-aminotetrazole. The flask was swirled in an ice bath during the gradual addition of 13.5 ml. of concentrated sulfuric acid, followed by 5.4 g. of (-)-α-ethylcapronitrile ($[\alpha]_D$ -9.85). The dropping funnel was then

replaced by a mechanical stirrer, and the reaction was stirred overnight. The temperature was maintained at 20-30°C. with a water bath.

The acid layer was separated, diluted with ice, and neutralized to litmus with 50% potassium hydroxide. After cooling, the resulting mixture was filtered and the filter cake extracted with a total of 100 ml. of hot isopropyl alcohol. This extract was evaporated to dryness at reduced pressure. The solid residue was rinsed out of the flask with a small amount of n-heptane and the slurry of crystals formed was decanted from the lower layer of yellow oil. Small amounts of heptane were added to the oil and decanted until no more crystals were obtainable. The crude product (3.2 g.) was filtered, dissolved in 14 ml. of 50% acetic acid, filtered, and treated with 7 ml. of water. The solution was heated on the steambath until clear and allowed to cool slowly. As the solution cooled a red, waxy material separated and collected on the surface. After this material was removed mechanically, the desired product separated from the remaining solution as colorless crystals. On repeated treatment of the red, waxy material with a mixture of 4 ml. of water and 2 ml. of glacial acetic acid, further separation of the product from the colored impurity was accomplished. The several fractions of colorless product were combined, washed with water and air-dried, m.p. 153-156°C., yield 1.6 g.

This product was recrystallized a second time from the same solvent mixture, filtered on a sintered glass funnel, and dried 40 minutes at 100°C., m. p. 156-157°C. The yield was 0.8 g. $[\alpha]_D$+9.05 (in ethyl alcohol).

Anal.[1] Calculated for $C_8H_{17}N_5$: C, 52.42%; H, 9.35%; N, 38.21%

Found: C, 52.47, 52.35; H, 9.43, 9.20; N, 37.93, 37.98

Optical rotation

All readings were taken at room temperature using a one-decimeter tube and the sodium D-line. Readings on the acid and the nitrile were made on the homogeneous liquid. The tetrazole sample was dissolved without heating in 95% ethyl alcohol to make 10 ml. of solution.

Substance	Reading	$[\alpha]_D$
(-)-α-ethylcaproic acid	-7.17	-7.94
(-)-α-ethylcapronitrile	-7.94	-9.85
(+)-1(3'-heptyl)-5-aminotetrazole (0.7511 g.)	+0.68	+9.05

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1 Analysis was done by Micro-Tech Laboratories, Skokie, Illinois.

SUMMARY

SUMMARY

1. An optically active 1-alkyl-5-aminotetrazole has been prepared by the reaction of an optically active nitrile with hydrazoic acid in the presence of sulfuric acid.

2. This observation supports the idea that the rearrangement involved is intramolecular and proceeds by a mechanism similar to that currently accepted for the Hofmann, Lossen, Curtius and Beckmann rearrangements.

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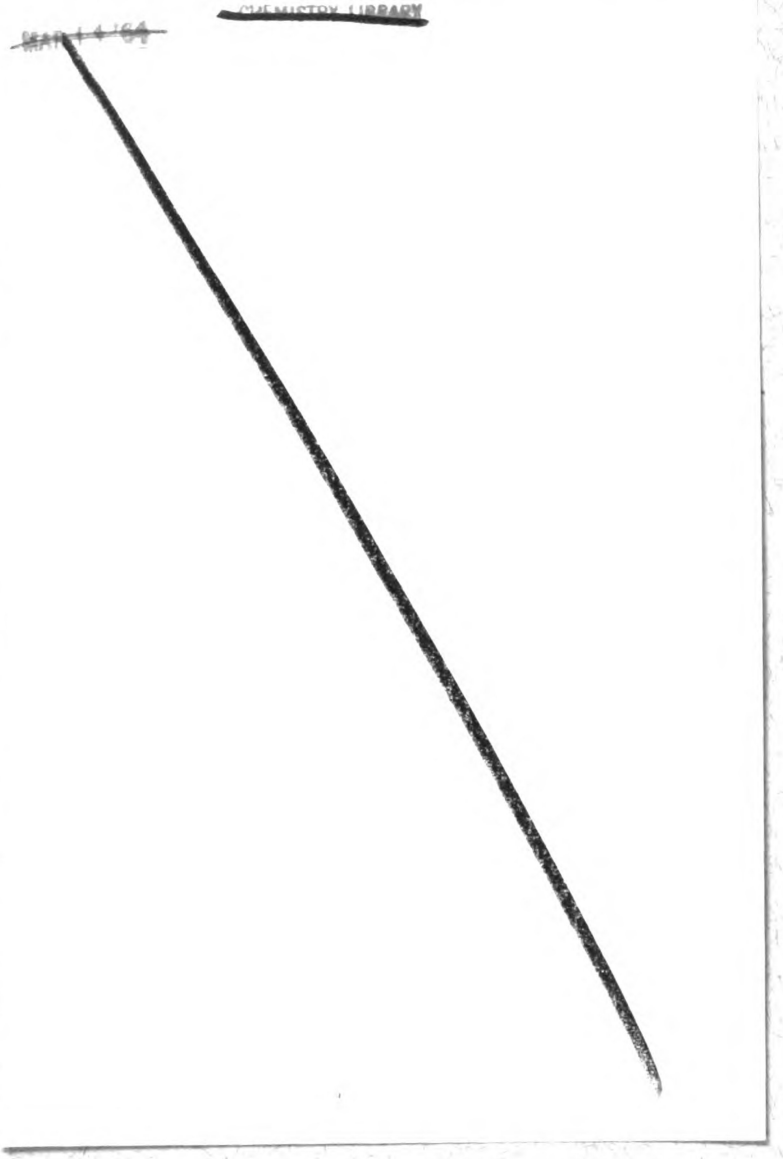

THE STEREOCHEMISTRY OF THE FORMATION OF AMINOTETRAZOLES FROM NITRILES

By

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AN ABSTRACT

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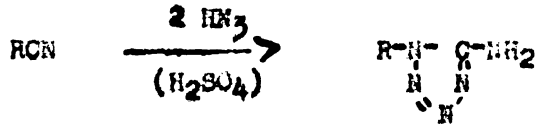
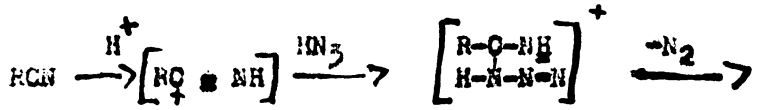
THE STEREOCHEMISTRY OF THE FORMATION OF AMINOTETRAZOLES FROM NITRILES

The 1-alkyl-5-aminotetrazoles may be formed from a number of different starting materials. Of the reactions employed, only one involves a rearrangement and a change in the position of attachment of a substituent group. This is the reaction between alkyl and aryl cyanides and hydrazoic acid in the presence of sulfuric acid.



A mechanism for this reaction has been suggested by Herbst, Roberts and Harvill, as follows:



The migration of the substituent group involves a typical 1,2 shift similar to that postulated for other common rearrangements involving adjacent carbon and nitrogen atoms such as the Beckmann, Curtius, Hofmann, Lossen and Schmidt reactions. If the above picture is the correct one, it should be possible to obtain an optically active tetrazole by starting with an optically active nitrile. The example chosen was the conversion of optically active α-ethylcapronitrile to 1-(3'-heptyl)-5-aminotetrazole.

The resolution of α-ethylcaproic acid was accomplished by repeated crystallization of its quinine salt from 50 % acetone. The (-)-α-ethylcaproic acid thus obtained was converted to its chloride by treatment with thionyl chloride. The crude chloride was distilled only once and used immediately to prepare the amide. The crude amide in turn was dehydrated to the nitrile by means of thionyl chloride without isolation or purification. The levorotatory nitrile, on treatment with sulfuric acid and a solution of hydrazoic acid in benzene, yielded dextrorotatory 1(3'-heptyl)-5-aminotetrazole. This tetrazole derivative has not previously been prepared in optically active form, and no method for resolution of the inactive compound is available. Consequently, it is not possible at present to show conclusively that no racemization took place during this rearrangement. However, the optical activity of the product obtained supports the mechanism suggested by Herbst, Roberts and Harvill. Considerable evidence has been presented to show that the related arrangements mentioned above proceed with retention of configuration as well as asymmetry.

On the basis of this evidence, it seems quite probable that both asymmetry and configuration are also retained in the formation of optically active 1-alkyl-5-aminotetrazoles, though rigid proof is impossible in the absence of an independent synthesis of the optically active product.