SUBSTITUTED PHENYL TETRAZOLES:

ALKOXY-NITROPHENYL TETRAZOLES AND ALKOXY-AMINOPHENYL TETRAZOLES

By

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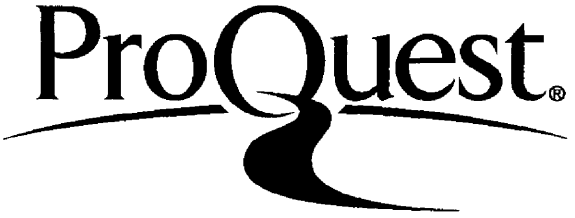
A THESIS

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

DOCTOR OF PHILOSOPHY

Department of Chemistry

1951



ACKNOWLEDGMENT

The writer wishes to express her sincere appreciation to Dr. Robert M. Herbst for his most helpful guidance and suggestions during the performance of this work. She is also indebted to Parke, Davis and Company for the fellowship given to her during the year 1950-1951.

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INTRODUCTION

INTRODUCTION

Although tetrazole itself does not appear to be characterized by any pronounced pharmacological action, the introduction of substituents into the 1 and 5 positions of the ring structure imparts definite and in many instances very profound actions to the resulting compounds. As outlined by Gross and Featherstone (1,2,3,4,5) as the result of a comprehensive study of 130 tetrazole derivatives, the pharmacological actions of these compounds generally involve the central nervous system. The substances exhibit stimulatory or depressant actions as well as varying degrees of mixed stimulatory and depressant action.

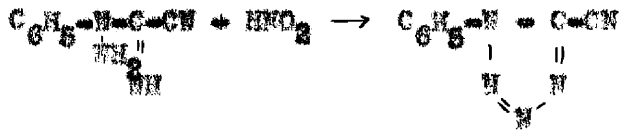
Herbst and co-workers (6) have synthesized a series of nitro- and aminophenyl tetrazole derivatives. It was interesting to observe that the introduction of a m-aminophenyl group at either the 1 or 5 position of the tetrazole nucleus resulted in compounds having primarily depressant action. They also synthesized several 1-methoxyphenyl-5-alkyl-tetrazoles (7). The presence of a p-methoxyphenyl group caused a similar depressant effect (7).

It is the purpose of this investigation to expand the knowledge of the relationship between chemical constitution and pharmacological properties in the tetrazole series. For this purpose, it appeared to be desirable to study the preparation of a series of substituted phenyl alkyl tetrazoles in which both an alkoxy and an amino group were included as substituents in different positions on the phenyl ring.

HISTORICAL.

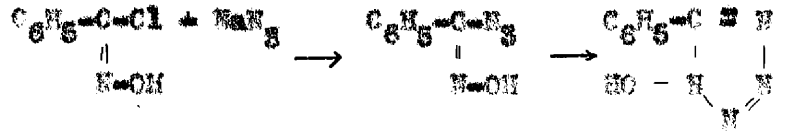
HISTORICAL

The first tetrazole was prepared in 1885 by the Swedish chemist J. A. Bladin (8) who observed that the action of nitrous acid on dicyanophenylhydrazine led to the formation of a compound $C_8H_5N_5$ to which he ascribed the formula $C_6H_5(CN)(CN_4)$. Hydrolysis, followed by decarboxylation, produced a compound having the formula $C_7H_6N_4$; the unit, $C_6H_5(CN_4)$, remained intact throughout the transformation (9). Bladin (10) proposed the name tetrazole for the new ring structure.

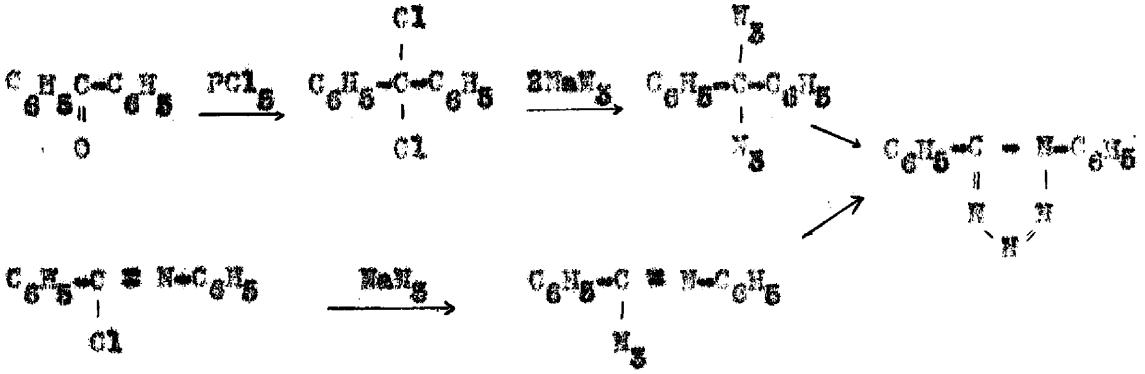


In 1892, Bladin (11) succeeded in preparing tetrazole itself by the following series of reactions.

Forster in 1900 (12) synthesized 1-hydroxy-5-phenyltetrazole by interaction of benzohydroxamyl chloride and sodium azide.

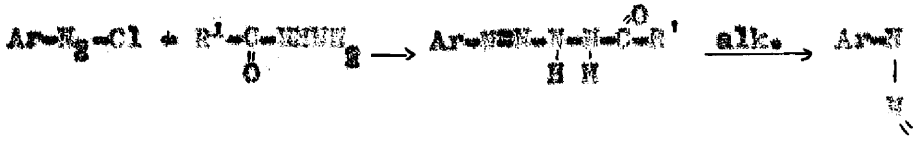


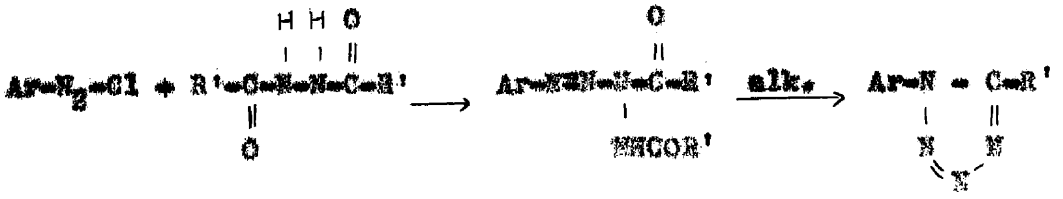
At about the same time, Schroeter (13,14) succeeded in converting benzophenone dichloride into 1,5-diphenyltetrazole by heating the former with silver azide or sodium azide. The constitution of 1,5-diphenyltetrazole was confirmed by the synthesis of this compound from N-phenyl benzimidyl chloride and sodium azide (14).



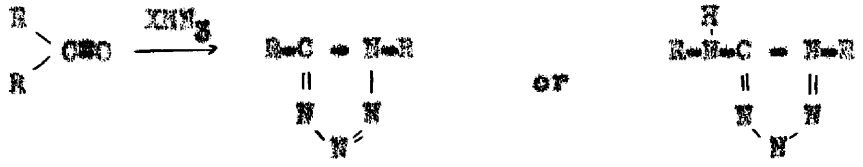
Schroeter (15) also examined the behavior of pivalophenone, an aromatic aliphatic ketone, in order to discover whether the aryl or the alkyl group migrated during the reaction. The formation of 1-t-butyl-5-phenyltetrazole indicated that the t-butyl group had migrated.

Another interesting synthesis of 1,5 disubstituted tetrazoles involving the condensation of aromatic diazonium salts with acyl hydrazines was described by Dimroth and de Montmollin (16). An initial condensation of the reactants to form diacylhydrazides was followed by conversion of the latter into tetrazole derivatives by treatment with aqueous alkali. Both monoacyl hydrazines and diacylhydrazines were used.



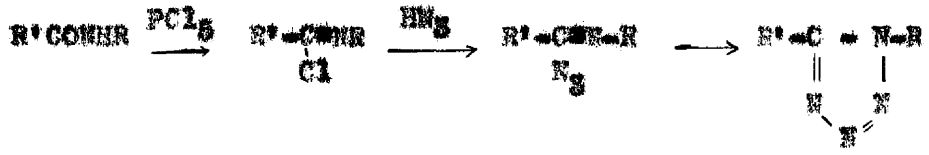


Schmidt in 1924 (17) described an apparently simple method for the conversion of ketones into 1,5 disubstituted tetrazoles. With one equivalent of hydrazoic acid, the product was an amide. Two or more equivalents of hydrazoic acid led to the formation of tetrazoles along with amides and some other products.



The mechanism offered by Schmidt to explain the reaction of hydrazoic acid in the presence of acid catalysts assumed the formation of an imine radical (>NH) which subsequently reacted with the ketone to give an oxime. The tetrazole formation was explained by the interaction of a second mole of hydrazoic acid with the oxime or some other intermediate formed by rearrangement of the oxime. Spielman and Austin (18), however, criticised Schmidt's mechanism and concluded that neither the imine radical nor the oxime was involved in the reaction between benzil and hydrazoic acid. Later, Smith (19) developed a more acceptable interpretation and discussed a carbonium ion mechanism for the formation of tetrazoles in the Schmidt reaction.

In 1941, von Braun and Rudolph (20) improved Schroeter's procedure (14) by treating the imide chloride with hydrazoic acid in benzene or chloroform solution. These investigators found that many imide chlorides which would not react with sodium azide yielded tetrazole derivatives if hydrazoic acid solution was used. Thus nitro substituted aromatic imide chlorides which were stable toward sodium azide could be converted into tetrazoles by this technique. Starting from N-alkyl or N-aryl benzamides, they succeeded in preparing a series of 1,5 diaryl- and 1-alkyl-5-aryltetrazoles by successive reaction with phosphorus pentachloride and hydrazoic acid.



The foregoing sequence of reactions was applied by von Braun and Rudolph (20) only to imide chlorides in which R' was aromatic and R was either aliphatic or aromatic. The restriction to imide chlorides derived from benzamides was explained by Herbst and co-workers (21) to be based on earlier work by von Braun and his co-workers (22,23,24) in which it was shown that imide chlorides of aliphatic amides of the type $R'CH_2-\underset{\underset{NR}{|}}{C}-Cl$, where R' was either H or an aliphatic group, were characterized by such reactivity that they could not be isolated.

In 1950, Herbst and co-workers (21) synthesized a group of twenty-six 1,5 disubstituted tetrazoles and demonstrated that the preparation of tetrazoles from N-substituted amides by conversion into imide chlorides and interaction of the latter with hydrazoic acid was not

limited to N-substituted benzamides as indicated by von Braun and Rudolph (20) but could be applied successfully to a great variety of substituted amides including completely aliphatic types. The stability of the imide chlorides was such that they could be prepared successfully in benzene solution. They showed that even with thermolabile imide chlorides, good results were obtainable when all procedures that involved warming prior to treatment with hydrazoic acid were avoided in so far as possible.

Recently, Herbst and co-workers (6) succeeded in extending von Braun's procedure to the preparation of a variety of nitrophenyltetrazoles from both N-alkyl nitrobenzamides and N-acyl nitroanilines. They converted the nitrophenyltetrazoles into the corresponding aminophenyltetrazoles by catalytic hydrogenation.

As a result of their investigations, Cross and Featherstone (1,2, 3,4,5) have drawn certain conclusions regarding the relationship between chemical structure and pharmacological action of the tetrazole derivatives. In a series of 1,5 disubstituted tetrazoles in which the substituents were hydrocarbon radicals, they concluded that central nervous stimulation was favored by a cycloaliphatic group in the 1 position or by increasing the size of a simple alkyl group in the same position. On the other hand, depressant action was favored by increasing the size of an alkyl group substituted in position 5. The introduction of a functional group such as an amino group as a substituent seemed to be a determining factor. When the amino group was attached directly to the tetrazole ring in position 5, compounds with purely stimulatory action resulted. When one or two carbon atoms were interposed

between the amino group and the tetrazole ring, still in position 5, a mixed action resulted, the degree of stimulation or depression being modified by the nature of other substituents in position 1. Interposing a cyclic system between the amino group and the tetrazole ring endowed the resulting compounds with a depressant action. The action was more purely depressant when the aminophenyl group was shifted from position 5 to position 1. The m-aminophenyltetrazoles appeared to be moderately effective as sedative and analgesic agents.

Schmeler, Wang, Featherstone and Cross (25) also investigated the absorption spectra of a series of thirty-one tetrazole derivatives and their possible significance in relation to the pharamacological action of these compounds. They found that the majority of the curves presented two maxima, one toward the higher wave lengths, designated as M_A, and one toward the lower wave lengths, designated as M_B. They concluded that, without exception, substances possessing a potent and purely stimulating action showed little or no absorption in the entire ultra violet region encompassed by the range of the Beckmann spectrophotometer. Also, and without exception, substances possessing a potent, purely depressant action exhibited a marked B peak. The height of the B peak (λ=222-226mμ) was roughly proportional to the potency. As any appreciable absorption in the ultra violet occurred only when substituents capable of appreciable "resonance conjugation" with the tetrazole system were present, they tentatively concluded that for the tetrazole derivatives, the substitution of groups at position 1 or 5 on the tetrazole nucleus capable of a high degree of "resonance conjugation" would be conducive to the production of a material possessing central depressant properties. The

conclusions of these authors are open to the criticism that a limited number of examples were selected from a large group of examples whose pharmacological actions had been studied. Apparently care was exercised not to include examples in which a high degree of "resonance conjugation" could be anticipated when the pharmacological action was primarily stimulatory.

DISCUSSION

DISCUSSION

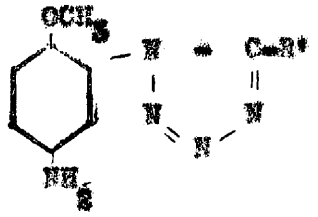
In this work, a series of alkoxy-aminophenyltetrazoles has been synthesized for the purpose of determining the effect of varying the point of attachment of both the alkoxy and the amino groups to the phenyl nucleus upon the pharmacological action of the compounds. The specific compounds chosen can be classified in five groups. The selection of the groups was based upon the pharmacological action of known aminophenyl- and methoxyphenyltetrazole derivatives and the availability or the ease of preparation of the requisite intermediates.

Group I 1-(3'-Amino-4'-methoxyphenyl)-5-alkyltetrazoles

R' = CH_3, C_2H_5, C_3H_7(n), C_3H_7(iso).

The compounds in group I contained an amino group *meta* and a methoxy group *para* to the tetrazole ring. As Cross and Featherstone (6,7) have shown that the substitution of a single m-aminophenyl or a single p-methoxyphenyl group on the tetrazole ring caused the resulting compounds to be central nervous depressants, it was thought that the introduction of both the amino and the methoxy groups into the same phenyl nucleus might lead to an additive effect. The alkyl group substituted in the 5 position was varied from methyl to ethyl, propyl and isopropyl in order to study the effect of the length and the branching of the chain.

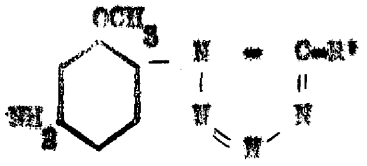
Group II 1-(2'-Methoxy-5'-aminophenyl)-5-alkyltetrazoles



R' = CH_3, C_2H_5, C_3H_7(n), C_3H_7(iso).

The only difference between compounds in group II and those in group I was the displacement of the methoxy group from the para position to one of the ortho positions.

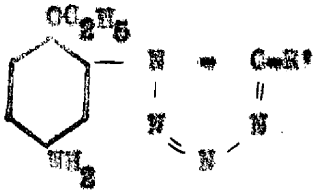
Group III 1-(2'-Methoxy-4'-aminophenyl)-5-alkyltetrazoles



R' = CH_3, C_2H_5, C_3H_7(n), C_3H_7(iso).

The compounds in group III contained an amino group para to the tetrazole ring as compared with those in groups I and II which contained an amino group substituted meta to the tetrazole ring. The methoxy group remained in the ortho position as in Group II.

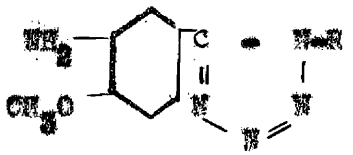
Group IV 1-(2'-Ethoxy-5'-aminophenyl)-5-alkyltetrazoles



R' = CH_3, C_2H_5 .

The compounds in group IV had the same points of attachment of the substituted amino and alkoxy groups as the compounds in group II with the exception that an ethoxy group was introduced instead of a methoxy group.

Group V 1-Alkyl-5-(3'-amino-4'-methoxyphenyl) tetrazoles



R = CH_3, C_2H_5 .

For compounds in group V, the substituents at the 1 and 5 positions of the tetrazole ring were reversed as compared with those in group I.

Several methods for the synthesis of the 1,5 disubstituted tetrazoles have been reviewed by Benson (26). Among them the von Braun, the Dimroth and the Schmidt procedure appeared to be the most promising. The von Braun procedure (20) has been well established as a method for the preparation of 1,5 disubstituted tetrazoles (6,21). It involves the interaction of N-substituted amides with phosphorus pentachloride and treatment of the imide chlorides so formed with hydrazoic acid. The steps involved in the use of this procedure for the preparation of the alkoxy-aminophenyltetrazoles described in this work are outlined in Figure 1. The Dimroth procedure (16) which involves coupling of diazotized aromatic amines with mono- and diacyl hydrazines and cyclization of the diacylhydrazides so formed in aqueous alkaline solution has not been extensively studied. We have investigated this method in order

to determine its limitations. The reactions involved are outlined in Figure 2. The Schmidt procedure (17) which involves simply the interaction of ketones with hydrazoic acid in the presence of concentrated sulfuric acid is complicated by side reactions which are not obvious at first glance. It has the disadvantage that substituted amides are formed as the major products accompanied by relatively small amounts of tetrazoles (21). Furthermore, in addition to 1,5 dialkyl or diaryl tetrazoles, amino tetrazoles may be formed (17,18) and when unsymmetrical ketones are employed, it becomes necessary to determine which group migrates in the simplest instance, or to separate mixtures of isomeric products if the migration of both groups is involved. For these reasons the Schmidt procedure was not considered as a satisfactory synthetic method for our purposes.

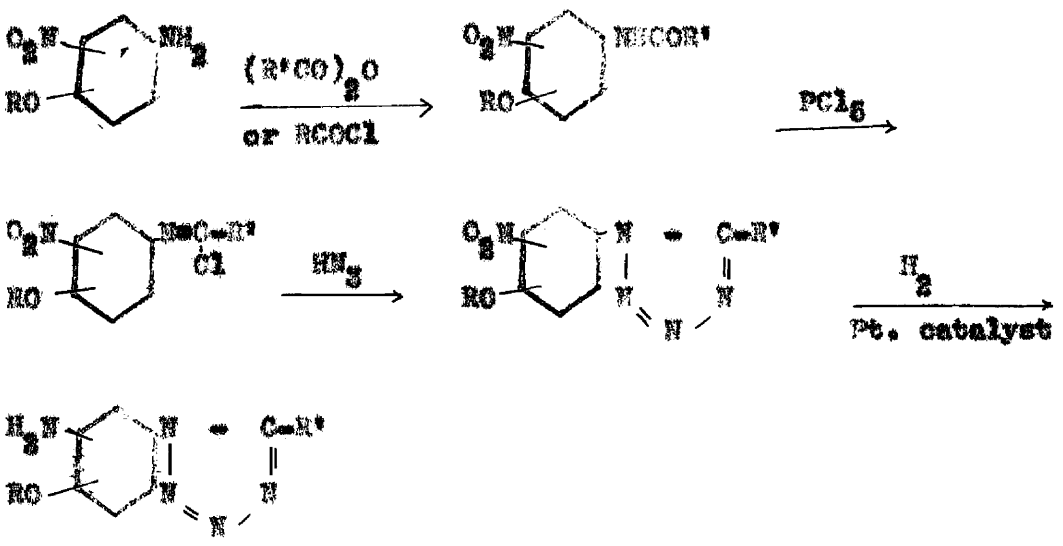
The same alkoxy-nitroanilines could be used as starting materials in both the von Braun and the Dimroth procedures. Of these, 2-amino-4-nitroanisole and 2-amino-3-nitroanisole, which would lead to the tetrazole derivatives of Groups II and III, respectively, were available from commercial sources. The tetrazoles in group I and IV, required the preparation of 2-nitro-4-amino-anisole and 2-amino-4-nitro-phenetole, respectively, or their acyl derivatives.

Several procedures were available for the preparation of the required nitroaminoanisoles or phenetoles. They may be considered in two groups (a) those involving nitrations of anisidines or phenetidines (27,28,29, 30,31,32,33) and (b) those involving partial reduction of dinitroanisoles or phenetoles (34,35,36).

FIGURE 1

von Braun Tetrazole Synthesis

a.



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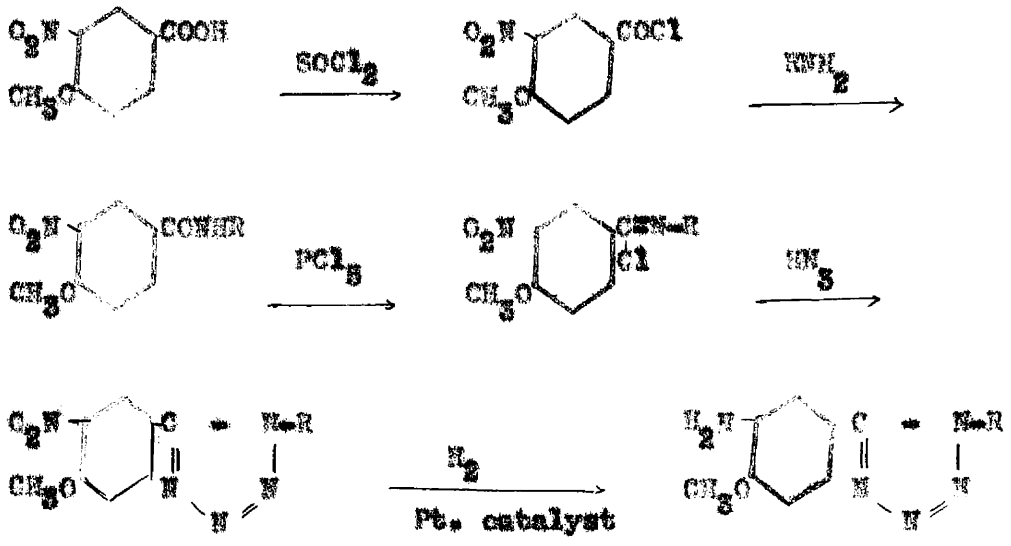
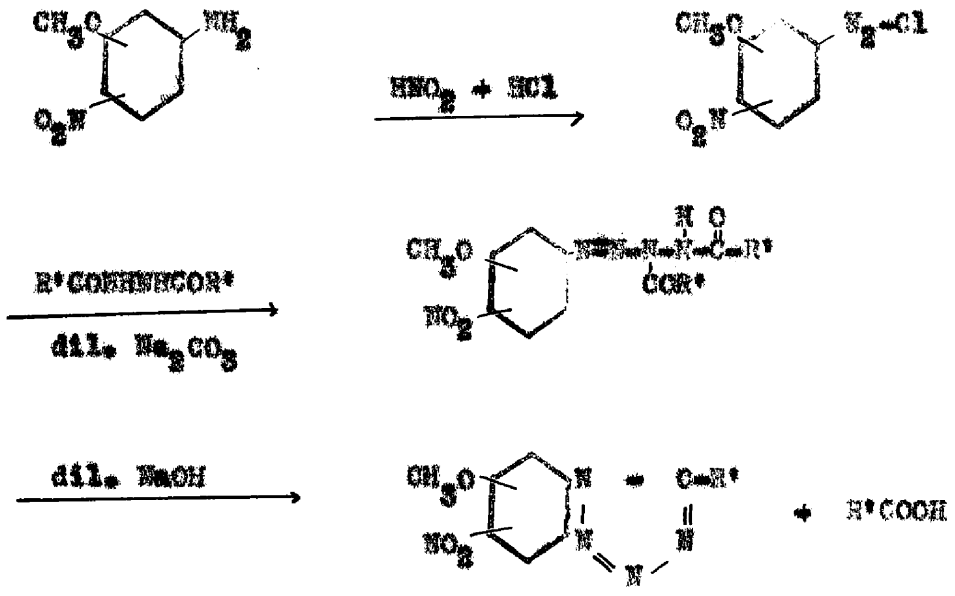


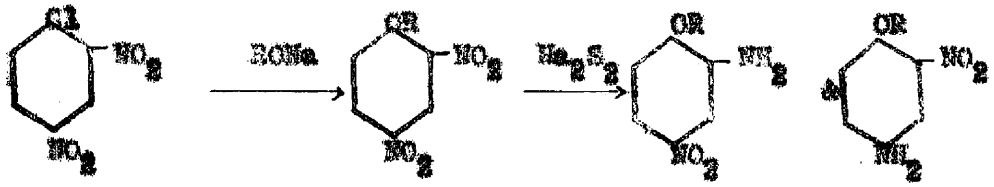
FIGURE 2

Dimroth Tetrazole Synthesis



(a)

(b)



Although in both instances mixtures of isomers may be formed, procedure (a) was selected for the preparation of the requisite intermediates because it was shorter and did not involve as many steps.

Since the directive influences of the alkoxy and amino groups are both ortho-para and are opposed in p-anisidine and o-phenetidine, it was essential to select conditions for the nitration of these compounds under which the directive influence of the alkoxy group would predominate. The use of concentrated sulfuric acid as a solvent for the nitration of p-anisidine alters the directive influence of the amino group in large measure from ortho-para to meta due apparently to the formation of an ammonium ion. Under such conditions the orienting effects of the alkoxy group and the amino group would be directed to the same position and the desired 2-nitro-4-amino-alkoxybenzene would be the major product. This technique was employed for the synthesis of the 2-nitro-4-aminoanisole. To avoid the formation of isomers, it is essential to regulate the conditions of nitration carefully. The best yields of 2-nitro-4-aminoanisole were obtained when p-anisidine was dissolved in concentrated sulfuric

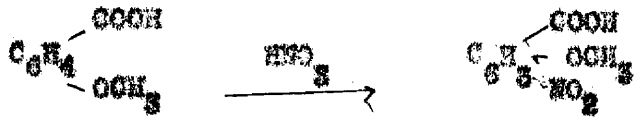
acid at 0° C., and treated at the same temperature with mixed acid diluted with a small amount of water. Under these conditions the desired isomer was obtained in 60 per cent yield. Acylation with acetic, propionic or n-butyric anhydride or with isobutyryl chloride led to the substituted anilides required for tetrazole synthesis (Table II).

Since the strength of the directive influence of the amino group may also be reduced by acylation, protection of the amino group in this manner prior to nitration was also investigated. The basicity of the acylated nitrogen would still permit salt formation with concentrated sulfuric acid so that the directive influence of the alkoxy group might be expected to predominate under these conditions as well. This sequence of reactions was chosen for the nitration of o-phenetidine because the overall yields were better in this instance. o-Phenetidine was acylated by treatment with acetic or propionic anhydride and the nitration was carried out at 0° C., in a mixture of concentrated sulfuric acid and acetic acid by the addition of mixed acid diluted with a small amount of water.

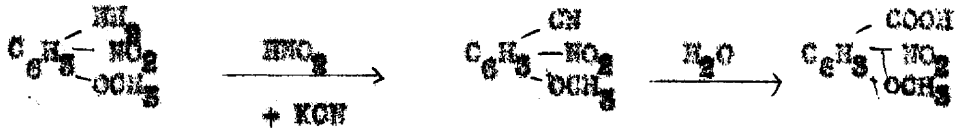
The tetrazoles of group V required N-substituted amides of nitroanisic acid as intermediates. Several approaches for the synthesis of nitroanisic acids would be (a) the nitration of the corresponding alkoxy benzoic acid (37,38,39,40,41,42), (b) the conversion of an amino-nitroanisole by the Sandmeyer reaction to the corresponding cyano compound followed by hydrolysis (43,44,45), and (c) the potassium permanganate oxidation of alkyl or chloroalkyl nitroanisoles (46,47,48). The second procedure was of some interest because the nitroanisidines which were

the starting material for the synthesis of the 1-aryl-5-alkyltetrazoles, could be converted into the nitroanisic acids which would serve as starting materials for the synthesis of the isomeric 1-alkyl-5-aryltetrazoles.

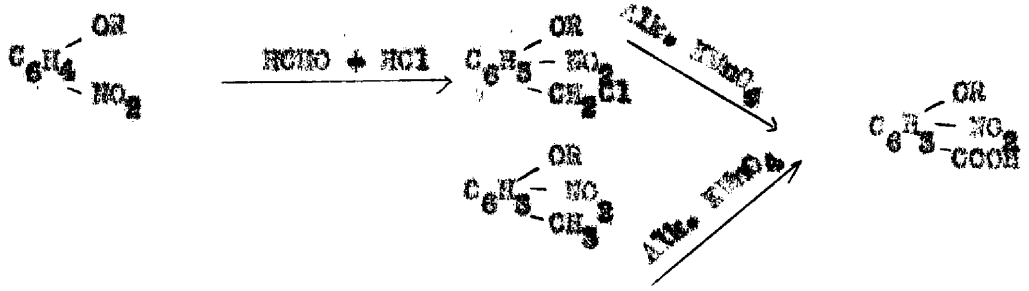
(a)



(b)



(c)



The nitration of anisic acid was selected as the simplest procedure and was accomplished by heating anisic acid with concentrated nitric acid at 70° C. Two isomeric nitrated anisic acids are possible, the 3-nitro-4-methoxybenzoic acid, m.p. 195°-196° C. (49) and the 3-nitro-4-methoxybenzoic acid, m.p. 195°-196° C. (49). Although it was expected that nitration of anisic acid would lead almost exclusively to the 3-nitro-4-methoxybenzoic acid, it was necessary to establish the identity of the product. This was accomplished by preparation of the anilide and of the methyl ester, both of which had been previously described in the case of 3-nitro-4-methoxybenzoic acid (49). The substituted amides

required as intermediates for tetrazole synthesis were prepared by treatment of the acid with thionyl chloride to form the acid chloride, and treatment of the latter with methylamine or ethylamine.

For the preparation of tetrazoles by the Dimroth procedure (16), a variety of diacylhydrazines was required in addition to the substituted aromatic amines. Stolle (50) had recommended the treatment of hydrazine hydrate with three moles of acetic anhydride and heating of the reaction mixture for the preparation of diacetyl hydrazine. Autenrieth and Spiess (51) prepared diacyl hydrazines by interaction of one mole of acid anhydride and one mole of hydrazine hydrate as 50 per cent aqueous solution at 0° C. Diacyl hydrazines were prepared by interaction of 85 per cent hydrazine hydrate solution with acetic anhydride, propionic anhydride, and n-butyric anhydride with minor modifications of the procedures recommended by Stolle and Autenrieth and Spiess.

The Dimroth procedure for tetrazole synthesis (Figure 2) was studied to determine the extent to which it could be applied and was used to provide an independent synthesis for a limited number of compounds. Although it could be applied to the preparation of 1-aryltetrazoles only, the procedure was attractive since it represented one of the few sequences of reactions by means of which tetrazole derivatives could be prepared without the use of hydrazoic acid or azides.

As Dimroth used only mono and diacetylhydrazine and mono-benzoylhydrazine for the preparation of 1-aryl-5-methyl- and 1-aryl-5-phenyltetrazoles, it seemed interesting to study whether this procedure could be extended to the synthesis of other 1-aryl-5-alkyltetrazoles. This

was shown to be possible and several 1-aryl-5-ethyl-, 5-n-propyl- and 5-i-propyltetrazoles were prepared by starting from dipropionyl, di-n-butyryl and di-i-butyryl hydrazine respectively. A series of diazotised nitroanilines and methoxy-nitroanilines including p-nitroaniline, m-nitroaniline, 2-nitro-4-aminoanisole, 2-amino-4-nitroanisole and 2-amino-5-nitroanisole, were coupled with diacetyl hydrazine and the products cyclised by treatment with aqueous sodium hydroxide. Furthermore, diazotised m-nitroaniline was coupled with dipropionyl and di-n-butyryl hydrazine and diazotised 2-amino-5-nitroanisole was coupled with di-propionyl, di-n-butyryl and di-i-butyryl hydrazine. In each case, the resulting diazohydrazides were cyclised to the tetrazole derivatives by treatment with dilute sodium hydroxide solution.

As di-n-butyryl and di-isobutyryl hydrazine are only slightly soluble in water, the coupling could not be carried out in dilute sodium carbonate solution as in the case of diacetyl and dipropionyl hydrazine. The di-n-butyryl or the di-i-butyryl hydrazine was, therefore, first suspended in dilute sodium carbonate solution buffered with sodium acetate and sodium hydroxide solution was added dropwise until the di-acyl hydrazine became soluble. In the resulting solution coupling took place very smoothly with diazotised aromatic amines with the formation of diazohydrazides.

The diazohydrazides were then cyclised to form the tetrazole derivatives by treatment with dilute sodium hydroxide solution. However, in the preparation of 1-(2'-methoxy-4'-nitrophenyl)-5-ethyl-, 5-n-propyl-, and 5-i-propyltetrazole, oily or semi-solid products separated after the treatment with sodium hydroxide solution. These products could be

caused to solidify completely by heating the reaction mixture to 60° C. In general, it was found that heating accelerated the cyclization and caused the reaction to be more complete.

The 1-nitrophenyl- and 1-alkoxy-nitrophenyl-5-alkyltetrazoles prepared by the Dimroth procedure are listed in Table I where the yields obtained by the von Braun procedure for the same compounds are included for comparison. In each instance the yield by the von Braun procedure was much better.

The von Braun procedure was applied to the synthesis of all tetrazoles described in this work. The starting points for the synthesis were either alkoxy-nitroanilines or nitro-methoxybenzoic acids. The alkoxy-nitroanilines were acylated by treatment with suitable acid anhydrides or acid chlorides, and the anilides so formed were treated successively with phosphorus pentachloride and hydrazoic acid to convert them into the desired alkoxy-nitrophenyltetrazoles. Catalytic hydrogenation was used to reduce the nitro groups to amino groups.

Starting with nitro-methoxybenzoic acids, the N-substituted benzamides were prepared by conversion of the acids to the acid chlorides by treatment with thionyl chloride, followed by interaction of the acid chlorides with suitable primary amines. Tetrazole formation was carried out in the same way as described for the anilides. The reactions involved in both processes are outlined in Figure 1.

In the preparation of alkoxy-nitrophenyltetrazoles, a five to ten per cent excess of phosphorus pentachloride was added to a benzene suspension of the substituted amide to convert the latter into the imide chloride. This could usually be done by stirring a mixture of the

TABLE I

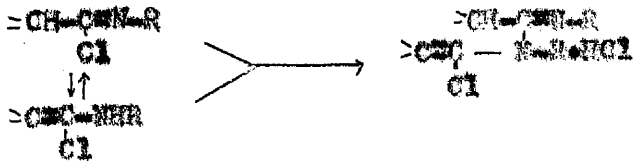
1-NITROPHENYL- AND 1-ALKOXY-NITROPHENYL-5-ALKYLTETRAZOLES

R	R'	M.P.* °C. (Corr.)		Yield %		Ref.
		Von Braun	Dimroth	Von Braun	Dimroth	
4-NO_2-C_6H_4	CH_3	132-133.5	132-133	66	40	6,16
3-NO_2-C_6H_4	CH_3	150-151	149.5-150	60	40	6
3-NO_2-C_6H_4	C_2H_5	122-123.5	122-123	79	35	6
3-NO_2-C_6H_4	n-C_3H_7	55-56*	53-54	47*	28	6
3-NO_2-4-OCH_3-C_6H_3	CH_3	149.5-150.5	149.5-150.5	65	28	
2-OCH_3-5-NO_2-C_6H_3	CH_3	174-175.5	175.5-176.5	70	20	
2-OCH_3-4-NO_2-C_6H_3	CH_3	140.5-141.5	140-141	78	45	
2-OCH_3-4-NO_2-C_6H_3	C_2H_5	116-116.5	114-116**	78	63	
2-OCH_3-4-NO_2-C_6H_3	n-C_3H_7	118-119	118.5-119.5	72	33	
2-OCH_3-4-NO_2-C_6H_3	i-C_3H_7	167-168	167.5-169	79	35	

* See Reference (21)
** Recrystallized from benzene

reactants suspended in benzene at room temperature. But in the case of N-acetyl and N-propionyl 3-nitro-4-methoxyaniline, and N-methyl and N-ethyl 3-nitro-4-methoxy-benzamide, no hydrogen chloride was evolved on treatment with phosphorus pentachloride under these conditions indicating that no imide chloride was formed at room temperature even after prolonged stirring. The reaction mixture was therefore warmed until hydrogen chloride evolution started. In the last two cases, boiling was required to initiate the reaction. It was unlikely that such decomposition or rearrangement of the imide chlorides took place even under the more drastic conditions required for their formation in the last examples since, even in these instances, excellent yields of the desired tetrazoles resulted on subsequent treatment with hydrazoic acid.

It has been stated by von Pechmann (52), Ley and Wolfenstein (53) and von Braun and co-workers (22,23,24,54), that most imide chlorides, $R'-C(Cl)=N-R$, excepting those derived from N-aryl aromatic amides were rather unstable and underwent thermal decomposition quite readily. For instance, imide chlorides in which R' was aromatic and R was aliphatic decomposed readily on heating with the formation of an alkyl chloride and an aromatic nitrile (52,53,54). Imide chlorides of aliphatic amides $R''CH_2-C(Cl)=N-R'$, where R'' was either hydrogen or an aliphatic group and R' was either aliphatic or aromatic, were even more unstable. The instability was conditioned chiefly by a hydrogen atom in the alpha position which could undergo a tautomeric shift to the nitrogen. Condensation of the tautomeric forms of the imide chloride led to amidine-like



condensation products (23,24,25). The change could be hindered if R was an aryl group containing a substituent in the ortho position to the nitrogen. As has been pointed out by Herbst and co-workers (21), the observations concerning the stability of imide chlorides were made during studies involving their isolation and purification by distillation techniques. They found that many imide chlorides, which according to von Braun's criteria should be unstable, could be prepared successfully in solution provided care was taken to avoid excessive heating.

It is interesting to note that the preparation of the imide chlorides from N-acetyl and N-propionyl 5-nitro-6-methoxyaniline required heating of the benzene suspension of the amide and phosphorus pentachloride to bring about reaction. These two examples exhibit structures that would according to von Braun favor tautomerism of the imide chloride since no substituents were present in the ortho positions. The good over-all yield of the tetrazoles in both of these instances indicated that the imide chloride had not suffered extensive decomposition. All of the tetrazoles prepared by the von Braun procedure are listed in Table IV. In Table I, the yields of a number of nitrophenyltetrazoles as prepared by the von Braun technique and by the Dimroth procedure are compared. It is apparent that the von Braun technique invariably gave the product in appreciably high yield.

The alkoxy-nitrophenyltetrazoles were then reduced to the amino-phenyltetrazoles by catalytic hydrogenation in the presence of platinum catalyst (6). Although Wedekind (55) succeeded in reducing

5-p-nitrophenyl-1-phenyltetrazole into its amino derivative by treatment with stannous chloride and hydrochloric acid, it still appeared more desirable to reduce the nitro group catalytically as it would give a purer product and furthermore the reduction could be stopped at the appropriate stage by observing the pressure drop during the reduction.

There was no evidence of a cleavage of the tetrazole ring during hydrogenation of the nitro compound comparable to that observed by Roblin and co-workers (66) during the reduction of 5-(p-nitrobenzenesulfonamido)-tetrazole. In most cases, the reduction proceeded smoothly to the amino derivatives as stated by Herbst and co-workers (6) but in a few instances, intensely colored by-products which might represent intermediate stages such as azo compounds were also formed. The formation of colored by-products appeared to be influenced by the speed at which reduction took place since it could usually be avoided by increasing slightly the amount of platinum catalyst. When they were present, these by-products could be removed by the conversion of the amine into its hydrochloride and liberation of the original amine after the separation and purification of the hydrochloride.

All the alkoxy-nitrophenyltetrazoles and the corresponding alkoxy-aminophenyltetrazoles as well as their acetyl derivatives and hydrochlorides are new compounds that have not been described in the literature.

Both the acetyl derivatives and the hydrochlorides were prepared from the alkoxy-aminophenyltetrazoles. The acetyl derivatives were used for the characterization of the aminophenyltetrazoles and the

hydrochlorides were of special interest as water-soluble salts of the amines. Some of the hydrochlorides, however, were hydrolyzed extensively in aqueous solution indicating that the corresponding amines were only weak bases.

In addition a group of four 1-nitrophenyl-5-alkyltetrazoles and the corresponding 1-aminophenyl-5-alkyltetrazoles were prepared. These included 1-m-nitrophenyl-5-methyl- and 5-ethyltetrazole and 1-p-nitrophenyl-5-methyl- and 5-ethyltetrazole and the corresponding amino compounds. Of these, only the 1-p-nitrophenyl- and the 1-p-aminophenyl-5-ethyltetrazole had not been previously described. These compounds were prepared in order to provide a basis for comparison in the pharmacological tests to which the group was subjected, and to permit a comparison of the Dimroth and the von Braun procedures with compounds whose identity had been previously established.

Most of the alkoxy-aminophenyltetrazoles have been submitted for screening of their pharmacological actions. We are indebted to the Research Laboratories of Parke, Davis and Company for preliminary reports which indicate that the compounds generally exhibit depressant actions upon the central nervous system. All of the compounds tested showed a mild sedative action, an anticonvulsant action as measured by their antagonism toward central nervous stimulants such as pentamethylenetetrazole (Metrazol), and moderate analgetic action. The results are not sufficiently complete at the present time to permit conclusions concerning the effect of structure upon pharmacological activity.

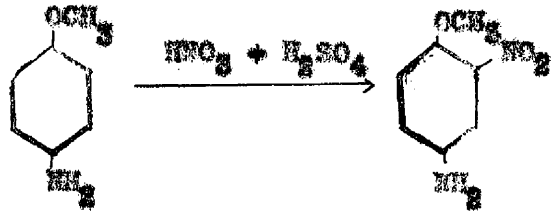
In conjunction with the pharmacological tests, experiments were carried out to detect other possible effects of the compounds. They were found to be devoid of bactericidal, fungicidal or amoebicidal actions.

EXPERIMENTAL

EXPERIMENTAL

PREPARATION OF INTERMEDIATES*

2-Nitro-4-aminoanisole



This compound was prepared by the nitration of p-anisidine. As the only reference in the literature for the preparation of this compound started from acetyl p-anisidine (27), the procedure employed here for its preparation by nitration of p-anisidine will be given.

One hundred and twenty-three grams (1 mole) of p-anisidine was added in small portions with stirring into 400 ml. of concentrated sulfuric acid kept at 0° C. A cooled mixture of 130 g. (1.14 moles) of nitric acid (sp. gr. 1.38) and 250 ml. of concentrated sulfuric acid was then added drop by drop at the same temperature. The stirring was continued for an hour after the addition of the mixed acid was complete. Upon pouring the reaction mixture onto 2500 g. of ice, a voluminous reddish yellow precipitate of amine sulfate separated. The amine sulfate was filtered and washed with water. The solid was suspended in water and treated with an excess of dilute aqueous ammonia to convert it into

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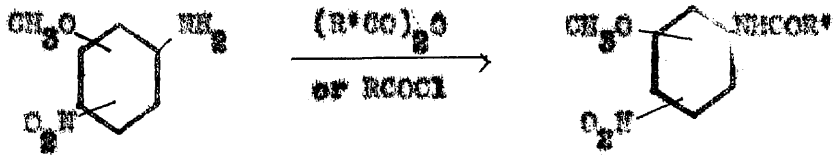
* Nitrogen analyses were carried out by the micro-Dumas method on all new compounds described in the experimental part of this thesis. About half of the analysis were carried out by the writer; the balance were done by the Micro-Tech Laboratories of Skokie, Illinois.

the amine. The amine separated as red crystals and, after chilling the suspension, was filtered by suction, washed with water and dissolved in ether. The ether solution was dried over anhydrous sodium sulfate and filtered to remove any other insoluble impurities. The solvent was then removed by evaporation and the residue recrystallized from toluene from which it separated as red prisms, m.p. 55-57° C. (corr.) (27,28,29, 30,35). An additional small amount of product was recovered by diluting the toluene filtrate with petroleum ether. The yield was 100 g. corresponding to 60 per cent of the theoretical.

N-Acyl amino-nitroanisoles



The N-acetyl, N-propionyl, N-n-butyryl and N-isobutyryl amino-nitroanisoles were prepared by treatment of the appropriate primary amines with acetic anhydride, propionic anhydride, n-butyric anhydride and isobutyryl chloride, respectively.

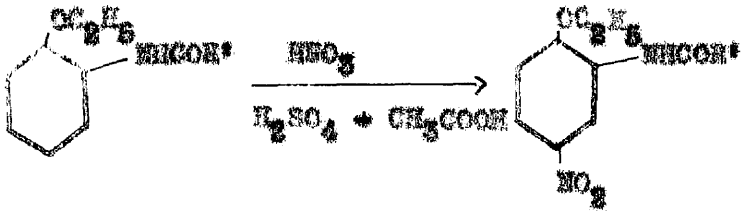
When acid anhydride was used, one mole of the amino-nitroanisole was treated with one and a half moles of acid anhydride. Most of the reactions were spontaneous but in several instances, particularly when n-butyric anhydride was used, the reaction mixture was warmed carefully to start the reaction. The solution was then cooled, diluted with water and the solid filtered. The precipitate, after washing successively with water, dilute sodium carbonate solution and water again to remove

any adhering acid or alkali, was recrystallized from the solvent indicated in Table II.

The N-isobutyryl derivatives were prepared by adding dropwise 50 g. of isobutyryl chloride (0.47 mole) with stirring and cooling to a benzene solution of 56 g. (0.33 mole) of the amino-nitroanisole and 31 g. of dried pyridine (0.39 mole). Stirring was continued for half an hour after complete addition of isobutyryl chloride, after which the reaction mixture was diluted with water to dissolve the pyridine hydrochloride. Some of the product separated as a solid at this stage and was filtered off and combined with the solid residue obtained by evaporation of benzene layer. The crude product was purified by recrystallization from the solvent indicated in Table II.

The yields, physical constants and analytical data for all the new N-acyl amino-nitroanisoles are summarized in Table II and Table III.

N-Acyl 2-amino-4-nitrophenetoles



N-Acetyl 2-amino-4-nitrophenetole was prepared by the method of Verkade and co-workers (33). The preparation of N-propionyl 2-amino-4-nitrophenetole was carried out in an analogous way and is given as a typical example for the nitration of N-acyl phenetoles.

Fifty-eight grams (0.3 mole) of N-propionyl 2-aminophenetole (m.p. 53.5-55° C.), prepared from o-phenetidine and propionic anhydride,

TABLE II

N-ACYL AMINO-NITROANISOLES

RNHCOR'

R = C_6H_3 (NO_2, OCH_3)	R'	M.P. °C. (corr.)	Yield %	Crystal Form	Solvent
3-NO_2-4-OCH_3	C_2H_5	109.5-110	77	Fine needles	80% ethanol
3-NO_2-4-OCH_3	n-C_3H_7	131.5-133	71	Prisms	80% ethanol
3-NO_2-4-OCH_3	i-C_3H_7	121.5-122.5	57	Small prisms	80% ethanol
2-OCH_3-5-NO_2	C_2H_5	121.5-122.5	77	Needles	95% ethanol
2-OCH_3-5-NO_2	n-C_3H_7	119-119.5	77	Prisms	95% ethanol
2-OCH_3-5-NO_2	i-C_3H_7	137.5-138.5	65	Fine needles	99% 2-propanol
2-OCH_3-4-NO_2	C_2H_5	101-101.5	94	Coarse needles	benzene
2-OCH_3-4-NO_2	n-C_3H_7	107.5-109.5	87	Coarse needles	benzene
2-OCH_3-4-NO_2	i-C_3H_7	124.5-126	65	Fine needles	80% ethanol

TABLE III

NITROGEN ANALYSES OF N-ACYL AMINO-ANISOLES

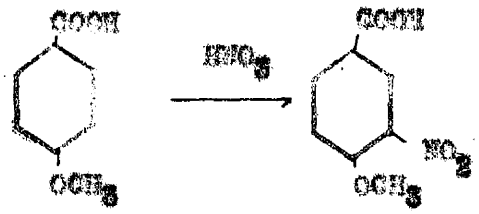
$RNHCOR'$

NH - C_6H_3 (NO_2, OCH_3)	R'	Formula	Analysis % N	
			Calculated	Found
3-NO_2-4-OCH_3	C_2H_5	$C_{10}H_{12}N_2O_4$	12.8	12.5
3-NO_2-4-OCH_3	n-C_3H_7	$C_{11}H_{14}N_2O_4$	11.8	11.8
3-NO_2-4-OCH_3	i-C_3H_7	$C_{11}H_{14}N_2O_4$	11.8	11.9
2-OCH_3-5-NO_2	C_2H_5	$C_{10}H_{12}N_2O_4$	12.8	12.4
2-OCH_3-5-NO_2	n-C_3H_7	$C_{11}H_{14}N_2O_4$	11.8	11.4
2-OCH_3-5-NO_2	i-C_3H_7	$C_{11}H_{14}N_2O_4$	11.8	12.0
2-OCH_3-4-NO_2	C_2H_5	$C_{10}H_{12}N_2O_4$	12.8	12.4
2-OCH_3-4-NO_2	n-C_3H_7	$C_{11}H_{14}N_2O_4$	11.8	11.9
2-OCH_3-4-NO_2	i-C_3H_7	$C_{11}H_{14}N_2O_4$	11.8	11.9

was added in small portions to a vigorously stirred mixture of 110 ml. of concentrated sulfuric acid and 100 ml. of glacial acid kept at 0° C. A mixture of 35 ml. of nitric acid (sp. gr. 1.40, 0.45 mole) and 50 ml. of concentrated sulfuric acid was added at the same temperature and stirring was continued for an hour after the addition was complete. The reaction mixture was then poured onto ice and the yellow precipitate which separated was filtered and washed successively with water, dilute sodium carbonate solution and water again to remove any acid or alkali present. The crude product was then recrystallised from 95 per cent alcohol from which it separated as long, fine needles. A yield of 48.1 g. of N-propionyl 2-amino-4-nitrophenetole corresponding to 67 per cent of the theoretical was obtained, m.p. 129.6-130.6° C. (corr.). Analysis. Calculated for $C_{11}H_{14}N_2O_4$: N, 11.8. Found: N, 11.8.

In order to determine the position of the entering nitro group, 3 g. of the N-propionyl 2-amino-4-nitrophenetole obtained by the above procedure was refluxed with 50 ml. of 6N hydrochloric acid until the reaction mixture became clear. The solution was then cooled and neutralised with ammonia. The precipitate which separated was filtered and recrystallised from ethyl alcohol. The resulting compound melted at 96.5-99° C., (corr.), corresponding to the known 2-amino-4-nitrophenetole (88).

3-Nitro-4-methoxybenzoic acid



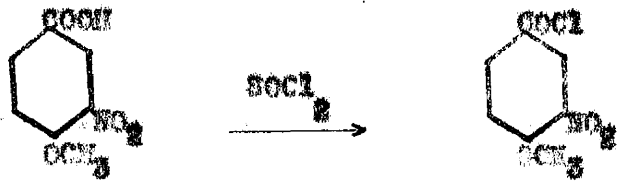
The 3-nitro-4-methoxybenzoic acid was prepared by the nitration of anisic acid (37,38,41). As no details of preparation were given in the literature, the procedure is described here.

One hundred grams of anisic acid (0.37 mole) was added in small portions to 750 ml. of vigorously stirred concentrated nitric acid (sp. gr. 1.42, 11.8 mole) in a three-necked round bottom flask equipped with a stirrer, a thermometer and a reflux condenser. The reaction mixture was warmed gradually to 70° C., during the addition of anisic acid and was kept at that temperature for half an hour after complete addition of the anisic acid after which the reaction mixture should be almost clear. The mixture was then filtered through a glass wool pad in a hot funnel to remove any insoluble material. The nitroanisic acid which separated out on cooling and subsequent dilution with water was filtered by suction. The crude product was purified by dissolving it in dilute aqueous ammonia and reprecipitating it by acidification with acetic acid. Any non-acidic impurities such as nitroanisoles and dinitroanisoles (41,57) were removed by virtue of their insolubility in aqueous ammonia. The product was recrystallised from dilute acetic acid and was obtained in a yield of 92.1 g., m.p. 193.5-194° C., (corr.), corresponding to 71 per cent of the theoretical.

As both the 2-nitro- and the 3-nitro-4-methoxybenzoic acids were reported to have the same melting point 195-196° C., (47,48), it seemed desirable to prepare several derivatives. The anilide and the methyl ester of the nitroanisic acid were therefore prepared. The anilide melted at 162.6-163.6° C., (corr.) (48) and the methyl ester at 109.5-110.5°

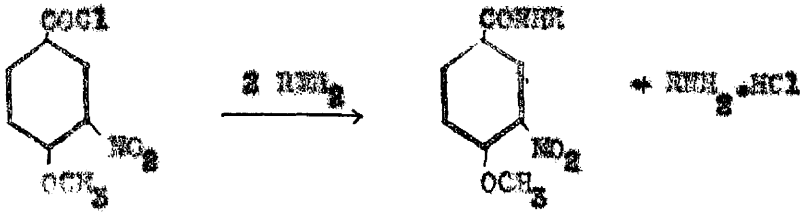
C., (corr.) (46), both in agreement with the same derivatives of 3-nitro-4-methoxybenzoic acid (49).

3-Nitro-4-methoxybenzoyl chloride



For the preparation of 3-nitro-4-methoxybenzoyl chloride, 75 g. of 3-nitroanisic acid (0.36 mole) was refluxed for two hours with 200 ml. of redistilled thionyl chloride (2.7 mole). The excess thionyl chloride was then distilled under reduced pressure and the residue stirred with 150 ml. of cold petroleum ether which dissolved any residual thionyl chloride and converted the product into a solid mass. The crude product was then filtered off and recrystallised from ether. Some ether-insoluble impurities were removed by filtration but were not identified. The yield was 68.7 g., 87 per cent, m.p. 53-53.5° C. (corr.) (41,47).

N-Alkyl 3-nitro-4-methoxybenzamides



A five per cent excess of alkyl amine was added dropwise with stirring to an ether solution of 0.5 mole of 3-nitro-4-methoxybenzoyl chloride, kept below 10° C. The stirring was continued for an hour after the complete addition of alkyl amine. The solid product was collected on a suction filter and washed thoroughly with water to dissolve any alkyl

amine or its hydrochloride. The filtrate was discarded as only very little of the desired product could be recovered after evaporation of the aqueous or the ethereal portion of the filtrate. The crude product was then recrystallised from 80 per cent ethyl alcohol.

The following were prepared in this manner:

N-Methyl 3-nitro-4-methoxybenzamide m.p. 163.5-164.5° C. (corr.)

Yield 86.2 g. (82%)

Analysis. Calculated for $C_9H_{10}N_2O_4$: N, 13.3 . Found: N, 13.3.

N-Ethyl 3-nitro-4-methoxybenzamide m.p. 116-117° C. (corr.)

Yield 88.6 g. (79%)

Analysis. Calculated for $C_{10}H_{12}N_2O_4$: N, 12.5 . Found: N, 12.6.

Diacyl hydrazines

$$(R'CO)_2O \quad \xrightarrow{NH_2NH_2 \cdot H_2O} \quad R'CONHNHCOR'$$

Diacetyl hydrazine

The diacetyl hydrazine was prepared by the addition of 3.3 moles of acetic anhydride drop by drop with stirring to one mole of hydrazine hydrate (85% solution) kept at 0° C. During the latter part of the addition, the acetic anhydride could be added in larger portions. The precipitate which separated was filtered, washed with ether and recrystallised from 95 per cent ethyl alcohol, m.p. 138.5-139.5° C. (corr.) (60). Yield 60-76 per cent.

Dipropionyl hydrazine

The dipropionyl hydrazine was prepared by the gradual addition of two moles of propionic anhydride to one mole of hydrazine hydrate

(85% solution) with cooling. The reaction mixture was then refluxed for one hour after which the solution was concentrated until the temperature of the reaction mixture reached 220° C. The residue in the distilling flask solidified after cooling. The solid was filtered off after dilution with petroleum ether and the crude product was recrystallised from acetone. m.p. 138.5-139° C. (corr.) (68). Yield 80 per cent.

Di-n-butyryl hydrazine

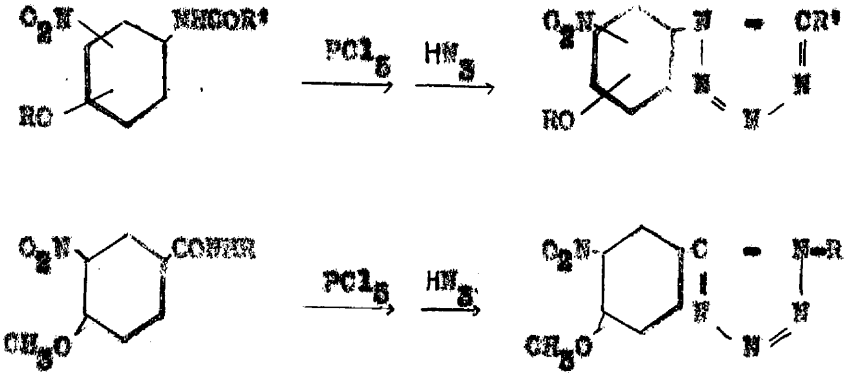
The di-n-butyryl hydrazine was prepared by the addition of 2.2 moles of n-butyric anhydride drop by drop with stirring to one mole of hydrazine hydrate (85% solution) kept at 0° C. The di-n-butyryl hydrazine separated out during the reaction and the reaction mixture after dilution with petroleum ether was filtered. The precipitate was washed with petroleum ether and recrystallised from 95 per cent ethyl alcohol. m.p. 169.5-171° C. (corr.) (51). Yield 60 per cent.

Di-i-butyryl hydrazine

The di-i-butyryl hydrazine was obtained from Mr. J. A. Garrison who had isolated it as a by-product during the preparation of 3,5-di-isopropyl-4-amino-1,2,4-triazole from isobutyric acid and hydrazine.

PREPARATION OF TETRAZOLES

1,5 Alkoxy-nitrophenyl-alkyltetrazoles (von Braun method)



All the alkoxy-nitrophenyl-alkyltetrazoles were prepared by the von Braun procedure (20). The following description of the preparation of 1-(2'-methoxy-5'-nitro)-5-n-propyltetrazole from 2-methoxy-5-nitro-n-butyranilide illustrates the general procedure employed for the synthesis of most of the products listed in Table III.

2-Methoxy-5-nitro-n-butyranilide (59.5 g., 0.25 mole) was suspended in 500 ml. of dry benzene in a 2 liter three-necked round bottom flask, fitted with a stirrer with a benzene seal and a reflux condenser surmounted by a calcium chloride tube. The third opening was connected to a 500 ml. Erlenmeyer flask containing 56 g. (0.27 mole) of phosphorus pentachloride. The benzene solution was stirred while the phosphorus pentachloride was added portionwise. The phosphorus pentachloride caused the evolution of hydrogen chloride. The stirring was continued until a clear solution was formed. The Erlenmeyer flask was then replaced by a dropping funnel through which 120 ml. of a benzene solution of hydrazoic

acid (15 g. of hydrazoic acid per 100 ml.) equivalent to 18 g. (0.42 mole) of hydrazoic acid was added in small portions. The reaction mixture was then warmed gradually to the boiling point on a water bath and maintained at this temperature until hydrogen chloride evolution ceased. The solvent was then removed under reduced pressure and the residue was treated with 250 ml. of ice water and 30 ml. of concentrated hydrochloric acid. The mixture was boiled under reflux for one hour in order to hydrolyse any unreacted amide. The tetrazole was only slightly soluble in the aqueous acid and was filtered off after chilling the suspension. After washing the crude product thoroughly with water, it was recrystallized twice from 95 per cent ethyl alcohol from which it separated as long, colorless needles, m.p. 140-141.5° C. (corr.). The yield was 60.1 g. equivalent to 92 per cent of the theoretical.

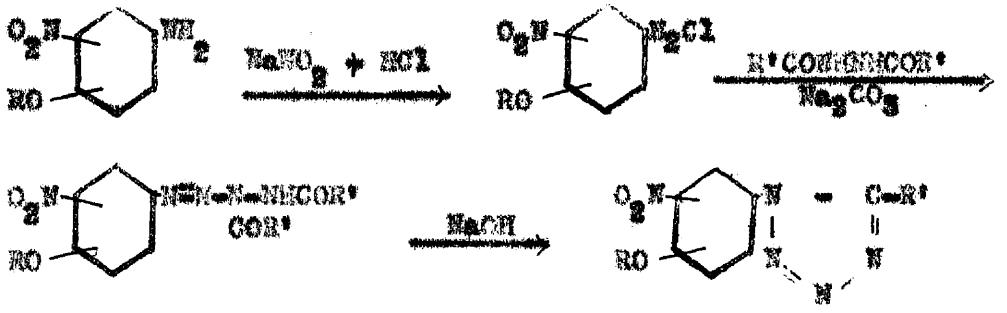
The amine formed by hydrolysis of the unreacted amide was soluble in the dilute aqueous acid and could be recovered by neutralization of the solution.

In most instances, the substituted amides were converted into imide chlorides by stirring with phosphorus pentachloride at room temperature. However, in the case of N-acetyl and N-propionyl 3-nitro-4-methoxyaniline, heating was necessary to start the reaction and in the case of N-methyl and N-ethyl 3-nitro-4-methoxybenzamide, boiling was required. The imide chlorides were soluble in the benzene except those derived from 3-nitro-4-methoxyacetanilide and 3-nitro-4-methoxypropionanilide which were only slightly soluble in benzene at room temperature. The addition of hydrazoic acid to the imide chloride solution usually caused the

separation of a solid product which dissolved when the reaction mixture was heated to boiling. In all instances, after the addition of hydrazoic acid solution there was copious evolution of hydrogen chloride when the reaction mixture was heated.

The nitrophenyltetrazoles and the alkoxy-nitrophenyltetrazoles prepared in this manner are listed in Table IV and Table V together with pertinent physical and analytical data.

1-Nitrophenyl- and 1-alkoxy-nitrophenyl-5-alkyltetrazoles (Dimroth method)



A group of ten nitrophenyl- and alkoxy-nitrophenyltetrazoles was also prepared by the Dimroth procedure (16). The preparation of 1-(2'-methoxy-4'-nitrophenyl)-5-methyltetrazole from diacetyl hydrazine and 2-amino-5-nitroanisole is described as a typical example.

To a mixture of 3.36 g. (0.02 mole) of 2-amino-5-nitroanisole in 14 ml. of 7 N hydrochloric acid kept at 0° C., a solution of 1.44 g. (0.021 mole) of sodium nitrite in 5 ml. of water was added gradually at the same temperature. The diazonium chloride solution was then treated with 5 g. of sodium acetate and 10 ml. of 5 N sodium hydroxide solution.

TABLE IV

1,5 NITROPHENYL- AND ALKOXY-NITROPHENYL-ALKYLTETRAZOLES

R= -C_6H_3(NO$_2$)(OAlk.) or (H)	R'	M.P. °C. (corr.)	Yield %	Crystal Form	Solvent
3-NO_2 (Ref. 6)	CH_3	150-151	80	Fine needles	95% ethanol
3-NO_2 (Ref. 6)	C_2H_5	122-123.5	79	Leaflets	95% ethanol
4-NO_2 (Ref. 6)	CH_3	132-133.5	66	Prisms	99%2-propanol
4-NO_2	C_2H_5	124.5-125.5	74	Needles	95% ethanol
3-NO_2-4-OCH_3	CH_3	140.5-150.5	65	Coarse needles	95% ethanol
3-NO_2-4-OCH_3	C_2H_5	119.5-121	66	Leaflets	90%2-propanol
3-NO_2-4-OCH_3	n-C_3H_7	105.5-106	68	Fine needles	90% ethanol
3-NO_2-4-OCH_3	i-C_3H_7	143-144.5	62	Fine needles	99%2-propanol
2-OCH_3-5-NO_2	CH_3	174-176.5	70	Long needles	95% ethanol
2-OCH_3-5-NO_2	C_2H_5	157.5-158.5	88	Long needles	95% ethanol
2-OCH_3-5-NO_2	n-C_3H_7	140-141.5	92	Long needles	95% ethanol
2-OCH_3-5-NO_2	i-C_3H_7	162-163.5	79	Leaflets	95% ethanol
2-OCH_3-4-NO_2	CH_3	140.5-141.5	78	Fine needles	90%2-propanol
2-OCH_3-4-NO_2	C_2H_5	116-116.5	78	Fine needles	90%2-propanol
2-OCH_3-4-NO_2	n-C_3H_7	118-119	72	Prisms	90%2-propanol
2-OCH_3-4-NO_2	i-C_3H_7	167-168	79	Coarse needles	95% ethanol
2-OC_2H_5-5-NO_2	CH_3	145.5-147	85	Long needles	99%2-propanol
2-OC_2H_5-5-NO_2	C_2H_5	129-130.5	85	Fine needles	80%2-propanol

R	R'= -C_6H_3(NO$_2$)(OCH_3)				
CH_3	3-NO_2-4-OCH_3	115-115.5	85	Long needles	95% ethanol
C_2H_5	3-NO_2-4-OCH_3	94.5-95	81	Fine needles	80% ethanol

TABLE V

NITROGEN ANALYSES OF 1,5 NITROPHENYL- AND ALKOXY-NITROPHENYL-ALKYLTETRAZOLES

R = $-C_6H_3$ (NO$_2$, (O Alk.) or (H))	R'	Formula	Analysis %N	
			Calculated	Found
4-NO_2	C_2H_5	$C_9H_9N_5O_2$	32.0	31.7
3-NO_2-4-OCH_3	CH_3	$C_9H_9N_5O_3$	29.8	29.5
3-NO_2-4-OCH_3	C_2H_5	$C_{10}H_{11}N_5O_3$	28.1	28.0
3-NO_2-4-OCH_3	n-C_3H_7	$C_{11}H_{13}N_5O_3$	26.6	26.7
3-NO_2-4-OCH_3	i-C_3H_7	$C_{11}H_{13}N_5O_3$	26.6	26.8
2-OCH_3-5-NO_2	CH_3	$C_9H_9N_5O_3$	29.8	29.6
2-OCH_3-5-NO_2	C_2H_5	$C_{10}H_{11}N_5O_3$	28.1	27.9
2-OCH_3-5-NO_2	n-C_3H_7	$C_{11}H_{13}N_5O_3$	26.6	26.6
2-OCH_3-6-NO_2	i-C_3H_7	$C_{11}H_{13}N_5O_3$	26.6	26.6
2-OCH_3-4-NO_2	CH_3	$C_9H_9N_5O_3$	29.8	30.0
2-OCH_3-4-NO_2	C_2H_5	$C_{10}H_{11}N_5O_3$	28.1	27.9
2-OCH_3-4-NO_2	n-C_3H_7	$C_{11}H_{13}N_5O_3$	26.6	26.5
2-OCH_3-4-NO_2	i-C_3H_7	$C_{11}H_{13}N_5O_3$	26.6	26.8
2-OC_2H_5-5-NO_2	CH_3	$C_{10}H_{11}N_5O_3$	28.1	28.4
2-OC_2H_5-5-NO_2	C_2H_5	$C_{11}H_{13}N_5O_3$	26.6	26.9

R	R' = $-C_6H_3$ (NO_2, OCH_3)			
CH_3	3-NO_2-4-OCH_3	$C_9H_9N_5O_3$	29.8	29.5
C_2H_5	3-NO_2-4-OCH_3	$C_{10}H_{11}N_5O_3$	28.1	28.3

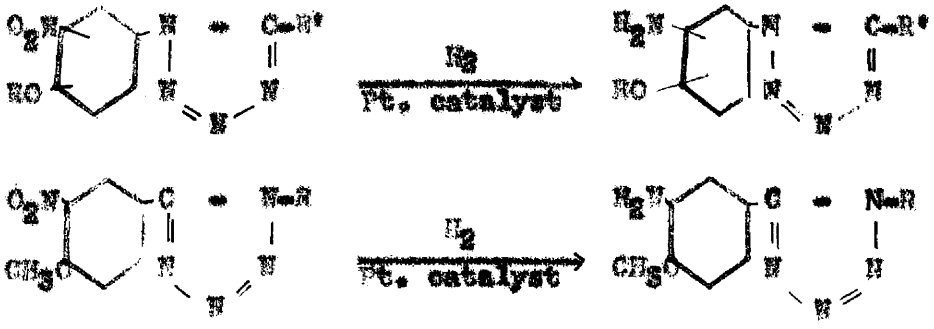
The diazonium chloride solution was added in small portions to a solution of 2.6 g. (0.021 mole) of diacetyl hydrazine in 60 ml. of 1.6 N sodium carbonate solution kept below 0° C. Without the isolation of the intermediate diazohydrazide which separated as a voluminous white precipitate, 40 ml. of 5 N sodium hydroxide solution was added with stirring. A clear solution resulted after the addition of sodium hydroxide solution and the tetrazole that separated after standing was filtered off, washed with water and dissolved in hot concentrated hydrochloric acid. The acid solution was filtered and diluted with water whereupon the tetrazole separated. The crude product was recrystallized from 96 per cent ethyl alcohol. Yield 2.1 g. (45%), m.p. 140.6-141.6° C. (corr.).

The above procedure was modified in several aspects in the preparation of some other tetrazole derivatives. In the preparation of 5-n-propyl and 5-i-propyl substituted tetrazoles, 0.02 mole of the di-n-butyryl- or di-i-butyryl hydrazine was first suspended in 50 ml. of 1 N sodium carbonate solution. After the addition of 20 g. of sodium acetate, 5 N sodium hydroxide solution was added drop by drop with occasional heating until the dicyl hydrazine became entirely soluble. Approximately 4-5 ml. of 5 N sodium hydroxide solution was required. The solution was then cooled to 0° C. and coupling with 0.02 mole of aromatic diazonium chloride at the same temperature was completed as described above. The diazohydrazides which separated after coupling were filtered off in most of the cases and treated with 40 ml. of 5 N sodium hydroxide solution to effect the cyclization. In the preparation of 1-(2'-methoxy-4'-nitrophenyl)-5-ethyl-, 5-propyl- and 5-isopropyl tetrazoles, oily or

semi-solid products separated after the addition of sodium hydroxide solution. These products were converted into solids by heating the reaction mixture to 80° C. In the case of 1-m-nitrophenyl-5-propyltetrazole, an oily product separated which could not be converted into the solid state by heating. A solid product, however, could be obtained by continuously grinding the diazohydrazide with 5 N sodium hydroxide solution in a mortar. The crude tetrazoles were usually first dissolved in concentrated hydrochloric acid and the solids which separated from the acid filtrate upon dilution with water were recrystallized from alcohol, aqueous alcohol or benzene. The treatment with concentrated hydrochloric acid was omitted if the crude tetrazole obtained was only slightly colored or when it was only slightly soluble in concentrated hydrochloric acid solution.

The tetrazoles prepared by the above procedure are listed in Table I where the physical constants are reported and the yields compared with those obtained in the von Braun procedure. Although analyses were not carried out on the compounds prepared by the Dimroth method, the products were identical with the corresponding compounds made by the von Braun method and showed no depression of the melting point when mixed with these.

1,5 Alkoxy-aminophenyl-alkyltetrazoles



This group of compounds was prepared by the catalytic hydrogenation of the corresponding alkoxy-nitrophenyltetrazoles according to the procedure of Herbst and co-workers (6). The preparation of 1-(2'-ethoxy-5'-aminophenyl)-5-ethyltetrazole is described as an example of the reduction of an alkoxy-nitrophenyltetrazole derivative.

To a solution of 0.1 mole (26.3 g.) of 1-(2'-ethoxy-5'-nitrophenyl)-5-ethyltetrazole in 210 ml. of glacial acetic acid 145 mg. of platinum oxide catalyst was added. The solution was reduced in the Burgess-Parr low pressure hydrogenation apparatus at an initial hydrogen pressure of 50 pounds per square inch and the reduction was complete within 30 minutes with a total drop in pressure of twenty-four pounds. After removal of the catalyst, the solvent was distilled off under reduced pressure. The residual material was taken up in 350 ml. of hot water containing 12 ml. of concentrated hydrochloric acid, boiled for a few minutes, chilled and filtered to remove any small amount of acid insoluble material. The chilled filtrate was made alkaline to litmus with aqueous ammonia and the amine which separated was filtered and washed with cold water. The crude base was recrystallized twice from 50 per cent ethyl alcohol from which it separated as colorless needles, melting at 149-150° C. (corr.). The yield was 18.4 g. corresponding to 79 per cent of the theoretical.

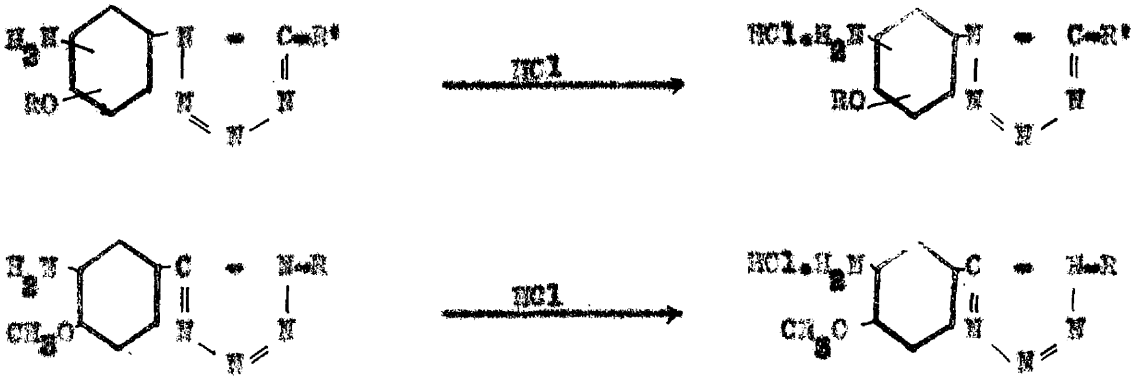
In case the alkoxy-nitrophenyltetrazole was not completely soluble in glacial acetic acid, the solid was pulverized and suspended in glacial acetic acid and the reduction carried out as usual. The solid dissolved rapidly as the hydrogenation progressed due both to the rise in the

temperature of the reaction mixture and to the reduction of the nitro group to an amino group.

In some instances, intensely colored reduction products were formed. The coloration could usually be avoided by increasing slightly the amount of platinum oxide catalyst or could be removed by the conversion of the amine into its hydrochloride and liberation of the amine again after crystallization of the hydrochloride. The addition of small amount of zinc when the amine was boiled in hydrochloric acid solution was frequently helpful in removing coloration.

The aminophenyl tetrazoles prepared in this manner are listed in Table VI and Table VII together with pertinent physical and analytical data.

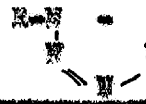
1,5 Alkoxy-aminophenyl-alkyltetrazole hydrochlorides



The hydrochlorides of the 1,5 alkoxy-aminophenyl-alkyltetrazoles were prepared by passing dry hydrogen chloride gas into a solution of the tetrazole in absolute isopropyl alcohol. If the hydrochloride separated from the alcoholic solution, as in the case of most of the

TABLE VI

1,5 AMINOPHENYL- AND ALKOXY-AMINOPHENYL-ALKYLTETRAZOLES



R= $-C_6H_3$ (NH$_2$, (O Alk.) or (H))	R'	M.P. °C. (corr.)	Yield %	Crystal Form	Solvent
3-NH_2 (Ref. 6)	CH_3	122-124	74	Fine needles	Water
3-NH_2 (Ref. 6)	C_2H_5	112.5-113	64	Fine needles	Water
4-NH_2 (Ref. 6)	CH_3	146-146	69	Small needles	Water
4-NH_2	C_2H_5	95.5-97	53	Prisms	Water
3-NH_2-4-OCH_3	CH_3	119.5-120.5	77	Needles	Water 30%
3-NH_2-4-OCH_3	C_2H_5	72.5-73.5	64	Fine needles	Ethanol 30%
3-NH_2-4-OCH_3	n-C_3H_7	90-91.5	60	Needles	Ethanol 30%
3-NH_2-4-OCH_3	i-C_3H_7	112-112.5	66	Prisms	Ethanol
2-OCH_3-5-NH_2	CH_3	130-132	69	Small prisms	Water 30%
2-OCH_3-5-NH_2	C_2H_5	173-175	72	Leaflets	Ethanol 30%
2-OCH_3-5-NH_2	n-C_3H_7	138-139.5	71	Needles	Ethanol 30%
2-OCH_3-5-NH_2	i-C_3H_7	210.5-211.5	61	Small needles	Ethanol
2-OCH_3-4-NH_2	CH_3	84-85	39	Fine needles	Water 25%
2-OCH_3-4-NH_2	C_2H_5	94-95	65	Leaflets	Ethanol 25%
2-OCH_3-4-NH_2	n-C_3H_7	119.5-120	74	Fine needles	Ethanol 25%
2-OCH_3-4-NH_2	i-C_3H_7	132.5-133.5	79	Needles	Ethanol
2-OC_2H_5-5-NH_2	CH_3	129.5-130.5	79	Small prisms	Water 30%
2-OC_2H_5-5-NH_2	C_2H_5	149-150	79	Fine needles	Ethanol
R	R'= $-C_6H_3$ (NH_2, OCH_3)				
CH_3	3-NH_2-4-OCH_3	153.5-154.5	71	Small needles	70% Ethanol 30%
C_2H_5	3-NH_2-4-OCH_3	90-91.5	66	Leaflets	Ethanol

TABLE VII

NITROGEN ANALYSES OF 1,5 AMINOPHENYL- AND ALKOXY-AMINOPHENYL-ALKYLTETRAZOLES

R = $-C_6H_3$ (NH$_2$, (O Alk.) or (R))	R'	Formula	Analysis % N	
			Calculated	Found
4-NH_2	C_2H_5	$C_9H_{11}N_5$	37.0	37.0
3-NH_2-4-OCH_3	CH_3	$C_9H_{11}N_5O$	34.1	34.6
3-NH_2-4-OCH_3	C_2H_5	$C_{10}H_{13}N_5O$	32.0	31.6
3-NH_2-4-OCH_3	n-C_3H_7	$C_{11}H_{15}N_5O$	30.0	29.9
3-NH_2-4-OCH_3	i-C_3H_7	$C_{11}H_{15}N_5O$	30.0	30.3
2-OCH_3-5-NH_2	CH_3	$C_9H_{11}N_5O$	34.1	34.1
2-OCH_3-5-NH_2	C_2H_5	$C_{10}H_{13}N_5O$	32.0	32.1
2-OCH_3-5-NH_2	n-C_3H_7	$C_{11}H_{15}N_5O$	30.0	30.0
2-OCH_3-5-NH_2	i-C_3H_7	$C_{11}H_{15}N_5O$	30.0	30.4
2-OCH_3-4-NH_2	CH_3	$C_9H_{11}N_5O$	34.1	33.9
2-OCH_3-4-NH_2	C_2H_5	$C_{10}H_{13}N_5O$	32.0	32.0
2-OCH_3-4-NH_2	n-C_3H_7	$C_{11}H_{15}N_5O$	30.0	30.2
2-OCH_3-4-NH_2	i-C_3H_7	$C_{11}H_{15}N_5O$	30.0	29.7
2-OC_2H_5-5-NH_2	CH_3	$C_{10}H_{13}N_5O$	32.0	32.4
2-OC_2H_5-5-NH_2	C_2H_5	$C_{11}H_{15}N_5O$	30.0	30.2

R	R' = $-C_6H_3$ (NH_2, OCH_3)			
CH_3	3-NH_2-4-OCH_3	$C_9H_{11}N_5O$	34.1	34.3
C_2H_5	3-NH_2-4-OCH_3	$C_{10}H_{13}N_5O$	32.0	32.1

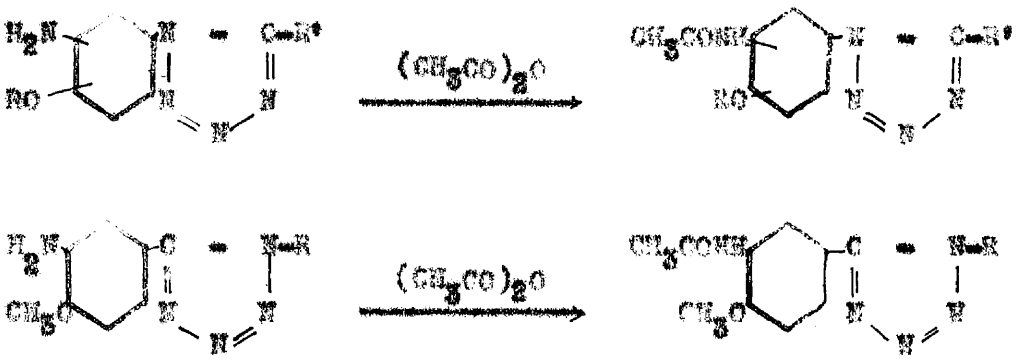
5-methyl or 1-methyl substituted tetrazoles, the hydrochloride was filtered off, washed with ether and recrystallized from absolute ethyl alcohol. In case the hydrochloride did not separate from the isopropyl alcohol solution, most of the solvent was evaporated and the residual solution cooled. If no hydrochloride separated out after cooling, the solution was diluted with ether. The hydrochloride precipitate was filtered, washed with ether and recrystallized from an appropriate combination of methyl alcohol, acetone and benzene. In case the addition of ether caused only the separation of an oily product, the product could be recovered as a solid by decanting the supernatant liquid and passing a slow current of dry air over the residue. Rubbing with a small amount of acetone was also helpful in some instances. The crude product was then suspended in ether, filtered, washed with ether and recrystallized from appropriate mixed solvents (see Table VIII) with the addition of a few drops of ether saturated with hydrogen chloride to assure the presence of excess acid.

Most of the hydrochlorides, excepting those having a methyl group substituted in position 1 or 5 of the tetrazole ring, are very soluble in alcohol, slightly or moderately soluble in acetone and only very slightly soluble in benzene and petroleum ether. By dissolving the hydrochloride in a small volume of methyl alcohol or acetone or a mixture of both with subsequent addition of benzene and partial evaporation of the more volatile solvents, a suitable mixture of solvents usually resulted from which the hydrochlorides separated as fine crystals.

The hydrochlorides were dried to constant weight over phosphorus pentoxide at 61° C., (b.p. of chloroform) and 2 mm. pressure in an Abderhalden drying pistol.

The hydrochlorides are listed in Table VIII and Table IX together with pertinent physical and analytical data.

1,5 Alkoxy-acetylaminophenyl-alkyltetrazoles



The acetyl derivatives were prepared by heating one gram of amino-phenyltetrazole with 1.5 g. of acetic anhydride. The reaction mixture was diluted with water, and the solid that separated was filtered and washed with water. The crude product was then recrystallized twice from water or aqueous isopropyl alcohol and dried to constant weight over phosphorus pentoxide at 100° C., and 15 mm. pressure in an Abderhalden drying pistol.

The acetyl derivatives are listed in Table X and Table XI together with pertinent physical and analytical data.

TABLE VIII

1,5 AMINOPHENYL- AND ALKOXY-AMINOPHENYL-ALKYLTETRAZOLE HYDROCHLORIDES

NH -C_6H_3 (O Alk.) or (H)	R'	M.P.* °C. (corr.)	Yields %	Crystal Form	Solvent
3-NH_2 (Ref. 6)	CH_3	207-210 (d.)	73	Small prisms	Absolute ethanol
3-NH_2 (Ref. 6)	C_2H_5	192.5-195.5	70	Prisms	Absolute ethanol
4-NH_2 (Ref. 6)	CH_3	215-215 (d.)	72	Leaflets	Absolute ethanol
4-NH_2	C_2H_5	203-206 (d.)	83	Small leaflets	Absolute ethanol
3-NH_2-4-OCH_3	CH_3	215.5-217.5 (d.)	95	Small needles	Absolute ethanol
3-NH_2-4-OCH_3	C_2H_5	188-191	80	Small Prisms	Methanol - acetone - benzene
3-NH_2-4-OCH_3	n-C_3H_7	171.5-174.5	77	Small prisms	Methanol - acetone - benzene
3-NH_2-4-OCH_3	i-C_3H_7	150-152	96	Small prisms	Methanol - acetone - benzene
2-OCH_3-5-NH_2	CH_3	230-232 (d.)	86	Small leaflets	Absolute ethanol
2-OCH_3-5-NH_2	C_2H_5	211.5-214.5 (d.)	86	Leaflets	99% 2-propanol
2-OCH_3-5-NH_2	n-C_3H_7	190-193	84	Small leaflets	99% 2-propanol
2-OCH_3-5-NH_2	i-C_3H_7**	173-176	75	Small prisms	Acetone - ether
2-OCH_3-4-NH_2	CH_3	204-206 (d.)	81	Small prisms	Absolute ethanol
2-OCH_3-4-NH_2	C_2H_5	168.5-171.5 (d.)	67	Small prisms	Acetone
2-OCH_3-4-NH_2	n-C_3H_7	167.5-170.5 (d.)	74	Small prisms	Acetone - benzene
2-OCH_3-4-NH_2	i-C_3H_7	183.5-186.5 (d.)	85	Small prisms	Methanol - acetone - benzene
2-OC_2H_5-5-NH_2	CH_3	207-210 (d.)	79	Small prisms	Methanol - acetone - benzene
2-OC_2H_5-5-NH_2	C_2H_5	190.5-193.5 (d.)	81	Small prisms	Methanol - acetone - benzene

R	R' = -C_6H_3 (NH_2, OCH_3)				
CH_3	3-NH_2-4-OCH_3	220.5-222.5 (d.)	91	Small prisms	Absolute ethanol
C_2H_5	3-NH_2-4-OCH_3	202-204 (d.)	76	Small needles	Methanol - acetone - benzene

* All the melting points are determined in a sealed capillary tube. The melting range depends on the rate of heating.

** Dried over phosphorus pentoxide at 111° C. and 2 mm. pressure in a drying pistol.

TABLE IX

NITROGEN ANALYSES OF 1,5 AMINOPHENYL- AND ALKOXY-AMINOPHENYL-ALKYLTETRAZOLE HYDROCHLORIDES

RR = C_6H_3(NH$_2$)(O Alk.) or (H)	R'	Formula	Analysis % N	
			Calculated	Found
4-NH_2	C_2H_5	$C_9H_{12}ClN_5$	31.0	30.9
3-NH_2-4-OCH_3	CH_3	$C_9H_{12}ClN_5O$	29.0	28.6
3-NH_2-4-OCH_3	C_2H_5	$C_{10}H_{14}ClN_5O$	27.4	27.4
3-NH_2-4-OCH_3	n-C_3H_7	$C_{11}H_{16}ClN_5O$	26.0	25.8
3-NH_2-4-OCH_3	i-C_3H_7	$C_{11}H_{16}ClN_5O$	26.0	25.8
2-OCH_3-5-NH_2	CH_3	$C_9H_{12}ClN_5O$	29.0	28.6
2-OCH_3-5-NH_2	C_2H_5	$C_{10}H_{14}ClN_5O$	27.4	27.1
2-OCH_3-5-NH_2	n-C_3H_7	$C_{11}H_{16}ClN_5O$	26.0	26.0
2-OCH_3-5-NH_2	i-C_3H_7	$C_{11}H_{16}ClN_5O$	26.0	25.8
2-OCH_3-4-NH_2	CH_3	$C_9H_{12}ClN_5O$	29.0	28.6
2-OCH_3-4-NH_2	C_2H_5	$C_{10}H_{14}ClN_5O$	27.4	27.6
2-OCH_3-4-NH_2	n-C_3H_7	$C_{11}H_{16}ClN_5O$	26.0	26.3
2-OCH_3-4-NH_2	i-C_3H_7	$C_{11}H_{16}ClN_5O$	26.0	26.0
2-OC_2H_5-5-NH_2	CH_3	$C_{10}H_{14}ClN_5O$	27.4	27.8
2-OC_2H_5-5-NH_2	C_2H_5	$C_{11}H_{16}ClN_5O$	26.0	25.8

R	R' = C_6H_3(NH$_2$)(OCH_3)			
CH_3	3-NH_2-4-OCH_3	$C_9H_{12}ClN_5O$	29.0	29.4
C_2H_5	3-NH_2-4-OCH_3	$C_{10}H_{14}ClN_5O$	27.4	27.6

TABLE X

1,5 ACETYLAMINOPHENYL- AND ALKOXY-ACETYLAMINOPHENYL-ALKYL-TETRAZOLES

R=	R'	M.P.°C. (Coor.)	Crystal Form	Solvent
4-$NHCOCH_3$	C_2H_5	133-136	Prisms	Water
3-$NHCOCH_3$-4-OCH_3	CH_3	200-200.5	Leaflets	30% 2-propanol
3-$NHCOCH_3$-4-OCH_3	C_2H_5	165.7-167	Needles	Water
3-$NHCOCH_3$-4-OCH_3	n-C_3H_7	157-158	Fine Needles	30% 2-propanol
3-$NHCOCH_3$-4-OCH_3	i-C_3H_7	154.5-156	Fine needles	30% 2-propanol
2-OCH_3-5-$NHCOCH_3$	CH_3	191-193	Small needles	Water
2-OCH_3-5-$NHCOCH_3$	C_2H_5	154.5-155.5	Small needles	30% 2-propanol
2-OCH_3-5-$NHCOCH_3$	n-C_3H_7	172.5-174.5	Small leaflets	30% 2-propanol
2-OCH_3-5-$NHCOCH_3$	i-C_3H_7	180.5-182.5**	Prisms	30% 2-propanol
2-OCH_3-4-$NHCOCH_3$	CH_3	187-188	Prisms	30% 2-propanol
2-OCH_3-4-$NHCOCH_3$	C_2H_5	141-142.5	Fine needles	Water
2-OCH_3-4-$NHCOCH_3$	n-C_3H_7	150.5-151.5	Fine needles	30% 2-propanol
2-OCH_3-4-$NHCOCH_3$	i-C_3H_7	128.5-129.5*	Prisms	30% 2-propanol
2-OC_2H_5-5-$NHCOCH_3$	CH_3	176-177	Small needles	30% 2-propanol
2-OC_2H_5-5-$NHCOCH_3$	C_2H_5	152-153.5	Small needles	30% 2-propanol

R	R'=	M.P.°C. (Coor.)	Crystal Form	Solvent
CH_3	3-$NHCOCH_3$-4-OCH_3	183.5-185	Fine needles	Water
C_2H_5	3-$NHCOCH_3$-4-OCH_3	109-110	Prisms	30% 2-propanol

* Anhydrous sample. Crystallised as a hydrate melting unsharply at about 65° C.

** Dried over phosphorus pentoxide at 111° C. and 15 mm pressure in a drying pistol.

TABLE XI

NITROGEN ANALYSES OF 1,5 ACETYLAMINOPHENYL- AND ALKOXY-ACETYLAMINOPHENYL-ALKYLTETRAZOLES

R=W	R'	Formula	Analysis % N	
			Calculated	Found
4-$NHCOCH_3$	C_2H_5	$C_{11}H_{13}N_5O$	30.3	30.1
3-$NHCOCH_3$-4-OCH_3	CH_3	$C_{11}H_{13}N_5O_2$	28.3	28.4
3-$NHCOCH_3$-4-OCH_3	C_2H_5	$C_{12}H_{15}N_5O_2$	26.8	26.9
3-$NHCOCH_3$-4-OCH_3	n-C_3H_7	$C_{13}H_{17}N_5O_2$	25.4	25.5
3-$NHCOCH_3$-4-OCH_3	i-C_3H_7	$C_{13}H_{17}N_5O_2$	25.4	25.6
2-OCH_3-5-$NHCOCH_3$	CH_3	$C_{11}H_{13}N_5O_2$	28.3	28.2
2-OCH_3-5-$NHCOCH_3$	C_2H_5	$C_{12}H_{15}N_5O_2$	26.8	26.7
2-OCH_3-5-$NHCOCH_3$	n-C_3H_7	$C_{13}H_{17}N_5O_2$	25.4	25.5
2-OCH_3-5-$NHCOCH_3$	i-C_3H_7	$C_{13}H_{17}N_5O_2$	25.4	25.7
2-OCH_3-4-$NHCOCH_3$	CH_3	$C_{11}H_{13}N_5O_2$	28.3	28.4
2-OCH_3-4-$NHCOCH_3$	C_2H_5	$C_{12}H_{15}N_5O_2$	26.8	26.9
2-OCH_3-4-$NHCOCH_3$	n-C_3H_7	$C_{13}H_{17}N_5O_2$	25.4	25.4
2-OCH_3-4-$NHCOCH_3$	i-C_3H_7	$C_{13}H_{17}N_5O_2$	25.4	25.0
2-OC_2H_5-5-$NHCOCH_3$	CH_3	$C_{12}H_{15}N_5O_2$	26.8	27.1
2-OC_2H_5-5-$NHCOCH_3$	C_2H_5	$C_{13}H_{17}N_5O_2$	25.4	25.5

R	R'= 3-$NHCOCH_3$-4-OCH_3			
CH_3		$C_{11}H_{13}N_5O_2$	28.3	28.5
C_2H_5		$C_{12}H_{15}N_5O_2$	26.8	27.1

SUMMARY

SUMMARY

1. A series of twelve new N-acyl alkoxy-nitroanilines and N-alkyl methoxy-nitrobenzamides has been prepared as intermediates for the preparation of a new group of tetrazole compounds.

2. A group of sixteen new 1,5 alkoxy-nitrophenyl-alkyltetrazoles has been prepared by the von Braun procedure which involves the interaction of both the N-acyl alkoxy-nitroanilines and the N-alkyl methoxy-nitrobenzamides with phosphorus pentachloride and treatment of the imide chlorides so formed with hydrazoic acid.

3. A group of sixteen new 1,5 alkoxy-aminophenyl-alkyltetrazoles has been prepared by catalytic hydrogenation of the corresponding nitro derivatives.

4. A group of four 1-nitrophenyl-5-alkyltetrazoles and the corresponding 1-aminophenyl-5-alkyltetrazoles has also been prepared by similar procedures. Of these, only the 1-p-nitrophenyl- and the 1-p-aminophenyl-5-ethyltetrazole have not been previously described.

5. The hydrochlorides and the acetyl derivatives of all the new alkoxy-aminophenyltetrazoles and the aminophenyltetrazole have also been prepared.

6. The Dimroth procedure for the preparation of 1-aryl-5-methyltetrazole by the coupling of diazotized aromatic amines with diacetyl hydrazine

and cyclisation of the diazohydrazides so formed in aqueous alkaline solution has been extended to the synthesis of 1-aryl-5-alkyltetrazoles. A group of ten 1-aryl-5-alkyltetrazoles has been prepared which includes the 5-methyl, 5-ethyl, 5-propyl and 5-isopropyl substituted tetrazoles. The cyclisation of diazohydrazides into tetrazoles can be accelerated by heating. The yields of tetrazoles obtained by the Einroth procedure, however, are lower than those obtained by the von Braun procedure.

7. The nitration of p-anisidine, o-acylphenetidine and anisic acid has been described.

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