[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE COLLEGE]

SUBSTITUTED PHENYLTETRAZOLES. ALKOXYNITROPHENYLTETRAZOLES AND ALKOXYAMINOPHENYLTETRAZOLES[1]

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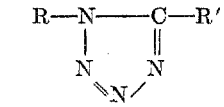
As a result of investigations of the pharmacological actions of a group of aminophenyltetrazoles Gross and Featherstone (1) concluded that a depressant action upon the central nervous system was common to certain compounds of this structure. The compounds investigated carried an aminophenyl group as a substituent in either position 1 or 5 of the tetrazole nucleus while alkyl groups of varying size were substituted in the other position (Ia and Ib). Curiously, compounds of this type were active only when the amino group occupied the *meta*-position. The corresponding *p*-aminophenyltetrazole derivatives were reported to be completely inactive in the dosage ranges studied.



I, a, R = $NH_2C_6H_4$; R′ = Alkyl

b, R = Alkyl; R′ = $NH_2C_6H_4$

Since the introduction of an alkoxy group as a substituent on an aromatic ring system frequently enhances the effectiveness of the resulting compound, it was of interest to investigate the effect of the addition of such a substituent to the aminophenyltetrazole structure. The observation that 1-*p*-methoxyphenyl-5-methyltetrazole exerted pronounced sedative action in rats (2), suggested that the inclusion of an alkoxy group in the aminophenyltetrazole structure might appreciably enhance the effectiveness of the resulting compounds. So that their pharmacological actions might be studied, the preparation of a number of alkoxyaminophenyltetrazoles was undertaken.

The usual procedures for the synthesis of tetrazole derivatives are not readily applicable to the direct preparation of aminophenyl substituted derivatives. However, the corresponding nitrophenyltetrazoles can be prepared without difficulty and these can be reduced easily to the desired aminophenyltetrazoles (3). Alkoxynitroanilines or alkoxynitrobenzoic acids would serve as the most useful starting points for the preparation of a variety of alkoxynitrophenyltetrazoles. The commercial availability or ease of synthesis of the alkoxynitroanilines and alkoxynitrobenzoic acids limited the variety of substituted tetrazole structures

[1] Based on a thesis submitted by Miss Du-Yung Wu to the School of Graduate Studies at Michigan State College in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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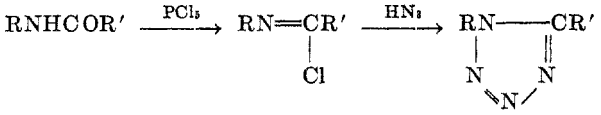
whose synthesis was undertaken at this time. The compounds prepared fall into five groups determined by the nature and orientation of the substituents.

Group 1. Formula Ia, R = 3-Amino-4-methoxyphenyl
R′ = Alkyl
Group 2. Formula Ia, R = 2-Methoxy-5-aminophenyl
R′ = Alkyl
Group 3. Formula Ia, R = 2-Methoxy-4-aminophenyl
R′ = Alkyl
Group 4. Formula Ia, R = 2-Ethoxy-5-aminophenyl
R′ = Alkyl
Group 5. Formula Ib, R = Alkyl
R′ = 3-Amino-4-methoxyphenyl

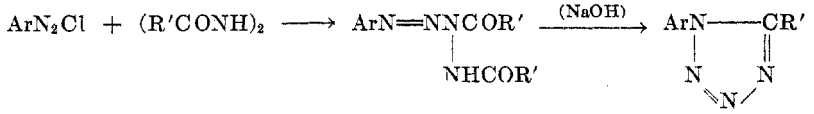
One method for the synthesis of compounds of these types based upon the tetrazole synthesis developed by von Braun and Rudolph (4) has recently been described (3). The procedure involved treatment of nitrophenyl-substituted amides, either anilides or N-alkylbenzamides, with phosphorus pentachloride and interaction of the resulting imide chloride with hydrazoic acid in benzene solution to form the tetrazole derivative. Catalytic hydrogenation served to reduce the nitrophenyltetrazoles to aminophenyltetrazoles.



(a) R = Aryl; R′ = Alkyl
(b) R = Alkyl; R′ = Aryl

Adaptation of this sequence of reactions to the synthesis of alkoxynitrophenyltetrazoles and eventually alkoxyaminophenyltetrazoles required only the preparation of suitable alkoxynitroacylanilides and N-alkylalkoxynitrobenzamides. It was applied to the synthesis of all tetrazoles described in Tables III and IV.

Another little used synthesis of 1,5-disubstituted tetrazoles was developed by Dimroth and deMontmollin (5). The procedure involved the coupling of diazonium compounds with acid hydrazides or *sym*-diacyl hydrazines followed by cyclization of the diazohydrazides formed in the coupling reaction. The synthesis is limited to the preparation of tetrazole derivatives with an aromatic substituent in position 1 and could be used only for the preparation of compounds of type Ia.



Although this sequence of reactions is one of the few leading to tetrazole formation that does not require the use of hydrazoic acid or azides, we have found no record of its application subsequent to Dimroth's publication. The possibility of

preparing 1,5-disubstituted tetrazoles without the use of hydrazoic acid made this procedure attractive to us. Furthermore, it seemed desirable to reinvestigate the procedure, to establish its limitations, and to compare its usefulness with that of the von Braun procedure for the synthesis of the same compounds.

Although Dimroth and deMontmollin (5) used both acid hydrazides and diacyl hydrazines for the formation of the intermediate diazohydrazides, best results were obtained with the diacyl hydrazines. For this reason we have limited our investigations to coupling reactions with diacyl hydrazines. We have repeated the preparation of 1-*p*-nitrophenyl-5-methyltetrazole by coupling diazotized *p*-nitroaniline with diacetyl hydrazine and cyclizing the resulting diazohydrazide in aqueous alkaline medium. Our results confirmed the observations of Dimroth and deMontmollin. It appears from Dimroth's work that the coupling reaction gave the lower yield while the cyclization proceeded in good yield, although the authors did not always differentiate clearly between over-all yields and yields in one or the other of the successive steps. Our observations, although we did not attempt to isolate the diazohydrazides, were in conformity with this interpretation. We have further studied the same sequence of reactions with diazotized *m*-nitroaniline and several nitroaminoanisoles not only with diacetyl hydrazine but with dipropionyl, di-*n*-butyryl, and diisobutyryl hydrazine as well. The results summarized in Table I indicate that the reaction is most useful with diacetyl and dipropionyl hydrazine and that the yield of tetrazole decreases as the acyl group becomes larger. This may be due in part to the technical difficulties presented by the lesser solubility of the higher diacyl hydrazines in the weakly alkaline coupling medium. Also included in Table I are the yields of the same products prepared by the von Braun procedure from which it can be seen that the over-all yield of tetrazole, calculated on the basis of amine required in both instances, is consistently better by the von Braun procedure.

The same alkoxynitroanilines could be used as starting materials in both the von Braun and the Dimroth reactions. Of these, 2-amino-4-nitroanisole and 2-amino-5-nitroanisole were available from commercial sources. In addition 2-nitro-4-aminoanisole and 2-amino-4-nitrophenetole or their acyl derivatives were desired as starting materials. 2-Nitro-4-aminoanisole was prepared by nitration at low temperature of *p*-anisidine dissolved in concentrated sulfuric acid. This procedure was found to be more advantageous than the nitration of acetyl-*p*-anisidine (6). The requisite anilides were prepared by acylation of the nitroaminoanisole. The acyl derivatives of 2-amino-4-nitrophenetole could be prepared most conveniently by nitration of the appropriate acyl phenetidine in a mixture of concentrated sulfuric acid and glacial acetic acid. Verkade and his co-workers (7) had prepared N-acetyl-2-amino-4-nitrophenetole in this manner. The orientation of the nitro group in the new acyl 2-amino-4-nitrophenetole was verified by hydrolysis to the known primary amine.

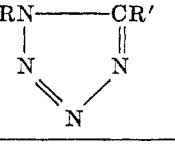
As an intermediate for the preparation of its N-alkyl amides, 3-nitro-4-methoxybenzoic acid was prepared by nitration of anisic acid (8). Treatment of the acid with thionyl chloride gave the acid chloride (9) which reacted readily with primary amines to form the desired N-alkyl amides.

The diacyl hydrazines used as intermediates in the Dimroth procedure were prepared by interaction of hydrazine in aqueous solution with the anhydrides of the lower fatty acids. The conditions chosen represent substantial modification of the procedures of Stollé (10) and Autenrieth (11). Diisobutyryl hydrazine was prepared in small quantity by the interaction of isobutyryl chloride and hydrazine, but this preparation was not developed since the intermediate became available as a by-product during an investigation of the formation of aminotriazole derivatives (12).

Pharmacological actions of the alkoxyaminophenyltetrazoles are being investigated in the Parke, Davis Research Laboratories through whose courtesy

TABLE I

1-NITROPHENYL- AND 1-ALKOXYNITROPHENYL-5-ALKYLTETRAZOLES PREPARED BY THE VON BRAUN AND THE DIMROTH METHODS



R = C_6H_3 (NO_2, H (or OR))	R′	M.P., °C.		YIELD, %[a]	
		von Braun	Dimroth	von Braun	Dimroth
4-NO_2	CH_3	132–133.5[b]	132–133[c]	60	40
3-NO_2	CH_3	150–151[b]	149.5–150	72	40
3-NO_2	C_2H_5	122–123.5[b]	122–123	68	25
3-NO_2	n-C_3H_7	55–56[d]	53–54	47[d]	26
3-NO_2-4-OCH_3	CH_3	149.5–150.5	149.5–150.5	66	26
2-OCH_3-5-NO_2	CH_3	174–175.5	175.5–176.5	58	20
2-OCH_3-4-NO_2	CH_3	140.5–141.5	140–141	62	45
2-OCH_3-4-NO_2	C_2H_5	116–116.5	114–116	73	53
2-OCH_3-4-NO_2	n-C_3H_7	118–119	118.5–119.5	63	33
2-OCH_3-4-NO_2	iso-C_3H_7	167–168	167.5–169	50	35

[a] The yields in both instances are over-all yields of tetrazole from the nitroaniline of the alkoxynitroaniline. [b] See also Reference 3. [c] See also Reference 5. [d] Data taken from Reference 3.

preliminary comments are available. In general the compounds of this group exhibit a depressant action on the central nervous system as evidenced by moderate sedative and anticonvulsant effects along with a mild analgesic action. The 1-alkyl-5-alkoxyaminophenyltetrazoles appear to have appreciably greater activity than the corresponding 1-alkoxy-aminophenyl-5-alkyltetrazoles.

EXPERIMENTAL[4]

Corrected melting points are reported for all compounds.

2-Nitro-4-aminoanisole. Prepared by a modification of Martin's procedure (13). *p*-Anisidine (123 g., 1 mole) was added to 400 ml. of concentrated sulfuric acid at 0° in small portions

[4] Micro-analyses were carried out on most of the compounds described in this paper by Micro-Tech Laboratories, Skokie, Illinois.

with stirring. A cooled mixture of 130 g. of concentrated nitric acid (*sp. gr.* 1.35) and 250 ml. of concentrated sulfuric acid was added dropwise at the same temperature with stirring which was continued for an hour after complete addition of the mixed acids. After pouring the nitration mixture onto 2.5 kg. of ice the voluminous reddish yellow precipitate of nitrated amine sulfate was separated and washed with cold water. The amine was liberated by suspension of the sulfate in cold water and treatment with an excess of dilute aqueous ammonia. The nitro amine separated as red crystals which were filtered and washed with cold water. The crude product was dissolved in ether and the solution dried over sodium sulfate. After evaporation of the solvent the residual material was recrystallized from toluene, red prisms, m.p. 55–57°, yield 100 g. (60%). The product was identical with material prepared by hydrolysis of the nitration product of acetyl-*p*-anisidine (6, 14, 15) and by the partial reduction of 2,4-dinitroanisole (16).

N-Acylaminonitroanisoles. The N-acetyl-, N-propionyl-, N-*n*-butyryl-, and N-isobutyryl-aminonitroanisoles were prepared by treatment of the primary amines with acetic anhydride, propionic anhydride, *n*-butyric anhydride, and isobutyryl chloride, respectively. Acyl derivatives of 2-nitro-4-aminoanisole, 2-amino-4-nitroanisole, and 2-amino-5-nitroanisole were prepared. When acid anhydrides were used, one mole of the aminonitroanisole

TABLE II

N-ACYLAMINONITROANISOLES RNHCOR′

R = C_6H_3(NO$_2$)(OCH$_3$)	R′	M.P., °C.	YIELD, %	RECRYSTALLIZED FROM	FORMULA	N	
						Calc'd	Found
3-NO_2-4-OCH_3	C_2H_5	109.5–110	77	80% Ethanol	$C_{10}H_{12}N_2O_4$	12.5	12.5
3-NO_2-4-OCH_3	*n*-C_3H_7	131.5–133	71	80% Ethanol	$C_{11}H_{14}N_2O_4$	11.8	11.8
3-NO_2-4-OCH_3	iso-C_3H_7	121.5–122.5	57	80% Ethanol	$C_{11}H_{14}N_2O_4$	11.8	11.9
2-OCH_3-5-NO_2	C_2H_5	121.5–122.5	77	95% Ethanol	$C_{10}H_{12}N_2O_4$	12.5	12.4
2-OCH_3-5-NO_2	*n*-C_3H_7	119–119.5	77	95% Ethanol	$C_{11}H_{14}N_2O_4$	11.8	11.4
2-OCH_3-5-NO_2	iso-C_3H_7	137.5–138.5	55	99% 2-Propanol	$C_{11}H_{14}N_2O_4$	11.8	12.0
2-OCH_3-4-NO_2	C_2H_5	101–101.5	94	Benzene	$C_{10}H_{12}N_2O_4$	12.5	12.4
2-OCH_3-4-NO_2	*n*-C_3H_7	107.5–109.5	87	Benzene	$C_{11}H_{14}N_2O_4$	11.8	11.9
2-OCH_3-4-NO_2	iso-C_3H_7	124.5–126	63	80% Ethanol	$C_{11}H_{14}N_2O_4$	11.8	11.9

was treated with 1.5 moles of the 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 initiate the reaction. After complete acylation of the amine the reaction mixture was cooled, diluted with water, and the solid product filtered. After successive washings with water, dilute sodium carbonate solution, and water again, the crude products were recrystallized from the solvents indicated in Table II.

The N-isobutyryl derivatives were prepared by adding dropwise with stirring 50 g. (0.47 mole) of isobutyryl chloride to a benzene solution of 56 g. (0.33 mole) of the aminonitroanisole and 31 g. (0.39 mole) of dry pyridine. Stirring was continued for a half-hour after complete addition of the isobutyryl chloride before the reaction mixture was diluted with water. Any product that precipitated at this stage was filtered off and combined with the residue left upon evaporation of the benzene solution. The crude products were crystallized from the solvents indicated in Table II where physical constants and analyses of all new compounds are recorded. None of the acetyl derivatives have been included in Table II since these are all described in the customary reference books.

N-Acetyl-2-amino-4-nitrophenetole was prepared by nitration of acetyl-*o*-phenetidine by the method of Verkade and co-workers (7).

N-Propionyl-2-amino-4-nitrophenetole. First, 58 g. (0.3 mole) of N-propionyl-2-amino-

phenetole, prepared from *o*-phenetidine and propionic anhydride, was dissolved in a mixture of 110 ml. of concentrated sulfuric acid and 100 ml. of glacial acetic acid at 0°. A mixture of 33 ml. of nitric acid (*sp. gr.* 1.40) and 50 ml. of concentrated sulfuric acid was added slowly at the same temperature with stirring which was continued for an hour after complete addition of the mixed acid. After completion of the nitration the reaction mixture was poured onto ice, and the precipitate was filtered, washed with water and sodium carbonate solution, and recrystallized from 95% ethanol; long, thin needles, m.p. 129.5–130.5°, yield 48 g. (67%).

Anal. Calc'd for $C_{11}H_{14}N_2O_4$: N, 11.8. Found: N, 11.8.

Orientation of the nitro group in the product was established by hydrolysis of the N-propionyl derivative with aqueous hydrochloric acid. After neutralization of the hydrolyzate with ammonia and crystallization of the product from ethanol an aminonitrophenetole, m.p. 98.5–99°, was obtained which was identical with 2-amino-4-nitrophenetole (16) and did not depress the melting point of an authentic sample.

3-Nitro-4-methoxybenzoic acid. Although this product had been prepared by the nitration of anisic acid (8, 9) or anise oil (17), no details of the procedure have been reported.

Anisic acid (100 g.) was added in small portions to 750 ml. of vigorously stirred nitric acid (*sp. gr.* 1.42) while the mixture was gradually warmed to 70° and maintained there for a half-hour after complete addition of the anisic acid or until a clear solution formed. The hot reaction mixture was filtered rapidly through a glass wool pad. Nitroanisic acid separated from the filtrate on cooling and on subsequent dilution with water. Purification was effected by dissolving the product in dilute aqueous ammonia and reprecipitating with acetic acid followed by crystallization from aqueous acetic acid solution. Yield 92 g. (71%), m.p. 193.5–194°. *Methyl ester*, m.p. 109.5–110.5° (18); *anilide*, m.p. 162.5–163.5° (18).

3-Nitro-4-methoxybenzoyl chloride was prepared by treatment of 72 g. of 3-nitro-4-methoxybenzoic acid with a large excess of thionyl chloride. After crystallization of the product from ether 69 g. (87%) of the acid chloride was obtained, m.p. 53–53.5° (9, 19).

N-Methyl-3-nitro-4-methoxybenzamide. A 25% aqueous solution of methylamine (1.05 moles) was added slowly with stirring to an ether solution of 0.5 mole of 3-nitro-4-methoxybenzoyl chloride kept below 10°. The solid product was separated, washed with water, and recrystallized from 80% ethanol. Yield 82%, m.p. 163.5–164.5°.

Anal. Calc'd for $C_9H_{10}N_2O_4$: N, 13.3. Found: N, 13.3.

N-Ethyl-3-nitro-4-methoxybenzamide was prepared from 33% aqueous ethylamine and an ethereal 3-nitro-4-methoxybenzoyl chloride solution as described for the N-methyl analog in 79% yield; m.p. 116–117°.

Anal. Calc'd for $C_{10}H_{12}N_2O_4$: N, 12.5. Found: N, 12.6.

DIACYL HYDRAZINES

The diacyl hydrazines were prepared by modifications of the procedures developed by Stollé (10) and Autenrieth and Spiess (11), for the preparation of diacetyl and di-*n*-butyryl hydrazine, respectively.

Diacetyl hydrazine was prepared by the dropwise addition with stirring of 3.3 moles of acetic anhydride to one mole of hydrazine as an 85% solution of the hydrate at 0°. During the latter part of the reaction the acetic anhydride could be added more rapidly. The precipitate of diacetyl hydrazine was filtered, washed with ether, and recrystallized from 95% ethanol, m.p. 138.5–139.5° (10); yield 60–78% in various experiments.

Dipropionyl hydrazine. Two moles of propionic anhydride were added slowly with cooling to one mole of hydrazine (85% solution of the hydrate). The reaction mixture was then heated slowly and boiled under reflux for one hour after which the solution was concentrated by distillation at atmospheric pressure until the temperature of the mixture reached 220°. The product, which solidified on cooling, was filtered after dilution with petroleum ether and recrystallized from acetone, m.p. 138.5–139° (20), yield 80%.

Di-n-butyryl hydrazine was prepared by interaction of 2.2 moles of *n*-butyric anhydride and one mole of hydrazine (85% solution of the hydrate) as described for the preparation

of diacetyl hydrazine. The crude product was washed with petroleum ether and recrystallized from 95% ethanol, m.p. 169.5–171° (11), yield 68%.

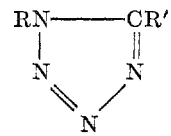
Di-isobutyryl hydrazine. This product became available as a by-product of another investigation in this laboratory (12) the results of which will be published at an early date.

1,5-ALKOXYNITROPHENYLALKYLTETRAZOLES

A. Preparation by the von Braun method. All of the alkoxynitrophenylalkyltetrazoles described in the following were prepared by the von Braun procedure (3, 4). The description of the preparation of 1-(2′-methoxy-5′-nitrophenyl)-5-*n*-propyltetrazole from 2-methoxy-

TABLE III

1-NITROPHENYL- AND 1-ALKOXYNITROPHENYL-5-ALKYLTETRAZOLES



R = C_6H_3(NO$_2$)(H (or OR))	R′	M.P., °C.	YIELD, %	RECRYSTALLIZED FROM	FORMULA	N	
						Calc'd	Found
3-NO_2 (Ref. 3)	CH_3	150–151	80	95% Ethanol	—	—	—
3-NO_2 (Ref. 3)	C_2H_5	122–123.5	79	95% Ethanol	—	—	—
4-NO_2 (Ref. 3)	CH_3	132–133.5	66	99% 2-Propanol	—	—	—
4-NO_2	C_2H_5	124.5–125.5	74	95% Ethanol	$C_9H_9N_5O_2$	32.0	31.7
3-NO_2-4-OCH_3	CH_3	149.5–150.5	83	95% Ethanol	$C_9H_9N_5O_3$	29.8	29.5
3-NO_2-4-OCH_3	C_2H_5	119.5–121	66	90% 2-Propanol	$C_{10}H_{11}N_5O_3$	28.1	28.0
3-NO_2-4-OCH_3	*n*-C_3H_7	105.5–106	88	90% Ethanol	$C_{11}H_{13}N_5O_3$	26.6	26.7
3-NO_2-4-OCH_3	iso-C_3H_7	143–144.5	82	99% 2-Propanol	$C_{11}H_{13}N_5O_3$	26.6	26.8
2-OCH_3-5-NO_2	CH_3	174–175.5	70	95% Ethanol	$C_9H_9N_5O_3$	29.8	29.6
2-OCH_3-5-NO_2	C_2H_5	157.5–158.5	88	95% Ethanol	$C_{10}H_{11}N_5O_3$	28.1	27.9
2-OCH_3-5-NO_2	*n*-C_3H_7	140–141.5	92	95% Ethanol	$C_{11}H_{13}N_5O_3$	26.6	26.6
2-OCH_3-5-NO_2	iso-C_3H_7	162–163.5	79	95% Ethanol	$C_{11}H_{13}N_5O_3$	26.6	26.6
2-OCH_3-4-NO_2	CH_3	140.5–141.5	78	90% 2-Propanol	$C_9H_9N_5O_3$	29.8	30.0
2-OCH_3-4-NO_2	C_2H_5	116–116.5	78	90% 2-Propanol	$C_{10}H_{11}N_5O_3$	28.1	27.9
2-OCH_3-4-NO_2	*n*-C_3H_7	118–119	72	90% 2-Propanol	$C_{11}H_{13}N_5O_3$	26.6	26.5
2-OCH_3-4-NO_2	iso-C_3H_7	167–168	79	95% Ethanol	$C_{11}H_{13}N_5O_3$	26.6	26.8
2-OC_2H_5-5-NO_2	CH_3	145.5–147	85	99% 2-Propanol	$C_{10}H_{11}N_5O_3$	28.1	28.4
2-OC_2H_5-5-NO_2	C_2H_5	129–130.5	85	80% 2-Propanol	$C_{11}H_{13}N_5O_3$	26.6	26.9

5-nitro-*n*-butyranilide illustrates the general procedure employed for the synthesis of the compounds listed in Table III.

2-Methoxy-5-nitro-*n*-butyranilide (59.5 g., 0.25 mole) was suspended in 500 ml. of benzene in a two-liter three-necked 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 by means of a short length of wide bore rubber tubing. The phosphorus pentachloride was added to the vigorously stirred benzene suspension in small portions. Hydrogen chloride was evolved as the reaction progressed and 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 portions. The reaction mixture was then gradually warmed to the boiling point on a water-bath and maintained at this temperature until hydrogen chloride evolution ceased. The solvent was removed under diminished pressure and the residue treated with 250 ml. of ice-water and 30 ml. of concentrated hydrochloric acid. The aqueous acid suspension was boiled under reflux for an hour to hydrolyze unreacted anilide 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% ethanol from which it separated as long, colorless needles, m.p. 140–141.5°, yield 60 g. (92%).

The amine formed by hydrolysis of the anilide could be recovered by neutralization of the acid solution.

In most instances the substituted amides could be converted into the imide chlorides by stirring in benzene solution or suspension with phosphorus pentachloride at room temperature. However, in the case of 3-nitro-4-methoxyacetanilide and the corresponding propionanilide heating was necessary to initiate interaction and in the case of N-methyl- and N-ethyl-3-nitro-4-methoxybenzamide the reaction mixture had to be boiled to bring about interaction of the amide and the phosphorus pentachloride. The imide chlorides were generally quite soluble in benzene except those derived from 3-nitro-4-methoxy acet- and propion-anilide. These latter 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 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 1-nitrophenyltetrazoles and the 1-alkoxynitrophenyltetrazoles prepared in this manner are listed in Table III together with pertinent physical and analytical data.

1-Methyl-5-(3'-nitro-4'-methoxyphenyl)tetrazole was prepared from N-methyl-3-nitro-4-methoxybenzamide by interaction successively with phosphorus pentachloride and hydrazoic acid in benzene solution as just described. Recrystallized from 95% ethanol as long needles, m.p. 115–115.5°, yield 85%.

Anal. Calc'd for $C_9H_9N_5O_3$: N, 29.8. Found: N, 29.5.

1-Ethyl-5-(3'-nitro-4'-methoxyphenyl)tetrazole was prepared from N-ethyl-3-nitro-4-methoxybenzamide by treatment first with phosphorus pentachloride and then with hydrazoic acid in benzene solution. Recrystallized from 80% ethanol as fine needles, m.p. 94.5–95°, yield 81%.

Anal. Calc'd for $C_{10}H_{11}N_5O_3$: N, 28.1. Found: N, 28.3.

B. Preparation by the Dimroth method. A group of ten nitrophenyl- and alkoxynitrophenyl-tetrazoles was also prepared by the Dimroth procedure (5). 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°, a solution of 1.44 g. (0.02 mole) of sodium nitrite in 5 ml. of water was added slowly. The diazonium salt solution was then treated with 5 g. of sodium acetate and 10 ml. of 5 *N* sodium hydroxide and added in small portions to a solution of 2.5 g. (0.02 mole) of diacetyl hydrazine in 60 ml. of 1.5 *N* sodium carbonate kept below 0°. Without isolation of the intermediate diazohydrazide which separated as a voluminous white precipitate, 40 ml. of 5 *N* sodium hydroxide was added with stirring. A clear solution resulted from which the tetrazole separated slowly at room temperature. The product was filtered off, washed with water, and dissolved in hot concentrated hydrochloric acid from which it separated after filtration upon dilution with water. The crude tetrazole was recrystallized from 95% ethanol, yield 2.1 g. (45%), m.p. 140.5–141.5°.

The above procedure was modified in several aspects in the preparation of some of the other tetrazoles. In the preparation of the 5-*n*-propyl and 5-isopropyl substituted tetrazoles, 0.02 mole of the di-*n*-butyryl or diisobutyryl hydrazine, respectively, was first suspended in 50 ml. of 1 *N* sodium carbonate. After addition of 20 g. of sodium acetate to the suspension,

5 *N* sodium hydroxide was added dropwise with gentle warming until the diacyl hydrazine had dissolved completely. Approximately 4–5 ml. of 5 *N* sodium hydroxide was required. The solution was then cooled to 0° and coupled with the diazonium compound as already described.

In most instances the diazohydrazides that separated after coupling were filtered off and, without further purification, treated with 40 ml. of 5 *N* sodium hydroxide to effect cyclization. In the preparation of 1-(2′-methoxy-4′-nitrophenyl)-5-ethyl-, -5-*n*-propyl-, and -5-isopropyl-tetrazoles, oily or semi-solid products formed upon treatment of the diazohydrazide with sodium hydroxide solution. These products could be made to solidify by heating the reaction mixture to about 50°. In the case of 1-*m*-nitrophenyl-5-*n*-propyltetrazole, an oily product formed at this stage which could not be converted into the solid state by heating but which did solidify on grinding in a mortar with 5 *N* sodium hydroxide. Generally it was helpful to dissolve the crude tetrazoles in concentrated hydrochloric acid and to reprecipitate by dilution with water before recrystallizing the products from alcohol, aqueous alcohol, or benzene. The treatment with hydrochloric acid was omitted when the crude tetrazole was only slightly colored or only sparingly soluble in concentrated hydrochloric acid.

The tetrazoles prepared by the Dimroth method are listed in Table I together with their melting points and yields for comparison with the results obtained by the von Braun method. In all cases the products obtained by both procedures were identical and no depression was observed when mixture melting points were taken.

1,5-ALKOXYAMINOPHENYLALKYLTETRAZOLES

This group of compounds was prepared by the catalytic hydrogenation of the corresponding alkoxynitrophenyltetrazoles by application of the procedure of Herbst, *et al.* (3). The preparation of 1-(2′-ethoxy-5′-aminophenyl)-5-ethyltetrazole is described as a typical example.

To a solution of 26.3 g. (0.1 mole) of 1-(2′-ethoxy-5′-nitrophenyl)-5-ethyltetrazole in 210 ml. of glacial acetic acid, 0.15 g. of Adams' platinum oxide catalyst was added. The mixture was shaken in the Burgess-Parr low pressure hydrogenation apparatus at an initial hydrogen pressure of 50 lbs./sq. in. and the reduction was complete in about 30 minutes. After removal of the catalyst the solvent was evaporated under diminished 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 a small amount of insoluble material. The filtrate was made alkaline to litmus with aqueous ammonia and the amine that separated was filtered and washed with cold water. The crude base was recrystallized twice from 30% ethanol, colorless needles, m.p. 149–150°, yield 18.4 g. (79%).

In case the alkoxynitrophenyltetrazole was not completely soluble in glacial acetic acid, the solid was pulverized and suspended in the solvent. Reduction was carried out as just described. The solid usually dissolved rapidly as the hydrogenation progressed. In some instances intensely colored reduction products were formed, but these could usually be avoided by increasing the speed of the reduction by the use of a slightly greater amount of catalyst. When they were present the colored by-products could best be removed by converting the amine into its hydrochloride which could be obtained colorless by recrystallization from suitable solvents, or by heating its aqueous solution with a small granule of zinc. The base liberated from the purified hydrochloride was generally colorless.

1-Methyl-5-(3′-amino-4′-methoxyphenyl)tetrazole was obtained by catalytic reduction of 1-methyl-5-(3′-nitro-4′-methoxyphenyl)tetrazole as just described. Recrystallized from 70% ethanol as small needles, m.p. 153.5–154.5°, yield 71%.

Anal. Calc'd for $C_9H_{11}N_5O$: N, 34.1. Found: N, 34.3.

Hydrochloride, small prisms from absolute ethanol, m.p. 220.5–222.5° with decomposition.

Anal. Calc'd for $C_9H_{12}ClN_5O$: N, 29.0. Found: N, 29.4.

Acetyl derivative, fine needles from water, m.p. 183.5–185°.

Anal. Calc'd for $C_{11}H_{13}N_5O_2$: N, 28.3. Found: N, 28.5.

1-Ethyl-5-(3'-amino-4'-methoxyphenyl)tetrazole was prepared from 1-ethyl-5-(3'-nitro-4'-methoxyphenyl)tetrazole by catalytic reduction as described in the preceding paragraphs. Recrystallized from 30% ethanol as leaflets, m.p. 90–91.5°, yield 66%.

Anal. Calc'd for $C_{10}H_{13}N_5O$: N, 32.0. Found: N, 32.1.

Hydrochloride, small needles from methanol-acetone-benzene, m.p. 202–204° with decomposition.

Anal. Calc'd for $C_{10}H_{14}ClN_5O$: N, 27.4. Found: N, 27.6.

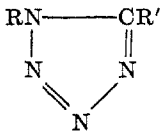
Acetyl derivative, prisms from 30% isopropyl alcohol, m.p. 109–110°.

Anal. Calc'd for $C_{12}H_{15}N_5O_2$: N, 26.8. Found: N, 27.1.

All other alkoxyaminophenylalkyltetrazoles are described in Table IV where physical constants and analytical data are recorded.

TABLE IV

1-AMINOPHENYL- AND 1-ALKOXYAMINOPHENYL-5-ALKYLTETRAZOLES



R = C_6H_3(NH$_2$)(H or OR)	R'	M.P., °C.	YIELD, %	RECRYSTALLIZED FROM	FORMULA	N	
						Calc'd	Found
3-NH_2 (Ref. 3).....	CH_3	122–124	74	Water	—	—	—
3-NH_2 (Ref. 3).....	C_2H_5	112.5–113	64	Water	—	—	—
4-NH_2 (Ref. 3).....	CH_3	146–148	69	Water	—	—	—
4-NH_2.....	C_2H_5	95.5– 97	53	Water	$C_9H_{11}N_5$	37.0	37.0
3-NH_2-4-OCH_3	CH_3	119.5–120.5	77	Water	$C_9H_{11}N_5O$	34.1	34.6
3-NH_2-4-OCH_3.....	C_2H_5	72.5– 73.5	64	30% Ethanol	$C_{10}H_{13}N_5O$	32.0	31.6
3-NH_2-4-OCH_3	*n*-C_3H_7	90–91.5	80	30% Ethanol	$C_{11}H_{15}N_5O$	30.0	29.9
3-NH_2-4-OCH_3	iso-C_3H_7	112–112.5	66	30% Ethanol	$C_{11}H_{15}N_5O$	30.0	30.3
2-OCH_3-5-NH_2	CH_3	130–132	69	Water	$C_9H_{11}N_5O$	34.1	34.1
2-OCH_3-5-NH_2	C_2H_5	173–175	72	30% Ethanol	$C_{10}H_{13}N_5O$	32.0	32.1
2-OCH_3-5-NH_2.....	*n*-C_3H_7	138–139.5	71	30% Ethanol	$C_{11}H_{15}N_5O$	30.0	30.0
2-OCH_3-5-NH_2.....	iso-C_3H_7	210.5–211.5	81	90% Ethanol	$C_{11}H_{15}N_5O$	30.0	30.4
2-OCH_3-4-NH_2.	CH_3	84–85	69	Water	$C_9H_{11}N_5O$	34.1	33.9
2-OCH_3-4-NH_2	C_2H_5	94–95	63	25% Ethanol	$C_{10}H_{13}N_5O$	32.0	32.0
2-OCH_3-4-NH_2	*n*-C_3H_7	119.5–120	74	25% Ethanol	$C_{11}H_{15}N_5O$	30.0	30.2
2-OCH_3-4-NH_2	iso-C_3H_7	132.5–133.5	79	25% Ethanol	$C_{11}H_{15}N_5O$	30.0	29.7
2-OC_2H_5-5-NH_2.....	CH_3	129.5–130.5	79	Water	$C_{10}H_{13}N_5O$	32.0	32.4
2-OC_2H_5-5-NH_2.....	C_2H_5	149–150	79	30% Ethanol	$C_{11}H_{15}N_5O$	30.0	30.2

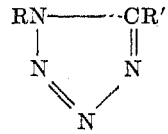
Hydrochlorides of the alkoxyaminophenylalkyltetrazoles were prepared by passing dry hydrogen chloride into an isopropyl alcoholic solution of the tetrazole. If the hydrochloride separated from the alcoholic solution, as in the case of most of the 5-methyl substituted tetrazoles, it was filtered off, washed with ether, and recrystallized from absolute alcohol. When the hydrochloride did not separate, the alcoholic solution was concentrated and carefully diluted with ether. The solid hydrochlorides could then be recrystallized from an appropriate combination of methanol-acetone-benzene. In a few instances addition of ether caused the hydrochloride to separate as a viscous syrup which usually solidified after decanting the supernatant liquid and drying in a stream of dry air or on trituration with a small amount of acetone.

Acetyl derivatives were prepared by heating a gram of the alkoxyaminophenyltetrazole

with 1.5 g. of acetic anhydride. The crude acetyl derivatives which separated on diluting the reaction mixture with water were recrystallized from water or aqueous isopropyl alcohol. Physical constants and analytical data for the hydrochlorides and acetyl derivatives are recorded in Table V.

TABLE V

HYDROCHLORIDES AND ACETYL DERIVATIVES OF 1-AMINOPHENYL- AND 1-ALKOXYAMINOPHENYL-5-ALKYLTETRAZOLES



R = C_6H_3(NH$_2$)(H (or OR))	R′	HYDROCHLORIDES[a]			ACETYL DERIVATIVES		
		M.P., °C.	N		M.P., °C.	N	
			Calc'd	Found		Calc'd	Found
3-NH_2 (Ref. 3)	CH_3	207–210 d.	—	—	—	—	—
3-NH_2 (Ref. 3)	C_2H_5	192–195 d.	—	—	—	—	—
4-NH_2 (Ref. 3)	CH_3	213–215 d.	—	—	—	—	—
4-NH_2	C_2H_5	203–206 d.	31.0	30.9	133–136	30.3	30.1
3-NH_2-4-OCH_3	CH_3	215–217 d.	29.0	28.6	200–200.5	28.3	28.4
3-NH_2-4-OCH_3	C_2H_5	188–191	27.4	27.4	165.5–167	26.8	26.9
3-NH_2-4-OCH_3	n-C_3H_7	171–174	26.0	25.8	157–158	25.4	25.5
3-NH_2-4-OCH_3	iso-C_3H_7	150–152	26.0	25.8	154.5–156	25.4	25.6
2-OCH_3-5-NH_2	CH_3	230–232 d.	29.0	28.6	191–193	28.3	28.2
2-OCH_3-5-NH_2	C_2H_5	211–214 d.	27.4	27.1	154.5–155.5	26.8	26.7
2-OCH_3-5-NH_2	n-C_3H_7	190–193	26.0	26.0	172.5–174.5	25.4	25.5
2-OCH_3-5-NH_2	iso-C_3H_7	173–176[b]	26.0	25.8	180.5–182.5[c]	25.4	25.7
2-OCH_3-4-NH_2	CH_3	204–206 d.	29.0	28.6	187–188	28.3	28.4
2-OCH_3-4-NH_2	C_2H_5	168–171 d.	27.4	27.5	141–142.5	26.8	26.9
2-OCH_3-4-NH_2	n-C_3H_7	167–170 d.	26.0	26.3	150.5–151.5	25.4	25.4
2-OCH_3-4-NH_2	iso-C_3H_7	183–186 d.	26.0	26.0	128.5–129.5[d]	25.4	25.0
2-OC_2H_5-5-NH_2	CH_3	207–210 d.	27.4	27.8	176–177	26.8	27.1
2-OC_2H_5-5-NH_2	C_2H_5	190–193 d.	26.0	25.8	152–153.5	25.4	25.5

[a] The melting points of all hydrochlorides were determined in sealed capillaries. The rate of heating often caused variation in the observed melting point. [b] After drying at 110 at 2 mm. over phosphorus pentoxide. [c] After drying at 110° at 15 mm. over phosphorus pentoxide. [d] Crystallized as a hydrate melting unsharply at 65°; m.p. of anhydrous acetyl derivative given.

SUMMARY

A series of twelve new N-acylalkoxynitroanilines and N-alkylmethoxynitrobenzamides has been prepared as intermediates for the preparation of a new group of tetrazole compounds.

A group of sixteen new 1,5-alkoxynitrophenylalkyltetrazoles has been prepared by interaction of both the N-acylalkoxynitroanilines and the N-alkylmethoxynitrobenzamides with phosphorus pentachloride and treatment of the imide chlorides so formed with hydrazoic acid. In each instance the nitro com-

pounds were reduced to the corresponding alkoxyaminophenylalkyltetrazoles catalytically and the latter were characterized as the bases, hydrochlorides, and acetyl derivatives.

The preparation of 1-aryl-5-alkyltetrazoles by the coupling of diazotized aromatic amines with diacyl hydrazines and cyclization of the diazohydrazides formed as intermediates has been reinvestigated and extended. A group of ten 1-aryl-5-alkyltetrazoles has been prepared including not only 5-methyl but 5-ethyl, 5-*n*-propyl and 5-isopropyl substituted tetrazoles. The cyclization of the diazohydrazides can be accelerated by heating them in aqueous alkaline solution. The over-all yields of tetrazoles obtained by this procedure are, however, lower than those obtained by the procedure involving formation of the N-substituted amides and intermediate formation of the imide chlorides.

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